

Synthesis, experimental and theoretical studies of two cocrystals in 1:1 stoichiometric ratio from 4,4'-bithiazole-2,2'-diamine with two hydrogen acceptor molecules

ZOHREH RASHIDI RANJBAR^{a,*} and ALI MORSALI^b

^aDepartment of Chemistry, Faculty of Sciences, Shahid Bahonar University of Kerman, P.O. Box 76169-133, Kerman, Iran

^bDepartment of Chemistry, Faculty of Sciences, Tarbiat Modares University, P.O. Box 14115-175, Tehran, Islamic Republic of Iran

e-mail: zoh.rashidi@uk.ac.ir; morsali_a@yahoo.com

MS received 30 May 2015; revised 1 September 2015; accepted 2 September 2015

Abstract. This paper reports synthesis, characterization and theoretical studies of two 1:1 stoichiometric ratio cocrystals of 4,4'-bithiazole-2,2'-diamine (DABTZ) with 2,5-bis(4-pyridyl)-1,3,4-oxadiazole (bpo) and 1,3-bis(4-pyridyl)ethane (bpa). These cocrystal compounds have been prepared by slow evaporation method and characterized by elemental and thermal analysis, FTIR, ¹H and ¹³C-NMR spectroscopies and X-ray crystallography. X-ray crystal analyses show that these structures [(DABTZ) (bpo)] and [(DABTZ) (bpa)] have crystallized in monoclinic forms with space groups of P2₁/n and C_{2/c}, respectively. These structures were studied theoretically and the results are in good agreement with the experimental data.

Keywords. Co-crystal; 4,4'-bithiazole-2,2'-diamine; X-ray crystallography; thermal analysis; theoretical studies; DFT.

1. Introduction

Cocrystal or multicomponent molecular compounds are solids at ambient temperatures and contain two or more distinct molecules with definite stoichiometric ratio.^{1,2} These molecular components interact with each other through non-covalent interactions, such as hydrogen bonding, π -interaction and van der Waals forces.^{3,4} In these systems, the donor and acceptor groups are different and complementary but the final structure may be predictable by saturated hydrogen bonding and π -interactions.^{5–8} Sometimes, these interactions are weaker in nature. For example, weak hydrogen interactions in which the donor group has very poor carbon acid, such as C–H groups or unconventional acceptor groups, such as a delocalized electron system.^{9,10} However, these crystalline structures with weaker or stronger bonds have recently found many applications in organic and inorganic chemistry, pharmaceutical (API) and electronic industry.^{11–20} Also, several theoretical studies have been performed on these structural molecules.^{21–26}

In this paper research, we report the synthesis and characterization of two novel cocrystals, [(DABTZ)

(bpo)] (1) and [(DABTZ) (bpa)] (2) by elemental and thermal analysis, spectroscopic data (FTIR, ¹H and ¹³C NMR) and single X-ray crystallography. Also, density functional theory (DFT) calculations for both cocrystals were performed at RB3LYP level of theory.

2. Experimental

2.1 Materials and Methods

Infrared spectra were measured on a Perkin-Elmer 597 and Nicolet 510P spectrophotometers in the range 400–4000 cm⁻¹ in KBr discs. The microanalyses were carried out using a Heraeus CHN-O-Rapid analyzer. The melting points were measured on an electrothermal 9100 apparatus. ¹H and ¹³C NMR spectra were measured with a BRUKER DRX-500 AVANCE spectrometer at 500 and 125 MHz, respectively. Thermal behavior was measured with PL-STA 1500 apparatus and TGA (Thermal Gravimetric Analysis)/DTA (Differential Thermal Analysis) diagrams were prepared.

Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallography Data Centre (CCDC) as deposition numbers CCDC-1050179 for [(DABTZ)(bpo)](1) and 1050178 for [(DABTZ)(bpa)](2). The data can be obtained, free

*For correspondence

of charge, from the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK via fax (+44-1223 336033) or e-mail (deposit@ccdc.cam.ac.uk).

