Spectroscopic evidence for cooperativity effects involving C–H···O hydrogen bonds: crystalline mestranol

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Combined crystallographic and IR spectroscopic study of the hydrogen bond network in the synthetic sex steroid mestranol indicates that a C≡C–H···O hydrogen bond can be considerably enhanced if the C≡C–H donor simultaneously accepts an O–H···C≡C interaction.

It is well known that in arrays of conventional hydrogen bonds such as O–H···O and N–H···O, the strengths of the individual constituents are enhanced by cooperativity effects. Best known is σ-bond cooperativity in chains such as $O^{\delta-}$–$H^{\delta+}\cdots O^{\delta-}$–$H^{\delta+}\cdots O^{\delta-}$–H, where the individual hydrogen bonds enhance each other's strengths by mutual polarisation of the O–H groups.[1] A current topic of hydrogen bond research is directional interactions of the types C–H···Y[2] and X–H··π.[3] In crystal structures, these types of weak hydrogen bonds are often found interconnected with 'normal' or other weak hydrogen bonds, forming motifs that are topologically analogous with conventional hydrogen bond patterns. Several authors have taken this as a manifestation of cooperativity phenomena,[4] although structural analogy alone does not prove such an effect. There are conflicting views that suggest that weak hydrogen bonds are additive in nature, similar to van der Waals contacts.

Here we present a combined structural and spectroscopic study of the crystalline synthetic sex steroid mestranol **1**, which contains a remarkable system of interconnected conventional and non-conventional hydrogen bonds.

The crystal structure† of **1** contains two symmetry-independent molecules of virtually identical conformation‡ (Fig. 1), but which have different intermolecular contacts. A section of the crystal packing is shown in Fig. 2. Symmetry-independent molecules A and B are arranged in a head-to-head fashion, with their hydroxy and ethynyl groups forming a two-dimensional hydrogen bond network. This system of intermolecular interactons is shown in detail in Fig. 3 [only the HC≡C–C(17)–OH moieties are drawn]; geometric data is given in Table 1. The two symmetry-independent ethynyl groups donate antiparallel C≡C–H···O hydrogen bonds of very similar geometries, with C···O separations differing by only 0.035 Å (Table 1). However, these two C≡C–H···O hydrogen bonds have completely different functions in the hydrogen bond array: C≡C(A)–H simultaneously accepts an O–H···π hydrogen bond, and is thereby part of an infinite chain O(B)–H···C≡C(A)–H···O(A′)–H···O(B′)–H *etc.*, for which cooperativity enhancement might be suggested for all participating hydrogen bonds. The other ethynyl residue forms only the isolated hydrogen bond C≡C(B)–H···O(B)–H.

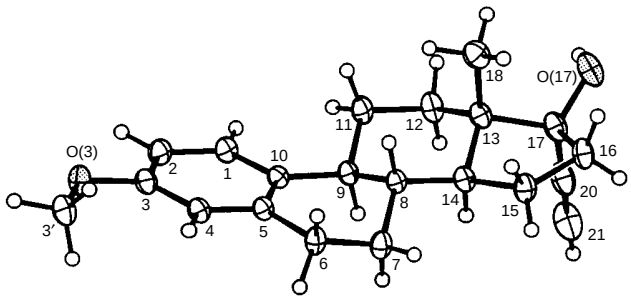

Fig. 1 Molecular structure and atomic numbering scheme of **1**, molecule A. Oxygen atoms are shaded. Displacement ellipsoids are drawn at the 30% probability level.

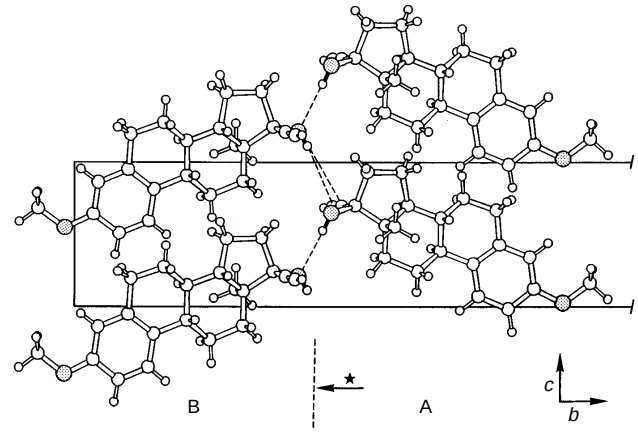

Fig. 2 Section around $y/b = 1/4$ of the crystal packing. Oxygen atoms are shaded. The arrow marked by a star indicates the projection of Fig. 3.

