Interaction between Aromatic Residues. Molecular Dynamics and ab Initio Exploration of the Potential Energy Surface of the Tryptophan−Histidine Pair

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Received: June 29, 1999; In Final Form: October 11, 1999

Empirical force fields for minimum searching in the tryptophan−histidine intermolecular energy surface were used. Fourteen principal minima were identified. For each of these structures the intermolecular energies were computed by using single point correlated ab initio calculation with a split valence and a correlation consistent valence double-ζ basis set. The force field determined complexes have much larger correlated ab initio stabilization energy than those reported in previous studies where a purely ab initio search method was used. The largest stabilization energy was found for a T-shaped complex stabilized by a NH···N hydrogen bond. Stacked structures with superimposed and parallel-displaced imidazole rings were also found to be very stable.

I. Introduction

The interaction between aromatic residues is of primary importance in many processes in chemistry and biology. This interaction can influence the stereochemistry of organic reactions[1] and the binding affinities in host−guest chemistry.[2] In biological molecular systems aromatic residues can engage in specific energetically favorable interactions. Base stacking, for example, certainly plays an important role in stabilizing the helical structure in DNA. Similarly the interactions between planar aromatic side chains can stabilize the protein's structure. Despite the relevance of the problem, the role of the various contributions to the interaction energy in stabilizing a given reciprocal arrangement of aromatic residues has not been fully understood.

The T-shaped structure, with the planes of the ring perpendicular to each other, is known to be the preferred arrangement for the benzene dimer in the gas-phase[3] and a T-shaped arrangement is also found in crystalline benzene.[4] The stacked "edge-displaced" [3] (i.e., with the ring planes parallely displaced) and "sandwich" structures (i.e., with superimposed planes) are also local minima for the benzene dimer, stabilized by concurrent dispersion interactions. In aromatic compounds with polar moieties, the energetics of these structures, characterized by weak and favorable dispersion interactions, is also strongly affected by electrostatic interactions and hydrogen bonds.[5] The correct representation of the potential energy surface (PES) for the interactions between aromatic compounds is a fundamental requirement for understanding the competition between T-shaped and stacked structures at finite temperatures. In the case of complex PES emerging from the intermolecular interactions that are the object of this paper, it is presently unfeasible, due to the prohibitive computational demand, to characterize it with a purely ab initio approach. Correlated ab initio methods allow the calculation of the energy and structure of molecular complexes within "chemical accuracy" but due to their computational demand can be used, at present, only to sample selected points of the PES. Less demanding semiempirical methods such as MNDO,[6] PM3,[7] or AM1[8] are known to perform poorly with respect to intermolecular PES.[9] Empirical *force fields* (FF), specifically devised for representing protein interactions, have been proven in several cases[10,9] to be quite reliable in representing the PES of the interaction of biological molecules. Empirical FFs are computationally convenient to explore, using molecular dynamics approaches, more thoroughly the PES, although the interaction energies obtained are only approximate.

In this paper a mixed approach has been adopted to take advantage on the one hand of the possibility of fully exploring the PES using classical molecular dynamics in conjunction with suitable FFs and on the other hand of the accuracy of the correlated ab initio methods to obtain interaction energies. The approach has been used specifically to study the interaction of the aromatic residues histidine (his) and tryptophan (trp) that

10.1021/jp992208g CCC: $19.00
Published on Web 01/13/2000

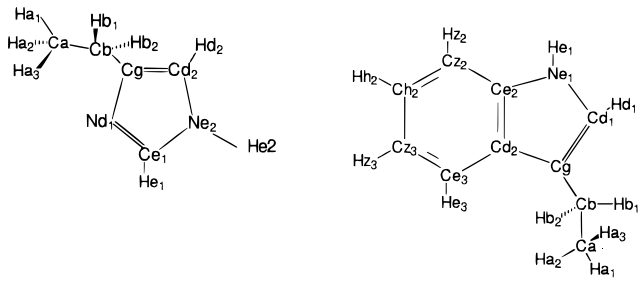

Figure 1. ϵ-protonated 5-ethylimidazole and 3-ethylindole.

are of intrinsic interest and seem to be implicated in interactions such as those of tachykinines with both peptide and non peptide antagonists.[11] The *global* search for minima conformations in the PES has been done by using classical molecular dynamics, while the intermolecular energy of the resulting conformations have been evaluated by means of correlated ab initio calculations using second-order Moeller−Plesset perturbation theory (MP2). This mixed FF/MP2 approach has been shown to sample efficiently the low-energy minima in the trp−his interaction space. In a recent paper Alagona et al.[12] studied the trp−his interaction by sampling the PES with a purely quantum mechanical approach along *selected* intermolecular coordinates, starting from experimental T-shaped or stacked arrangements. According to their findings, stacked structures are strongly favored with respect to T-shape arrangements in vacuo. In the present paper, using the same quantum chemical approach but an entirely different PES scanning procedure, it is shown that T-shaped structures, stabilized by hydrogen bonds, are actually as stable as, or more stable than, stacked arrangements, in agreement with previous studies on the interaction of trp with aromatic residues.[13] In this work, at the MP2 level, very stable T-shaped and X-shaped structures were found which were completely missed in previous studies.[12]

