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ORIGINAL PAPER

Preparation, Mechanism, and Supramolecular Structure Study of a Novel Benzimidazole-Hydrate

Yong Hong · Jing-Yi Xiao · Ke-Long Huang · Jin-Gang Yu · Du-Shu Huang

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Abstract A novel bis[2-(2-chloro-4-fluorophenyl)-1H-Benzimidazole]-hydrate was prepared from Schiff base, and its single crystalline was obtained. The single crystalline was characterized by X-ray crystallography, and the results shows that the title complex belongs to the triclinic system, space group (P1) with lattice parameters $a = 7.592$ (2) Å, $b = 7.595(2)$ Å, $c = 11.886$ (3) Å, $V = 574(3)$ Å^3, $Mr = 352.33$, $Dc = 1.478$ g/cm^3, $\mu(MoK\alpha) = 0.33$ mm^{-1}, $F(000) = 262$, $Z = 1$, the final $R = 0.090$ and $wR = 0.209$ for 2,315 observed reflections ($I > 2\sigma(I)$). The crystal structure is formed by two benzimidazole molecules which are linked by a water molecule. A UV–Vis spectrophotometer and a fluorophotometer were used to detect the benzimizadole-hydrate crystal transformation process, which shows that benzimidazole-hydrate can only be formed from Schiff base effectively when ortho-hydroxyl group does not exist in benzaldehyde. The synthesis mechanism was also discussed. Compared with its Schiff base, benzimidazole-hydrate displays stronger fluorescence.

Keywords Benzimidazole · Schiff base · Crystal structure · UV–Vis spectrophotometer · Fluorophotometer

Y. Hong · J.-Y. Xiao · K.-L. Huang (✉) · J.-G. Yu · D.-S. Huang
College of Chemistry and Chemical Engineering, Central South University, 410083, Changsha, Hunan, China
e-mail: klhuang@mail.csu.edu.cn

J.-G. Yu
e-mail: yujg_zhoufl@yahoo.com

Introduction

Benzimidazole and its derivatives are important bioactive molecules in pharmaceutical fields [1]. Not only can they be used for producing medicines such as Omeprazole and Pimobendan, but also have they exhibited significant activities against some viruses including RSV [2], herpes (HCV) [3], HIV [4] and human cytomegalovirus (HCMV) [5]. Preparation of 2-substituted benzimidazoles from phenylene diamines and carboxylic acids or carboxylic acid derivatives was usually carried out under rigorous dehydrating conditions [4], and addition of Lewis acids [5], inorganic clays [6], mineral acids [7], or PyBOP [8] could improve their yields and purity. However, toxic or environment-hazardous byproducts will be produced under most of these procedures. Moreover, these procedures are time-consuming, labour-consuming and/or low output. A two-step procedure that includes oxidative cyclodehydrogenation of aniline Schiff bases has also been reported [9, 10], which is an in situ condensation reaction of phenylenediamines and aldehydes. However, special oxidants are urgently needed.

In this work, we demonstrated that benzimidazole derivatives could be prepared from Schiff base compounds directly. The mechanism of the reaction was also discussed.

Experimental

Synthesis of Bis[2-(2-Chloro-4-Fluorophenyl)-1H-Benzimidazole]-Hydrate

A mixture of *o*-phenylenediamine (108 mg, 1 mmol), 2-chloro-4-fluorobenzaldehyde (317 mg, 2 mmol) and ethanol (5 mL) was stirred in an ice bath for 1 h to prepare Schiff base (3.8 g, yield 85%). The Schiff base (3.45 g,

Table 1 Crystal data and structure refinement

Compound	II
Empirical formula	$C_{26}H_{18}Cl_2F_2N_4O$
Formula weight	511.34
Crystal size (mm)	0.19 × 0.07 × 0.05
Crystal system	Triclinic
Space group	*P*1
a (Å)	7.569(2)
b (Å)	7.595(2)
c (Å)	11.886
α (°)	82.559
β (°)	73.479
γ (°)	61.286
V (Å)	574.5(3)
Z	1
Dc (g cm^{-3})	1.478
μ (mm^{-1})	0.33
F(000)	262
Index ranges	$-9 \leqq h \leqq 9$
	$-9 \leqq k \leqq 9$
	$-9 \leqq l \leqq 14$
Reflns measured	2,315
R int	0.025
S on F_2	1.08
R_1, WR_2 ($I > 2$)	0.070, 0.167
R_1, WR_2 (all data)	0.090, 0.209

yield 90%) was purified using ethyl acetate. The benzimizadole-hydrate single crystalline suitable for X-ray measurements were obtained using a mixed solution of ethyl acetate and water.

