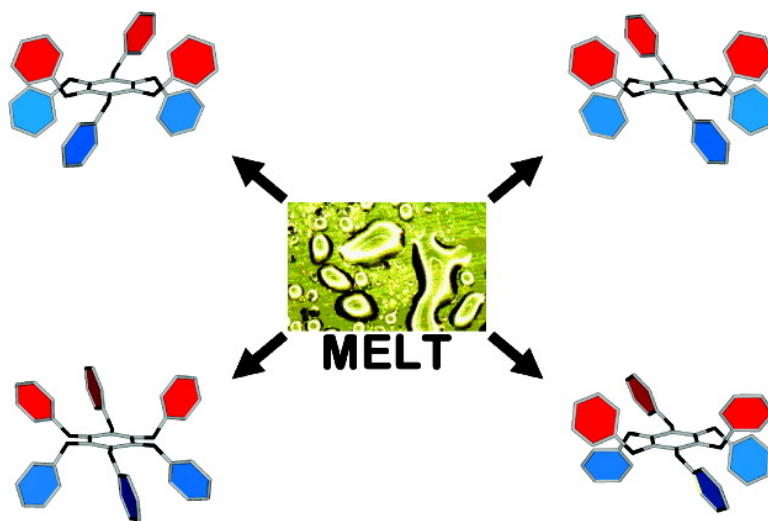


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Polymorphism of a Hexa-host: Isolation of Four Different Single-Crystal Phases by Melt Crystallization

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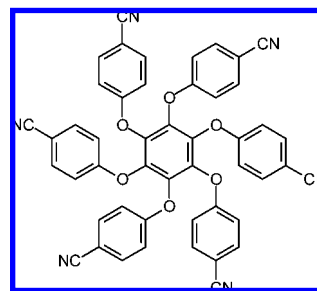
According to its most accepted definition, polymorphism occurs when a chemical substance possesses at least two different arrangements in the crystalline solid state.¹ This phenomenon can be troublesome in the pharmaceutical and specialty chemical industries—different polymorphic forms generally have different physical and chemical properties, thus adversely affecting the processing or formulation of the desired product.² It is therefore of critical importance to characterize all the polymorphs of a commercially viable chemical substance and to understand the conditions under which each is formed. In this regard, single-crystal diffraction (SCD) analysis can be viewed as the ultimate characterization tool, but it suffers from the often insurmountable challenges relating to the availability of suitable crystals. For this reason, it is not always possible to characterize a series of polymorphs by SCD methods. When only polycrystalline materials are available, X-ray powder diffraction (XRPD) is the most convenient method for the identification of polymorphs.³

In most of the documented cases, polymorphs have been crystallized as a result of leads from structure prediction,⁴ attempted cocrystallization,⁵ cross-nucleation,⁶ employing additives,⁷ *in situ* flash cooling,⁸ and various other methods.⁹ It is often difficult to prepare solvent-free single crystals of molecules that have a strong tendency to crystallize as solvates. In such cases, the solvent molecules provide extra stability through hydrogen bonding or packing effects,¹⁰ and desolvation under reduced pressure or by thermal treatment usually results in structural rearrangement with concomitant loss of single crystallinity.¹¹ In many cases, solvent-free single crystals can be obtained by judicious choice of the solvent of crystallization,¹² melt crystallization,¹³ or sublimation.¹⁴ Indeed, crystallization by controlled melting on a hot-stage microscope is used routinely to screen for polymorphs of pharmaceutical compounds.¹⁵

The structures and properties of host–guest complexes of hexa-substituted benzene derivatives (known as hexa-hosts) have been well studied.¹⁶ However, these compounds have not received any attention in the context of polymorphism. Here we report the preparation of four polymorphs of hexa-host **1** (Scheme 1) by melt crystallization (referred to here as **M1**–**M4**). To the best of our knowledge, this is the first report of the occurrence of more than two polymorphs of any normally solid compound obtained exclusively by melt crystallization as single crystals (we have obtained single-crystal X-ray structures of all four forms). We also describe both concomitant¹⁷ and conformational polymorphism¹⁸ exhibited by **1**, noting that two of the polymorphs (**M3** and **M4**) are derived from an amorphous phase by the introduction of thermal stress. We note that Yu et al. have reported a record nine polymorphs of the compound ROY, among which two polymorphs are obtained by melt crystallization.¹⁹

Compound **1** was synthesized using a slightly modified literature procedure.²⁰ As anticipated, all attempts at crystallization from various solvents yielded solvates; therefore, we could not grow

Scheme 1. Hexakis(4-cyanophenoxy)benzene (**1**)



apohost crystals (i.e., without inclusion of solvent) by solvent-mediated crystallization. Subsequent attempts at producing an unsolvated crystalline phase of **1** by sublimation also failed to yield crystals suitable for SCD studies; although the material was heated to its melting point (278–282 °C) under reduced pressure in a glass oven, no sublimation was apparent. Upon slow cooling to room temperature, part of the melt phase crystallized while the rest remained in a glassy state. Several crystals suitable for SCD studies were isolated, and two distinct crystal structures of compound **1** (**M1** and **M2**) were obtained. A separate batch of material yielded yet a third polymorph (**M3**) in addition to **M1** after rapid cooling caused by dipping the molten substance into hexane. Heating compound **1** to 300 °C results in the formation of an amorphous phase that does not crystallize upon cooling or reheating. However, crystallization was induced by the application of thermal stress resulting from insertion of the tip of a steel needle into the molten amorphous phase. All of the material immediately recrystallized as polymorph **M4**, which was characterized by SCD as well as XRPD analysis.

