Theor Chem Acc (1999) 101:143–150
DOI 10.1007/s00214980m119

Theoretical
Chemistry Accounts

Regular article

Theoretical investigation of histidine-tryptophan preferential interactions*

Giuliano Alagona[1], **Caterina Ghio**[1], **Alessandro Giolitti**[2], **Susanna Monti**[2]

[1] CNR – ICQEM, Institute of Quantum Chemistry and Molecular Energetics, Via Risorgimento 35, I-56126 Pisa, Italy
[2] Menarini Ricerche SpA, Via Sette Santi 3, I-50131 Florence, Italy

Abstract. Several histidine-tryptophan complexes (either stacked or T-shaped), derived from the crystal structures available in the Brookhaven Protein Data Bank, have been examined with molecular mechanics (MM), using the Tripos force field with Gasteiger-Hückel charges, whose trend was found to be analogous to the AMBER or CHARMM ones. The MM results were compared to the ab initio MP2 results, with and without counterpoise (CP) correction, previously obtained using extended basis sets on 5-methylimidazole and indole as model systems. MM seems to underestimate the interaction energy between the two monomers when compared to the uncorrected MP2 results, while the agreement is much better after including the CP correction at the MP2 level in all cases. MM was thus used to qualitatively analyse the dependence of the stacking energy on the ring rotation at a variable distance and ring centroid displacement for these systems, while keeping the rings in parallel planes. An analogous study was carried out for a T-shaped adduct.

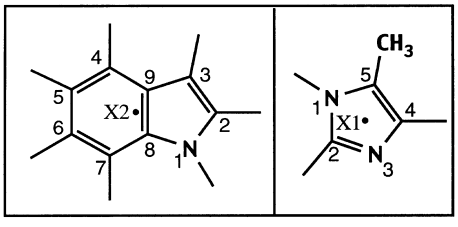
Key words: Molecular mechanics interaction energy – π complexes – T-shaped adducts – Stacking interactions – Molecular mechanics/quantum mechanics comparison – Indole···5-methylimidazole

1 Introduction

The ligand-receptor interactions to form a complex responsible for a given biological activity primarily occur through the side chains of the protein amino acids and suitable moieties from the ligand. Some of these interactions are preferentially established between well-defined pairs (or more terms) of residues, which are therefore able to drive specificity and selectivity in the complex formation. An example can be found in the neurokinin receptor family, belonging to the G-protein coupled receptor superfamily, where a typical interaction involves two or three histidines (His) defining the binding site. In some instances the most favourable interaction takes place when the ligand has indolyl moieties, such as peptides enclosing tryptophan (Trp) in their sequence. With the aim of shedding some light on this experimental result, a computational study was undertaken, examining systematically all the parallel and perpendicular adducts reachable with the chosen rotation and translation steps.

2 Methodology

The Protein Data Bank (PDB) was searched as described in our previous paper [1] to determine several different structures containing Trp and His in stacked or T-shaped orientations. The Trp/His adducts, examined after adding hydrogens to the side chains and optimising their positions, while keeping all the other atoms fixed, with molecular mechanics (MM), using the SYBYL force field [2], the Gasteiger-Hückel charges [3] and dielectric constant $\varepsilon = 1$, showed δ protonated imidazole rings (H on N_1) in all cases. A model system, indole···5-methylimidazole (Scheme 1), as for the ab initio calculations, was used for the sake of comparison.



Scheme 1

The MM interaction energies (obtained with SYBYL, AMBER [4] and CHARMM [5]) for variable centroid separations at fixed mutual orientations, were compared to the ab initio results obtained in Ref. [1] at the SCF and MP2 [6] levels, both without and with counterpoise (CP) corrections [7] to the basis set superposition error (BSSE), on internal geometries optimised with the 6-31G* basis [8] in the isolated partners. Internal geometries optimised with MM in the isolated partners were also used for the classical calculations, because the MM interaction energies can be heavily affected by internal strains.

* Contribution to the Proceedings of Computational Chemistry and the Living World, April 20–24, 1998, Chambery, France

Correspondence to: G. Alagona

Reference is made to the ab initio study [1] for the definition of the various terms and for a detailed discussion of quantum mechanical results obtained exploiting Dunning's double-zeta plus polarisation (DZP) [9] or 6-31G* with the *d* exponents reduced to 0.25 [10] (6-31G* (0.25) [11]) basis sets. For the density functional theory (DFT) 6-31G* calculations we made use of the Gaussian94 program [12] running on the IBM/RS6000-590 and SGI Indigo^2 workstations at ICQEM. Geometries were visualised with SYBYL.

3 Results and discussion

3.1 Validation of the MM results

The arrangements used (named after the PDB file they belong to) are shown in Fig. 1. Structure resolutions, values of the angle between the ring planes, ring centroid separations as measured from the distance *d*(X1-X2) of the imidazole and indole ring centres, and stereo pictures can be found in Table 1 and Figs. 1-3 of Ref. [1].

