J Chem Crystallogr
DOI 10.1007/s10870-012-0386-6

ORIGINAL PAPER

Unusual C–H···π Interactions in the Structure of 3,4,5-Trimethoxy-N-*p*-tolylbenzamide

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Received: 16 June 2012 / Accepted: 6 November 2012

Abstract 3,4,5-trimethoxy-*N*-*p*-tolylbenzamide, $C_{17}H_{19}NO_4$, (**1**), is a benzanilide derivative derived from *p*-toluidine and 3,4,5-trimethoxybenzoyl chloride. The structure was identified from spectroscopic and elemental analysis data and unambiguously confirmed by the single crystal X-ray diffraction studies in space group $P2_1$, with $a = 5.1065(7)$ Å; $b = 13.9148(18)$ Å; $c = 11.2054(14)$ Å; $\beta = 103.118(7)°$; $Z = 2$. In the X-ray structure packing is predictably influenced by strong N–H···O hydrogen bonds, augmented by C–H···O contacts generating $R_1^2(6)$ ring motifs and forming chains of molecules along the *b* axis. Chains are also linked in a head-to-tail fashion by an additional weak Ar–C–H···O contact involving the tolyl methyl group. A particularly unusual feature of the packing in this structure however, is the extensive contribution of C–H···π interactions, involving two hydrogen atoms from each of the methyl groups of the 3- and 5-methoxy substituents. These link the chains into a three-dimensional network. A CSD investigation of intermolecular interactions involving both phenyl-bound and methoxy methyl groups is also presented.

Keywords Benzamides · Tri-methoxy benzene derivatives · Spectroscopic characterisation · Crystal structure · Hydrogen bonding · C–H···π interactions

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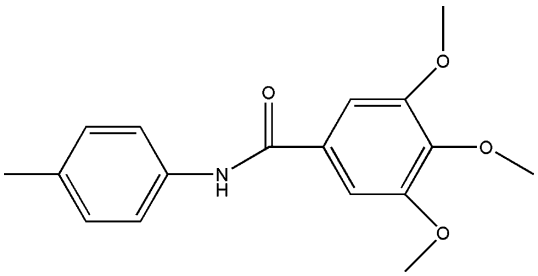
Introduction

N-substituted benzamides are an important class of structurally simple compounds with a wide range of medicinal, commercial and synthetic applications. For example declopramide (3-chloroprocainamide) is a well known anticancer compound [1]. The cytotoxic effects of *N*-(3-chloro-1, 4-dioxo, 4-dihydro-naphthalen-2-yl)-benzamide on androgen-dependent and independent prostate cancer cell lines have also been reported [2]. 2-Oxy-6-fluoro-*N*-((S)-1-hydroxy-3-phenylpropan-2-yl)-benzamides are inhibitors of hepatitis C virus polymerase [3] while alo-nitrobenzamides find potential applications against human African trypanosomiasis [4] and aminopiperidine benzamides have been identified as MCHr1 antagonists [5].

A diversity of benzamides can be prepared by systematically changing the substituents on either of the benzene rings. Introduction of various electron-donating or withdrawing substituents affects the hydrogen-bonding ability of the amide carbonyl which depends, *inter alia* upon the acidity of the −NH proton [6, 7]. While derivatives of 1,2,3-trimethoxybenzene abound, 535 entries in the Cambridge Structural Database, CSD, [8] only 32 of these have C(O)–NH substituents, with hydrazine derivatives predominating, [9–11]. Furthermore only eight of the compounds whose structures have been reported have aromatic substituents on the amide N atom forming phenyl-3,4,5-trimethoxybenzamides such as [12–16]. Interest in the potential medical applications of these compounds prompted us to continue our investigations of these derivatives with the preparation and structure determination of 3,4,5-trimethoxy-*N*-*p*-tolylbenzamide (**1**), Scheme 1. Crystal packing in this structure is shown to be influenced particularly by intermolecular interactions involving the methyl groups of the tolyl and tri-methoxy benzene rings. These and related contacts are therefore examined in some detail in what follows.

Published online: 17 November 2012



Scheme 1 3,4,5-trimethoxy-N-*p*-tolylbenzamide (**1**)

Experimental

Materials and Measurements

The melting points were recorded using a digital Gallenkamp (SANYO) model MPD.BM 3.5 apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were determined in DMSO-d_6 at 300 MHz and 75.4 MHz, respectively, using a Bruker spectrophotometer. The FTIR spectrum was recorded on an FTS 3000 MX spectrophotometer. The mass spectrum (EI, 70 eV) was obtained using a GC-MS instrument, Agilent technologies, and elemental analysis was conducted using a LECO-183 CHNS analyzer.

