

## Total CCl<sub>4</sub> guest alignment in a *quasiracemic* clathrate closely related to Dianin's compound

 Christopher S. Frampton<sup>\*a</sup>, James H. Gall<sup>b</sup> and David D. MacNicol<sup>\*b</sup>

 Received 00th January 20xx,  
 Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Single crystal X-ray analysis at 100 K reveals that in the trigonal CCl<sub>4</sub> *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 compound **1**, (±)-4-*p*-hydroxyphenyl-2,2,4-trimethylchroman **1**, and related compounds have been the subject of substantial sustained interest for more than half a century<sup>2</sup>, 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 energies<sup>3</sup>, host response to the nature of the guest<sup>4</sup>, hydrogen bond reorientation<sup>5</sup>, guest transport<sup>6</sup>, and, of immediate relevance to the present communication, guest alignment, *vide infra*.

Typically, the racemic clathrates of **1**, and those formed by synthetic analogues<sup>7</sup>, crystallise in the premier clathrate space group *R*3̄, with a single crystallographically independent host molecule in the asymmetric unit<sup>1</sup>; and the host packing is characterised by infinite stacking of *C*<sub>3v</sub>-symmetric hydrogen-bonded [OH]<sub>6</sub> 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

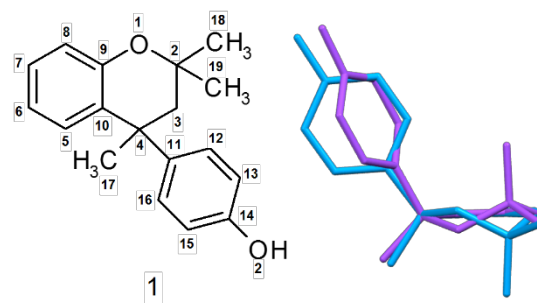


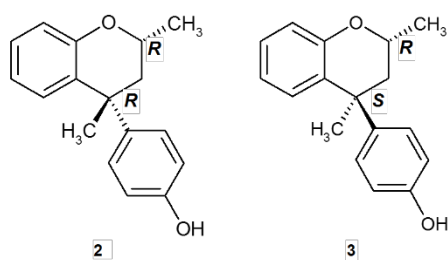
Figure 1. Overlay of the proximal (purple) and distal (blue) conformations of Dianin's compound **1**, illustrated for the *S*-enantiomer, the atom numbering scheme used for torsion angle discussion is shown. In this view the fused benzene ring is hidden.

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 ago<sup>8</sup>. 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*<sup>†</sup> chiral clathrate, space group *R*3̄, formed from the *R*-enantiomeric form of **1** and the *S*-enantiomeric form of its direct thiachroman counterpart<sup>9</sup>, that there was partial alignment of the CCl<sub>4</sub> 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]<sub>3</sub> hexamer replacing the conventional [OH]<sub>6</sub> host hexamer.<sup>10</sup> NQR has also been employed to study the motion of the CCl<sub>4</sub> guest molecule in host **1** itself<sup>11</sup>. We now present detailed single-crystal X-ray analyses at 100K of these earlier prototypical *quasiracemic* polar structures, space group *R*3̄, which reveal a novel complete guest orientation phenomenon and an unprecedented host conformation. The CCl<sub>4</sub> clathrates

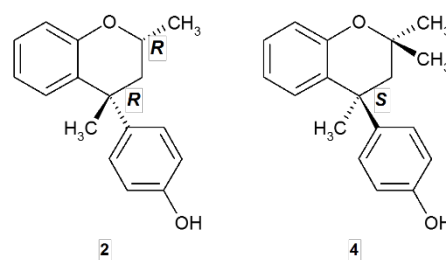
<sup>a</sup> Wolfson Centre for Materials Processing, Brunel University, Kingston Lane, Uxbridge, Middlesex UB8 3PH, UK, Tel: +44 (0)1895 265337; Fax: +44 (0)1895 203376; Email: chris.frampton@brunel.ac.uk.

<sup>b</sup> Department of Chemistry, University of Glasgow, Glasgow G12 8QQ, Scotland, UK, Tel: +44 (0)141 330 4479; Email: david.macnicol@glasgow.ac.uk.

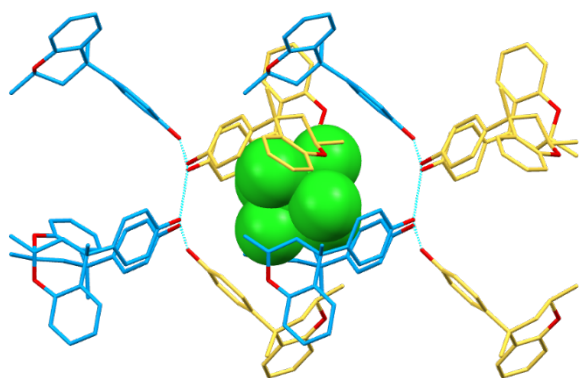
Electronic Supplementary Information (ESI) available: Full experimental details and crystal structure data. [CCDC Deposition numbers 1541892, 2/3, 1541849, 2/4, 1558621, 5 and 1558622, 6]. See DOI: 10.1039/x0xx00000x



