Water mediated self assembly of 5-(2-benzoimidazole-1-yl-ethoxy)-3-methyl-1-phenyl-*1H*-pyrazole-4-carboxylic acid methyl ester through C—H···O and O—H···N interactions

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ABSTRACT

Single crystal X-ray structure analysis of 5-(2-benzoimidazole-1-yl-ethoxy)-3-methyl-1-phenyl-*1H*-pyrazole-4-carboxylic acid methyl ester (**2**).0.5H$_2$O provided experimental proof for H···O=C, C—H···O—H and H—O···N interactions. The embedded water molecule bridges between molecules **2** via non-covalent interactions. Thus this molecule behaves as a preorganized host molecule for water, presenting a minimum ring-size molecular environment for water binding. Single crystal X-ray structure analysis of 5-(2-benzoimidazole-1-yl-ethoxy)-3-methyl-1-phenyl-*1H*-pyrazole-4-carboxylic acid methyl esterhemihydrate provided experimental proof for six hydrogen bonds by one molecule of water. The embedded water molecule bridges six molecules by two types of hydrogen bonding. Theoretical calculations showed that the conformation of the bicyclic hetero-ring alters only slightly due to the presence of the water molecule. Thus this organic molecule behaves as a very interesting preorganized host molecule for water, presenting maximum binding environment for water binding.

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1. Introduction

Weak non-covalent interactions play subtle role in construction of supramolecular architectures. Among them, C—H···O, C—H···π and π···π interactions are very important as they are widely active in organic crystals and biological macromolecules. Water is known to participate actively in molecular recognition processes both in chemical and especially in biological systems, by mediating the interactions between binding partners and contribute to either enthalpic or entropic stabilization. Also, it is known to play an important role in the recognition and hence stabilization of the interactions, specifically through C—H···O networks as observed in 5-(2-benzoimidazole-1-yl-ethoxy)-3-methyl-1-phenyl-*1H*-pyrazole-4-carboxylic acid methyl ester which is highly stabilized through C—H···O and O—H···N interactions due to the involvement of water. Crystal structures of molecular solids are determined by large number of weak directional forces responsible for generating self assembly of molecules. Role of water in the crystal structures is well documented [1]. Stronger water–water interactions are formed around non-polar organic molecules in order to compensate weak water–non-polar molecular interactions. The entropy of dissolution decreases when (**2**) comes in contact with

water. Interactions of water generally reduce non-polar surface area of organic molecule exposed to the solvent and reduce the amount of structured water providing favorable entropy of association. Interactions play key role in the construction of supramolecular architecture [2,3] through supramolecular synthons [4]. The aggregation of aromatic compounds can also be caused by alternative interactions between π systems which are used to manipulate the organization of molecular subunits in the solid state [5]. Among the weak interactions, C—H···O [6], C—H···π [7] and π···π interactions [8] are important in generating symmetry non-equivalence in the crystal lattice [9,10]. They are also known to control drug action [11], and polymorphism [12]. It has been established interactions that among these forces, C—H···O hydrogen bonds [13] exist as significant secondary interaction and occasionally dominant interaction [14] in molecular solids and therefore they are widely implicated as important structural determinants in organic crystals [13] and biological macromolecules [15]. For example, water molecules at protein–DNA interface contribute to the complex formation and potentially play important role in mediating specific interactions [16–18]. The chemistry of pyrazole derivatives has been the subject of research due to their importance in various applications and their wide spread of potential biological and pharmacological activities governed by specific interactions between host and receptors [19–33]. In the present study, self assembly of compound (**2**) mediated through water molecules is reported which reveals an C—H···O contact between

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(**2**) and water molecules in the solid state. The water molecule is also hydrogen bonded through O—H···π interactions to the π-electron cloud over 5-membered ring of benzimidazole.

