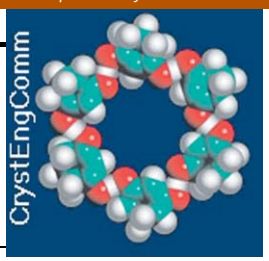

Multiple molecules in the crystallographic asymmetric unit. Self host–guest and doubly interpenetrated hydrogen bond networks in a pair of keto-bisphenols

Paper

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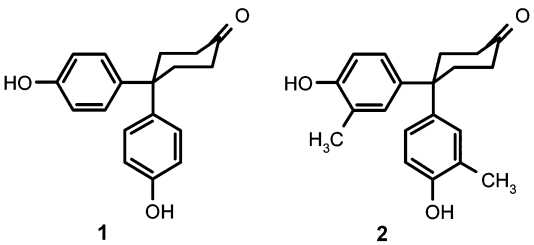
The presence of two molecules in the crystallographic asymmetric unit in a pair of closely related keto-bisphenols that differ by a methyl substituent only, leads to open frameworks that fill space through self-inclusion in one case, and through interpenetration in the other.

Introduction

The combination of a symmetrical molecular scaffold, a degree of rigidity, and the presence of good hydrogen bonding groups (OH, CO_2H, C=O) is an effective way to engineer open framework structures.[1–3] β-Quinol,[4] trimesic acid[5] and adamantane-1,3,5,7-tetracarboxylic acid[6] are classic examples of the two routes available to an open network to solve the close packing problem—guest inclusion or interpenetration. A number of cases have been reported that illustrate these two situations.[7,8]

In this paper we report the crystal structures of 4,4-bis(4-hydroxyphenyl) cyclohexanone, **1**, and 4,4-bis(3-methyl-4-hydroxyphenyl)cyclohexanone, **2**. Both structures consist of hydrogen bonded networks. In both cases there are two symmetry independent molecules. Apparently, minor differences in the conformations of the two molecules in the asymmetric unit lead to different hydrogen bond motifs, and in turn to rare variations of the guest inclusion and interpenetration themes for close packing. Bisphenol **1** may be viewed as a self host–guest structure while **2** exhibits interpenetration of non-identical networks.



Experimental

1. Synthesis

A mixture of cyclohexane-1,4-dione (0.5 g, 4.46 mmol) and phenol (1.3 g, 13.89 mmol) in 1,4-dioxane (10 mL) and water (10 mL) at 0 °C was treated dropwise with concentrated H_2SO_4 (6 mL). The reaction mixture was stirred at room temperature for 6 h, neutralized with $NaHCO_3$ solution and extracted with ether to yield **1**. Compound **2** was made using the same procedure with cyclohexane-1,4-dione and *o*-cresol as starting compounds. **1**: ^{1}H–NMR δ (DMSO-d_6) 8.79 (s, 2 H), 6.69 (d, *J* 8, 4 H), 6.23 (d, *J* 8, 4 H), 2.08 (t, *J* 5, 4 H), 1.81 (t, *J* 5, 4 H). IR (KBr): 3368, 1696, 1611, 1512, 1440, 1371, 1236, 1181, 1013, 874, 831, 735 cm^{-1}. Crystallised from EtOAc/hexane. **2**: ^{1}H-NMR δ (DMSO-d_6) 9.09 (s, 2 H), 7.03 (s, 2 H), 6.95 (d, *J* 8, 2 H), 6.66 (d, *J* 8, 2 H), 2.50 (t, *J* 6, 4 H), 2.23 (t, *J* 6, 4 H), 2.07 (s, 6 H). IR ν (KBr): 3287, 1680, 1609, 1512, 1412, 1366, 1258, 1127, 891, 819, 762, 731 cm^{-1}. Crystallised from MeCN.

2. X-Ray crystallography

X-Ray data for both compounds were collected at 100 K using a KUMA CCD detector[9] and graphite-monochromated Mo K_α radiation. The structures were solved by direct methods using SHELXS[10] and refined using SHELXL[11] program. All atoms were included in the refinement with anisotropic (non H atoms) and isotropic (H atoms) displacement parameters. Table 1 gives the pertinent crystallographic data for bisphenols **1** and **2**. CCDC reference numbers 211016–211017. See http://www.rsc.org/suppdata/ce/b3/b312085f/ for crystallographic data in CIF or other electronic form.

