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CRYSTAL STRUCTURES OF TWO 4-PHENYLBENZOPHENONES

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Two 4-phenylbenzophenones (**I**) and (**II**) are synthesized via Friedel—Crafts reactions. There are four crystallographically independent molecules with different conformations in the crystal structure of [1,1′-biphenyl]-4-yl(2-chlorophenyl)methanone (**I**). Crystals are orthorhombic, $Pca2_1$, $C_{19}H_{13}ClO$, $a = 13.699(3)$ Å, $b = 8.9385(17)$ Å, $c = 46.836(9)$ Å; $V = 5735(2)$ Å^3, $Z = 16$, $d_x = 1.356$ g/cm^3. Torsion angles between the biphenyl rings are between 28.5° and 30.8°. Several C—H…O and C—H…Cl hydrogen bonds and weak π—π stacking contacts consolidate the crystal. Crystals of [1,1′-biphenyl]-4-yl(3-methoxyphenyl)methanone (**II**) are orthorhombic, $Pbca$, $C_{20}H_{16}O_2$, $a = 7.8179(15)$ Å, $b = 16.003(3)$ Å, $c = 23.345(5)$ Å; $V = 2920.7(10)$ Å^3, $Z = 8$, $d_x = 1.311$ g/cm^3. The torsion angle between the biphenyl rings is 28.1° and C—H…O hydrogen bonds are observed in compound (**II**).

Keywords: 4-phenylbenzophenone, [1,1′-biphenyl]-4-yl(2-chlorophenyl)methanone, [1,1′-biphenyl]-4-yl(3-methoxyphenyl)methanone, crystal structure, single crystal XRD, torsion angle, hydrogen bond, π—π contact.

INTRODUCTION

Biphenyl is a challenging molecule from the structural point of view because its conformations in crystals, gas and other condensed phases can differ substantially. In the crystalline state at room temperature, biphenyl owns a coplanar conformation [1]. In the gas phase, Almenningen *et al.* found by electron diffraction that the equilibrium torsion angle between the two phenyl planes was 44.4±1.2° [2]. However, in solution, twisted conformations depend largely on the nature of the solvent and the temperature [3], and for a biphenyl melt the dihedral angle was 32±4° [4]. These torsion angles of biphenyl are driven by the π-conjugation of phenyl rings, electron exchange, and steric repulsion between the adjacent hydrogen atoms in *ortho* positions [5]. Furthermore, the debate for nonplanarity is still ongoing with the viewpoint that an unfavorable lengthening of the central C—C bond might cause a hydrogen-hydrogen interaction once the planes become more coplanar [6].

Substituted biphenyls can be used as functional materials and the biphenyl moiety is also a part of many compounds possessing potential biological activities. It is believed that degrees of the torsion angles play a critical role in bioactivities. Among imidazolylmethylbenzophenones, biphenyl-4-yl-(3-imidazol-1-ylmethylphenyl)methanone was found to be the most potent cytochrome P450 aromatase (CYP19) inhibitor with an IC_{50} value of 5.3 nM, comparable to currently marketed drugs. Docking stimulations showed that the twisted biphenyl rings could establish interactions in a homology-built aromatase model (PDB 1TQA), such as π—π interactions with His475 and His480 or hydrophobic contacts with Ala223 and Ala226 [7]. X-ray cocrystals of peroxisome proliferators-activated receptor

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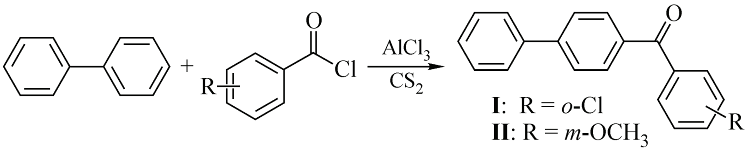
gamma (PPARγ) inhibitors revealed that compounds with a twisted 4-phenylbenzophenone tail part could extend deeper into the pocket entrance of the protein (PDB 3GBK) and make extensive hydrophobic contacts with the surrounding residues [8]. Moreover, in search for one subtype multidrug resistance-associated protein (ABCC2/MRP2) inhibitor, it was concluded that in various biphenyl-substituted heterocycles, the degrees of twisting between the two phenyl rings are crucial to the inhibition of ABCC2/MRP2 [9].

