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The distinctively singular self-assembly of a "molecular stair": observation of a quadrilateral C–H···O hydrogen bonding cycle in the crystal structure of a tetracyclic oligo-tetrahydrofuran

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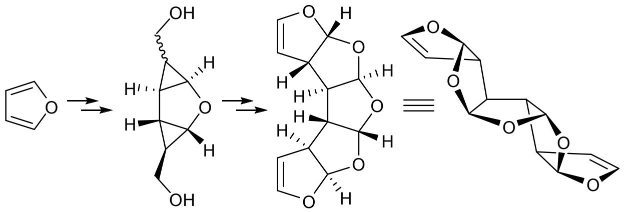
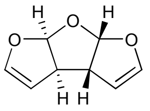
A comparative analysis of the C–H···O hydrogen bonded crystal structures of three structurally related 'molecular stairs' (*anti*-fused oligoannelated tetrahydrofurans) has led to the identification of a scarcely encountered quadrilateral C–H···O hydrogen bonding cycle, involving a pair of bifurcated H-bonds and two lactone carbonyl oxygens, in a chiral trigonal space group.

Quite recently, a modular approach to "molecular stairs" (anti-fused oligoannelated tetrahydrofurans), emanating from furan via an iterative two-fold cyclopropanation-reduction-oxidation sequence, was reported by Werz et al. (Scheme 1).[1] While single crystal XRD analysis was employed extensively as a tool for structural elucidation in this reported synthetic endeavour, details of crystal packing in any of the newly crafted "molecular stairs" **1-6** were not presented. An examination of the crystal data available for **1-6** (CCDC 764650, 764651, 720562, 764653, 720971, 764656)[1b] in the CCDC database reveals a general trend in the space group preferences and crystal packing, namely: (a) lack of lattice symmetry higher than orthorhombic, (b) presence of both C(sp^3)–H···O and C(sp^2)–H···O hydrogen bonds, and (c) participation of both terminal double bonds in the C(sp^2)–H···O hydrogen bonds.



Scheme 1. Werz's modular approach to anti-fused oligoannelated tetrahydrofurans ("molecular stairs").



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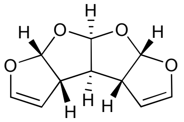

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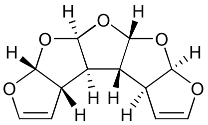

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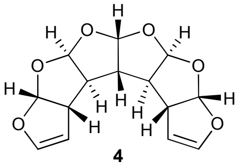

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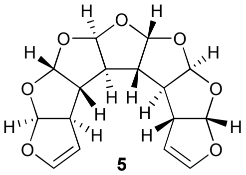

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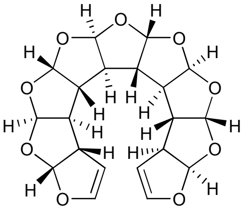

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The decisive role played by the peripheral double bonds in all the reported crystal structures of Werz's "molecular stairs" goaded us to investigate the overall effect that a complete disablement of the C(sp^2)–H donors might have on the packing of these crystalline *anti*-fused oligoannelated tetrahydrofurans. The initial impetus for undertaking such a comparative case study came from the ready availability of single crystal X-ray diffraction data of *anti*-fused oligo-tetrahydrofurans, such as **7-9**, that were afforded from our own recently concluded synthetic endeavour towards "molecular stairs" based on a regenerative γ-butyrolactone annulation stratagem.[2] We recognized that besides the obvious lack of any C(sp^2)–H donor, the unsymmetrical oligo-tetrahydrofurans **7-9** differ from the C_2/C_s symmetric Werz variants **1-3** by bearing an additional C–H···O acceptor (in form of a γ-lactone) on one of the peripheral rings. Since this feature invariably leads to a dissymmetry in the potential H-bond donors and acceptors in **7-9**, we opted to make our postulated comparative study more holistic by including a

