Evaluation of stabilization energies in π–π and cation–π interactions involved in biological macromolecules by *ab initio* calculations

2009 J. Phys.: Condens. Matter 21 064243

(http://iopscience.iop.org/0953-8984/21/6/064243)

J. Phys.: Condens. Matter **21** (2009) 064243 (7pp) doi:10.1088/0953-8984/21/6/064243

Evaluation of stabilization energies in π–π and cation–π interactions involved in biological macromolecules by *ab initio* calculations

Masaru Tateno[1] **and Yohsuke Hagiwara**

Center for Computational Sciences, University of Tsukuba, Tennodai 1-1-1, Tsukuba Science City, Japan

E-mail: tateno@ccs.tsukuba.ac.jp

Received 18 July 2008
Published 20 January 2009
Online at stacks.iop.org/JPhysCM/21/064243

Abstract

Non-covalent interactions involving aromatic rings contribute significantly to the stability of three-dimensional structures of biological macromolecules. Therefore, accurate descriptions of such interactions are crucial in understanding the functional mechanisms of biological molecules. However, it is also well known that, for some cases where van der Waals interactions make a dominant contribution, conventional *ab initio* electronic structure calculations, such as density functional theory, do not produce accurate interaction energies. In this study, we evaluated molecular mechanics (MM) calculations for two types of interactions involving aromatic rings, π–π interactions and cation–π interactions, by comparing our results with those obtained by advanced *ab initio* calculations at the coupled-cluster with singles, doubles and perturbative triples level. In structures with stacked aromatic rings, interaction energies obtained by MM calculations are overestimated. On the other hand, for cation–π interactions, the energies in MM calculations are significantly underestimated. In both cases, addition of an induction energy based on polarization effects also fails to improve the estimate given by MM calculations. The results indicate that current effective pairwise potentials are inappropriate to represent π–π and cation–π interactions.

(Some figures in this article are in colour only in the electronic version)

1. Introduction

Non-covalent interactions involving aromatic rings, such as cation–π interaction and stacking of rings, are widely observed in biological macromolecules. In particular, statistical analyses in the Protein Data Bank show a high frequency of occurrence for cation–π interactions (1 per 77 amino acid residues) and indicate that 26% of tryptophan (Trp) residues are involved in cation–π interactions [1].

For stacking of aromatic rings, which occurs between planar residues in biological molecules such as Trp, phenylalanine (Phe), tyrosine (Tyr) and bases of nucleotide residues, there are two types of structures: 'parallel' stacking, where each residue stacks parallel to the next, and 'T-shaped' stacking, where each ring stacks perpendicularly to the next. In DNA, parallel stacking contributes significantly to the stabilization of double helix conformations. For instance, the stabilization energy by stacking of A·T and G·C base pairs has experimentally been determined to be -11.9 and -16.5 kcal mol^{-1}, respectively [2]. In proteins, in addition to parallel stacking, T-shaped stacking is also frequently involved.

In the case of Trp-cage, which has a hydrophobic core where proline (Pro), Tyr and Trp interact with each other through both parallel and T-type stacking, the melting temperature, T_m, is increased from 42 to 57 °C by a mutation of Pro to Trp inside the core [3]. In protein–drug recognition, stacking of aromatic rings also plays an important role in stabilization of the structure. For instance, in the complex

[1] Author to whom any correspondence should be addressed.

of acetylcholinesterase (AChE) with E2020 (a drug for Alzheimer's disease), single mutations such as W86A and W286A increase the free energy upon binding of the drug by +3.4 and +4.4 kcal mol^{-1}, respectively [4]. Those results indicate that stacking interactions of aromatic rings actually contribute to stabilization of three-dimensional structures of biological molecules, and therefore accurate descriptions of those interactions are required to understand molecular recognition in biological molecules.

Theoretical investigations have been carried out to gain an understanding of stacking of aromatic rings and cation–π interactions. Those analyses showed that the stabilization energy of cation–π interactions originates from both electrostatic and cation-induced polarization interactions. In contrast, the origin of the stacking of aromatic rings has been indicated to be van der Waals (vdW) interactions. However, accurate descriptions of vdW interactions require intensive treatments of electron correlation effects; therefore, high-level *ab initio* calculations, such as second-order Møller–Plesset perturbation (MP2), coupled-cluster with singles, doubles and perturbative triples (CCSD(T)) or quantum Monte Carlo calculations, are necessary, but their computational costs are prohibitive. Density functional theory (DFT) calculations are widely used to investigate electronic structures of biological molecules, because their computational costs are much lower than those of high-level *ab initio* calculations. However, if one adopts commonly used density functionals, such as the local density approximation (LDA) or the generalized gradient approximation (GGA), DFT fails to estimate vdW interactions [5–7].