2.2 Method of calculation

In this study, both structures are optimized by DFT using the X-ray structure data as input with RB3LYP exchange correlation functional and 6-31G(d) basis sets. The optimized structures of the investigated compounds are shown in figure 3. To validate the optimization of the structures, frequency calculations were performed and the results showed no negative frequency.

2.3 Synthesis of the co-crystals

2.3a Preparation of [(DABTZ)(bpo)](1): This compound was prepared by adding 10 mL solution of 2,5-bis(4-pyridyl)-1,3,4-oxadiazole (bpo) (0.244 g, 1 mmol) in MeOH to 10 mL methanolic solution of [4,4'-bithiazole]-2,2'-diamine (0.198 g, 1 mmol) and stirred for 1 h at room temperature. The prepared solution was allowed to evaporate slowly for 10 days at room temperature (*ca.* 25°C). Yellowish crystals of the desired product precipitated, washed by acetone and dried in air (M.p. 60°C). IR (KBr, cm⁻¹): 545w, 686w, 816w, 1040m, 1247w, 1327w, 1400w, 1523s, 1585m, 1628m, 3095s and 3255m. ¹H-NMR ([D₆]-DMSO): 6.6 (s, 2H); 7.7 (d, 4H); 7.2 (d, 4H); 8.5 (s, 4H) ppm. ¹³C{¹H} NMR ([D₆]-DMSO): 170.7; 150.2, 142.7; 137.9, 124.7, 120.9, 102.6 ppm. Yield: 0.3 g, 78%. C₁₈H₁₄N₈OS₂: calc. (%) C 51.2, H 3.32, N 26.50; found (%): C 50.8, H 3.10, N 26.4.

2.3b Preparation of [(DABTZ)(bpa)](2): This compound was prepared by dissolving 2,2'-diamino-4,4'-bis(1,3-thiazole) (0.198 g, 1 mmol) in MeOH (10 mL) and adding to a MeOH solution of 1,3-bis(4-pyridyl)ethane (0.184 g, 1 mmol). The resulting solution was stirred for 1 h at room temperature and allowed

to stand for 5 days at room temperature (*ca.* 25°C). Yellowish precipitated crystals were filtered off and dried in air (M.p. 75°C). IR (KBr, cm⁻¹): 490w, 553w, 707m, 1246m, 1330m, 1338m, 1405m, 1523s, 1584w, 1606m, 3088s, 3268w. ¹H-NMR ([D₆]-DMSO): 1.8 (t, 4H); 6.6 (s, 2H); 6.8 (d, 4H); 7.3 (d, 4H) and 7.9 (s, 4H) ppm. ¹³C{¹H} NMR ([D₆]-DMSO): 23.0, 102.0, 121.7, 147.8, 151.1, 169.5 ppm. Yield: 0.3 g, 82%. C₉H₉N₃S₄: calc (%) C 28.27, H 2.35, N 10.99; found (%): C 28.15, H 2.30, N 11.20.

3. Results and Discussion

The infrared spectra of these two compounds (KBr pellets) show some harmonic vibrational frequencies in the range of 400-4000 cm⁻¹. The vibrational analysis enables the characterization of a given molecular structure.

The asymmetric and symmetric stretching vibrations of the -NH₂ groups are observed as strong bands centered at 3500 and 3660 cm⁻¹ for [(DABTZ)(bpo)] (1) and at 3650 and 3340 cm⁻¹ for [(DABTZ)(bpa)] (2). Also, the rotational mode bands of NH₂ groups appear at 1670 cm⁻¹ and 1680 cm⁻¹, respectively. The relatively medium absorption bands at 3183 cm⁻¹ and 3200 cm⁻¹ are due to the C-H modes in or out of the aromatic plane. The IR spectra of both compounds show absorption bands from the skeletal vibrations of aromatic rings in the 1400-1600 cm⁻¹ range. The experimental ¹H and ¹³C NMR chemical shifts (δ) of the two compounds 1 and 2 are given in table 1. By analyzing the proton signals of pyridyl and thiazole in compound 1, four series of signals with different intensities were observed at room temperature. In cocrystal 1, seven distinct ¹³C-NMR peaks are observed (table 1). The ¹H-NMR spectrum of compound 2 in DMSO-d₆ shows two characteristic signals at δ = 7.1 and 7.0 ppm for NH₂ group and the proton in the thiazole ring. For the other protons of H₂C-CH₂ group and some protons of pyridyl rings, three series of signals with different intensities were observed. Also, seven distinct peaks in ¹³C-NMR

Table 1. ¹H NMR and ¹³C NMR spectroscopy data for [(DABTZ)(bpo)] (1) and [(DABTZ)(bpa)] (2).

