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From Molecular to Supramolecular: An Exploration into the Modes of Self-assembly in Conformationally Locked Polycyclitols

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Abstract: This brief account highlights the notable findings of our investigation into the supramolecular chemistry of conformationally locked polycyclitols in the solid state. The study was aimed at analyzing the crystal packing and unraveling the modalities of non-covalent interactions (particularly, intramolecular vis-à-vis intermolecular O–H···O hydrogen bonds) in polyols. The know-how obtained thereof, was successfully utilized to engineer self-assemblies of designer polycyclitols, having hydrogen bond donors and acceptors fettered onto a *trans*-decalin scaffold. The results seek to draw particular attention to the intrinsic attribute of this rigid carbocyclic framework to lock functional groups into spatially invariant positions and bring potential intramolecular hydrogen bonding partners into favorable interaction geometry to engender predictability in the self-assembly patterns.

Keywords: Conformational locking · Crystal engineering · Hydrogen bonding · Polycyclitols · Supramolecular chemistry

Goverdhan Mehta was born in Jodhpur, India. After his PhD from the University of Poona and post-doctoral research at the Michigan and the Ohio State Universities, he held faculty appointments at IIT Kanpur, University of Hyderabad (Vice Chancellor, 1994–1998) and the Indian Institute of Science, Bangalore (Director, 1998–2005). He is presently National Research Professor and Lilly-Jubilant Chair. He has published extensively, and is a recipient of numerous academic and civilian honours/awards and honorary doctorate degrees. He is a Fellow of the Royal Society (FRS) as well as of other Academies in India and abroad. His research interests encompass synthesis of bioactive natural products, creation of new and aesthetically pleasing molecular entities and incisive probing of stereo-electronic effects.

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1. Introduction

Supramolecular chemistry, aptly termed by Lehn as the study of molecular sociology, is the chemistry of the intermolecular bond, focusing on the structures and functions of 'supermolecules' – chemical systems formed by the association between two or more molecular components.[1] While interrelated, supramolecular chemistry forges beyond the domain of traditional molecular chemistry and blends the comprehensive resources of molecular chemistry with a designed control of the intermolecular interactions. Not surprisingly, it has been stated that *supermolecules are to molecules and the intermolecular bond what molecules are to atoms and the covalent bond*.[1a] In the realm of molecular crystals, the focus of supramolecular chemistry converges with that of a rather recent, but rapidly emerging interfacial subdiscipline of crystal engineering.[2] Coined nearly four decades ago in conjunction with photodimerization reactions in crystalline cinnamic acids,[3] the term 'crystal engineering' has since then broadened its expanse considerably and is, at present, most appropriately defined as "the understanding of intermolecular interactions in the context of crystal packing and the utilization of such understanding in the design of new solids with desired physical and chemical properties".[2a]

A basic paradigm can be therefore expounded from any crystal engineering strategy, *viz.* design molecular building blocks with a prior knowledge of the possible non-covalent interactions, such that they are pre-ordained to self-assemble in a manner that leads to the desired crystal structure. Like tools in a crystal engineer's kit, non-covalent interactions in molecular crystals are varied in nature, and broadly include the directional hydrogen bonds (and other dipole-dipole interactions, *i.e.* $\overset{\delta-}{D}–\overset{\delta+}{X}\cdots\overset{\delta-}{A}$, where X ≠ H) and isotropic van der Waals forces.[2a,4,5] Among the archetypes of hydrogen bonding interactions, the classical O–H···O hydrogen bond, well recognized to be vital for life itself, has been thoroughly studied and extensively documented.[6]

Many biologically important polyhydroxylated compounds, such as carbohydrates and inositols, have long served as model systems for the systematic study of O–H···O hydrogen bonds.[6a,b,d] The large database of accurately determined crystal structures of these biomolecules has, over the years, stimulated research in identifying the commonalities in the patterns of their O–H···O hydrogen bonding in the solid state. In his seminal review 'Crystallographic Studies of Carbohydrates',[6a] Jeffrey pointed out that hydrogen bonding in carbohydrates tends to follow certain rules that are based on two primary concepts: (a) maximize the total number of hydrogen bonds per molecule, using as many donor/acceptor oxygens as possible, and (b) maximize cooperativity by forming as many finite and infinite chains of hydrogen bonds as possible.

The first of the two concepts could be validated in crystal structures of not only

carbohydrates, but also a variety of mono- and polyhydroxylated (polyols) species as well. In fact, it underlines a vital aspect of molecular self-assembly, known after Robertson as the *principle of maximum hydrogen bonding*.[7] Non-covalent interactions, being much weaker than covalent bonds, derive their strength (the ability to control and direct crystal packing) from their sheer numbers. Hence, a crystal packing would generally be able to adjust itself in a way that ensures the involvement of as many available hydrogen atoms, bonded to electronegative groups, as possible in hydrogen bonding.

