Density-Functional, Density-Functional Tight-Binding, and Wave Function Calculations on Biomolecular Systems†

Tomáš Kubař, Petr Jurečka, Jiří Černý, Jan Řezáč, Michal Otyepka, Haydée Valdés, and Pavel Hobza*

Institute of Organic Chemistry and Biochemistry, Czech Academy of Sciences and Center of Biomolecules and Complex Molecular Systems, Flemingovo nám. 2, 166 10 Praha 6, Czech Republic

Received: December 22, 2006; In Final Form: February 23, 2007

Recently, two computational approaches that supply a density-functional-based quantum-chemical method with an empirical term accounting for London dispersion were introduced and found use in the studies of biomolecular systems, namely, DFT−D and SCC−DFTB−D. Here, we examine the performance and usability of these combined techniques for dealing with several tasks typically occurring in the research of biomolecules. The interaction energy of small biomolecular complexes agrees very well with the reference data yielded by correlated ab initio quantum chemical methods. In real-life studies aimed at interaction energy, structure, and infrared spectra, the mentioned methods provide results in good agreement with each other and with experiment (where available). The very favorable time demands of these approaches are discussed, and for each of them, a suitable area of use is proposed on the basis of the results of our analysis.

Introduction

Molecular modeling is a powerful approach to examine the properties of biomolecular systems like nucleic acids and proteins and their interactions with other substances. Dealing with extended molecules and, moreover, aiming at their dynamics, the researcher is forced to introduce the molecular-mechanics methods, which exhibit very low computational demands while not sacrificing accuracy. This obvious advantage is counterweighted by a similarly obvious limitation: the electronic structure of the molecular complex investigated is considered constant throughout the entire simulation. So, it is impossible to have a covalent bond created or broken to describe the process of charge transfer and so forth.[1−3]

As a way of resolving this problem, it would be desirable to have at our disposal a quantum-chemical method, which would allow the change of electronic structure in a certain region of the molecular complex of interest. This means either to use a standalone quantum-chemical method to describe the entire system or to employ a hybrid quantum-chemical-molecular-mechanics approach (QM/MM, also known as embedding) where a region of changing electronic structure is treated by means of a quantum-chemical method. Either case, there are the following requirements on the method of choice: (1) accuracy to describe both intra- and intermolecular interactions and (2) speed and other demands on computational resources.

As for accuracy, the intermolecular interactions are the more likely source of error in the calculation. Low-cost computational methods often yield completely misleading results, in particular, if there is an interaction of highly polarizable electron systems (such as π orbitals), which goes to the account of correlation energy and is termed London dispersion. It turns out that it is necessary to employ a high-level correlated ab initio treatment to advance toward reality. The second-order perturbation theory (MP2) represents the simplest approach. However, the MP2 method frequently overestimates the interaction energy, so it is necessary to proceed toward the coupled-cluster method (CCSD-(T)). Because of its extreme computational demands, CCSD-(T) cannot be considered the method of choice for simulations. On the other hand, there is a variety of methods with modest computational requirements. Most frequently, they are based on density-functional theory (DFT). The substantial drawback brought by DFT, namely, the inability to describe the London dispersive forces properly,[4,5] may be resolved in several ways.

In this work, we present a thorough analysis of performance of two approaches recently developed in our laboratory.[6,7] Both use a supplementary term (E^{disp}) added to the calculated electronic energy ($E^{\mathrm{DFT-like}}$) of the system, which is accounted for by the London dispersion $E^{\mathrm{total}} = E^{\mathrm{DFT-like}} + E^{\mathrm{disp}}$. The E^{disp} term is calculated as the sum of pairwise contributions for every pair of atoms in the molecule/complex, which scales with the inverse sixth power of the distance of atoms (i.e., in the same way as in empirical force fields, the attractive branch of Lennard−Jones potential). On short distances, such a simple correction term rises beyond limitations and, hence, it needs to be damped[8,9] so that proper balance is achieved between the attraction (from the empirical correction) and the repulsion, which is described correctly by DFT. (To see how a damping function works, cf. Figure 1.) These approaches are hereafter called D methods. Such a correction brings no extra computational cost, so the computer time needed for the calculation is determined solely by the DFT or DFT-like method.

