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Syntheses and crystal structures of two soybean isoflavone derivatives

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Two soybean isoflavone derivatives, 7-methoxy-4′-hydroxyisoflavone (**1**) and 4′, 7-diethoxyl-5-hydroxyisoflavone (**2**) were synthesized and their crystal structures were determined by single-crystal X-ray diffraction. Two derivatives crystallize in the monoclinic crystal system, space group $P2_1/c$. The cell dimensions of **1** are $a = 8.696(4)$ Å, $b = 11.947(5)$ Å, $c = 12.078(5)$ Å, $\beta = 93.594(7)^\circ$, $D_c = 1.423$ Mg/m^3, $V = 1252.3(10)$ Å^3, $Z = 4$, and those of **2** are $a = 37.672(12)$ Å, $b = 11.228(4)$ Å, $c = 7.582(3)$ Å, $\beta = 94.150(6)^\circ$, $D_c = 1.355$ Mg/m^3, $V = 3198.6(18)$ Å^3 and $Z = 8$. They have the same isoflavone skeleton which is composed of a benzopyranone moiety and a phenyl moiety. Hydrogen bonding and $\pi \cdots \pi$ stacking interactions assemble **1** into supramolecule with a three-dimensional network. And in the crystal structure of **2**, hydrogen bonding and C—H$\cdots\pi$ stacking interactions lead to the formation of a two-dimensional network.

KEY WORDS: Soybean isoflavone; 7-methoxy-4′-hydroxyisoflavone; 4′,7-diethoxyl-5-hydroxy-isoflavone; crystal structure; hydrogen bonding; $\pi \cdots \pi$ stacking.

Introduction

Daidzein (4′,7-dihydroxy-isoflavone) and genistein (4′,7-dihydroxy-isoflavone), as two effective principals of soybean isoflavone, display a wide range of biological activities. They have been pharmacologically shown with the effects of antidysrhythmic,[1] antioxidant,[2,3] potential phytoestrogen,[4,5] getting rid of hyperkinesias[6] and inhibiting cancer cells growth.[7,11] Studies have also found daidzein and genistein effective in inhibiting cardiovascular disease[12] and tyrosine kinases,[13] and accelerating the formation of bone cells.[14,15] The structures of flavonoids have the close relations with their biological activities, for instance, Meng *et al.*[16] found neither genistein nor daidzein, in their aglycone form, have antioxidant properties of Low Density Lipoprotein (LDL), while the fatty acid esters of both genistein and daidzein have antioxidant properties of LDL; Eun-AH Bae *et al.*[17] have investigated the inhibitory effect of eight isoflavones on the growth of *Helicobacter pylori* (HP), their activities have large difference due to the different substituents in the isoflavone skeletons. In order to study the possible biological effects, we have synthesized the derivatives of genistein, 4′,7-dimethoxyl-5-hydroxyisoflavone, and studied its crystal structure.[18] In this paper, two soybean isoflavone derivatives, 7-methoxy-4′-hydroxyisoflavone (**1**) and 4′,7-diethoxyl-5-hydroxyisoflavone (**2**) were

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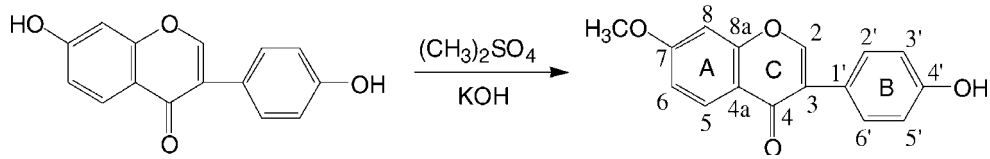


Scheme 1. Route of synthesis of **1**.

synthesized and their crystal structure were examined by single-crystal X-ray diffraction.

Experimental

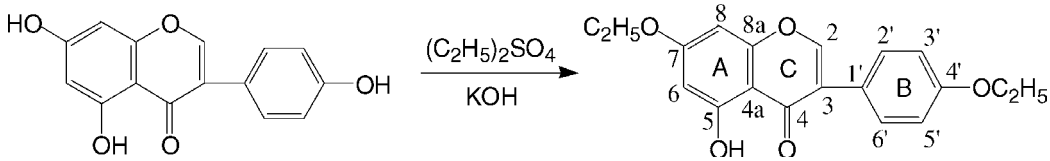
Reagent grade chemicals were used directly without further purification. The infrared spectra were recorded as KBr pellets on a Nicolet 170SX FT-IR spectrometer. The ^{1}H NMR Spectra were recorded on a Bruker-1000 CCD spectrometer with TMS as internal reference and DMSO-d_6 as solvent. The crystal structures were determined with a Bruker Smart-1000 CCD diffractometer.