Crystallography Measurements

A benzimizadole-hydrate single crystal sample with dimensions of 0.19 mm × 0.07 mm × 0.05 mm was used for X-ray measurements, and data collection was carried out on a CCD area detector diffractometer (Mo K_α, $\lambda = 0.07107$ nm) at 273 K. The data were corrected for absorption empirically by the psi-scan method. The structure was solved by direct and difference Fourier methods and refined by full-matrix least-squares on F^2. All non-H atoms were refined with anisotropic displacement parameters. All H atoms were generated automatically except for the H atoms of water which generated manually, that is, generated theoretically. The crystallographic computing was performed using SHELXL97 [11]. The crystal parameters, data collection and refinement results for the compound are listed in Table 1. Selected bond lengths and angles are listed in Table 2.

Table 2 Hydrogen-bond geometry (Å, °)

D–H···A	D–H	H···A	D···A	D–H···A
O1W–H1WA···N1	0.85	1.96	2.791(8)	165
O1W–H1WB···N4	0.85	2.20	2.811(8)	129
N2–H2B···O1W(i)	0.86	2.03	2.876(8)	168
N3–H3A···O1W(ii)	0.86	2.09	2.904(8)	158

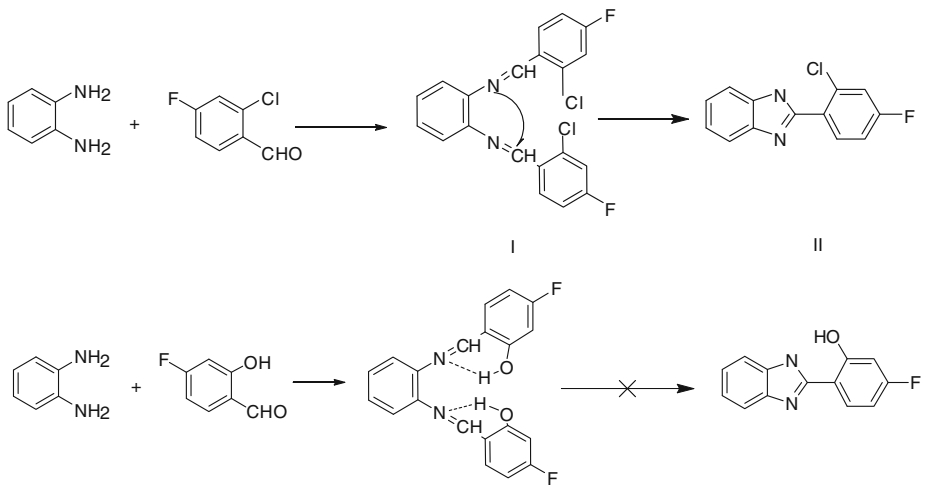
Symmetry codes: (*i*) $x - 1, y, z$; (*ii*) $x, y + 1, z$

Results and Discussion

Structure Properties

The structure of compound II (Scheme 1) is shown in Fig. 1. The water molecules participate in the hydrogen bonds with the azido nitrogen molecules are shown in Table 2, the bond lengths and bond angles are shown in Table 3. In all essential details, the geometrical parameters of the molecules in terms of bond lengths and angles show general values. The bond lengths of C–C and C–N are similar to those in 2-(2-ethoxyphenyl)-1-ethyl-1H-

Scheme 1 Mechanism of synthesis benzimidazole



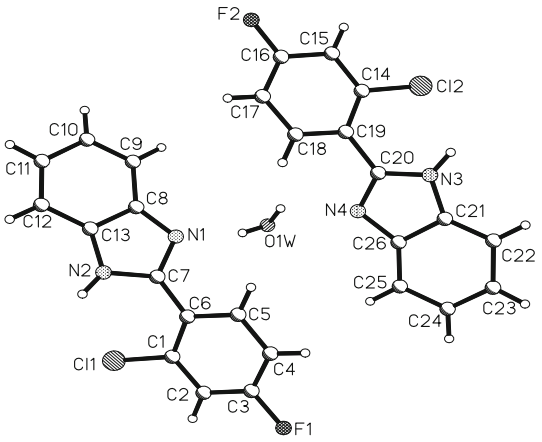


Fig. 1 Perspective drawing of the title complex bis[2-(2-chloro-4-fluorophenyl)-1H-Benzimidazole]-hydrate with the atomic numbering. Displacement ellipsoids are shown at the 30% probability level

benzimidazole [12] and 2-(2,4-dichlorophenyl)-1H-benzimidazole [13]. For compound II, the benzimidazole ring is a plane with a torsional angle of C7–N1–C8–C9 being 179.96° and a dihedral angle being 40.697° between the benzimidazole ring and benzene ring.