The first approach, DFT−D, combines a standard DFT calculation with the empirical correction.[7] Certain (roughly 10-fold) acceleration is achieved by using the resolution-of-identity approximation in the DFT calculation. The extra input necessary to calculate the dispersive energy is two parameters of the damping function. These parameters need to be optimized for the used combination of DFT functional and basis set. Several combinations and the optimized parameters were presented in the original work, where the optimization and testing is

† Part of the "DFTB Special Section".

* To whom correspondence should be addressed. Phone: +420 220 410 311; fax: +420 220 410 320; e-mail: pavel.hobza@uochb.cas.cz.

10.1021/jp068858j CCC: $37.00
Published on Web 04/06/2007

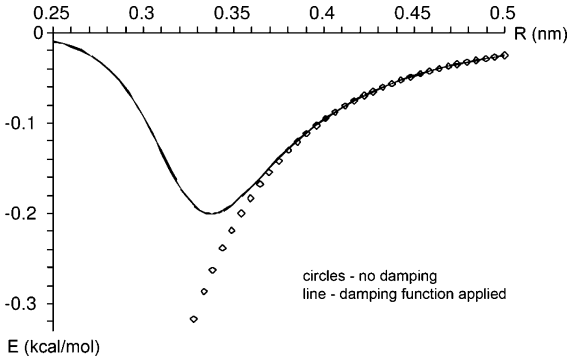

Figure 1. The empirical correction to dispersive energy for two carbon atoms depending on their distance. The correction is most significant on distances typical for intermolecular complexes while it drops steeply on shorter distances.

performed on an extended set of molecular complexes.[6] Above all, it is the size and diversity of the testing set of complexes that distinguish this flavor of DFT−D from similar approaches proposed recently.[10−14]

The other approach, SCC−DFTB−D, uses a density-functional tight-binding scheme augmented by a self-consistent-charge procedure.[15,16] The correction for dispersive forces works here similarly as in the previous case. The approximations introduced (i.e., the tight-binding scheme) make this method even orders of magnitude faster than the previously mentioned one.

Here, we demonstrate the performance of both DFT−D and SCC−DFTB−D on a variety of biomolecular systems. The accuracy of results obtained will be discussed critically on the basis of comparison with quantum-chemical data, and the computational demands of D methods will be assessed.

Methods

To demonstrate the performance of a traditional DFT approach to describe the biomolecular complexes, the B3-LYP functional[17,18] was used with the TZVP basis set.[19]

The calculations within the DFT−D framework were accomplished with the TPSS functional[20] and the TZVP basis set; in this case, the damping-function parameters in the calculation of dispersion energy were set to $\alpha = 35$ and $S = 0.98$ following the results of optimization in the original work. The DFT calculations with TPSS functional involved the resolution-of-identity approximation,[21] and all DFT calculations were performed using the Turbomole package (version 5.8).[22] The correction for dispersive energy was evaluated using a program written by the authors.

The density-functional tight-binding scheme was used in the form of SCC−DFTB−D[15] by means of a stand-alone program developed by the authors of the original work.

As reference data, we use our previous results obtained at the CCSD(T) level with the extrapolation to the complete-basis-set limit (CBS).[6,23−26] These data represent the most accurate interaction energy available to date.

Molecular Complexes Studied

In this work, we present an application of DFT−D and SCC−DFTB−D to several groups of noncovalently bound biomolecular complexes, which may be divided into two classes: First, those that were the subject of accurate quantum-chemical calculations using CCSD(T) extrapolated to the complete basis-set limit (if possible); these are the reference data that we use to validate the new methods. Second, there are extended molecular systems, which cannot be treated at such a high computational level. The latter class represents the area of proposed applications of the DFT-based methods for real problems. These examples spread across the spectrum of noncovalent biomolecular interactions. Thus, the performance of DFT-based approaches reviewed in this work may be judged by various criteria.

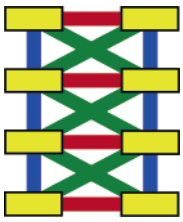

Figure 2. The interactions between bases in double-stranded DNA. Yellow boxes, bases; red lines, hydrogen bonding; blue lines, intrastrand stacking; green lines, interstrand stacking.

1. Complexes Used for Validation. *Nucleic Acid Base Pairs.* These are energy-minimized dimers of DNA bases, adenine...thymine and guanine...cytosine, in both hydrogen-bonded and stacked orientation. Also considered are methylated bases to mimic the presence of the deoxyribose unit of the nucleoside. The interaction energy of these complexes has been previously evaluated using high-level techniques in our laboratory.