Synthesis of derivative **1**

Daidzein (1.0 g) was dissolved into acetone (30 mL), and KOH (1 mL, 0.3%) added. Then dimethyl sulfate (1 mL) was added dropwise to the solution with strong stirring. After the mixture was stirred at room temperature for 4 h, it was poured into water (50 mL) and white precipitation appeared. The precipitate was filtered off and dissolved in NaOH (50 mL, 3 mol/L). After that, the solution was filtered and the filtrate was adjusted to pH = 10 with H_2SO_4 (3 mol/L), and some white precipitate came into being. The precipitate was filtered off and washed with water until the pH of the filtrate was 7 to obtain the derivative **1**. Finally, it was recrystallized from ethanol to give hexagonal colorless blocks. ^{1}H NMR(DMSO-d_6, ppm): 10.02 (s, 1H, HO$-C_{4'}$), 8.28 (s, 1H, H$-C_2$), 8.01 (d, 1H, J = 9.0 Hz, H$-C_5$), 7.34 (d, 2H, J = 8.4 Hz, H$-C_{2'}$, $C_{6'}$), 7.12 (s, 1H, H$-C_8$), 7.07 (d, 1H, J = 9.0 Hz, H$-C_6$), 6.72 (d, 2H, J = 8.4 Hz, H$-C_{3'}$,$C_{5'}$), 3.90 (s, 3H, OCH_3).

Synthesis of derivative **2**

Genistein (1.0 g) was dissolved into acetone (30 mL), and KOH (1 mL, 0.3%) added. Then, diethyl sulfate (1 mL) was added dropwise to the solution with strong stirring. After the mixture was stirred at room temperature for 4 h, it was poured into 50 mL water and white precipitation appeared. The precipitate was filtered off and dissolved in 50 mL NaOH (2 mol/L). After that, the solution was filtered off and washed with water until the pH of the filtrate was 7 to obtain the derivative 2. Finally, it was recrystallized from ethyl acetates to give prismatic crystal. ^{1}H NMR(DMSO-d_6, ppm): 12.92(s, 1H, HO$-C_5$), 8.43(s, 1H, H$-C_2$), 7.49 (d, 2H, J = 8.4 Hz, H$-C_{2'}$, $C_{6'}$), 6.98(d, 2H, J = 8.4 Hz, H$-C_{3'}$, $C_{5'}$), 6.64(s, 1H, H$-C_8$), 6.39 (s, 1H,



Scheme 2. Route of synthesis of **2**.

H−C_6), 4.12(m, 4H, −OCH_2−), 1.34 (m, 6H, −OC−CH_3).

X-ray crystal structure determinations

In the determination of the structures of the crystals **1** and **2**, X-ray determination data were collected on a Bruker Smart-1000 CCD diffractometer with graphite-monochromated Mo K_α radiation ($\lambda = 0.71073$ Å) using $\omega - 2\theta$ scan technique. The structures were solved by direct methods and refined on F^2 by full matrix least-squares with the Bruker's SHELXL-97 program. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were treated using a riding model. The crystals used for the diffraction study showed no decomposition during data collection. The crystals data, experimental details, and refinement results are summarized in Table 1. The selected bond lengths and angles of **1** and **2** are listed in Tables 2 and 3, respectively.

