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N-Methylformamide−Benzene Complex as a Prototypical Peptide N−H···π Hydrogen-Bonded System: Density Functional Theory and MP2 Studies

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Although the existence of peptide N−H···π hydrogen bonds recently has been reported in protein structures, little is known about their strength and binding nature and, therefore, the relative importance of the interaction. To shed light on this binding, the *N*-methylformamide−benzene complex, as a model of the peptide N−H···π hydrogen bonding, was studied by using density functional theory and Møller−Plesset second-order perturbation (MP2) methods. The geometry of the complex was fully optimized at the B3LYP/6-31G(d,p) and MP2/6-31G(d,p) levels. The optimized interaction distances are about 3.6 and 3.2 Å, respectively, at the two levels. The binding energy corrected by basis set superposition error with the MP2/cc-pVTZ method based on the MP2/6-31G** geometry is −4.37 kcal/mol, which is as strong as the conventional hydrogen bonding. The calculated results suggest that the peptide N−H···π hydrogen bonding is of sufficient strength to play an important role in the stabilization of protein structures. These results are helpful to better understand the characteristics and nature of the peptide N−H···π interaction as well as to modify current force fields to better represent this special interaction.

1. Introduction

Noncovalent interaction plays a crucial role in the determination of the structures and functions of many biological molecules. The three-dimensional (3D) architectures of proteins are stabilized by many different noncovalent interactions. Biological recognition is also operated mainly by this mechanism, and the molecular mobility required for biological processes is directly connected with the rapid formation and breaking of the noncovalent interaction as well.[1] One of the most important noncovalent interactions is hydrogen bonding. The ubiquitousness of the hydrogen bond has made it an active topic of research for many decades.[1−3] Conventional hydrogen bond interaction (A−H···B) involves two electronegative atoms (A and B are usually nitrogen, oxygen, or fluorine), A being attached to a hydrogen atom as a donor and B bearing lone electron pairs as an acceptor.[3]

However, the hydrogen bond as a very broad phenomenon, covering a wide and continuous energy scale from around −0.5 to over −30 kcal/mol,[4] should not be only restricted to N, O, and F atoms, but may involve less electronegative atoms or groups. Recently, a general concept of hydrogen bonding has emerged, which involves not only N−H and O−H as donor groups, but also C−H, and not only N and O as acceptor groups, but also π systems.[1,4−7] For example, C−H···O,[8−18] C−H···N,[18−20]

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O−H···π,[21−25] N−H···π,[25−30] X−H···π,[31] and even C−H···π[4,5,32−40] hydrogen bonds have been reported. Now, the principle that π systems can act as hydrogen bond acceptors in certain circumstances has become a part of mainstream chemistry.[4−7,21−41] For example, benzene, acting as an acceptor, can form a hydrogen bond with ammonia.[25−27] The ammonia−benzene complex was determined experimentally by spectroscopic techniques and predicted theoretically by ab initio MP2/6-31G** (MP2 = Møller−Plesset second-order perturbation) calculation.[26] The calculated MP2/6-31G** interaction energy without basis set superposition error (BSSE) correction for the monodentate structure was −2.4 kcal/mol.[26] The reported binding energy from density functional theory (DFT) calculation was −0.9 kcal/mol.[27] Tsuzuki et al.[25] performed high-level ab initio calculations to evaluate the interaction between ammonia and benzene as a model of N−H···π interaction. The calculated MP2/cc-pVTZ interaction energy between ammonia and benzene, after BSSE correction, is −2.07 kcal/mol.[25] There are a few other studies of the N−H···π hydrogen bond. For instance, Park and Lee[29] investigated theoretically the structure and energy of the pyrrole dimer at the RHF/6-31G**, RHF/6-31++G**, and MP2/ 6-31G** levels of theory. Kim and Friesner[41] studied the N−H···π hydrogen bond interaction among acetamide, NH_2COCH_3, and benzene with the PS−HF method using the 6-31G** basis set.