Polymorphs **M1**, **M2**, and **M4** crystallize in the monoclinic system with $Z' = 1, 0.5,$ and $1,$ respectively, while **M3** crystallizes in the orthorhombic system with $Z' = 0.5$. Since **M1** and **M2** were obtained concurrently from the same batch of molten material and under similar conditions, they can be considered to be concomitant polymorphs.¹⁷ Owing to the different conformations of **1** in the crystal structures of **M1**–**M4**, these forms can also be termed “conformational polymorphs”.¹⁸

In general, hexa-host molecules assume a conformation in which the substituent groups alternate in positions above and below the plane of the central benzene ring (i.e., *ababab*).²¹ However, alternative conformations have been observed for some thioether derivatives²² and are also present in the crystal structures of **M1** and **M4**. The conformation of **1** is exclusively *ababab* in both **M2** and **M3**, whereas it is exclusively *aaabbb* in **M4**. Both *ababab* and *aaabbb* conformations are present in **M1**. An analysis of the crystal packing in all four polymorphs reveals that the molecules are held together by weak C–H···N hydrogen bonds.

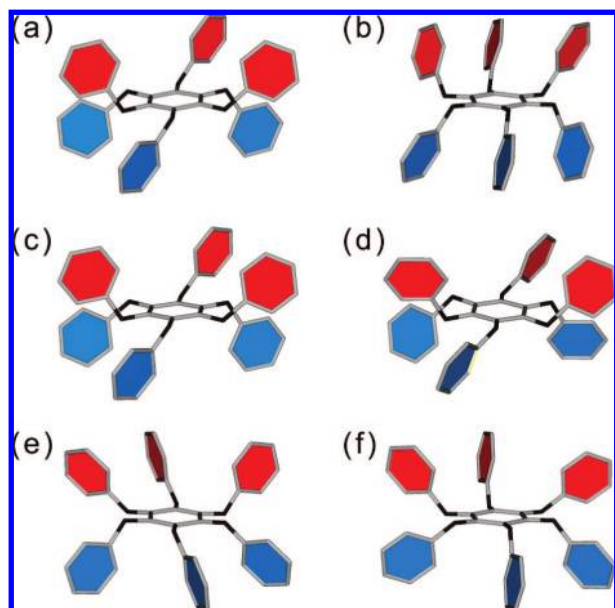


Figure 1. Conformation of **1** in (a,b) **M1**, (c) **M2**, (d) **M3**, and (e,f) **M4**. Hydrogen atoms and nitrile groups are omitted for clarity. Colors: C, gray; O, black; aromatic rings extending above the central ring, red; aromatic rings extending below the central ring, blue.

XRPD analysis reveals that desolvation of a range of solvates of **1** by heating to 200 °C yields polymorph **M1**. This phase was thus used as the starting material in a systematic study of the polymorphic nature of **1** by differential scanning calorimetry (DSC) and hot-stage microscopy. A DSC thermogram (Figure S8, Supporting Information (SI)) shows that **M1** undergoes an endothermic phase transition with $T_{on} = 252$ °C to form **M2**, followed by melting at $T_{on} = 270$ °C (T_{on} = onset temperature). Irreversible transition of **M1** to **M2** on a hot stage heated to 260 °C for 24 h was confirmed by XRPD (Figure S6), but a similar experiment with **M4** does not result in a phase transition. It was not possible to study **M3** by DSC because of the difficulty involved in obtaining the pure phase. However, it is interesting to note that, of the polymorphs **M1**, **M2**, and **M4**, **M4** has the highest melting point ($T_{on} = 275$ °C, Figure S9, SI) (implying highest thermodynamic stability) despite having the lowest density and not having the lowest value of Z' .²³ Generally, high Z' structures are thermodynamically less stable than low Z' structures.²⁴ Lattice energy calculations (Table S1, SI) also indicate higher stability of **M4**, most likely because this phase has the most extensive hydrogen-bonded network among the four phases studied (Table S2, SI).

In summary, we describe polymorphism of a hexa-host for the first time. Furthermore, compound **1** exhibits both concomitant and conformational polymorphism and yields an unprecedented set of four polymorphic forms by means of melt crystallization. Considering the current intense interest in the phenomenon of polymorphism, together with its importance to the field of crystal chemistry, it is remarkable that the formation of only two polymorphs by melt crystallization has been reported to date. All four of the polymorphs described here can apparently only be obtained as single crystals from the melt phase, and these preparations are reproducible. The

crystal structures have been elucidated by SCD methods, and polymorphic phase transitions have been studied by DSC and XRPD analysis. Form **M1** converts irreversibly to form **M2** at 252 °C, and the formation of polymorphs **M3** and **M4** can be triggered by the introduction of thermal stress to the molten state. Further study aimed at rationalizing the thermodynamic stability of all four polymorphs of **1** is in progress.

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Supporting Information Available: Crystallographic data (CIF) for **M1**, **M2**, **M3**, and **M4**, packing diagrams, hydrogen bond tables, hot-stage micrographs, DSC thermograms, XRPD patterns, and database search results. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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