Results and discussion

The molecular structures of two derivatives are illustrated in Figs. 1 and 2, respectively. Compound **1** is composed of a benzopyranone moiety, a phenyl moiety, a hydroxyl and a methoxyl group. The atoms of benzopyranone moety, including ring A(C4−C9) and ring C(C1−C4,C9,O1), display a coplanar configuration with a mean deviation to the least square plane of 0.0031 Å. To avoid steric conflicts, the two rigid ring systems, phenyl ring B (C10−C15) and benzopyranone moiety are rotated by 43.2° with respect to each other. The methoxyl group at C7 is nearly planar with its corresponding rings, ring A and ring C, the torsion angle C16−O3−C7−C8

Table 1. Crystal Data and Structure Refinement for **1** and **2**

Crystal data	Compound **1**	Compound **2**
CCDC deposit no.	258208	258209
Empirical formula	$C_{16}H_{12}O_4$	$C_{19}H_{18}O_5$
Formula weight	268.26	326.33
Crystal size (mm)	0.43 × 0.29 × 0.25	0.58 × 0.48 × 0.11
Temperature (K)	298(2)	273(2)
Crystal system	Monoclinic	Monoclinic
Space group	P2(1)/*c*	P2(1)/*c*
Unit cell dimensions		
a (Å)	8.696(4)	37.672(12)
b (Å)	11.947(5)	11.228(4)
c (Å)	12.078(5)	7.582 (3)
β (°)	93.594(7)	94.150(6)
Volume, *Z* (Å^3)	1252.3(10), 4	3198.6(18), 8
Density(calculated, Mg/m^3)	1.423	1.355
Absorption coefficient (mm^{-1})	0.103	0.098
Θ range for data collection (°)	2.35 to 25.03	1.63 to 25.03
Limiting indices	$-10 \le h \le 10$	$-44 \le h \le 40$
	$-14 \le k \le 13$	$-13 \le k \le 12$
	$-13 \le l \le 14$	$-9 \le l \le 8$
Reflections collected/unique	6282/2205 [$R_{int} = 0.0321$]	15936/5501 [$R_{int} = 0.0733$]
Max. and min. transmission	0.9748 and 0.9572	0.9893 and 0.9453
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	2205/0/229	5501/0/433
Goodness-of-fit on F^2	1.021	1.007
Final *R* indices [$I > 2\sigma(I)$]	$R_1 = 0.0384$, $wR_2 = 0.0877$	$R_1 = 0.0688$, $wR_2 = 0.1587$
R indices (all data)	$R_1 = 0.0681$, $wR_2 = 0.1054$	$R_1 = 0.1472$, $wR_2 = 0.2057$
Largest diff. peak and hole (eA^{-3})	0.140 and −0.168	0.266 and −0.183

Table 2. Selected Bond Lengths (Å) and Angles (°) for **1**

Bond lengths (Å)			
O(1)−C(1)	1.358(2)	C(4)−C(9)	1.381(2)
O(2)−C(3)	1.238(2)	C(4)−C(5)	1.409(3)
O(3)−C(7)	1.356(2)	C(6)−C(7)	1.400(3)
O(3)−C(16)	1.429(3)	C(8)−C(9)	1.393(3)
O(4)−C(13)	1.362(2)	C(10)−C(11)	1.392(3)
O(4)−H(9)	0.93(3)	C(10)−C(15)	1.396(3)
C(1)−C(2)	1.336(3)	C(11)−C(12)	1.375(3)
C(2)−C(10)	1.484(3)	C(13)−C(14)	1.383(3)
C(3)−C(4)	1.451(3)	C(14)−C(15)	1.383(3)
Bond angles (°)			
C(1)−O(1)−C(9)	118.09(15)	C(6)−C(5)−C(4)	121.2(2)
C(7)−O(3)−C(16)	118.11(18)	O(3)−C(7)−C(8)	124.76(18)
C(13)−O(4)−H(9)	109.5(19)	C(8)−C(7)−C(6)	120.16(19)
C(2)−C(1)−O(1)	126.31(19)	O(1)−C(9)−C(4)	121.01(16)
C(1)−C(2)−C(3)	121.01(16)	C(4)−C(9)−C(8)	123.57(18)
O(2)−C(3)−C(4)	122.50(17)	C(11)−C(10)−C(15)	121.19(17)
C(4)−C(3)−C(2)	115.64(16)	C(12)−C(11)−C(10)	121.63(19)
C(9)−C(4)−C(5)	116.56(18)	C(11)−C(12)−C(13)	120.3(2)
O(4)−C(13)−C(14)	123.23(17)	C(13)−C(14)−C(15)	120.08(19)
C(14)−C(13)−C(12)	119.18(19)	C(14)−C(15)−C(10)	121.49(19)