Amino Acid (AA) Pairs. Similarly as in the case of DNA-base pairs, we analyze the interaction energy of several amino acid complexes. There are (1) pairs of AA's with nonpolar aromatic side chains, (2) complexes of an aromatic AA with *N*-methylacetamide (the model of a peptide bond), and (3) salt bridges, complexes of AA's carrying opposite charge.

2. Applications. *DNA Bases in Double-Stranded Octamers.* We performed an extended analysis of interaction energy in 128 B-DNA double-stranded octamers.[27] The interaction energy was calculated for every pair of neighboring bases in every octamer. These pairs were divided into three groups: hydrogen-bonded (red lines in Figure 2), intrastrand stacked (two bases placed one on top of the other within a DNA-strand; blue lines), and interstrand stacked (one base in each strand, not forming a hydrogen bond; such a pair usually has a smaller overlap and thus smaller interaction energy than an intrastrand one; green lines). The massive amount of calculation requested prevented us from using the demanding coupled-cluster method. So, the low-cost DFT-based procedures were the option.

Double-Stranded DNA Tetramer with a Ligand. Another important aspect of nucleic acid chemistry is the interaction of these with small organic molecules, which may act as either toxins or drugs (sometimes both). It is widely accepted that the interaction energy of such a complex correlates with the strength of binding and hence with the biological activity of the drug, and this leads to the application of such calculation in the drug design. In this case, it is the size of the molecular system investigated which limits the choice of the computational method. Again, any high-level correlated procedures are exceedingly demanding whereas DFT draws attention. Here, we study the binding of the anticancer drug ellipticine[28] (cf. Figure 3) with a double-stranded DNA tetramer.[29] The ligand binds both to the minor groove and in the intercalative fashion (cf. Figure 4); the comparison of these binding modes is of considerable interest.

The Core of the INK4 Tumor Suppressor. The INK4-family proteins[30] contain a distinct hydrophobic core, which constitutes of 8−10 helical regions connected by loops (e.g., as in Figure

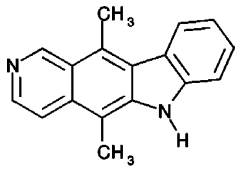

Figure 3. The DNA binding drug ellipticine.

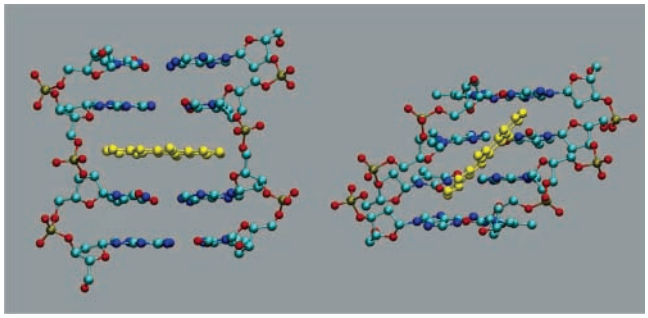

Figure 4. The binding modes of ellipticine to B-DNA. Intercalation, left; minor-groove binding, right.

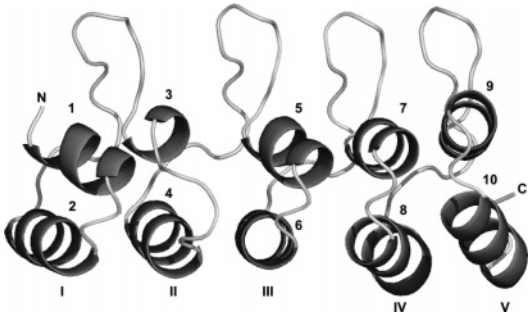

Figure 5. The hydrophobic core of an INK4 tumor suppressor.

5). The three-dimensional structure of this core is maintained by forces of both electrostatic and dispersive character, and this is why a balanced description of these kinds of interaction is vitally required. In our study of this molecule,[31] we aimed at the estimate of the free-energy profile of the folding-like conformational change, and the interaction energy of the complexes of helices were one of the components that was necessary to evaluate in such a task.