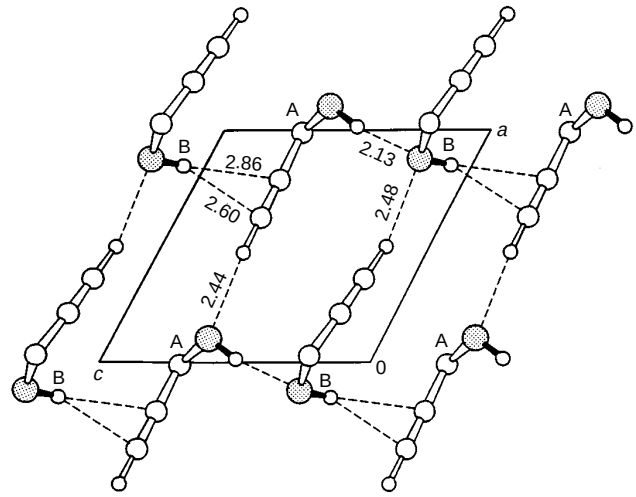

Fig. 3 Hydrogen bond pattern in a projection perpendicular to Fig. 2. Oxygen atoms are shaded. Normalised H-positions are shown.

The infrared spectra were recorded§ for crystals and a dilute solution of **1** in CCl_4 (Table 2 and Fig. 4). As is to be expected, the spectrum shows two distinct O–H and two ≡C–H absorption bands present in the crystal phase, corresponding to the two symmetry-independent molecules. Of the two O–H bands, one is quite narrow and red-shifted by -90.7 cm^{-1} compared to the 'free' O–H group in CCl_4 solution. This is typical for O–H···π hydrogen bonding, and the band is assigned to O(B)–H. The other O–H absorption band is significantly broader and more intense, and is therefore assigned to the conventionally hydrogen bonding O(A)–H. The two ≡C–H bands are shifted by -21.3 and -59.8 cm^{-1} compared to free ethynyl groups, both values being indicative of C–H···O hydrogen bonding. Since these two red shifts differ by almost a factor of three, the two C≡C–H···O hydrogen bonds in the crystal must be markedly different despite their similar donor–acceptor separations.

The two C≡C–H···O interactions are formed by chemically identical groups; therefore, the large difference in the corresponding $\nu_{\equiv C-H}$ shifts can only be due to differences in the intermolecular environment. It is straightforward to suggest that the C–H···O interaction in the infinite chain is the stronger one, because it is donated by an ethynyl group which simultaneously accepts an O–H···π interaction. Therefore, the strongly shifted band is assigned to residue A, and the weakly shifted band to residue **B**; the difference is interpreted as a direct consequence of the cooperative effect.¶ This is compatible with spectroscopic investigations on 2-ethynyladamantan-2-ol,[5] where an unusually large $\nu_{\equiv C-H}$ red shift was found for a O–H···C≡C–H···O coupled system; that system, however, contains no non-cooperative C–H···O bonds for comparison.[4c]

These observations show conclusively that C–H···O interactions can be strongly influenced by their environment. The structural and spectral data for **1** are incompatible with the view that C–H···O and X–H·π interactions are too subtle to experience or to generate significant non-additivity effects. This is not relevant only to ethynyl groups. For all other residues that can simultaneously act as C–H donors and π acceptors, similar effects must be expected. A most important example is the phenyl group.