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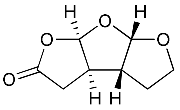
saturated variant of Werz's "molecular stairs". The tetracyclic *anti*-fused oligo-tetrahydrofuran **10** was readily crystalline and best suited our needs in this regard.[2] The present communication is therefore an initial endeavour to compare the molecular packing of three structurally related "molecular stairs", viz. **2**, **8** and **10**, and throw a spotlight *en route* on the distinctively singular crystal structure observed for **8**.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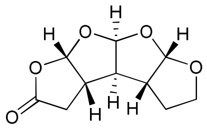
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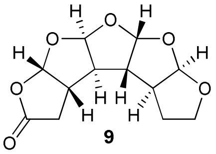
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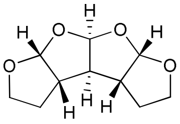
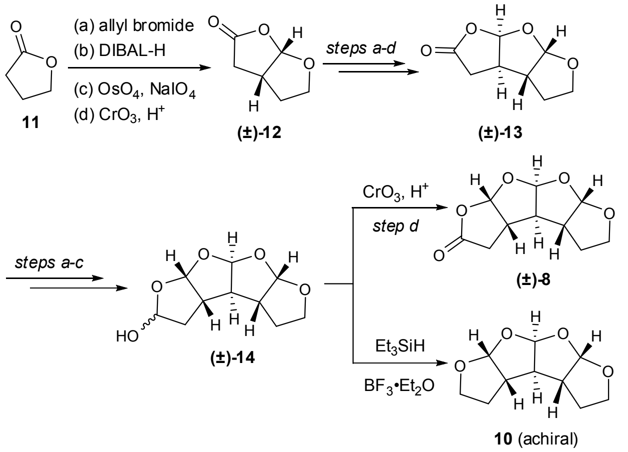
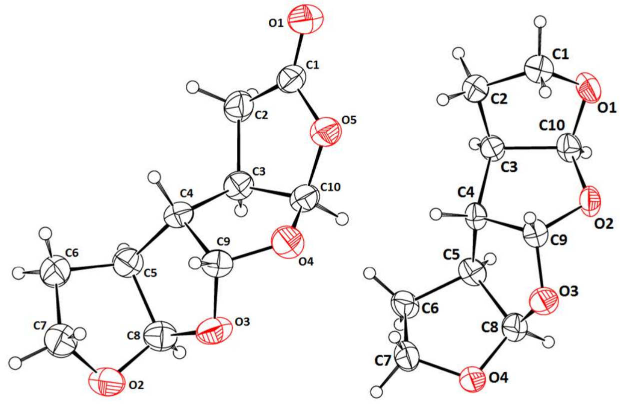

10

The tetracyclic lactone **8** was crafted as a racemic modification from γ-butyrolactone **11** with an overall yield of around 13% *via* a four step iterative protocol, namely (a) LiHMDS mediated α-alkenylation of the lactone with allyl bromide, (b) DIBAL-H mediated reduction of the lactone moiety, (c) Lemieux-Johnson oxidation of the allyl side-arm and subsequent *in situ* oligoacetal formation and (d) Jones oxidation of the newly created hemiacetal moiety. The achiral C_s-symmetric oligo-tetrahydrofuran **10**, a saturated variant of achiral C_s-symmetric **2**, was prepared in turn from the racemic tetracyclic hemiacetal **14** via a Lewis acid promoted reductive deoxygenation with triethylsilane (Scheme 2).[2]



Scheme 2. Overview of the synthetic strategy adopted for the preparation of **8** and **10** (see Ref. 2 for details).

Crystals of **8**and **10**, suitable for single crystal X-ray diffraction studies, were grown at ~5 °C by the slow solvent evaporation technique from their solutions in 1:2 EtOAc-hexane and 1:1 THF-EtOAc respectively. Though obtained as a racemic modification following the synthetic route described above, the tetracyclic oligo-tetrahydrofuran-lactone **8** underwent spontaneous resolution during crystallization[3,4] so that the crystal structure of **8** was solved and refined in the chiral trigonal space group $P3_22$ (Z = 6).[‡] The possible absolute configuration of **8** in the crystal structure was deduced as most likely being (1*R*,2*R*,6*R*,8*S*,10*R*,14*S*)-5,7,9,11-tetraoxatetracyclo $[6.6.0.0^{2,6}.0^{10,14}]$tetradecan-4-one by refinement of the Flack parameter[5] (Figure 1a). Interestingly, even the achiral C_s-symmetric **10** crystallized in the chiral monoclinic space group $C2$ (Z = 4) (Figure 1*b*).[§] On one hand, this observation tallies well with the precedence that the unsaturated variant - the C_s-symmetric **2** - too crystallized in $P2_1/c$ (Z = 4), a monoclinic space group with no *m* symmetry,[1b] so that the molecular symmetry of neither **2** nor **10** is reflected in the crystal structure. On the other hand, the fact that achiral **10** opted for a chiral molecular packing was unanticipated and can be considered a departure from the known preference for achiral molecules, such as **2**, to crystallize in centrosymmetric space groups.[6,7,8]



