# Concomitant polymorphs of 2,2′,6,6′-tetramethyl-4,4′-terphenyldiol: the β-quinol network reproduced in a metastable polymorph†

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**The striking resemblance of the rhombohedral and monoclinic forms of the title molecule to β- and γ-quinol provides a crystal engineering approach to new polymorphic systems.**

H. M. Powell[1] reported the crystal structure of hydroquinone (1,4-benzenediol, quinol in the older literature) and its polymorphs and clathrates in the 1940s and 50s. α-Hydroquinone is the stable form (*R*-3, $a_h$ = 38.46, $c$ = 5.65 Å) with 54 molecules in the triple primitive hexagonal unit cell. The metastable γ modification crystallizes in the monoclinic system $P2_1/c$ ($a$ = 8.07, $b$ = 5.20, $c$ = 13.20 Å, $\beta$ = 107.0°). β-Hydroquinone clathrates are the most well studied forms because of the resemblance of the rhombohedral host lattice to β-polonium and its ability to include small and large guest molecules (Ne, HF, $H_2S$, MeOH, $C_{60}$)[2] in the doubly interpenetrated cubic cage (*R*-3, $a_h$ = 16.61, $c$ = 5.47 Å, no guest). A dense δ form is obtained at high pressure.[3] The structural chemistry of hydroquinone is the genesis of clathrate, host–guest and lattice inclusion compounds in modern-day supramolecular chemistry.[4] *It is therefore surprising that the fascinating rhombohedral structure of β-hydroquinone has not been reproduced in another diphenolic compound for over half a century.* We report a fourfold interpenetrated rhombohedral structure of 2,2′,6,6′-tetramethyl-4,4′-terphenyldiol (**1**)† as well as a monoclinic modification, referred to as forms **1a** and **1b**. These structures are strikingly similar to β- and γ-hydroquinone. Our "phenylogous series" crystal engineering approach for developing a new polymorphic system is novel in the extensive literature on polymorphism.[5,6]

Crystallization of **1** from EtOAc/ether afforded wine-red colored hexagonal-shaped single crystals. The X-ray structure of form **1a** ($R\bar{3}$ space group in the hexagonal setting)‡ shows a chair cyclohexane ring of O–H···O hydrogen bonds (1.79 Å, 163.0°; neutron-normalized geometry) with the terphenyl groups oriented axially. The inversion-related phenol group is part of an identical O–H···O hexamer having length of 2.75 Å on each side. Each oxygen atom behaves as a three-connected 3D node which builds up to produce the $6.10^2$ network of β-quinol.[7] The rhombohedral cage structure of **1a** (Fig. 1), constructed by joining the centers of O–H···O hexamers, is about twice as long compared to β-hydroquinone (10.13 *vs.* 17.96 Å). The fourfold interpenetrated dense network of **1a** (packing fraction 71.7%) eschews guest inclusion in contrast to the doubly interlocked β-hydroquinone inclusion clathrates.

Crystallization of **1** from EtOAc gave needle-shaped crystals of form **1b** (monoclinic $P2_1/c$).‡ Screw-axis related molecules form an infinite chain of O–H···O hydrogen bonds (1.84 Å, 153.5°; Fig. 2), similar to the structure of γ-hydroquinone. The ring and chain polymorphs of **1** have different topologies[8] mediated *via* phenol O–H···O hydrogen bonds. Photomicrographs in Fig. 3 show that the hexagonal and needle-shaped crystals, **1a** and **1b**, can be grown from EtOAc/ether and EtOAc without any morph contamination.

Crystallization of **1** from MeOH afforded crystals of both hexagonal and needle morphology that correspond to the unit cell of the rhombohedral and monoclinic forms. Mechanical grinding[9] with a drop of MeOH or *n*-PrOH added also afforded both modifications in the same batch. The exact amount of these forms varies in different experiments but hexagonal crystals far outnumbered needle-shaped ones. Thus, concomitant polymorphs **1a** and **1b** can be isolated from the same flask by employing appropriate crystallization solvents or the solvent-drop grinding method.[9] Since the central phenyl ring adopts different conformations in these structures,† the dimorphic cluster of **1** is classified as concomitant, conformational polymorphs.[6] These observations suggest that crystal lattice energies must be comparable (form **1a** −45.16 kcal mol$^{-1}$, form **1b** −46.57 kcal mol$^{-1}$, per molecule of **1**).§ However, crystal density of the metastable form **1a** is higher than that of **1b** (1.261 vs. 1.231 g/cm$^3$)[10] but packing fraction of **1b** (72.1%) is higher. That the kinetic polymorph **1a** is the dominant form in the grinding experiment is judged from powder X-ray diffraction (PXRD).†