The paper is organized as follows: In section II the methodology for determining the relevant local minima for the interaction using the empirical FFs is discussed. Results and comparison of two popular FFs with respect to the PES representation are also discussed in this section. In section III calculation at the MP2 level for the most significant local minima of the residues' interaction are presented and the ab initio stabilization energies are compared with the results given by the empirical FFs. Conclusive remarks appear in section IV.

II. Determination of PES of the trp−his Interaction Using Empirical Force Fields

A. PES Scanning and Quenching Methodology for Local Minima Search. The aromatic compounds considered in the present report are the ϵ protonated 3-ethylindole (trp) and 5-ethylimidazole (his) (see Figure 1). The ethyl substitution was introduced to mimic the effect of the steric hindrance of the peptide backbone. In the present section the PES of intermolecular interactions between trp and his is characterized by using the AMBER[14] and CHARMM[15] FFs. These FFs parametrize the internal energy as a series of valence contributions such as stretching, bending, and torsions and the intermolecular energies as a sum of Lennard-Jones and charge−charge interactions. On the basis of the potential databases,[14,15] all constants referring to intra- or intermolecular potentials can be easily deduced from the knowledge of the molecular topology and of the atomic FF types. The CHARMM and AMBER atomic types are assigned according to the types reported in the databases for the atoms of trp and his in the protein backbone (see Table 1). In the case of the AMBER FF, as prescribed in ref 14, the atomic charges are determined by using a ESP procedure.[16] The gridded electrostatic potential is computed at the MP2/6-31G* level. The ESP atomic charges are reported in Table 1. In the CHARMM protocol the charges on the protein residues are simple parameters selected in order to reproduce interaction energies and minimum energy geometries for model supermolecules and are not derived by special procedure such as ESP. In the case of CHARMM, therefore, we used the original charges[15] devised for trp and his in the protein backbone (see Table 1).

The minima in the AMBER and CHARMM PES for the total interaction energy for the trp−his complex were determined by quenching 1000 structures sampled from a molecular dynamics (MD) simulation at 300 K lasting for 0.3 ns. The program ORAC[17] was used in all the MD simulations and energy minimizations. During the configurational sampling by MD, the two molecules were tethered together by a weak dummy bond between the two terminal ethyl carbons. Structures were stored to disk at regular intervals of 0.3 ps. The saved structures were then minimized after elimination of the dummy bond using the conjugate gradient method.[18] Some of the minimized structures were discarded either because their energy was more than 10 kJ/mol above the average energy of the local minima, because they corresponded to saddle points, or because their population was too scarce (less than 0.1%). After this filtering, the MD/quenching procedure resulted in 21 and 23 distinct principal minima for the CHARMM and for the AMBER FF, respectively. The normalized population $p_i = N_i/N_{tot}$, with N_i and N being the number of quenched minima of type i and the total number of quenched structures, respectively, measures the size of the "energy basin" of the i-th local minimum at the simulation temperature of 300 K. The convergence of the population was checked by performing further 0.3 ns of MD/quenching for each of the FFs. New minimum structures did not appear and significant changes in the populations p_i were not observed. The effect of the dummy bond was also evaluated by performing 3 different 0.3-ns MD/quenching simulations, using the AMBER suite, with bonds 5, 7, and 9 Å. In all the cases, neither new minima were found nor any significant difference in the final populations was noticed.

B. Structures and Energetics of the AMBER and CHARMM Complexes. Since the interest of this work was in the interaction energy of the aromatic rings and not in the position of the ethyl chains, all the structures which differ mainly in the position of the ethyl moiety were grouped together. In this way we were left with seven groups of minima for CHARMM and seven for AMBER.

The structures of the most energetically favorable conformers within each group are shown in Figures 2 and 3 for AMBER and CHARMM, respectively. In the figures the intermolecular energy E_s, the population p, the distance D between the centroids of the his and trp rings, and the angle θ between the vectors perpendicular to the planes are reported for each structure. The intermolecular energy E_s of the complex, reported in the figures, is defined as $E_s = E_c(0) - E_{trp}(0) - E_{his}(0)$, where E_c refers to the total potential energy of the complex and the individual energies of trp and his, $E_{trp}(0)$ and $E_{his}(0)$, were calculated by using the coordinates of these molecules in the complex. With this choice for the intermolecular energy definition, the deformation contribution to the energy of the complex was deliberately excluded. The AMBER FF predicts two principal stacked minima with comparable stabilization energy, labeled from now on as AS1 and AS2. These complexes are stabilized mainly by