In this study, we investigated the reliability of present molecular mechanics (MM) potentials to describe cation–π and π–π interactions by comparing them with the results of CCSD(T) calculations. As a model system of cation–π interactions, we employed a structure composed of an aromatic ring and a metal. In actual biological systems, metals have been found to interact with aromatic rings: a coordination of Na^+ with a tryptophan ring has been reported in crystal structures of the hen-egg-white lysozyme [8] and in a thermophilic triosephosphate isomerase mutant [9] and thermoalkalophilic lipase [10]. Other examples involving coordination of Cs^+ with an aromatic residue have been found in crystal structures of rhodanese [10], glutamine synthase [11] and methylamine dehydrogenase [12]. Further, stacking between an aromatic ring and a peptide group was investigated in this study, since that is also often found in protein structures. As a result, it should be noted that the stacking found in real biological systems is not limited to that between two aromatic rings, but occurs widely in various molecular components involving planar systems with delocalized electrons.

2. Methodology

2.1. BSSE

The basis set superposition error (BSSE) is one of the serious problems involved in electronic structure calculations that use localized molecular orbitals [13]. A standard method applied to correct that problem is the counterpoise (CP) procedure [14], which calculates a correction term using a set of ghost orbitals located in the place of partner molecules. In the case of complexes of molecules A and B (AB), BSSE is estimated as

$$E_{\mathrm{BSSE}} = [E_A^{AB}(A) - E_A^{AB}(AB)] + [E_B^{AB}(A) - E_B^{AB}(AB)] \quad (1)$$

where $E_I^J(K)$ represents energy of molecule I in geometry J when a basis set of K is used. The counterpoise-corrected interaction energy, ΔE^{CP}, is written as

$$\Delta E^{\mathrm{CP}} = E_{AB}^{AB}(AB) - E_A^A(A) - E_B^B(B) + E_{\mathrm{BSSE}}. \quad (2)$$

2.2. Estimation of CCSD(T) energy using a complete basis set

CCSD(T) calculations are known to be dependent on the basis sets used; in order to accurately estimate stacking energy, larger basis sets are required. However, computational costs increase significantly with the size of basis sets used. In this study, CCSD(T) energy is estimated at a basis set limit ($E_{\mathrm{CCSD(T)(limit)}}$), which mimics the energy calculated using a complete basis set by exploiting a procedure proposed by Tsuzuki *et al* [15]. According to this scheme, $E_{\mathrm{CCSD(T)(limit)}}$ is calculated on the basis of the following equation:

$$E_{\mathrm{CCSD(T)(limit)}} = E_{\mathrm{MP2(limit)}} + \Delta\mathrm{CCSD(T)(limit)} \quad (3)$$

where ΔCCSD(T)(limit) denotes the CCSD(T) correction term, i.e. $\Delta\mathrm{CCSD(T)} = E_{\mathrm{CCSD(T)}} - E_{\mathrm{MP2}}$ at the basis set limit. E_{MP2} and $E_{\mathrm{CCSD(T)}}$ denote stacking energies obtained at the MP2 and CCSD(T) levels, respectively. Here, stacking energy at the MP2 level with use of the basis set limit ($E_{\mathrm{MP2(limit)}}$) is estimated by the following equation:

$$E_{\mathrm{MP2(limit)}} = E_{\mathrm{HF(limit)}} + E_{\mathrm{corr(MP2)(limit)}}. \quad (4)$$

$E_{\mathrm{HF(limit)}}$ and $E_{\mathrm{corrMP2(limit)}}$ denote stacking energies at the Hartree–Fock (HF) level (E_{HF}) and MP2 level correlation energies ($E_{\mathrm{corr(MP2)}} = E_{\mathrm{MP2}} - E_{\mathrm{HF}}$), respectively, at the basis set limit. In practice, $E_{\mathrm{MP2(limit)}}$ is obtained by extrapolation of the correlation energy. The value of ΔCCSD(T)(limit) is estimated by the following equation:

$$\Delta\mathrm{CCSD(T)(limit)} = \Delta\mathrm{CCSD(T)(M)} + \Delta(\mathrm{M})\mathrm{CCSD(T)}. \quad (5)$$