Trp-Gly-Gly Tripeptide. This molecule is considered as a model to study the process of peptide/protein folding. It is accessible both to accurate spectroscopic studies in vacuo and to quantum-chemical calculations, so, for instance, computational chemistry may be used to interpret the experimental results. Indeed, using efficient computational approaches like DFT−D or even SCC−DFTB−D, it is perfectly possible to perform energy minimization and even molecular-dynamics simulations of this molecule. Such a simulation may yield a description of the potential- and free-energy surface of the respective molecule. Moreover, vibrational analysis may be performed in a straightforward way, giving another valuable data set to be compared with the infrared spectroscopy results. All this was the subject of our recent studies.[32,33]

Results

Nucleic Acid Base Pairs. Recently, we have evaluated the interaction energy of various pairs of nucleic acid bases using the coupled-cluster approach (CCSD(T)) and the extrapolation to the complete-basis-set limit (CBS). We use these data as a reference (cf. Figure 6, striped bars) for our present calculations using DFT-based methods.

First, we discuss the performance of a density-functional commonly used in the studies of biomolecular systems, namely, B3-LYP with the TZVP basis set. What we can see (cf. Figure 6, white bars) is that this method does very well for hydrogen-bonded pairs (in Figure 6: W, Watson−Crick-like; H, Hoogsteen-like). Indeed, as previous studies revealed,[2] virtually every computational method describes hydrogen-bonded complexes correctly. On the other hand, severe discrepancies arise when we look at the stacked pairs (in Figure 6, S). In these cases, the B3-LYP functional fails to render the stabilization, which is actually present (as reported by CCSD(T)) and which goes to the account of dispersive forces, and the use of B3-LYP (as well as many other common functionals) may lead to a complete breakdown of the calculation.[34] Similar conclusions can be made concerning the TPSS functional (cf. Figure 6, striped bars).

So, even these simple complexes are one of the cases that require a proper treatment of the dispersion energy. The most economical approaches are represented by the DFT-based methods describing the dispersion energy by an empirical term. Here, both DFT−D and SCC−DFTB−D reproduce the interaction energy of all base pairs (hydrogen-bonded as well as stacked) very well. The only apparent deviation touches the SCC−DFTB−D and hydrogen-bonded pairs; these complexes are underbound by about 20%. In other respects, the D methods perform excellently.

Further, let us compare the interaction energy yielded by the TPSS functional itself and the DFT−D approach involving a TPSS calculation. There is no significant difference in case of hydrogen-bonded complexes. Conversely, in the stacked complexes, the plain DFT (TPSS) gives nearly negligible and sometimes even repulsive interaction. Obviously, the major part of interaction energy is rendered by the dispersive-energy correction.

Amino Acid Pairs. Similarly as in the case of nucleic acid base pairs, we tested the performance of the D methods to describe the interaction of amino acids.

Looking at the first group of complexes (cf. Table 1), we see that the attractive forces acting between bulky nonpolar side chains (Phe, Lys, Leu, Tyr) are not at all described at the DFT level (TPSS functional used; we expect similar results with B3-LYP and others). However, the introduction of dispersion-energy correction in both DFT−D and SCC−DFTB−D leads to a perfect agreement with reference data. The same is true for the interaction of aromatic residue with the model of peptide bond (Phe-PB in Table 1). The interaction of charged amino acids is dominated by electrostatic forces, and so it is described at the uncorrected DFT level correctly; the D methods do perfectly as well.

To summarize the results of calculations on these simple complexes, we can say that the DFT-based methods including the empirical dispersion-energy term give accurate enough values of interaction energy. The only slight shortcoming exhibited by the SCC−DFTB−D method is an about 20%-underestimate of the hydrogen-boding interaction energy, similarly as in the case of hydrogen-bonded DNA-base pairs.

Double-Stranded DNA, Interaction of Bases. We calculated the interaction energy for every base pair in 185 double-helical DNA oligomers with 5−12 base pairs. Then, we obtained the average values for every kind of interaction in our set of DNA species. These averages together with standard deviations are presented in Table 2.

From these data, we may derive the idea of relative importance of the interactions between bases to the stabilization of the 3D DNA structure. Hydrogen bonding seems responsible