TABLE 1: Atomic Types and Charges in Electrons for the AMBER and CHARMM Force Fields

3-ethylindole (trp)					5-ethylimidazole (his)				
	AMBER		CHARMM			AMBER		CHARMM	
label	type	*q*/e	type	*q*/e	label	type	*q*/e	type	*q*/e
ca.	ct	−0.162 992	CT3	−0.27	ca.	ct	0.059 585	CT3	−0.27
ha1	hc	0.042 488	HA	0.09	ha1	hc	−0.005 752	HA	0.09
ha2	hc	0.042 488	HA	0.09	ha2	hc	−0.005 751	HA	0.09
ha3	hc	0.042 488	HA	0.09	ha3	hc	−0.005 752	HA	0.09
cb	ct	0.118 634	CT2	−0.18	cb	ct	−0.156 343	CT2	−0.08
hb1	hc	0.013 542	HA	0.09	hb1	hc	0.042 949	HA	0.09
hb2	hc	0.003 977	HA	0.09	hb2	hc	0.042 949	HA	0.09
cg	c*	−0.245 828	CY	−0.03	cg	cc	0.355 155	CPH1	0.22
cd1	cw	−0.109 004	CA	0.035	nd1	na	−0.503 272	NR2	−0.70
hd1	h4	0.168 916	HP	0.115	ce1	cr	0.145 401	CPH2	0.25
ne1	na	−0.415631	NY	−0.61	he1	h5	0.099172	HR1	0.13
he1	h	0.363 488	H	0.38	ne2	na	−0.249721	NR1	−0.36
ce2	cn	0.186 576	CPT	0.13	he2	h	0.326 098	H	0.32
cz2	ca.	−0.285 681	CA	−0.115	cd2	cw	−0.339 718	CPH1	−0.05
hz2	ha	0.158 022	HP	0.115	hd2	h4	0.195 000	HR3	0.09
ch2	ca.	−0.111 906	CA	−0.115					
hh2	ha	0.119 982	HP	0.115					
cz3	ca.	−0.149 149	CA	−0.115					
hz3	ha	0.125 199	HP	0.115					
ce3	ca.	−0.286 737	CA	−0.115					
he3	ha	0.174 946	HP	0.115					
cd2	cb	0.206 182	CPT	−0.02					

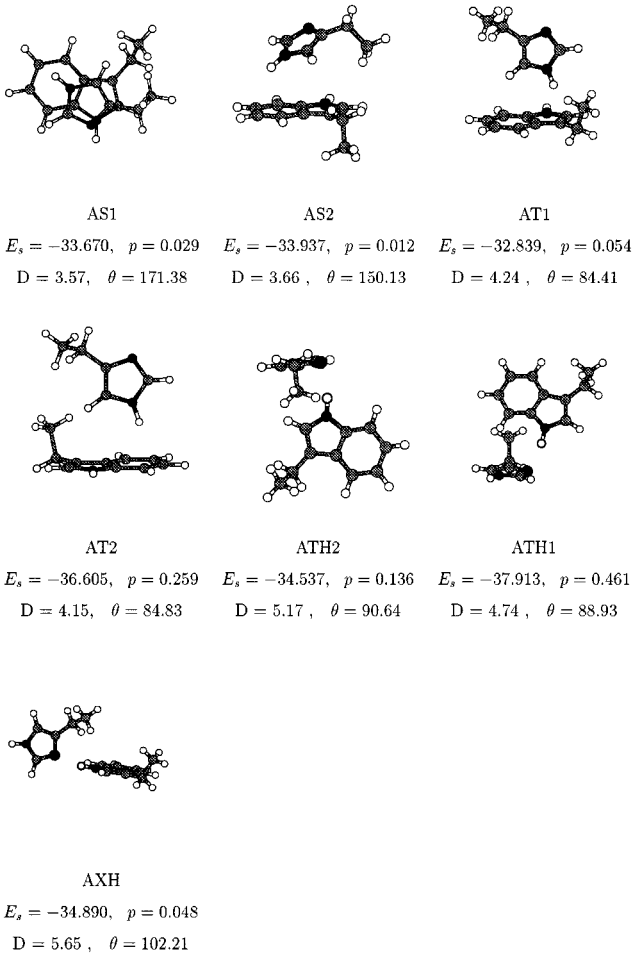

Figure 2. AMBER local minimum structures (see text for details).