Here, ΔCCSD(T)(M) shows ΔCCSD(T) obtained using a medium-size basis set, and Δ(M)ΔCCSD(T) shows a correction term for ΔCCSD(T) obtained using the medium-size basis set, since ΔCCSD(T) is dependent on the size of the basis sets used in calculations. This term is estimated by the following equation:

$$\begin{aligned}\Delta(\mathrm{M})\Delta\mathrm{CCSD(T)} &= F_{\Delta\mathrm{CCSD(T)}} \times \Delta(\mathrm{M})E_{\mathrm{corr(MP2)}} \\ &= F_{\Delta\mathrm{CCSD(T)}} \times [E_{\mathrm{corr(MP2)(limit)}} - E_{\mathrm{corr(MP2)(M)}}], \end{aligned} \quad (6)$$

where $E_{\mathrm{corr(MP2)(M)}}$ denotes $E_{\mathrm{corr(MP2)}}$ obtained using the medium-size basis set. $\Delta(\mathrm{M})E_{\mathrm{corr(MP2)}}$ is a correction term for $E_{\mathrm{corr(MP2)}}$ due to the dependence of the basis set size used in MP2 calculations. $F\Delta_{\mathrm{CCSD(T)}}$ is a scaling factor applied to estimate Δ(M)ΔCCSD(T).

Interaction energies of benzene, thiophene and naphthalene dimers, calculated using various basis sets (6-31G*, 6-311G*, 6-311G*, cc-pVDZ and a modified cc-pVTZ basis set), have shown that ΔCCSD(T) is about 20–29% of the absolute value of $E_{\mathrm{corr(MP2)}}$ [16–21]. These results suggest that Δ(M)ΔCCSD(T) is approximately 25 ± 5% of the absolute value of $\Delta(\mathrm{M})E_{\mathrm{corr(MP2)}}$. Therefore, $F_{\Delta\mathrm{CCSD(T)}}$ can be set to −0.25. In this way, CCSD(T) energies for the model systems were calculated to obtain their potentials. All calculations were performed using the Gaussian 03 package [22].

2.3. Estimation of induction energy

The induction energy in MM calculations has been described using the isotropic polarization model, where atomic point charges polarize other atoms and interact with their induced atomic dipole moments. The electrostatic field that induces a dipole moment on atom i is calculated self-consistently in an iterative way, and the polarization energy is then calculated according to

$$E_{\mathrm{pol}} = -\tfrac{1}{2}\sum_i \alpha_i \mathbf{E}_i^{(0)} \cdot \mathbf{E}_i. \qquad (7)$$

Here, α_i is the isotropic polarizability of atom i and $\mathbf{E}_i$ is the electrostatic field on atom i due to all other charges and induced dipoles. E is the electrostatic field on atom i resulting from permanent atomic charges only. All MM calculations were performed using the AMBER 9 package [23].

2.4. Model systems

Na^+–benzene and Na^+–imidazole complexes were employed as model systems for cation–π interactions (figure 1(a)). In both models, cations were aligned perpendicular to the aromatic rings and with the centre of mass of the six-membered rings. For π–π interactions, complexes of a benzene ring and a peptide plane, which is capped with hydrogen atoms, were used as the model systems (figure 2(a)).

3. Results and discussion

3.1. Cation–π interaction

Figure 1(b) shows profiles of the interaction energy with respect to the distance between Na^+ and the aromatic rings. The energy profiles obtained by the CCSD(T) calculations at the basis set limit show that, in both cases, minimum-energy states are found to be at a distance of 2.5 Å between the cation and the rings, and that the interaction energy between Na^+ and the imidazole ring is larger than that of the Na^+–benzene system; this energy difference between energy-minimum states of the two systems is 5.3 kcal mol^{-1}. This is a result of the difference in the sizes of the aromatic rings analysed: π electrons of the imidazole ring are more abundant than those of the benzene ring, and therefore the stabilization energy between the cation and π electrons is increased more in the Na^+–imidazole system than in the Na^+–benzene system. The energy profile obtained by the DFT calculations shows a slight overestimation of interaction energy between the cation and aromatic rings. However, the energy-minimum geometries obtained by the DFT and CCSD(T) calculations are very similar (figure 1(b)). Further, in the DFT calculations, interaction energies of the Na^+–imidazole system are larger than those of the Na^+–benzene system. Those results show that the cation–π interactions can be estimated by the DFT calculations.

