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Molecular Mechanisms of Imidazole and Benzene Ring Binding in Proteins

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Abstract—Aromatic bonds of amino acid radicals play an important role in arrangement of protein primary structure. Previously, the existence of a number of preferable conformations of aromatic dimers was shown theoretically and experimentally, the best known of which are parallel-displaced and perpendicular T conformations. To reveal principles that define preference of various conformations for His-His and Phe-His dimers, non-empirical quantum-chemical calculations of diimidazole and benzene-imidazole were carried out. Calculations were performed using the 6-31G** basis with account for electronic correlations in frames of MP2 and MP4 methods of perturbation theory. Comparative analysis of energetic and geometric parameters of the systems points to the preference of stacking contact or classical hydrogen bond in diimidazole. On the contrary, T conformation is maximally advantageous for benzene-imidazole.

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Key words: stacking interaction, hydrogen bond, diimidazole, benzene-imidazole

Present-day achievements in molecular biology and X-ray analysis as well as improvements in computer modeling technologies and methods stimulate vigorous development of theoretical approaches to structural and functional investigation of proteins. The establishment of a connection between amino acid sequence and structure of different intra-protein domains reveals the role of particular amino acid residues in arrangement of spatial structure. Prediction of the protein tertiary structure, of inter-protein, ligand–receptor, and enzyme–substrate interactions should be based on detailed understanding of molecular mechanisms responsible for formation of selective and directed contacts between their functional groups.

Weak noncovalent interactions that are mainly responsible for arrangement of the spatial structure of a biomolecule can be rather critical towards mutual orientations of reacting residues and their nearest environment. Among them, there are hydrogen bonds as well as interactions between side aromatic radicals of Phe, Tyr, Trp, and His, which play an important role in formation of native protein conformation [1, 2]. Different variants of bonds between aromatic residues appear in proteins [3]. Among them stacking-interaction should be distinguished, which is characterized by parallel orientation of planes of two aromatic rings, namely PD and S conformations with displacement of the ring centers relative to each other or without it, respectively. The main contribution to the stacking contact energy probably belongs to dispersion forces that, together with electrostatic forces, define also the geometry of these systems [4]. Typical are also the T-shaped and "inclined" (sloping) conformations in which one ring is perpendicular to the plane of another or, respectively, at an acute angle to it [2]. In some cases, the last hydrogen atom in T conformation is oriented towards the π-electron system of the partner [2, 5], which is interpreted as a special type of hydrogen bond with π-electron cloud as the proton acceptor.

The energy of an aromatic bond depends both on the chemical nature of reacting residues and on their mutual orientation. The latter is responsible for the incidence of PD-, T-, and sloping conformations in proteins and preference of formation of any of them for particular amino

Abbreviations: MP2, Meller–Plesset method of second order perturbation theory; b, benzene-imidazole; a, imidazole dimer; 0, the initial dimer conformation.

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acids. Thus, PD conformation is most characteristic of benzene ring dimers in Phe [6], although T conformation and a number of intermediate ones are rather frequent in proteins. Quantum-chemical calculations of the optimal geometry of dibenzene also give ambiguous results: different authors consider different conformations either as stable ones, corresponding to local minimum points on the surface of potential energy, or to a number of transitory between them and unstable ones [7-11]. As a rule, conformation T and/or PD are usually considered as stable. Their energy with correction for zero point energy (ZPE) is, respectively, 2.4 and 2.7-2.8 kcal/mol. In this case, in PD conformation the distance between aromatic planes is 3.4-3.6 Å, while the shift of the ring centers is 1.6-1.8 Å. According to different estimations, experimentally measured energy of dibenzene is (1.6-2.4) ± 0.2 kcal/mol [12, 13]. The flat image of the dibenzene potential surface with difference in the energy of transfer between PD and T minima ~0.2 kcal/mol defines the alteration of the stability system character even in the case of a slight overestimation of contributions to the binding energy produced by different type interactions, such as electrostatic and dispersion [14]. Probably the same is responsible for the presence in macromolecules of a broad spectrum of diphenylalanine conformations. Structural context also has a pronounced effect on the residue orientations. At the same time, the tendency for selection of individual conformations is able to define a general trend in protein folding and the character of functional alterations of its structure in native state.