Cocrystal	¹ H NMR chemical shift δ(Hz)	Assignment	¹³ C NMR chemical shift δ(Hz)	Assignment
(1)	6.62	-C-H _{thiazole}	102.6, 146.8, 168.61	C _{thiazole}
	7.10	-NH ₂	120.86, 124.7, 13786	C _{ph}
	5.90 and 6.10	-CH _{py}	150.19	C _{Ar}
(2)	6.6	-C-H _{thiazole}	104.6, 139, 169	C _{thiazole}
	7.28, 8.60	-C-H _{py}	149, 123, 147	C _{py}
	7.0	-NH ₂		
	2.8	-CH _{2ethan}	37.5	C _{ethan}

spectrum of the other cocrystal **2** have been observed. All data are shown in table 1.

Crystallographic measurements were made at 273(2) K for [(DABTZ)(bpo)] (**1**) and [(DABTZ)(bpa)] (**2**) using a Bruker APEX area-detector diffractometer using graphite monochromated Mo-K α radiation. The structure was solved by direct methods and refined by full-matrix least-squares techniques on F². Structure solution and refinement were accomplished using SHELXL97. Cocrystal [(DABTZ)(bpo)] (**1**) is yellowish cubic crystals in P2₁/n space group (table 2). Each unit cell consists of one molecule of DABTZ and bpo as shown in an ORTEP (Oak Ridge Thermal Ellipsoid plot) diagram (figure 1a). This cocrystal lies in the inversion center with the symmetry transformation code -x, y, -z+1/2. The key structural feature of **1** is involvement of simultaneous hydrogen bonding (N-H...N) between amine groups (NH₂) of DABTZ molecule and two different nitrogen atoms of the neighboring molecule moieties, pyridine (N5) and oxidazole

(N7) groups from two distinct bpo molecules (table 3). These hydrogen bonds form two dimensional (2D) assembly as shown in figure 1b. The π - π stacking is the other weak interaction to stabilize cocrystal **1** structure. This interaction has been observed between the pyridine ring of bpo and the imidazole ring of DABTZ. The plane-to-plane distance between rings is 3.61 Å and two component assemblies stack in a parallel manner (figure 1c). Thereby, these interactions connect two dimensional assemblies and a three dimensional (3D) supramolecular structure was formed.

Cocrystal **2**, [(DABTZ)(bpa)] was crystallized in C_{2/c} space group (table 2). The unit cell contains two molecules of DABTZ and bpa (figure 2a). This assembly was formed through N-H...N hydrogen bonds, parallel and offset π - π stacking interactions (figure 2b). In addition, surprisingly per hydrogens of amine group (NH₂) in DABTZ molecule interact with two distinct nitrogen atoms (N3) from pyridine ring of bpa molecule and (N1) from thiazole ring of the other DABTZ

Table 2. Crystal data and structure refinement for compounds [(DABTZ)(bpo)](**1**) and [(DABTZ)(bpa)](**2**).

