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Total CCl₄ guest alignment in a *quasiracemic* clathrate closely related to Dianin's compound

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Single crystal X-ray analysis at 100 K reveals that in the trigonal CCl₄ *quasiracemic* clathrate, space group *R*3̄, formed from host components *S*-(-)-Dianin's compound and its (+)-2*R*,4*R* 2-nor methyl analogue there is an unprecedented complete ordering of a C-Cl bond of the guest with respect to the *c*-axial direction. In this clathrate and that formed from the (+)-2*R*,4*R* and (+)-2*R*,4*S* epimers the participation of an unexpected host conformation is reported for the first time.

Although the clathrates formed by Dianin's compound¹, (±)-4-*p*-hydroxyphenyl-2,2,4-trimethylchroman **1**, and related compounds have been the subject of substantial sustained interest for more than half a century², only recently has increased emphasis been placed on quantitative elucidation of host-guest interactions and host consolidation in these fascinating systems. For example, current studies have thrown new light on host-guest interaction energies³, host response to the nature of the guest⁴, hydrogen bond reorientation⁵, guest transport⁶, and, of immediate relevance to the present communication, guest alignment, *vide infra*.

Typically, the racemic clathrates of **1**, and those formed by synthetic analogues⁷, crystallise in the premier clathrate space group *R*3̄, with a single crystallographically independent host molecule in the asymmetric unit¹; and the host packing is characterised by infinite stacking of *C*_{3v}-symmetric hydrogen-bonded [OH]₆ units along the *c*-axis such that *achiral* centrosymmetric voids are left between adjacent hexamers. A universal feature of molecular conformation of the heterocyclic ring of host **1** and related hosts is the *proximal* relationship between the *p*-hydroxyphenyl substituent and the *syn*-related methyl group, Figure 1. By contrast these substituent groups

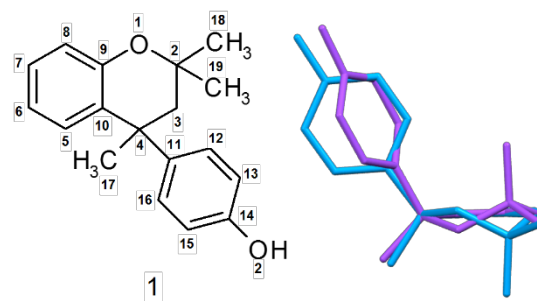


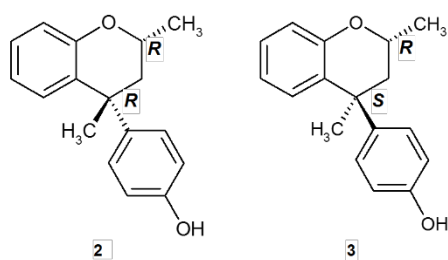
Figure 1. Overlay of the proximal (purple) and distal (blue) conformations of Dianin's compound **1**, illustrated for the *S*-enantiomer, the atom numbering scheme used for torsion angle discussion is shown. In this view the fused benzene ring is hidden.

have a *distal* relationship in the unsolvated, optically pure molecular crystals. The first successful design of analogous *polar* Dianin-type host structures, possessing *chiral* voids between hexameric units was described by Collet and Jacques 40 years ago⁸. Until now however, only the unit cell and space group, (*R*3̄), were known (ref 7). We have recently shown that in a related *quasiracemic*[†] chiral clathrate, space group *R*3̄, formed from the *R*-enantiomeric form of **1** and the *S*-enantiomeric form of its direct thiachroman counterpart⁹, that there was partial alignment of the CCl₄ guest with respect to the *c*-axial direction. It is also noteworthy that a higher degree of templated polar order has been achieved for the same guest molecule in the *quasiracemic* host formed by the *R*-enantiomeric form of **1** and the *S*-enantiomeric form of its direct 4-*p*-mercaptophenyl counterpart and that this system exhibits a significant second harmonic generation (SHG) effect. Interestingly, in this case the clathrate features a novel [OH⋯SH]₃ hexamer replacing the conventional [OH]₆ host hexamer.¹⁰ NQR has also been employed to study the motion of the CCl₄ guest molecule in host **1** itself¹¹. We now present detailed single-crystal X-ray analyses at 100K of these earlier prototypal *quasiracemic* polar structures, space group *R*3̄, which reveal a novel complete guest orientation phenomenon and an unprecedented host conformation. The CCl₄ clathrates

