Ab Initio Study of Energetics of X−H···π (X = N, O, and C) Interactions Involving a Heteroaromatic Ring

Uttamkumar Samanta,[‡] Pinak Chakrabarti,*[,‡] and Jayaraman Chandrasekhar*[,§]

Division of Physical Chemistry, National Chemical Laboratory, Pune 411008, India, Department of Biochemistry, Bose Institute, P1/12 CIT Scheme VIIM, Calcutta 700054, India, and Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, India

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The possibility of the π-face of a heterocyclic ring acting as a hydrogen-bond acceptor has considerable significance in the structure and binding of cofactors and nucleic acids to proteins. This interaction has been modeled using ab initio calculations on various complexes of pyridine with water, ammonia, methane, and benzene. Both Hartree−Fock (HF) and MP2/6-31G(d,p) calculations, including counterpoise corrections, have been carried out on a number of representative geometries. In addition to the expected hydrogen-bonded structure involving the nitrogen lone pair, a number of other orientations in which X−H is placed above the π-face are also found to be energetically favorable. The maximum stabilization is found directly above the pyridine nitrogen for water and ammonia, whereas for methane it is shifted to a point halfway toward the ring center. The corresponding complexation energies are 2.9 (X = O), 1.8 (N), and 0.8 (C) kcal mol^{-1}, which are 0.45, 0.56, and 0.71, respectively, of the values obtained when the interaction is in the conventional hydrogen-bonded geometry. Bifurcated structures, with the XH_2 group above the pyridine ring but displaced from the center toward the nitrogen, are also found to be fairly stabilized. A herringbone structure with two of the benzene C−H bonds facing the pyridine ring is computed to have a stabilization energy of 2.7 kcal mol^{-1}, which is greater by 0.4 kcal mol^{-1} than that for the linear C−H···N hydrogen-bonded geometry involving the nitrogen lone pair. The interaction energies with the π-face are of comparable magnitude for benzene and pyridine. The computed relative energetics for various geometries should be useful in developing potential functions for modeling the binding of cofactors and nucleic acids with proteins.

Introduction

Hydrogen bonding plays a central role in the structure and function of all biological molecules.[1] Derived from the wealth of information available in small molecule structures,[2] the concept of hydrogen bonding has been used in protein structures quite early on.[3] Traditionally it was assumed to involve an essentially electrostatic interaction between a proton attached to an electronegative atom (OH or NH as the proton donor) and another oxygen or nitrogen atom (as the proton acceptor).[4] However, many features in small molecule structures as well as in macromolecular structures have led to a refining of this limited perspective of hydrogen bonding. Thus, over the years it has been realized that less electronegative atoms can act as proton donors and acceptors.[5] For example, the proton donor could be a CH group, leading to CH···O/N interaction.[6] Another manifestation of an unusual hydrogen-bonding motif was recognized by Perutz and co-workers,[7] on the basis of a few hemoglobin−drug complex structures. It was noted that an OH or NH group placed on top of an aromatic ring represents an energetically favorable ensemble. Termed X−H···π interactions, these have now been observed in the solid-state structures of many proteins as well as small molecules.[8,9] The structural features have been detected in solution and gas phase, and their existence has been confirmed by theoretical studies.[10−12] In addition to providing stability, the interactions have functional utility also.[8b,d]

The concept of the O/NH···π hydrogen bond has also been extended to CH···π-type interactions.[13] The latter is stabilized especially if the CH group is polarized, as in an aromatic ring,[14,15] or if it is attached to a positively charged group.[16−18] Alternatively, the acceptor site can also be modulated by making it more electron-rich with the incorporation of nitrogen atoms in the aromatic ring. The resultant CH(aliphatic)···π(heterocyclic) interaction is observed in protein structures that bind adenine-containing cofactors.[19] However, in the absence of any knowledge of the coordinates of the hydrogen atoms in protein crystal structures, the precise position of the CH group on the face of the heterocyclic ring cannot be ascertained, as also is the case for the energetics.