(*a*) (*b*)

Figure 1. ORTEP diagrams of (a) the tetracyclic oligo-tetrahydrofuran-lactone **8** and (b) the tetracyclic oligo-tetrahydrofuran **10**, with the atom numbering schemes for the asymmetric units. Displacement ellipsoids have been drawn at 30% probability level and H atoms are shown as small spheres of arbitrary radii.

Much like that of the symmetrical congener **2**, the molecular structures of both **8** and **10** show a corkscrew arrangement of the five membered rings in the solid state (Figure 2).[1b] Analysis of the ring puckering parameters[9] in **8** pointed towards an approximate envelope (*E*) conformation forthe two inner THF moieties and close to a twisted (*T*) conformation for the outer lactone and THF rings. In case of **10**, ring puckering analysis indicated an approximate twisted (*T*) conformation for the two outer and one inner THF rings, and close to an envelope (*E*) conformation for the remaining inner THF moiety.

Crystal packing in **8** is mediated by an intricate array of C–H···O hydrogen bonds, the shorter of them being observed solely away from the longest *c* axis and serving to connect the molecules into three different sets of interlinked molecular chains. Thus, a pair of C–H···O H-bonds, involving C8 and O4, links each molecule to its translationally related neighbours to form chains parallel to the *a* and *b* axes, and the (-1,1,1) plane. An interesting quadrilateral C–H···O hydrogen bonding cycle, involving a pair of bifurcated H-bonds at H10 and two carbonyl

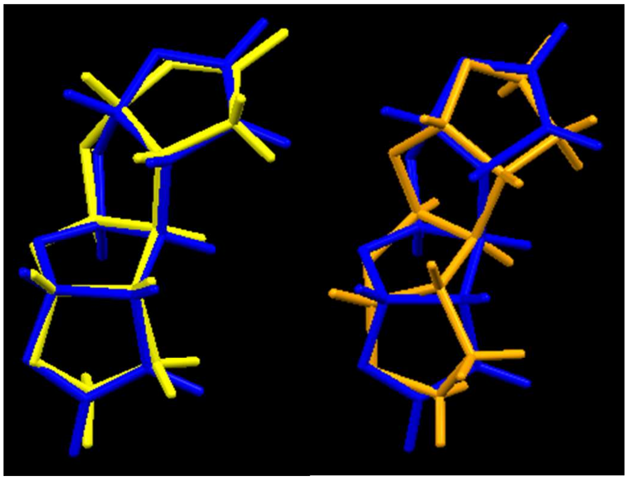


Figure 2.(*left*) Molecular overlay diagram of the tetracyclic oligo-tetrahydrofurans**8**(yellow) and **2**(blue). Calculated RMS deviation = 0.228 Å. (*right*) Molecular overlay diagram of the tetracyclic oligo-tetrahydrofurans**10**(orange) and **2**(blue). Calculated RMS deviation = 0.638 Å

oxygens (O1), now connects (a) each molecular chain along *b* axis to its neighbour across the 2_1 axis at (1/2, 0, 1/3) to form dimers, and then links each such dimer to its translationally related neighbours along the *a* axis (Sets a of interlinked molecular chains, colored yellow in Figure 3); (b) each molecular chain along *a* axis to its neighbour across the 2_1 axis at (0, 1/2, 2/3) to form dimers, and then links each such dimer to its translationally related neighbours along the *b* axis (Sets b of interlinked molecular chains, colored blue in Figure 3); (c) each molecular chain, growing parallel to the (-1,1,1) plane, to its neighbour across the 2_1 axis, lying on the *ab* plane and (-4 4 0), to form dimers, and then links each such dimer to its translationally related neighbours roughly along the [-1 1 0] direction (Sets c of interlinked molecular chains, colored green in Figure 3). The longer of the C–H···O hydrogen bonds in the crystal packing of **8** serves to consolidate further the supramolecular assemblies of molecular chains thus formed and then link them along the *c* axis (Figure 3, Table 1).