The shapes of the energy profiles obtained by the MM calculations are similar to those of the CCSD(T) and DFT calculations; geometries of energy-minimum states are in close agreement with those obtained by the CCSD(T) and DFT calculations (both the Na^+–benzene and Na^+–imidazole distances are about 2.3 Å); and the stabilization energy of the Na^+–imidazole system is larger than that of the Na^+–benzene system (the difference of those energies is about 1.7 kcal mol^{-1}). However, the absolute values of interaction energies are significantly underestimated in both the benzene and imidazole systems: MM energies of energy-minimum geometries of the benzene and imidazole systems are −13.8 and −15.5 kcal mol^{-1}, respectively, while the corresponding CCSD(T) energies are −21.4 and −26.7 kcal mol^{-1}, respectively. It has been shown that the origin of the cation–π interaction is both the electrostatic and induction energies; the origin of the induction energy is the induced polarization of the π electron by the electric field produced by the cation metals [24, 25]. Thus, the underestimation in the MM calculations is presumably caused by the absence of induction effects. Accordingly, we examined whether a classical model based on equation (7) can describe such effects.

Figure 1(c) shows that the induction energy significantly increases stabilization energy obtained by the MM calculations; when distances between the cation and the aromatic rings are large (<2.5 Å), their stabilization energies are in good agreement with those obtained by CCSD(T) at the basis set limit. In contrast, for short distances between the cation and the aromatic rings, the MM calculations overestimate the interaction energies. In addition, for the Na^+–imidazole system, the minimum-energy state in the MM energy profile is shifted to a shorter distance between the cation and the aromatic rings (2.0 Å).

Figures 1(d) and (e) show interaction energy profiles resulting from replacing Na^+ with Mg^{2+} in the Na^+–benzene and Na^+–imidazole systems. As expected, an increase in the charge of the cation led to a drastic change in interaction energies; energy profiles obtained by CCSD(T) at the basis set limit show that interaction energies for energy-minimum geometries of model systems including Mg^{2+} are approximately fivefold stronger than those of systems including Na^+ (the stabilization energies are −108.2 and −127.2 kcal mol^{-1}, respectively) and that energy-minimum geometries in both systems are shifted to a shorter distance of 2.0 Å, in comparison with the Na^+ systems. Energy profiles obtained by the DFT calculations show that energy-minimum geometries are consistent with energy profiles obtained by CCSD(T) at the basis set limit, but interaction energies of energy-minimum geometries are slightly overestimated at −115.4 and −131.2 kcal mol^{-1} for Mg^{2+}–benzene and Mg^{2+}–imidazole systems, respectively.

