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Chloral Hydrate Polymorphs and Cocrystal Revisited: Solving Two Pharmaceutical Cold Cases

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ABSTRACT: Chloral hydrate has the distinction of perhaps being the first reported example of a pharmaceutical compound to exhibit polymorphism (1877) and the first use of a pharmaceutical cocrystal in a drug product (Beta-Chlor®, 1960's). Nevertheless, chloral hydrate represents a microcosm of contemporary issues in solid-state chemistry and its importance to pharmaceutical science. Ironically, the single crystal structures of the **β**-form of chloral hydrate and its pharmaceutical cocrystal with betaine have not yet been reported. In this contribution, the single crystal structures and physical properties of these crystal forms are reported for the first time. The previously termed "high temperature" **β**-form of chloral hydrate was obtained by melting the **α**-form of chloral hydrate and crystallizing from the melt. The **α**-form of chloral hydrate is comprised of diol-diol homodimers that further assemble into a sheet of 6-membered rings. The **β**-form is sustained by head-to-tail OH···O hydrogen bonds that form a sheet built from two types of 3- and 5- membered rings. The diol-diol interactions that sustain these polymorphs are placed in context through a CSD analysis. The chloral hydrate–betaine cocrystal (CHOBTN) was obtained by slow cooling from water, exhibits higher thermal stability than the chloral hydrate polymorphs, and is sustained by a previously known 2-point diol-carboxylate supramolecular heterosynthon that could be of general utility.

INTRODUCTION

McCrone's seminal work[1] described how polymorphs can sometimes impact physicochemical properties of relevance to drug delivery. Regulatory requirements for drug substances to be subject to crystal form screening for the existence of polymorphs, solvates and hydrates were subsequently introduced in 1987[2a] and remain a key step in the early stages of drug development.[2b,c] The relevance of polymorphism to the pharmaceutical industry is a contemporary subject of interest since predicting the existence of polymorphs before they are made remains a scientific challenge[3] and there could be intellectual property opportunities that accompany the discovery of new crystal forms.[4] In this context, the subject of pharmaceutical cocrystals has risen to prominence in recent years since it has become apparent that pharmaceutical cocrystals can offer much greater changes in physicochemical properties than can occur in polymorphs, solvates and hydrates.[5]

Benzamide,[6] a polymorphic molecular compound that is still being explored in the 21st century,[7,8] was first reported to be polymorphic in 1832 by Liebig and Wöhler. The same year, Liebig also synthesized chloral hydrate (2,2,2-trichloroethane-1,1-diol): "by passing dry chlorine gas over hot alcohol until no more HCl was produced".[9] Chloral hydrate quickly found utility as a sedative/hypnotic and was widely used throughout the 19th century for this purpose. However, as safer and more effective sedatives were discovered and developed, chloral hydrate fell out of favor. Nevertheless, chloral hydrate remained on the market as an "unapproved drug" after the US congress passed the Federal Food, Drug, and Cosmetic act of 1938.[10]

Groth, in 1872, reported studies concerning crystal forms of chloral hydrate,[11] however, having received crystals from a local factory, may not have observed polymorphism. Berthelot (1877) noticed oddities in the latent heat of fusion in chloral hydrate,[12] suggesting that it may have something to do with the plasticity of the re-solidified compound. However, it was Pope (1899) who recognized Berthelot's findings as polymorphism.[13] He obtained two crystal forms through recrystallization experiments and polarized micrographs were taken. However, the **β**-form was found to be too unstable to be studied with a goniometer. X-ray crystallography was subsequently used to study the **α**-form by Ogawa[14] and neutron diffraction studies were later reported by Levy.[15] The unit cell parameters reported from these experiments disagree with measurements by Pope, Dufet,[16] and Des Cloizeaux.[17]

Chloral hydrate (CHO) has also been used as a coformer in a 1:1 pharmaceutical cocrystal with betaine (N, N, N-trimethylglycine, BTN), CHOBTN. CHOBTN could represent the first use of a pharmaceutical cocrystal as a drug substance in a pharmaceutical product, Beta-Chlor®. Petrow *et al.* were issued US patent 3,028,240 in 1962. This

patent details the preparation of CHOBTN and how it exhibits the same medicinal properties as chloral hydrate but with less antagonistic effects and a higher melting point.[18] CHOBTN was later marketed by Mead Johnson in 1963 and to our knowledge represents the first pharmaceutical cocrystal to be marketed in the US.[19]

In this contribution, the single crystal structures of the polymorphs of chloral hydrate and CHOBTN are reported for the first time and we also address the physical properties of these crystal forms and their implications for crystal engineering of diol compounds.