Apart from the theoretical study of small organic molecules, numerous N−H···π hydrogen bonds have been observed in experimentally determined protein structures.[1,4,6] For example, Steiner and Koellner[4] recently found 519 aromatic hydrogen bonds with N−H donors in the inspection of 592 published high-resolution crystal structures (<1.6 Å), peptide N−H groups of which are major constituent donors in the samples. The interaction between a peptide N−H bond and a π system was described as a peptide N−H···π hydrogen bond.[4] In proteins, because the main-chain N−H is involved in a conventional N−H···O═C hydrogen bond, the peptide N−H···π hydrogen bond cannot be formed in the central parts of the regular secondary structure elements, such as β-sheets and α-helices. It usually exists at the ends and edges of sheets and the *N*-termini of helices aside, and at structural irregularities within strands and helices. Though it is generally thought to be weaker than the conventional N−H···O═C hydrogen bond, peptide N−H···π hydrogen bonding is generally considered to be operative in edge and terminus stabilization.[4]

Despite the finding of numerous peptide N−H···π interactions in protein structures,[1,4,6] there are only a few investigations that are mainly on the NH_3−benzene complex.[25−27] However, the sp^3-hybridized N−H···π hydrogen bond in the NH_3−benzene complex cannot represent the peptide N−H···π interaction properly, because the structure of the peptide bond is planar, and the N atom in the peptide bond unit is more likely sp^2 hybridized. Therefore, the nature and characteristics of the peptide N−H···π interaction remain open questions. To shed light on the nature of these interactions, a model system composed of *N*-methylformamide (MF) and benzene was used for this theoretical investigation to explore how the peptide N−H group interacts with a π system. We chose this model because the interaction between the N−H of MF and benzene can serve as a prototype for most peptide N−H···π hydrogen bonds found in protein structures, while it is small enough to be calculated by using advanced quantum chemistry methods. The information released from this model system should be helpful in understanding peptide N−H···π hydrogen bonding. The methods employed in this study are DFT and MP2 with different basis sets as large as cc-pVTZ. This is because a very large basis set is necessary for ab initio calculations to accurately evaluate this kind of noncovalent interaction.[42]

2. Computational Methods

The geometry of a peptide N−H···π hydrogen-bonded complex is possibly very flexible, even softer than that of conventional hydrogen bonds. Considering the initial structure might seriously affect the final conformations of the peptide N−H···π hydrogen bond complexes, six possible initial structures of the MF−benzene complex were designed for geometry optimization (see Figure S1 in the Supporting Information). All the geometries of complexes and free monomers were optimized with the 6-31G** basis set at the B3LYP[43,44] and MP2[45−48] levels, respectively. No symmetry constraint was imposed during the optimization. Frequency calculations were

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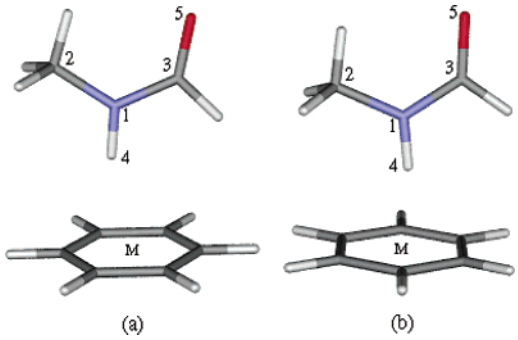

FIGURE 1. B3LYP/6-31G**-optimized geometry (a) and MP2/6-31G**-optimized geometry (b). (M represents the center of the benzene ring.)

then performed for each optimized structure to test whether they were real minimum energy structures on the potential surfaces.

To obtain more reliable binding energies, BSSE correction was estimated by the Boys−Bernardi counterpoise method.[49] In addition, the common practice of running a high-level single-point energy calculation on the geometry computed by use of a cheaper method is as effective as performing all calculation at the higher level of theory. Thus, on the basis of the B3LYP/6-31G**- and MP2/6-31G**-optimized geometries, single-point energy calculations and BSSE corrections using larger basis sets were carried out as well.

All the calculations were performed using the Gaussian98 program[50] on a supercomputer.