The interaction energies for the adducts in Fig. 1a, kept at the experimental mutual orientation (namely a T-shaped structure, 1lla with indole hydrogens pointing towards the imidazole ring (imidazole-across), and two stacked couples, 1s01 almost parallel and 1esaB antiparallel but slightly distorted), are shown in Fig. 2 for various centroid separations in comparison to the DZP/HF, MP2 and CP corrected MP2 (CPMP) curves. The MM interaction energies computed with the three MM force fields (SYBYL, AMBER with the RESP/6-31G* charges [13] and CHARMM[1]) turn out to be fairly consistent with the CPMP ones, although decidedly steeper in the repulsive branch. Their trend however is much better than the uncorrected HF and MP2 ones. Of course the CP corrected HF curves are even less favourable than the uncorrected HF ones and thus are not reported here.

The relevant equilibrium values are reported and compared to the ab initio ones in Table 1. The skew antiparallel structure (1esaB) turns out to be the most favourable in the set as at the ab initio level. The order of stability is maintained and the equilibrium distances are well-reproduced by MM when compared to the best ab initio results (CPMP/DZP).

The structures in Fig. 1b, corresponding to two T-shaped (1spbB and 1aoz) and two parallel (1frbA and 1esaA, but both slightly displaced) arrangements, differ in the imidazole position (located either below or above the indole plane) and the ring centroid separation, while the angles between the ring planes are similar. Both T-shaped adducts are indole-across, because an imidazole H points towards the indole ring π orbitals. Due to the very similar trend of various MM descriptions of the system, only the SYBYL results, often referred to as MM, are taken into account from now on. The MM interaction energies are compared in Fig. 3 to the 6-31G*(0.25) HF and MP2 values, because the DZP or CPMP results are not available. Actually the basis set was found to affect only slightly the results [1], with the

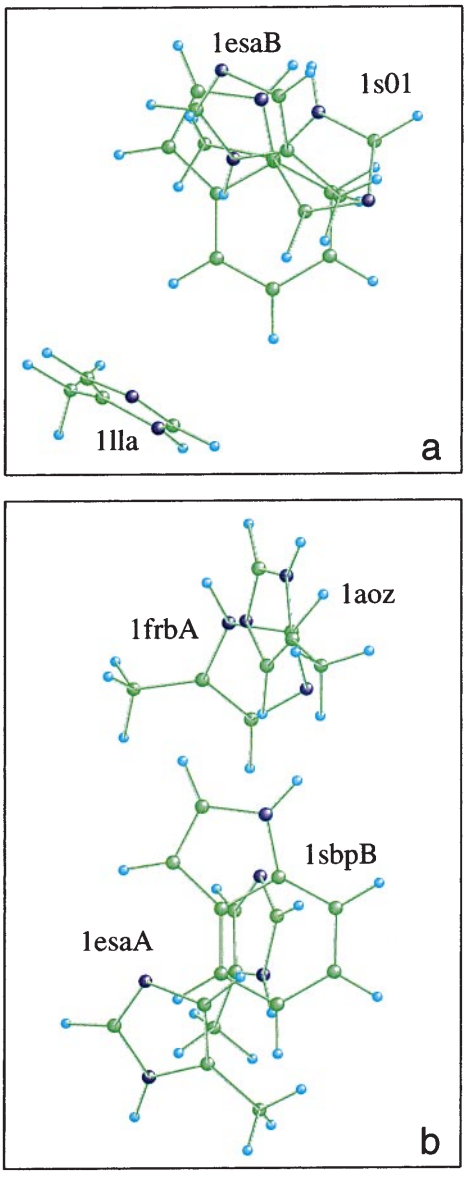


Fig. 1. Mutual orientation of a few adducts, drawn with coinciding indole rings, corresponding to **a** a T-shaped arrangement, *1lla* (imidazole-across) and two stacked structures, *1s01*, nearly parallel, and *1esaB*, skew antiparallel; **b** two T-shaped indole-across structures with imidazole below, *1spbB*, and above, *1aoz*, the indole plane, and two displaced parallel structures, *1frbA* and *1esaA*. *Light blue* = H; *green* = C; *blue* = N

6-31G*(0.25) basis set giving slightly more favourable interaction energies with respect to DZP. The CP-corrected interaction energy should be located nearly halfway between the HF and MP2 curves. Therefore the MM trend is satisfactory for the displaced parallel structures (1frbA and 1esaA), whereas it is somewhat dismaying for the T-shaped indole-across adducts. For the T-shaped imidazole-across adduct of Fig. 1a (1lla), however, the trend is fairly satisfactory as for the stacked complexes. Since the 6-31G*(0.25) basis set at the MP2 level produces stronger interaction at a shorter separation than at the CPMP level, the corresponding results represent a lower limit to the true energy curve

[1] The charges, derived from the internal database, were suitably modified in order to maintain electroneutrality

that, as stated earlier, should be placed somewhere halfway between the MP2 and HF values. Consequently, the MM equilibrium values are likely to be very close to reality.