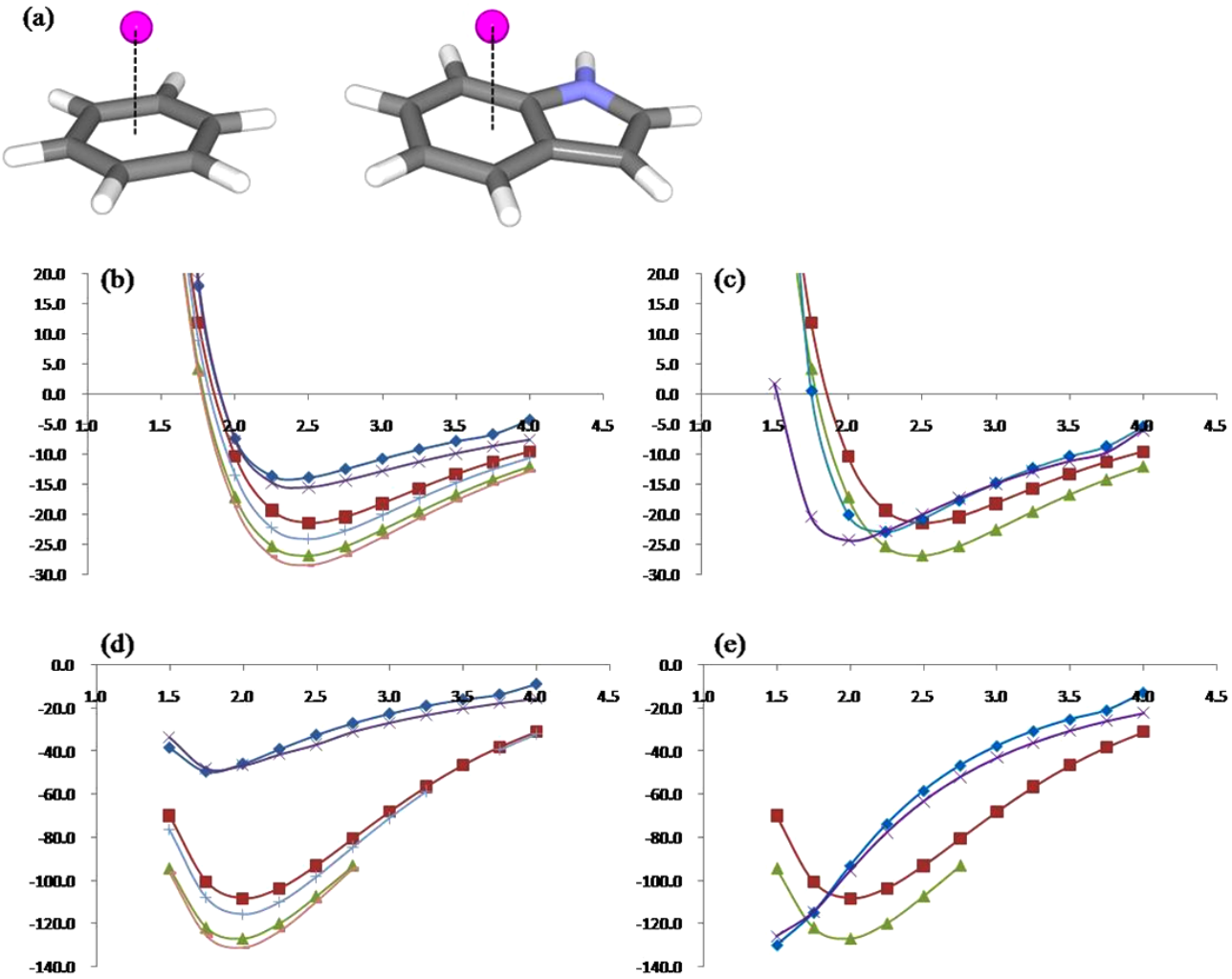

Figure 1. (a) Model structures for cation–π interactions. The metal is shown as a sphere. The left panel shows a metal–benzene system, where the metal is placed on a line perpendicular to the benzene ring and passing through the centre of mass of the benzene ring. The right panel shows a metal–imidazole ring system, where the metal is placed on a line perpendicular to an imidazole ring and passing through the centre of mass of the six-membered ring moiety in the imidazole ring. (b) Energy profiles of interaction energies of Na^+ and benzene/imidazole rings. The horizontal axis shows the distance between the metal and the benzene/imidazole rings. The interaction energies of a Na^+-benzene system obtained by CCSD(T) at the basis set limit, MM and DFT, are shown in square (■), diamond shape (♦), and a cruciform (+), respectively. Interaction energies of a Na^+-imidazole system obtained by CCSD(T), MM and DFT, are shown in triangle (▲), a cross (+) and hyphen (−), respectively. (c) Energy profiles of interaction energies of Na^+ and benzene/imidazole rings. Markers are the same as in (b). In the MM calculations, an induction term is added to the energy function used (see the methodology section). (d) Energy profiles of the interaction energies of Mg^{2+} and benzene/imidazole rings. Markers are the same as in (b). (e) Energy profiles of interaction energies of Mg^{2+} and benzene/imidazole rings. Markers are the same as in (b). In the MM calculations, an induction term is added to the energy function used (see the methodology section).

With respect to the MM calculations, similar trends are also observed for the Mg^{2+}-bound systems as are found in the Na^+ systems: interaction energies are underestimated in the absence of an induction term. However, for the Mg^{2+} systems, the MM calculations, including the induction energy defined by equation (7), still lead to significant differences in stabilization energies in comparison with those obtained by the CCSD(T) calculations at the basis set limit. In particular, noticeable differences in stabilization energy are observed for shorter distances between the cation and the aromatic rings (<1.8 Å); this indicates that the magnitude of redistribution effects of electrons becomes larger as the distances decrease, suggesting that interaction energies between Mg^{2+} and aromatic rings cannot readily be described using energy functions used in the MM calculations. In addition, stabilization energies between the benzene and imidazole systems estimated by the MM calculations are −48.1 and −49.4 kcal mol^{-1}, respectively; these stabilization energies are very different from those of the CCSD(T) calculations at the basis set limit.