	[(DABTZ)(bpo)] (1)	[(DABTZ)(bpa)] (2)
Identification code	[(DABTZ)(bpo)] (1)	[(DABTZ)(bpa)] (2)
Empirical formula	C ₁₈ H ₁₄ N ₈ OS ₂	C ₉ H ₉ N ₃ S ₄
Formula weight	422.49	191.25
Temperature	273(2)K	273(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	monoclinic	monoclinic
Space group	P2 ₁ /n	C _{2/c}
Unit cell dimensions	a = 11.367(5) Å b = 12.163(6) Å c = 14.206(6) Å α = 90.00° β = 101.561(9)° γ = 90.00°	a = 7.3236(9) Å b = 18.193(2) Å c = 14.5443(18) Å α = 90.00° β = 101.096(2)° γ = 90.00°
Volume	1924.1(15) Å ³	1901.7(4) Å ³
Z	4	8
Density (calculated)	1.458 g cm ⁻³	1.336 g cm ⁻³
Absorption coefficient	0.305 mm ⁻¹	0.294 mm ⁻¹
F(000)	872	800
Crystal size	0.46 x 0.28 x 0.22 mm ³	0.28 x 0.17 x 0.15 mm ³
Theta range for data collection	2.1 to 25.30	2.24 to 25.30°
Index ranges	-10 ≤ h ≤ 13 -13 ≤ k ≤ 14 -17 ≤ l ≤ 16	-8 ≤ h ≤ 8 -21 ≤ k ≤ 20 -17 ≤ l ≤ 10
Reflections collected	3484	5064
Independent reflections	3064	1464
Absorption correction	Multi-scan	Multi-scan
Max. and min. transmission	0.8723 and 0.59	0.9572 and 0.9221
Refinement method	Fullmatrix leastsquares on F ²	Fullmatrix leastsquares on F ²
Data / restraints / parameters	3484 / 4 / 278	1730 / 2 / 124
Goodness of fit on F ²	1.196	1.167
Final R indices [I > 2σ(I)]	R1 = 0.0636 wR2 = 0.1404	R1 = 0.0728 wR2 = 0.1526
R indices (all data)	R1 = 0.0730 wR2 = 0.1463	R1 = 0.0877 wR2 = 0.1606