Synthesis and Characterization of 3,4,5-Trimethoxy-*N*-*p*-tolylbenzamide (**1**)

Freshly prepared 3,4,5-trimethoxybenzoyl chloride (1 mmol) in $CHCl_3$ was treated with p-toluidine (1.0 mmol) under a nitrogen atmosphere at reflux for 3.5 h. Upon cooling, the reaction mixture was diluted with $CHCl_3$ and washed consecutively with 1 *M* aqueous HCl and saturated aqueous $NaHCO_3$. The organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure. Crystallization of the residue from ethanol twice afforded (**1**) (83 %) as colourless crystals. mp 168–169 °C; IR (ATR cm^{-1}): 3273 (NH amide), 3096 (C sp^2-H), 2918 (Csp^3-H), 1681 (C=O amide), 1575 (C=C aromatic); ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.65 (s, 1H, NH), 8.1 (d, 2H, $J = 6.2$, Ar), 7.83 (d, 2H, $J = 6.2$, Ar), 7.71 (s, 2H, Ar), 3.81 (s, 9H, OMe × 3), 2.51 (s, 3H, $ArCH_3$), ^{13}C NMR: (75.4 MHz, DMSO-d_6): δ 169.9 (CONH), 167.2, 147.2, 148.11, 138.4, 134.42, 133.39, 128.92, 125.61, 114.69, 56.7 (OMe), 22.4 ($ArCH_3$); GC–MS *m*/*z* (%) 301(36), 219 (28), 206 (52), 195 (100); Anal. calcd. for $C_{17}H_{19}NO_4$: C, 67.76; H, 6.36; N, 4.65 %; found: C, 67.54; H, 6.67; N, 4.49 %.

Crystallography

Crystallographic data for (**1**) are listed in Table 1. Diffraction data were collected on a Bruker APEXII CCD diffractometer using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å). The crystal was mounted on a mylar loop in a thin film of Paratone N oil. Data collection was controlled by *APEX2* [17] software using 60 s ω scans and cell refinement and data reduction was performed with *SAINT* [17]. Multi-scan absorption corrections were applied using *SADABS* [17]. The structure was solved with *SHELXS* [18] and refined by full-matrix least-squares on F^2 using *SHELXL-97* [18] and *TITAN2000* [19]. All non-hydrogen atoms were assigned anisotropic displacement parameters. The H atom on N1 was located in a difference Fourier map and its coordinates refined with the atomic displacement parameter set to $1.2U_{eq}$(N). All other H-atoms were

Table 1 Crystal data and structure refinement for (**1**)

CCDC number	871199
Crystal data	
Molecular formula	$C_{17}H_{19}NO_4$
Molecular weight	301.33
Crystal system	Monoclinic
Space group	$P2_1^a$
Temperature	90(2) K
a (Å)	5.1065(7)
b (Å)	13.9148(18)
c (Å)	11.2054(14)
β (°)	103.118(7)
V (Å^3)	775.43(18)
Z	2
Dc (g cm^{-3})	1.291
Absorption coeff. (mm^{-1})	0.092
F(000)	320
Crystal size (mm)	0.30 × 0.26 × 0.10
Data collection and structure solution	
Range/indices (*H*,*K*,*L*)	−7/6; −19/18; −15/15
Data collected	12461
Independent reflections	2207
Observed reflections [$I > 2\sigma(I)$]	1959
R(int.)	0.0346
Completeness	98.9 %
T_{max}/T_{min}	1.000/0.850
Data/restraints/parameters	2207/0/206
R1[$I > 2\sigma(I)$][b]	0.0377
*wR*2 (all data)[c]	0.0924
GooF, *S*, on F^2	1.040
Largest difference peak and hole (eÅ^{-3})	0.230/−0.238

[a] The absolute structure could not be reliably determined and no Flack parameter is reported

[b] $R1 = ||F_o| - |F_c||/|F_o|$

[c] $wR2 = \left\{\Sigma\left[w\left(F_o^2 - -F_c^2\right)^2\right]/\Sigma\left[w\left(F_o^2\right)^2\right]\right\}^{1/2}$;
$w = 1/\left[\sigma^2\left(F_o^2\right) + (0.0445P)^2 + 0.1496P\right]$ where $P = \left(F_{o2} + 2F_c^2\right)/3$.

