Seeking structural repetitivity in systems with interaction interference: crystal engineering in the *gem*-alkynol family

N. N. Laxmi Madhavi,[a] Clair Bilton,[b] Judith A. K. Howard,*[b] Frank H. Allen,[c] Ashwini Nangia[a] and Gautam R. Desiraju*[a]

[a] *School of Chemistry, University of Hyderabad, Hyderabad 500 046, India. E-mail: grdch@uohyd.ernet.in*
[b] *Department of Chemistry, University of Durham, South Road, Durham, UK DH1 3LE*
[c] *Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, UK CB2 1EZ*

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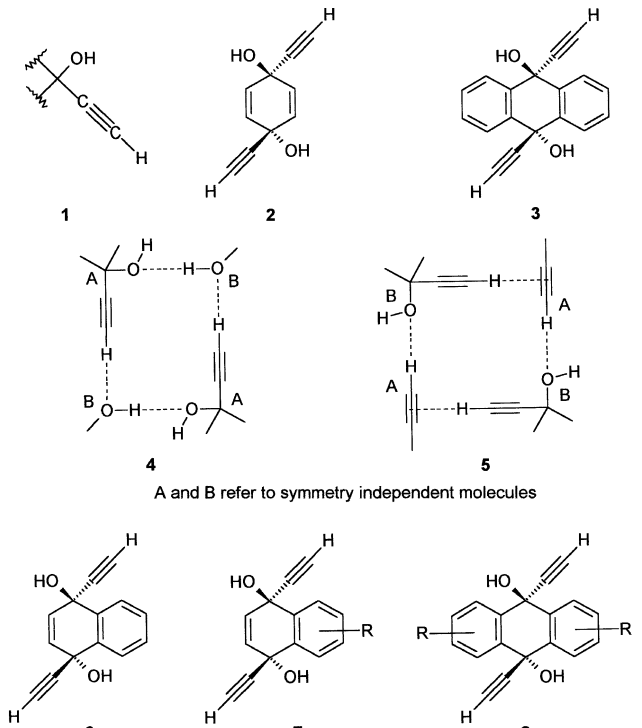
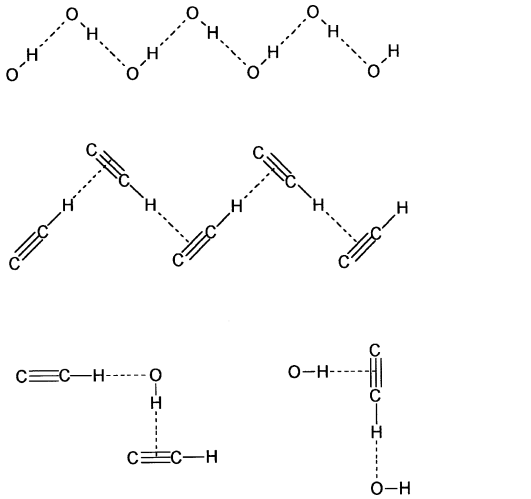
Synthon repetitivity has been demonstrated in a pair of *gem*-alkynols, despite the high degree of interaction interference typical of this family of compounds.

Crystal engineering methodologies attempt to identify common patterns in a series of crystal structures, so as to understand them in terms of mutual interplay between particular intermolecular interactions.[1,2] Since interactions arise from molecular functionalities, one of the important aims of crystal engineering is, in effect, to establish correspondences between molecular and crystal structures.[3] This aim, however, is challenged by a group of 90 or so compounds with a geminal ethynyl hydroxy moiety, **1**. The 94 published structures† in this category exhibit a bewildering variety of intermolecular interaction patterns.[1,4,5] Analysis of these structures showed 16 O–H···O, 28 C–H···O, 6 O–H···π and 14 C–H···π contacts in the normal ranges for these interactions‡ [Cambridge Structural Database (CSD), Version 5.16, October 1998, 190 307 entries][6] and where all donor and acceptor atoms originate exclusively from moiety **1**. The diversity of the more extended patterns formed with these interactions is shown in Scheme 1 by the synthons that occur more or less frequently in this group.