Interactions of other aromatic residues, in particular, of His with an imidazole ring in the side radical, are not so thoroughly studied. His aggregates are characteristic of metal-binding sites [15]. This residue also appears in enzyme catalytic centers, which is due to its ability to easily bind and release protons at physiological pH values. The "parallel" conformation is probably dominant for His complexes with aromatic amino acids within proteins [15]. Experimental data obtained for the His-Phe dimer are not quite unambiguous: according to earlier data of the same authors [15], the edge region of His is mainly oriented at an angle to the plane of the benzene ring [2]. In this case, the N–H or C–H bond in His is directed towards the π-electron region of the Phe ring by involvement in the hydrogen bond formation. Choosing preferable orientation largely depends on the distance between residues in amino acid sequence. Close position of amino acids in a peptide applies restriction on possible His conformations in complexes with aromatic side radicals [16].

Quantum-chemical non-empirical calculations of aromatic bonds suggest leaving the limits of the traditional Hartree–Fock–Rutan method and are due to regard for effects of electronic correlations. In particular, the latter can be realized in frames of the Meller–Plesset method of second order perturbation theory (MP2) [17]. The stable bond in dibenzene [4] and dipyridine [18] is realized only with the Hartree–Fock energy (E_{HF}) correction for energy of electron correlations (E_{CORR}). The use of the MP2 technique gives excessive (by ~1-2 kcal/mol) levels of energy of dispersion interactions of aromatic rings compared to the more precise method of coupled clusters (CCSD(T)) [4]. Estimation of correlations in the context of the method of fourth order perturbation theory (MP4) can be useful for solution of this problem, but it is associated with significant time and equipment expenses. Calculations with the mean quality bases of electron functions on atoms also require correction of the basis set superposition error (BSSE) due to which levels of binding energy are somewhat overestimated. Geometric parameters of bound fragments are less dependent on the chosen methods of calculation; therefore, the use of the CCSD(T) technique instead of MP2 has practically no effect on the level of parallel displacement in dibenzene [8]. This makes possible carrying out initial steps of the system geometry optimization using less precise methods with following re-estimation of energy level in the region of a local minimum. When the energy difference for two conformations is about several tenths kcal/mol and is within the limits of energy of thermal fluctuations, both conformations as well as intermediate ones will be represented with sufficient probability in real biological systems.

If high-precision calculations are impossible due to complexity of systems under study, comparative analysis of energy and geometric parameters of different aromatic dimers can be useful for understanding basic principles of dimerization. Imidazole as the simplest heteroaromatic compound within a protein has a number of properties that define specific character of its interactions with nonpolar benzene. We have performed non-empirical quantum-chemical calculations of optimal diimidazole and benzene-imidazole geometry *in vacuo* that model binding of Phe and His residues. Comparison of energy values and geometric parameters determined with known accuracy for different chemical systems and conformations of one system allows one to judge about the mechanisms that are the basis for bond formation and selection of preferable conformers.

METHODS OF INVESTIGATION

Initial construction of monomers and dimers as well as estimation of geometrical parameters of the system before and after optimization were carried out using the program package VegaZZ 2.0.8 [19]. The imidazole dimer is designated in this paper by letter "a", benzene-imidazole by letter "b", and initial dimer conformation is designated by the figure "0" (Tables 1 and 2). Aromatic rings of monomers in diimidazole were initially oriented parallel without centroid displacement. The middle of a fragment joining two N atoms in an imidazole ring was con-

ventionally considered as the centroid. Initial distance between ring planes was 3.5 Å, which is characteristic of stacking contact in dibenzene. We have chosen structures in which processes of geometry optimization are most characteristic examples of system evolution. A number of conformations were obtained by one ring rotation for the angle α in a parallel plane – a01-a06 (Fig. 1). Two limiting cases of rotation, a01/a02 (α = 0°) and a03 (α = 180°), as well as a number of intermediate ones, were chosen as starting structures. The sense of rotation at which the N(H) atom is converted to N in the shortest way is considered as positive. The geometry for two variants of diimidazole T conformation, a07 and a08, was also optimized (Fig. 1). The initial benzene-imidazole geometry corresponded to a parallel conformation (without regard for a) inclined to three different variants of T conformation – b01-b05 (Fig. 1). The middle of a stretch joining C3 and C6 atoms was conventionally considered as the centroid of the benzene molecule.