In this paper, we report a detailed computational examination of the strength of hydrogen-bonding interactions involving the π cloud of a heteroaromatic ring. We have carried out ab initio calculations on the interaction of a pyridine ring (as a model for a heterocyclic system) with water, ammonia, and methane. As an additional reference, we have evaluated the magnitude of interaction with the C−H bond of a benzene molecule. We have considered several relative orientations in all the systems to probe the ability of the π framework to act as a hydrogen-bond acceptor. The conventional hydrogen-bonded structures involving the pyridine nitrogen lone pair offer ideal internal

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* Address correspondence to these authors: (P.C.) Fax +91-33-334-3886, E-mail pinak@boseinst.ernet.in; (J.C.) Fax +91-80-344-3529, E-mail jc@orgchem.iisc.ernet.in.

[‡] National Chemical Laboratory. Present address: Bose Institute.

[§] Indian Institute of Science.

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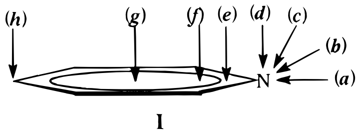

Figure 1. Different idealized sites, ***a***−***h***, at which the hydrogen-bonding ability of pyridine was examined.

comparison. After analyzing the computed energetics, we discuss their potential implications for biomolecular structures.

Methods

In all the systems considered, it is likely that conventional hydrogen-bonded structures involving the pyridine nitrogen lone pair are the only minima on the potential energy surface. Alternative forms utilizing the pyridine π-face as the hydrogen atom acceptor may collapse to the classical forms during geometry optimization. Therefore, rather than attempting to locate probably elusive local minima with X−H···π interactions, we have followed a different objective of quantifying the magnitude of the interactions in a range of idealized geometries. To keep the comparisons uniform, we have chosen the experimental geometries[20] of the individual monomers.

Figure 1 shows various idealized orientations in which one of the X−H bonds of water, ammonia, or methane is allowed to interact with the pyridine molecule (1H bonding mode). The sites of interaction of the pyridine ring, I, considered in this study are labeled ***a***−***h***. Geometry ***a*** corresponds to the conventional hydrogen-bonded form. In ***b***, ***c***, and ***d***, the X−H unit is oriented at an angle of 30°, 60°, and 90°, respectively, with respect to the 2-fold axis of pyridine. Thus, the X−H bond directly interacts with the nitrogen p(π) orbital in ***d***, while ***b*** and ***c*** correspond to intermediate geometries between the classical hydrogen-bonded form and one of the X−H···π bonded forms. Structures ***d***−***h*** probe the hydrogen-bond acceptor efficiency of different parts of the π-cloud of the ring. The forms ***e***−***h*** are generated from ***d*** by translating the X−H unit along the 2-fold axis by distances of *R*/8, *R*/4, *R*/2, and *R* away from nitrogen, *R* being the distance between N and C_4.

For each of the possibilities ***a***−***h***, several idealized orientations of the hydrogen atom donor unit were considered. For the water molecule, the non-hydrogen-bonded O−H unit can be syn, anti, or orthogonal to the nitrogen lone pair. The corresponding structures have been labeled II−IV in Figure 2. Equivalent structures in the case of ammonia are V−VII. For the methane−pyridine complex, geometries VIII and IX, both with C_s symmetry, were considered.

A series of structures with bifurcated (2H) hydrogen bonds in which XH_2 units interact with pyridine at sites ***a***−***h*** were also examined (Figure 3). For example, the water molecule can be in the plane of the N−C_4 axis or orthogonal to it, leading to structures X and XI, respectively. Similar bifurcated hydrogen-bonded structures involving ammonia and methane are XII,XIII and XIV,XV, respectively. In the case of ammonia and methane, structures with XH_3 units forming hydrogen bonds were additionally taken into account. These 3H bonded forms, XVI−XIX, were chosen to have C_s symmetry (Figure 4).