Studies on the conformations of substituted biphenyls have long attracted the attention of researchers who have made considerable efforts on theoretical and experimental investigations. Numerous theoretical studies have been performed on substituted biphenyls [10], several of which were accompanied by experimental studies [11, 12]. Recently, Grineva has analyzed the conformations of 139 *para*-X—C_6H_4—C_6H_4—*para*-Y molecules and intermolecular contacts formed by these molecules in 95 homo- and heteromolecular crystals based on the data of the Cambridge Structural Database (CSD) [13]. The *para*-substituents X and Y were limited to H, halogens, CH_3, OH, COOH, NH_2, NO_2, and CN moieties.

Herein, we synthesized two 4-phenylbenzophenones (**I**) and (**II**) via Friedel—Crafts reactions, as shown in Scheme 1, and discussed their crystallographic properties.



Scheme 1

EXPERIMENTAL

Melting points were taken on an X-4 apparatus and are uncorrected. Infrared spectra (IR) were obtained on a Thermo Nicolet Avatar 370 FT—IR spectrophotometer. Ultraviolet spectra (UV) were obtained on a Jasco V-550 UV/VIS spectrophotometer. ^{1}H NMR spectra were recorded on a Brucker AVANCE III spectrometer operating at 500 MHz.

[1,1′-Biphenyl]-4-yl(2-chlorophenyl)methanone (**I**) was obtained as follows [14, 15]. To a solution of biphenyl (9.3 g, 60 mmol) and anhydrous aluminum chloride (9.6 g, 72 mmol) in dry carbon disulfide (40 ml) *ortho*-chlorobenzoyl chloride (11.6 g, 66 mmol) in carbon disulfide (20 ml) was added dropwise at room temperature. The reaction mixture was refluxed for 8 h and poured onto ice-water containing 10 % hydrochloric acid. The mixture was extracted by carbon disulfide and the organic layer was washed by water and brine, and dried over anhydrous sodium sulfate. The crude product was purified by recrystallization in 95 % ethanol to give colorless solid, 14.0 g (yield: 79.7 %); T_m: 94—97 °C (T_m: 94 °C [16]); IR (KBr)/cm^{-1}: 3063, 1670, 1603, 1295, 931, 744; ^{1}H NMR ($CDCl_3$, 500 MHz)/ppm: 7.89 (d, $J = 8.5$ Hz, 2H, Ar), 7.69 (d, $J = 8.5$ Hz, 2H, Ar), 7.63 (d, $J = 7.0$ Hz, 2H, Ar), 7.49—7.43 (m, 4H, Ar), 7.42—7.37 (m, 3H, Ar).

[1,1′-Biphenyl]-4-yl(3-methoxyphenyl)methanone (**II**) was obtained in the same manner, with the corresponding *meta*-methoxybenzoyl chloride (11.3 g, 66 mmol), as colorless solid, 14.6 g (yield: 67.6 %); T_m: 99—105 °C (T_m: 105—106 °C [14]); IR (KBr)/cm^{-1}: 1658, 1592, 1278, 778; 1H NMR ($CDCl_3$, 500 MHz)/ppm: 7.80 (d, $J = 9.0$ Hz, 2H, Ar), 7.70 (d, $J = 9.0$ Hz, 2H, Ar), 7.65 (d, $J = 7.5$ Hz, 2H, Ar), 7.48 (t, $J = 7.5$ Hz, 2H, Ar), 7.42—7.38 (m, 4H, Ar), 7.15—7.13 (m, 1H, Ar), 3.87 (s, 3H, OCH_3).

Single crystals of compounds (**I**) and (**II**) suitable for the XRD analysis were grown from ethanol by slow evaporation at room temperature. The crystal data were collected on a Rigaku AFC10/Saturn 724+ diffractometer equipped with graphite monochromated MoK_α ($\lambda = 0.71073$ Å) radiation by φ—ω scanning in a range to $2\theta = 55°$ using the *CrystalClear* program [17]. The structures were solved by direct methods and refined on F^2 by full-matrix least-squares techniques with SHELXS97 and SHELXL97 [18]. All of the hydrogen atoms were located in theoretical positions and refined isotropically. The C—H distances were 0.95 Å for aromatic C atoms and 0.98 Å for the sp^3 C atom. Crys-