EXPERIMENTAL

Synthesis. Chloral hydrate was purchased from Sigma Aldrich and used without further purification. Single crystals of the **α**–form were obtained by slow evaporation of the as-received chloral hydrate (331 mg, 2.00 mmol) in acetone (220 μl) from an open vial under ambient conditions. After six weeks, colorless prismatic crystals were obtained and harvested. Single crystals of the **β**–form (992 mg, 6.00 mmol) were obtained by recrystallization of the melted **α**–form via heating to 60 °C and cooling to room temperature. A powder X-ray diffraction (PXRD) study indicated that the **α**–form of chloral hydrate converts to the **β**–form after the first melt. Repeating this process three times afforded needles of the **β**–form. PXRD further revealed that the **β**–form reverts to the **α**–form over a period of seven days. CHOBTN was obtained by dissolving as-received chloral hydrate (32.0 mg, 0.193 mmol) and betaine (22.6 mg, 0.193 mmol) in 200 μl deionized H_2O. This solution was placed on a watch glass and heated to 60 °C. Square plates were observed to form upon cooling to room temperature. Microcrystalline powders of CHOBTN were obtained by solvent-drop grinding at room temperature using the same quantities as above.

Single Crystal X-ray Diffraction (SXRD). The crystallographic and structural parameters for the polymorphs of chloral hydrate and CHOBTN are presented in Table 1. Reflection data for the **α**– and **β**–form of chloral hydrate and CHOBTN were collected on a Bruker D8 Quest single crystal X-ray diffractometer with sealed tube MoKα source (λ = 0.71073) and TRIUMPH mirror. Absorption corrections were carried out using the multi-scan method in SADABS. XPREP in APEX3 was used for spacegroup determination. The structures were solved in the APEX3 program using intrinsic methods in SHELXT and refined against all F_o using SHELXL in the program SHELXLE. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms in the **α**-form of chloral hydrate and CHOBTN were refined with torsion angles derived from a difference Fourier synthesis and refined as a rigid group. Hydrogen atoms in the **β**–form were refined using a riding model. Due to the difficulty in obtaining the **β**-form, a small poorly diffracting crystal was used for data collection. Further to this, due to the **β**-form existing at higher temperatures, data collection was carried out at room temperature. Ultimately, these restrictions, as well as the instability of the **β**-form which decomposed during data collection, led to the mediocre quality of crystal data. See ESI for further details.

Table 1 Crystallographic parameters for the α and β, forms of chloral hydrate and its betaine cocrystal, CHOBTN

	α	β	CHOBTN
Formula	$C_2H_3Cl_3O_2$	$C_2H_3Cl_3O_2$	$C_7H_{14}Cl_3NO_4$
M	165.40	165.40	282.55
T (K)	273(2)	301(2)	298(2)
Crystal System	Monoclinic	Monoclinic	Monoclinic
Spacegroup	$P\,2_1/c$	$P\,2_1/n$	$P2_1/c$
a (Å)	10.5714(10)	10.0216(16)	9.2451(9)
b (Å)	5.9647(6)	5.9870(9)	11.5444(11)
c (Å)	9.6727(8)	39.612(6)	11.5227(10)
β (°)	111.226(2)	92.446(4)	91.390(2)
Volume (Å^3)	568.54(9)	2374.5(6)	1229.4(2)
Z, Z′	4, 1	16, 4	4, 1
μ, mm-1	1.494	1.431	0.739
Reflections	7341	30976	20272
Unique Reflections	1305	3426	2080
R_{int}	0.0382	0.1362	0.0227
Final R_1 [I>2σ(I)]	0.0378	0.0852	0.0403
Final $wR(F^2)$ [I>2σ(I)]	0.1123	0.1470	0.1096
R_1 (all data)	0.0539	0.1280	0.0440
wR(F^2) (all data)	0.1246	0.1570	0.1146
GooF	0.925	1.150	1.188