2. Experimental procedure

2.1. Instrumentation

All reactions were carried out under simple conditions at room temperature. Commercially available reagents and solvents were used without further purification. ^1H and ^{13}C NMR spectra were recorded on a JEOL AL300 FTNMR spectrometer in $CDCl_3$. TMS is used as internal reference and chemical shift values are expressed in δ, ppm units. The X-ray diffraction data collected on Bruker SMART APEX CCD area detector diffractometer. The structure was solved and refined by using SHELXTL [34] program. Molecular graphics were designed by using ORTEP-3 version. 1.08. Crystal structure of compound (**2**)·H_2O is shown in ortep diagram with labelling in Fig. 1.

The crystal data are given in Table 1 and the selected geometrical parameters of inter and intramolecular hydrogen bonds are summarized in Table 2a and b. In solution growth technique, the formation of X-ray quality single crystals depends on the choice of the solvent. In order to select the proper solvent for growing large-size single crystals, the solubility of (**2**) was checked in various solvents. 3% Ethyl acetate in hexane mixture was found to be the best solvent for growing single crystals of (**2**) because of its good solubility as compared to other solvents. Well-defined single crystals of good transparency were obtained.

2.2. Materials

To the suspension of benzimidazole (0.17 g, 0.00147 mol) and anhydrous K_2CO_3 (0.20 g, 0.0015 mol) in DMF (10 ml) stirred at r.t. for 30 min was slowly added compound **1** (0.5 g, 0.0015 mol) with constant stirring (Scheme 1). The reaction mixture was stirred at room temperature for 24 h. Completion of the reaction was confirmed via TLC. DMF was removed under reduced pressure using rotavap and the product was treated with 1:1 $CHCl_3$–H_2O system (100 ml). The organic layer was collected and the aqueous layer was washed two times with 100 ml of $CHCl_3$. The organic layers were combined and washed with water (100 ml) and dried over anhydrous Na_2SO_4). Removal of $CHCl_3$ under reduced pressure gave
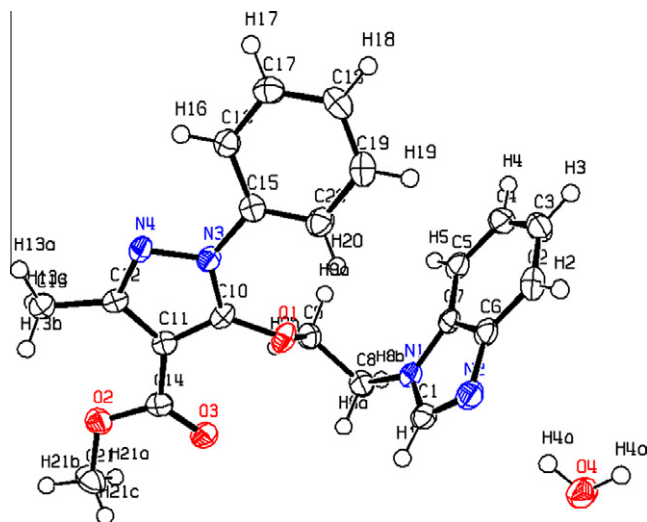

Fig. 1. Ortep diagram of compound (**2**)·H_2O with labelling.

Table 1
Crystallographic data of compound **2**.

Compound	**2**
Compound name	5-(2-Benzoimidazol-1-yl-ethoxy)-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic acid methyl ester; hydrate $C_{21}H_{20}N_4O_3$·0.5H_2O
Empirical formula	770.84
Formula weight (g mol^{-1})	100 (2)
Temperature (K)	0.71073
Wave length (Å)	Monoclinic, C 2/c
Crystal system, space group	a = 25.990 (3)
Unit cell dimensions (Å)	b = 10.8447 (12), β = 108.15 (3)
	c = 15.950 (2) 2468.83
Cell volume, V (Å^3)	1.351
Dcalc. (Mg m^{-3})	1624
F (000)	8
Z	0.50 × 0.25 × 0.23
Crystal size (mm)	1.86–25.03
Theta range for data collection (°)	$-30 \leqslant h \leqslant 27$, $-12 \leqslant k \leqslant 12$, $-17 \leqslant l \leqslant 18$
Limiting indices	3315/3186 [R (int) = 0.0295]
Reflections collected/ unique	Full-matrix least-squares on F^2
Refinement method	331–333
Melting point (K)	$R1$ = 0.0495, w$R2$ = 0.0965
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0528, w$R2$ = 0.0983
R indices (all data)	1.055
Goodness-of-fit on F^2	0.23/−0.20
$\Delta\rho$ max/$\Delta\rho$ min (e Å^{-3})	

Table 2
(a and b): Geometry of C—H···π and O—H···N interactions in compound **2**.