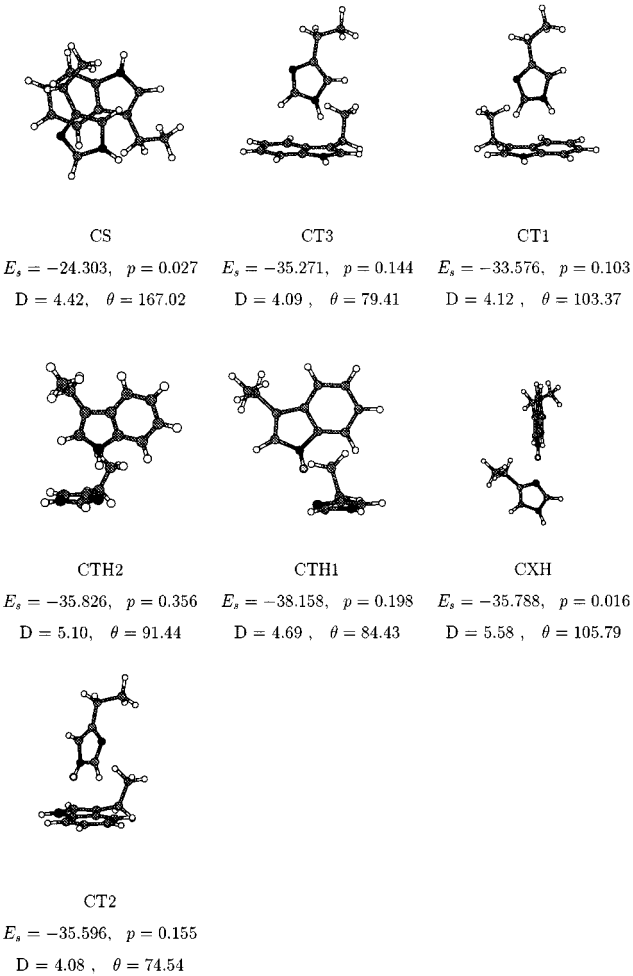

Figure 3. CHARMM local minimum structures (see text for details).

the dispersive Lennard-Jones interaction (≃60% of the stabilization energy comes from Lennard-Jones interactions). The AS1 structure corresponds to a sandwich structure with almost perfect superposition of the five-membered ring of trp with the his ring, whereas AS2 is an edge-displaced structure with parallel displacement of the two five-membered rings. T-shaped minima are characterized by the presence of hydrogen bonds (ATH1, ATH2) or by a NH bond perpendicular to a ring (AT1, AT2). In the former case the stabilization energy is mostly electrostatic (≃70%), while in the latter the electrostatic contribution is approximately equivalent to that of the dispersive term. The

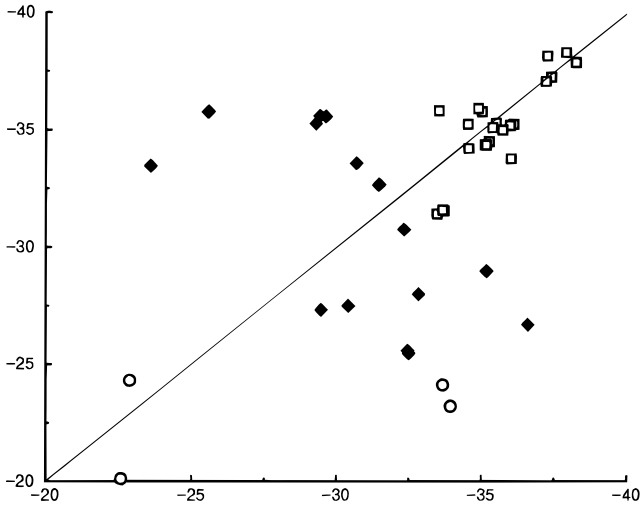

Figure 4. Correlation diagram for the interaction energies (kJ/mol) of the complexes calculated by AMBER (*x* axis) and CHARMM (*y* axis) FFs. Squares refer to H-bonded structures (X- and T-shaped). Diamonds refer to T-shaped structures without H-bonds. Circles refer to stacked structures.

minimum corresponding to an edge-to-edge (or X-shaped) structure is also stabilized by electrostatic interactions. The most stable structure are the T-shaped ATH1 and AT2 conformations.

The CHARMM FF fails to predict the stacked structures found with AMBER and so common in proteins,[12] predicting only one stacked structure (CS) with strongly displaced rings and low stabilization energy (≃24 kJ/mol). The minimum structures corresponding to H-bonded T-shaped and to X-shaped structures found using the CHARMM FF are practically identical to those obtained with AMBER and also have similar stabilization energies: the structures labeled as CTH1, CTH2, and CXH in Figure 2 are closely related to ATH1, ATH2, and AXH in Figure 3.

Non-H-bonded T-shaped minima found by CHARMM are similar to those found by AMBER except for the CT3 structure, which corresponds to a T-shaped arrangement stabilized by a nonlinear hydrogen bond *NH*···*NH*. No such minimum structure is found using the AMBER FF.