Powder X-ray Diffraction (PXRD). Diffraction studies of microcrystalline samples were performed in Bragg-Brentano geometry on a Panalytical Empyrean diffractometer (40 kV, 40 mA, CuKα1,2 (λ = 1.5418 Å). A scan speed of 0.5 s/step (6°/min) with a step size of 0.05° in 2θ was used at room temperature.

Differential Scanning Calorimetry (DSC). Thermal analysis was conducted using a TA Q2000 heat flux DSC. Microcrystalline samples of chloral hydrate were hermetically sealed in aluminum pans and a ramp rate of 20 °C/min between -20 °C and 120 °C was applied under a N2 atmosphere. Measured heat flow was compared with that of an empty aluminum pan.

Survey of the Cambridge Structural Database (CSD). Conquest v5.37 with the November 2015 update was used to survey organic geminal and vicinal diols. Filters were as follows: 3D coordinates determined; no ions; R ≤ 0.075. The intermolecular distance between –OH groups was 2.7 ± 0.3 Å and entries were analyzed using Mercury 3.7.

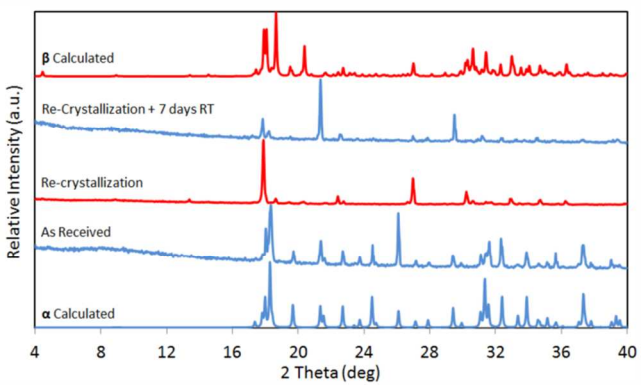

Figure 1. Comparisons of the calculated PXRD patterns of the **α** and **β** polymorphs of chloral hydrate with experimentally measured PXRD patterns.

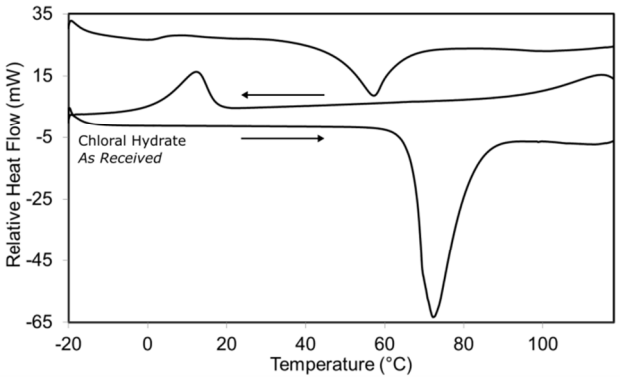

Figure 2. DSC thermograms of the **α**–form of chloral hydrate melting (bottom) and re-crystallizing as the **β**–form (middle) and the melt of the **β**–form (top).