Table 3. Selected Bond Lengths (Å) and Angles (°) for **2**

Bond lengths (Å)			
O(1)−C(1)	1.360(4)	C(10)−C(15)	1.383(5)
O(2)−C(3)	1.249(4)	C(11)−C(12)	1.375(5)
O(3)−C(5)	1.341(4)	C(16)−C(17)	1.506(6)
O(4)−C(7)	1.368(5)	C(18)−C(19)	1.498(5)
O(5)−C(13)	1.372(4)	C(20)−C(21)	1.339(5)
O(6)−C(20)	1.356(4)	C(23)−C(28)	1.387(5)
O(7)−C(22)	1.243(4)	C(25)−C(26)	1.402(5)
O(8)−C(24)	1.346(4)	C(27)−C(28)	1.373(5)
O(9)−C(26)	1.356(5)	C(29)−C(34)	1.382(5)
O(10)−C(32)	1.381(4)	C(30)−C(31)	1.377(5)
C(1)−C(2)	1.348(5)	C(33)−C(34)	1.377(5)
C(4)−C(9)	1.384(5)	C(35)−C(36)	1.504(6)
C(7)−C(8)	1.381(5)	C(37)−C(38)	1.476(6)
Bond angles (°)			
C(1)−O(1)−C(9)	118.8(3)	O(4)−C(16)−C(17)	108.3(4)
C(7)−O(4)−C(16)	118.2(3)	O(5)−C(18)−C(19)	109.2(3)
C(13)−O(5)−C(18)	118.1(3)	C(21)−C(20)−O(6)	126.2(4)
C(20)−O(6)−C(28)	118.9(3)	C(20)−C(21)−C(22)	117.7(4)
C(26)−O(9)−C(35)	118.7(3)	O(7)−C(22)−C(23)	121.3(3)
C(32)−O(10)−C(37)	118.5(3)	C(23)−C(22)−C(21)	116.0(3)
C(2)−C(1)−O(1)	125.8(3)	C(28)−C(23)−C(24)	116.2(4)
O(2)−C(3)−C(4)	120.9(3)	C(24)−C(23)−C(22)	122.1(3)
C(4)−C(3)−C(2)	116.0(3)	O(8)−C(24)−C(25)	119.4(4)
C(9)−C(4)−C(5)	117.1(4)	C(25)−C(24)−C(23)	121.4(4)
C(5)−C(4)−C(3)	121.9(3)	O(9)−C(26)−C(27)	123.9(4)
O(3)−C(5)−C(6)	119.8(4)	C(27)−C(26)−C(25)	120.9(4)
C(6)−C(5)−C(4)	120.6(4)	C(27)−C(28)−O(6)	116.0(3)
C(5)−C(6)−C(7)	119.9(4)	C(27)−C(28)−C(23)	124.6(4)
O(4)−C(7)−C(8)	123.6(4)	O(6)−C(28)−C(23)	119.4(4)
C(8)−C(7)−C(6)	121.3(4)	C(34)−C(29)−C(30)	116.6(3)
O(1)−C(9)−C(4)	120.6(3)	C(30)−C(29)−C(21)	122.8(3)
C(4)−C(9)−C(8)	123.2(4)	C(30)−C(31)−C(32)	120.4(3)
C(15)−C(10)−C(11)	116.3(4)	C(33)−C(32)−O(10)	125.1(3)
C(12)−C(11)−C(10)	120.5(4)	O(10)−C(32)−C(31)	115.4(3)
O(5)−C(13)−C(14)	124.8(3)	C(34)−C(33)−C(32)	119.4(3)
C(14)−C(13)−C(12)	118.9(4)	O(9)−C(35)−C(36)	107.8(3)
C(14)−C(15)−C(10)	123.5(3)	O(10)−C(37)−C(38)	109.0(3)

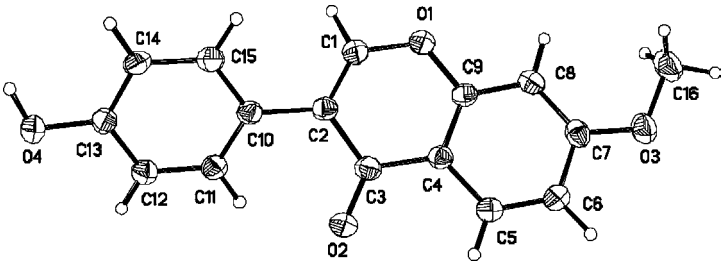


Fig. 1. The molecular structure of **1** showing 30% probability displacement ellipsoids.