Those results demonstrate the difficulty involved in efforts to precisely describe induction effects in cation–π complexes using classical polarization treatments. The induction energies used in this study were calculated with non-polarizable partial charges, even when surrounding interactions were changed; therefore, classical polarization treatments cannot

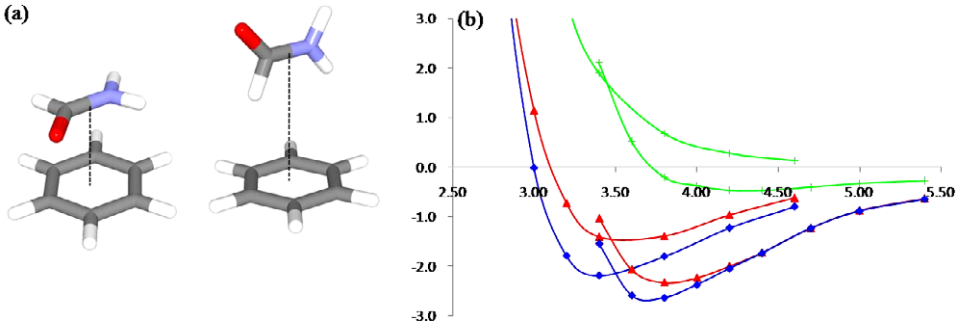

Figure 2. (a) Model structures for stacking of peptide and benzene. Left panel shows a parallel-type conformation: the peptide and benzene planes are parallel. Right panel shows a T-type conformation: the peptide and benzene planes are orthogonal. (b) Energy profiles of interaction energies of a peptide group and benzene. The horizontal axis represents the distance between the centre of mass of the benzene ring and the midpoint of the bond between C and N atoms. The interaction energy profiles obtained by CCSD(T), MM and DFT are shown in triangle (▲), diamond shape (♦) and a cross shape (+), respectively.

account for effects of changes in π-electron clouds induced by interactions with a cation. We observed that, for both systems at longer distances between cations and aromatic rings where induction effects are smaller, inconsistency with the CCSD(T) calculations at the basis set limit declines, although at shorter distances, where induction effects become larger, discrepancies between the MM and CCSD(T) calculations become significant.

3.2. Stacking

Peptide–benzene systems were used as model systems of π–π stacking (figure 2(a)). Two structures were used for calculations: one of the 'parallel' type, where the plane of the peptide group is parallel to that of the benzene, and the other of the 'T-type, where the peptide plane is orthogonal to that of the benzene.

Profiles of interaction energies with respect to distances between peptide groups and the centres of mass of benzenes are shown in figure 2(b). According to those obtained by the CCSD(T) calculations at the basis set limit, energy-minimum geometries for the T and parallel types are distances of 3.8 and 3.4 Å, respectively, while the corresponding interaction energies of the energy-minimum geometries are -1.42 and -2.33 kcal mol^{-1}, respectively. Thus, the T-type conformation is found to be more stable than that of the parallel type by 0.91 kcal mol^{-1}. Actually, the parallel-type conformation of the peptide–benzene system is changed to the T-type through geometric optimization using the resolution identity (RI)–MP2 calculation with cc-pVTZ basis sets, whereas the geometric changes are moderate in optimization if one starts the calculation from the T-type conformation [26].

The origin of stabilization energy in stacking has been shown to be vdW interactions. In reality, the DFT calculations fail to estimate interaction energies for both model systems; rather, repulsion even occurs at energy-minimum distances of CCSD calculations at the basis set limit. The small stabilization energy obtained in the T-type conformation is presumed to be due to electrostatic interactions, which can be accurately estimated by DFT calculations, while vdW interactions are the most dominant [21, 26]. On the other hand, for the parallel-type conformation, electrostatic interactions decrease stabilization energies in π–π interactions, while vdW interactions, which the DFT calculations completely fail to estimate, are crucial for stabilization of the systems [21, 26].

Energy profiles obtained by the MM calculations show that stabilization energies can be reliably estimated by using MM potentials, and that energy-minimum geometries of both the parallel- and T-type conformations are consistent with those of the CCSD(T) calculations at the basis set limit. In contrast to calculations of cation–π interactions discussed above, stabilization energies in the stacking are overestimated by the MM calculations for both types of conformations; in fact, minimum-energy geometries of both the T- and parallel-type conformations are -2.38 and -2.20 kcal mol^{-1}, respectively. In particular, the magnitude of such overestimations is larger in the case of the parallel-type conformation rather than the T-type. MM energies are 1.6-fold larger than CCSD(T) energies, leading to the incorrect conclusion that a T-type conformation is almost isoenergetic to a parallel type, although the energy difference of 0.91 kcal mol^{-1} does exist in the CCSD(T) calculations at the basis set limit.