Table 1

Crystallographic data, main experiment characteristics, and refinement parameters for structures **I** *and* **II**

Compound No.	**I**	**II**
Gross formula	$C_{19}H_{13}ClO$	$C_{20}H_{16}O_2$
Molecular weight	292.74	288.33
Crystal system	Orthorhombic	Orthorhombic
Space group	$Pca2_1$	*Pbca*
a, b, c, Å	13.699(3), 8.9385(17), 46.836(9)	7.8178(15), 16.003(3), 23.345(5)
V, Å^3	5735(2)	2920.7(10)
Z	16	8
d_x, g/cm^3	1.356	1.311
T, K	133(2)	103(2)
Size, mm	0.55×0.37×0.12	0.40×0.37×0.37
Color / shape	Colorless / platelet	Colorless / block
μ, cm^{-1}	0.26	0.08
Reflections meas. / indep.	49265 / 12983	21095 / 3353
Reflections with $[I > 2\sigma(I)]$	10971	2790
R_{int}	0.086	0.038
Refined parameters	758	200
Final R indices	$R_1 = 0.070$, $wR_2 = 0.176$	$R_1 = 0.050$, $wR_2 = 0.125$
GOOF	1.00	1.00
CCDC deposit no.	818747	818748

tallographic data, main experiment characteristics, and refinement parameters for the structures of (**I**) and (**II**) are given in Table 1.

CIF files containing complete information on the studied structures were deposited with CCDC, deposition number 818747 and 818748, and are freely available upon request from the following web site: www.ccdc.cam.ac.uk/data_request/cif.

RESULTS AND DISCUSSION

As shown in Table 2, the bond lengths and angles in compounds (**I**) and (**II**) are within the normal range and in good agreement with the values reported for some analogous structures, and the lengths of bonds joining two phenyl rings C(11)—C(14) are in a range of 1.478(6) Å to 1.496(5) Å, quite close to the values of similar structures and to the standard value for a single bond length between trigonally linked C atoms [19, 20]. The three internal ring bond angles, C(9)—C(8)—C(13), C(10)—C(11)—C(12) and C(15)—C(14)—C(19), are generally smaller than the ideal angle of 120°, but similar to those found in the related compounds [20]. In both compounds the carbonyl moieties (C(1)/C(7)/C(8)/O(1)) adopt a planar triangle geometry. There are four crystallographically independent molecules (***A***, ***B***, ***C***, and ***D***) with slightly different conformations in the crystal structure of (**I**) (Fig. 1) and the C—Cl distances are between 1.732(5) Å and 1.753(5) Å in four independent molecules. In the crystal structure of (**I**), each ring is almost planar with the maximum deviation of 0.0258 Å. The dihedral angles between the aromatic rings A (C1—C6), B (C8—C13), and C (C14—C19) in four independent molecules in the asymetric unit are not the same. In the molecule ***A***, the *ortho*-chlorophenyl group is inclined at a dihedral angle of 110.5° to the adjacent phenyl group of biphenyl. And the two biphenyl rings are not coplanar, twisted with a dihedral angle of 30.7°. In the molecule ***B***, the dihedral angles are A/B = 68.0°, B/C = 28.8°; in the molecule ***C***, the dihedral angles are A/B = 71.9°, B/C = 30.8°; and in the molecule ***D***, the dihedral angles are A/B = 68.2°, B/C = 28.5° respectively. In the crystal structure of compound (**II**), each ring is almost planar with the maximum deviation of

Table 2

Main bond lengths d (Å), *bond angles* ω (deg.) *and torsion angles* φ (deg.) *in compounds* **I** *and* **II**