Table 1. Hydrogen bond geometry in the tetracyclic oligo-tetrahydrofuran **8**

D–H···A^{a}	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
C5–H5···O4^{i}	0.98	2.62	3.341(3)	130
C7–H7B···O2^{ii}	0.97	2.63	3.489(4)	148
C8–H8···O4^{iii}	0.98	2.52	3.461(4)	160
C10–H10···O1^{iv}	0.98	2.38	3.221(3)	144
C10–H10···O1^{v}	0.98	2.59	3.158(3)§§	117

^{a}symmetry codes: (i) *x* – 1, *y*, *z*; (ii) *x* – *y*, –*y* + 1, –*z* + 1/3; (iii) *x*, *y* + 1, *z*; (iv) *x* + 1, *y*+ 1, *z*; (v) –*x* + 1, –*x* + *y* + 1, –*z* + 2/3

It is pertinent to mention at this point that the quadrilateral C–H···O hydrogen bonding cycle – the singularly notable feature in the hydrogen bonding pattern of **8** - has scarcely been encountered in the crystal structures of organic compounds.[10] Indeed, a Cambridge Structural Database search [CSD version 5.35 (November 2013 + 2 updates)] with a fragment, as shown

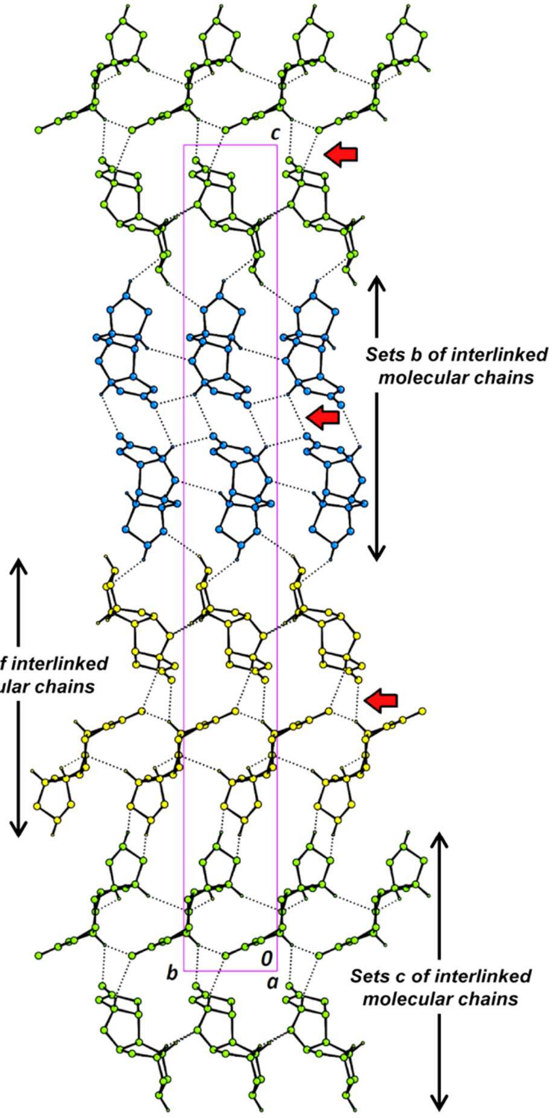
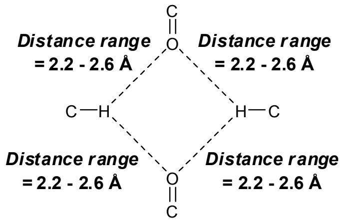


Figure 3. Molecular packing in the tetracyclic oligo-tetrahydrofuran**8** as viewed along the *a* axis. Dotted lines indicate C–H···O hydrogen bonds while the block arrows mark the quadrilateral C–H···O hydrogen bonding cycles. Non-interacting H atoms have been omitted for clarity.

in Figure 4, generated only 18 hits (CSD codes: BESDUA, COFGIO, DUXYUQ, FEDPEK, FMESIB, GELRUL, IJOPEC, JEMHAL, KINGUJ, LASLEY, MINBOB, MUBVIP, NUBTOU, PEGDAH,QENCIV, SODCEU, WIBHAR, XAQFUS).[11] All of the crystal structures within this coterie were centrosymmetric and none possessed a space group symmetry higher than orthorhombic. In addition, the quadrilateral C–H···O hydrogen bonding cycle did in none of the 18 CSD hits involve the C=O group of a γ-lactone – attesting further to the maverick nature of the H-bonded assembly in crystalline **8**.