Results and discussion

Fig. 1a is a superposition of the two symmetry independent molecules in the crystal structure of keto-bisphenol **1**. The two molecules superpose quite well except for the conformations of one of the phenyl rings and the two hydroxyl groups. The environments around the two molecules in the crystal structure are totally different as would be expected for symmetry independent molecules. Fig. 2 shows that the crystal structure of **1** may be considered as a self host–guest complex, and that it closely resembles channel type structures. The host molecules (blue) form a square network with strong O–H···O (1.86 Å, 174°) and weak C–H···O (2.58 Å, 157°) and C–H···π (2.69 Å, 146°, to ring centroid) hydrogen bonds. The guest molecules (red) are arranged in columns, perpendicular to the plane of the figure and assembled with O–H···O (1.81 Å, 177°) and C–H···π (2.84 Å, 153°) hydrogen bonds. A number of hydrogen bonds link host and guest molecules (O–H···O, 1.96 Å, 170°, 1.90 Å, 175°; C–H···O, 2.73 Å, 139°, 2.65 Å, 127°, 2.79 Å, 175°) but

Table 1 Crystallographic data for **1** and **2**

Compound	**1**	**2**
Empirical formula	$C_{18}H_{18}O_3$	$C_{20}H_{22}O_3$
Formula wt.	282.32	310.38
Melting point/K	508	480
Crystal system	monoclinic	monoclinic
Space group	*Cc*	$P2_1/n$
T/K	100(1)	100(1)
a/Å	14.391(3)	10.004(2)
b/Å	20.228(4)	15.783(3)
c/Å	9.782(2)	20.253(4)
β/°	91.96(3)	94.79(3)
Z	8	8
V/Å^3	2845.9(10)	3186.7(11)
λ/Å	0.71073	0.71073
D_{calc}/g cm^{-3}	1.318	1.294
F [000]	1200	1328
μ/mm^{-1}	0.089	0.086
2*θ*/°	3.34–27.49	2.10–27.48
Index ranges	$-18 \leqslant h \leqslant 12$	$-12 \leqslant h \leqslant 9$
	$-26 \leqslant k \leqslant 26$	$-19 \leqslant k \leqslant 20$
	$-12 \leqslant l \leqslant 12$	$-23 \leqslant l \leqslant 26$
Reflections collected	12728	29031
Unique reflections	4288	7270
Observed reflections	4029	5516
R_{int}	0.050	0.056
R_1 [$F_0 > 4\sigma(F_0)$]	0.0373	0.0697
wR_2	0.0800	0.1263

there is no guest···guest connection between columns. So while the number and types of hydrogen bridges of the host···host, guest···guest and host···guest types are comparable, there is an obvious topological difference between the two symmetry independent molecules.

The term 'self host–guest' needs some explanation. Generally, it is assumed that the host and guest in a host–guest compound are different chemical species (at a molecular level). Here the difference between 'host' and 'guest' is at a conformational and supramolecular level. The 'host' forms its own network that girdles the 'guest' molecules, and so the descriptor 'self host–guest' is used. In a sense, what is being conveyed is that the solid does not have Kitaigorodskii type close packing wherein a molecule is surrounded by twelve supramolecularly identical molecules. By definition, symmetry independent molecules must have a different supramolecular networking. In cases of self host–guest complexation, the network associated with one of the symmetry independent molecules encircles in some way the other molecule. Whether or not these network definitions are in themselves subjective is quite another issue but this is a more general question. For the present it suffices to state that the visualization of structure **1** as a self host–guest complex is as appropriate as the concept itself, but the idea needs more discussion and analysis. However, early examples were identified in the work of Herbstein and Marsh on trimesic acid hydrate[12] and of Bishop, Dance and co-workers on oxabicyclononane.[13] Other examples of self-inclusion are known[14] including a structure from the group of Weber wherein the host and guest are symmetry independent molecules.[15] The term 'pseudo host–guest' has been used by some of these authors but we prefer the terms 'self host–guest' or 'self inclusion'.

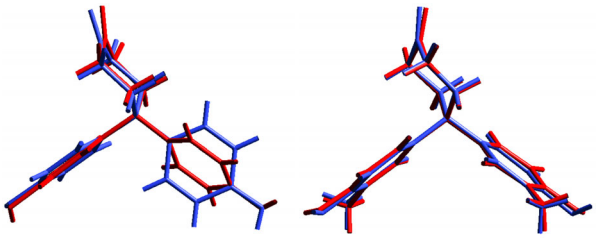


Fig. 1 Overlay diagram of the two symmetry independent molecules in the crystal structures of keto-bisphenols, (a) **1** and (b) **2**.

