Isostructurality in crystalline oxa-androgens: a case of C–O–H···O and C–H···O interaction mimicry and solid solution formation

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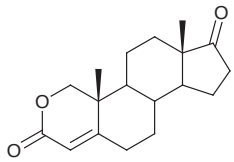
A C–H···O interaction in 2-oxa-4-androstene-3,17-dione is replaced by a C–O–H···O hydrogen bond in the isostructural 6α-hydroxy analogue, and these compounds form a binary solid solution, showing the similarity of these two crystal structures.

As part of an ongoing study on androgens[1] and their 2-oxa analogues,[2] the crystal structures of 2-oxa-4-androstene-3,17-dione **1**[3] and 6α-hydroxy-2-oxa-4-androstene-3,17-dione



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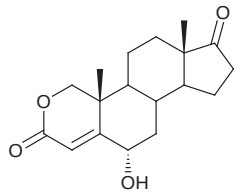

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2[2] were determined. Crystals of these compounds were obtained from EtOAc–MeOH mixtures. Both these lactones were found to have similar crystal structures. Isostructurality in steroids has been studied previously for compounds that are related by an exchange of functional groups or by epimerisation. Thus, the pairs of compounds gamabufotalin/arenobufagin, cinobufagin/cinobufotalin and digitoxigenin/digirezigenin form solid solutions which are isostructural with the respective individual components while the crystal structures of epimeric 5α- and 5β-androstane-3α,17β-diol are similar, if only to a slightly lesser degree.[4] The conformation of the oxa-steroid skeletons in **1** and **2** are identical.† Accordingly, the crystal structures of **1** and **2** were scrutinised further.‡

Both **1** and **2** adopt the same monoclinic space group, $P2_1$ and the value of the *a*-axis parameter is nearly equal (6.2321 and 6.2214 Å). This is the direction of the hydrogen bond interactions and an inspection of Fig. 1–3 is instructive. In hydroxy lactone **2**, O6–H and C6–H are hydrogen bonded to the lactone carbonyl atom O3 of different screw-axis related molecules, thereby forming chains of alternating O–H···O (1.86 Å) and C–H···O (2.38 Å) hydrogen bonds§ (Fig. 1 and 3). Effectively, O6 behaves as an O–H···O donor and O3 as a bifurcated acceptor. In lactone **1**, the C6 methylene hydrogens are linked to the O3 atom of 2_1-related molecules to give chains of C–H···O hydrogen bonds (2.38 and 2.67 Å) (Fig. 2 and 3). The metrics of these hydrogen bonded chains along [100] in the two structures are given in Fig. 3, from which it is clearly seen that the shorter of the C–H···O hydrogen bonds in**1** behaves as a surrogate of the C–O–H···O bond in**2**. We note that the near equality of the *a*-axis parameter in the two structures allows for the replacement of four links between translationally related O3 atoms in **1** (two weak O···H interactions and two C–H bonds) by five links in **2** (strong O···H interaction, weak O···H interaction, C–H bond, C–O bond and O–H bond).

When a 1:1 mixture of **1** and **2** was crystallised from EtOAc–MeOH, crystals **3**‡ were obtained in the space group $P2_1$ with cell dimensions very similar to those of pure **2**. Structure solution and refinement with partial positional occupancy for O6 yielded a converged model with partial occupancies of 0.28 and 0.720(6) for **1** and **2** respectively, showing that **3** is a binary solid solution.§ While there are examples of equivalence between N–H···O and C–H···O hydrogen bonds in isostructural crystals,[6] the formation of solid solution has not been reported in these cases. Additionally, interaction mimicry between C–O–H···O and C–H···O is a novel occurrence. The present example is therefore unprecedented and offers valuable clues regarding crystal packing in general.

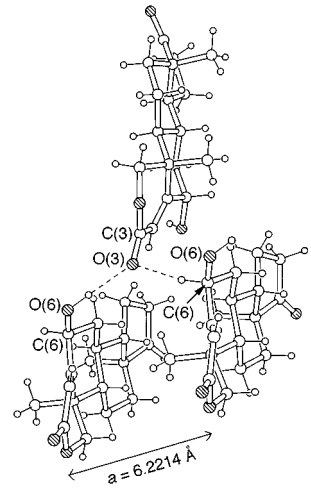


Fig. 1 Hydrogen bonding in hydroxy lactone **2** along [100] to show the O6–H···O3 and C6–H···O3 interactions between 2-related molecules. Oxygen atoms are shaded.

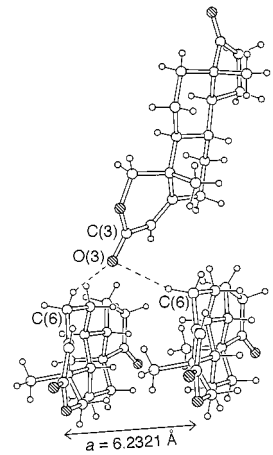
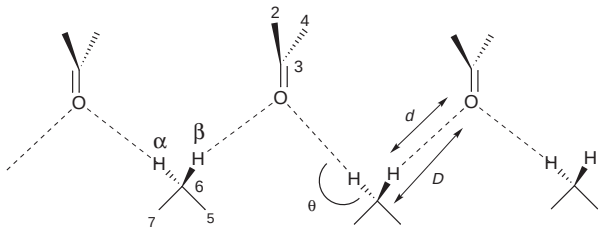


Fig. 2 Hydrogen bonding in lactone **1** along [100] between C6-methylene H-atoms and the carbonyl O3 atom of different 2_1-related molecules. Oxygen atoms are shaded. Notice the identity of *a*-axis and the similarity in hydrogen bonded chains and arrangement of molecules in the structure shown here and in Fig. 1.