The complete gradient of all structures was optimized using versions PC GAMESS 7.0 (Granovskii, A. A., http://classic.chem.msu.su/gran/gamess/index.html) of program complex GAMESS [20]. Calculations were done by the Hartree–Fock–Rutan method using the basis set 6-31G** [21] with regard for electronic correlations in Meller–Plesset second order perturbation theory (MP2). Evidence of the system existence in local minimum follows from calculation of the dimer fluctuation frequencies in the same basis in MP2. Calculations of full energy with account for MP4(SDQ) contribution (1-, 2-, and 4-fold electron excitations were performed for systems with preliminarily optimized geometry. Total energy of the molecule is composed of Hartree–Fock and correlation components: $E_t = E_{HF} + E_{MP2/MP4}$. Bond energy in dimers is:

$$\Delta E_t = E_t(\text{dimer}) - [E_t(\text{monomer1}) + E_t(\text{monomer2})].$$

BSSE energy was corrected for optimized dimers using the GAUSSIAN 03 program [22] in basis 6-31G with account of MP4(SDQ), or without it for dimers optimized without account for electronic correlations. E_{DIM} is bond energy in the dimer with correction for BSSE.

All structures were visualized using the VMD program [23].

RESULTS

In the course of complete optimization of the diimidazole and benzene-imidazole dimer space structures the system under consideration reaches one of the local energy minima, getting into each of them depends on the initial geometric parameters of the system (Tables 1 and 2). Correlation contribution of MP4 decreases absolute value of bond energy compared to that calculated using MP2. The BSSE correction influences the bond energy in the same way, especially for cases of stacking interaction, which agrees with calculations for dibenzene [8]. At the same time, a general tendency for energy changes upon dimer conversion from one stable conformation to another is independent of the order of considered correlations and correction for BSSE.

Geometry of diimidazole initial state a01 at α = 0° (Fig. 2a) is unfavorable for bond formation: monomers come apart in space (a1). However, due to proton migration from one N atom to the oppositely located N atom (a02), monomers pass to the PD state (a2, Fig. 2b), which corresponds to stacking contact with energy –2.2 kcal/mol (Table 1). Antiparallel dimer conformation with displacement is realized upon optimization from initial state a03 (α = 180°) (a3, Fig. 2c). Binding energy for it increases somewhat (–2.5 kcal/mol), while angle α and centroid displacements along coordinate axes differ from those in a2. In both cases Δz displacement after optimization decreases to 3.0 Å. Similar spatial orientation of heteroatoms in conformations a2 and a3 attracts attention: N atoms are located above polarized hydrogen atoms of N(H) groups at a distance of 2.9-3.0 Å. Some proton displacement from the imidazole plane towards the partner's

Table 1. Geometry of aromatic ring arrangement and energy of stacking interactions in imidazole dimers

1	2	3	4	5	6	7	8
a01	0	a1	0.4				
a02	0	a2	–7.9 (–5.6)	–2.2	8	3.0	–0.1; 1.6; 3.0
a02 (without MP2)	0	a2'	–3.1	–2.1	9	3.4	0.1; 1.8; 3.4
a03	180	a3	–8.1 (–5.9)	–2.5	177	3.0	–0.1; 1.4; 3.0

Note: 1) original structure; 2) angle α before optimization (degrees); 3) structure after optimization; 4) ΔE_t (kcal/mol); ΔE_t value calculated with account of MP4 contribution is given in parentheses; 5) E_{DIM} bond energy (kcal/mol) with account of BSSE correction; 6) angle β between planes in the optimized dimer (degrees); 7) inter-plane distance (Δz) after optimization (Å); 8) centroid displacement along coordinate axes (Δx, Δy, Δz) after optimization (Å).