RESULTS & DISCUSSION

Interconversion of Chloral Hydrate Polymorphs. Pope's contribution over a century ago gave insight into how to obtain single crystals of both polymorphs of chloral hydrate. Experiments varying the temperature, solvent, and crystallization method (slow evaporation, recrystallization from the melt, and supersaturated slurries) were conducted to study the relationship between the two polymorphs. As-received chloral hydrate was determined to be the **α**–form by comparison of experimental powder X-ray diffractograms with that calculated for the single crystal structure (Figure 1). Melting and cooling of the **α**–form resulted in clusters of colorless needles which were observed to be brittle and become opaque upon being stressed by touching with a needle. Repetitive melting and recrystallizing in an oven (heat to 60 °C, slow cool to RT, repeat) afforded larger and more stable single crystals of the **β**–form and allowed for an SXRD study. DSC experiments conducted on the **α**–form revealed that onset of the melt occurred at approximately 56 °C and that, upon cooling, a recrystallization event occurred at approximately 20 °C (Figure 2). Reheating this recrystallized sample resulted in a broad melting event at a lower temperature than before; suggesting that a new, less stable, phase had been formed. Reproduction of this experiment on a hotplate enabled isolation of the **β**-form of chloral hydrate and for measurement of its PXRD pattern. We observed that the metastable **β**-form survives for ca. seven days under ambient conditions before full conversion to the more stable **α**-form occurs (Figure 1). The crystal habits and melting points can distinguish between the two forms of chloral hydrate. DSC, PXRD, and SXRD experiments also indicate that the **β**-form can be readily prepared by cooling the melted **α**-form. The polymorphic behavior of chloral hydrate is consistent with an enantiotropic system. The narrow temperature range within which these polymorphs exist suggests that the crystal forms are of similar energy. Pope's assertion, that the peculiar melting points of chloral hydrate were due to polymorphism, is therefore validated by our study.

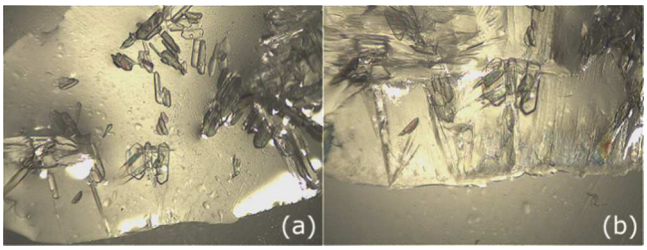

Figure 3. (a) Prismatic crystals of the **α**-form of chloral hydrate; (b) Emergence of **β**–form needles from the mother liquor already containing **α**–form prisms.

Synthesis and Structural Analysis of Chloral Hydrate Polymorphs. Single crystals of the **α**-form were obtained by slow evaporation from an acetone solution of chloral hydrate in a scintillation vial. Removal of **α**–form crystals and mother liquor from the vial in order to obtain images of these crystals resulted in fast evaporation of solvent and crystals of the **β**-form needles were observed to appear within minutes (Figure 3). The difference between crystal habits (i.e. prismatic **α**-form and needle-like **β**-form) that allows for distinction between the polymorphs is in good agreement with Pope's study[13] and was verified by measurement of the respective unit cell parameters. Room temperature slow evaporation of chloral hydrate in ethanol resulted in the formation of 2,2,2-trichloroethyl acetate, consistent with the known instability of geminal-diol compounds (see ESI for crystallographic data).

The crystal structure of the **α**-form of chloral hydrate packs with four molecules per unit cell in $P2_1/c$ with $Z' = 1$. Chloral hydrate molecules form hydrogen-bonded homodimers through diol–diol interactions which exhibit an $R^2_2(8)$ graph set[20] motif with OH···O distances of 2.837(3) Å. The motif and atoms involved in the diol – diol dimers are reminiscent of the supramolecular heterosynthons[21] formed by carboxamides[22] which result in exterior H-bond donors that remain to be satisfied and thereby tend to afford extended H-bond networks. In the structure of the **α**-form, the extra two donors on the periphery of each dimer form hydrogen bonds to open acceptor sites on neighboring dimers, thereby forming 4,4 sheets that are corrugated (Figure 4). A schematic illustration of how four diol-diol dimers engage to form a larger $R^4_4(16)$ motif that sustains the 4,4 sheets is given in Figure 5(a). The larger ring motif appears to be stabilized by bifurcated