S. No.	Interaction	C/O—H···π/N/ C (Å)	C/O—H···π/N/ C (°)
(a) Intramolecular			
1	C(20)—H(20)···π (benzim-5-membered ring)	3.16	153
2	C(19)—H(19)···π (benzim-6-membered ring)	3.20	125

S. No.	Interaction		O/C—H/π···π/N/O (Å)
(b). Intermolecular			
1	π···π (2 benzim-5-membered rings)		3.86
2	C(1)—H(1)···N(4)		2.58 (153°)
3	C(5)—H(5)···O(4)		2.57 (152°)
4	C(17)—H(17)···O(3)		2.51 (168°)
5	C(18)—H(18)···π (pyrazole)		3.04 (100°)
6	O(4)—H(40)···N(2)		2.06 (167°)

solid residue which was crystallized from 3% ethyl acetate–hexane solution along with a drop of water to give pure compound **2**.

Yield: 0.12 g (22.15%); mp 58–60 °C. ^1H NMR (300 MHz, $CDCl_3$, δ ppm): 2.436 (s, 3H, CH_3), 3.775 (s, 3H, OCH_3), 4.48–4.53 (q, 4H, CH_2 X 2, J = 3.3, 5.1, 4.5 Hz), 7.19–7.83 (m, 9H, Ar-H), 7.83 (s, 1H, H); ^{13}C NMR ($CDCl_3$, δ ppm): 15.18, 44.56, 51.03, 72.67, 99.43, 109.20, 120.33, 122.71, 127.61, 128.88, 133.42, 136.68, 143.10, 143.66, 150.67, 154.09, 163.23.