Table 2. Geometry of aromatic ring arrangement and dimerization energy in diimidazole and benzene-imidazole with hydrogen bond

1	2	3	4	5	6	7
a04 (−108), a05 (−144), a06 (144), a07, a08	a4	−11.5 (−10.3)	−7.7	90	3.0	178
a03 (180) (without MP2)	a4'	−8.3	−7.3	89	3.1	176
a02 protonated	a4"	−31.5 (−28.8)		83	2.6	178
a04 (−108)	a5	−8.2 (−6.4)	−3.4	48	3.1	142
b01, b03, b04	b1	−6.8 (−5.0)	−2.2	90	3.2	177
b1 protonated	b1"	−15.5 (−13.03)		89	3.0	160
b04 (without MP2)	b1'	−3.0	−2.3	88	3.6	172
b02	b2	−2.9 (−1.8)	0.0	87	3.5	176
b05	b3	−4.3 (−2.8)	−0.5			145

Note: 1) initial structure. Angle α before optimization (degrees) is shown in parentheses; 2) structure after optimization; 3) ΔE_t (kcal/mol). The ΔE_t value calculated with account of MP4 contribution is shown in parentheses; 4) energy of E_{DIM} bond (kcal/mol) with account of BSSE correction; 5) angle β between planes in optimized dimer (degrees); 6) distance between proton donor and acceptor (Å); 7) angle of donor-proton-acceptor hydrogen bond (degrees). The aromatic ring centroid is considered as the acceptor region in the benzene molecule.

N ring is characteristic: the proton "senses" increased electron density on the adjacent molecule. The shift of electron density towards nitrogen atoms should be favorable for electrostatic interaction of positive charges in the centroid region with negative charges on N in N(H). Evidently, electrostatic interactions largely define the diimidazole geometry with parallel rings.

Relative orientation of aromatic rings in His107 and His81 in adenosine kinase [15] is very close to a2, but the distance between the ring planes is much longer (3.85 Å). This may be due to a steric hindrance for tighter approaching from CH_2 fragments of the His residues. It is also known that the BSSE correction gives somewhat higher (by ~0.2 Å) values of equilibrium inter-plane distances in the aromatic dimer [8]. The MP4 and BSSE contribution was not considered during optimization, which made impossible detailed analysis of potential surface using more precise methods compared to MP2. We calculated energy for a2 in MP4 without BSSE correction in the case of step-by-step displacement of one ring along the coordinate axes. Binding energy is characterized by a rather flat potential surface: ΔE_t changes within 0.5 kcal/mol upon displacement by the order of 0.5 Å. Energy minimum is achieved by the monomers moving apart along the z axis by 0.1 Å; the absolute value of ΔE_t increases by 0.15 kcal/mol compared to a2. In the case of parallel shift, the maximal energy advantage is 0.05 kcal/mol. Thus, MP4 accounting during geometry optimization results in a certain divergence of monomers in space and has practically no effect on the level of parallel displacements, which are probably defined by electrostatic interactions in the system.

For initial structures a04, a05, and a06 ($0° << |\alpha| << 180°$) numerous intermediate unstable conformations are achieved during optimization in which the N–H bond of one monomer is oriented towards the N atom of the partner's ring. This makes possible formation of a polar bond between them, which probably defines a lower value of dimer energy compared to a3 (Table 1). In particular, for inclined a5 conformation (Fig. 2e) at N–H = 1.0 Å and H...N = 2.2 Å, E_{DIM} is −3.4 kcal/mol. The angle N–H...N (142°) is not optimal for hydrogen bond formation: the distance between donor and acceptor on the order of 2.6-3.2 Å and bonding angle 155-180° are usually considered as optimal conditions for hydrogen bond formation.