Two possible types of interactions were considered for the pyridine−benzene complex (Figure 5). In one set of calculations, a single C−H bond was oriented toward the pyridine lone pair or π-face (XX). In another, a pair of adjacent C−H bonds pointed toward the pyridine ring (XXI). In both sets of calculations, the benzene ring and the N−C_4 axis of pyridine were kept in the same plane, corresponding to the herringbone-type geometry.

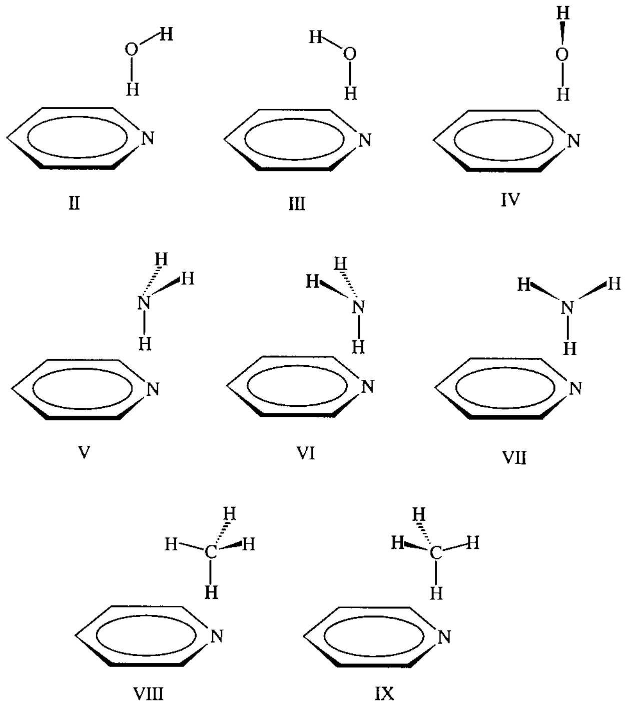

Figure 2. Various conformations involving 1H mode of interaction of water, ammonia, and methane with pyridine.

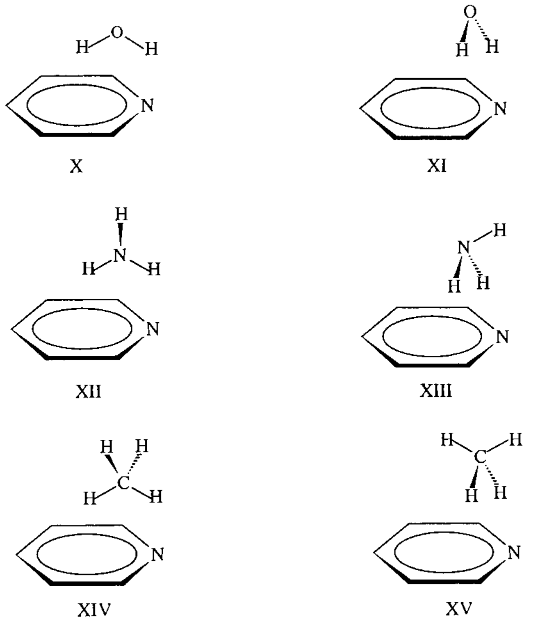

Figure 3. Various conformations involving 2H mode of interaction of water, ammonia, and methane with pyridine.

To obtain a comparison, a few representative complexes formed by benzene with water, ammonia, and methane have also been examined. The interaction energies of XH, XH_2, and XH_3 units placed directly above the ring center and above a carbon atom, which correspond to structural types ***g*** and ***d***, respectively, have been computed.