3. Results and Discussion

3.1. Geometries. The lowest energy structures revealed from both B3LYP/6-31G** and MP2/6-31G** geometry optimizations are very similar to each other as depicted in Figure 1. Vibrational frequency analysis on these two optimized structures gave no imaginary frequencies, suggesting that they are true minimum energy structures and that the peptide N−H···π hydrogen-bonded complex is stable. All the bond lengths in the complexes are almost the same as those in free monomers, suggesting that the binding between MF and aromatics does not significantly affect the geometries of the monomers in the complexes. The optimized interaction distances are shown in Table 1. The data demonstrate that the peptide N−H bond points toward the benzene ring. It has a T-shape binding characteristic

TABLE 1. Geometry Parameters of the MF−Benzene Complex[a]

	complex		free MF or benzene	
	B3LYP	MP2	B3LYP	MP2
^{R}(1,M)[b] (Å)	3.564	3.206		
^{R}(4,M)[b] (Å)	2.573	2.208		
A(2,1,3) (deg)	122.56	122.37	122.79	122.25
A(1,4,M)[b] (deg)	166.9	171.5		
D(4,1,3,5) (deg)	180.0	180.0	180.0	180.0

[a] All geometries are optimized with 6-31G** basis set. [b] M represents the centroid of benzene ring.

similar to that of the NH_3–benzene complex.[25−27] The N−centroid distances are 3.206 and 3.564 Å for the MP2/6-31G** and B3LYP/6-31G** methods, respectively (Table 1). A rather shorter interaction distance for the MP2 method than that for the B3LYP method by about 0.36 Å indicates that the MP2 binding strength might be stronger than that of B3LYP. Both B3LYP and MP2 results did not show a significant change in aromatic C−C bond and C−H bond lengths (<0.01 Å) during the complexation reaction, suggesting that the interaction between MF and benzene is not very strong.

An important feature of the MF−benzene complex is that the N atom of MF slightly shifts away from the normal axis of the benzene ring. The calculated N−H···M angles are 166.8° and 171.5° at the B3LYP/6-31G** and MP2/6-31G** levels, respectively. This nonlinear structural characteristic of the N−H···M unit is in agreement with the database analysis result on the peptide N−H···π interaction by Steiner,[4] which shows that the mean N···M distance is 3.71 Å and the mean N−H···M angle is 146.7° in experimentally determined protein structures.

3.2. Energies. Table 2 summarizes the calculated binding energies, BSSEs, and binding energies corrected by the BSSEs. At the MP2/6-311G** and MP2/cc-pVTZ levels, the BSSE-corrected binding energies are −3.52 and −4.99 kcal/mol, respectively. Rodhan et al.[26] reported that, for the N−H···π interaction of the NH_3−benzene complex, the MP2/6-31G** binding energy without BSSE correction was −2.4 kcal/mol. Recently, Seiji Tsuzuki et al.[25] evaluated this N−H···π interaction at the MP2/6-311G** and MP2/cc-pVTZ levels with BSSE corrections as −1.45 and −2.07 kcal/mol, respectively, only about 2/5 of the values of the MF−benzene complex. With an influence from the electronegative carbonyl group, the H atom attached to the sp^2-hybridized N atom should be more positively charged than that in ammonia. This could be one of the reasons that the peptide N−H···π interaction in the MF−benzene complex is much stronger than the ordinary sp^3 N−H···π interaction in the NH_3−benzene complex.

The BSSE-corrected interaction energies in the benzene−water complex are −2.34 and −2.81 kcal/mol,[25] respectively, for the MP2/6-311G** and MP2/cc-pVTZ levels. Therefore, the peptide N−H···π interaction is also stronger than the O−H···π interaction of the benzene−water complex. Meanwhile, at the level of MP2/cc-pVTZ, the predicted BSSE-corrected binding energy of a conventional O−H···O hydrogen bond between two water molecules in the gas phase, based on MP2/6-31G**-optimized structure, is −4.17 kcal/mol (unpublished data), still about 0.8 kcal/mol smaller than that of the