For all these adducts the MM results are much better than the HF ones even computed with extended basis sets because they cannot take into account the dispersion attraction which plays an important role in stabilising interaction energies and in shortening equilibrium distances. Therefore the MP2 electron correlation, which after the inclusion of CP corrections gives a reliable estimate of the dispersion attraction, seems to be adequately parameterised in the force field.

An additional test was carried out using DFT, which has gained popularity even for treating H-bond interactions [14-18] and thus it has been proposed as a computational method less expensive than MP2 to account for intermolecular electron correlation. It is, however, necessary to carefully evaluate its applicability every time new types of interactions need to be investigated. The most stable compound (1esaB) was chosen as a test case for the Becke III-Lee-Yang-Parr (B3LYP) exchange-correlation functional [19, 20] at the 6-31G* level on the HF/6-31G* optimised internal geometries of the partners. The relevant results are shown in Fig. 4 without and with CP corrections, together with the 6-31G*/HF and MP2 curves. It is apparent that the B3LYP functional considerably underestimates the interaction energy, which turns out to be only slightly more favourable when uncorrected than at the HF level. After CP correction the interaction energy is even less favourable than at the HF level in the region of the minimum. For this kind of complexes it is therefore not advisable to use the B3LYP/6-31G* functional.

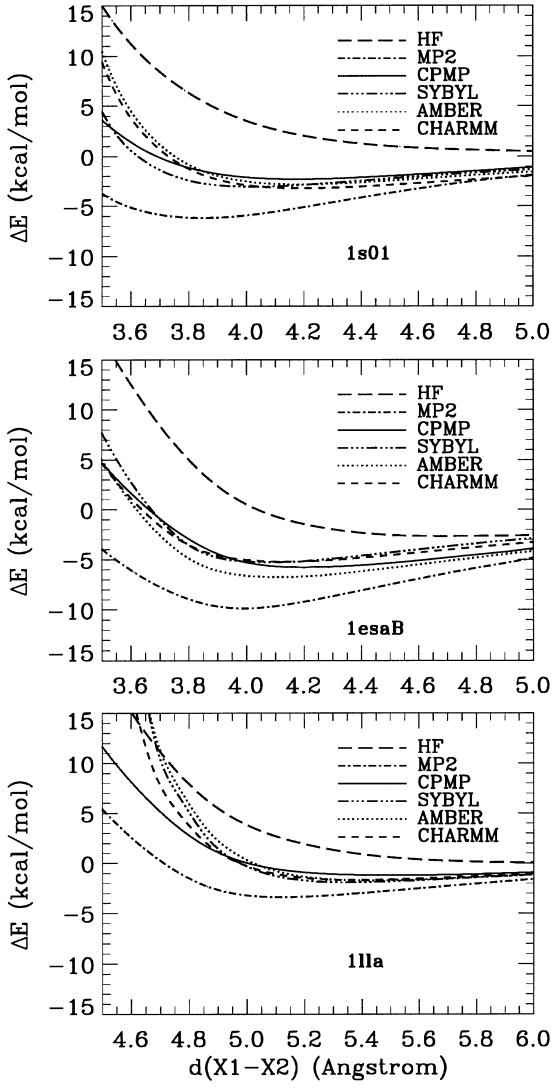


Fig. 2. Molecular mechanics (MM) interaction energies along the approaching path computed with SYBYL (*three dots-dash*), AMBER (*dot*), and CHARMM (*short dash*) for *1s01* (*upper plot*), *1esaB* (*mid plot*), and *1lla* (*lower plot*) in comparison to the interaction energy at the DZP/HF (*long dash*), DZP/MP2 (*dot-dash*), and DZP/counterpoise-corrected MP2 (CPMP) (*solid line*) levels

3.2 MM dependence of the stacking energy on the partner mutual position

The MM empirical potential was therefore used to examine the qualitative dependence of the stacking energy from the mutual rotation and translation of the partners. Starting with the two ring systems (indole and 5-methylimidazole) in parallel planes and with their centroids, X1 and X2, connected by the normal to the indole plane (arrangement defined "exactly superimposed" in what follows) and at a distance of 3.2 Å, 5-methylimidazole was rotated in 10° steps about the axis passing through X1 and perpendicular to the ring (θ rotation, defined by the indole C_8, X2, X1 and the imidazole C_5). Looking from imidazole down to indole, when θ is zero the C—CH_3 bond is roughly parallel to the indole NH group, while anticlockwise rotations of methylimidazole are considered to be positive. For each value of θ the interaction energy was minimised as a function of the distance, *d*, between the ring planes. The most stable conforma-

Table 1. Molecular mechanics (MM) equilibrium distances (Å) and corresponding interaction energies (kcal/mol) along the approaching paths for a few adducts (see text), obtained with SYBYL, AMBER and CHARMM, as compared to the counterpoise-corrected MP2 (CPMP) results obtained with the DZP basis set CPMP/DZP results from Ref. [1]