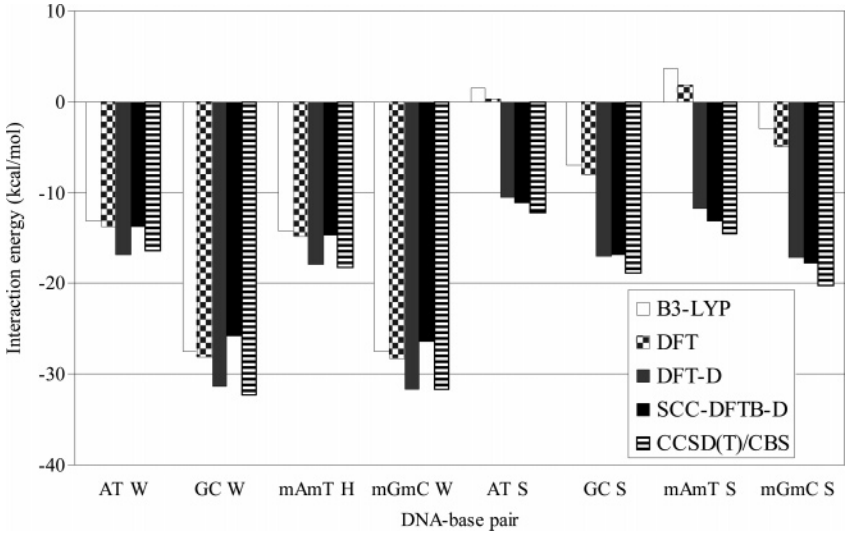

Figure 6. Interaction energy of DNA-base pairs calculated using various approaches.

TABLE 1: Interaction Energy of Amino Acid Pairs Calculated Using Various Approaches

E^{int} kcal/mol	PDB	amino acids	DFT	DFT−D	SCC−DFTB−D	CCSD(T)/CBS
aromatic amino acid with nonpolar	1BRF	Phe30-Lys46	−0.7	−3.5	−2.9	−3.1
	1BRF	Phe30-Leu33	−0.6	−6.5	−4.6	−5.0
	1BRF	Phe30-Tyr13	−0.4	−4.5	−3.7	−3.9
aromatic with peptide bond	1BRF	Phe49-PB(4-5)	−0.3	−3.5	−2.4	−2.8
	1BRF	Phe49-PB(5-6)	−1.4	−7.3	−8.2	−8.2
strong salt bridges	1IU5	Glu47-Lys6	−73.9	−78.2	−76.9	−80.7
	1BQ9	Glu49-Lys6	−105.5	−110.1	−108.7	−113.4
	1BRF	Glu50-Lys30	−60.8	−61.0	−60.0	−60.4

TABLE 2: Average Interaction Energy by Type of Interaction in Double-Stranded DNA Oligonucleotides of Varied Length

E^{int}	DFT−D	SCC−DFTB−D
hydrogen bonding	−24.4 ± 8.5	−19.3 ± 7.4
intrastrand stacking	−5.5 ± 2.3	−6.2 ± 2.8
interstrand stacking	−1.5 ± 2.3	−1.4 ± 2.7

for the major part of the total interaction energy. Again, the SCC−DFTB−D approach yields 20% smaller interaction energy for hydrogen bonding, consistently with what we learned previously. Otherwise, the results provided by both methods used are in acceptable agreement.

The vast amount of calculation engaged in this study, the interaction energy, was evaluated for the total of 12 938 base pairs. Thus, the efficiency of used methods represented the crucial factor.

DNA Interaction with Ligand. We present the results obtained for the complex of DNA with ellipticine. The drug was considered both in neutral form and protonated because it may take on either of these forms depending on pH; the interaction energy is resumed in Table 3.

We see that the major role in the binding of neutral ellipticine to DNA is played by the dispersive forces, and at the DFT level, the binding is severely underestimated. In case of the intercalator, the entire interaction energy stems from dispersion, and DFT itself fails to predict any binding. On the other hand, the dispersion-corrected methods produce decent interaction energy in mutual accordance. With the protonated ligand, the major part of interaction goes to the account of electrostatic energy, which is described well already at the DFT level. Even so, we miss a certain amount of stabilization, and this is corrected by the D methods.

Hydrophobic Core of INK4 Tumor Suppressor. This is another example of an extended molecular complex, for which the computational method of choice is either of the D approaches.

The calculation of energy of the entire core formed by 10 helices, which contain no less than 1400 atoms altogether, was possible only at the SCC−DFTB−D level. Subtracting the sum of energy of the individual helices forming the core, we obtained the interaction energy of −513 kcal/mol, a huge value describing the stabilization of a large complex.

However, it was perfectly possible to calculate the interaction energy for every pair of neighboring helices forming the core, even at the DFT−D level, and so we decided to compare the performance of both methods at this task (cf. Figure 7).

Several pairs exhibit large stabilization which are those composed of oppositely charged helices, where strong charge−charge forces act. In the others, weaker electrostatic and dispersion interaction drives the formation of complex. The absence of any positive interaction energy means that the interaction of all neighboring helices is favorable for the complex formation.