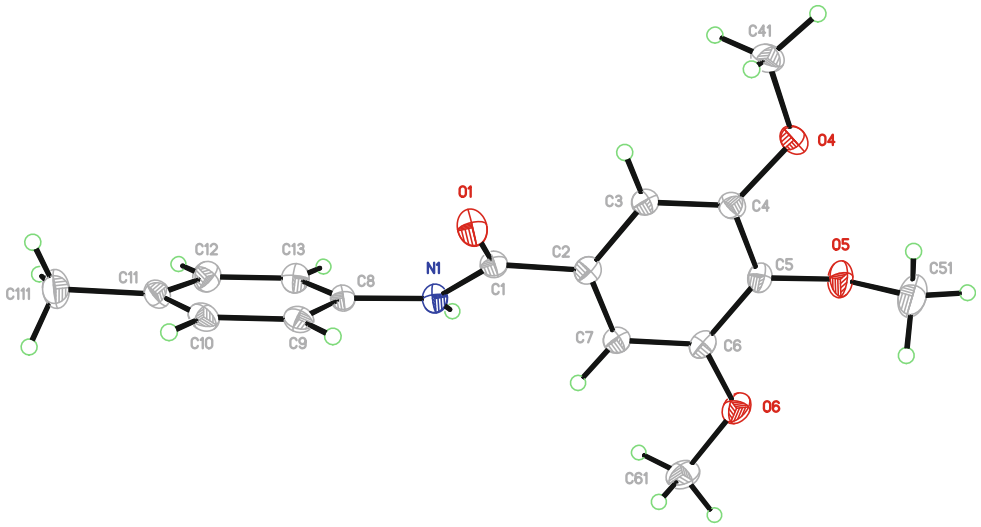


Fig. 1 The molecular structure of (**1**) with displacement ellipsoids drawn at the 50 % probability level

positioned geometrically and refined using a riding model with d(C–H) = 0.95 Å, $U_{iso} = 1.2U_{eq}$(C) for aromatic 0.99 Å and 0.98 Å, $U_{iso} = 1.5U_{eq}$(C) for CH_3 atoms. Figure 1 was produced using XP in SHELXTL [18] and packing diagrams were drawn using Mercury [20]. Other calculations were performed using PLATON [21].

Results and Discussion

Synthesis and Characterization

The synthetic pathway to the title compound (**1**) is depicted in Scheme 2. Thus, 3,4,5-trimethoxybenzoic acid was converted to the corresponding acid chloride by a standard procedure. Freshly prepared trimethoxybenzoyl chloride was refluxed with an equimolar amount of *p*-toluidine in dry chloroform under nitrogen for 2 h to give the amide which was recrystallised twice from ethanol to afford crystals suitable for the X-ray diffraction study.

In the FTIR spectrum, a broad signal attributed to the N–H stretch appeared at 3,273 cm^{-1} while the amide carbonyl and aromatic C=C stretching vibrations, were observed at 1,681 and 1,575 cm^{-1}, respectively. The ^{1}H-NMR spectrum of the compound was also consistent with the proposed structure. Thus, in addition to the signals for the amide N–H proton at δ 8.6, two 2H doublets typical of a *p*-disubstituted aromatic ring appeared at δ 8.1 and δ 7.83 together with a 2H singlet at δ 7.71 ppm, respectively. A singlet for the nine methoxy protons appeared at δ 3.81 with that for aromatic methyl group at δ 2.51 ppm. In the ^{13}C NMR the amide carbonyl was observed at δ 169.9 with all other carbon resonances in their characteristic regions. The mass spectrum showed the molecular ion peak at *m/z* 301 and a base peak derived from the trimethoxycarbonyl cation at *m/z* 195.

Molecular Structure

In the structure of (**1**), Fig. 1, Table 2, the two benzene rings are inclined at 75.91(5)° to one another and linked by a planar C8, N1, C1, O1, C2 amide unit (rms deviation 0.0053 Å) which makes dihedral angles of 34.00(7)° and 41.95(7)° with the trimethoxybenzene and tolyl ring systems, respectively. The 3 and 5-methoxy substituents, O4, C41 and O6, C61, lie close to their benzene ring plane, with maximum deviations 0.162(4) Å for C41 and 0.134(4) Å for C61, in opposite directions. In contrast, the C5–O5–C51 plane of the central 4-methoxy substituent subtends an angle of 72.04(15)° to the benzene plane. A similar configuration is found in several other phenyl-3,4,5-trimethoxybenzamides [12–16].