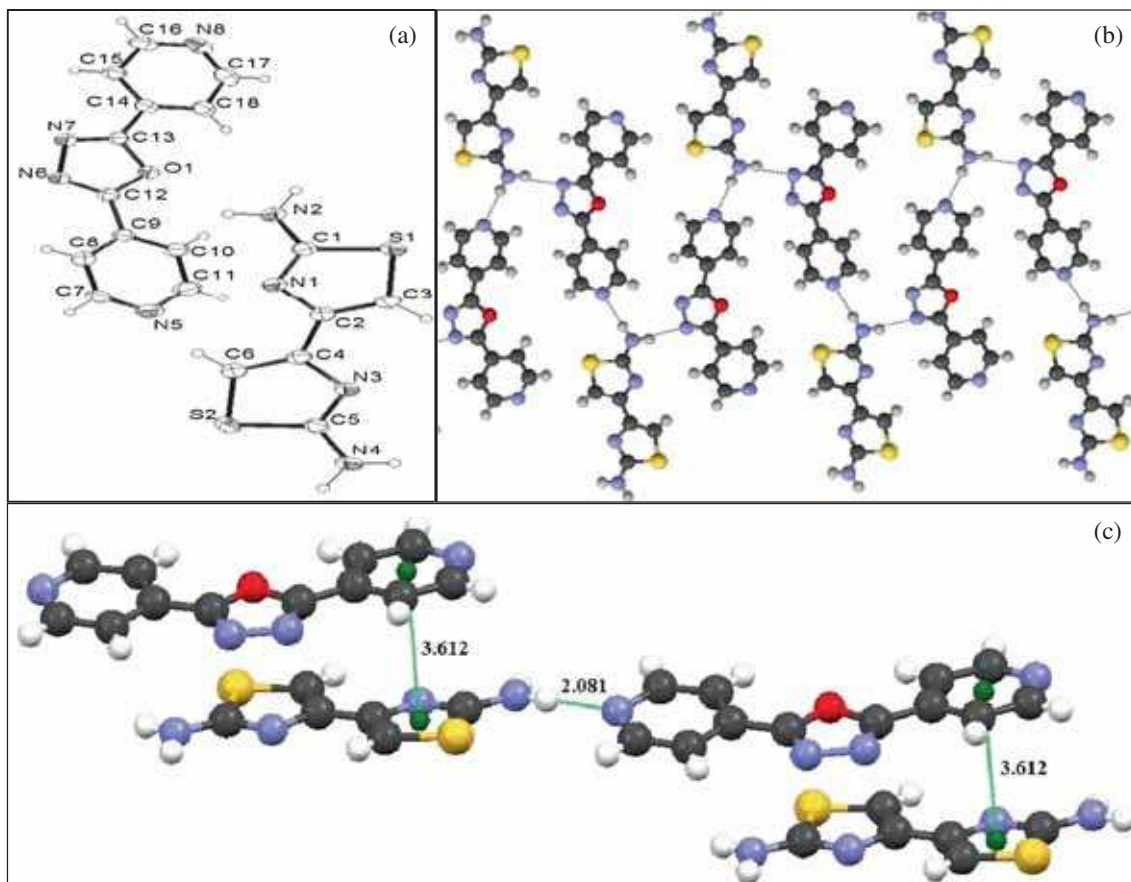


Figure 1. (a) ORTEP plot (with ellipsoids of 30% probability). (b) A perspective view of hydrogen bonded 2D assembly. (c) Parallel π - π stacking view between 2D assemblies of cocrystal **(1)**, [(DABTZ)(bpo)].

molecule in adjacent chain (table 3). These hydrogen bonds lead to an infinite two-dimensional supramolecular assembly (figure 2b). As figure 2b shows the π - π stacking feature between imidazole and pyridine rings are located offset. But, this bonding feature between two adjacent pyridine rings are parallel, approximately (figure 2b).

The geometry of both compounds was optimized using DFT method with the RB3LYP function. In order to get more stable structures, the molecules were optimized at RB3LYP/6-31(d) level of theory and the results are shown in figure 3. According to selected parameters, bond lengths (Å) and angles ($^{\circ}$), there is a good agreement between structural parameters from DFT calculation and X-ray crystallography results.

Geometrical calculated parameters are listed for better comparison in table 4. Maximum deviations are 0.041 and 0.035 Å for the C(1)-N(2) bond in cocrystals **1** and **2**, respectively. Also, maximum deviations in angles are 1.56° for N(1)C(1)N(2) in cocrystal **1** and 1.89° for C(4)N(3)C(8) in cocrystal **2**. The small differences between experimental and theoretical data refer to the fact that the experimental data belong to the solid state and the lattice with interactions in the crystal structure, while the calculated values refer to a single molecule in the gas phase.

The thermal decomposition behavior of these two new cocrystals [(DABTZ)(bpo)](**1**) and [(DABTZ)(bpa)](**2**) were investigated in static air atmosphere

Table 3. Hydrogen bond lengths (Å)/angles ($^{\circ}$) in the structure of [(DABTZ)(bpo)] (**1**) and [(DABTZ)(bpa)] (**2**).

Cocrystal No.	D-H...A	d(D-H)	d(H...A)	d(D...A)	\angle (DHA)
(1)	N(2)-H(2A)...N(5)	0.905	2.081	2.985	176.66
	N(2)-H(2B)...N(7)	0.899	2.097	2.952	158.38
(2)	N(2)-H(2A)...N(1)	0.86	2.180	3.032	171.31
	N(2)-H(2B)...N(3)	0.86	2.074	2.926	171.02