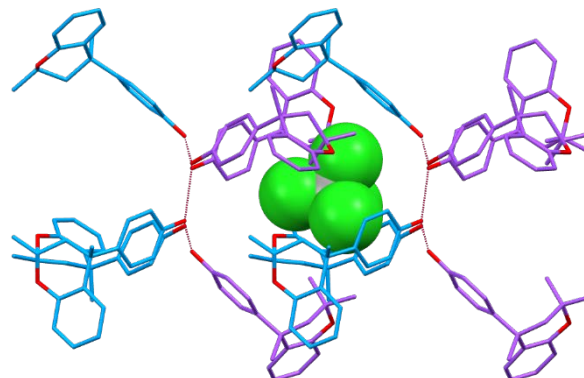
**Scheme 1.** 2-nor methyl epimers of Dianin's compound, (+)-2*R*,4*R*, **2** and (+)-2*R*,4*S*, **3**.



**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 CCl<sub>4</sub> clathrate formed from the nor-methyl components (+)-2*R*,4*R*, **2** and (+)-2*R*,4*S*, **3**, shown in blue and yellow respectively.



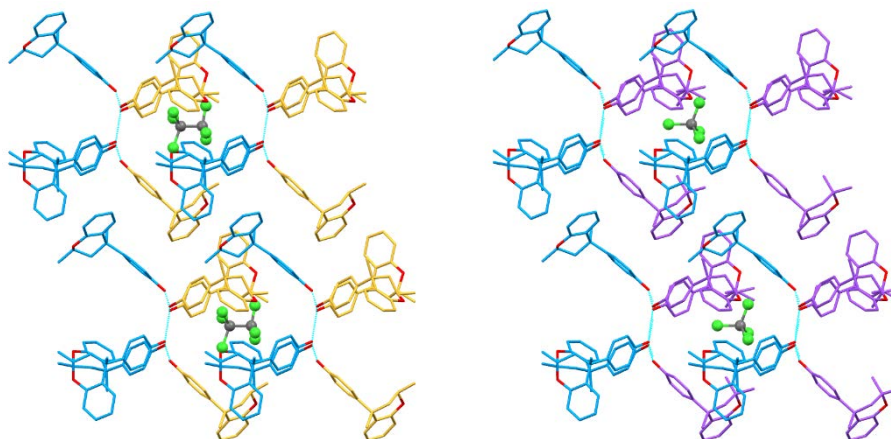
**Figure 3.** View down the *b*-axis, *c*-axis horizontal of the CCl<sub>4</sub> clathrate formed from the (+)-2*R*,4*R* epimer, **2** and *S*(-)-Dianin's compound, **4**, shown in blue and purple respectively.

studied were prepared by recrystallisation of equimolar host components from neat CCl<sub>4</sub>, as described in the literature<sup>8</sup>.

The host-guest packing in the CCl<sub>4</sub> 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* CCl<sub>4</sub> clathrate formed from host components the 2*R*,4*S*/2*S*,4*R* 2-nor methyl enantiomers<sup>12</sup>. Despite the very close correspondence of the unit cell parameters for the CCl<sub>4</sub> clathrate of Dianin's compound<sup>4</sup> 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 CCl<sub>4</sub> clathrate<sup>4</sup> of **1** are +57.5 and -57.5°.

Figure 3 illustrates the host-guest crystal packing of the isomorphous structure of the CCl<sub>4</sub> 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 CCl<sub>4</sub> 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 CCl<sub>4</sub> 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]<sub>6</sub> hexamer to which its molecule contributes. It is apposite to consider the relative cavity volumes, (calculated using the program *Mercury*<sup>14</sup>, with contact surface, probe radius, 1.2 Å, grid spacing 0.25 Å) for the CCl<sub>4</sub> clathrates of **1**, **2/4** and **2/3** which are 694.73, 782.54 and 889.36 Å<sup>3</sup>, 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

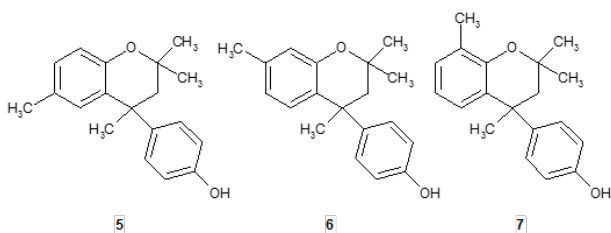


**Figure 4.** Intercolumn packing diagrams as viewed down the *b*-axis of the unit cell for structures **2/3** (left) and **2/4** (right). The structure colour codes are as for Figures 2 and 3. In these views the three-fold screw axis by which adjacent columns are related, parallel to the *c*-axis, runs 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 identified<sup>3</sup> 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 CCl<sub>4</sub> clathrate with space group  $R\bar{3}$ , in which the guest is of course statistically disordered<sup>7</sup>; whilst the 6- and 7- counterparts<sup>13</sup> 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.