Trp-Gly-Gly Tripeptide: Molecular Dynamics Simulation and Vibrational Spectrum. The molecular dynamics/quenching technique using SCC−DFTB−D method was applied to identify the conformers of the Trp-Gly-Gly tripeptide coexisting in the gas phase. It is very important that sufficiently long simulation time was allowed by the efficiency of SCC−DFTB−D method (see also below).

The several conformers with the lowest potential energy were then selected for further reoptimization using the DFT−D method. As an example, we present the structure of the conformer that corresponds to the global minimum on the potential energy surface. Its structure features dispersive interac-

TABLE 3: Interaction Energy (kcal/mol) of a DNA/Ligand Complex Calculated by Various Approaches

binding	intercalation			minor-groove binding		
method	DFT	DFT−D	SCC−DFTB−D	DFT	DFT−D	SCC−DFTB−D
ellipticine	−0.1	−44.9	−48.0	−9.6	−39.9	−37.5
protonated elli	−198.3	−245.6	−255.4	−204.9	−236.2	−242.7

TABLE 4: Frequency (cm^{-1}) of Selected Normal Vibrational Modes of the Selected Conformer of Trp-Gly-Gly

	stretching modes				in-plane bending modes		
method	NH_{indole}	NH_{pept1}	NH_{pept2}	$CO_{carboxy}$	NH_{ipb2}	NH_{ipb1}	OH_{ipb}
experiment	**3381**	**3419**	**3431**	**1771**	**1551**	**1504**	**1421**
DFT−D (TPSS/TZVP)	3445	3493	3429	1750	1526	1498	1417
scaled[a]	*3352*	*3469*	*3404*	*1724*	*1504*	*1476*	*1395*
MP2/cc-pVDZ	3499	3587	3608	1826	1579	1545	1485
scaled[a]	*3352*	*3411*	*3431*	*1746*	*1510*	*1477*	*1420*

[a] Scaling factors. DFT−D: 0.975 (NH_{indole}), 0.989 (NH_{pept}), 0.985 (others). MP2: 0.958 (NH_{indole}), 0.951 (NH_{pept}), 0.956 (others).

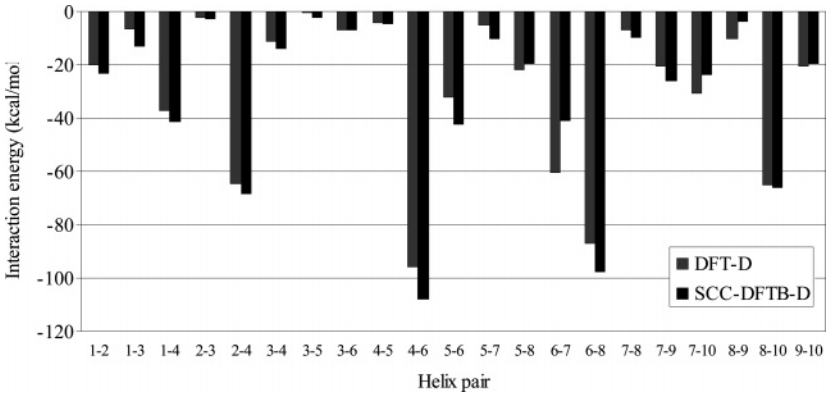

Figure 7. Interaction energy of helix pairs (helices labeled 1−10) in the hydrophobic core of INK4 calculated by D methods.

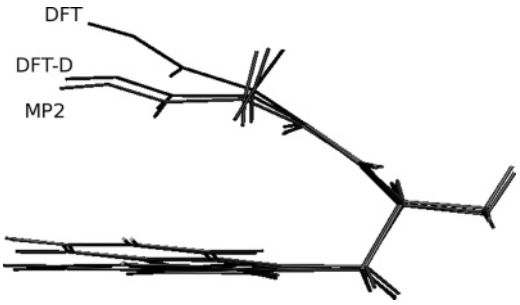

Figure 8. The structure of the Trp-Gly-Gly tripeptide energy-minimized using various methods.

tion between the aromatic side chain of tryptophan and the peptide backbone, compare Figure 8 for the structure of this conformer energy-minimized using several common methods, namely, DFT, MP2, and DFT−D. We can see that the DFT minimum is widely open, resulting from the deficiency of DFT to describe the attraction driven by dispersive forces. On the contrary, the MP2 method is known to overestimate such attraction slightly, and this feature is reflected in a too much closed structure of the peptide. Finally, the DFT−D approach yielded a somewhat more open structure than MP2, thus exhibiting a correct trend. However, some testing procedures had to be employed to prove the fitness of DFT−D for energy minimization.