Adduct	SYBYL		AMBER		CHARMM		CPMP/DZP	
	R_{eq}	ΔE_{eq}	R_{eq}	ΔE_{eq}	R_{eq}	ΔE_{eq}	R_{eq}	ΔE_{eq}
1esaB	4.1	−5.3	4.1	−6.7	4.1	−5.2	4.2	−5.8
1s01	4.0	−3.1	4.2	−2.8	4.2	−3.2	4.1	−2.3
1lla	5.4	−1.9	5.4	−1.7	5.4	−1.7	5.5	−1.2

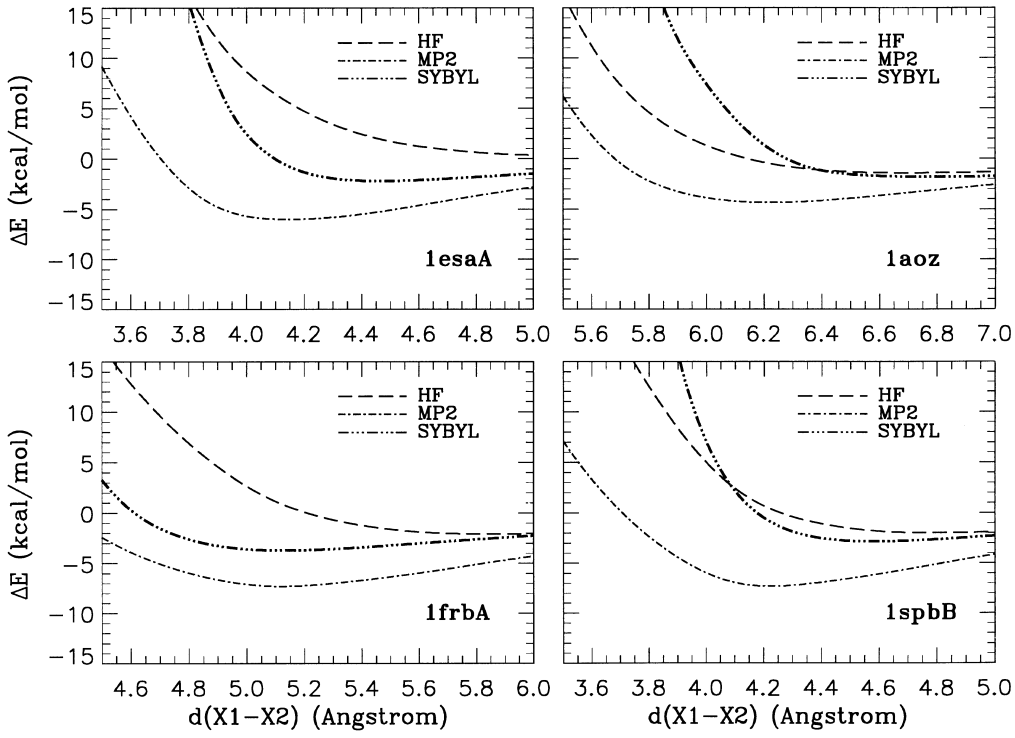


Fig. 3. MM interaction energy along the approaching path computed with SYBYL (*three dots-dash*) for *1esaA* (*upper left plot*), *1aoz* (*upper right plot*), *1frbA* (*lower left plot*), and *1spbB* (*lower right plot*) in comparison to the interaction energy at the 6-31G*(0.25)/HF (*long dash*), and 6-31G*(0.25)/MP2 (*dot-dash*) levels

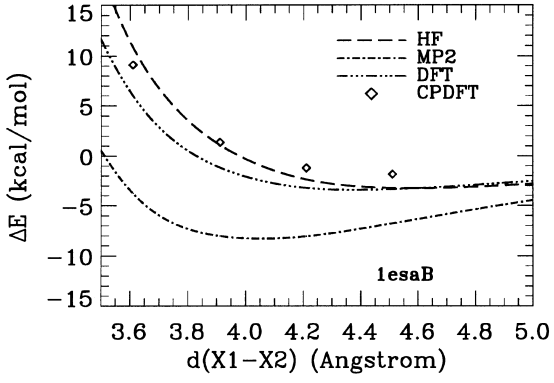
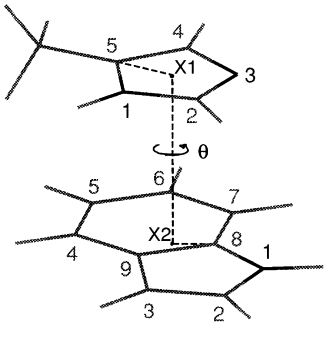


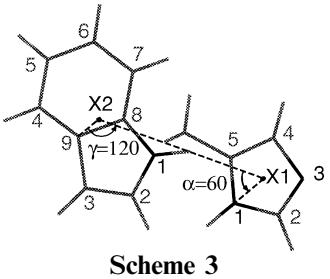
Fig. 4. B3LYP/6-31G* interaction energy along the approaching path (*three dots-dash*) for *1esaB* in comparison to the 6-31G* HF (*long dash*) and MP2 (*dot-dash*) interaction energy. The *diamonds* stand for the CP corrected B3LYP/ 6-31G* interaction energy

tion, displayed in Scheme 2, is obtained for $d = 3.2$ Å and $\theta = 150°$, when the imidazole N_3 lone pair is facing the indole NH group.