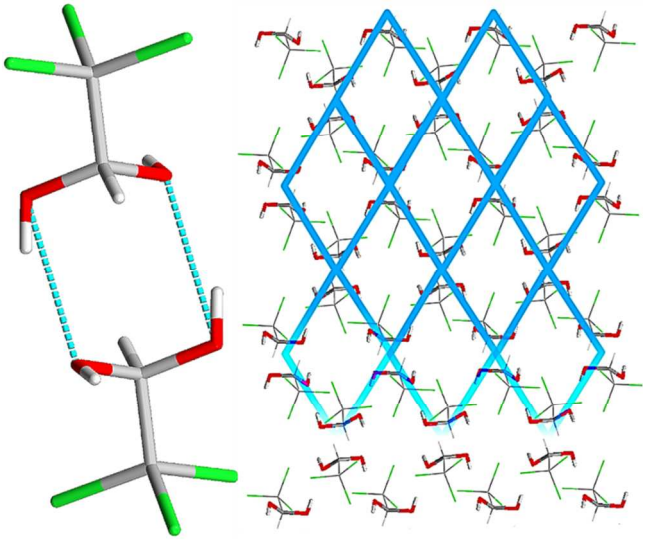

Figure 4. Self-assembly of diol-diol homodimers (left) results in corrugated 4,4 sheets (right) in the **α**-form of chloral hydrate.

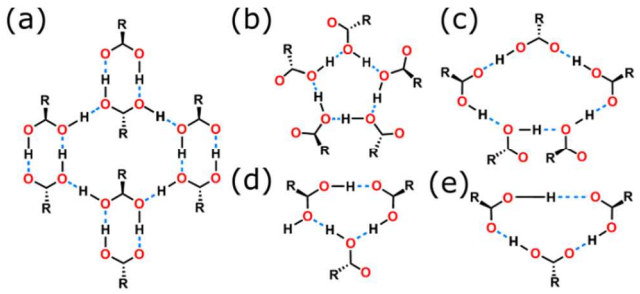

Figure 5. (a) Self-assembly of diol-diol dimers in the **α**-form of chloral hydrate result in self-assembly as shown; (b) First pentagonal ring of the **β**-form generated from head-to-tail interactions of five hydroxyl groups; (c) Second pentagonal ring of the **β**-form generated by hydrogen bonding between three geminal diols and two hydroxyl groups; (d) First triangular ring of the **β**-form sustained by two geminal diols and one hydroxyl group; (e) Second triangular ring of the **β**-form containing three geminal diols (R = -CCl_3, non-interacting hydrogen atoms removed for clarity).

Cl···O interactions with distances of 3.0777(2) and 3.1883(19) Å. Chloral hydrate molecules are arranged in such a manner that the –CCl_3 functional groups are oriented at the surface of each layer. This results in stacking of the 4,4 sheets with the closest distance between layers being the result of Cl···Cl interactions[23] (3.6406(3) Å).

The crystal structure of the **β**-form of chloral hydrate is a high Z' structure with 16 molecules per unit cell in $P2_1/n$ and $Z' = 4$. The crystal packing of the **β**-form can also be described as sheets but these sheets are not based upon self-assembly of diol-diol dimers. Indeed, the diol–diol dimers seen in the **α**-form are not even present in the **β**-form. Instead, the hydroxyl groups on chloral hydrate molecules form head-to-tail assemblies that generate rings. Specifically, two types of pentagonal ring and two types of triangular ring afford the observed sheet-like assembly and help to explain the high Z' value. The first pentagonal ring is sustained by the hydrogen bonding of one –OH group from each of five chloral hydrate molecules (Figure 5(b)). The OH···O bond distances within the first pentagonal ring range between 2.667(8) Å - 2.930(9) Å.

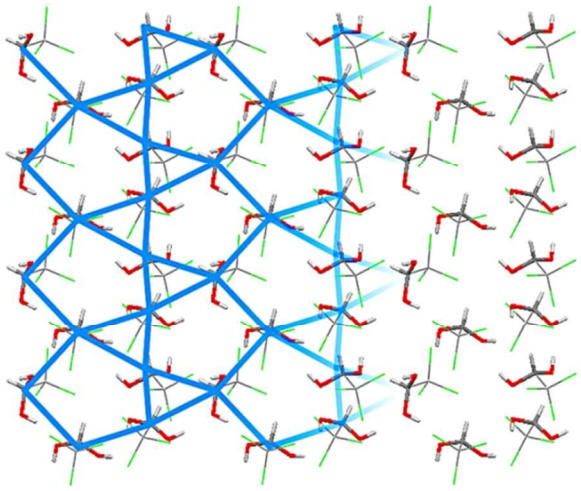

Figure 6. Self-assembly of heat-to-tail hydrogen bonds forming pentagonal and triangular rings in the **β**-form of chloral hydrate