For each chosen geometry, the separation between the molecular subunits at which maximum interaction occurs was first determined from MP2/6-31G(d) calculations. Single point calculations were then carried out using the larger 6-31G(d,p) basis set at the MP2 level. To remove basis set superposition errors (BSSE), counterpoise corrections were made.[21] This level of theory has been shown to yield interaction energies very close to those obtained with MP2 calculations using near-Hartree−

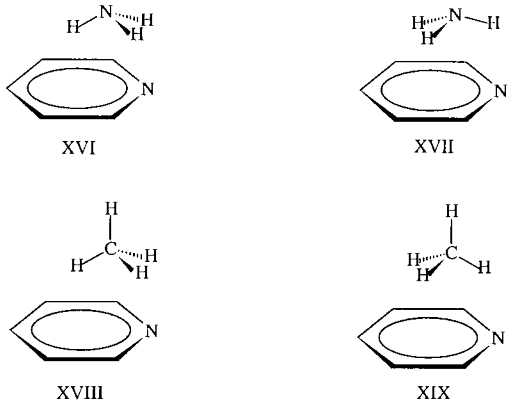

Figure 4. Various conformations involving 3H mode of interaction of ammonia and methane with pyridine.

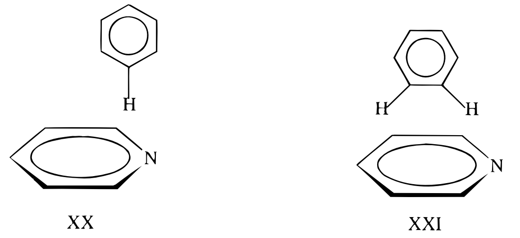

Figure 5. The 1H and 2H modes of interaction of benzene with pyridine.

Fock-limit basis sets for a number of hydrogen-bonded systems.[22] Nevertheless, while the uncorrelated energies are undoubtedly overestimated, there have been reports that the BSSE-corrected interaction energies are underestimated, especially in the biological molecular systems.[23] Only the conventional hydrogen-bonded systems were studied by Novoa et al.,[22a] and even in these systems the energies were found to be underestimated. For weaker benzene complexes, full BSSE-corrected interaction energies between the benzene and other molecules are highly underestimated;[24] furthermore, the BSSE-corrected energies are sometimes less consistent than the uncorrected energies.[25] Therefore, instead of the full BSSE correction, 50% BSSE correction has often been used.[25] Consequently, it was assumed that a 50% BSSE correction would provide realistic values of interaction energies for these aromatic ring complexes. Unless stated otherwise, 50% BSSE-corrected MP2/6-31G(d,p) data are used in all subsequent discussion. All calculations were performed with the Gaussian 94 series of programs.[26] Full details of computed energetics and geometries employed are provided as Supporting Information.

Results

Interaction with Water. The classical hydrogen-bonded structure with one O−H bond directed toward the pyridine lone pair is calculated to have a large interaction energy [6.44 kcal mol^{-1} at MP2/6-31G(d,p) with 50% BSSE corrections]. As the water molecule is pulled out toward the pyridine π unit, the stability is lowered. The relative interaction energies are similar for the three different orientations, II−IV, considered for the water molecule with respect to the pyridine ring. However, the maximum interaction energy is obtained for the structural type II, for which the computed results are summarized in Table 1. In orientation ***d*** with the O−H unit pointing toward the nitrogen π orbital, the stabilization is quite substantial (2.91 kcal mol^{-1}). The magnitude of interaction tapers off as the water molecule is moved above the ring from nitrogen to C_4. Significantly, the interaction is calculated to be favorable along the entire series of structures, ***d*−*h***.

In the bifurcated (2H) mode, the hydrogen-bonding energy is uniformly lower. The interaction with the nitrogen lone pair is 3.84 kcal mol^{-1} and is reduced further as the water molecule is moved over the ring. Table 1 includes data of stabilization energies computed for orientation X, which are larger compared to those for XI. The interaction with the π cloud is maximum when the oxygen atom is located above the ring between the nitrogen and the ring center. Such a geometry allows one of the hydrogen atoms of water to be closer to the pyridine nitrogen.