Lengths, angles	**I**				**II**
	A	***B***	***C***	***D***	
C(1)—C(7)	1.515(6)	1.505(6)	1.499(6)	1.500(6)	1.501(2)
C(7)—C(8)	1.496(5)	1.501(5)	1.503(6)	1.487(5)	1.497(2)
C(7)—O(1)	1.219(5)	1.229(5)	1.216(5)	1.220(5)	1.221(2)
C(11)—C(14)	1.492(5)	1.478(6)	1.481(5)	1.496(5)	1.487(2)
C(2)—Cl(1)	1.732(5)	1.741(5)	1.753(5)	1.740(5)	—
C(3)—O(2)	—	—	—	—	1.370(2)
O(2)—C(20)	—	—	—	—	1.426(2)
C(1)—C(7)—C(8)	117.2(3)	119.5(4)	116.1(4)	120.5(4)	120.7(1)
C(1)—C(7)—O(1)	121.7(4)	119.1(4)	122.3(4)	118.6(4)	119.6(1)
C(8)—C(7)—O(1)	121.0(4)	121.1(4)	121.6(4)	120.7(4)	119.8(1)
C(9)—C(8)—C(13)	119.2(4)	120.2(4)	119.8(4)	117.8(4)	118.8(1)
C(10)—C(11)—C(12)	118.6(4)	117.1(4)	118.3(4)	118.8(4)	118.0(1)
C(15)—C(14)—C(19)	118.4(4)	118.0(4)	117.8(4)	117.9(4)	117.8(1)
C(10)—C(11)—C(14)—C(15)	29.5(6)	28.3(6)	30.8(6)	28.0(6)	27.2(2)
ring A/ring B	110.5(2)	68.0(2)	71.9(2)	68.2(2)	46.0(2)
ring B/ring C	30.7(2)	28.8(2)	30.8(2)	28.5(2)	28.1(2)

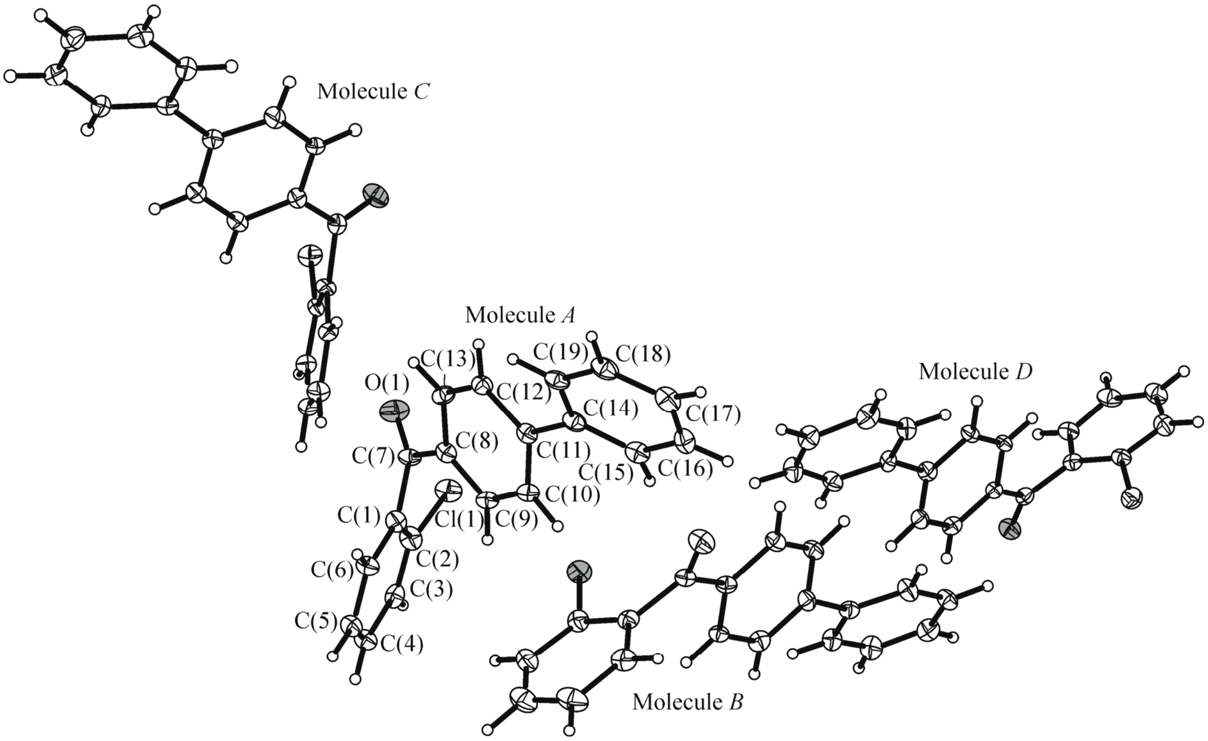


Fig. 1. Structure of compound (**I**) with atoms shown as ellipsoids of thermal vibrations with a probability of 0.3

0.0121 (2) Å (Fig. 2). The dihedral angles of the A (C1—C6), B (C8—C13), and C (C14—C19) rings are: A/B = 46.0°, B/C = 28.1°. These torsion angles between benzene rings are also presented in Table 2.