The second pentagonal ring is an expanded ring because it results from a different motif formed by both hydroxyl groups of three geminal diols and a single hydroxyl group of two other chloral hydrate molecules (Figure 5(c)). Similar to the first pentagonal ring, this motif is also an irregular pentagon with intermolecular hydrogen bond distances ranging from 2.740(9) Å to 2.798(9) Å. The first triangular ring forms via self-assembly of two diols and a single hydroxyl group of a third chloral hydrate molecule (Figure 5(d)). One of the diols uses both donor contacts in the ring while the other utilizes both acceptor contacts. The hydroxyl group closes the ring as a triangle. The hydrogen bond distances found within this ring range from 2.703(9) Å to 2.798(9) Å. The second triangular ring is constructed through OH···O interactions between three diol functional groups (Figure 5(e)). Hydrogen bond distances range from 2.667(8) Å to 2.930(9) Å. Figure 6 reveals how these triangular and pentagonal ring motifs combine to form sheets which in turn stack with –CCl_3 functional groups at the surface. The closest contacts between the sheets are Cl···Cl interactions[23] with distances of 3.5178(3) Å.

The First Pharmaceutical Cocrystal to Reach Market? Chloral Hydrate – Betaine. The subject of pharmaceutical cocrystals has been thoroughly reviewed in recent years.[24] The history of pharmaceutical cocrystals dates back to at least the 1930's with the complexation of APIs to hydrotropic agents.[30] In 1934 Von Heyden AG was awarded what may be the first patent of a molecular cocrystal with the potential for pharmaceutical utility.[25] However, there is no evidence that these multicomponent materials (barbiturate – pyridine derivative cocrystals) were ever used as drug substances in drug

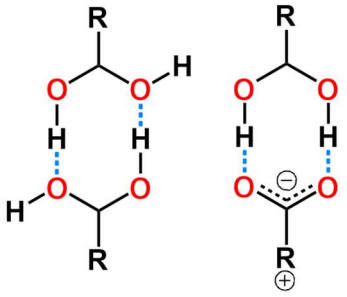

Figure 7. Diol-diol homodimers as observed in the α-form of chloral hydrate (left) and the charge-assisted diol-carboxylate heterodimers that sustain CHOBTN (right).

products. Our review of the literature suggests that the 1:1 cocrystal of chloral hydrate and betaine, CHOBTN, could be the first use of a pharmaceutical cocrystal as the drug substance in a drug product, Beta-Chlor®; which first appeared on the US market in 1963. To our knowledge, the only other examples to date are the active ingredients of Depakote®,[26] Entresto®,[27] Cafcit®[28] and Lexapro®,[29] most of which are ionic cocrystals.[24a]

The concepts of crystal engineering[31] can be exploited for the design of new pharmaceutical cocrystals from first principles.[32] Rational design of novel cocrystals requires an understanding of supramolecular synthons,[33] in particular the propensity of a given functional group to form specific hydrogen-bonded supramolecular heterosynthons in the presence of competing interactions. Our research group has systematically addressed the hierarchy of several supramolecular synthons that are of general relevance to drug molecules.[34] Figure 7 illustrates that there is in effect a competition between diol homodimers, as observed in the α-form of chloral hydrate, and the diol-carboxylate supramolecular heterosynthon that sustains CHOBTN.[22] That CHOBTN and the cocrystal between vitamin C and betaine, ASCBTN,[34c] exist suggests that the carboxylate-diol charge-assisted supramolecular heterosynthon is favored over diol-diol supramolecular homosynthons (Figure 7). The single crystal structure of CHOBTN revealed that chloral hydrate molecules and betaine zwitterions form $R^2_2(8)$ heterodimers with the geminal diol of chloral hydrate hydrogen bonding to the carboxylate moiety of the betaine zwitterion (OH···O distances of 2.635(3) and 2.648(3) Å, Figure 8). These chloral