Scheme 2

Using this arrangement as a starting conformation, the dependence of the interaction energy on the centroid displacement by 1, 2 or 3 Å in the horizontal plane, with respect to the exactly superimposed location, was considered for rotations about the imidazole centroid, while keeping the rings in parallel planes. After moving X1 to its displaced location, the whole space above the indole ring was spanned by rotating (γ rotation) the imidazole centroid in 30° steps about the perpendicular to the indole plane passing through the indole centroid. The angle definitions with imidazole projected onto the indole plane in a 3 Å displaced generic arrangement are shown in Scheme 3.



Scheme 3

For each γ value, 5-methylimidazole was rotated (α rotation) in 10° steps about the axis perpendicular to its ring and passing through X1, and the equilibrium distance between the two ring planes was determined for the α rotation producing the lowest interaction energy. In Table 2 only the lowest energy arrangement for each displacement is reported, together with the corresponding values of the geometrical parameters and the interaction energy components, while in Table 3 the least stable minima for each displacement are shown. The most favourable interaction energy ($\Delta E = -6.7$ kcal/

mol) was found for a displacement of 2 Å with respect to the exactly superimposed position of X1 and X2, at a distance between the ring planes of 3 Å (**p2**). Some 1 Å displaced complexes were found to have interaction energies lower than the exactly superimposed ones, and MP2/DZP results, uncorrected for BSSE, confirmed that the displaced complex is more stable than that with the exactly superimposed centroids. Actually the MM highest minimum was found for that kind of arrangement (*p0*) with the ring planes located at a distance of 3.4 Å for a rotation of $\theta = -90°$ (Table 3).

In general the most stable complexes show favourable electrostatic interaction, as can be seen by examining the interaction energy components in Tables 2 and 3, whereas the highest minima show unfavourable electrostatic interaction. This suggested the analysis of the molecular electrostatic potential and the dipole moments of these complexes.

3.3 Molecular electrostatic potential (MEP) and dipole moment features

The MEP [21] around the stacked complexes was visualised using colour-coded isopotential surfaces. The MEP of the highest minimum adduct, displayed in Fig. 5a, shows a decidedly dipolar trend, while the MEP for the most stable arrangement from the same point of view shows (Fig. 5b) a more complicated trend, that appears to be like a quadrupolar one when observed from a side view (Fig. 5d). This is due to the fact that in these arrangements the molecular dipoles lying in the molecular plane (the 5-methylimidazole one is almost parallel to $N_1 \cdots N_3$, while the indole one divides the two ring system going from the middle of the N—H bond to C_4—C_5), drawn as pointing from the positive to the negative charge, are either nearly parallel (making an angle ≈15°, Fig. 6a) or antiparallel (angle ≈163°, Fig. 6b).

The most stable adduct with the exactly superimposed centroids, whose electrostatic contribution is slightly unfavourable, shows, however, an overwhelming van der Waals component, which is sharply stabilising. Its MEP, shown in Fig. 5c, is again mainly dipolar, even though both the positive and negative lobes are not spherical and present a very thick "banana" shape. The molecular dipoles, shown in Fig. 6c, in this case cross each other with an angle of about 135° producing skew banana lobes due to the separation between the ring planes.

There is a fair linear correlation between the interaction energy and the adduct dipole moments (regression coefficient $r = 0.915$, considering the lowest minima for each displacement). The correlation between the interaction energy and the interaction energy of the dipole moments of each molecule in the relevant mutual orientation (such as those reported in Fig. 6) is even slightly better ($r = 0.928$).

Table 2. MM geometrical parameters (Å, degrees) and corresponding interaction energies (kcal/mol) with van der Waals (*vdW*) and electrostatic components (*Elect*) for the most stable parallel (**p**) and perpendicular (**P**) displaced complexes

Displaced by	θ	γ	α	*d*	vdW	Elect	Δ*E*
p0[a]	150	–	–	3.2	−5.6	0.2	−5.4
p1	–	150	−40	3.2	−5.2	−0.6	−5.8
p2	–	150	−30	3.0	−4.9	−1.8	−6.7
p3	–	60	110	3.1	−4.6	−1.1	−5.7
Displaced by	γ	φ′	α	*d*	vdW	Elect	Δ*E*
P0[a]	–	–	–	4.5	−2.7	−1.6	−4.3
P1	180	−50	−110	4.3[b]	−2.7	−1.5	−4.2
P2	−150	−20	−110	4.3[b]	−2.5	−1.4	−3.9
P3	0	20	−90	4.2[b]	−2.1	−1.2	−3.3

[a] Exactly superimposed centroids
[b] Distance between the imidazole centroid (X1) and its projection onto the indole plane