Melting point determination (Fisher–Johns) shows that both forms melt at 257–259 °C. $T_{onset}$ of the melting endotherm in differential scanning calorimetry (DSC) is also very close: **1a** 257.62 °C, **1b** 257.74 °C (Fig. 4). Closer inspection of phase **1a** (see insert) reveals a micro-endotherm at 251 °C just before the onset of melting, whereas the DSC profile of **1b** shows melting only. This difference in thermal behavior[11] could mean that the metastable polymorph **1a** transforms to the thermodynamic form **1b** before melting (enantiotropic situation).[5,12] The dimorphic cluster **1** follows Ostwald's Rule of Stages:[13] the metsatable form is isolated first which then transforms to the stable modification upon heating. That the micro-endotherm in form **1a** is a phase transition was confirmed by heat–cool–heat cycle in DSC. The metastable form **1a** was heated to 251 °C (just beyond the micro-endo peak) and cooled to room temperature; reheating to 300 °C now shows only the major melting endotherm at 257–258 °C for the stable phase **1b**. We did not observe any phase transition in crystallization batches from MeOH/PrOH on the laboratory time scale of hours to days.

† Electronic supplementary information (ESI) available: Synthesis of **1** and **2**, conformation overlay diagram, and PXRD pattern of polymorphs. See http://www.rsc.org/suppdata/cc/b5/b500665a/

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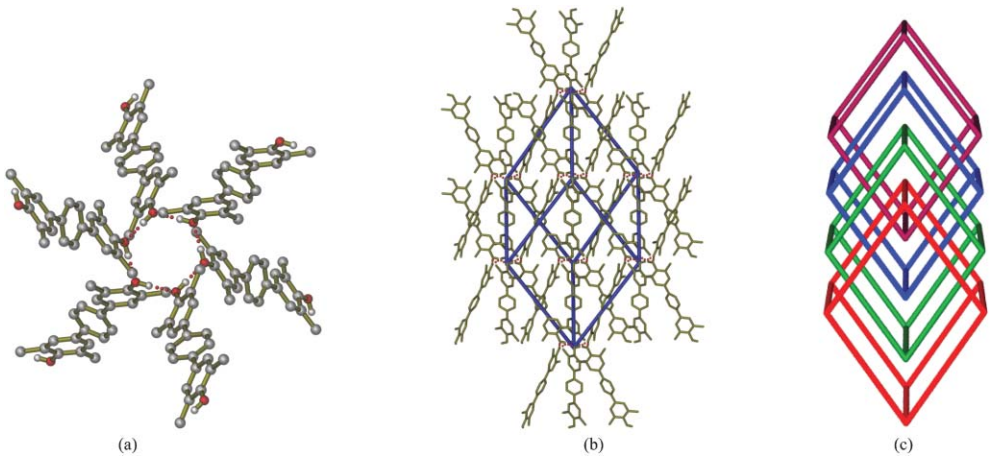


**Fig. 1** (a) Chair cyclohexane ring of O–H···O hydrogen bonds in polymorph **1a**. (b) Hydrogen bonding of the axially oriented terphenyl groups to six different O–H···O hexamers forms the super cube of the rhombohedral β-quinol network (blue lines). H atoms are omitted except OH groups. (c) Fourfold interpenetrated network of the cubic lattice in **1a**.