3. Theoretical calculations

Theoretical molecular models of molecules were calculated by B3LYP/6-31+G(d,p) level DFT chemical calculations as implemented in Gaussian '03[35]. An initial model of the **2**·H_2O was taken from the XRD experiment or rebuilt [36] for the anhydrous (**2**).
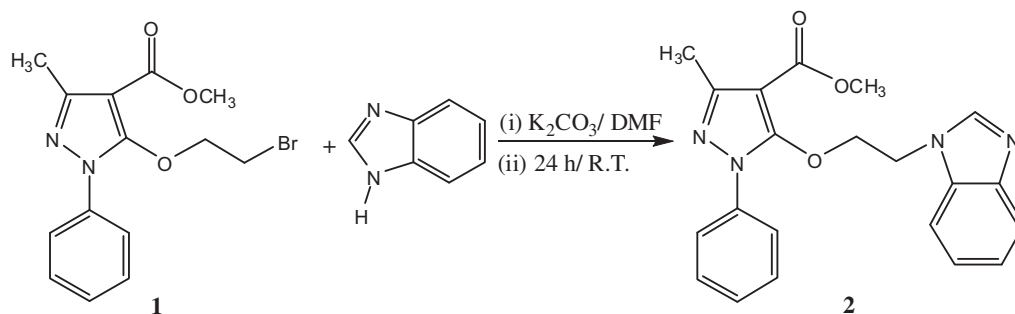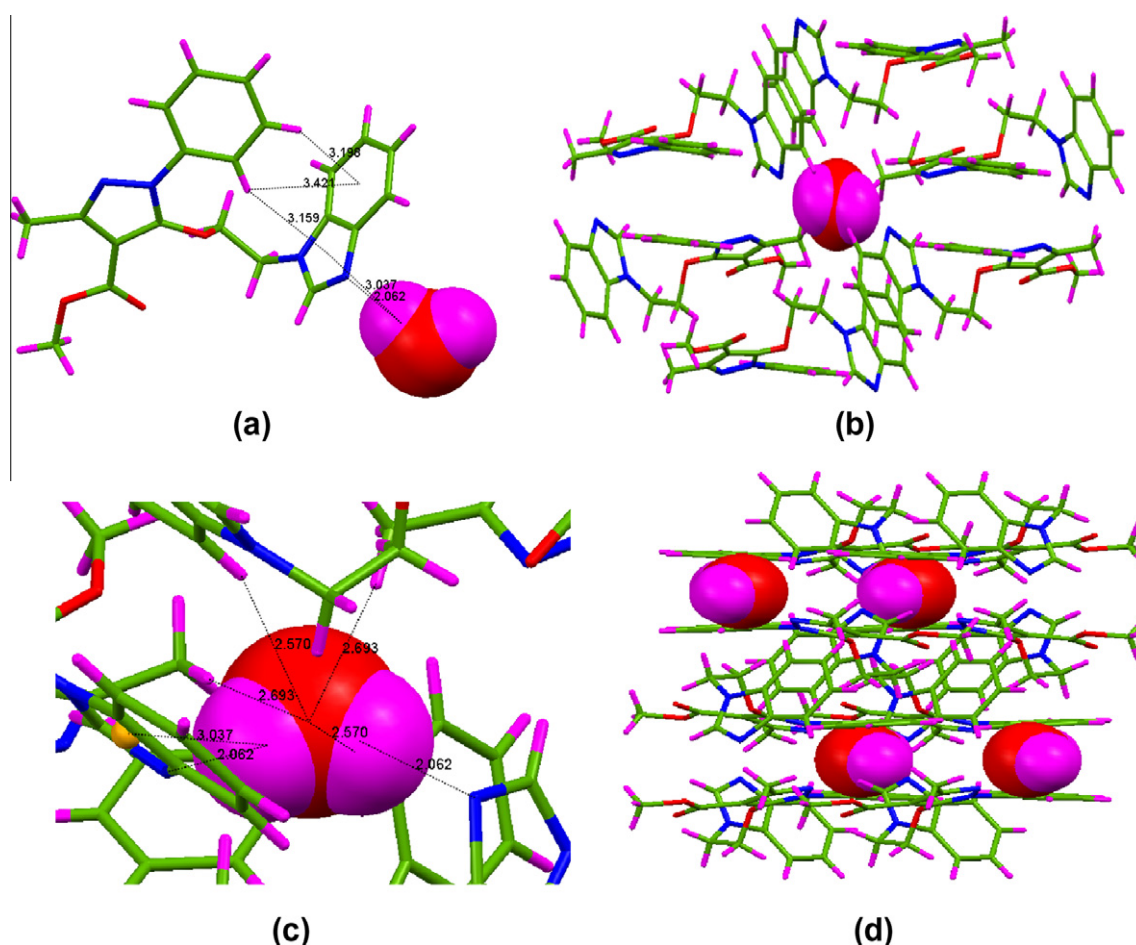
Scheme 1.

Fig. 2. (a) Single molecule with water; (b)–(d) pictorial representation of water mediated assembly of (**2**) through O—H···N, O—H···π and C—H···O interactions.

The force constants matrices of the fully optimized structures were always positive. The intra and intermolecular interactions were analyzed with the aid of Mercury [37] and GaussView.

4. Results and discussion

Compound **2** possesses intramolecular as well as intermolecular network of π···π, C—H···π, C—H···N, C—H···O and O—H···N interactions which actively participate in stabilizing the structure leading to self assembly of molecules (Fig. 2a).

Compound **2** is an unsymmetrical molecule in which the pyrazole and benzimidazole residues are joined through an ethylene linker. The molecule is not planar and all aromatic rings are in different plane that is highly influenced by interactions of these rings with embedded water.