Table 3. MM geometrical parameters (Å, degrees) and corresponding interaction energies (kcal/mol) with van der Waals (*vdW*) and electrostatic (*Elect*) components for the least stable minima among the parallel (*p*) and perpendicular (*P*) displaced complexes

Displaced by	θ	γ	α	*d*	vdW	Elect	Δ*E*
p0[a]	−90	–	–	3.4	−4.8	2.0	−2.8
p1	–	−60	80	3.2	−5.8	1.2	−4.6
p2	–	−30	40	3.4	−4.3	0.1	−4.2
p3	–	−30	80	3.3	−3.7	−0.4	−4.1
Displaced by	γ	φ′	α	*d*	vdW	Elect	Δ*E*
P0[a]	–	–	–	4.5	−2.4	−0.6	−3.0
P1	−90	140	−100	4.5[b]	−2.3	−1.4	−3.7
P2	−30	−100	−100	4.3[b]	−2.2	−0.8	−3.1
P3	150	0	−90	4.3[b]	−2.1	−0.3	−2.4

[a] Exactly superimposed centroids
[b] Distance between the imidazole centroid (X1) and its projection onto the indole plane

3.4 MM dependence of the T-shaped energy on the partner mutual position

Some indole-across T-shaped complexes were also examined to evaluate the dependence of their energy on the mutual rotation and translation of the two monomers. Starting with the two ring systems in perpendicular planes with X1 placed along the normal to the indole plane at X2, and the angle α among the imidazole C_5, X1 and X2 equal to 90°, 5-methylimidazole was rotated about the X1-X2 axis (φ rotation defined by the torsion C_9, X2, X1 and the imidazole N_1, anticlockwise rotations of N_1 taken as positive) and the lowest interaction energy for changes in α ($90° \le \alpha \le 270°$) and in *d*(X1-X2) was determined [$\Delta E = -4.3$ kcal/mol for $\varphi = -90°$, $\alpha = 100°$ at *d*(X1-X2) = 4.5 Å]. The corresponding highest minimum ($\Delta E = -3.0$ kcal/mol) was found at $\varphi = 150°$, with α and *d*(X1-X2) unaltered. The complexes with the methyl group pointing towards indole were not taken into account because the methyl group stands for the β carbon atom of the histidine amino acid.

The displacement of the centroids was again performed by 1, 2 and 3 Å in the horizontal plane, and the space above the indole ring was scanned by rotating the projection of X1 onto the indole plane about X2 in 30° steps (γ rotation), according to what was described in Sect. 3.2 for the parallel arrangement. For each value of γ the imidazole ring was rotated about the perpendicular to the indole plane passing through X1 (φ′ rotation). The angle definition is shown in Scheme 4 for a T-shaped adduct in a generic arrangement after a 3 Å displacement with X1 projected onto the indole plane. 5-Methylimidazole was also rotated about the axis perpendicular to its ring and passing through X1 (α rotation), using the same limits as above to prevent the methyl group from pointing toward indole.

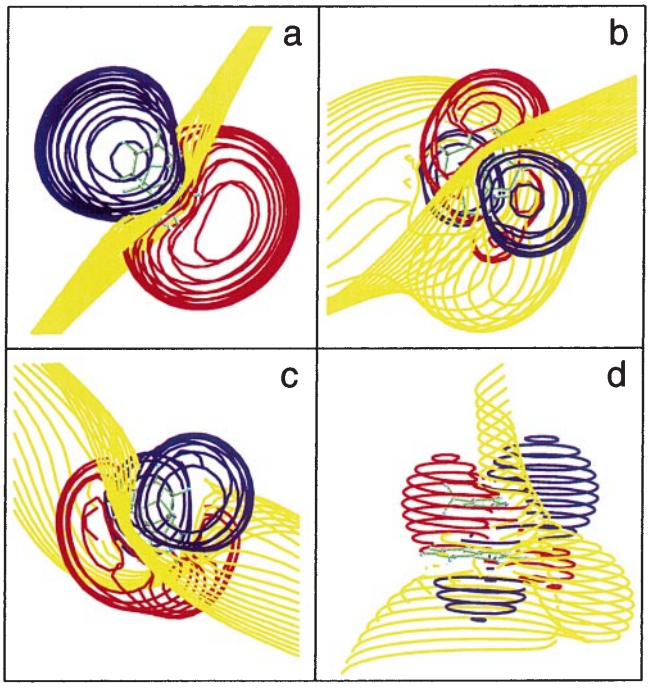
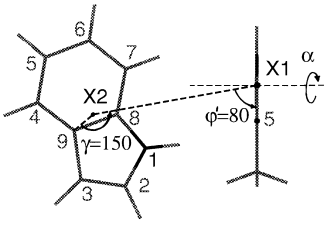


Fig. 5. Colour-coded isopotential surfaces (*blue* = −5, *yellow* = 0 and *red* = +5 kcal/mol, respectively) for **a** the highest minimum complex, *p0*, **b** the most stable complex, **p2**, **c** the most stable adduct with exactly superimposed centroids, **p0**, and **d** the most stable complex, **p2** (side view)