These 94 *gem*-alkynols are a diverse group, though the majority of them (61) are steroids with moiety **1** at the C17 position.§ The list also contains other disparate compounds, such as 4 phenyl-rich molecules and 6 molecular complexes, that have been investigated with considerations other than crystal engineering in mind. The lack of structural repetitivity among these compounds may arise from the close juxtaposition of two hydrogen bond donors and two acceptors. In this sterically hindered situation, and also with their incorporation into cooperative networks, the four possible interactions, O–H···O, C–H···O, O–H···π and C–H···π, become competitive.[1] The packing adopted by any particular compound then becomes extremely sensitive to other molecular features. In practice, the unusually high level of interaction interference generates several quite different networks (Scheme 1), so that it is not at all easy to establish the molecule–supermolecule correspondences[3] that are so important in crystal engineering. The problem, then, is quite simple—how does one predict that a particular *gem*-alkynol will form a particular hydrogen bond pattern?

Given that the molecular structures of the 94 CSD examples are diverse and sometimes complex, it was felt that the first step in the understanding of crystal packing of the *gem*-alkynols would be to simplify the kind of molecule being



Scheme 1 Some common supramolecular synthons in the crystal structures of *gem*-alkynols.

studied. About half of these CSD compounds (45) contain other functional groups that are capable of acting as strong hydrogen bond donors and acceptors, leading to an unnecessary and avoidable complication in a system as fragile as the present one. The fact that 72 of the crystal structures contain single enantiomers is a further complication in that centrosymmetrical packing patterns are precluded in these cases.¶ Accordingly, *trans*-1,4-diethynyl-1,4-dihydroxy-2,5-cyclohexadiene, **2**, was identified as a starting point in the crystal engineering exercise. The symmetry of the molecule virtually dictates a centrosymmetric packing, while the small size and the absence of functional groups other than the alkynol fragment was expected to result in further simplification, leading to a packing that could be rationalised and subsequently repeated in another derivative.

Alkynol **2** was prepared by the addition of excess TMS–C**3**C–Li to 1,4-benzoquinone, hydrolysis of the TMS group with methanolic KOH, and purification by column chromatography followed by recrystallisation from ethyl acetate.‖ Fig. 1 shows that the crystal packing is, as expected, simple.** Infinite cooperative O–H···O–H···O–H··· (*d* 2.12 Å, θ 163°) chains are formed along [010] while C–H···O (2.39 Å, 142°) and C–H···π (2.90 Å, 127°) hydrogen bonds are formed in the (100) plane. The long H···O distance may be noted. Though the structure is straightforward, it was hardly predictable. Fig. 1(*b*) shows that each of the C(sp^2)–H groups is important in the densely packed layer parallel to (100). The structure of alkynol **2** is therefore another example of heavy structural interference in this family. The various functional groups (hydroxy, ethynyl, alkenic) are intimately involved with one another and they also interact with the hydrocarbon residues. Disturbing any of these interactions will result in a total change in the structure, so that substitutional manipulation at any of the alkenic positions was not expected to preserve this structure type.

Attention shifted therefore to the *trans*-dibenzoalkynol **3**, prepared analogously from 9,10-anthraquinone‖ and whose crystal structure** is shown in Fig. 2. There are two symmetry independent half-molecules, each lying on a distinct inversion centre. The alkynol groups from these two sets of molecules result in the centrosymmetric cooperative synthons, **4** and **5**. Both these overlapping synthons involve both of the symmetry-independent molecules (A and B in the scheme), but while **4** is constituted with O–H···O (1.90 Å, 160°) and C–H···O (2.07 Å, 163°) hydrogen bonds, **5** is constituted with C–H···O (2.07 Å, 163°) and C–H···π (2.84 Å, 157°) bonds. The synthon arrangement is detailed in Fig. 2(*a*). There are several encouraging features here: (1) synthon **4** had previously been noted by us in the crystal structure of 2-ethynyladamantan-2-ol,[7] where it is also formed from portions of two symmetry-independent molecules and this is the first instance of structural repetitivity of a major synthon in this family between two compounds with widely different substituent groups; (2) synthons **4** and **5** lie within (1$\bar{1}$0) and form a sheet structure that consists exclusively of strong and weak