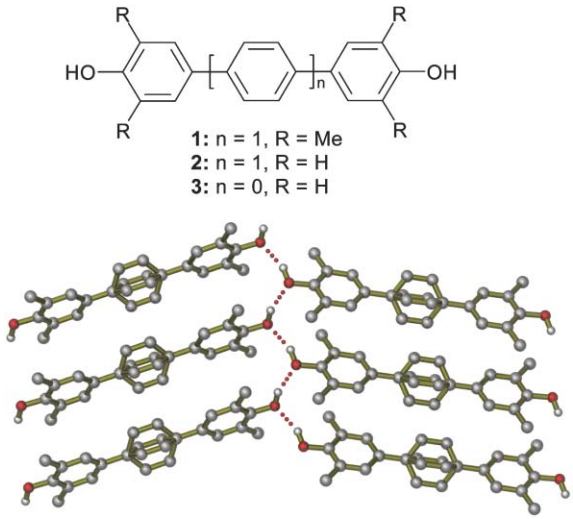


**Fig. 2** Infinite chain of O–H···O hydrogen bonds along [010] in polymorph **1b**. The middle phenyl ring is disordered over two orientations (s.o.f. 0.69, 0.31). H atoms are omitted except OH groups.

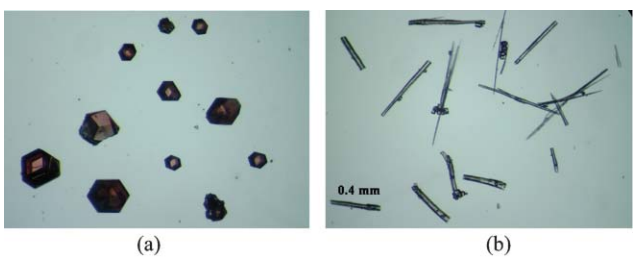


**Fig. 3** Hexagonal crystals of the rhombohedral form **1a** (a) and needle-shaped crystals of the monoclinic form **1b** (b), grown from different solvents.

Why is the hydrogen-bonded hexamer **1a** formed faster than the infinite chain **1b**? We surmise that clusters of 5–6 hydrogen-bonded molecules are dominant in solution because this is the taper-off limit for cooperative stabilization in O–H···O chains.[14] The formation of cyclohexane ring polymorph **1a** through

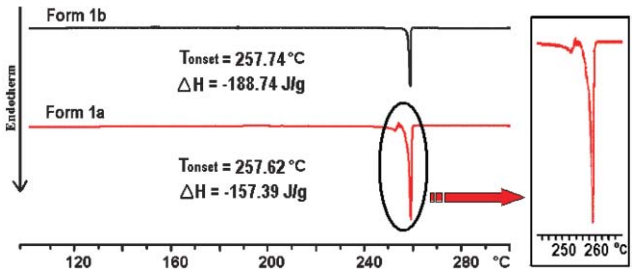


**Fig. 4** DSC thermogram to show the phase transition of **1a** (see insert) prior to the melting endotherm. Form **1b** is stable. Note the absolutely flat background in DSC runs.

intramolecular H-bonding is kinetically favored due to entropic factors. The infinite O–H···O chain of form **1b** is thermodynamically stable because of extended σ-bond cooperativity. Our model is consistent with the observation that solvent-drop grinding with MeOH/*n*-PrOH type solvents affords both forms concomitantly. Both types of crystal nuclei form extended clusters with these hydrogen bond donor–acceptor solvents, and then loose the solvent as the nucleus grows to give form **1a** and **1b** simultaneously. On the other hand, EtOAc and ether are hydrogen bond terminating type solvents and so substrate O–H···O hydrogen bond synthons are able to discriminate in the outcome of crystallization, giving either form **1a** or form **1b**.

Crystal engineering[15] is about structural control and modular self-assembly. Polymorphism is its antithesis, wherein hydrogen bonding and packing motifs cannot be easily predicted. We have designed a new polymorphic system from hydroquinone using the idea of structural insulation through phenyl spacer units. Hydroquinone led us to think of 4,4′-terphenyldiol **2** so that the inversion center would reside on the central phenyl ring and the hydrogen bonding groups will extend out. Crystallization of **2** from DMSO afforded a solvated form (**2**.dmso,‡ Fig. 5), suggesting that the phenol OH groups should be made less accessible to the solvent. The addition of *ortho*-methyl groups resulted in the title molecule **1** which exhibits polymorphism and network structures akin to hydroquinone. We have therefore

 