Those results show that the MM calculations are not precise enough to estimate energies of stacked systems, even if vdW energies are included in the energy functions. This failure is presumably due to existing descriptions of vdW energies, which are based on two-body interactions calculated using atomic-pair parameters, while stabilization of stacking could have originated from interactions between the π-electron 'clouds' of aromatic rings and a peptide group. Consequently, effective potentials based on schemes independent of atom-pair-based two-body interactions must be developed, in order to precisely describe stabilization energies of π–π and cation–π interactions involving aromatic rings. Effective potentials can also be used to perform fast calculations of such interaction energies, which are available even in molecular dynamics simulations.

We have recently developed a scheme to obtain an effective vdW potential, which is a functional of the electron density of the system, by optimizing its parameters. Our functional can be highly and readily parallelized for

Table 1. BSSE with six different basis sets for the peptide–benzene system in the T- and parallel-type conformations, and for the Na^+–benzene system. E_{BSSE} is BSEE energy in kcal mol^{-1}, and the ratio of error is the ratio of E_{BSSE} to an interaction energy corrected by the CP method, $E_{BSSE}/\Delta E_{CP}$.

	T-type		Parallel type		Na^+–benzene	
Basis set	E_{BSSE} (kcal mol^{-1})	Ratio of error (%)	E_{BSSE} (kcal mol^{-1})	Ratio of error (%)	E_{BSSE} (kcal mol^{-1})	Ratio of error (%)
3-21G*	2.16	72.80	2.83	179.90	15.62	43.24
6-31G*	1.52	48.90	2.28	106.20	5.89	20.69
6-31 + G*	1.81	48.40	2.45	77.30	4.33	17.89
6-311G*	1.24	40.00	2.14	85.23	4.43	17.78
6-311 + G*	1.75	44.60	2.47	71.17	3.62	15.43
6-311G+**	1.53	41.40	2.20	64.70	3.33	15.12

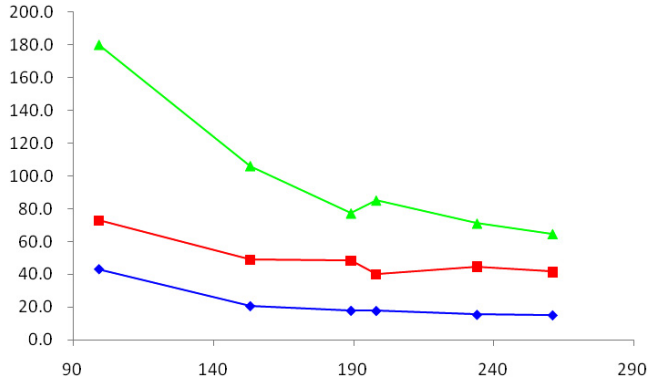

Figure 3. The magnitude of effects of BSSE. The vertical axis represents the ratio of E_{BSSE} to the interaction energy corrected by the CP method, ΔE_{CP}, and the horizontal axis represents the size of the basis sets used. The energy profiles obtained using the Na^+-benzene system, the T-type conformation of a peptide-benzene system and the parallel type conformation of the same system, are shown in diamond (♦), square (■) and triangle (▲) shape, respectively.

calculation, and thus it enables us to precisely and rapidly calculate vdW energies and forces of stacking of aromatic rings, even though the accuracy is equivalent to that of CCSD(T) at the basis set limit [27].

3.3. Effects of BSSE

In order to investigate the effects of BSSE, we calculated interaction energies of the stacking of peptide and benzene in T- and parallel-type conformations, as well as that of the Na^+–benzene system, using MP2 with six distinct basis sets (3-31G*, 6-31G*, 6-31 + G*, 6-311G*, 6-311 + G* and 6-311 + G**). The modelled structures used in the calculations were taken from the energy-minimum geometries in the energy profiles. In figure 3, ratios of BSSE to the interaction energy corrected by the CP method, $E_{BSSE}/\Delta E_{CP}$, are plotted with respect to the size of the basis sets used. It was found that the effects of BSSE are larger in the peptide–benzene system in comparison with the Na^+–benzene system, and that the effects of BSSE on the parallel-type conformation are more significant than those on the T-type conformation.