Complete optimization of geometric parameters of a04-a06 systems results in stable condition a4 (Fig. 2d) in which the N–H bond is directed towards the unshared electron pair of the partner's N ring and is located in the same plane as the latter. Bonding energy E_{t_MP4} (−7.7 kcal/mol) is maximal compared to energy of other conformers. Monomer planes are oriented perpendicularly forming edge-to-edge structure. Probably, a hydrogen bond with mean energy 4-6 kcal/mol plays the key role in stabilization of this structure. The a4 condition is also achieved upon diimidazole optimization from T conformation where bond N–H or C–H is oriented perpendicularly to the plane of the partner's ring (a07, a08). This means that T conformation of diimidazole is energetically unstable. Optimization of a02 and a07 with protonated imidazole results in a structure similar to a4 with bonding energy $E_{t\_MP2/MP4} = -31.5/-28.8$ kcal/mol (a4″), which is close in value to the ionic bond energy. Thus, protonation stabilizes a hydrogen bond in diimidazole, although its energy value may be significantly lower in real conditions due to correction for dielectric permeability of the medium.

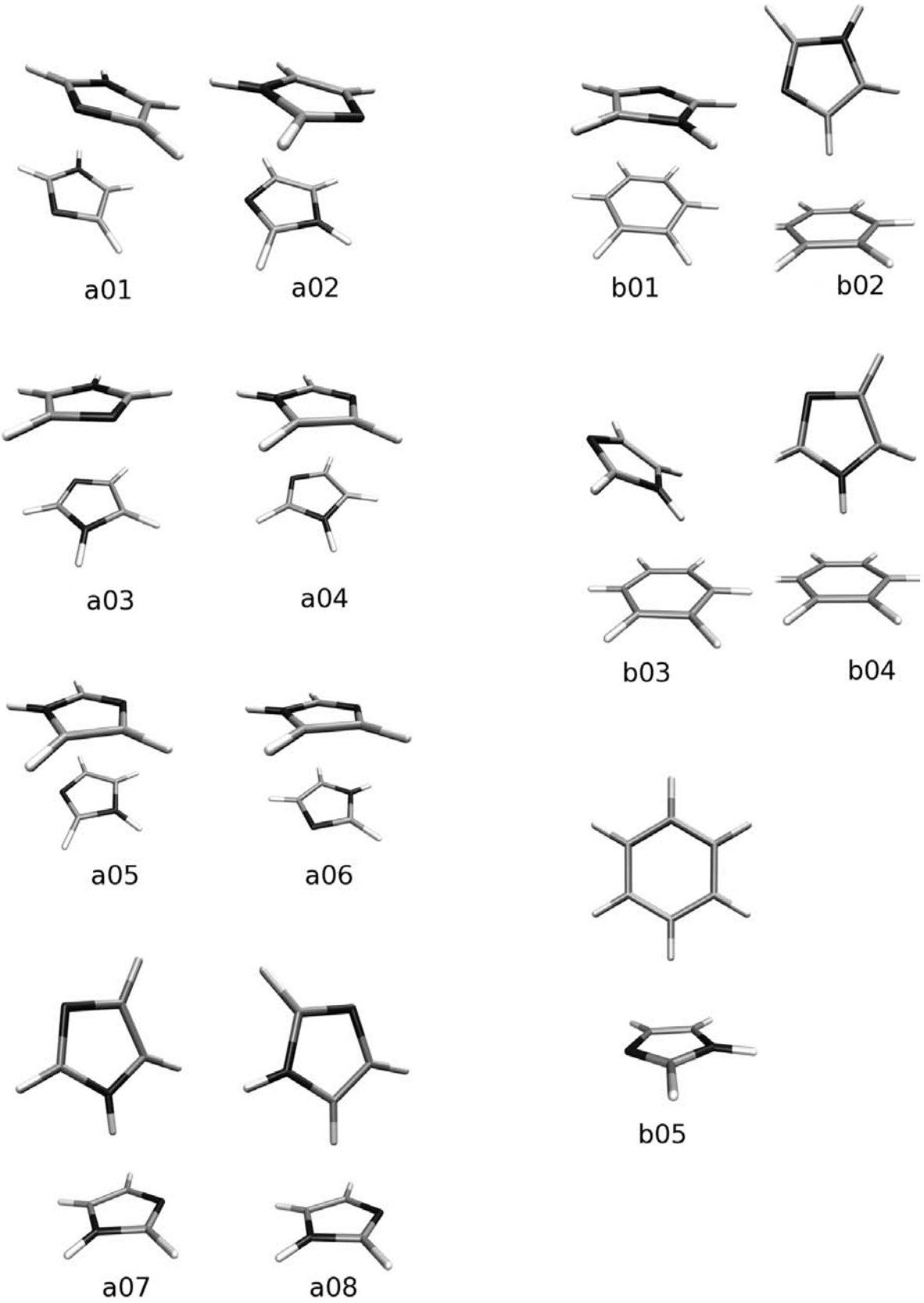

Fig. 1. Initial conformations of diimidazole and benzene-imidazole. Nitrogen atoms are shown in black, carbon atoms in gray, and hydrogen atoms in white.

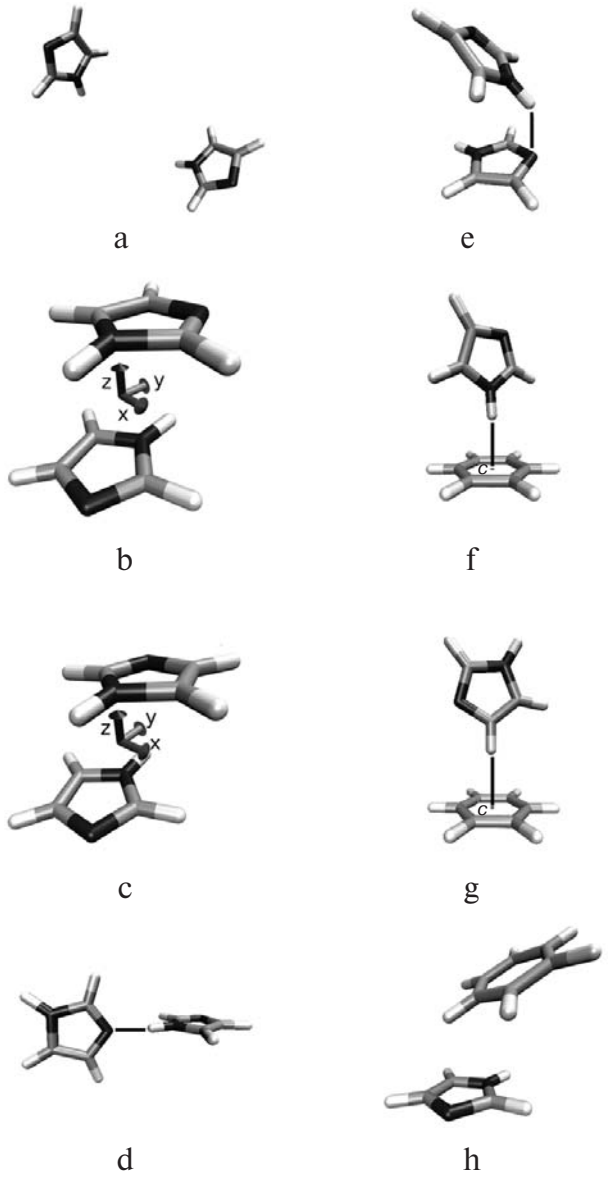

Fig. 2. Spatial (three-dimensional) structure of diimidazole and benzene-imidazole molecules (data of *ab initio* calculations). a) Initial structure of the diimidazole molecule before optimization (a01); b) diimidazole with stacking contact in parallel conformation (a2); c) diimidazole with stacking contact in antiparallel conformation (a3); d) diimidazole molecule with hydrogen bond between monomers, perpendicular orientation of aromatic rings (a4); e) imidazole dimer with hydrogen bond at intermediate step of geometry optimization, inclined conformation (a5); f) benzene-imidazole dimer in T conformation, variant 1 (b1); g) benzene-imidazole dimer in T conformation, variant 2 (b2); h) benzene-imidazole dimer in inclined conformation (b3). Nitrogen atoms are shown in black, carbon atoms in gray, and hydrogen atoms in white. Solid line designates hydrogen bonds. Letter *c* points to centroid positions. *x*, *y*, and *z* show direction of coordinate axes.