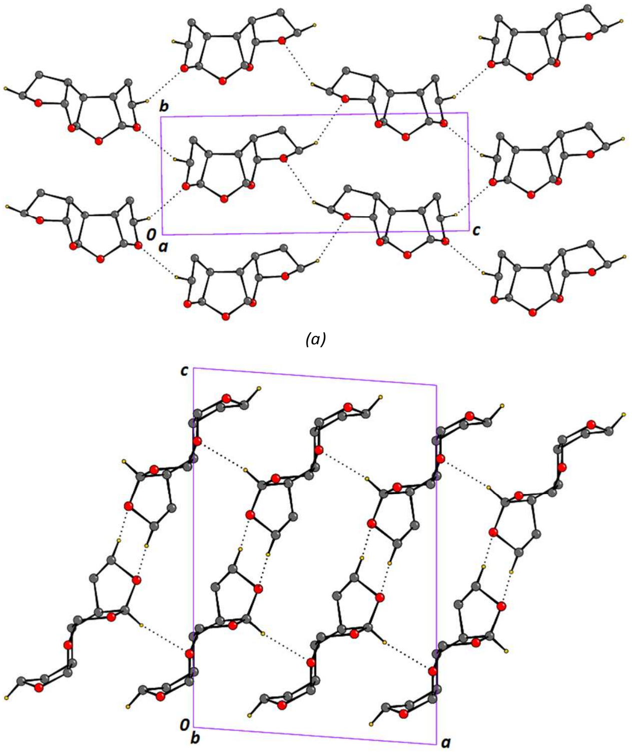
In comparison, such a C–H···O H-bonding motif was inevitably absent in the crystal structures of the tetracyclic oligo-tetrahydrofurans **2** and **10**. However, similarities between the molecular packing of **8** and **10** were easily noticeable in the manner in which the oxygen atoms of the THF rings in **10**



Filters applied:
3D coordinates determined
No errors
No ions
Not disordered
Not polymeric
No powder structures
Only organics

Figure 4. The C–H···O H-bonding motif and filters employed in the CSD search.

participated in C(sp^3)–H···O hydrogen bonds. Thus, a pair of C–H···O H-bonds [C(7)–H(7B)···O(4)], involving one of the two terminal THF moieties in **10**, linked each molecule to its neighbour, related by the 2-fold symmetry, to form zig-zag chains growing parallel to the *b* axis [Figure 5*a*]. Another pair of C–H···O H-bonds [C(1)–H(1A)···O(1)], involving the other terminal THF ring, connected these molecular chains to form sheets essentially parallel to the (4 0 -4) plane. Each such molecular sheet is in turn linked to the ones, over and underneath it essentially along the [1 -1 0] direction, by the shortest C–H···O H-bonds, involving C(10)···O(3) [Figure 5*b*, Table 2].



(a)

(b)

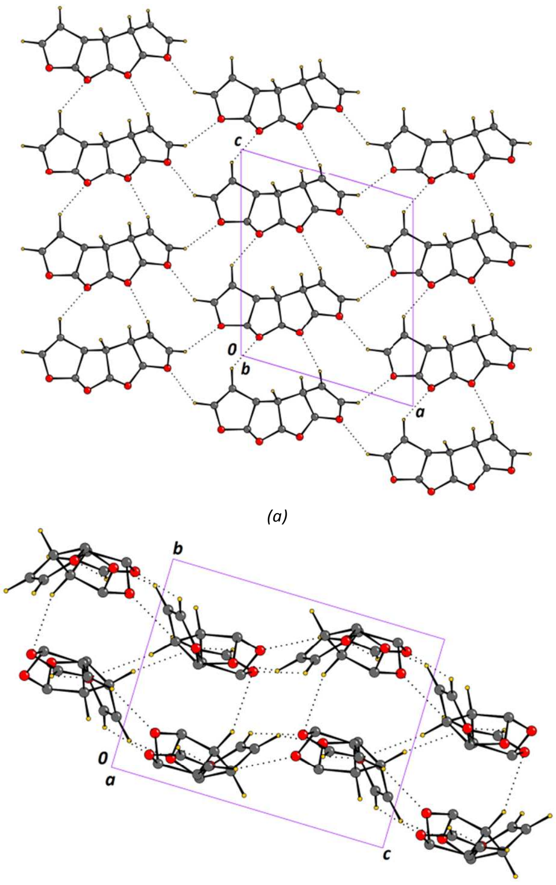
Figure 5. Molecular packing in the tetracyclic oligo-tetrahydrofuran **10** as viewed (a) along the *a* axis, and (b) along the *b* axis. Dotted lines indicate C–H···O hydrogen bonds. Non-interacting H atoms have been omitted for clarity