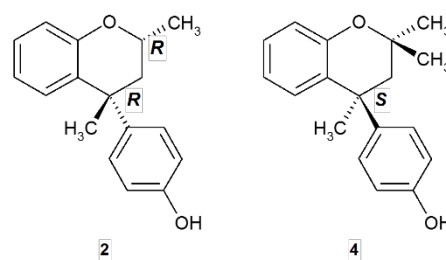
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Electronic Supplementary Information (ESI) available: Full experimental details and crystal structure data. [CCDC Deposition numbers 1541892, 2/3, 1541849, 2/4, 1558621, 5 and 1558622, 6]. See DOI: 10.1039/x0xx00000x



Scheme 1. 2-nor methyl epimers of Dianin's compound, (+)-2*R*,4*R*, **2** and (+)-2*R*,4*S*, **3**.



Scheme 2. (+)-2*R*,4*R* 2-nor methyl epimer of Dianin's compound, **2** and (-)-*S*-Dianin's compound, **4**.

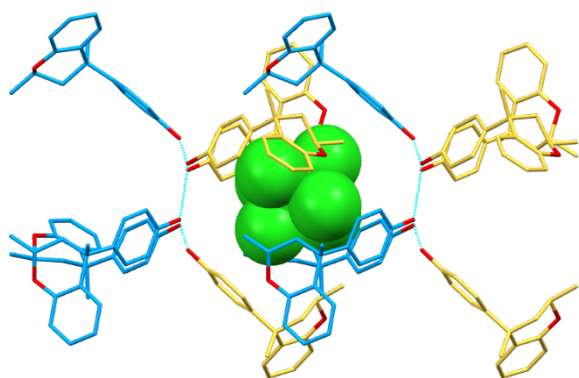


Figure 2. View down the *b*-axis, *c*-axis horizontal, of the CCl₄ clathrate formed from the nor-methyl components (+)-2*R*,4*R*, **2** and (+)-2*R*,4*S*, **3**, shown in blue and yellow respectively.

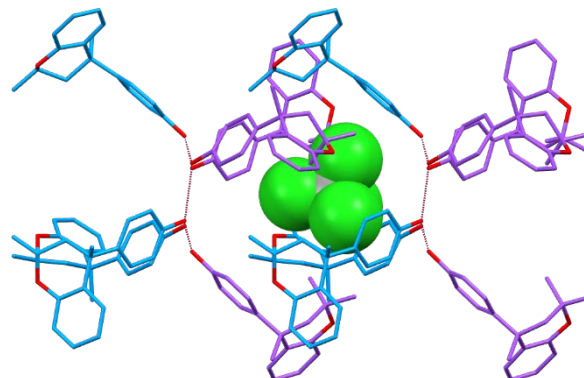


Figure 3. View down the *b*-axis, *c*-axis horizontal of the CCl₄ clathrate formed from the (+)-2*R*,4*R* epimer, **2** and *S*-(-)-Dianin's compound, **4**, shown in blue and purple respectively.

studied were prepared by recrystallisation of equimolar host components from neat CCl₄, as described in the literature⁸.

The host-guest packing in the CCl₄ clathrate formed from the 2-nor methyl epimers, (+)-2*R*,4*R*, **2**, and (+)-2*R*,4*S*, **3**, (Scheme 1), is illustrated in Figure 2§. In this case a partial ordering of a C-Cl bond of the guest molecule is observed with respect to the *c*-axial direction, with a ratio of the two disordered components refining to 70.7:29.3. In this structure the conformation of the (+)-2*R*,4*S* epimer corresponds directly to that found for Dianin's compound itself as characterised by the *proximal* relationship of the 4-*p*-hydroxyphenyl substituent with the non-sterically demanding hydrogen atom on C(2). This conformation is also found in the structurally related *racemic* CCl₄ clathrate formed from host components the 2*R*,4*S*/2*S*,4*R* 2-nor methyl enantiomers¹². Despite the very close correspondence of the unit cell parameters for the CCl₄ clathrate of Dianin's compound⁴ and the present structure, [$a = 26.8671$, $c = 10.8701$ Å and $a = 26.3307$, $c = 11.1874$ Å respectively], the conformation of the (+)-2*R*,4*R* epimer in this structure came as a complete surprise in that it does not exhibit the expected *proximal* relationship possessed by racemic Dianin type host structures but rather corresponds to ring inversion of the heterocyclic ring to give a *distal* relationship of the 4-*p*-hydroxyphenyl substituent with its *syn* related methyl group. The C(2)-C(3)-C(4)-C(11) torsion angles for molecule **2**, (*Distal*), and molecule **3**, (*Proximal*), conformations are 159.1(2) and -74.9(3)° respectively; the corresponding torsion angle for racemic Dianin's compound has magnitude 80.67° (ref. 4). The torsion angle O(1)-C(2)-C(3)-C(4), defining the heterocyclic ring