The CSD [8] reveals that bond distances in this molecule compare well with those reported for the 30 other structurally characterised 3,4,5-trimethoxybenzene structures with C(O)–NH substituents at position 1.

Scheme 2 The synthesis of 3,4,5-trimethoxy-*N*-p-tolylbenzamide (**1**)

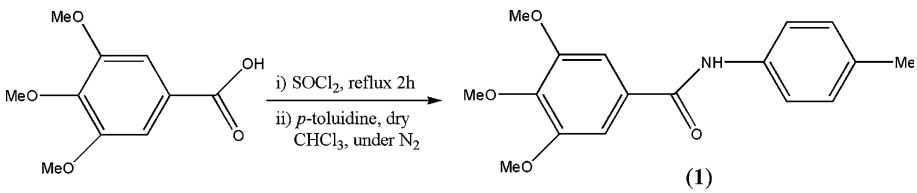


Table 2 Selected bond distances, angles and torsion angles (Å, °) for (**1**)

N1–C1	1.358 (3)	C4–O4	1.362(3)
N1–C8	1.424 (3)	O4–C41	1.425(3)
C1–O1	1.235 (2)	C5–O5	1.372(2)
C1–C2	1.495 (3)	O5–C51	1.434(3)
C11–C111	1.511(3)	C6–O6	1.364(3)
		O6–C61	1.424(3)
C1–N1–C8	124.18 (17)	C4–O4–C41	117.14 (17)
O1–C1–N1	123.19 (18)	C4–C5–O5	120.46 (19)
O1–C1–C2	120.94 (18)	C6–C5–O5	119.56 (19)
N1–C1–C2	115.87 (17)	C5–O5–O51	114.07 (18)
C10–C11–C111	120.77 (19)	C5–C6–O6	115.24 (18)
C12–C11–C111	121.6 (2)	C7–C6–O6	124.74 (18)
C3–C4–O4	124.76 (18)	C6–O6–C61	117.08 (17)
C5–C4–O4	115.04 (18)		
C8–N1–C1–O1	0.8 (3)	C4–C5–O5–C51	75.0 (3)
C8–N1–C1–C2	−178.91 (17)	C6–C5–O5–C51	−108.9 (2)
C3–C4–O4–C41	−1.9 (3)	C5–C6–O6–C61	178.90 (17)
C5–C4–O4–C41	177.60 (18)	C7–C6–O6–C61	−1.4 (3)

Table 3 Hydrogen bond geometry (Å, °) for (**1**)

D–H···A	D–H	H···A	D···A	D–H···A
N1–H1 N···O1^{i}	0.91(3)	2.06(3)	2.945(2)	163(2)
C13–H13···O1^{i}	0.95	2.66	3.330(3)	128
C111–H11C···O4^{ii}	0.98	2.72	3.409(3)	128

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

Crystal Packing

In the crystal structure, packing is predictably influenced by strong intermolecular N1–H···O1 hydrogen bonds, which combine with C13–H13···O1 contacts, Table 3, to generate $R_1^2(6)$ ring motifs and link the molecules in chains along the *a* axis, Fig. 2. A search of the CSD for benzanilide derivatives with intramolecular N–H···O hydrogen bonds similarly supported by C–H···O contacts involving an *ortho*-H atom of the aniline ring was conducted and revealed 46 instances of similar motifs, with comparable intermolecular bond distances and angles to those observed here. These include, for example, *N*-(3-methylphenyl)benzamide and *N*-(4-chlorophenyl)-3-methylbenzamide [22, 23] and the even more closely related 3,4,5-trimethoxy-*N*-(2-methoxyphenyl)benzamide [12]. Similarities between (**1**) and these systems suggest this to be a reasonably common packing motif in such compounds.

Molecules are also linked in a head-to-tail fashion into chains running along *b*, Fig. 3, by weak C111–H11C···O4 hydrogen bonds between the tolyl methyl group and the O4 atom of one of the outer methoxy groups.