While the overall crystal structure of **2** (CCDC 764651)[1b] bears a strong resemblance to that of its saturated variant **10**, molecular packing in **2** is mediated by an intricate array of bothC(sp^3)–H···O and C(sp^2)–H···O hydrogen bonds, and a decided participation by all four terminal olefinic methine H-atoms. Thus, a pair of C(sp^2)–H···O H-bonds [C(1)–H(1)···O(2) and C(9)–H(9)···O(3)] link each molecule to its neighbour, related by the *c* glide symmetry, to form zig-zag chains growing along the *c* axis [Figure 6*a*]. A further pair of C(sp^2)–H···O H-bonds [C(2)–H(2)···O(4) and C(10)–H(10)···O(1)] connect these molecular chains translated along the *a* axis to form corrugated sheets essentially parallel to the *ac* plane. Each such molecular sheet is in turn linked to the ones, over and underneath it along the b axis, by C(sp^3)–H···O H-bonds, involving C(5)···O(1) and C(7)···O(4) [Figure 6*b*, Table 3].

Table 2. Hydrogen bond geometry in the tetracyclic oligo-tetrahydrofuran **10**

D–H···A[a]	D–H (Å)	H···A(Å)	D···A(Å)	D–H···A (°)
C1–H1A···O1[i]	0.97	2.68	3.534(8)	147
C7–H7B···O4[ii]	0.97	2.63	3.500(8)	150
C10–H10···O3[iii]	0.98	2.54	3.501(7)	167

[a]symmetry codes: (i) –*x* + 3/2, *y* + 1/2, –*z* + 1; (ii) –*x* + 5/2, *y* + 1/2, –*z* + 2; (iii) *x* – 1/2, *y* + 1/2, *z*.



(a)

(b)

Figure 6. (a) Molecular packing mediated by C(sp^2)–H···O hydrogen bonds in the tetracyclic oligo-tetrahydrofuran **2** as viewed along the *b* axis. (b) Molecular packing mediated by both C(sp^2)–H···O and C(sp^3)–H···O hydrogen bonds in the tetracyclic oligo-tetrahydrofuran **2** as viewed along the *a* axis. Dotted lines indicate C–H···O hydrogen bonds. Non-interacting H atoms have been omitted for clarity.

Table 3. Hydrogen bond geometry in the tetracyclic oligo-tetrahydrofuran **2**

D–H···A^a	D–H (Å)	H···A (Å)	D···A (Å)	D–H···A (°)
C(1)–H(1)···O(2)^{i}	1.09	2.51	3.3794(7)	136
C(2)–H(2)···O(4)^{ii}	1.08	2.43	3.2463(7)	131
C(5)–H(5)···O(1)^{iii}	1.10	2.50	3.5312(7)	157
C(7)–H(7)···O(4)^{iv}	1.10	2.55	3.5774(7)	156
C(9)–H(9)···O(3)^{i}	1.09	2.36	3.2514(7)	138
C(10)–H(10)···O(1)^{vi}	1.08	2.46	3.3447(7)	138

^{a}symmetry codes: (i) *x*, –*y* + 1/2, *z* + 1/2; (ii) *x* – 1, *y*, *z*; (iii) –*x*, *y* + 1/2, –*z* + 1/2; (iv) –*x* + 1, –*y*, –*z* + 1; (v) *x* + 1, –*y* + 1/2, *z* + 1/2.