It is very interesting that the crystal structure is formed by two benzimidazole molecules, which were linked by a H_2O molecule as center. The structure is similar to the complex of benzimidazole and can increase the stability of the molecule. The angle of N_1–O_1–N_4 is 117.89°. The angle of the plane between phenyls of the benzimidazole derivative molecules is 43.588°.

As shown in Fig. 2 and Table 2, two molecules of compound II are linked by O1W–H1W·N(1,2,3,4) intermolecular hydrogen bonds along *a* axis and *b* axis (symmetry code as in Table 2) and a two dimensional plane is formed. The packing of compound I (Fig. 2) viewed along c axis shows that one layer of molecules is connected by O_1W–H_1W·N hydrogen bonds (dashed lines). Both hydrogen bonds and π–π stacking interactions between the adjacent molecules devote to the three-dimensional network. Therefore, both of them play a critical role to the stability of the crystal lattice.

Spectral Analysis

Absorption and fluorescence spectra were measured using a UV–Vis spectrophotometer (Unico 7200) and a fluorophotometer (Hitachi F-2500), respectively.

Chen et al. [14] have developed a fluorescence spectroscopic system for detecting the conversion procedure of phenolic Schiff base to benzoxazoles. Herein, the relationship between the molecules and spectral changes was discussed, and the reaction process was monitored using UV–Vis and fluorescence spectroscopy.

Table 3 Selected bond lengths (Å) and angles (°)

F1–C3	1.369(11)	C12–C13	1.420(12)
F2–C16	1.325(11)	C13–N2	1.350(11)
Cl1–C1	1.741(8)	C14–C15	1.367(13)
Cl2–C14	1.758(8)	C14–C19	1.392(11)
C1–C2	1.360(12)	C15–C16	1.410(14)
C1–C6	1.391(11)	C16–C17	1.358(15)
C2–C3	1.344(14)	C17–C18	1.397(14)
C3–C4	1.328(16)	C18–C19	1.379(11)
C4–C5	1.403(14)	C19–C20	1.485(12)
C5–C6	1.399(10)	C20–N4	1.292(10)
C6–C7	1.426(12)	C20–N3	1.341(10)
C7–N1	1.344(10)	C21–N3	1.357(10)
C7–N2	1.416(10)	C21–C22	1.383(11)
C8–N1	1.362(10)	C21–C26	1.423(11)
C8–C13	1.403(10)	C22–C23	1.411(14)
C8–C9	1.417(11)	C23–C24	1.362(15)
C9–C10	1.361(14)	C24–C25	1.401(15)
C10–C11	1.399(13)	C25–C26	1.348(12)
C11–C12	1.335(14)	C26–N4	1.409(11)
C2–C1–C6	121.1(8)	C19–C14–Cl2	120.6(6)
C2–C1–Cl1	118.4(7)	C14–C15–C16	116.9(9)
C6–C1–Cl1	120.5(6)	F2–C16–C17	120.9(9)
C3–C2–C1	119.9(9)	F2–C16–C15	117.4(10)
C4–C3–C2	122.6(9)	C17–C16–C15	121.8(9)
C4–C3–F1	118.3(9)	C16–C17–C18	119.1(8)
C2–C3–F1	119.1(10)	C19–C18–C17	121.4(9)
C3–C4–C5	119.2(9)	C18–C19–C14	117.2(8)
C6–C5–C4	120.0(9)	C18–C19–C20	118.1(8)
C1–C6–C5	117.3(8)	C14–C19–C20	124.8(7)
C1–C6–C7	124.4(7)	N4–C20–N3	113.4(7)
C5–C6–C7	118.2(8)	N4–C20–C19	121.1(6)
N1–C7–N2	109.0(7)	N3–C20–C19	125.4(7)
N1–C7–C6	125.2(6)	N3–C21–C22	132.5(8)
N2–C7–C6	125.5(6)	N3–C21–C26	105.9(7)
N1–C8–C13	110.0(6)	C22–C21–C26	121.7(8)
N1–C8–C9	132.2(7)	C21–C22–C23	116.3(9)
C13–C8–C9	117.8(7)	C24–C23–C22	121.6(10)
C10–C9–C8	119.6(8)	C23–C24–C25	121.5(10)
C9–C10–C11	120.3(9)	C26–C25–C24	118.4(9)
C12–C11–C10	123.4(9)	C25–C26–N4	132.6(8)
C11–C12–C13	116.7(8)	C25–C26–C21	120.4(8)
N2–C13–C8	106.3(6)	N4–C26–C21	106.8(7)
N2–C13–C12	131.4(7)	C7–N1–C8	106.9(6)
C8–C13–C12	122.2(7)	C13–N2–C7	107.7(6)
C15–C14–C19	123.6(7)	C20–N3–C21	107.9(6)
C15–C14–Cl2	115.7(6)	C20–N4–C26	106.1(6)