In this case, a straightforward way to verify the computational results is to calculate the vibrational frequency of normal modes for the molecule and to compare the results with measured infrared spectra. For this analysis, we chose the second most stable conformer, which possesses a clear "opening" normal mode. The results are presented in Table 4 together with frequency calculated by the MP2 method for the purpose of comparison. We can see that the spectrum calculated by DFT−D overlaps quite nicely with the experimental one, thus giving us confidence in this methodology when aiming at the minimum-energy structure. Moreover, DFT−D proves applicable to calculate the frequency of vibrational modes itself, without the need to scale the results by a certain factor, which is often necessary when using a different computational approach. (Of course, slightly better results may be achieved if the frequency is scaled even with DFT−D, cf. Table 4.) This is the case of MP2, which requires the introduction of a scaling factor significantly deviating from unity. After such a modification, we may not be able to decide the source of inaccuracy, that is, if it is the inability of MP2 to calculate frequency or a wrong structure in the minimum of energy.

Considerations of Computational Speed. It is necessary to discuss the computational requirements of the D methods. It takes little extra time to calculate the correction to dispersive energy, and thus the quantum-chemical component rules the computational demands. While DFT itself belongs to efficient quantum-chemical tools (especially if the resolution-of-identity approximation is employed), the approximative SCC−DFTB performs even orders of magnitude faster and with smaller demands on hardware.

This may be illustrated on the example of ellipticine bound to double-stranded DNA (tetranucleotides were considered). The proportions and the complex electronic structure of the molecules studied make the quantum-chemical calculations quite demanding. The SCF and SCC procedures (in DFT−D and SCC−DFTB−D, respectively) converge slowly, leading to prolonged computational time. The SCC−DFTB procedure is

finished within at most 2 min whereas the DFT task may take as long as 40 h to complete (timing recorded on a one-CPU PC).

These observations make us believe that only the SCC−DFTB−D approach is really useful for molecular dynamics (MD) simulations, whereas the DFT−D framework remains perfectly suitable for the minimization and the calculation of vibrational frequency, which require improved accuracy.

Conclusions

- The approaches combining a density-functional-based approach with the empirical correction for dispersion energy, DFT−D, and SCC−DFTB−D were tested on biomolecular systems. Both provided us with balanced and reliable description of the interactions inside biomolecules, comparing perfectly with the results of the most accurate and highly demanding quantum-chemical methods.
- The SCC−DFTB−D method yields very good energy data; the only shortcoming observed consisted in the interaction energy of hydrogen-bonded complexes being underestimated by 20%. If this inaccuracy is eliminated, the performance will be considered perfect.
- The DFT−D framework produces high-quality structure (by means of energy minimization) and also vibrational frequency close to the experimental values.
- The efficiency of DFT−D makes it possible to perform energy minimization and vibrational analysis of extended molecular complexes (hundreds of atoms).
- The SCC−DFTB−D method is even a few orders of magnitude faster, not relinquishing accuracy. For this reason, it is extremely useful in both (1) quantum-chemical MD simulations and (2) calculations carried out for massive numbers of extended molecular complexes.

Acknowledgment. This work is a part of the research project Z40550506, and it was supported by grants from the Grant Agency of the Academy of Sciences of the Czech Republic (grant No. A400550510), the Ministry of Education of the Czech Republic (Center for Biomolecules and Complex Molecular Systems, LC512, and grant No. MSM6198959216), and Grant Agency of the Czech Republic (grants No. 203/05/H001 and 203/05/009).