Table 2 Summary of CSD Survey

Molecule Type	Assembly	Synthon	CSD Refcode
Geminal Diol	Ribbon	$R^4_4(8)$	SENZIW[36]
			SENZOC[36]
			TUGXAU[37]
Vicinal Diol	Ribbon	$R^3_3(6)$	SEFRIE[38]
	Tape	$R^2_2(8)$	WUXGIF[39]
	Sheet	$R^2_2(8)$	CATCOL01[40]
		$R^2_2(8)$	SIJJAX[41]

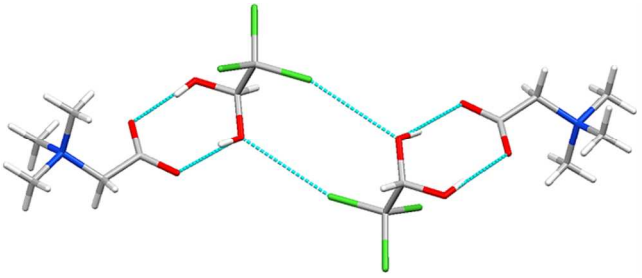

Figure 8. Two carboxylate-diol heterodimers of CHOBTN form tetramers through Cl···O interactions

hydrate – betaine heterodimers self-assemble to form a discrete tetrameric assembly through two identical Cl···O interactions (3.2608(2) Å) which generate a second $R^2_2(8)$ motif. The next closest Cl···O distance, 3.6437(2) Å, is outside the sum of Van der Waals radii. Upon heating above 150 °C under N2, chloral hydrate is released to afford betaine (See ESI for thermogravimetric and crystallographic analysis). This observation indicates that CHOBTN imparts improved thermal stability to chloral hydrate since chloral hydrate is itself only thermally stable to *ca*. 56 °C. Betaine was isolated in the form of a previously known hydrate of betaine.[35]

Survey of the CSD for Geminal/Vicinal Diol – Diol Interactions. The differences in the diol–diol interactions exhibited by the α and β polymorphs of chloral hydrate prompted us to consider what other supramolecular synthons between diols are feasible and/or known. A CSD survey of geminal and vicinal diols revealed that OH···O hydrogen bond distances average 2.7 ± 0.3 Å. When the hitlist was refined to include only those structures with diol–diol interactions, there are only seven unique entries as summarized in Table 2: three geminal diols and four vicinal diols. That hydroxyl groups can serve as both hydrogen bond donor and acceptor sites affords diols a degree of freedom in their mode of packing that is more promiscuous than that of carboxylic acids and carboxamides. Of the vicinal diols, WUXGIF forms dimers that extend through their extra donor/acceptor sites to generate a tape, a classic motif seen in amide structures[24b] (Figure 9(a)) This motif is repeated in SIJJAX, however, there are two diols present in SIJJAX, which enables the formation of a sheet. Similar to the interactions displayed in the α-form of chloral hydrate, catechol (CATCOL) produces dimers, with each hydroxyl group acting as both a hydrogen bond donor and a hydrogen bond acceptor. CATCOL thereby forms a 4,4 network (Figure 9(b)). The four remaining structures generate what can be best described as tubes wherein each diol generates a

head-to-tail hydrogen bonded ring with one hydroxyl group and a head-to-tail chain with the other hydroxyl group. The result is a tubular hydrogen bonded network. SEFRIE exhibits three hydrogen bonded chains that cross-link to create trimeric assemblies with three molecules adding one hydroxyl group to a ring. In each of the geminal diol structures (SENZIW, SENZOC, and TUGXAU), two catemers are produced which are double cross-linked to generate tetrameric assemblies (Figure 9(c)). These