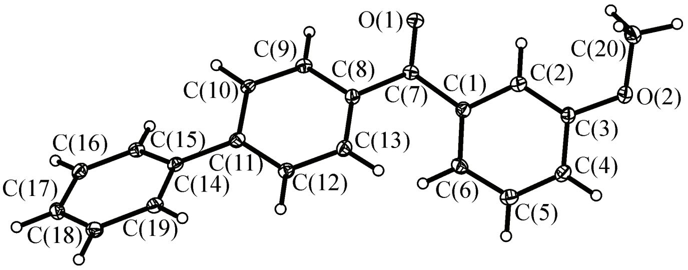


Fig. 2. Structure of compound (**II**) with atoms shown as ellipsoids of thermal vibrations with a probability of 0.3

In the crystal of (**I**), eleven kinds of hydrogen bonds exist among the phenyl, carbonyl, and chloro groups, which can be classified into seven types according to symmetry positions (Fig. 3). Details of all C—H…O and C—H…Cl hydrogen bond lengths and angles are given in Table 3. The C…O distances

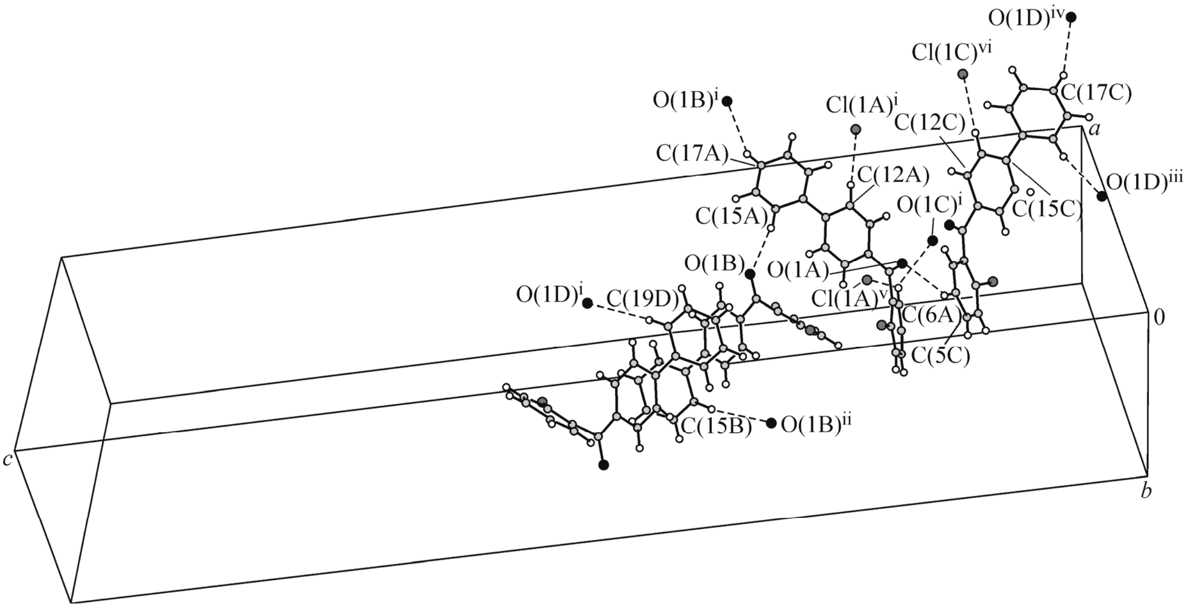


Fig. 3. Hydrogen-bonding in compound (**I**) with atoms shown as ellipsoids of thermal vibrations with a probability of 0.1 for clarity, and hydrogen bonds are indicated by dashed lines

Table 3

Hydrogen bond geometry in compound **I** (Å, deg.)