chirality, has values of -63.1(3) and -64.2(3)° for **2** and **3** respectively, in the **2/3** clathrate. The corresponding values for the enantiomers in the CCl₄ clathrate⁴ of **1** are +57.5 and -57.5°.

Figure 3 illustrates the host-guest crystal packing of the isomorphous structure of the CCl₄ clathrate formed from the host components, (+)-2*R*,4*R* 2-nor methyl epimer, **2** and *S*-(-)-Dianin's compound, **4**. In this structure the conformation of the *S*-(-)-Dianin's molecule is virtually identical to that found in its racemic CCl₄ clathrate, however its *quasiracemic* partner again exhibits the unexpected *distal* relationship as described above. In this case, reflecting a significantly altered cavity shape from that of racemic Dianin's compound, the complete ordering of the CCl₄ guest molecule occurs. The C(2)-C(3)-C(4)-C(11) torsion angles for molecule **2** (*Distal*), and molecule **4**, (*Proximal*), are 157.5(2) and -79.4(3)° respectively. The chirality-defining torsion angle O(1)-C(2)-C(3)-C(4), has values of -62.6(3) and -57.8(3)° for **2** and **4**, respectively, in the **2/4** clathrate. It should be noted that in this structure unlike Dianin's structure itself there are only three "waist" methyl groups rather than six. The remaining methyl group on C(2) of the 2-nor methyl component is displaced significantly by about $\frac{1}{3}c$ from its expected the waist position, away from the [OH]₆ hexamer to which its molecule contributes. It is apposite to consider the relative cavity volumes, (calculated using the program *Mercury*¹⁴, with contact surface, probe radius, 1.2 Å, grid spacing 0.25 Å) for the CCl₄ clathrates of **1**, **2/4** and **2/3** which are 694.73, 782.54 and 889.36 Å³, respectively. In the centrosymmetric classical hour glass-shaped cavity of **1** there is necessarily a statistical 50-50 guest orientation distribution. However, in the *larger* cavity of

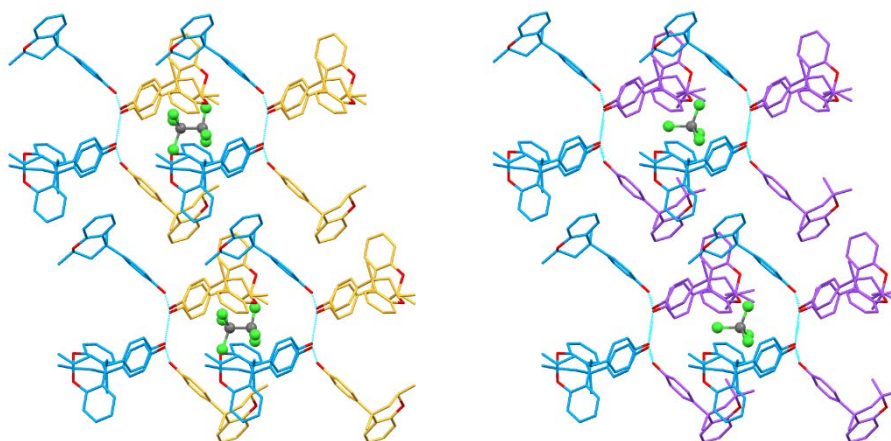
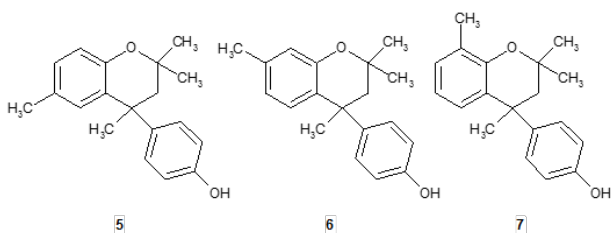


Figure 4. Intercolumn packing diagrams as viewed down the *b*-axis of the unit cell for structures **2/3** (left) and **2/4** (right). The structure colour codes are as for Figures 2 and 3. In these views the three-fold screw axis by which adjacent columns are related, parallel to the *c*-axis, runs horizontally.