The formation of benzimizole can be confirmed by comparing the spectrum of compound I and compound II (Fig. 3). The first peak can be assigned to the $\pi \rightarrow \pi^*$

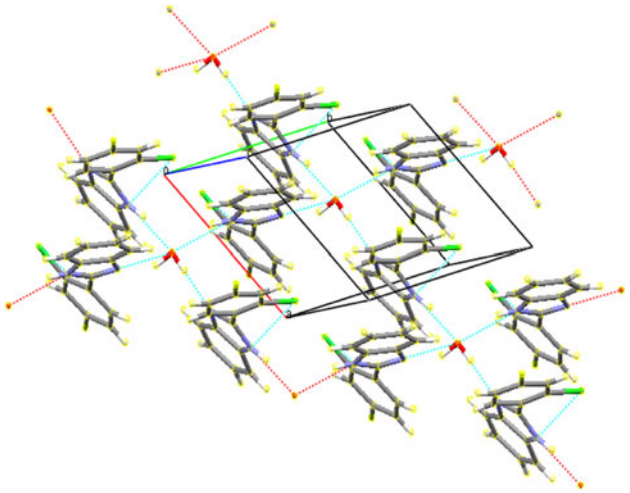


Fig. 2 The packing of (I), viewed down the *a* axis, shows one layer of molecules connected by O1W–H1W···N hydrogen bonds (*dashed lines*). H atoms which don't devote to form hydrogen bonds have been omitted

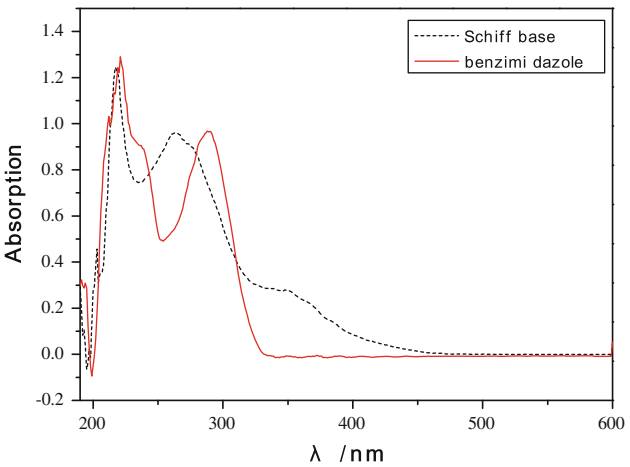


Fig. 3 Absorption changes of Schiff base and benzimidazole

transition due to the imine nitrogen atoms in conjugation with phenyl group. The compound II showes a decreased absorption peak at 272 nm ($\varepsilon = 0.85 \times 104$), and a new increased absorption peak at 299 nm ($\varepsilon = 0.92 \times 104$) can be attributed to the benzimidazole.

The fluorescence properties of the Schiff base and benzimidazole were investigated at room temperature in solid state (Fig. 4). No fluorescence emission can be detected from the Schiff base. However, benzimidazole-hydrate showes a high fluorescence peak. Due to presence of the lone pair electrons of the donor atoms in the Schiff base, whose fluorescence is probably quenched by the occurrence of a photoinduced electron transfer (PET) process. Because two benzimidazoles are linked by a O_1W–H_1W·N(1,2,3,4) intermolecular hydrogen bonds and a perfect plane is formed, the so obtained benzimidazole-hydrate shows excellent fluorescence properties.