being 2.1°. In the crystal structure of **2**, the basic asymmetric unit contains two molecules, and the isoflavone skeletons of them are A(C4−C9)C(O1,C1−C4,C9)–B(C10−C15) and A(C23−C28) C(O8, C20−C23, C28)–B(C29−C34), respectively. The atoms in the benzopyranone moiety of two molecules are nearly coplanar, and the dihedral angle between ring A and C are 1.1° and 2.4°, respectively. To avoid steric conflicts, the two rigid ring systems, phenyl ring and benzopyranone moiety are rotated by 35.90° and 31.10° with respect to each other, respectively. The ethoxyl group at C-7, C-26 are slightly twisted out of phenyl ring with the torsion angle C(16)−O(3)−C(7)−C(8) = 0.1° and C(35)−O(10)−C(26)−C(25) = 7.5°, and the etholxy group at C-13, C32 are slightly oriented out of the benzopyranone moiety, as indicated by the torsion angle C(18)−O(4)−C(13)−C(14) = −3.1°, C(37)−O(11)−C(32)−C(33) = 0.4°.

As is shown in Fig. 3, in the crystal structure of **1**, there are two kinds of hydrogen bonds that link the molecules into a sheet (Details of hydrogen bond lengths and angles are given in Table 4). The carbonyl oxygen atom accepts proton from the adjacent molecule to form the hydrogen bond O2 · · · H9#−O4#, which link the molecules into an infinite zig-zag chain. The zig-zag chain is further extended into a sheet along $(\bar{1}, 0, 1)$ direction by hydrogen bond C6*−H3* · · · O1**.** In addition, $\pi \cdots \pi$ stacking interactions exist in crystal structure of **1** (Fig. 4). The ring B (C1−C4,C9,O1) of one molecule is nearly parallel to the ring C (C10−C15) of a neighboring molecule, the

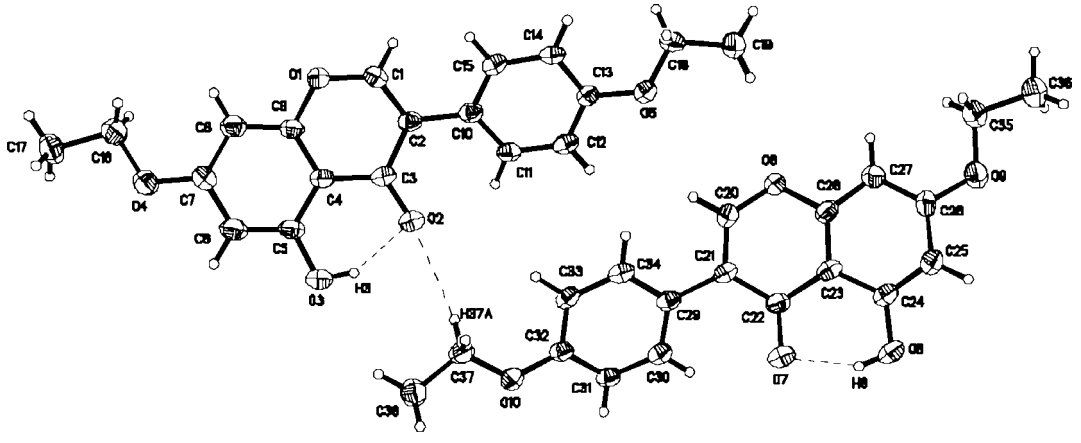


Fig. 2. A general view of the asymmetric unit of **2**. Ellipsoids are drawn at the 30% probability. Thin *dashed lines* represent the hydrogen bonds.