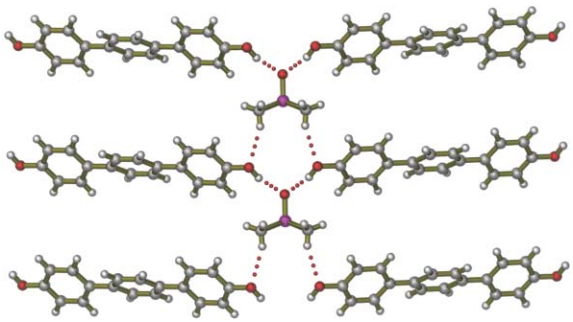

**Fig. 5** O–H···$O_{dmso}$ hydrogen bonding in linear chains of molecular complex **2.**dmso and C–H···O interactions between the chains (O–H···O: 1.80 Å, 163.8°; C–H···O: 2.28 Å, 158.7°).

reproduced the fascinating rhombohedral network of β-quinol after more than five decades by deliberate design, and not just as a chance observation. Several crystallizations of 4,4′-biphenyldiol **3** afforded the reported monoclinic cell[16] of the close-packed γ-hydroquinone type structure. We are searching for an open framework structure of **3**, or its tetramethyl derivative, to complete this phenylogous series of polymorphic structures.¶ Supramolecular homology is not common in crystal engineering, and only two well documented examples are known: benzene, biphenyl, *p*-terphenyl; and phenylogous-diol–diamine complexes.[17] We now show that even the less predictable polymorphic systems are amenable to a degree of structural control. This result has wider implications because the search for polymorphs and a better control over new solid forms is a major challenge in pharmaceutical formulations[18] and nonlinear optical materials.[19]

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## Notes and references

‡ X-ray data for **1a** and **1b** were collected on Bruker SMART APEX CCD area detector and for **2.dmso** on Nonius Kappa CCD detector with graphite-monochromated Mo–Kα radiation. Crystal data. **Form 1a**. $C_{22}H_{22}O_2$, $M$ = 318.40, hexagonal, space group $R\bar{3}$, $a = b$ = 20.8580(12), $c$ = 10.0116(12) Å, $V$ = 3772.1(5) Å$^3$, $Z$ = 9, $D_c$ = 1.261 g cm$^{-3}$, $T$ = 100 K, F(000) = 1530, $\lambda$ = 0.71073 Å, $\mu$ = 0.079 mm$^{-1}$, $R1$ = 0.0392 for 1514 $Fo > 2\sigma(Fo)$. **Form 1b**. $C_{22}H_{22}O_2$, $M$ = 318.40, monoclinic, space group $P2_1/c$, $a$ = 9.553(2), $b$ = 4.5252(11), $c$ = 20.210(5) Å, $\beta$ = 100.555(3), $V$ = 858.9(4) Å$^3$, $Z$ = 2, $D_c$ = 1.231 g cm$^{-3}$, $T$ = 100 K, F(000) = 340, $\lambda$ = 0.71073 Å, $\mu$ = 0.077 mm$^{-1}$, $R1$ = 0.0632 for 1393 $Fo > 2\sigma(Fo)$. **2.dmso**. $C_{20}H_{20}O_3S$, $M$ = 340.42, orthorhombic, space group *Pnma*, $a$ = 7.1305(14), $b$ = 34.505(7), $c$ = 6.8846(14) Å, $V$ = 1693.9(6) Å$^3$, $Z$ = 4, $D_c$ = 1.335 g cm$^{-3}$, $T$ = 100 K, F(000) = 720, $\lambda$ = 0.71073 Å, $\mu$ = 0.206 mm$^{-1}$, $R1$ = 0.0577 for 1883 $Fo > 2\sigma(Fo)$. Crystal structures were solved by direct methods using SHELXS-97 and refined by full-matrix least-squares refinement on $F^2$ with anisotropic displacement parameters for non-H atoms using SHELXL-97. All H atoms in **2.**dmso and hydroxy H atoms in **1a** and **1b** are refined isotropically. All other non-hydroxy H atoms in **1a** and **1b** were placed in calculated positions. CCDC 261093–261095. See http://www.rsc.org/suppdata/cc/b5/b500665a/ for crystallographic data in CIF or other electronic format.

§ Computed in Cerius$^2$, Compass force field. www.accelrys.com.

¶ The Cambridge Structural Database (http://www.ccdc.cam.ac.uk) has only one phenylogous pair of PhOH polymorphs, phenol (PHENOL) and biphenylol (BOPSAA). These structures have infinite O–H···O chains as the common motif. They are not a case of polymorph engineering.

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