the **2/4** host complete ordering of a C-Cl bond of the guest occurs, caused by the introduction of pronounced topological asymmetry with respect to the *c*-axial direction. This effect arises from the displacement of three cavity-wall methyl groups from their anticipated waist positions due to the novel host conformation adopted by the host molecule **2**; a second guest orientation is now precluded by prohibitive short contacts which would occur between the 'displaced' methyl groups and three chlorine atoms of the guest. For the **2/3** clathrate, whose expanded cavity volume corresponds to the replacement of the remaining bulky waist methyl groups of **2/4** by hydrogen atoms, both guest C-Cl bond orientations, (in non-equal proportions, *vide supra*) are present since neither is sterically prohibited. Thus, for strict guest orientation control, as found in the quasiracemate **2/4**, a combination of limited available space and suitable cavity topology is critical.

In view of the significant role of intercolumn packing identified³ for host consolidation in clathrates of **1**, it is important to note that the intervention of the unexpected *distal* host conformation does not disrupt the efficiency of intercolumn packing for **2/3** and **2/4**, as is nicely illustrated in Figure 4. Figures showing the different cavity shapes for **2/3** and **2/4** are included in the ESI.

Parentetically, it may be added that when a methyl group is substituted onto compound **1**, at the 6-, 7- or 8-positions, (Scheme 3), varied behaviour is observed, though the molecule always maintains a *proximal* conformation. The 8-methyl counterpart of **1** forms a CCl₄ clathrate with space group $R\bar{3}$, in which the guest is of course statistically disordered⁷; whilst the 6- and 7- counterparts¹³ crystallise unsolvated in the common



Scheme 3. 6-methyl, (**5**), 7-methyl, (**6**) and 8-methyl, (**7**) Dianin's compound counterparts.

centrosymmetric space group $P2_1/n$, $Z=4$, with infinite head-to-tail linking of molecules by O-H...O hydrogen bonds of lengths 2.795(1) and 2.812(1) Å, respectively, [see ESI for full structure details]. This almost certainly reflects a greater degree of potential intercolumn disruption by the more outward-projecting, (formally introduced), methyl groups, situated on the exterior of the columns for the 6-methyl and 7-methyl cases.

In conclusion, this work describes the discovery of two unique features. The first is the observation of an unprecedented host conformation for Dianin-type clathrate systems in which a *proximal* relationship does not exist between the *p*-hydroxyphenyl group and the corresponding substituent on C(2). The second feature is the total alignment of a non-polar guest in the cavity of a polar Dianin-type clathrate. Thus, it now becomes attractive to attempt to align suitable inherently polar molecules to enhance potential second harmonic generation (SHG) properties.

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Notes and references

†Whilst the prototypical rhombohedral Dianin host structure has universally $Z'(\text{host}) = 1$, $Z'(\text{host}) = 4$ has been found for a clathrate of **1** at low temperature, (J. J. Lee, R. O. Fuller, A. N. Sobolev, H. F. Clausen, J. Overgaard, G. A. Koutsantonis, Bo B. Iversen and M. A. Spackman, *Chem. Commun.*, 2013, **47**, 2029); and a maximum $Z'(\text{host}) = 16$ has very recently been observed at low temperature for the direct thia- and selenachroman analogues of **1** (C. S. Frampton, K. A. Ketuly, H. B. M. Ali, A. H. S. Azizan, J. H. Gall and D. D. MacNicol, *Cryst. Eng. Comm.*, 2017, **19**, 2653.)

‡For a comprehensive description of the term quasiracemate see K. A. Wheeler, R. C. Grove, R. E. Davis and W. S. Kassel. *Angew. Chem. Int. Ed.*, (2008), **47**, 78.