Only two stable structures in T conformation, differing in bonding energy, are realized for the benzene-imidazole dimer during geometry optimization (Table 2). Optimization from initial states in parallel (b01), inclined (b03), and T conformations with the N–H bond perpendicular to the benzene plane (b04) results in total local minimum b1 (Fig. 2f). The b1 geometry corresponds to T conformation with N–H bond directed towards the centroid. E_{DIM} = –2.2 kcal/mol, which suggests hydrogen bonding N(H) with aromatic π-electron cloud of the benzene ring. The b2 conformation (Fig. 2g) is achieved upon optimization of the benzene-imidazole T conformation with the C–H bond oriented towards the centroid. E_{DIM} in b2 is close to 0. Besides, the distance from H to the benzene ring centroid in b2 is 0.3 Å longer. The differences are probably due to the low polarity of the C–H bond in imidazole. Step-by-step calculations of ΔE_t in MP4 show that the optimal state is achieved by displacement of the imidazole ring from the benzene ring plane by 0.1 Å in the case of b1 and by 0.2 Å in the case of b2. In this case, the absolute value of ΔE_t increases by 0.8 and 0.1 kcal/mol, respectively. Bonding energy in b1 is lower than that in dibenzene T conformation ($E_{t\_MP2/MP4}$ = –3.5/–2.1 kcal/mol).

In the case of optimization of T conformation, in which the benzene edge is directed towards imidazole plane (b05), the inclined conformation b3 ($E_{t\_MP2/MP4}$ = –4.3/–2.8 kcal/mol) is achieved. However, the stability of the structure is doubtful because the possibility of its transition to b1 state during optimization is shown.

Optimization of b1 dimer with protonated imidazole results in b1″ structure in T conformation with bonding energy ($E_{t\_MP2/MP4}$ = –15.5/–13.0 kcal/mol) (Table 2). The distance between proton donor and benzene ring centroid is reduced by 0.2 Å, and the hydrogen bond angle (160°) declines comparing to that in b1. Thus, imidazole protonation significantly decreases energy of dimer in T conformation, which agrees with data on stabilizing effect of His(H^+)–Phe interaction in helical peptides [5].

In the case of dimer a02 and a03 geometry stabilization without accounting for electron correlations, stable conformations, similar to a2 and a4 (a2′ and a4′) with bonding energy E_{DIM} = –2.1/–7.3 kcal/mol, respectively, are realized. In a2′ the distance between ring planes is 3.4 Å, and distinctions from a2 are also observed in values of α angle and centroid displacement along the coordinate axes (Table 2). In b1′ dimer, calculated without contribution of correlations, the distance between donor and acceptor atoms is 3.6 Å. Thus, the accounting for correlations changes the character of system stability and parameters of its geometry.

DISCUSSION

The data point to energetic preference of the PD conformation and of the "edge-to-edge" type conformation with hydrogen bond for diimidazole and to the T conformation energetic preference for benzene-imida-

zole *in vacuo*. Electrostatic interactions significantly define diimidazole geometry in PD conformation. The inclined conformation is characterized by polar interaction N–H...N. Probably the imidazole hydrogen bonds N–H or C–H with the aromatic ring of benzene playing an important role in the stabilization of the benzene-imidazole structure. Imidazole protonation increases energy of both classical and non-standard hydrogen bonds in dimers.

Bonding energy (in absolute value) in diimidazole significantly exceeds that in dibenzene. For a3 conformation, this energy calculated using the high quality electron basis aug-cc-pVTZ with accounting for MP2 and BSSE is –7.9 kcal/mol (–4.7 kcal/mol for dibenzene in PD conformation [8]). The dibenzene optimization in MP2 using electronic basis 6-31G** results in PD conformation with energy –3.4 kcal/mol and inter-plane distance Δz = 3.4 Å [24]. Recalculation of this dimer energy in MP4 gives a value of –0.88 kcal/mol.