In Figure 4 the energy correlation diagram for all the 44 structures corresponding to minima of AMBER (23) and CHARMM (21) FFs is shown. The energies corresponding to structures with strong hydrogen bonds (TH and X structures) are well correlated, while stacked and T-shaped "aromatic" interactions are not. The AMBER local minima corresponding to the T-shaped structures without the presence of linear hydrogen bonds are predicted to be much less stable with CHARMM, and vice-versa, similar T-shaped structures, corresponding to CHARMM local minima, have much lower stabilization energy when computed with AMBER. For both FFs, however, the hydrogen bond interactions in the trp−his complex appear to favor T-shaped, edge-to-face structures. T-shaped conformers, either with (ATH1, ATH2, and CTH2) or without strong hydrogen bonds (like AT2, CT2, and CT3) are in fact those with the largest energy basins in both the AMBER and CHARMM PES (see Figures 2 and 3). The stacked structures, despite their relatively high stabilization energy and the edge-to-edge crossed geometry, on the contrary, are scarcely populated.

The observed high populations and high stabilization energy for the T-shaped complex in the gas-phase contrasts with the relatively small incidence of these structures found in proteins.[12,19] Several studies[12,13,19,20] on databases of well resolved protein structures taken from the Brookhaven Protein Data Bank have shown that T-shaped structures are favored for aromatic interactions involving nonpolar residues such as trp and phenylalanine (phe). The stacked structures are instead favored when the strongly polar residue his interacts with other aromatic amino acids.[13] The destabilization of T-shaped complexes involving his in real proteins is probably a solvent effect. As previously stated, the electrostatic contribution to the stabilization energy in T-shaped complexes is much larger than that found in stacked structures. The dielectric screening for the his/aromatic complexes, being his is a polar residue usually exposed to the solvent, is therefore probably responsible for the destabilization of the T-shaped arrangements in favor of stacked structures which are less affected by the presence of the solvent. For complexes involving nonpolar aromatic residues, buried in the protein interior and hence with little interaction with the solvent, T-shaped structures are not destabilized and hence are more abundant than stacked conformations.[19]

III. Ab Initio Calculations

To verify the reliability of the intermolecular energies as determined by the CHARMM and AMBER FF for the various structure of the trp/his complex, ab initio single point calculations of the intermolecular energy for the 14 structures reported in the Figures 2 and 3 were performed. The intermolecular energy of the complex was calculated as the sum of the Hartree−Fock and a electronic correlation contributions, i.e., $E_s = E_s(\mathrm{HF}) + E_s(\mathrm{COR})$. $E_s(\mathrm{COR})$ was calculated at the MP2 level with the "frozen core" approximation.[31] The full function counterpoise method of Boys and Bernardi[21] was applied to both energy components to eliminate the superposition error (BSSE). Recently the correctness of the Boys and Bernardi scheme for evaluating intermolecular energies at all level of basis set completeness has been demonstrated.[22,23] The geometry used for the three calculations (two for the isolated monomers with "ghost" partners and that for the complex) was identical to that of the MD quenched structures.

A. Basis Set Selection. The selection of the basis set in intermolecular energy computations is indeed a crucial point. To obtain reliable intermolecular energies, polarization functions must be included[24,25] in the basis set. The standard split valence 6-31G* basis set with diffuse *d* orbitals is known to significantly underestimate the *zz* polarizability tensor element[26] (with *z* being the component perpendicular to the ring in aromatic compounds) and hence also the correlation energy. The use of a significantly larger basis set in aromatic systems is not recommended[27] at the MP2 level since it would lead to an overestimation of the correlation energy, especially for stacked structures where the dispersion contribution is larger.

Therefore a 6-31G*(0.25) basis set was used. This basis set relies on *dispersion* energy-optimized, rather than simply energy-optimized, diffuse functions with an orbital exponent of 0.25 for C, N, and O. While in general the use of split valence basis sets is not recommended for the intermolecular interactions,[24,3] this particular split valence basis set, possibly because of error cancellations, gave good values for the energy in the case of DNA bases interactions[27] and was used by Alagona et al. in their study of trp−his interactions.[12]

However, for structures stabilized by mainly electrostatic interactions, like T-shaped complexes (A,C)TH2, it is not yet clear[27,26] whether the basis set size corresponding to the 6-31G*-(0.25) (580 primitive Gaussians for the trp−his complex) is appropriate at the MP2 level. Therefore, for comparison, calculations were also carried with a segment optimized cc-