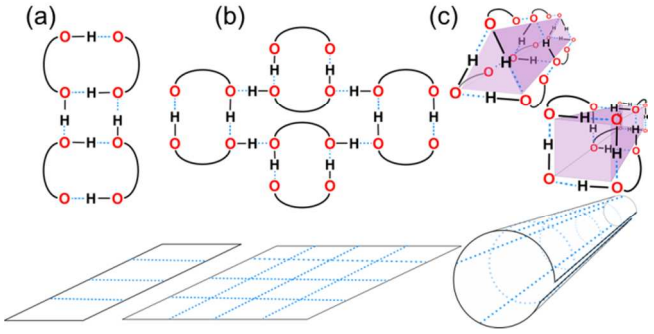

Figure 9. (a) Tapes (b) Sheets and (c) Tubes generated from OH···O hydrogen bonds found in vicinal and geminal diol crystal structures. Below are schematic representations of tapes, sheets, and the conceptual "rolling-up" of tapes/sheets to form tubes

ring assemblies are also exhibited by carboxylic acids[42], with amides being more prone to forming tapes. Conceptually, the tubular networks can be viewed as "rolling-up" a sheet to generate packing efficiency (Figure 9).

While the supramolecular synthons found in the **α**-form of chloral hydrate also sustain the structure of CATCOL, the synthons that hold together the **β**-form of chloral hydrate were not found in any existing structures. Indeed, the unusual packing of the **β**-form is validated by a survey of the CSD for any hydroxyl groups that form the same motif resulting in zero hits.

CONCLUSIONS

Encapsulated within the historical significance of chloral hydrate polymorphism are contemporary issues in solid-state chemistry and pharmaceutical science. Berthelot's studies into the melting points of chloral hydrate place knowledge of its polymorphism at nearly 140 years ago. However, the single crystal structure of the **β**-form of chloral hydrate is only now elucidated. This remains a contemporary issue for several reasons: understanding of polymorphism is still a scientific challenge; polymorphism can play a role in the efficacy of a drug substance and its ability to be formulated and processed; there are also intellectual property implications to polymorphism. Although the structural motifs sustaining the **α**-form of chloral hydrate are found in other structures utilizing diol-diol interactions, the structural motifs of the **β**-form have not been found elsewhere in the CSD.

The molecular cocrystal, CHOBTN, which we believe to be the first example of a pharmaceutical cocrystal to be used in a marketed drug product in the 1960's, also represents a contemporary subject, i.e. the potential utility of pharmaceutical cocrystals in drug products thanks to improved physicochemical properties. The superior properties of CHOBTN over chloral hydrate polymorphs are that CHOBTN exhibits much better thermal stability while maintaining its efficacy. Indeed, both polymorphs of chloral hydrate melt below 60° C whereas CHOBTN melts above 120° C.

The crystal structures of the polymorphs of chloral hydrate and CHOBTN exhibit just some of the supramolecular synthons that are possible for diols. In principle, geminal and vicinal diols are more promiscuous in terms of possible motifs than carboxylic acids and amides. This makes diols less predictable but does not impact their propensity to form cocrystals through supramolecular heterosynthons. However, further studies are required concerning the hierarchy of supramolecular synthons in diols before broader conclusions can be drawn.

ASSOCIATED CONTENT

Supporting Information

Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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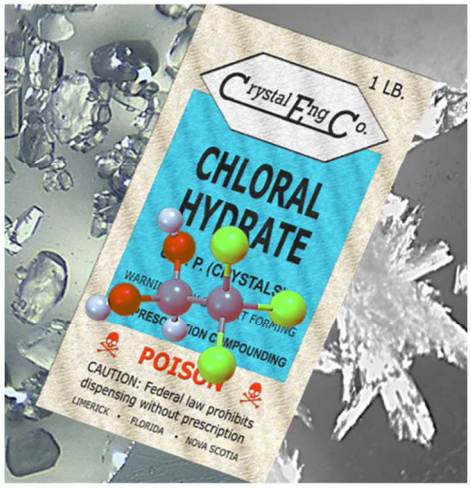

Chloral hydrate is arguably the earliest-known example of pharmaceutical polymorphism and also the first use of a pharmaceutical cocrystal in a drug product. The **α**- and **β**-form of chloral hydrate as well as the cocrystal have been obtained and intermolecular interactions characterized by X-ray diffraction.