Table 1 The hydrogen bonds of **1**; M = centroid of C(20)≡C(21) (for normalized H positions with C–H = 1.09 and O–H = 0.98 Å)

	H···A/Å	D···A/Å	D–H···A (°)
O(17A)–H···O(17B)	2.13	3.098(7)	170
O(17B)–H···C(20B)	2.86	3.835(6)	175
O(17B)–H···M(B)	2.67	3.636(7)	170
O(17B)–H···C(21B)	2.60	3.524(8)	158
C(21A)–H···O(17A)	2.44	3.443(5)	153
C(21B)–H···O(17B)	2.48	3.478(5)	151

Table 2 Stretching frequencies

Sampling	ν_{O-H}/cm^{-1}	$\nu_{\equiv C-H}$/cm^{-1}
Dilute solution in CCl_4 at r.t.	3614.0	3308.6
Crystal (KBr) at r.t.	3523.3, 3481.4	3287.3, 3248.8
Crystal (KBr) at 92 K[a]	3505.1, 3471.3	3278.9, 3233.8
Shift $\Delta\nu_{cryst-soln}$ at r.t.	−90.7, −132.6	−21.3, −59.8

[a] The low temperature data are not discussed in the text, because no corresponding X-ray crystal structure is available. The increase of the red shifts indicates further strengthening of all hydrogen bonds upon cooling. r.t. = room temperature.

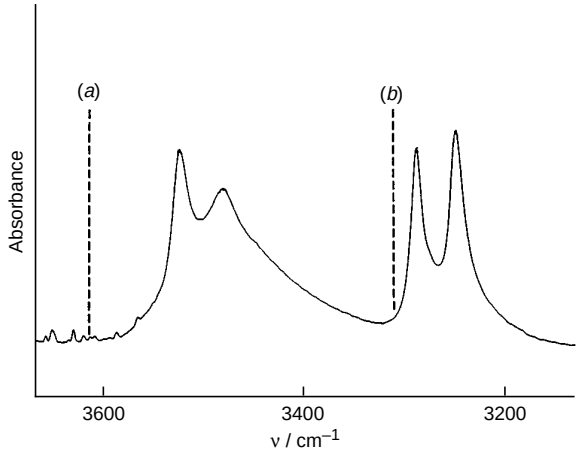

Fig. 4 Section of the IR absorption spectrum of crystalline **1** at room temp. (KBr); numerical values are listed in Table 2: (*a*) ν_{OH} in CCl_4, (*b*) $\nu_{\equiv C-H}$ in CCl_4. The two left bands represent hydrogen bonding O–H, and the two right bands hydrogen bonding C≡CH groups.

Footnotes

† Mestranol: 17α-ethynyl-3-methoxestra-1,3,5[10]-trien-17β-ol $C_{21}H_{26}O_2$, M = 310.4 (commercially available from Sigma). Solvent-free crystals were obtained by slow evaporation of solutions in EtOH. Monoclinic, space group $P2_1$, a = 6.8622(8), b = 39.71(3), c = 6.997(5) Å, β = 117.6(2)°, V = 1690(2) Å^3, Z = 4, D_c = 1.22 g cm^{-3}. Enraf-Nonius FAST area-detector, Mo-Kα (λ = 0.71073 Å), graphite monochromator, 0.5 × 0.2 × 0.2 mm^3 crystal, room temperature, 14262 measured reflections, 8704 unique reflections (R_{int} = 0.064), 6670 with $F^2 > 2\sigma(F^2)$, no absorption correction. Structure solution and refinement with standard methods (SHELXS-86, SHELXL-93). H-atoms refined isotropically. Final R = 0.070 (for observed reflections), $wR(F^2)$ = 0.164 (for all reflections). Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Informations for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/305.

‡ The steroid skeleton does not significantly differ from 17α-ethynylestradiol as observed in the hemihydrate crystal structure; V. J. van Geerestein, *Acta Crystallogr., Sect. C*, 1987, **43**, 1206.

§ IR spectroscopy: Mattson Research Series spectrophotometer equipped with a DTGS detector. Cryostate Specac P/N 21.000 variable temperature cell. Scanning parameters: region 4000–500 cm^{-1}, resolution 2 cm^{-1}, 64 scans and triangular apodization.

¶ There is a further difference in the surroundings of the two ethynyl groups: as a consequence of the double-acceptor function of O17(B), there might be electrostatic repulsion between C(21B)–H and O(17A)–H donating hydrogen bonds to O(17B). This could destabilize the C(21B)–H···O interaction, and be responsible for a reduced red shift of $\nu_{C(21B)-H}$. Since the H[C(21B)]···H [O(17A)] distance is rather long (2.80 Å), it is assumed that this interaction is of only secondary importance compared to the O–H··π interaction accepted by the residue A. C(21A)–H does not form such a, possibly unfavourable, contact.

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