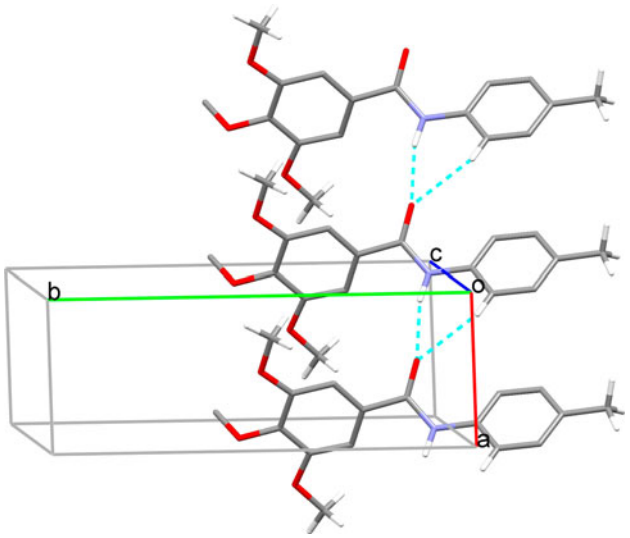


Fig. 2 Supported N–H···O hydrogen bonds that form $R_1^2(6)$ ring motifs and generate chains along the *a* axis. Hydrogen bonds are drawn as *dashed lines*

The crystal structure of (1) appears also to be stabilised to a considerable extent by a series of C–H···π interactions, involving two hydrogen atoms from each of the C41 and C61 methyl groups of the 3 and 5 methoxy substituents, Table 4, Fig. 4.

Doubts have been raised concerning the appropriateness of invoking any kind of intermolecular hydrogen bonding contact that involves methyl groups on the basis that, even at low temperatures, rapid rotation of the groups occurs reducing the possibility of meaningful non-classical hydrogen bonding contacts [24, 25]. As this structure appears to provide strong evidence for the involvement of both C–H···O and C–H···π contacts in the packing of these molecules, we have undertaken database searches targeting both types of methyl based contacts to examine their generality and applicability more closely. A recent detailed study has looked at the energetics of weak hydrogen bonding interactions as a function of D–H···A angles [26] and recommends limiting C–H···X angles to a minimum of no less than 120° for the contact to be considered significant. We have used these criteria as a guide to investigate initially C–H···O contacts involving phenyl bound methyl groups such as those as shown in Fig. 3.

Interrogating the CSD for Ar–CH_3···O contacts involving a methyl group bound in a *para* position on a benzene ring as found in (**1**) with C···O distances in the range 2.7–3.5 Å and with C–H···O angles limited to 120°–180° (other search limitations: 3-D-coordinates determined; $R < 0.1$; only organics) produced 1,536 hits involving 1,815 discrete contacts. Analysis of the metrical data using Mercury [20] showed a mean C···O contact distance of 3.4(4) Å while the C–H···O angles examined in the same search over the range 120°–180° showed a mean angle of

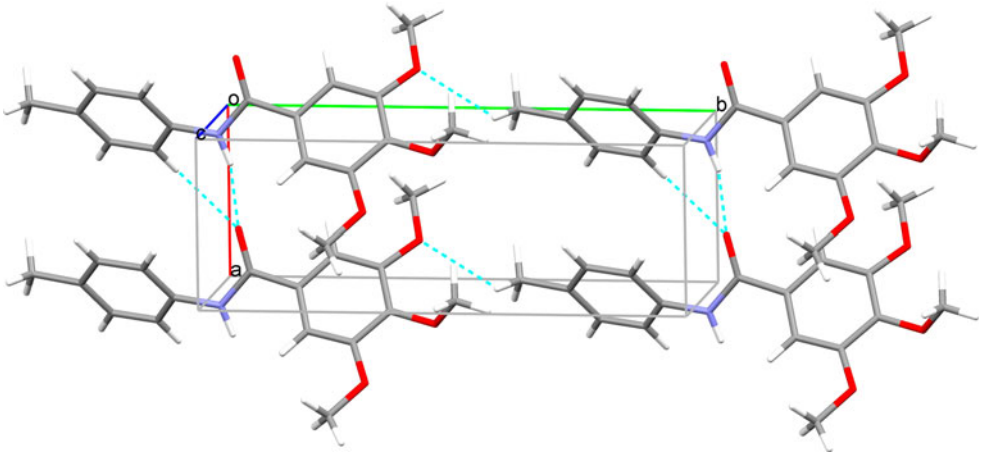


Fig. 3 Chains formed along the *b* axis by weak C–H···O hydrogen bonds

Table 4 Potential C–H…π contacts (Å, °) for (**1**)