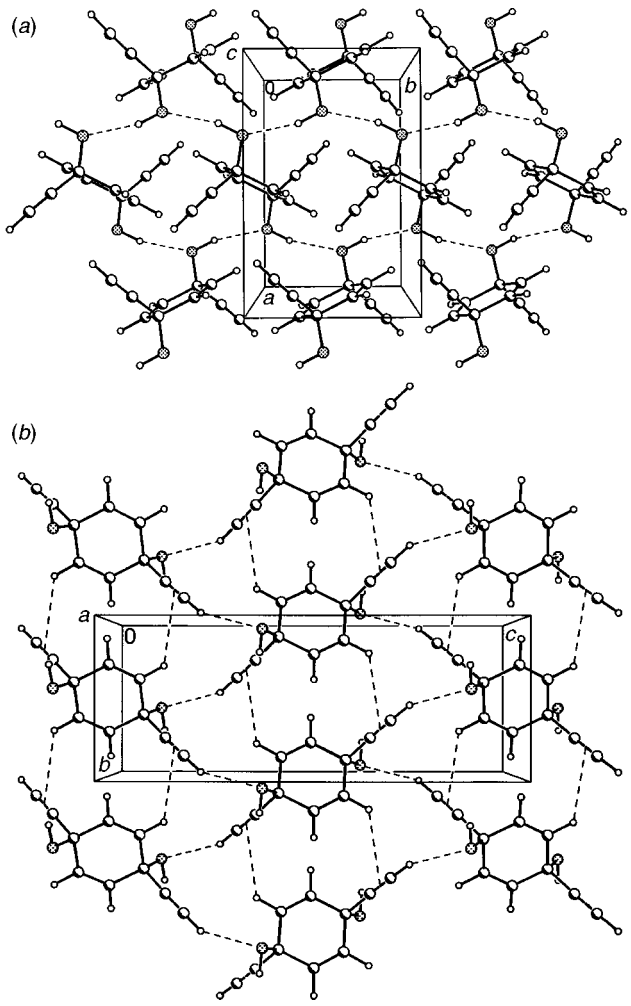


Fig. 1 (*a*) Crystal structure of alkynol 2. Note the infinite cooperative O–H···O–H··· chains formed between *b*-glide related molecules. (*b*) Densely packed layer structure parallel to (100) in the structure of 2. Notice the C–H···O and C–H···π hydrogen bonds. Replacement of any of the alkenic H atoms with a substituent is expected to change the structure.

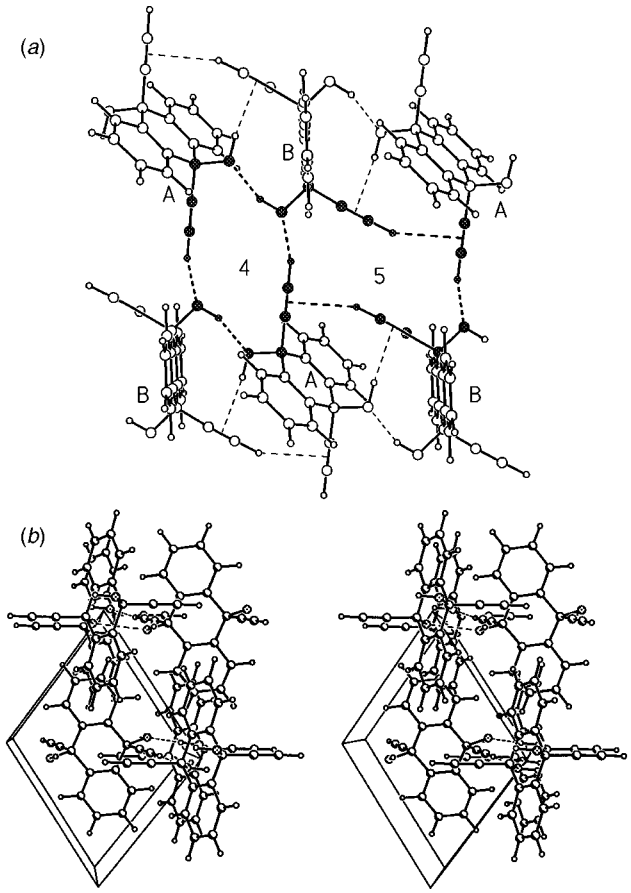


Fig. 2 (*a*) Crystal structure of alkynol 3 in (1$\bar{1}$0), showing the cyclic synthons 4 and 5. Notice the elaborate cooperative network of strong and weak hydrogen bonds. (*b*) Stereoview of the crystal structure of 3 down [001], showing the interdigitation of the anthryl residues. The view is perpendicular to that shown in (*a*).

hydrogen bonds; (3) the fused phenyl rings protrude from either side of the hydrogen bonded sheet and interdigitate with the corresponding rings in the adjacent sheets. This is shown in Fig. 2(*b*). The hydrogen bonded and close-packed domains here are structurally orthogonal, and clearly the interaction interference between the hydrogen bonding groups and the fused ring hydrocarbon portions of alkynol **3** is minimal.††