Interaction with Ammonia. Two classical N−H···N hydrogen-bonded structures, with the orientation of the ammonia unit corresponding to V (VI) and VII, are computed to be quite stable. The latter has a marginally higher interaction energy (3.4 kcal mol^{-1}). For structures characterized by N−H···π interactions, orientation V is uniformly favored. The energetics for this set of geometry are given in Table 1. The interaction energy for the structure in which the N−H unit is directly placed above the pyridine nitrogen is 1.8 kcal mol^{-1}. The stabilization remains nearly constant (~1.6 kcal mol^{-1}) as it is shifted toward the ring center.

The bifurcated hydrogen-bond structure of ammonia with the pyridine nitrogen lone pair is relatively weak (1.8 kcal mol^{-1}, Table 1). The interaction with the ring π cloud is roughly of the same magnitude (1.6−1.7 kcal mol^{-1}), especially in the range of structures ***d*−*g***. In all these geometries, one of the hydrogen atoms of the ammonia unit is relatively close to the nitrogen p(π) orbital of the pyridine ring. The stabilization disappears as the ammonia nitrogen is moved above C_4 of pyridine.

In the 3H bonding mode involving ammonia, the interaction is uniformly repulsive at the HF level when all three hydrogen atoms are directed toward the pyridine π cloud. At the correlated level, the maximum stabilization (1.3 kcal mol^{-1}) is obtained for the structure ***f***.

Interaction with Methane. The stabilization resulting from a single C−H bond of methane directed toward the pyridine nitrogen lone pair is 1.2 kcal mol^{-1}. The corresponding interaction energies in the bifurcated and trifurcated modes are much smaller. In contrast, the interaction between methane and the pyridine aromatic ring is uniformly favorable, although only at the correlated level. Indeed, a value (1.0 kcal mol^{-1}) comparable to the above is obtained for XIV(***f***) when the methane C atom is halfway between N and the ring centroid. The stabilization is nearly the same for the methane unit oriented as in VIII, IX, XIV, XVIII, or XIX. Representative energetics for three sets of structures are given in Table 1.

Interaction with Benzene. Two features are notable in the computed interaction energies for the pyridine−benzene complex (Table 1). First, the nitrogen lone pair interacts nearly equally effectively with benzene in the linear C−H···N as well as in the bifurcated modes. Further, the interaction of benzene with the pyridine π cloud is also quite stabilizing. With one C−H bond placed above the pyridine ring at various sites, the interaction energies range from 1.4 to 2.1 kcal mol^{-1}. The stabilization energies are even larger when two C−H bonds are oriented toward the pyridine ring. In structure ***f***, the stabilization (2.7 kcal mol^{-1}) is even greater than that calculated for the complex involving the nitrogen lone pair (2.3 kcal mol^{-1}).

Discussion

Classical Hydrogen-Bonded Structures. The lone pair on pyridine offers an ideal hydrogen atom acceptor site. The

TABLE 1: Corrected (50% BSSE) HF/6-31G(d,p) and MP2/6-31G(d,p) Interaction Energies[a] of Pyridine with Water, Ammonia, Methane, and Benzene in Various Geometries[b]