This is consistent with the magnitude of the contribution of vdW interaction energies, demonstrating that it is crucial to consider BSSE for accurate descriptions of vdW energies, and that sufficiently large basis sets should be used, since ratio of E_{BSSE} is 64.7% for the parallel-type conformation, even when a larger basis set, 6-311G+**, is used (table 1).

4. Conclusions

In this study, we evaluated MM potentials to estimate the stabilization energies for stacking involving aromatic rings. For stacking of a peptide and aromatic ring complex, vdW interactions are the origin of the stabilization. For cation–π interactions, electrostatic and induction energies are the origin of the stabilization, while vdW interactions are negligible. In both cases, the interaction energies obtained by the MM calculations are not consistent with those of the CCSD(T) calculations at the basis set limit. These features suggest that current effective pairwise potentials are not appropriate to represent such interactions. Therefore, effective potentials based on schemes independent of atom-pair-based two-body interactions must be developed in order to describe stabilization energies of π–π and cation–π interactions involving aromatic rings, and to perform fast calculations of such interaction energies as well. For that purpose, BSSE should be chosen to fit potential parameters, since it cannot be ignored using even large basis sets.

Acknowledgments

This work is partly supported by grants-in-aid from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) under contract Nos 19019003, 19340108 and 20051003. Computations were performed using the computer facilities under the 'Interdisciplinary Computational Science Program' at the Center for Computational Sciences, University of Tsukuba and the Computer Center for Agriculture, Forestry, and Fisheries Research, MAFF, Japan.

References

[1] Gallivan J P and Dougherty D A 1999 *Proc. Natl Acad. Sci.* **96** 9459
[2] Meyer E A, Castellano R K and Diederich F 2003 *Angew Chem. Int. Edn* **42** 1210
[3] Bunagan M R, Yang X, Saven J G and Gai F 2006 *J. Phys. Chem.* B **110** 3759

[4] Saxena A, Fedorko J M and Vinayaka C R 2003 *Eur. J. Biochem.* **270** 4447
[5] Kristyán S and Pulay P 1944 *Chem. Phys. Lett.* **229** 175
[6] Pérez-Jordá J M and Becke A D 1995 *Chem. Phys. Lett.* **233** 134
[7] Meijer E J and Sprik M 1996 *J. Chem. Phys.* **105** 8684
[8] Wouters J 1998 *Protein Sci.* **7** 2472
[9] Wouters J and Maes D 2000 *Acta Crystallogr.* D **56** 1201
[10] Matsumura H, Yamamoto T, Leow T C, Mori T, Salleh A B, Basri M, Inoue T, Kai Y and Rahman R N 2008 *Proteins* **70** 592
[11] Kooystra P J, Kalk K H and Hol W G 1988 *Eur. J. Biochem.* **177** 345
[12] Liaw S H, Kuo I and Eisenberg D 1995 *Protein Sci.* **4** 2358
[13] Ransil B J 1961 *J. Chem. Phys.* **34** 2109
[14] Boys S F and Bernardi F 1970 *Mol. Phys.* **19** 553
[15] Tsuzuki S, Uchimaru T and Mikami M 2006 *J. Phys. Chem.* A **110** 2027
[16] Hobza P, Selzle H L and Schlag E W 1996 *J. Phys. Chem.* **100** 18790
[17] Tsuzuki S, Honda K, Uchimaru T, Mikami M and Tanabe K 2002 *J. Am. Chem. Soc.* **124** 104
[18] Sinnokrot M O, Valeev E V and Sherrill C D 2002 *J. Am. Chem. Soc.* **124** 10887
[19] Tsuzuki S, Honda K, Uchimaru T and Mikami M 2004 *J. Chem. Phys.* **120** 647
[20] Tsuzuki S, Honda K, Uchimaru T and Mikami M 2005 *J. Chem. Phys.* **122** 144323
[21] Tsuzuki S, Honda K and Azumi R 2002 *J. Am. Chem. Soc.* **124** 12200
[22] Cubero E, Luque F J and Orozco M 1998 *Proc. Natl Acad. Sci.* **95** 5976
[23] Frisch M J *et al* 2004 *Gaussian03* (Wallingford, CT: Gaussian)
[24] Case D A *et al* 2006 *AMBER 9* University of California, San Francisco
[25] Tsuzuki S, Yoshida M, Uchimaru T and Mikami M 2001 *J. Phys. Chem.* A **105** 769
[26] Bendoza L, Jurecka P, Hobza P and Vondrasek J 2006 *J. Phys. Chem.* B **111** 9975
[27] Hagiwara Y and Tateno M 2008 in preparation