The intramolecular stacked structure of compound **2** is stabilized preferably through edge to face C—H···π interactions. This generates a bent structure of molecule **2** with formation of a cavity within the molecule. The water molecule appears in the cavity which is developed by six molecules of compound **2**. The distance between 6-membered ring centroid of benzimidazole and H(19) of phenyl ring was found to be 3.20 Å (C—H···π). This indicates that the H(19) proton of the phenyl ring is affected by the π-electron orbitals located over the 6-membered ring of benzimidazole. Similar interaction is observed between the phenyl H(20) and 5-membered ring of benzaimidazole (C—H···π = 3.16 Å C—H···π angle = 153°).

Table 3
Comparison of selected bond lengths, torsion angles and H-bond dimensions calculated by theoretical methods (B3LYP/6-31+G(d,p) level) with the experimental structural model from X-ray diffraction with their e.s.d.'s where applicable (XRD, distances in Å, angles in u).

Geometry	**1** (anhydrous)	**1**:H$_2$O	XRD
C17 C18	1.398	1.398	1.384(4)
C18 C19	1.396	1.397	1.387(3)
C19 C20	1.397	1.397	1.385(3)
C9 O1 C10	118.2	118.2	116.7(2)
C14 O2 C21	115.8	115.9	115.0(2)
C1 N1 C7	106.0	106.2	106.5(2)
C1 N1 C8	126.6	126.3	125.9(2)
C7 N1 C8	127.4	127.4	127.3(2)
C1 N2 C6	104.6	105.1	104.2(2)
N4 N3 C10	111.1	111.1	110.5(2)
N4 N3 C15	119.4	119.3	118.8(2)
C10 N3 C15	129.5	129.6	130.6(2)
N3 N4 C12	106.3	106.4	105.5(2)
N1 C1 N2	114.2	113.8	114.2(2)
N1 C1 H1	120.6	121.1	122.9(2)
N2 C1 H1	125.3	125.2	122.9(2)
H4O O4 H4O	105.6	111(3)	
C7 N1 C1 N2	−0.5	−0.4	−0.3(3)
C7 N1 C1 H1	179.7	179.9	179.7(2)
C8 N1 C1 N2	−176.7	−177.2	−174.2(2)
C8 N1 C1 H1	3.4	3.1	5.8(4)
C1 N1 C7 C5	179.7	179.5	178.0(2)
C1 N1 C7 C6	0.5	0.4	−0.5(2)
C8 N1 C7 C5	−4.1	−3.7	−8.2(4)
C8 N1 C7 C6	176.7	177.2	173.3(2)
C1 N1 C8 H8A	−26.4	−25.2	−10.1(3)
C1 N1 C8 H8B	−143.7	−142.6	−127.9(2)
C1 N1 C8 C9	94.8	95.9	111.0(2)

The crystal structure of **2** shows the presence of water molecules in the crystal packing diagram, which play an important role in the crystal packing as they act as mediator and facilitate the network of weak interactions throughout the crystal packing involving C—H···O, and O—H···N donor–acceptor interactions. The distance between H4O (water) and *N2* of benzimidazole 5-membered ring (O—H···N) was 2.06 Å. Packing diagram reveals that one water molecule is engaged in stabilizing six molecules of **2** as shown in Fig. 2b–d. Incorporation of water generates channel like regular arrangement of molecules of **2** in which water molecule is trapped in crystal packing through short C—H···O contacts of 2.57 Å with an angle of 151.91°. This (**2**)–water aggregate enhances the H-bond acceptor strength of the water oxygen (O4) by the polarization of the O—H bonds of the water molecule. Inter-

estingly, a short N···O contact (2.92 Å) is also observed among the N2 of pyrazole and O4 of water molecule. The crystal packing structure also revealed the presence of important parallel displaced π···π (3.86 Å) interactions among the benzimidazole 5-membered rings of two different molecules of **2**, indicating that the two rings form stacked arrangement. The distance between centroid of benzimidazole 5-membered ring and N1 (benzimidazole 5 membered ring) and that of H5 of benzimidazole 5 membered ring (N···π and C—H···π) of adjacent molecule is 3.59 Å and 3.78 Å, respectively. In the second case, (C—H···π interaction), the bond angle is 80.84° which indicated that the H5 is nearly orthogonally placed over the benzimidazole ring; it means these two rings create perpendicular planes against each other. Intermolecular C—H···N interaction among N4 (pyrazole) to H1 (benzimidazole) of two adjacent molecules is 2.58 Å (153.24°).