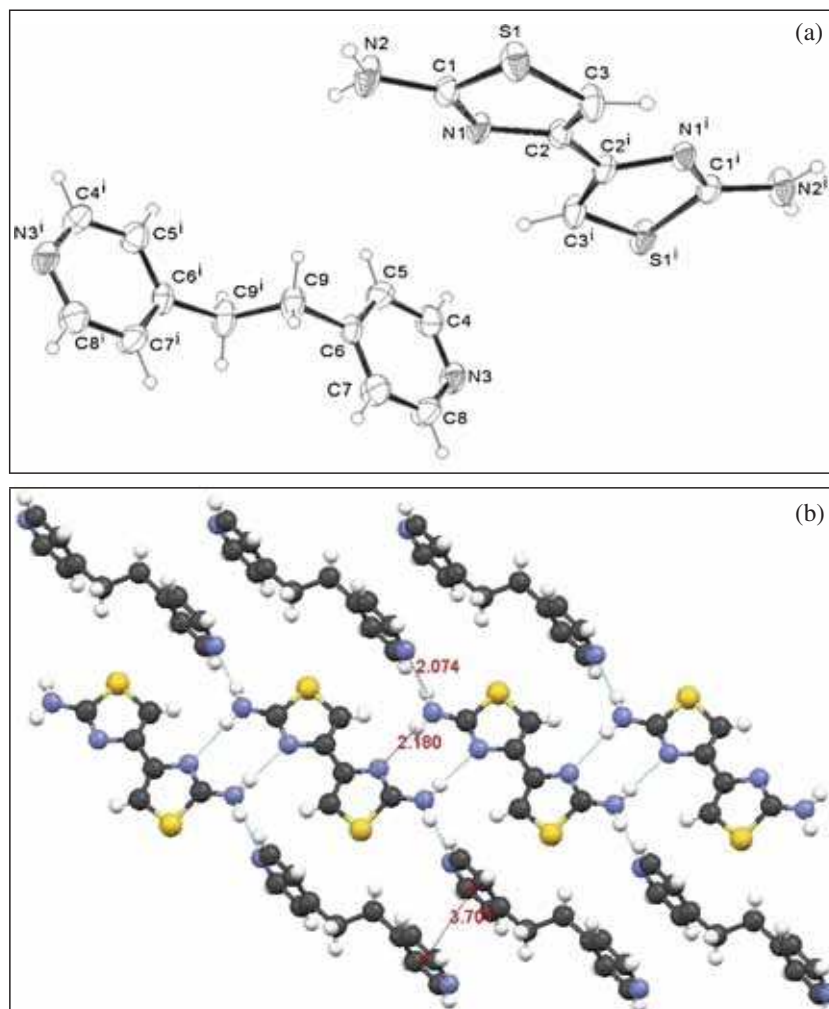


Figure 2. (a) ORTEP plot (with ellipsoids of 30% probability) (b) A perspective view of hydrogen bonded and parallel π - π stacking of co-crystal (2), [(DABTZ)(bpa)].

from ambient temperature upto 700°C. Co-crystal **1** is stable up until 200°C and above this temperature, release of one DABTZ molecule in two steps has started until 370°C (observed 41%, calc. 47%). This fragment exited by two endo and exothermic processes. The

weight loss of 58% from 370 to 600°C is equivalent to the loss of bpo molecule [calc: 53%] with an exothermic event at 450°C (figure 4a).

Thermal decomposition of co-crystal **2** takes place from 150°C. At this temperature, the bpa molecule exit

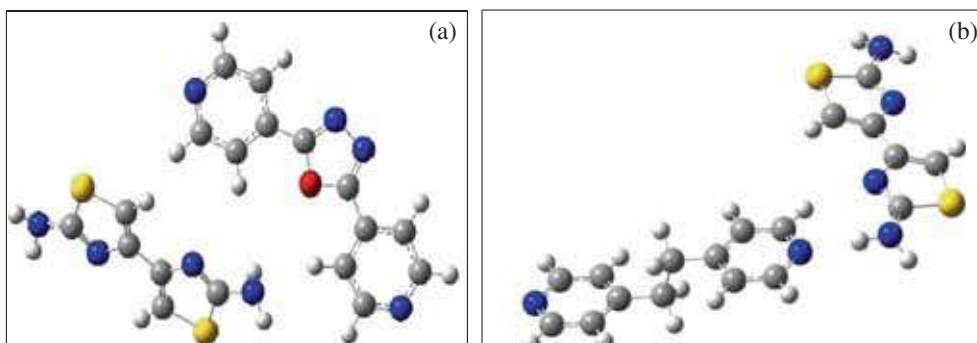
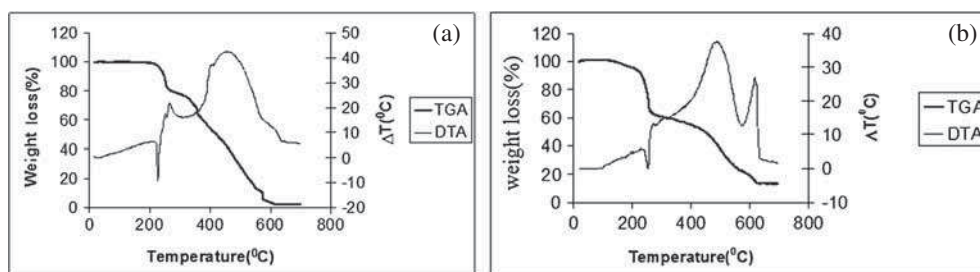


Figure 3. Optimized structure of the title co-crystals; (a) [(DABTZ)(bpo)](1) and (b) [(DABTZ)(bpa)](2).