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TABLE 2. Energy Properties (kcal/mol) of the MF−Benzene Complex Evaluated by the B3LYP and MP2 Methods

method	ΔE	BSSE	ΔE^{BSSE}	ΔZPVE	$\Delta E^{BSSE+ZPVE}$ [a]
B3LYP/6-31G**	−2.73	1.04	−1.69	0.39	−1.30
B3LYP/6-31++G**//B3LYP/6-31G**	−1.89	0.46	−1.43		−1.04
B3LYP/6-311G**//B3LYP/6-31G**	−2.32	0.78	−1.54		−1.15
B3LYP/6-311++G**//B3LYP/6-31G**	−1.83	0.40	−1.43		−1.04
B3LYP/cc-pVTZ//B3LYP/6-31G**	−1.86	0.45	−1.41		−1.02
MP2/6-31G**	−6.02	2.96	−3.06	0.62	−2.44
MP2/6-31++G**//MP2/6-31G**	−7.04	3.71	−3.33		−2.71
MP2/6-311G**//MP2/6-31G**	−6.31	2.79	−3.52		−2.90
MP2/6-311++G**//MP2/6-31G**	−7.19	3.35	−3.84		−3.22
MP2/cc-pVTZ//MP2/6-31G**	−6.33	1.34	−4.99		−4.37

[a] The binding energy corrected with the ZPVE at the 6-31G** level.

MF−benzene complex. Therefore, the peptide N−H···π interaction is even stronger than the conventional O−H···O hydrogen bond. Thus, the peptide N−H···π hydrogen bonds are of sufficient strength to make a significant contribution toward the edge and terminus stabilization in protein structures.

The data in Table 2 also indicate that the calculated binding energy is sensitive to the methods used. In agreement with the binding distance, the binding strength predicted at the MP2 level is stronger than that predicted by the B3LYP approach. Using the 6-31++G** basis set as a reference, the MP2-calculated binding energy is −2.71 kcal/mol, more stable than the B3LYP-predicted result of −1.04 kcal/mol by 1.9 kcal/mol. The great differences between MP2 and B3LYP binding energies indicate that the dispersion interaction, which is not given by the DFT B3LYP level of theory,[42,51−53] is one of the dominant ingredients of the binding energy in the MF−benzene complex. It should also be the reason that the MP2 interaction distance is shorter than the B3LYP interaction distance. Therefore, the B3LYP method should not be recommended for the peptide N−H···π system calculations. To further clarify the importance of the dispersion, the decomposition of the binding energy was performed using version 3.2 of the ORIENT program developed by Stone,[54] in which a precise distributed multipoles model is obtained from the MP2/6-31G** wave functions using CADPAC version 6.[55] The decomposition result shows that the total binding energy (−7.42 kcal/mol) is composed of electrostatic energy (−5.25 kcal/mol), repulsion energy (4.86 kcal/mol), induction energy (−1.69 kcal/mol), and dispersion energy (−5.35 kcal/mol), also demonstrating that dispersion is essential to the binding of peptide N−H with the π system.

The B3LYP-predicted binding energies are not very sensitive to the basis sets used. All B3LYP calculations with the 6-31++G**, 6-311++G**, and cc-pVTZ basis sets give similar values of the BSSE- and zero-point vibrational energy (ZPVE)-corrected binding energy. Enlarging the basis set from 6-311++G** to cc-pVTZ, the binding energy varies from −1.04 to −1.02 kcal/mol only. However, the MP2-calculated binding energy is sensitive to the basis sets. Similar basis set dependence has also been observed in other calculations.[56,57] The small 6-31G** basis set (205 basis functions for the MF−benzene complex) leads to a considerable underestimation of the attraction compared with the cc-pVTZ basis set (454 basis functions). The BSSE-corrected MP2 interaction energies at the levels of 6-31G**, 6-31++G**, 6-311G**, and 6-311++G** are −2.44, −2.71, −2.90, and −3.22 kcal/mol, respectively, while that at the cc-pVTZ basis set level is −4.37 kcal/mol. Adding two sets of the Gaussian s- and p-type diffusion functions results in an increase of about 0.3 kcal/mol in the binding energy for the MF−benzene complex. Unlike the B3LYP method, the MP2 method with the 6-311++G** basis set still underestimates the interaction energy by as much as 26% compared with the MP2/cc-pVTZ-predicted value. These results also illustrate that a large basis set is essential for studying the peptide N−H···π system if teh MP2 method is used.