structure	level	***a***	***b***	***c***	***d***	***e***	***f***	***g***	***h***
water	HF	5.16	4.68	3.26	1.37	1.23	0.87	0.65	0.60
1H (II)	MP2	6.44	6.01	4.53	2.91	2.64	2.42	2.33	1.90
water	HF	3.20	2.98	2.24	0.90	1.32	1.20	0.45	0.04
2H (X)	MP2	3.84	3.65	3.11	2.45	2.72	2.72	2.17	1.13
ammonia	HF	1.90	1.76	1.22	0.37	0.07	−0.07	−0.10	0.25
1H (V)	MP2	3.18	3.08	2.48	1.79	1.63	1.56	1.63	1.33
ammonia	HF	1.11	1.05	0.54	0.24	0.21	0.12	0.04	−0.31
2H (XII)	MP2	1.79	1.75	1.55	1.59	1.71	1.76	1.55	0.80
ammonia	HF	0.42	0.43	0.11	−0.27	−0.30	−0.31	−0.17	−0.44
3H (XVII)	MP2	0.98	1.02	0.98	1.10	1.20	1.27	1.22	0.55
methane	HF	0.27	0.19	−0.05	−0.28	−0.65	−0.68	−0.70	−0.26
1H (IX)	MP2	1.18	1.12	0.96	0.84	0.76	0.79	0.83	0.65
methane	HF	−0.31	−0.28	−0.44	−0.59	−0.61	−0.66	−0.58	−0.48
2H (XIV)	MP2	0.30	0.36	0.45	0.78	0.55	1.00	0.95	0.58
methane	HF	−0.55	−0.53	−0.53	−0.76	−0.63	−0.76	−0.97	−0.53
3H (XVIII)	MP2	0.24	0.29	0.43	0.71	0.77	0.76	0.70	0.64
benzene	HF	0.81			−0.47		−1.28	−1.24	−0.53
1H (XX)	MP2	2.32			1.88		1.87	2.10	1.42
benzene	HF	0.65			−1.14		−0.82	−0.94	−1.05
2H (XXI)	MP2	2.39			2.72		2.58	2.21	2.05

[a] Given in kilocalories per mole. A positive value denotes stabilization. [b] See Figures 1−5 and text for definition of structural symbols used.

corresponding hydrogen-bonded structures with water and ammonia are therefore highly favored. The C−H···N-type interaction involving methane provides moderate stability. In all these cases, the 1H bonding mode represents the preferred orientation. The bifurcated structures have much lower complexation energies. The results obtained for the pyridine−benzene complex provide a contrast. The 2H interaction is as effective as the 1H mode. The interaction energies are also relatively large in magnitude.

The qualitative nature of the interaction can be inferred from the method dependence of the complexation energies. The HF method adequately describes polarization, charge transfer, and electrostatic interactions, but does not take into account dispersion forces.[4] If the interaction is computed to be attractive at the HF level, conventional hydrogen bonding can be assumed to be operative. On the other hand, repulsive interaction at the HF level but stabilization at the correlated level of theory implies that the system is best described as a van der Waals complex. On this basis, type ***a*** O−H···N and N−H···N complexes involving water and ammonia correspond to classical hydrogen bonds. The corresponding structures with methane are best described as van der Waals complexes.

Intermediate Structures. As the hydrogen-bond donor molecule is moved away from the pyridine nitrogen lone pair, the interaction energy rapidly decreases. The intermediate structural types ***b*** and ***c*** for water and ammonia complexes derive their stability mainly from the extent of overlap possible between the X−H bond and the lone pair. As a consequence, the 2H- and 3H-type interactions, which bring a proton closer to the pyridine lone pair, are relatively favored. The stabilization of the methane complex in the intermediate structures is also comparable to that in the conventional hydrogen-bonded structure ***a***, since dispersion forces, which are relatively insensitive to direction, are the primary source of binding in this system.

Interaction with the Pyridine π-Electron Cloud. The computed energetics for the structures ***d−h*** show that the ability of the heteroaromatic ring to act as a hydrogen-bond acceptor is not insignificant. The interaction energies involving water and ammonia complexes show a measure of direction dependence that is characteristic of typical hydrogen bonds. The nitrogen end of the π cloud is energetically preferred. The interaction above the C_4 center is the weakest. The donor unit is also calculated to prefer the 1H bonding mode, as in the classical hydrogen-bonded structures. In the complexes involving 2H- and 3H-type interactions, greater energies are obtained for those structures in which the position of the X atom is displaced slightly away from the pyridine nitrogen. In such a geometry, a proton is brought closer to the nitrogen, leading to greater stabilization.

The interaction between the π framework and the C−H bonds of methane is also attractive. However, this is so only at the MP2 level. Hence the interaction is predominantly due to London forces. This conclusion is also true for the complex involving the C−H bonds of benzene and the π cloud of pyridine. Of all the orientations and positions of the methane unit above the ring, the maximum interaction is possible in the 2H mode, when the unit is in the middle between N and the ring centroid.