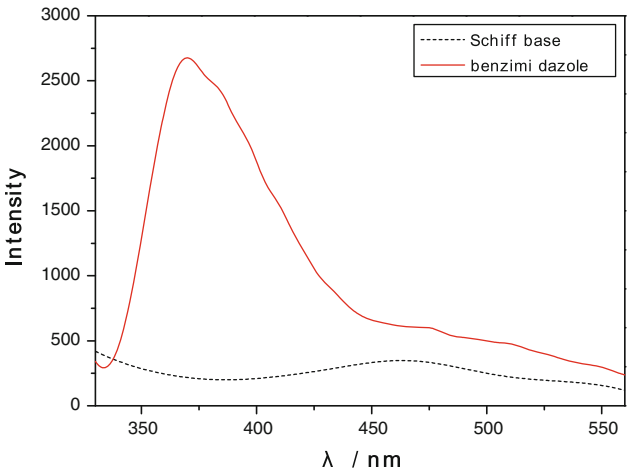


Fig. 4 Fluorescence intensity changes of Schiff base and benzimidazole

Mechanism of the Reaction

The reaction can usually be carried out effectively in various solvents such as DMF and alcohol. The reaction rate can be greatly enhanced in the presence of mineral acids. We have also found a not complex procedure for the formation of benzimidazoles by reaction of phenylenediamines with benzaldehyde. It can greatly reduce reaction time and enhance yields. Over 85% yields were obtained in our experiments.

However, if there were a hydroxyl group in the ortho-position of the benzaldehyde, the reaction will be difficult to occur. When 2-hydroxy-4-fluorobenzaldehyde was used to synthesis benzimidazole, it was found that the reaction could hardly be carried out under the same condition, which showed that the conversion of benzimidazole from Schiff base could only be carried out effectively when

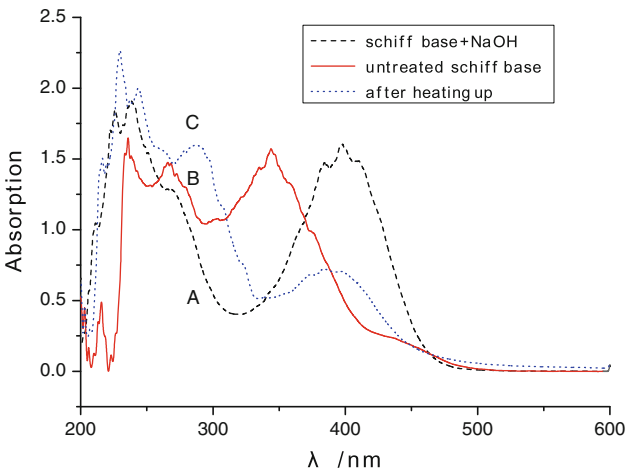
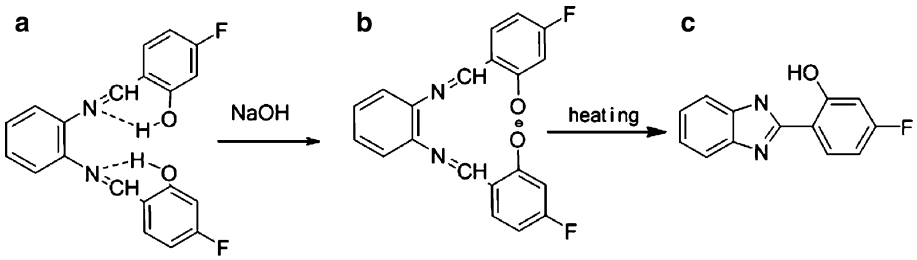


Fig. 5 Absorption changes of compound a (*A* untreated; *B* with NaOH addition; *C* with NaOH addition and heating up)

Scheme 2 Synthesis of benzimidazole from compound (a)



o-hydroxyl does not exist in the benzimizadole. However, the reaction can be carried out by heating in presence of NaOH, which may be useful for synthesizing benzimidazole derivatives.

A plausible pathway for preparation of benzimidazole by an intra-molecular participation of imine of the intermediate Schiff base to form the cyclic adduct was proposed. The existence of *o*-hydroxyl leads to the formation of hydrogen-bonds between the nitrogen atom and oxygen atom, and the cyclization was blocked (Scheme 1).

The reaction was carried out under different conditions to prove the possibility and reliability of the synthesis procedure. The absorption changes of compound (a) in ethanol with addition of NaOH are presented in Fig. 5. A decreased adsorption at 342 nm and two new concomitant increased absorptions at 400 nm corresponding to compound (b) are from –OH deprotonation, which are similar to the reported results [14]. However, no change can be found at 254 nm. Due to the weaker electronegative properties, the intra-molecular carbon–nitrogen bond of benzimidazole is harder to form than the carbon–oxygen bond of benzoxazolebut the reaction mechanism is very similar. By heating up, the absorption band at 400 nm decreases along with the increase of new absorption band at about 290 nm, as shown in Fig. 5. The reaction may undergo the pathway as shown in Scheme 2.

Conclusions

A 2-(2-chloro-4-fluorophenyl)-1H-Benzimidazole was synthesized by a convenient method from Schiff base. Its geometric structure and spectroscopic properties were investigated by X-ray crystallography, UV–Vis spectrophotometer and fluorophotometer. The reaction mechanism was also proposed.

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