D—H…A	D—H	H…A	D…A	∠DHA
C(6A)—H(6A)…O(1C)^{i}	0.95	2.84	3.566	134
C(15A)—H(15A)…O(1B)	0.95	2.64	3.578	169
C(17A)—H(17A)…O(1B)^{i}	0.95	2.69	3.483	141
C(15B)—H(15B)…O(1B)^{ii}	0.95	2.81	3.738	167
C(5C)—H(5C)…O(1A)	0.95	2.65	3.242	121
C(15C)—H(15C)…O(1D)^{iii}	0.95	2.63	3.562	169
C(17C)—H(17C)…O(1D)^{iv}	0.95	2.70	3.486	141
C(19D)—H(19D)…O(1D)^{i}	0.95	2.82	3.745	166
C(6A)—H(6A)…Cl(1A)^{v}	0.95	3.00	3.638	126
C(12A)—H(12A)…Cl(1A)^{i}	0.95	2.91	3.817	160
C(12C)—H(12C)…Cl(1C)^{vi}	0.95	2.96	3.872	161

Symmetry codes: (i) $1/2+x$, $1-y$, z; (ii) $-1/2+x$, $2-y$, z; (iii) $1-x$, $1-y$, $-1/2+z$; (iv) $3/2-x$, $-1+y$, $-1/2+z$; (v) $1/2+x$, $2-y$, z; (vi) $1/2+x$, $-y$, z.

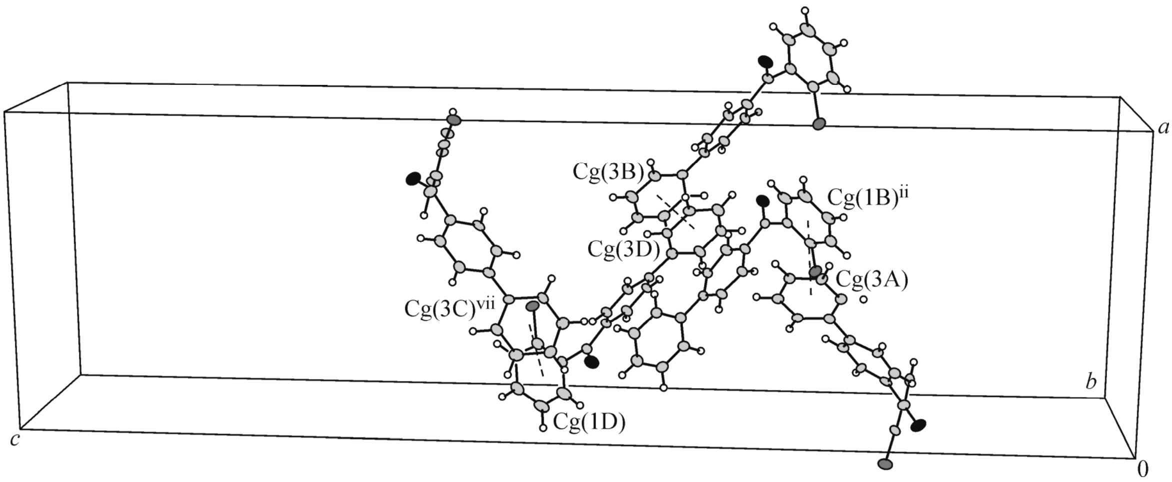


Fig. 4. π—π Stacking contacts in compound (**I**) with atoms shown as ellipsoids of thermal vibrations with a probability of 0.3

of the C—H...O hydrogen bonds are in the range of 3.242—3.745 Å, the H...O distances are in the range of 2.63—2.84 Å, and the bond angles of them range from 121° to 169°. These hydrogen bonds not only link the molecules into a hydrogen bonding network, but also play very important roles in the formation, stability, and crystallization of compound (**I**).

In addition, aromatic π—π stacking contacts are observed between a part of molecules in the crystal of (**I**) (Fig. 4), and the centroid-centroid distances are slightly more than 4.0 Å, as listed in Table 4. These π—π stacking contacts further consolidate the crystal packings.

Table 4

Parameters of the π—π *contacts in compound* **I** (Å, deg.)