It is instructive to compare the stabilization energies of structures involving the nitrogen lone pair and the π cloud. The latter is about 0.45 times as effective as the lone pair in the interaction with water. In the complexes involving ammonia, the ratio rises to 0.56. In the primarily van der Waals-type complex with methane, the π interaction is 0.71 times that of the lone pair. With benzene, the complex utilizing the π cloud is more stable (1.17 times) than the one involving the lone pair.

Comparison of π Interactions Involving Pyridine and Benzene. It is of interest to compare the relative abilities of the π-clouds of benzene and pyridine to engage in hydrogen bonding. A number of studies have considered X−H···π interactions involving benzene,[10] as it represents the prototypical aromatic molecule. Weak complexes of water and ammonia with benzene have also been experimentally characterized.[11] Geometry optimization at the ab initio level yields low-symmetry structures with the hydrogen-bond donor unit placed nearly above the center of the aromatic ring. For the benzene−water complex, the C_2 axis of water and the C_6 axis of benzene make an angle of 24°, halfway between those of the 1H (53°)

TABLE 2: (50% BSSE) Corrected HF/6-31G(d,p) and MP2/6-31G(d,p) Interaction Energies[a] of Benzene with Water, Ammonia, and Methane in Various Geometries[b]

		pyridine		benzene	
structure	level	***d***	***g***	***d***	***g***
water 1H (II)	HF	1.37	0.65	1.52	1.10
	MP2	2.91	2.33	2.70	2.79
water 2H (X)	HF	0.90	0.45	0.73	1.07
	MP2	2.45	2.17	1.96	2.80
ammonia 1H (V)	HF	0.37	−0.10	0.37	0.09
	MP2	1.79	1.63	1.66	1.82
ammonia 2H (XII)	HF	0.24	0.04	−0.10	−0.21
	MP2	1.59	1.55	1.20	1.76
ammonia 3H (XVII)	HF	−0.27	−0.17	0.03	−0.09
	MP2	1.10	1.22	1.05	1.36
methane 1H (VIII)	HF	−0.28	−0.70	−0.34	−0.59
	MP2	0.84	0.83	0.74	0.96
methane 2H (XIV)	HF	−0.59	−0.58	−0.46	−0.73
	MP2	0.78	0.95	0.64	0.86
methane 3H (XVIII)	HF	−0.76	−0.97	−0.53	−0.74
	MP2	0.71	0.70	0.67	0.71

[a] Given in kilocalories per mole. A positive value denotes stabilization. [b] See Figures 1−4 and text for definition of structural symbols used.

and 2H (0°) modes of interaction.[11a] In the case of the benzene−ammonia complex, the C_3 axis of the ammonia unit is calculated to be tilted by 58° with respect to the C_6 axis of benzene,[11b] predominantly in the 1H mode.

To have a uniform basis for comparison with the calculations on the pyridine complexes, we have calculated the interaction energies of water, ammonia, and methane with benzene on idealized orientations. The 1H, 2H, and 3H (where appropriate) modes were considered. Interactions above the ring center (***g***) as well as above a carbon atom (***d***, ***h***) were examined. As in the pyridine systems, MP2/6-31G(d,p) calculations with counterpoise corrections (50%) were carried out after preliminary optimization of the interaction distance at the MP2/6-31G(d) level.

The complexation energies involving pyridine and benzene in representative geometries are compared in Table 2. There are subtle differences between the two series of complexes. While with pyridine the preferred interaction is in the 1H bonding mode (except for methane, when it is the 2H mode) and the interaction is generally greater above the nitrogen atom, benzene offers the maximum magnitude of interaction above the ring center with the 1H and 2H modes being nearly isoenergetic.