To study the complex formation between **2** and water in solution state, ^{1}H NMR titration was performed by incremental addition of water in a solution of **2** in CDCl$_3$. No shift in any proton peak was observed indicating that **2** does not form complex with water in solution which may be due to increased contribution of hydrophobic effects.

The structural models of **2**·H$_2$O, as well as that of water-free **2** were evaluated by quantum chemical calculations. The results of B3LYP/6-31+G (d,p) level density functional calculations together with the model obtained from the XRD measurement are summarized in Table 3 and the so-optimized structures are shown in Fig. 3. The total binding energy for the water to **2** was calculated to be 76 kJ mol^{-1} using BSSE corrected B3LYP/6-31+G (d,p) wave functions. This value aligns with literature data [38] and naturally implies not only energy gains due to H-bridges, but also other, albeit minor, changes in shape and geometry. Only a difference of a few degrees was found between the torsion angle of the experimental and calculated structures of **2**·H$_2$O. There are two types of intramolecular interactions in the calculated model of the 5-(2-Benzoimidazole-1-yl-ethoxy)-3-methyl-1-phenyl-*1H*-pyrazole-4-carboxylic acid me-thyl ester molecule. The oxygen atom of the ester function interacts with the suitable H-atom of the methylene group. The lengths of this H-bond are 2.44 Å, 2.66 Å and 2.46 Å, 2.55 Å in both calculations respectively. Furthermore, a bicyclic aromatic ring approaches the water hydrogen at a distance of 1.92 Å. This contact is replaced in the crystal by an inter-associate contact of a bicyclic aromatic ring to water at a distance 2.06 Å. Similar calculated molecular models were found for both the anhydrous and the hydrate forms **2** and **2**·H$_2$O, respectively. Thus, water exerts a moderate effect on the geometry of the 5-(2-benzoimidazole-1-yl-ethoxy)-3-methyl-1-phenyl-*1H*-pyrazole-4-carboxylic acid methyl ester.
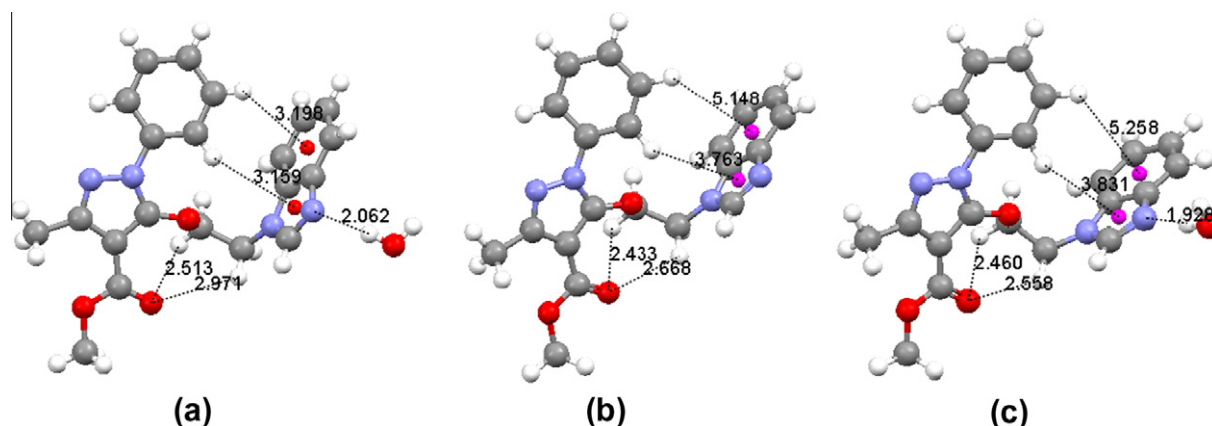
Fig. 3. Near-identical perspective views of 5-(2-benzoimidazole-1-yl-ethoxy)-3-methyl-1-phenyl-*1H*-pyrazole-4-carboxylic acid methyl ester·H$_2$O (a) XRD model; (b) of the calculated anhydrous **1**; (c) of calculated **1**·H$_2$O (all calculated models are at the B3LYP/6-31+G(d,p) level of theory).