The characteristic feature of imidazole is high polarity of the N–H bond as well as heterogeneous distribution of electron density in the aromatic ring, which results in the electrostatic interaction contributions to dimer stabilization. The inter-plane distance in diimidazole is less by 0.4 Å. At the same time, stacking interaction in a2 and a3 is realized in PD conformation with centroid displacements by 1.4-1.6 Å, which is close to that for dibenzene. In conformation a4, the gain in energy is probably achieved due to hydrogen bond formation. The N–H bond in a4 is elongated by 0.02 Å compared to an isolated monomer, and the frequency of its fluctuations decreases by 309 cm^{-1}. This corresponds to data of spectral shift to longer wavelength, which accompanies formation of a classical hydrogen bond [25].

In proteins, in aromatic dimers with inclined and T conformations, where the His plane is directed towards the amino acid edge region, Phe is the least preferable partner for His, while another His is the most preferable one [16]. The inclined conformation of benzene-imidazole, where the C–H bond of benzene is oriented towards the partner's N ring with the possibility of hydrogen bonding, is transformed into the b1 type T conformation. The probable reason is low polarity of the C–H bond in benzene and, as a result, low energy of hydrogen bond. Conformation of the dimer with imidazole inclined to the benzene plane is also converted to b1. This means that formation of a hydrogen bond with central electron density of the aromatic ring appears to be energetically more advantageous than that with C atoms. Unlike diimidazole, in this case the length of the N–H bond is practically unchanged, its fluctuation frequency somewhat increases (by 8 cm^{-1}), which is specific of non-standard hydrogen bonds with π-electron proton acceptors [25].

Owing to the electron density shift to heteroatoms, N–H...N bond formation is more preferable for diimidazole. In this case, β angle between monomer planes can vary within broad limits, because high (in absolute value) values of bonding energy were also obtained for unstable conformations realized at intermediate steps of geometry optimization. Thus, bonding energy E_{t_MP4} = –3.4 kcal/mol in diimidazole corresponds to inclined conformation a5 with a polar N–H...N bond.

Experimental data on the advantage of parallel conformation of His dimers in proteins [15] do not contradict the calculated results: geometry optimization reveals two energy maxima with imidazole parallel and antiparallel orientations. The "inclined" variants of His-His conformation are also well represented in proteins, which is probably due to incidence of the a5 type transient conformations on the diimidazole potential surface. The existence of a classical hydrogen bond is shown only for 10% of dimers [15]. In conformation a4, establishment of hydrogen bonds between His residues can be difficult for steric reasons.

The b1/b2 type conformation for His-Phe is most frequent in proteins [15]. At the same time the authors point to the preference of PD conformation: real structure frequency in this case is compared with the theoretically expected one calculated on the basis of frequencies of structures obtained from the first either by ring displacement or by changing the flat angle between them. Thus, the PD preference is defined by low frequency in proteins of S and parallel "edge-to-edge" conformations whose instability is also confirmed by calculations in this work. The abundance in proteins of inclined benzene-imidazole conformation with adjacent ring edges is confirmed by existence of b3 conformation with sufficiently high (in absolute value) bonding energy. Thus the calculated data agree well with the experimental data. The high frequency in proteins of b05 conformation along with b1 can be explained by its nearness to b3 and by the possibility of the C–H... π bond formation for Phe-His dimer.

In His-Phe complexes of proteins, the mean length of the X...C bond of the benzene aromatic ring (where X is N/C atom of imidazole) is 3.5/3.7 Å [2]. For b1 and b2 dimers, optimized with accounting for MP4, these values are 3.55/3.91 Å. Calculations without accounting for electron correlations give significantly higher values of interatomic distances of 3.85 and 4.47 Å, respectively.

Optimization of the model dimer spatial structure reveals only more or less stable system conformations that might differ from that in proteins due to the effect of amino acid environment and continuous energy changes. The system movement along a multicoordinate surface of potential energy encounters a number of local minima and energy barriers, and the possibility of overcoming them depends both on their relative value and algorithm of calculations. Realization of different bond types within a macromolecule depends on initial orientation of reactive residues. At the same time, prediction of the dimer optimal geometry reveals tendencies to their preferable interaction. On the whole, both facts can serve

as the basis for understanding mechanisms of specificity of protein folding and inter-protein interactions.

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