Table 4. Experimental (X-ray) and calculated [RB3LYP/6-31G(d)] selected bond lengths (Å), angles (°) and torsion angles (°) for [(DABTZ)(bpo)](1) and [(DABTZ)(bpa)](2).

Cocrystal No.	Bond (ex.)	Bond length(Å)		Angle (ex.)	Angel(°)		Torsion angle (ex.)	Torsion angel(°)	
		Exp.	Theo		Exp.	Theo		Exp.	Theo
(1)	C(2)-N(1)	1.385	1.387	N(1)C(1)N(2)	125.58	124.02	N(1)C(2)C(4)N(3)	-177.39	179.00
	C(1)-N(1)	1.305	1.300	N(2)C(1)S(1)	119.74	120.85	C(3)C(2)C(4)C(6)	-174.11	175.68
	C(1)-N(2)	1.336	1.377	C(1)N(1)C(2)	110.27	110.76	N(6)C(12)C(9)C(8)	175.98	-178.41
	C(3)-S(1)	1.727	1.746	C(13)N(7)N(6)	106.73	106.69	C(8)C(9)C(12)O(1)	177.35	-177.78
	C(1)-S(1)	1.749	1.773	C(12)N(6)N(7)	105.80	106.72			
	C(7)-N(5)	1.322	1.339	C(11)N(5)C(7)	116.70	117.05			
	C(11)-N(5)	1.333	1.341						
	C(12)-N(6)	1.280	1.304						
	N(6)-N(7)	1.402	1.384						
	C(13)-N(7)	1.280	1.303						
(2)	C(2)-N(1)	1.385	1.389	C(5)C(6)C(9)	121.67	121.57	C(5)C(6)C(9)C(9)	89.45	90.08
	C(1)-N(1)	1.309	1.298	C(6)C(9)C(9)	112.45	112.23	C(3)C(2)C(2)C(3)	162.77	-174.91
	C(1)-N(2)	1.345	1.380	N(2)C(1)S(1)	120.52	120.67	N(1)C(2)C(2)N(1)	160.86	-175.36
	C(3)-S(1)	1.726	1.747	N(2)C(1)N(1)	124.35	124.94	C(6)C(9)C(9)C(6)	174.00	179.92
	C(1)-S(1)	1.739	1.773	C(1)N(1)C(2)	110.00	111.01			
	C(4)-N(3)	1.319	1.342	N(1)C(2)C(2)	119.06	119.54			
	C(8)-N(3)	1.308	1.340	C(4)N(3)C(8)	115.52	117.41			

**Figure 4.** TGA and DTA diagrams of (a) [(DABTZ)(bpo)] (1) and (b) [(DABTZ)(bpa)] (2).

by an endothermic process and the experimental mass loss of 40% is consistent with the calculated value 48% until 230°C. In the final step, elimination of bpa molecule (observed 50%, calc. 52%) follows with two exothermic feature at 600°C (figure 4b).

4. Conclusions

Herein, we have succeeded to synthesize two cocrystal compounds, [(DABTZ)(bpo)] (1) and [(DABTZ)(bpa)] (2), in the 1:1 stoichiometry ratio of DABTZ as hydrogen donor moiety two distinct coformers (bpo, bpa) as hydrogen acceptors. Both cocrystals were characterized by elemental and thermal analysis, FT-IR, ¹H-NMR, ¹³C-NMR spectroscopies. Also, the structures of (1) and (2) were determined by single crystal X-ray diffraction. Crystallography data showed that non-covalent interactions, H-bond and π - π stacking control

the packing of both structures. DFT calculations were done at B3LYP level of theory to predict the structural geometry. Comparison of theoretical results and experimental data shows a good agreement between them.