One may now extrapolate to the unsymmetrical *trans*-benzoalkynol, **6**, which was prepared similarly from 1,4-naphthoquinone‖ and the structure of which is shown in Fig. 3.** The extended hydrogen bonded sheet seen in **3** (with overlapping synthons **4** and **5**) is retained intact here. Because the molecule lacks a centre of symmetry, this is possible with two symmetry-independent molecules ($P2_1/c$, $Z = 8$) and with each molecule situated on a general position. The crystal structures of alkynols **3** and **6** are actually very closely related, with a minor difference in the disposition of the fused benzo rings. In **6**, the rings are situated on the same side of the hydrogen bonded sheets so that one finds aromatic–aromatic interdigitation alternating with sheet–sheet close-packing. In **3**, the molecules lie on inversion centres so that interdigitation occurs on both sides of the molecular plane. These alternative modes of interdigitation may be compared by examining Fig. 2(*b*) and 3(*b*).

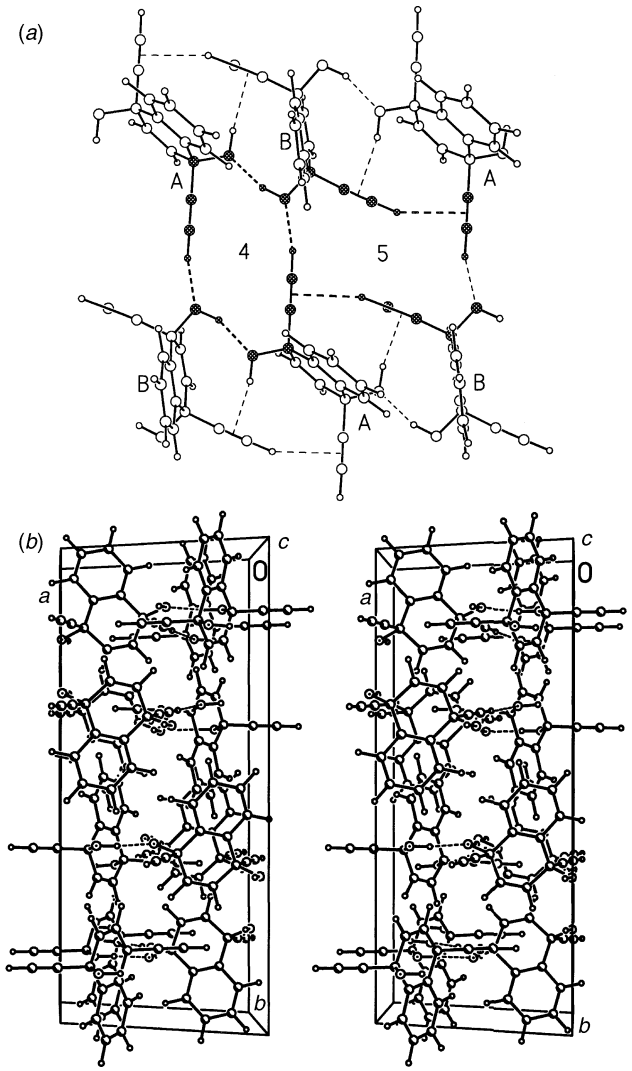


Fig. 3 (*a*) Crystal structure of alkynol 6. Notice the near identity to 3 in Fig. 2(*a*). (*b*) Interdigitation of naphthyl residues in the crystal structure of 6. Compare this with Fig. 2(*b*).

Nevertheless, the manner of interdigitation of benzo rings in **3** and **6** is very similar. In general, one may expect that the substituted benzo rings in compounds **7** and **8** (**R** = simple substituent groups) might also interdigitate in the same way. Accordingly, we predict that other members of this family are likely to adopt similar crystal structures, thereby leading to structural repetitivity.

It is noteworthy that a fairly abstruse hydrogen bonded network is repeated in alkynols **3** and **6**. Anticipation of the structure of **6** was possible because of the orthogonal and non-interfering arrangement of hydrogen bonding and phenyl-phenyl interactions in **3**. This situation is similar to the crystal structure of 4-aminophenol[3*a*] in which the OH···NH_2 and phenyl···phenyl interactions are insulated from each other and in contrast to the structures of 2- and 3-aminophenol,[3*b*] which show a high degree of interaction interference. Interaction orthogonality is of key importance in establishing the beginnings of structural repetitivity in systems where severe structural interference is likely.

Notes and references

† These structures were obtained from the CSD. Screens 57 (organic only), −55 (charged species removed), 153 (3D coordinates present) were applied; duplicate hits were removed manually.