TABLE 2: Interaction Energies in kJ/mol for the 14 Structures Reported in Figures 2 and 3[a]

	interaction energy						
	ab initio MP2			FF			
	cc-pVDZ(0.15,0.25)	6-31G*(0.25)	Δ	AMBER	Δ	CHARMM	Δ
			AMBER Local Minima				
AXH	−40.7466	−39.0847	−1.662	**−34.890**	−4.1947	−35.926	−3.1587
AS1	−37.5814	−34.2849	−3.297	**−33.670**	−0.6149	−24.114	−10.1709
ATH1	−36.9963	−35.4736	−1.523	**−37.913**	2.4394	−38.310	2.8364
AS2	−35.9888	−33.9467	−2.042	**−33.937**	−0.0097	−23.209	−10.7377
AT2	−30.7706	−30.8817	0.111	**−36.605**	5.7233	−26.694	−4.1877
AT1	−30.0856	−30.3135	0.228	**−32.839**	2.5255	−27.997	−2.3165
ATH2	−27.1508	−26.4726	−0.678	**−34.537**	8.0644	−35.260	8.7874
			CHARMM Local Minima				
CXH	−39.1732	−37.5577	−1.616	−35.025	−2.5327	**−35.788**	−1.7697
CTH1	−32.0954	−30.8232	−1.272	−37.267	6.4438	**−38.158**	7.3348
CT1	−30.8331	−30.7045	−0.129	−30.693	−0.0115	**−33.576**	2.8715
CT2	−27.0683	−27.0986	0.030	−29.436	2.3374	**−35.596**	8.4974
CT3	−26.3385	−26.6123	0.274	−29.292	2.6797	**−35.271**	8.6587
CTH2	−23.3838	−22.9768	−0.407	−33.541	10.5642	**−35.826**	12.8492
CS		−20.1824		−22.881	2.699	**−24.303**	−4.1206

[a] Computed using MP2 with the 6-31G*(0.25) and cc-pVDZ(0.15,0.25) basis sets (see text) and empirical FFs. The ab initio reference energies are those obtained with the 6-31G*(0.25) basis set at the MP2 level. The entries in bold in the FF columns refer to true local minima.

pVDZ basis set[28] (727 primitive Gaussian for the trp−his system) where the exponents of the polarization functions for N, C, and H are replaced by more diffuse ones ($\alpha(d) = 0.25$, $\alpha(p) = 0.15$). The exponents were originally proposed by Kroon-Batenburg et al.[29] and were optimized for the correlation interaction energy. The same modified cc-pVDZ basis set was also used in a recent MP2 study of the benzene dimer,[3] yielding results comparable to those obtained with augmented basis sets.

The calculations with the 6-31G*(0.25) basis set were performed by using the GAMESS program[30] (release 6) on a SP2 computer. The calculation with the cc-pVDZ(0.25,015) basis were done on an Origin 2000 with 16 nodes using the Gaussian98 package.[31]

In Table 2 the ab initio stabilization energies for all complexes reported in Figures 2 and 3, computed at the MP2 level with the 6-31G*(0.25) and cc-pVDZ(0.25,015) basis set, are collected. For comparison the energy calculated with the AMBER and CHARMM FFs are also shown.

The two basis set differ mainly in the stabilization energy of the stacked structures with the cc-pVDZ(0.25,015) basis predicting for, e.g., AS1 a further 3 kJ/mol of stabilization. For the structures where electrostatic interactions are important, the energies computed with two basis sets differ in most cases by less than 1 kJ/mol. The coincidence of intermolecular energies with the two basis set for nonstacked structures is actually due to error cancellation: the relative weight of the dispersion-correlation energy ΔE_{COR} and of Hartree−Fock electrostatic-repulsion contribution ΔE_{HF} using the two basis sets can be assessed by inspection of Table 3. In general we observe that the smaller basis set 6-31G*(0.25) underestimates repulsive and *positive* HF energy as much as it underestimates attractive and *negative* MP2 energy, giving overall roughly the same total ΔE obtained with the larger cc-pVDZ basis. The only exceptions to this trend are precisely the entries corresponding to the stacked minima AS1 and AS2. In this case the Hartree−Fock contribution is negative and practically the same for the two basis, whereas ΔE_{COR} is much larger for the cc-pVDZ(0.25,0.15) basis set. It can also be noted that for both basis sets ΔE_{COR} reaches its maximum value in correspondence of the stacked minima AS1 and AS2. According to recent studies on aromatic complexes[27] where several basis sets were tested for the intermolecular energy against accurate coupled cluster calculations, the 6-31G*(0.25) result for the stacked structures appear to be more reliable than that obtained with the larger cc-pVDZ-(0.25,015) basis set. This is due, as previously stated, to the overestimation of the dispersive interactions with large basis sets at MP2 level.

TABLE 3: Energy Decomposition Analysis for the Structures Reported in Figures 2 and 3[a]

	6-31G*(0.25)		cc-pVDZ(0.15,0.25)	
	ΔE_{HF}	ΔE_{COR}	ΔE_{HF}	ΔE_{COR}
ATH2	2.06475	−28.5373	2.05257	−29.2034
AXH	−15.959	−23.1257	−15.5002	−25.2464
AS1	12.4331	−46.718	12.088	−49.6694
ATH1	−7.03584	−28.4378	−5.89005	−31.1062
CTH1	−0.758662	−30.0645	0.574533	−32.6699
CTH2	4.86771	−27.8445	6.70421	−30.088
CT2	9.14406	−36.2427	12.0442	−39.1125
CT1	5.44057	−36.1451	8.32249	−39.1556
AS2	9.9334	−43.8801	10.8955	−46.8843
AT2	6.00305	−36.8847	9.48923	−40.2598
AT1	4.64269	−34.9562	7.60571	−37.6913
CT3	8.65657	−35.2689	11.7393	−38.0778
CXH	−14.9539	−22.6038	−14.5795	−24.5937

[a] See text for definitions. All values are in kJ/mol.