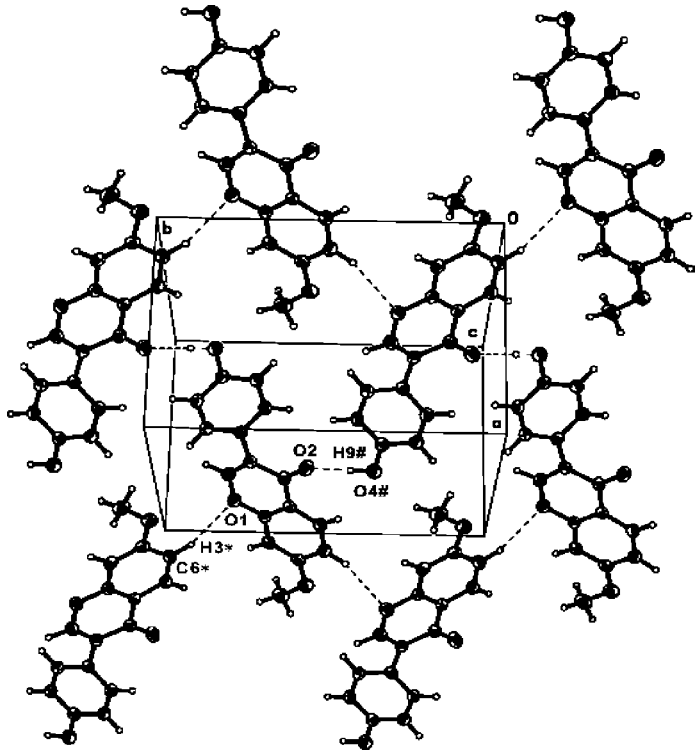


Fig. 3. The sheet of molecules formed *via* two kinds of hydrogen bonds in **1**. Symmetry code: *$(2-x, y+0.5, 2.5-z)$; #$(1-x, 1-y, 1.5-z)$.

angle between them being 8.3°. They stack with each other and its centriod-centriod distance is 3.706 Å, which is in the normal range of 3.3–3.8 Å.[19] $\pi\cdots\pi$ stacking interactions and hydrogen bonding assemble **1** into supramolecule with a three-dimensional network (Fig. 5).

Two intramolecular hydrogen bonds, O3—H3 · · · O2 and O8—H8 · · · O7 exist in the crystal structure of **2.** The carbonyl oxygen atom O2 accepts proton from the other molecule to form intermolecular hydrogen bond C37—H37A · · · O2, which links two molecules of the asymmetry unit together (Fig. 2).

The asymmetry units are further linked into a chain along the $(\bar{3}, 0, 2)$ direction by the hydrogen bond C18—H18B · · · O7. (Details of hydrogen bond lengths and angles are also given in Table 4). Additionally, the C—H $\cdots\pi$ stacking exists in the

Table 4. Typical Hydrogen Bond Lengths (Å) and Bond Angles (°) for **1** and **2**

	D—H · · · A	D—H (Å)	H · · · A (Å)	D · · · A (Å)	D—H · · · A(°)
1	O4#—H9# · · · O2	0.928	1.772	2.770	177.63
	C6*—H3* · · · O1	0.966	2.552	3.435	161.53
2	O3—H3 · · · O2	0.821	1.830	2.563	147.94
	O8—H8 · · · O7	0.819	1.836	2.557	146.23
	C37—H37A · · · O2	0.970	2.564	3.325	139.39
	C18—H18B · · · O7	0.970	2.587	3.449	148.21

Note. Symmetry code: *$(2-x, y+0.5, 2.5-z)$; #$(1-x, 1-y, 1.5-z)$.

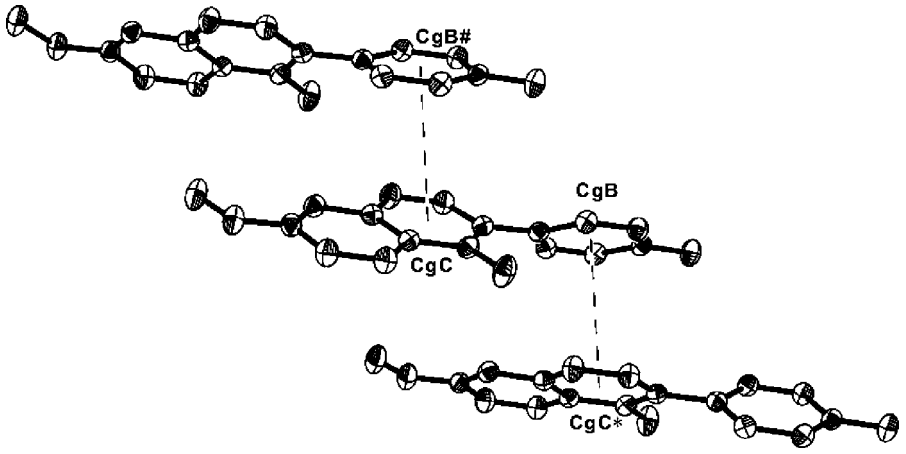


Fig. 4. The $\pi \cdots \pi$ stacking interactions in **1**. Symmetry code: #(x, $1.5 - y$, $z + 0.5$); *(x, $1.5 - y$, $z - 0.5$).