Differences between the experimental $2 \cdot H_2O$ and the calculated model were also characterized by means of the root mean square standard deviation (r.m.s.d.) values of the superposed structures. Thus comparisons of the anhydrous form geometry of 2 against those of the calculated one for $2 \cdot H_2O$ and the one from the crystal structure of $2 \cdot 0.5H_2O$ show only a slight adjustment of the host molecule upon water binding (Fig. 3).

Theoretical MP2 calculation is also done to study the role of multipoles in the system because Coulombic interactions can be expressed as the sum of the attraction terms between charges and/or permanent multipoles. The orientation of the system is same as in the DFT calculation, it means, this is the most stable orientation of the system by theoretical calculations. Various coulombic interactions taking part in the molecular system by the presence of charge, dipole moment, quadrupole moment, octapole moment and hexadecapole moment in the system. In the case of the CH/π interaction, π-base is generally not dipolar. Even if the C—H group can be a strong dipole when the carbon atom is substituted with more than one electronegative group or the ring is attached with many groups, the interaction cannot be so strong as to be observable in polar solvents. Actually CH/π interactions are shown to persist even in polar solvent. Thus, the CH/π interaction is clearly different from Coulombic interaction. The aromatic π-system has a large quadrupole/or mutipole which can enhance the CH/π interactions [39]. In the calculation of compound $(2) \cdot H_2O$ by MP2 method there is dipole moment, quadrupole moment, octapole moment, hexadecapole moment, these multipoles enhances the CH/π interactions (values are given in the Supplementary information).

On the basis of these findings, host **2** may well be considered as a preorganized compound for water fixation. As expounded by Cram [40], Lehn [41], Reinhoudt and Dijkstra [42] and Schmidtchen et al. [43] in many details a preformed molecular scaffold has lots of advantages in host–guest chemistry from some aspects. Firstly energy costs of providing a nearly ideal molecular recognition cavity, pocket, cleft or frameworks are already paid off at the covalent synthesis step of the target host. Thus, creating a supramolecular assembly will not be prohibitive in energy terms as, e.g. entropy loss of guest binding may be rewarded by enthalpy gain from well-placed hydrogen bonding attachment sites. As pointed out earlier, [41] binding of neutral species such as water may require more assistance, as neutral guests have much smaller free energies of complexation. Molecule **2** with its deformed conformation, with the linked O—H···N bridge and the juxtaposed PLO functions at proper distances all qualify for a preorganized minimum-size ring system. It must be noted that the hydrophobic outer skin of **2** and the hydrophilic internal region should also promote water binding by the PLO functions. Thus, an ideal micro-environment is provided by the molecule **2**.

5. Conclusions

The crystal structure of $2 \cdot 0.5H_2O$ corroborates the existence of the proposed O—H···N interaction. The solid state structure indicates marked activity of the aromatic-CH group in both intra- and intermolecular C—H···π hydrogen bridge with aromatic rings. Due to its high electron density, the five-membered ring of benzoimidazole fragment may tightly bind to water molecule. Such a binding is certainly facilitated by the well-known interactions behind classic intra-associate O—H···N, O—H···π and H-bridges as well as those behind both inter- and intra-associate O—H···N contacts. Comparisons of the experimental $2 \cdot 0.5H_2O$ structure and the theoretical models for **2** and $2 \cdot H_2O$ also present **2** as a kind of suitable ring of molecule for water binding. Apparently, the hygroscopic compound **2** may provide a model for water sensing

purposes. These studies help us to design the molecule having aromatic moiety with hydrophilic in nature.

Appendix A. Supplementary material

Crystallographic data for the structure **2** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication No. CCDC – 654472. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.molstruc.2011.09.004.

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