Supplementary Information

All additional information pertaining to characterization of the cocrystals using IR spectra (figure S1), ¹H NMR spectra (figures S2) and CIF word file are given in Supplementary Information which is available at www.ias.ac.in/chemsci.

Acknowledgments

Support of this work by Iran National Science Foundation is gratefully acknowledged.

References

1. Arenas-Garcia J I, Herrera-Ruiz D, Mondragon-Vasquez K, Morales-Rojas H and Hopfl H 2012 *Cryst. Growth Des.* **12** 811
2. Leyssens T, Springuel G, Montis R, Candoni N and Veessler S ph 2012 *Cryst. Growth Des.* **12** 1520
3. Sokolov A N, Friscic T and MacGillivray L R 2006 *J. Am. Chem. Soc.* **128** 2806
4. Karunatilaka Ch, Bucar D-K, Ditzler L R, Friscic T, Swenson D C, MacGillivray L R and Tivanski V 2011 *Angew. Chem. Int. Ed.* **50** 8642
5. Oliveira M A, Peterson M L and Davey R J 2011 *Cryst. Growth Des.* **11** 449
6. Janiak C 2000 *J. Chem. Soc. Dalton Trans.* 3885
7. Rashidi Ranjbar Z, Morsali A and Ghoreishi Amiri M 2014 *Helv. Chim. Acta* **97** 701
8. Rashidi Ranjbar Z, Morsali A and Zhu L G 2007 *J. Mol. Struct.* **826** 29
9. Garcia H C, Cunha R T, Diniz R and de Oliveira L F C 2012 *J. Mol. Struct.* **1010** 104
10. Springuel G, Norberg B, Robeyns K, Wouters J and Leyssens T 2012 *Cryst. Growth Des.* **12** 475
11. Nauha E and Nissinen M 2011 *J. Mol. Struct.* **1006** 566
12. Kucharski T J, Oxsher J R and Blackstock S C 2006 *Tetrahedron Lett.* **47** 4569
13. Velaga S P, Basavoju S and Bostrom D 2008 *J. Mol. Struct.* **889** 150
14. Sander J R G, Bucar D-K, Henry R F, Zhang G G Z and MacGillivray L R 2010 *Angew. Chem. Int. Ed.* **49** 7284
15. Sander J R G, Bucar D-K, Henry R F, Baltrusaitis J, Zhang G G Z and MacGillivray L R 2010 *J. Pharm. Sci.* **99** 3676
16. Bucar D-K, Henry R F, Zhang G G Z and MacGillivray L R 2014 *Cryst. Growth Des.* **14** 5318
17. Sanphui P, Devi V K, Deepa C, Nidhi M, Somnath G and Desiraju G R 2015 *Mol. Pharmaceutics* **12** 1615
18. Rajput L, Sanphui P and Desiraju G R 2013 *Cryst. Growth Des.* **13** 3681
19. Mahapatra S, Thakur T S, Joseph S, Varughese S and Desiraju G R 2010 *Cryst. Growth Des.* **10** 3191
20. Sanphui P, Mishra M K, Ramamurty U and Desiraju G R 2015 *Mol. Pharmaceutics* **12** 889
21. Du Y, Xia Y, Zhang H and Hong Zh 2013 *Spectrochim. Acta Part A* **111** 192
22. Zhang G Ch, Lin H L and Lin Sh Y 2012 *J. Pharm. Biomed. Anal.* **66** 162
23. Lin H-L, Zhang G-Ch, Po-Ch Hsu and Lin Sh-Y 2013 *Microchem. J.* **110** 15
24. Ravikumar N, Gaddamanugu G and Solomon K A 1033 *J. Mol. Struct.* 272
25. Eshtiagh-Hosseini H, Aghabozorg H, Mirzaei M, Beyramabadi S A, Eshghi H, Morsali A, Shokrollahi A and Aghaei R 2011 *Spectrochim. Acta Part A* **78** 1392
26. Yenikaya C and Ogretir C 2005 *J. Mol. Struct. Theochem.* **731** 1