crystal structure of **2** (Fig. 6). The distance of the H15 to Cg*, the centroid of ring B, is 2.710 Å, which lies in the normal range of the C—H $\cdots \pi$ stacking.[20–22] The C—H $\cdots \pi$ stacking interactions link the chains into a two-dimensional network.

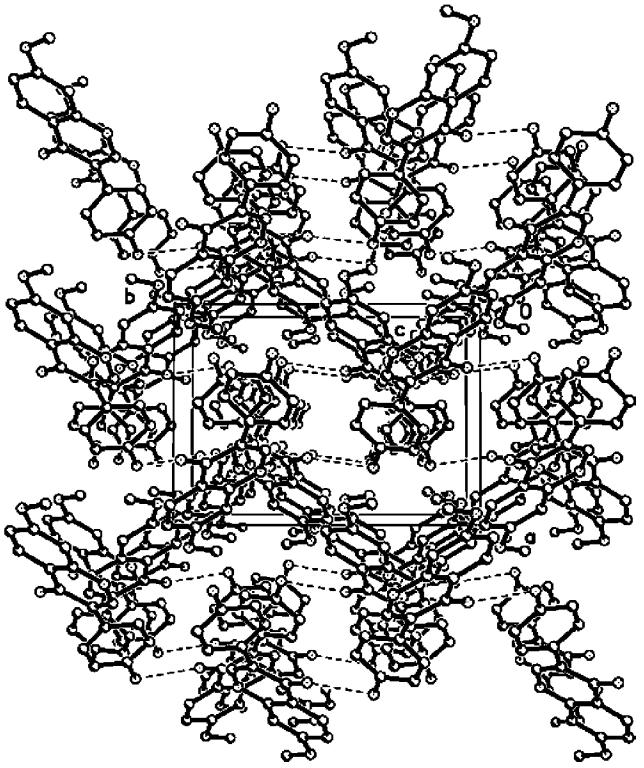


Fig. 5. The packing diagram of **1**.

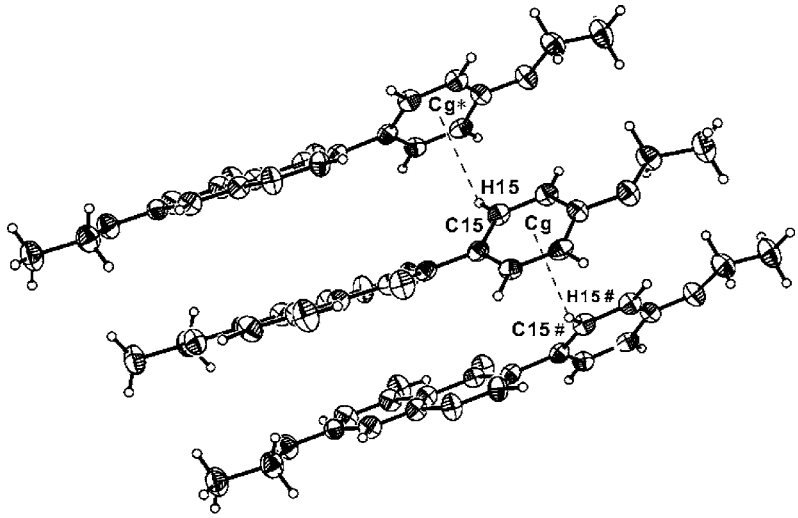


Fig. 6. The intermolecular C−H $\cdots$ π stacking in **2**. Symmetry code: # (x, 1.5 − y, z + 0.5); *(x, 1.5 − y, z − 0.5).

Supplementary material "CCDC-258208 and 258209 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)12 23-336033; e-mail: deposit@ccdc.cam.ac.uk]."

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