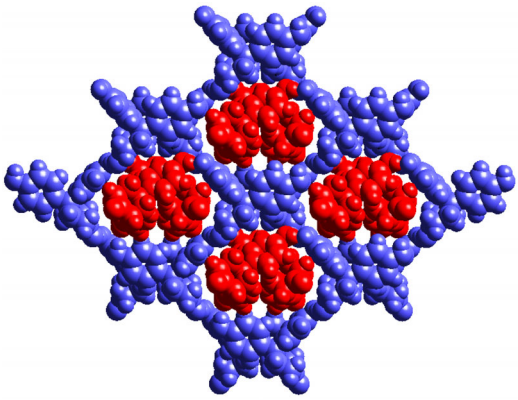


Fig. 2 Self host–guest complex. Symmetry independent molecules of keto-bisphenol **1** form host (blue) and guest (red) arrays in the crystal. Click here to access a 3D view of Fig. 2.

In the dimethyl derivative, **2**, the carbon skeletons of the two symmetry independent molecules are virtually superimposable (Fig. 1b). The only difference between the two molecules lies in the conformations of the two hydroxyl groups. However, there are deep-seated differences at the crystal packing level. Each of the two symmetry independent molecules forms its own two-dimensional hydrogen bonded network. These are shown in Fig. 3. The first is a square network (Fig. 3a) made up with quartets of molecules held together by O–H···O hydrogen bonds (to hydroxyl oxygen, 1.92 Å, 175°; to carbonyl oxygen, 1.95 Å, 160°) and miscellaneous C–H···O hydrogen bonds (2.61–2.71 Å, 120–130°). This square network is quite different from the square network formed by molecule **1**. In the second network (Fig. 3b), the hydrogen bonded (O–H···O, 1.83 Å,

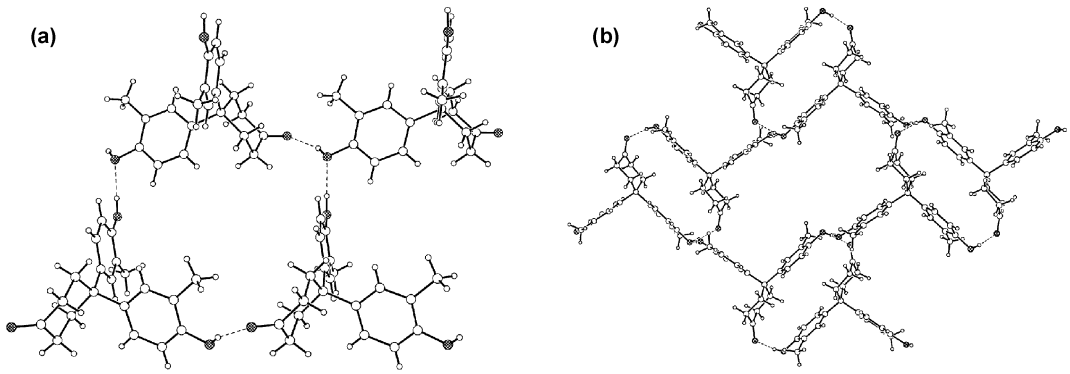


Fig. 3 Two distinct hydrogen bonded networks in the crystal structure of keto-bisphenol **2**, (a) square net, (b) parquet floor.

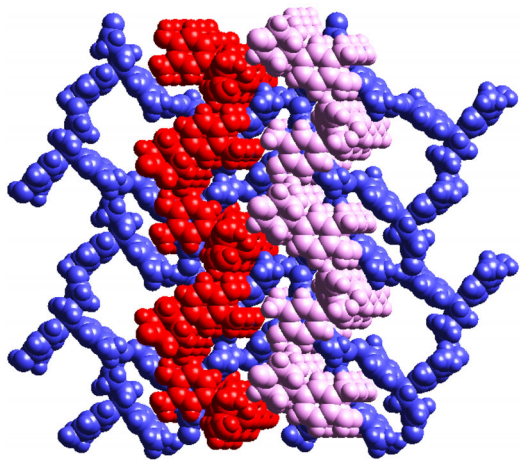


Fig. 4 Interpenetration of distinct networks in the crystal structure of **2**. The parquet floor network in Fig. 3 is coloured blue and the square net is coloured red. The pink network is related to the red network by a centre of inversion. Click here to access a 3D view of Fig. 4.

170°, 1.89 Å, 175°) molecules are arranged with a parquet floor shape (if not topology) with unequal tile sizes.[13,16] There are no notable hydrogen bonds between the two networks and close packing is achieved by an inclined interpenetration of the networks at an angle of 68° as shown in Fig. 4. Interpenetration of non-identical networks is a novel feature even for coordination polymers,[17] wherein interpenetration is more common. We believe that this is the first report of this phenomenon in an all-organic system.

That different conformations of the molecular skeletons and OH-group orientations of the independent molecules in **1** and **2** lead to quite different hydrogen bond motifs may be concluded from the summary presented in Table 2.