References and Notes

(1) Hobza, P.; Zahradník, R.; Müller-Dethlefs, K. *Collect. Czech. Chem. Commun.* **2006**, *71*, 443−531.
(2) Müller-Dethlefs, K.; Hobza, P. *Chem. Rev.* **2000**, *100*, 143−167.
(3) Castleman, A. W., Jr., Brutschy, B., Hobza, P., Eds. Van der Waals complexes I, II, III. *Chem. Rev.* **1988**, *88* (6); **1994**, *94* (7); **2000**, *100* (11).
(4) Hobza, P.; Šponer, J.; Reschel, T. *J. Comp. Chem.* **1995**, *16*, 1315−1325.
(5) Kristyan, S.; Pulay, P. *Chem. Phys. Lett.* **1994**, *229*, 175−180.
(6) Jurečka, P.; Šponer, J.; Černý, J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2006**, *8*, 1985−1993.
(7) Jurečka, P.; Černý, J.; Hobza, P.; Salahub, D. R. *J. Comp. Chem.* **2007**, *28*, 555−569.
(8) Hepburn, J.; Scoles, G.; Penco, R. *Chem. Phys. Lett.* **1975**, *36*, 451−456.
(9) Ahlrichs, R.; Penco, R.; Scoles, G. *Chem. Phys.* **1977**, *19*, 119−130.
(10) Grimme, S. *J. Comp. Chem.* **2004**, *25*, 1463−1473.
(11) Grimme, S. *J. Comp. Chem.* **2006**, *27*, 1787−1799.
(12) Wu, Q.; Yang, W. T. *J. Chem. Phys.* **2002**, *116*, 515−524.
(13) Zhechkov, L.; Heine, T.; Patchkovskii, S.; Seifert, G.; Duarte, H. A. *J. Chem. Theory Comput.* **2005**, *1*, 841−847.
(14) Zimmerli, U.; Parrinello, M.; Koumoutsakos, P. *J. Chem. Phys.* **2004**, *120*, 2693−2699.
(15) Elstner, M.; Hobza, P.; Frauenheim, T.; Suhai, S.; Kaxiras, E. *J. Chem. Phys.* **2001**, *114*, 5149−5155.
(16) Elstner, M.; Porezag, D.; Jungnickel, G.; Elsner, J.; Haugk, M.; Frauenheim, T.; Suhai, S.; Seifert, G. *Phys. Rev. B* **1998**, *58*, 7260−7268.
(17) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648−5652.
(18) Lee, C. T.; Yang, W. T.; Parr, R. G. *Phys. Rev. B* **1988**, *37*, 785−789.
(19) Schafer, A.; Horn, H.; Ahlrichs, R. *J. Chem. Phys.* **1992**, *97*, 2571−2577.
(20) Tao, J. M.; Perdew, J. P.; Staroverov, V. N.; Scuseria, G. E. *Phys. Rev. Lett.* **2003**, *91*, 146401.
(21) Sierka, M.; Hogekamp, A.; Ahlrichs, R. *J. Chem. Phys.* **2003**, *118*, 9136−9148.
(22) Ahlrichs, R.; Bär, M.; Häser, M.; Horn, H.; Kölmel, C. *Chem. Phys. Lett.* **1989**, *162*, 165−169.
(23) Jurečka, P.; Hobza, P. *J. Am. Chem. Soc.* **2003**, *125*, 15608−15613.
(24) Jurečka, P.; Šponer, J.; Hobza, P. *J. Phys. Chem. B* **2004**, *108*, 5466−5471.
(25) Šponer, J.; Jurečka, P.; Hobza, P. *J. Am. Chem. Soc.* **2004**, *126*, 10142−10151.
(26) Vondrášek, J.; Bendová, L.; Klusák, V.; Hobza, P. *J. Am. Chem. Soc.* **2005**, *127*, 2615−2619.
(27) Řezáč, J.; Hobza, P. *Chem.−Eur. J.* **2007**, *13*, 2983−2989.
(28) Stiborová, M.; Bieler, C. A.; Wiessler, M.; Frei, E. *Biochem. Pharmacol.* **2001**, *62*, 1675−1684.
(29) Kubař, T.; Hobza, P. *Nucleic Acids Res.*, submitted for publication, 2007.
(30) Venkataramani, R.; Swaminathan, K.; Marmorstein, R. *Nat. Struct. Biol.* 1998, *5*, 74−81.
(31) Otyepka, M.; Sklenovský, P.; Horinek, D.; Kubař, T.; Hobza, P. *J. Phys. Chem. B* **2006**, *110*, 4423−4429.
(32) Černý, J.; Jurečka, P.; Hobza, P.; Valdés, H. *J. Phys. Chem. A* **2007**, *111*, 1146−1154.
(33) Valdés, H.; Řeha, D.; Hobza, P. *J. Phys. Chem. B* **2006**, *110*, 6385−6396.
(34) Černý, J.; Hobza, P. *Phys. Chem. Chem. Phys.* **2005**, *7*, 1624−1626.