B. Intermolecular Energies at the FF Minima. The ab initio calculations predict a very stable T-shaped ATH1 structure in agreement with the FF calculations. For the local minima found with the AMBER protocol, the generally good agreement between the MP2/6-31G*(0.25) energy and the AMBER energy is indeed quite surprising. In four cases (AS1, AS2, ATH1, and AT1) the ab initio and FF energies differ by less than 3 kJ/mol. The almost perfect agreement between 6-31G*(0.25) and AMBER intermolecular energy for the stacked complexes may well be fortuitous. Nevertheless, we stress again that empirical FFs are known to perform quite accurately for dispersive interactions and at the same time, due to error cancellation, the 6-31G*(0.25) basis seems to yield in general[28,25] reliable energies at the MP2 level for the stacked interaction with large dispersive contributions.

The present calculations were done with the same basis set (6-31G*(0.25)) used by Alagona et al.[12] in their study of trp−his interactions. Unfortunately, a comparison for the energy is possible only for the structures labeled 1esab, 1s01, and 1lla in their paper, for which counterpoise corrections were applied. The AS1 and AS2 structures are similar to the structures 1esaB

TABLE 4: Moduli of the Dipole Moments (in debye) of the Complexes Reported in Figures 2 and 3 and of the Corresponding Monomers[a]

	complex		his		trp		$\Delta\mu$
MP2 with	6-31G*	cc-pVDZ	6-31G*	cc-pVDZ	6-31G*	cc-pVDZ	6-31G*
			AMBER Local Minima				
AS1	1.681 557	1.5426	3.406 041	3.3218	1.814 937	1.8776	0.353 079 151
AS2	2.699 337	2.5615	3.367 928	3.3066	1.847 993	1.8916	0.660 814 582
AT1	4.961 081	4.3850	3.388 648	3.3384	1.887 296	1.9091	1.110 291 45
AT2	5.294 176	5.1281	3.373 874	3.341	1.909 255	1.9292	1.182 331 92
ATH1	4.446 255	4.3144	3.555 271	3.4267	1.820 231	1.9079	0.757 286 275
ATH2	5.297 157	5.2728	3.519 637	3.3925	1.781 598		1.062 262 81
AXH	6.788 16	6.7352	3.672 61	3.5322	1.797 057	1.8922	1.387 415 73
			CHARMM Local Minima				
CS	4.303 663		3.338 208		1.868 931		0.426 492 141
CT1	3.704 168	3.598	3.341 341	3.2767	1.823 416	1.8427	0.957 549 649
CT2	5.296 931	5.1753	3.423 323	3.3755	1.830 77	1.8426	1.240 472 23
CT3	5.169 269	5.0413	3.317 863	3.2565	1.832 055	1.8452	1.214 951 74
CTH1	4.231 682	4.0967	3.541 164	3.4277	1.742 972	1.8474	1.174 221 84
CTH2	5.330 616	5.306	3.537 624	3.4179	1.734 397	1.8399	1.176 706 68
CXH	6.563 829	6.4916	3.675 404	3.5419	1.746 894	1.8409	1.531 565 19

[a] Calculated at the MP2 level with the 6-31G*(0.25) and cc-pDVZ(0.15,0.25) basis sets. $\Delta\mu$ is the modulus of the vector difference between the dipole of the complex and the vector sum of the dipoles of the monomers. The experimental value of the dipole for imidazole is 3.8 ± 0.4 D,[32] for indole is 2.1 ± 0.1 D.[33]

and 1s01, respectively. In the AS1−1esaB stacked pair the his are superimposed while for the AS2 and 1s01 the his is parallely displaced over trp. In both cases our centroid distances are sensibly smaller than those found by Alagona et al. by minimizing along the intercentroid distance while keeping the mutual molecular orientation fixed. Correspondingly, our stabilization energies are almost 8 kJ/mol larger in the case of AS1 with respect to 1esab, and more than 24 kJ/mol for AS2 with respect to 1s01. The PES scanning using the FFs constitutes therefore a much more efficient searching method for stable complexes with respect to the approaching path technique starting from experimental structures, used by Alagona et al.