Table 2 also shows that, in comparison with the BSSE values, the ZPVE corrections are small, only 0.39 and 0.62 kcal/mol at the B3LYP/6-31G** and MP2/6-31G** levels, respectively.

It is worthy to stress that failure to correct the BSSE would result in erroneous conclusions. Consistent with our previous studies of cation−π interactions,[53,58−59] the calculated BSSE values at the MP2 level are substantially larger than those using the B3LYP approach. The MP2 calculation with small 6-31G** gives a large BSSE value (2.96 kcal/mol), which is close to the size of the calculated interaction energies. Even if the MP2/cc-pVTZ method is used, the BSSE value (1.34 kcal/mol) is still as large as about 31% of the total corrected binding energy, suggesting that there is a problem of basis set incompleteness associated with the MP2 calculation. More complete basis sets should be used to reach the MP2 convergence on binding energy. A previous study with

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TABLE 3. Sum of Atomic Mulliken and ChelpG Charges

		B3LYP/6-31G**	MP2/6-31G**
Mulliken	MF	−0.0237	−0.0281
	benzene	0.0237	0.0281
CHelpG	MF	−0.0602	−0.0757
	benzene	0.0602	0.0757

the NH_3−benzene complex showed that, however, the binding energy difference between MP2/cc-pVTZ and MP2/cc-pVQZ is very small, only 0.3 kcal/mol.[25] Therefore, our calculations at the MP2/cc-pVTZ level should be acceptable and reliable. Hence, the binding strength in the peptide N−H···π system is more likely as strong as −4.37 kcal/mol.

3.3. Charge Population Analysis. Mulliken and ChelpG charges are calculated using both the B3LYP and MP2 levels of theory, to see whether charge transfer is important in the binding of MF with benzene. Each optimized structure was divided into two parts in terms of benzene and MF. Table 3 summarizes the total atomic charges of these two parts. It is clear that some of the π-electron is transferred from the benzene ring to MF. However, the amount of transferred charge in the MF−benzene complex is significantly smaller than that in the NH_4^+−benzene complex, in which charge transfer plays a very important role in the binding.[59] This indicates that the charge transfer in peptide N−H···π hydrogen-bonding systems is not as significant as in cation−π complexes; subsequently the peptide N−H···π hydrogen bond is weaker than the cation−π interaction.

3.4. Molecular Orbital Analysis. In an effort to study whether any orbital interaction is involved in the binding, as well as to better understand the nature of the peptide N−H···π hydrogen bond, an orbital analysis on the MF−benzene complex at the MP2/6-31G** level for structure b in Figure 1 was performed. Schematic diagrams of the orbital interactions are presented in Figure 2, and the bonding molecular orbital compositions are listed in Table 4. With the influence of MF, the degenerated HOMOs 20 and 21 in benzene split; one becomes the main contributor to the HOMO−1 in the MF−benzene complex, and the other mixes with a minor contribution from the HOMO of MF, forming the HOMO of their complex. The HOMO−2 in the MF−benzene complex comes mostly from the HOMO of MF, mixed with p_x orbitals of the carbon atoms of benzene. The LUMO is basically the LUMO of benzene. Quantitatively, the HOMO in MF−benzene contains 83.47% p_x orbital from benzene carbon atoms and 13.96% p_z orbital from MF, and the LUMO contains 97.11% p_x orbital from benzene.

In a conventional hydrogen bond, the charge transfer can be understood in a frontier orbital picture in terms of mixing of the HOMO in one monomer and the LUMO in the other monomer.[60] The contour maps of the molecular orbitals, as shown in Figure 2, indicate that the orbital interaction is involved as well in the binding between peptide N−H and aromatics, but it is quite weak. This might be the reason that little charge transfer was found during the complexation between MF and benzene (see the discussion in Charge Population Analysis).