Cg(*i*)...*Cg*(*j*)	*d*(*Cg*...*Cg*)	α	β	Γ	*Cg*(i)_p	*Cg*(j)_p
Cg(3A)...*Cg*(1B)^{ii}	4.116	27.73	15.52	39.75	3.164	3.966
Cg(3B)...*Cg*(3D)	4.039	0.72	18.77	19.17	3.815	3.824
Cg(1D)...*Cg*(3C)^{vii}	4.180	27.38	40.66	16.85	4.000	3.171

Cg(3A), *Cg*(1B), *Cg*(3B), *Cg*(3D), *Cg*(1D) and *Cg*(3C) are the centroids of the C(14A)—C(19A), C(1B)—C(6B), C(14B)—C(19B), C(14D)—C(19D), C(1D)—C(6D) and C(14C)—C(19C) rings respectively.
Symmetry codes: (ii) –1/2+*x*, 2–*y*, *z*; (vii) 3/2–*x*, *y*, –1+*z*.

Table 5

Hydrogen bond geometry in compound **II** (Å, deg.)

D—H...A	D—H	H...A	D...A	∠DHA
C(17)—H(17)...O(1)^{i}	0.95	2.59	3.253	127
C(18)—H(18)...O(2)^{ii}	0.95	2.68	3.376	131
C(19)—H(19)...O(2)^{ii}	0.95	2.91	3.491	121
C(20)—H(20B)...O(2)^{iii}	0.98	2.61	3.443	142

Symmetry code: (i) *x*, 1/2–*y*, 1/2+*z*; (ii) 1/2–*x*, 1–*y*, 1/2+*z*; (iii) 1–*x*, 1–*y*, –*z*.

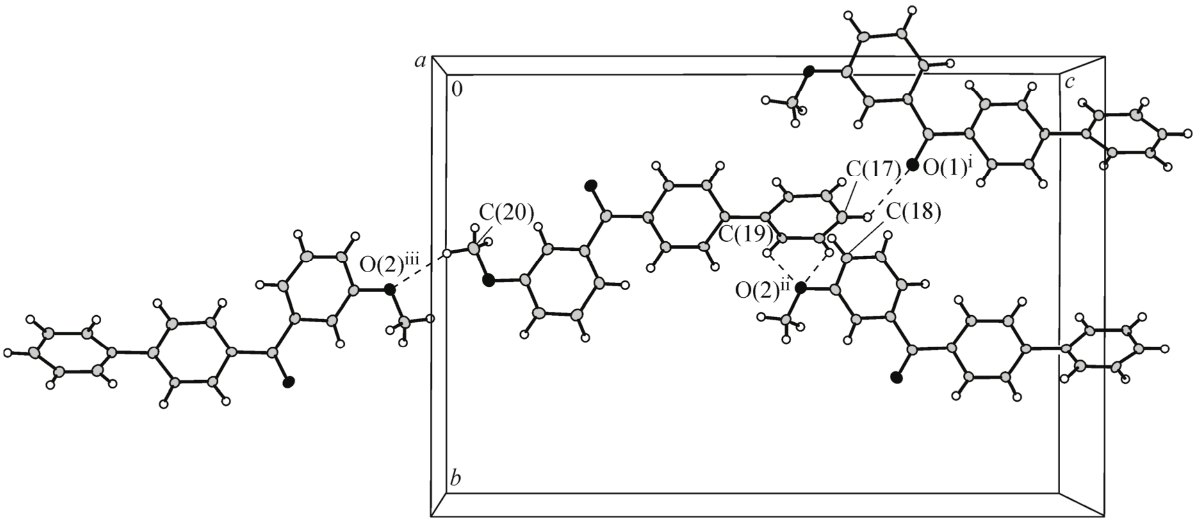


Fig. 5. Hydrogen-bonding in compound (**II**) with atoms shown as ellipsoids of thermal vibrations with a probability of 0.3, and hydrogen bonds are indicated by dashed lines

The crystal structure of (**II**) exhibits four kinds of intermolecular C—H...O hydrogen bonds (Fig. 5). Details of the hydrogen bonding geometry are listed in Table 5. One ether O(2)^{ii} [symmetry code: 1/2–x, 1–y, 1/2+z] atom is involved in a weak bifurcated hydrogen bond to two aromatic H atoms, H(18) and H(19), while the aromatic H(17) atom forms a shorter hydrogen bond with carbonyl O(1)^{i} [symmetry code: x, 1/2–y, 1/2+z]. Besides, methyl C(20) also participates in the C—H...O^{iii} [symmetry code: 1–x, 1–y, –z] hydrogen bonding. The molecules are packed as infinite layers parallel to the bc plane with an interplanar separation at 3.9 Å and no hydrogen bonding or obvious π—π stacking contacts are observed between the layers (Fig. 6).