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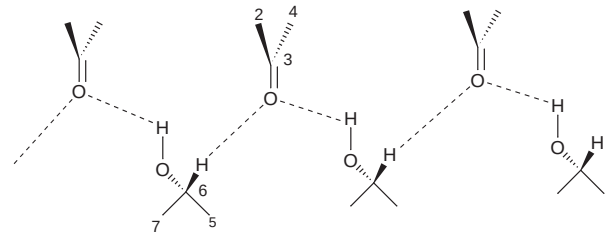

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Fig. 3 Supramolecular synthons **4** and **5** in the structures of **1** and **2** along [100]. The geometrical parameters (*d*, *D*, *θ*) of the hydrogen bonds with normalised O–H and C–H distances are for **4**: C6–αH···O3: 2.38, 3.381(4) Å, 154° and C6–βH···O3: 2.67, 3.693(4) Å, 157°; **5**: O6–αH···O3: 1.8602(5), 2.831(4) Å, 171° and C6–βH···O3: 2.38 Å, 3.409(4) Å, 158°.α and β refer to the bottom and top faces of the somewhat flattened steroid skeleton.

Firstly, this example shows the equivalence of O–H···O and C–H···O hydrogen bonding and confirms yet again that the structure directing effects of these two interactions can often be the same. It is noteworthy that the C6 H-atoms in Δ^4-steroids are allylic in nature and, as such, activated as C–H donors.[7] Secondly, the formation of a solid solution in such cases is *per se* noteworthy. Binary solid solution formation is the most stringent criterion for isostructurality[8] and occurs here because **1** and **2** have similar overall molecular shapes and also because the hydrogen bonds and recognition patterns in the structure-forming domain, that is along [100], are virtually identical. These patterns are the supramolecular synthons[9] **4** and **5** and they play a significant structural role in all three crystals. Thirdly, the fact that the **3** adopts the structure of **2** rather than that of **1** could be ascribed to the larger size of the OH group compared to the H substituent,[10] while the excess of **2** over **1** in the solid solution might be because of the relative strengths of O–H···O and C–H···O hydrogen bonds in the individual structures.[11] Finally, we note that solid solution formation occurs for this pair of compounds **1** and **2** even though the *b*, *c* and β parameters are significantly different. While the unit cell similarity index Π[8,12] is fortituously close to zero (Π = 0.002), this index could be misleading here. Since the monoclinic axial lengths are quite different (9.926 and 12.050 Å), the other packing features in the crystals, in this case the general coordination arrangements of molecules, are different leading to a degree of isostructurality index,[8,12] I^{21}_{D} of only 75%. Despite this, solid solution formation has been observed leading to the thought that isostructurality along one direction is sufficient to observe mimicry effects,[13] if that direction is important as a structure determinant. The implications of such 'one-dimensional isostructurality' have a bearing on the analysis of similarities in crystal packing that are mediated by robust supramolecular synthons.[14] Such synthons could play an active role during all stages of crystallisation events from nucleation to growth to the final appearance of a single crystal.

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Notes and references

† This was determined from an overlay diagram which shows an overall rms deviation of 0.075 Å.

‡ *Crystal data* for **1**: $C_{18}H_{24}O_3$, M = 288.37, mp 185–186 °C, monoclinic, space group $P2_1$, a = 6.2321(3), b = 9.9264(6), c = 12.8120(8) Å, β = 97.079(5)°, V = 786.54(8) Å^3, Z = 2, D_c = 1.218 g cm^{-3}, KM-4 diffractometer, T = 293 K, Cu-Kα, ω–2θ scan mode, 1597 unique reflections, 1434 with $I > 2\sigma(I)$, no absorption corrections. Structure solution and refinement with standard methods (SHELXS86 and SHELX97); H-atoms fixed, final R = 0.0342 (observed), 0.0412 (all), wR = 0.0865 (observed), 0.0919 (all). For **2**: $C_{18}H_{24}O_4$, M = 304.37, mp 244–246 °C, monoclinic, space group $P2_1$, a = 6.2214(7), b = 12.050(1), c = 10.888(1) Å, β = 103.07(1)°, V = 795.10(14) Å^3, Z = 2, D_c = 1.271 g cm^{-3}, KM-4 diffractometer, T = 293 K, Cu-Kα, ω–2θ scan mode, 1514 unique reflections, 1458 with $I > 2\sigma(I)$, no absorption corrections. Structure solution and refinement with standard methods (SHELXS86 and SHELX97); H-atoms fixed, final R = 0.0359 (observed), 0.0378 (all), wR = 0.1013 (observed), 0.1033 (all). For **3**: solid solution of **1** and **2**, $(C_{18}H_{24}O_3)_{0.28}$ + $(C_{18}H_{24}O_4)_{0.72}$, M = 299.89, mp 244–245 °C, monoclinic, space group $P2_1$; a = 6.2246(7), b = 12.014(1), c = 10.915(1) Å, β = 103.09(1)°, V = 795.04(14) Å^3, D_c = 1.252 g cm^{-3}, KM-4 diffractometer, T = 293 K, Cu-Kα, ω–2θ scan mode, 1542 unique reflections, 1497 with $I > 2\sigma(I)$, no absorption corrections. Structure solution and refinement with standard methods (SHELXS86 and SHELX97); H-atoms fixed, final R = 0.0321 (observed), 0.0334 (all), wR = 0.0862 (observed), 0.0880 (all). CCDC 182/1056.

§ The presence of **1** and **2** in single crystals of **3** was further confirmed by IR analysis and their ratio was found to be in the range 3:7 to 4:6 by ^{1}H NMR integration.

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