Cambridge structural database search

A CSD search (Version 5.24, July 2003) was carried out to determine the frequency of symmetry independent molecules of interest. The search first identifies error-free phenyl ring containing structures that have at least one methyl substituent at the ring, and with $Z' \geqslant 2$. The search was limited to organic, non-ionic and non-polymeric structures with $R < 0.10$. Disordered and empty (no co-ordinates) entries were excluded. In total, 575 entries were found. Individual searches were then performed for each of the corresponding *nor*-structures wherein the methyl group(s) is replaced by an H-atom, and further with the condition that $Z' \geqslant 2$. The number of such searches is necessarily greater than 575 because some of the compounds contain multiple methyl groups in different locations. Only 14 hits were obtained, and the 14 pairs of compounds were considered. Five pairs, wherein either of the compounds is pseudosymmetric, were discarded. The remaining nine structural pairs were analysed in detail (Me-compound, H-compound; GOJROM, MNBZAC01; YUYLAF, CLPHOL02; AFOLUC, PHBORA; NUCBUI, NUCBOC; PADTOD, PADVAR; VILPEL, UHENUQ; CRESOL02, PHENOL03; MCRSOL, PHENOL03; OCRSOL, PHENOL03). Considering that among them are three cresol/phenol pairs that are nearly equivalent, we may conclude that it is indeed rare that a pair of compounds that differ by a single methyl group should *both* have symmetry independent molecules in the asymmetric unit. These nine molecules (in either set) show no obvious similarities and this merely reaffirms that it will be difficult to predict if a crystal structure will have $Z' > 1$ on the basis of molecular structure alone.

Conclusions

There are two common situations where multiple molecules are found in the asymmetric unit. In pseudosymmetric structures, the presence of symmetry independent molecules is more or less a technical necessity. In cases like the two structures described here, however, the symmetry independent molecules fulfill entirely different roles in the crystal packing and their occurrence must follow from a more fundamental packing requirement. In this case, the requirement is that an open hydrogen bonded network is formed and that it needs to close pack. Such packing is not possible with symmetry related networks and so a second symmetry independent molecule is utilised. What is noteworthy is that while the crystal structures of keto-bisphenols **1** and **2** illustrate known solutions to the close packing problem for networks, namely host–guest complex formation and interpenetration, the crystal structures that are obtained in the process are quite unusual because of the presence of two symmetry independent molecules in the crystal.

The occurrence of multiple molecules in the asymmetric unit has been analysed only sporadically.[18] A recent review by Steed[19] is a brave attempt to bring some order into what many crystal chemists have dismissed as a crystallographic oddity. Rigorously, it is very difficult to explain why this phenomenon is even resorted to. As stated above, it is impossible today to predict from the molecular structural formula of a compound if the crystal structure will contain multiple molecules in the asymmetric unit. Crystal engineering or prediction (CSP) of such a structure is therefore only a matter for dreams. It is easy to say that if a molecule has some conformational flexibility, two different conformations may occur in the crystal. But most flexible molecules crystallize with only one molecule in the asymmetric unit. The phenomenon is uncommon and as mentioned above we regard it as most unusual that two closely related molecules like **1** and **2** both adopt $Z' = 2$ crystal structures. $Z' > 1$ structures are adopted because there may be some difficulty in close packing if $Z' = 1$ and the molecule lies on a general position. What exactly is the difficulty with bisphenols **1** and **2**? Are they too rigid? Are they not rigid enough? These questions have concerned us throughout this

Table 2 Hydrogen bonding between symmetry-independent molecules (blue and red)[a] in structures of keto-bisphenols **1** and **2**

	Functional group	Blue molecule	Red molecule
1		*Host*	*Guest*
	axial OH	donate to C=O (blue), accept from eq. OH (red)	donate to C=O (red), accept from eq. OH (blue)
	equatorial OH	donate to ax. OH (red), accept C–H···O from blue	donate to ax. OH (blue)
	carbonyl group	accept from ax. OH (blue)	accept from ax. OH (red)
2		*Parquet*	*Square*
	axial OH	donate to eq. OH (blue)	donate to C=O (red), accept from eq. OH (red)
	equatorial OH	donate to C=O (blue), accept from ax. OH (blue)	donate to ax. OH (red)
	carbonyl group	accept from eq. OH (blue)	accept from ax. OH (red), accept C–H···O from red

[a]The colour coding shows the extent of interdependence of the symmetry independent molecules in the respective hydrogen bonding schemes.

study and we place them before the reader without further comment.

While the fundamental issues concerning this phenomenon may remain an enigma for some time to come, what is clear is that many interesting network topologies will be observed in this category, even in all-organic systems, as the number and variety of molecules examined for crystal engineering applications increases. In this sense, a closer study of $Z' > 1$ structures is bound to be worthwhile.

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