The IR and UV absorption spectra of compounds (**I**) and (**II**) are presented in Fig. 7. The carbonyl absorption bands lie at 1670 cm^{-1} and 1658 cm^{-1} for compounds (**I**) and (**II**) respectively in the IR spectra. From UV spectra, compound (**I**) exhibits two peaks at $\lambda_{\max}^{\mathrm{EtOH}}$ 205 nm ($\varepsilon_{\max}$ 42000) and 295 nm ($\varepsilon_{\max}$ 24000), along with a shoulder peak at around 216—218 nm, while compound (**II**) displays three peaks at $\lambda_{\max}^{\mathrm{EtOH}}$ 205 nm ($\varepsilon_{\max}$ 45000), 221 nm ($\varepsilon_{\max}$ 31000), and 292 nm ($\varepsilon_{\max}$ 25000) respectively. A red shift of an absorption maximum in compound (**II**) moves towards longer wavelength at 221 nm than in compound (**I**) with a shoulder peak at around 216—218 nm. On the whole, the absorption intensity in compound (**II**) increases with an increase in the extent of the chromophore, indicating a hyperchromic effect compared with compound (**I**). It may be produced by the presence of a stronger auxochrome of methoxyl group substituted to biphenyl.

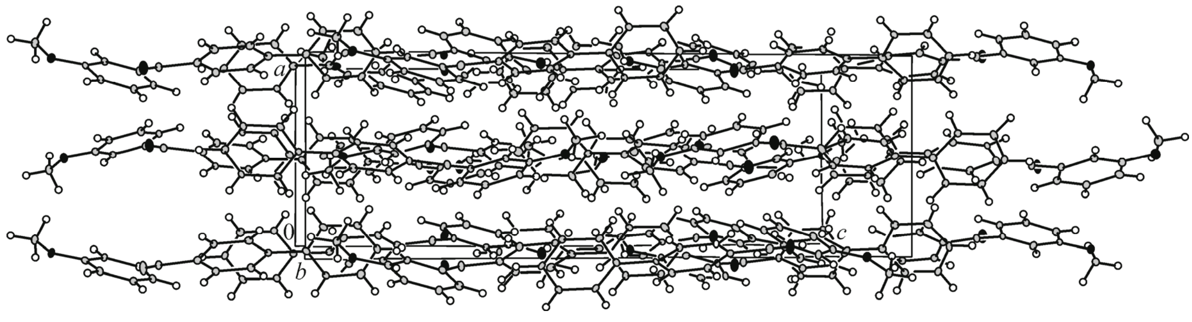


Fig. 6. The molecular packing for (**II**) viewed down the b axis, showing the layers parallel to the bc plane. Hydrogen bonds are omitted for clarity

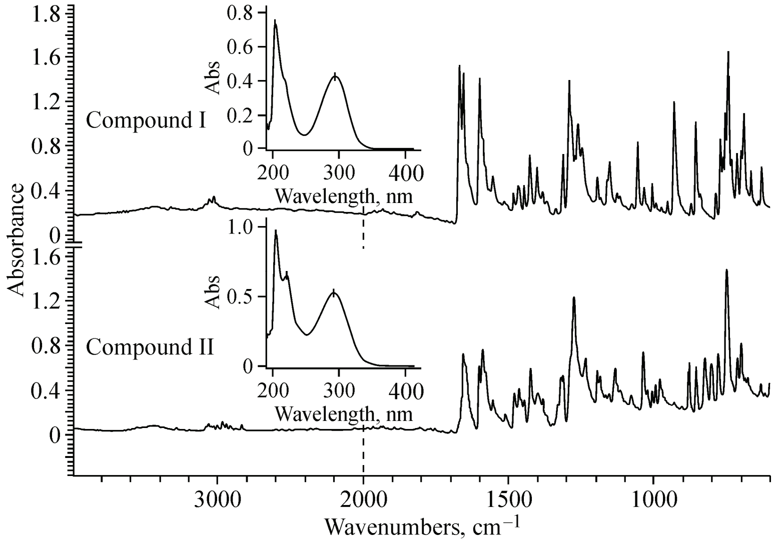


Fig. 7. IR and UV absorption spectra for crystalline compounds (**I**) and (**II**)

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