‡ The d,θ ranges are 1.7–2.1, 140–180; 2.0–2.9, 110–180; 2.0–2.9, 110–180; and 2.5–3.1 Å, 110–180°, respectively. All O–H and C–H distances are neutron-normalised. That the number of these interactions (64) is less than the number of compounds (94) is because many of the molecules have hydrogen bonding donor and acceptor groups other than those in moiety **1**.

§ Some trivial packing similarities do exist in the steroid sub-category but these isostructuralities may be largely ascribed to the steroid skeleton itself with the role of the 17-substituents (hydroxy and ethynyl) being innocuous to supportive at best.

¶ Whether this is, or is not, advantageous from the viewpoint of crystal engineering is still polemical. However, the work of Kitaigorodskii[8] would tend to suggest that the anticipation of the crystal packing of a centrosymmetrical molecule is easier because a centre of symmetry would almost always be found in the crystal.

‖ Spectroscopic data. **2:** ^{1}H NMR δ 6.10 (s, 4H), 2.55 (s, 2H), 1.70 (br s, 2H); IR (cm^{-1}) 3468, 3267, 2924, 2102, 1413, 1367, 1221, 1086, 1041, 1003, 916, 787, 686; mp 179–180 °C (sublimes). **3:** ^{1}H NMR δ 8.10 (dd, *J* 8, 3 Hz, 4H), 7.41 (dd, *J* 8, 3 Hz, 4H), 2.90 (s, 2H), 2.80 (s, 2H); IR (cm^{-1}) 3516, 3408, 3273, 3207, 2110, 1483, 1446, 1381, 1329, 1244, 1020, 974, 916, 763, 736, 646; mp 206–207 °C. **6:** ^{1}H NMR δ 7.85 (d, *J* 8 Hz, 2H), 7.46 (d, *J* 8 Hz, 2H), 6.22 (s, 2H), 2.65 (s, 2H), 2.60 (s, 2H); IR (cm^{-1}) 3342, 3312, 3283, 3273, 3146, 3050, 2957, 2114, 1635, 1487, 1452, 1394, 1313, 1161, 1128, 989, 945, 763, 655; mp 134 °C.

** Crystal data. **2**: ($C_{10}H_8O_2$, $M = 160.16$). Orthorhombic, *Pbca*; $a = 8.8316(2)$, $b = 5.900\,30(10)$, $c = 15.6123(4)$ Å, $U = 813.54(3)$ Å^3, $Z = 4$, $D_c = 1.308$ g cm^{-3}, 934 unique reflections, 837 with $F^2 > 2\sigma(F^2)$. Final $R = 0.036$ (observed), 0.041 (all); $wR(F^2) = 0.088$ (observed), 0.095 (all). **3**: ($C_{18}H_{12}O_2$, $M = 260.28$). Triclinic, $P\bar{1}$; $a = 8.7684(18)$, $b = 8.9558(18)$, $c = 10.315(2)$ Å, $\alpha = 113.78(3)$, $\beta = 102.06(3)$, $\gamma = 102.59(3)°$, $U = 682.2(2)$ Å^3, $Z = 2$, $D_c = 1.267$ g cm^{-3}, 3623 unique reflections, 2404 with $F^2 > 2\sigma(F^2)$. Final $R = 0.054$ (observed), 0.097 (all); $wR(F^2) = 0.108$ (observed), 0.133 (all). **6**: ($C_{14}H_{10}O_2$, $M = 210.22$). Monoclinic, $P2_1/c$; $a = 10.8247(3)$, $b = 22.6384(8)$, $c = 10.4783(3)$ Å, $\beta = 118.1850(10)°$, $U = 2263.28(12)$ Å^3, $Z = 8$, $D_c = 1.234$ g cm^{-3}, 6159 unique reflections, 3713 with $F^2 > 2\sigma(F^2)$. Final $R = 0.060$ (observed), 0.108 (all); $wR(F^2) = 0.140$ (observed), 0.160 (all). All data were collected on a Bruker SMART CCD diffractometer at 150 K using Mo-Kα radiation ($\lambda = 0.710\,73$ Å), in the ω-scan mode. Absorption correction was made by the ψ-scans method. Structure solution and refinement was carried out with SHELX-97. CCDC reference number 440/157. See http://www.rsc.org/suppdata/nj/2000/a908233f/ for crystallographic files in .cif format.

†† Whether structural orthogonality (effective insulation) also calls for physical orthogonality is a matter for future discussion.

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