D–H…A	D–H	H…A	D…A	D–H..A
C41–H41C···Cg1^{iii}	0.98	2.91	3.873(2)	167
C41–H41A···Cg2^{iv}	0.98	2.78	3.377(2)	120
C61–H61C···Cg1^{i}	0.98	2.72	3.491(2)	136
C61–H61B···Cg2^{v}	0.98	2.85	3.763(2)	155

Symmetry codes: (i) $x+1, y, z$; (ii) $x-1, y, z$; (iii) $-x+1, y+1/2, -z+1$; (iv) $-x+3, y+1/2, -z+2$. Cg1 and Cg2 are the centroids of the C2···C7 and C8···C13 benzene rings, respectively

140(14)° suggesting that there is some substance to the suggestion that such contacts can indeed support crystal packing. The distance observed here for (1), 3.409 (3) Å, is close to this mean bond distance, while the C–H···O angle, 128°, is at the lower end of the range suggesting that in this case the interaction may be relatively weak. Nonetheless this investigation confirms that this interaction will indeed contribute to the crystal packing in this instance.

Similarly we have also sought evidence for the involvement of intermolecular O–C–H···π contacts involving the methyl groups of methoxy substituents on aromatic rings. These interactions certainly appear to be fairly common, as a search of the CSD for Ar–O–CH_3···π contacts involving one H atom from an individual methoxy group with C···Cg distances in the range 3.0–3.9 Å and C–H···Cg angles within the range 120–180° produced no fewer than 4,919 hits (limitations 3D coordinates determined; $R < 0.1$; only organics). Applying the same criteria, 212 of these structures were found to be 3,4,5-trimethoxybenzene derivatives. Restricting the search to 3,4,5-trimethoxybenzene compounds in which a methoxy group formed contacts via two discrete H atoms from different outer (3 & 5) methyl groups limited the number of contacts to 44. Analysis of

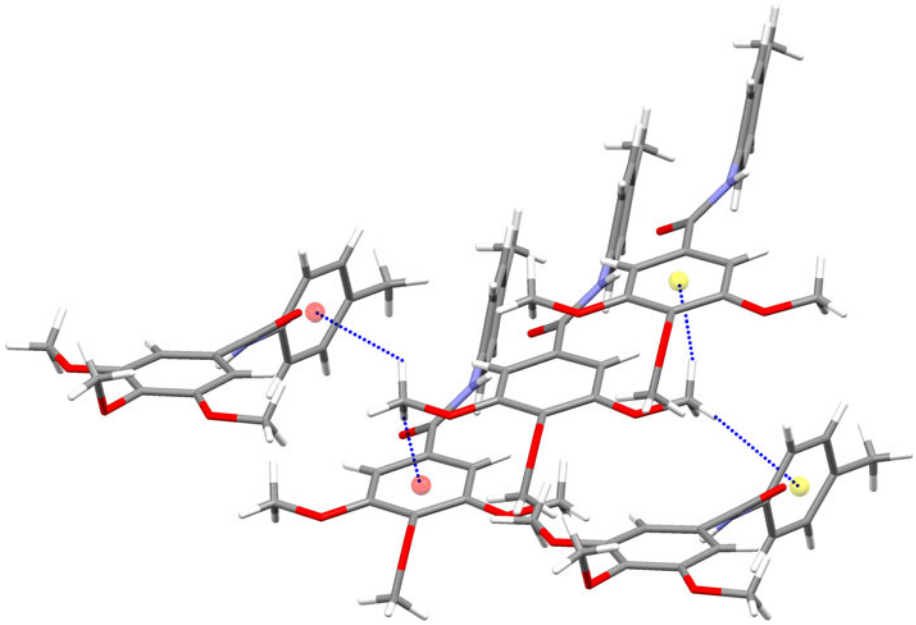


Fig. 4 C–H···π contacts (*dotted lines*) emanating from a single molecule of (**1**). *Red* and *yellow* spheres represent the centroids of the C2···C7 and C8···C13 benzene rings, respectively (Color figure online)