In ref 12 the most stable T-shaped structure is that labeled 1spbB with the his NH group pointing toward the center of the trp six-membered ring, a structure similar to the AT2 complex. In this case the FF minimum energy centroid distances and the purely MP2 minimum of Alagona et al. are practically coincident, indicating a smaller dependence of this coordinate on the mutual molecular orientation. Unfortunately the counterpoise MP2 energy is not available for 1spbB. However, even the MP2 uncorrected stabilization energy for 1spbB of about 30 kJ/mol is smaller than our counterpoise corrected value of 36.605 kJ/mol for AT2, and the MP2 stabilization energy of 1spbB is expected to drop by about 50% when counterpoise corrections are included. Again it can be argued that also for the T-shaped arrangements, our PES searching using MD is able to locate much more stable complexes with respect to the purely MP2 PES scanning method used by Alagona et al.[12] The highly stable hydrogen bonded T-shaped complexes ATH1 and ATH2 were completely missed in ref 12 as the starting experimental structures did not have the correct orientation for establishing a hydrogen bond when brought in close contact along the approaching path.

In Table 2 intermolecular MP2 energies at the CHARMM local minimum geometries are also reported. Remarkably, like in the case of the AMBER minima with large electrostatic stabilization energy, for the two basis sets little differences in the stabilization energies are detected also at the CHARMM geometries. The CHARMM energies compare less favorably to the MP2 calculations than AMBER energies do. CHARMM predicts a large stabilization energy for the CXH and CTH1 structures as in the MP2 calculation, although for the T-shaped complexes CHARMM appears to significantly overestimate the stabilization energy. For all other minima the MP2 values are consistently smaller (by 12 kJ/mol in the worse case of CT3) than the CHARMM counterpart. This can be due in part to the fact that for the T-shaped or crossed geometries CHARMM predicts centroid distances shorter than those predicted by AMBER. As the CHARMM potential is targeted for condensed phase properties,[15] comparison with ab initio stabilization energies of isolated complexes is not fair in this case. Nonetheless, the inability of the CHARMM potential to predict stable stacked structures in the gas-phase has to be remarked. In fact, the only stable structure with parallel rings predicted by CHARMM (CS) is not a truly stacked structure as there is practically no superposition of the aromatic rings and the centroid distance is almost 1 Å larger than that found with AMBER.

In Table 4 we report the molecular dipoles at the AMBER and CHARMM minima for the complexes and the isolated monomers including the ghost atoms of the partner. The $\Delta\mu$s in the last column are therefore counterpoise corrected differential dipoles and are a measure of electron density rearrangements due to electronic polarization or charge transfer in the monomers upon complex formation. The computed dipoles are weakly dependent on the basis set with the cc-pVDZ values being generally few percent smaller than the 6-31G*(0.25) counterpart. The smallest $\Delta\mu$s are obtained for the stacked structures, indicating that little density rearrangement takes places in this case. The largest $\Delta\mu$s are found for the T-shaped and X-shaped structures. The AXH and CXH complexes with hydrogen bonds have about $\Delta\mu = 1.5$ D. It is indeed noticeable that large discrepancies between ab initio and AMBER FF calculations (e.g., AXH, AT2, and ATH2 in Table 1) are detected for the structures with the largest $\Delta\mu$, whereas a better agreement is found for those with a small $\Delta\mu$ (e.g., AS1, AS2, and ATH1 in Table 1). For the former structures, where polarization effects are more important, the fixed charges description ($\Delta\mu = 0$) of the FF is probably also not adequate.

IV. Conclusions

In this paper the PES for the interaction of the aromatic compounds trp and his *in vacuo*, calculated with AMBER and

CHARMM FFs, have been compared. In both cases, seven principal minima of the complex were found, corresponding to stacked, T-shaped, and X-shaped structures. For the AMBER protocol, formation of hydrogen bonds in the complex stabilizes the T-shaped structures with respect to stacked conformations. Also in CHARMM the T-shaped structures are stabilized by the hydrogen bond, but no true stacked structures are found among the local minima. For both FFs, the largest energy basins at 300 K (i.e., the minima with the largest population) are those corresponding to T-shaped structures, indicating that this local minima are likely to play an important role in determining the potential of mean force for the interactions of aromatic compounds. AMBER predicts two stable, although scarcely populated, stacked complexes corresponding to a sandwich and an edge-displaced structure, while CHARMM fails to predict stable stacked structures. The empirical PES were tested by using single point ab initio calculations at the MP2 level. The ab initio calculations compare favorably with the AMBER FFs. In agreement with AMBER, the ab initio calculations predict the largest stabilization energy of trp−his complexes for T-shaped structures. Comparison of ab initio calculations with the CHARMM results is less satisfactory. CHARMM appears to consistently overestimate stabilization energies for complexes involving hydrogen bonds.

Acknowledgment. This work was supported by the Italian Ministero dell′Università e della Ricerca Scientifica e Tecnologica (MURST) and by the Consiglio Nazionale delle Ricerche (Progetto finalizzato Biotecnologie). We thank CINECA for providing us with calculation time on the Origin 2000 computer and prof. A. D. MacKerell for useful suggestions on the implementation of CHARMM FF.

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