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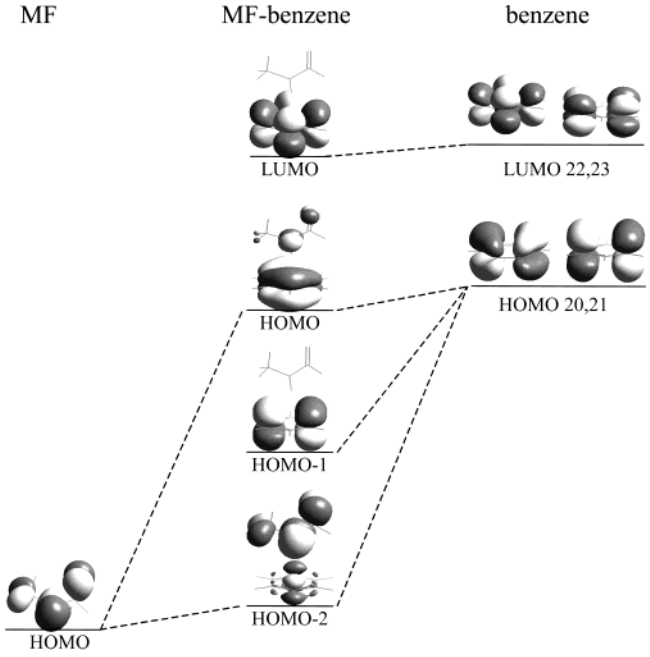

FIGURE 2. Orbital interaction in the MF−benzene complex at the MP2/6-31G** level. The isosurface value of MF and benzene is 0.1, and that of the complex is 0.08.

TABLE 4. Relevant Molecular Orbital Energies and Compositions at the MP2/6-31G Level for Structure b in Figure 1**

		MF orbital (%)		benzene orbital (%)	
MO	*E* level (au)	s	p_z	p_x	p_y
HOMO − 2	−0.3756	6.08	85.67	7.52	
HOMO − 1	−0.3538	1.05		97.17	0.96
HOMO	−0.3500	1.38	13.96	83.47	0.76
LUMO	0.1218	0.80	0.60	97.11	0.90

4. Conclusions

Peptide N−H···π interactions have been observed in crystal structures of proteins. As the peptide bond exhibits partial double bond character, and the peptide unit is relatively rigid and planar, the previous sp^3-hybridized N−H···π hydrogen bond model in ammonia−benzene complex is not a proper model for the study of the peptide N−H···π interaction.

In this study, by means of the B3LYP density functional method and the ab initio MP2 method at various basis sets, the properties of the MF−benzene complex, which can represent the peptide N−H···π interaction found in protein structures, have been investigated. These data provide the first reliable estimate for the strength of the peptide N−H···π interaction. The optimized geometries show that the intermolecular binding distances are quite short, about 3.6 and 3.2 Å, respectively, at the B3LYP and MP2 levels of theory.

The binding energy for the MF−benzene complex predicted at the MP2/cc-pVTZ level is about −4.37 kcal/mol, even stronger than the hydrogen bond of O−H···O in a water dimer, suggesting that the peptide N−H···π hydrogen bond must be considered as an important factor affecting the protein structure and properties. We found that the dispersion energy is the first important component in the binding of peptide N−H with aromatics.

Therefore, the MP2 method using cc-pVTZ or larger basis sets should be used in the computational studies of peptide N−H···π hydrogen bond interactions.

The charge population analysis indicated that a small amount of charge transfer occurred when MF was bonded to the benzene ring. The molecular orbital analysis showed that the orbital interactions between the two monomers are weak.

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Supporting Information Available: Figure S1 showing the six initial structures in the geometry optimization, in which the N−H points perpendicularly toward the center of the acceptor benzene ring (a, d), to the middle of the acceptor aromatic C−C bond (b, c), or to one carbon atom (e, f), Tables S1 and S2 listing the effects of basis sets (the comparison of cc-pVTZ with 6-31G** basis sets at the MP2 level) on charge population analysis and molecular orbital analysis, respectively, Table S3 listing the absolute energies (hartrees) for the optimized geometries at different levels of theory, and the Cartesian coordinates of the finally optimized geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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