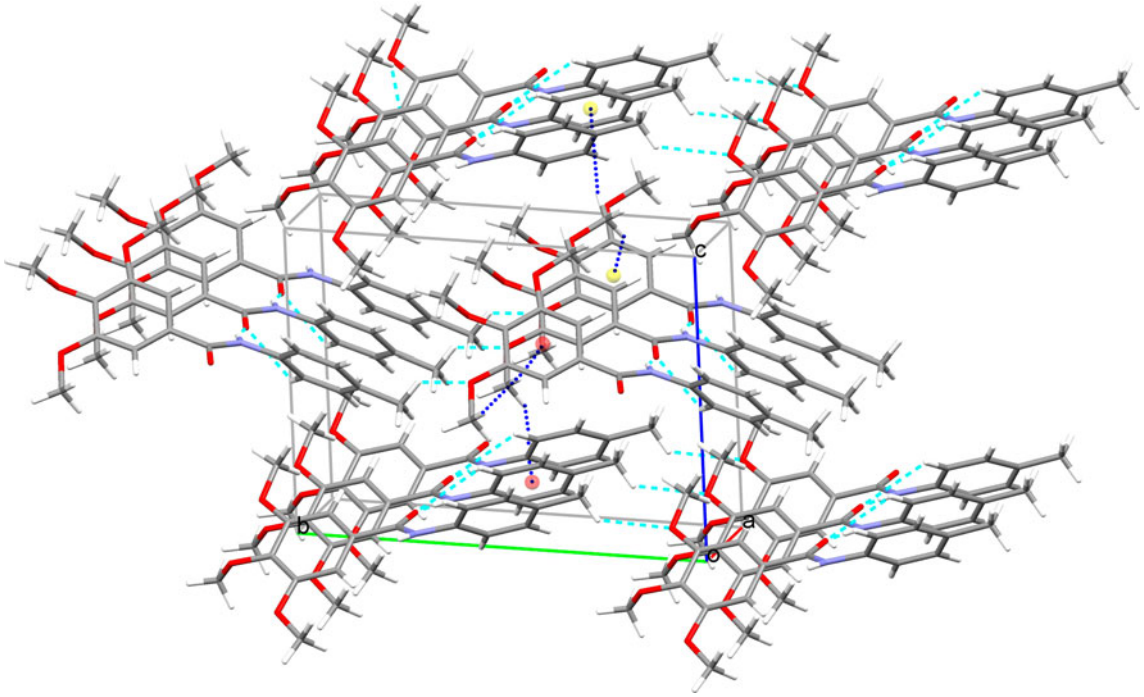


Fig. 5 Packing diagram for (**1**) showing molecules stacked along *a*. N–H···O and C–H···O contacts are shown as *dashed lines* with a representative set of C–H···π interactions drawn as *dotted lines*

these [20] gave mean C···centroid distances of 3.67(2) Å and 3.685(19) Å, respectively, with corresponding mean C–H···centroid angles of 144(12)° and 147(11)°. A similar search in which the two C–H···π contacts emanated from the same outer (3 or 5) methoxy group revealed 14 structures only one of which was a benzamide [3,4,5-trimethoxy-*N*-methyl-*N*-(4(1H-pyrrol-2-yl)phenyl)-benzamide] but its packing was not discussed [27]. Similar analysis gave mean C···centroid distances of 3.66(16) Å and 3.75(11) Å, respectively, with corresponding mean C–H···centroid angles of 138(13)° and 141(14)°. This suggests that where two H atoms from the same methyl group are involved in such C–H···π interactions the resulting contacts are slightly weaker. Extending this search still further to include one or two additional C–H···π contacts involving both 3,5-methoxy substituents in 3,4,5-trimethoxybenzene compounds produced no hits demonstrating the complete novelty of the range of contacts observed in the crystal packing of (**1**). Clearly the metrical data for the compound reported here, Table 4, show that these contacts lie well within the norms observed previously in similar molecules. This is however the first situation where such an extensive set of O–C–H···π contacts have been observed in a 3,4,5-trimethoxybenzene derivative.

The overall effect of these classical and non-classical hydrogen bonding interactions is the generation of a three dimensional network structure with molecules stacked in a regular fashion along the *a* axis, Fig. 5.

Conclusions

While the molecular structure of this compound is unremarkable, the crystal packing involves some novel interactions. Classical N–H···O hydrogen bonds are supported by C–H···O contacts from the adjacent tolyl ring. CH_3···O contacts from the tolyl methyl group are also found. A significant contribution to the packing also comes from OCH_3···π contacts involving two hydrogen atoms from each of the outer (3 & 5) methoxy groups. These provide a structural motif that is shown to be unique to this molecule.

Acknowledgments We thank the University of Otago for purchase of the diffractometer.

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