Scheme 4

The lowest energy complexes and the highest minima are also reported in Tables 2 and 3. The perpendicular complexes, as expected, show large centroid separations (measured as the distance between X1 and its projection onto the indole plane). They turn out to be less stable than the parallel ones, because the stabilising van der Waals term is more feeble (though the electrostatic contribution is always more favourable) than in the

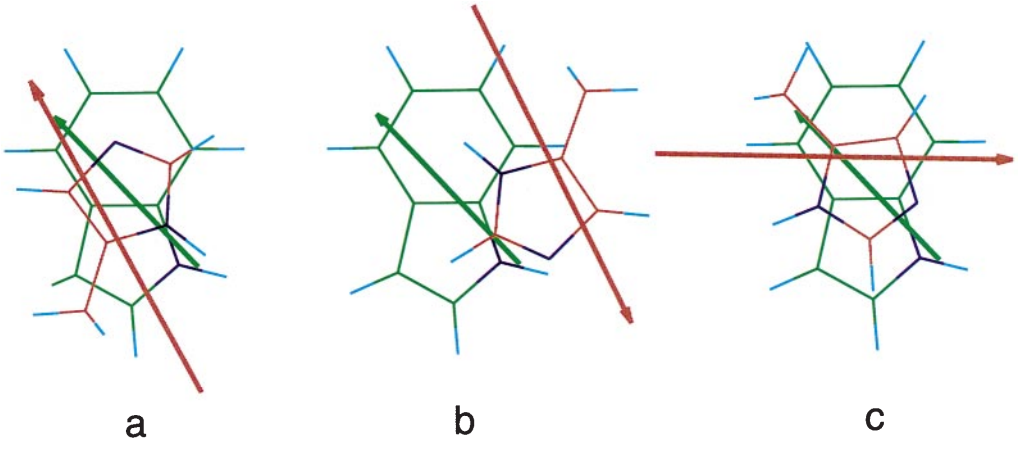


Fig. 6. Orientation of the molecular dipole moments, drawn pointing from the positive to the negative charge, for indole and 5-methylimidazole in **a** the highest minimum complex, *p0*, **b** the most stable complex, **p2** and **c** the most stable adduct with exactly superimposed centroids, **p0**

parallel arrangement. This suggests that the T-shaped complexes are similar to H-bonded systems and are not mainly governed by van der Waals interactions as are the stacked adducts.

3.5 MM dependence of the interaction energy on the angle between the planes

For the exactly superimposed complexes, the dependence of the interaction energy on the inclination of the imidazole ring with respect to the indole one was examined. When the imidazole rotation axis, passing through X1 and C_2, is parallel to the indole axis passing through the midpoint of the C_5—C_6 bond and X2, the most stable arrangement is obtained at a separation of 3.10 Å with the imidazole ring rotated by only 5° (the imidazole N_1 is driven slightly farther from the indole plane).

4 Conclusions

The picture of the interaction in several stacked or T-shaped arrangements of His and Trp, extracted from the PDB crystal structures, derived from MM calculations employing either SYBYL with Gasteiger-Hückel charges or AMBER with the RESP charges, or CHARMM (see footnote 1 for the description of the charge derivation) is in satisfactory agreement with the ab initio extended basis set results including electron correlation at the MP2 level and counterpoise corrections. Indole and 5-methylimidazole were used as model systems. On the other hand, the DFT performance, checked with the B3LYP/6-31G* functional on the HF/6-31G* optimised internal geometries of the partners, noticeably underestimates the interaction energy, which turns out to be only slightly more favourable than at the HF level.

Therefore SYBYL, which is friendlier than AMBER and CHARMM, was used in a systematic study of parallel or perpendicular (indole-across) arrangements of the indole and 5-methylimidazole aromatic rings. In the most stable conformation, obtained by minimising the interaction energy as a function of the centroid separation for rotations about the centroid axis of imidazole while keeping the rings in parallel planes with their centroids exactly superimposed, the rings are at a distance of 3.2 Å with the imidazole N lone pair parallel to the indole NH group. By releasing the parallelism condition, the most stable arrangement is obtained at a centroid separation of 3.10 Å with the imidazole ring rotated by only 5°, with the imidazole protonated N slightly farther apart from the indole plane. The main stabilising component of the interaction energy is the van der Waals term, while the electrostatic contribution is more favourable for the lowest-energy adducts than for the highest minima obtained in each set of rotations. This suggests that the charge distribution of each partner and hence its dipole moment plays an important role in stabilising such complexes. The molecular dipoles of the most stable parallel adduct are nearly antiparallel thus giving rise to a quadrupolar charge distribution also shown by the molecular electrostatic potential behaviour.

The perpendicular arrangements (T-shaped with indole placed across with respect to 5-methylimidazole) are generally less stable and at a larger separation than the stacked ones.