Financial support from the Malaysia HIR MOHE, Grant No. F000009-21001, is gratefully acknowledged. We wish to thank the Collège de France for a generous donation of samples.

## 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**:  $3(\text{C}_{17}\text{H}_{18}\text{O}_2)$ ,  $3(\text{C}_{17}\text{H}_{18}\text{O}_2)$ ,  $\text{CCl}_4$ ,  $M = 1679.69$ ,  $a = 26.3307(3)$  Å,  $b = 26.3307(3)$  Å,  $c = 11.1874(3)$  Å,  $\alpha = 90.00^\circ$ ,  $\beta = 90.00^\circ$ ,  $\gamma = 120.00^\circ$ ,  $V = 6717.1(2)$  Å<sup>3</sup>,  $T = 100(1)$  K, trigonal, space group  $R3$ ,  $Z = 3$ ,  $\mu(\text{Cu K}\alpha) = 1.694$  mm<sup>-1</sup>, 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*:  $3(\text{C}_{18}\text{H}_{20}\text{O}_2)$ ,  $3(\text{C}_{17}\text{H}_{18}\text{O}_2)$ ,  $\text{CCl}_4$ ,  $M = 1721.77$ ,  $a = 26.5576(5) \text{ \AA}$ ,  $b = 26.5576(5) \text{ \AA}$ ,  $c = 11.1274(4) \text{ \AA}$ ,  $\alpha = 90.00^\circ$ ,  $\beta = 90.00^\circ$ ,  $\gamma = 120.00^\circ$ ,  $V = 6796.8(4) \text{ \AA}^3$ ,  $T = 100(1) \text{ K}$ , 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 SHELX<sup>15</sup> 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

- 1 L. Pang, E. A. C. Lucken and G. Bernardinelli, *J. Am. Chem. Soc.*, 1990, **112**, 8754.
- 2 J. H. Gall, A. D. U. Hardy, J. J. McKendrick, and D. D. MacNicol, *J. Chem. Soc., Perkin Trans. 2*, 1979, 376.
- 3 Previously only the space group and unit cell dimensions had been determined; A. D. U. Hardy, J. J. McKendrick and D. D. MacNicol, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1072.
- 4 C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek and P. A. Wood, *J. Appl. Crystallogr.*, 2008, **41**, 466-470.
- 5 G. M. Sheldrick, *Acta Crystallogr. Sect A: Found. Crystallogr.*, 2008, **64(1)**, 112-122; G. M. Sheldrick, *Acta Crystallogr. Sect C: Cryst. Struct. Commun.*, 2015, **71**, 3-8.
- 6 A. P. Dianin, *J. Russe. Phys. Chem. Soc.*, 1914, **46**, 1310.
- 7 See, for example, P. Finocchiaro and S. Failla, Other Potentially Important Hosts, in *Comprehensive Supramolecular Chemistry*, Eds. D. D. MacNicol, F. Toda and R. Bishop, Elsevier Science, Oxford, 1996, **Vol. 6, Ch. 18**, pp. 618-632; R. Bishop, *Synthetic Clathrate Systems*, in *Supramolecular Chemistry; From Molecules to Nanomaterials*, Eds. P. A. Gale and J. W. Steed, John Wiley & Sons, Ltd., 2012, pp. 3033-3056.
- 8 E. Eikeland, M. A. Spackman, and Bo B. Iversen, *Cryst. Growth Des.*, 2016, **16**, 6858.
- 9 J. J. Lee, A. N. Sobolev, M. J. Turner, R. O. Fuller, Bo B. Iversen, G. A. Koutsantonis, M. A. Spackman, *Cryst. Growth Des.*, 2014, **14**, 1296.
- 10 A. Nemkevich, M. A. Spackman, and B. Corry, *J. Am. Chem. Soc.*, 2011, **133**, 18880.
- 11 A. Nemkevich, M. A. Spackman, and B. Corry, *Chem. Eur. J.*, 2013, **19**, 2676.
- 12 D. D. MacNicol, *Structure and design of inclusion compounds: the clathrates of hydroquinone, phenol, Dianin's compound and related systems*, in *Inclusion Compounds*, Ed. J. L. Atwood, J. E. D. Davies and D. D. MacNicol, Academic Press, 1984, **Vol. 2, Ch. 1**, pp. 12-32; see also Ref. 2
- 13 A. Collet and J. Jacques, *Isr. J. Chem.*, 1976/1977, **15**, 82.
- 14 C. S. Frampton, K. A. Ketuly, A. H. A. Hadi, J. H. Gall and D. D. MacNicol, *Chem. Commun.*, 2013, **49**, 7198.
- 15 T. Jacobs, M. W. Bredenkamp, P. H. Neethling, E. G. Rohwer and L. J. Barbour, *Chem. Commun.*, 2010, **46**, 8341.