§ *Crystal data* for **2/3**: $3(\text{C}_{17}\text{H}_{18}\text{O}_2)$, $3(\text{C}_{17}\text{H}_{18}\text{O}_2)$, CCl_4 , $M = 1679.69$, $a = 26.3307(3)$ Å, $b = 26.3307(3)$ Å, $c = 11.1874(3)$ Å, $\alpha = 90.00^\circ$, $\beta = 90.00^\circ$, $\gamma = 120.00^\circ$, $V = 6717.1(2)$ Å³, $T = 100(1)$ K, trigonal, space group $R3$, $Z = 3$, $\mu(\text{Cu K}\alpha) = 1.694$ mm⁻¹, 15436 reflections measured,

5891 independent ($R_{\text{int}} = 0.0168$). The final R_1 value was 0.0489 for 5838 reflections with $I > 2\sigma(I)$, the final $wR^2(F^2)$ value was 0.1363 (all data). Goodness of fit on F^2 was 1.061, Flack parameter = 0.037(10). Maximum and minimum residual density = 0.900 and $-0.477 \text{ e } \text{\AA}^{-3}$. CCDC deposition number 1541892. *Crystal data for 2/4*: $3(\text{C}_{18}\text{H}_{20}\text{O}_2)$, $3(\text{C}_{17}\text{H}_{18}\text{O}_2)$, CCl_4 , $M = 1721.77$, $a = 26.5576(5) \text{ \AA}$, $b = 26.5576(5) \text{ \AA}$, $c = 11.1274(4) \text{ \AA}$, $\alpha = 90.00^\circ$, $\beta = 90.00^\circ$, $\gamma = 120.00^\circ$, $V = 6796.8(4) \text{ \AA}^3$, $T = 100(1) \text{ K}$, trigonal, space group $R\bar{3}$, $Z = 3$, $\mu(\text{Cu K}\alpha) = 1.687 \text{ mm}^{-1}$, 16141 reflections measured, 5821 independent ($R_{\text{int}} = 0.0245$). The final R_1 value was 0.0331 for 5617 reflections with $I > 2\sigma(I)$, the final $wR^2(F^2)$ value was 0.0931 (all data). Goodness of fit on F^2 was 1.001, Flack parameter = 0.012(6). Maximum and minimum residual density = 0.419 and $-0.420 \text{ e } \text{\AA}^{-3}$. CCDC deposition number 1541849. *Crystal data for 5*: $\text{C}_{19}\text{H}_{22}\text{O}_2$, $M = 282.36$, $a = 14.14913(16) \text{ \AA}$, $b = 6.42088(6) \text{ \AA}$, $c = 18.3566(2) \text{ \AA}$, $\alpha = 90.00^\circ$, $\beta = 111.973(1)^\circ$, $\gamma = 90.00^\circ$, $V = 1546.55(3) \text{ \AA}^3$, $T = 100(1) \text{ K}$, monoclinic, space group $P2_1/n$, $Z = 4$, $\mu(\text{Cu K}\alpha) = 0.603 \text{ mm}^{-1}$, 13535 reflections measured, 3154 independent ($R_{\text{int}} = 0.0187$). The final R_1 value was 0.0355 for 2924 reflections with $I > 2\sigma(I)$, the final $wR^2(F^2)$ value was 0.0934 (all data). Goodness of fit on F^2 was 1.019. Maximum and minimum residual density = 0.305 and $-0.200 \text{ e } \text{\AA}^{-3}$. CCDC deposition number 1558621. *Crystal data for 6*: $\text{C}_{19}\text{H}_{22}\text{O}_2$, $M = 282.36$, $a = 9.77030(15) \text{ \AA}$, $b = 12.02971(18) \text{ \AA}$, $c = 12.7860(2) \text{ \AA}$, $\alpha = 90.00^\circ$, $\beta = 90.657(1)^\circ$, $\gamma = 90.00^\circ$, $V = 1502.69(4) \text{ \AA}^3$, $T = 100(1) \text{ K}$, monoclinic, space group $P2_1/n$, $Z = 4$, $\mu(\text{Cu K}\alpha) = 0.620 \text{ mm}^{-1}$, 6135 reflections measured, 3058 independent ($R_{\text{int}} = 0.0133$). The final R_1 value was 0.0350 for 2866 reflections with $I > 2\sigma(I)$, the final $wR^2(F^2)$ value was 0.0928 (all data). Goodness of fit on F^2 was 1.026. Maximum and minimum residual density = 0.299 and $-0.180 \text{ e } \text{\AA}^{-3}$. CCDC deposition number 1558622. All structures were solved and refined with the SHELX¹⁵ suite of programs.

Electronic Supplementary Information (ESI) available: Full experimental details, crystal structure data, orpep diagrams for **2/3**, **2/4**, **5** and **6**, packing diagrams for **5** and **6**, void space figures for structures **2/3** and **2/4**. [CCDC Deposition numbers 1541892, **2/3**, 1541849, **2/4**, 1558621, **5** and 1558622, **6**]. See DOI: 10.1039/x0xx00000x

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