Conclusions

This comparative study into the crystal packing of three structurally related "molecular stairs" is the first attempt to shed light on the nuances of self-assembly in this newly introduced class of molecular entities. Each of the three tetracyclic oligo-tetrahydrofurans investigated displayed its individualistic complement of C–H···O hydrogen bond donors and acceptors, from which an unorthodox quadrilateral C–H···O hydrogen bonding motif stood out. However, themodes of self-assembly in the three 'molecular stairs', despite the differences in their C–H···O hydrogen bonding, converged in the ubiquitous role played by the peripheral tetrahydrofuran moieties in their C–H···O H-bonded assemblies. Indeed, this trend is noticeable in all the crystal structures of Werz's "molecular stairs", and should stimulate further investigation into the hydrogen bonding preferences of oligocyclic oligo-tetrahydrofurans with the present study as an archetype for understanding the self-assembling processes in these novel molecular constructs.

Acknowledgment

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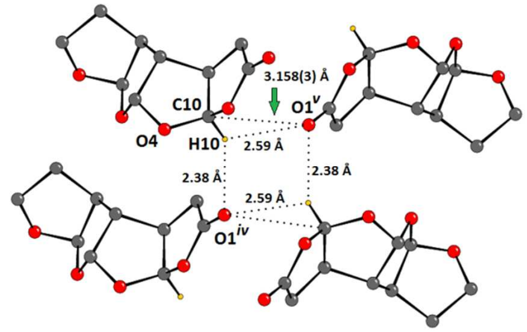
Notes and references

‡Single crystal X-ray data for **8** was collected at 291 K on a Agilent Xcalibur X-ray diffractometer, equipped with Cu–Kα radiation (λ = 1.5418 Å) source. Data reduction was carried out with *CrysAlisPro* version 1.171.35.19. The crystal structure were solved by direct methods using *SIR92* and refined by full-matrix least-squares methods on F^2 using *SHELXL97*. Crystal data of **8**: $C_{10}H_{12}O_5$, *M* = 212.20, trigonal, $P3_22$, *a* = 6.0046(6), *c* = 45.980(6) Å, *V* = 1435.7(4) Å^3, *Z* = 6, ρ_{calcd} = 1.473 g/cm^3, 3117 reflections measured, 1752 unique (R_{int} = 0.0315), *R1* = 0.0420 and *wR2* = 0.0981 for 1454 observed reflections, CCDC 1026652.

§Single crystal X-ray diffraction data for **10** was collected on a Bruker AXS SMART APEX CCD diffractometer at 291 K using Mo–Kα radiation (λ = 0.7107Å). Data reduction was carried out with *SAINTPLUS*. The crystal structures were solved by direct methods using *SIR92* and refined by full-matrix least-squares methods on F^2 using *SHELXL97*. Crystal data for **10**: $C_{10}H_{14}O_4$, *M* = 198.21, monoclinic, *C2, a* = 10.420(5), *b* = 5.899(3), *c* = 15.377(8) Å, *β* = 94.096(7)°, *V* = 942.7(8) Å^3, *Z* = 4, ρ_{calcd} = 1.397 g/cm^3, 3444 reflections measured, 967 unique (R_{int} = 0.022), *R*1 = 0.0778 and *wR2* = 0.1887 for 878 observed reflections, CCDC 1412443.

§§This close C10···O1 contact might result from an alignment of the electron rich O1 with the σ*C–O orbital of the C10–O4 atoms (*see figure below; symmetry codes refer to those given in Table 1*) and explain partly the formation of the quadrilateral C–H···O hydrogen bonding cycle.



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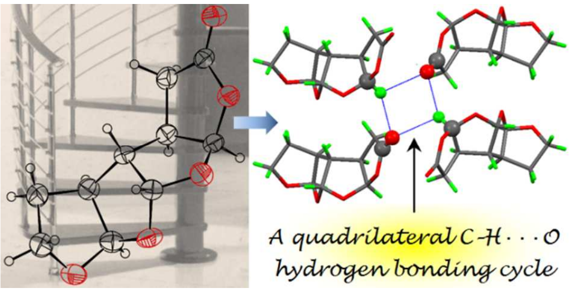
Graphical abstract



The first comparative analysis of the C–H···O hydrogen bonded crystal structures of three structurally related 'molecular ladders' (*anti*-fused oligocyclic oligotetrahydrofurans) has been presented. The study not only identified a rare quadrilateral C–H···O hydrogen bonding motif in a chiral trigonal space group setting for one of the oligo-tetrahydrofurans, but also have revealed that the terminal moieties in such molecular stairs play a ubiquitous role in their C–H···O H-bonded assemblies.