In the most stable arrangements involving X−H···π interactions, the complexation energies for benzene and pyridine do not differ much. The PE surface is indicated to be flatter above the benzene ring, while the polarized charge cloud in pyridine causes the nitrogen end to be relatively more attractive.

Implications for Biomolecular Structures. Heterocyclic systems abound in biology as various cofactors, nucleic acid bases, and amino acid residues (tryptophan and histidine). Although these residues are generally involved in conventional hydrogen bonding, there is evidence[19] that face-specific interactions can also be important in their binding and recognition in biological systems. The present study with pyridine as a model confirms the validity of these proposals.

Structures with attractive interactions, even if they are not minima in the gas phase, may be realized in the condensed phase due to additional constraints present and therefore are of significance. For example, C−H···π interactions involving heteroaromatic rings are likely to contribute to overall stabilization in many systems. In proteins the adenine ring in a majority of cases is found sandwiched between branched side-chains such that more than one CH group interacts with any given face.[19] If we assume the contribution of CH···π interaction obtained in this study to be additive, two such interactions will make a substantial contribution to binding. Our calculations also suggest that placing the edge of an aromatic ring on the face of an adenine ring may provide similar energy. However, there may be two reasons why aromatic rings are not usually found near the adenine site. First, a T-shape arrangement with an aromatic ring may not cover enough surface area[15a] of a large adenine ring system for efficient binding. Further, it may be noted that an aromatic ring may not be equally stabilizing in all orientations. The present study reveals that optimum interaction is found only when the benzene ring is coplanar with the N−C_4 axis of pyridine.

Compared to CH···π interactions, OH···π and NH···π bonds are stronger. Systems with the latter-type interactions have been characterized in the solid state as well as in solution.[7−9] It is therefore surprising that OH···π and N−H···π bonds with heteroaromatic rings are not very common in protein structures.[19,27] It is likely that a protein will gain a lot more in terms of energy if it can associate its O/N−H group with another electronegative atom rather than engaging it with a π-electron cloud. As is generally the case, for optimal crystal packing the strongest hydrogen-bond donor is paired up with the strongest acceptor, followed by a matching of the next strongest donor and acceptor.[28] Presumably, the donor and acceptor abilities of a CH group and the face of an aromatic ring are evenly poised, and an O/N−H···π interaction is used only under special circumstances of functional relevance.

Conclusions

To understand the binding features of heterocyclic rings in biomolecules, the energetics and geometries of interaction between pyridine and ammonia, water, methane, and benzene have been computed by ab initio methods. The presence of the nitrogen atom with a lone pair of electrons leads to the formation of conventional hydrogen-bonded structures. However, the ring is capable of forming π-facial hydrogen bonds, especially with O−H and N−H bonds. These interactions are fairly orientation-sensitive. For the proton donor, the 1H bonding mode is generally preferred. Facial interaction is larger near the nitrogen atom. The interaction with C−H bonds is primarily due to dispersion forces and hence relatively constant over the ring. The strength of π-facial hydrogen bonding is nearly the same for benzene and pyridine, but the latter shows a greater variation over the ring surface. The interaction between the C−H bonds of benzene and the π-face of pyridine is also quite strong.

The computed energetics imply that heteroaromatic rings in proteins and other biomolecules are likely to take advantage of π-facial hydrogen bonding with X−H units as an additional source of stabilization. It is therefore essential that these interactions are adequately described by potential functions used for modeling molecules containing polarizable π-clouds. The variations in the interaction energies noted in the present study provide a qualitative guide for parametrizing force fields to include π-facial hydrogen bonding. These may be especially relevant in the modeling of nucleic acid and cofactor binding and in the design of aromatic substrates to be used for ligation to specific sites of protein molecules.

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Supporting Information Available: Eleven tables, showing HF and MP2/6-31G(d,p) total energies and counterpoise corrections for the complexes of pyridine with water, ammonia, methane, and benzene, as well as for benzene with water, ammonia, and methane (4 pages). Ordering information is given on any current masthead page.

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