Of course the specific lowest-energy structures found depend on the path followed while performing the rotations. However, the main result sought from this investigation was an overview of the possible arrangements of these side chains and the understanding of the origin of their supposed stabilising interaction as stated in the Introduction.

Acknowledgements. S.M. is grateful to Menarini for a fellowship allowing her to carry out research activity at ICQEM.

References

1. Alagona G, Ghio C, Monti S (1998) J Phys Chem A 102:6152
2. SYBYL, Tripos Associates. St Louis, MO 63144-2913, USA
3. (a) Gasteiger J, Marsili M (1980) Tetrahedron 36:3219; (b) Gasteiger J, Saller H (1985) Angew Chem Int Ed Eng 24:687; (c) Hückel E (1932) Z Phys 76:628
4. (a) Pearlman DA, Case DA, Caldwell JW, Ross WS, Cheatham III TE, Ferguson DM, Seibel GL, Chandra Singh U, Weiner PK, Kollman PA (1995) AMBER 4.1. University of California, San Francisco; (b) Cornell WD, Cieplak P, Bayly CI, Gould IR, Merz KM Jr, Ferguson DM, Spellmeyer DC, Fox T, Caldwell JW, Kollman PA (1995) J Am Chem Soc 117:5179
5. (a) Brooks BR, Bruccoleri RE, Olafson BD, States DJ, Swaminathan S, Karplus M (1983) J Comput Chem 4:187; (b) MacKerell AD Jr, Wiorkeiwicz-Kuczera J, Karplus M (1995) J Am Chem Soc 117: 11946
6. (a) Møller C, Plesset MS (1934) Phys Rev 46:618; (b) Pople JA, Binkley JS, Seeger R (1976) Int J Quantum Chem 10 s:1; (c) Krishnan R, Frisch MJ, Pople JA (1980) J Chem Phys 72:4244
7. Boys SF, Bernardi F (1970) Mol Phys 19:553
8. (a) Ditchfield R, Hehre WJ, Pople JA (1972) J Chem Phys 56:2257; (b) Hariharan PC, Pople JA (1973) Theor Chim Acta 28:213
9. Dunning TH, Hay PJ (1976) Modern theoretical chemistry. Plenum, New York, p 1
10. Van Duijneveldt-Van De Rijdt JGCM, Van Duijneveldt FB (1982) J Mol Struct (Theochem) 89:185
11. (a) Hobza P, Mehlhorn A, Čársky P, Zahradník R (1986) J Mol Struct (Theochem) 138:387; (b) Šponer J, Hobza P (1994) J Biomol Struct Dyn 12:671; (c) Hobza P, Šponer J, Polášek M (1995) J Am Chem Soc 117:792; (d) Šponer J, Leszczynski J, Hobza P (1996) J Phys Chem 100:1965; (e) Šponer J, Leszczynski J, Vetterl V, Hobza P (1996) J Biomol Struct Dyn 13:695; (f) Šponer J, Hobza P (1997) Chem Phys Lett 267:263
12. Frisch MJ, Trucks GW, Schlegel HB, Gill PMW, Johnson BG, Robb MA, Cheeseman JR, Keith T, Petersson GA, Montgomery JA, Raghavachari K, Al-Laham MA, Zakrzewski VG, Ortiz JV, Foresman JB, Cioslowski J, Stefanov BB, Nanayakkara A, Challacombe M, Peng CY, Ayala PY, Chen W, Wong MW, Andres JL, Replogle ES, Gomperts R, Martin RL, Fox DJ, Binkley JS, Defrees DJ, Baker J, Stewart JP, Head-Gordon M, Gonzalez C, Pople JA (1995) Gaussian 94 revision D4. Gaussian, Pittsburgh, Pa
13. (a) Bayly CI, Cieplak P, Cornell WD, Kollman, PA (1993) J Phys Chem 97:10269; (b) Cornell WD, Cieplak P, Bayly CI, Kollman PA (1993) J Am Chem Soc 115:9620

14. Latajka Z, Bouteiller Y (1994) J Chem Phys 101:9793
15. Novoa JJ, Sosa C (1995) J Phys Chem 99:15837
16. Pudzianowski AT (1996) J Phys Chem 100:4781
17. Hamann DR (1997) Phys Rev B 55:10157
18. Dobado JA, Molina J, Portal D (1998) J Phys Chem A 102:778
19. Lee C, Yang W, Parr RG (1988) Phys Rev B 37:785
20. Becke AD (1993) J Chem Phys 98:5648
21. (a) Scrocco E, Tomasi J (1973) Top Curr Chem 42:95; (b) Scrocco E, Tomasi J (1978) Adv Quantum Chem 11:115; (c) Tomasi J (1982) In: Ratajczak H, Orville-Thomas WJ (eds) Molecular interactions, vol 3. Wiley, New York, p 119; (d) Politzer P, Murray JS (1991) In: Lipkowitz KB, Boyd DB (eds) Reviews in computational chemistry, vol 2. VCH, New York, p 273