The second concept propounded by Jeffrey,[6a] namely, the occurrence of cooperative O–H···O hydrogen bonding chains, was however shown by Taylor and Macrae to be strongly dependent on not only the number of OH groups in a particular polyhydroxylated species, but also the steric environment (the degree of substitution) around each hydroxyl functionality.[8] The pivotal role played by steric effects in the crystal packing of a polyol was again underlined in a contemporary CSD study on *vic*-diols by Brock, wherein it was observed that the extent of O–H···O bond formation itself depends on the degree of substitution of the *vic*-diol, an $R^2_2(10)$ dimer being the preferred motif in fully hydrogen bonded crystal structures.[9] The importance of molecular bulk or shape in dictating the choice of H-bonded motifs adopted by alcohols was also advanced by Bishop *et al.* in a separate CSD analysis on the occurrence of ladder-like supramolecular architectures in certain diols.[10]

While these generalizations serve as useful guidelines for understanding the predilection of polyols for certain O–H···O hydrogen bonding motifs over others, predicting a precise model for the mode of molecular association through intermolecular O–H···O H-bonds in any polyhydroxylated molecule, to paraphrase Jeffrey,[6a] is a difficult proposition.[11] In this context, orientational flexibility of the C–OH groups poses a particular inconvenience, since a variable C–OH···O torsion-angle parameter has to be associated with each hydrogen bond considered. Hence, proposing the hydrogen bonded architecture in conformationally flexible polyols, having little or no constraints on the internal degrees of freedom, becomes even more complicated because the final spatial disposition of both the hydrogen bond donors and acceptors – the hydroxy groups – in the crystal structure of such molecules is often largely determined by the crystal packing itself.

Against this background, we decided to examine the possibility of limiting the O–H···O hydrogen bonding patterns in polyols by locking their hydroxy groups into pre-destined conformations, which would be unaffected by molecular packing. As would be elaborated in the succeeding sections, the primary impetus for this undertaking came from an in-house know-how of the means to polyhydroxylate a rigid *trans*-decalin framework – a synthetic stratagem which transforms aromatic hydrocarbons into a class of exotic constructs called *conformationally locked polycyclitols*.

2. Polycyclitols, Conformational Locking and the *trans*-Decalin Scaffold

From a purely chronological standpoint, the basic design of conformationally locked polycyclitols, such as the annulated inositols **1** (Fig. 1),[12] was amply inspired by the preceding syntheses of the polycyclitols **2** and **3**, in which the hydroxy functionalities were embedded in a *cis*-hydrindane and *cis*-decalin framework respectively.[13] Spurred by the intriguing inhibitory activity of two stereochemically defined analogs of **2** and **3**, *viz.* **4** and **5**, specifically towards yeast α-glucosidase,[13b] it appeared inherently interesting to investigate the properties of polycyclitols which might be conceived by transcribing the dense hydroxy pattern, present in **2** and **3**, on to the rigid carbocyclic framework of either a *trans*-hydrindane or a *trans*-decalin. Unlike **2** and **3**, polyhydroxylated *trans*-hydrindanes/decalins of prototype **1** would evidently exhibit a spatial locking of the hydroxy substituents and thus define a novel class of polyols, namely the '*conformationally locked polycyclitols*'.

Annulated inositols, wherein conformational locking of the hydroxy groups stemmed from an archetypical 9,10-dihydroxy-*trans*-decalin (or hydrindane) core, formed the first representative category of such polyhydroxylated molecules.[12] While retaining the natural configuration of the parent inositol, these inositol analogues were destined to be frozen in a high-energy 'unnatural' conformation of the cyclitol moiety. For example, while *myo*-inositol, the most prevalent natural inositol diastereomer, exists in the stable conformation **6** with five equatorial and one axial hydroxy groups (5e/1a),[14] the synthetic annulated *myo*-inositol **7** was found to be locked in a five axial and one equatorial conformation (5a/1e) (Fig. 1).[12]

Such ground-state *axial-rich* conformations of hydroxy groups were subsequently observed in various intermediates and end products, obtained along synthetic routes devised by our group for annulated hexoses **8**,[15] inosito-inositols **9**[16] and conjoined inositols **10** (Fig 2).[17] In each of these synthetic endeavors, the 9,10-dihydroxy-*trans*-decalin framework could be reliably employed as a prototypical path for locking the hydroxy substituents in spatial orientations which might not have been realized otherwise.

From annulated to conjoined inositols, our endeavors to evolve a general synthetic protocol for the stereo- and regioselective polyhydroxylation of the *trans*-decalin framework stemmed from the expectation that such a tactic would lead to novel variants of naturally occurring cyclitols with hydroxy groups destined to be locked in an unnatural *axial-rich* conformation. It was conjectured that such a conformational

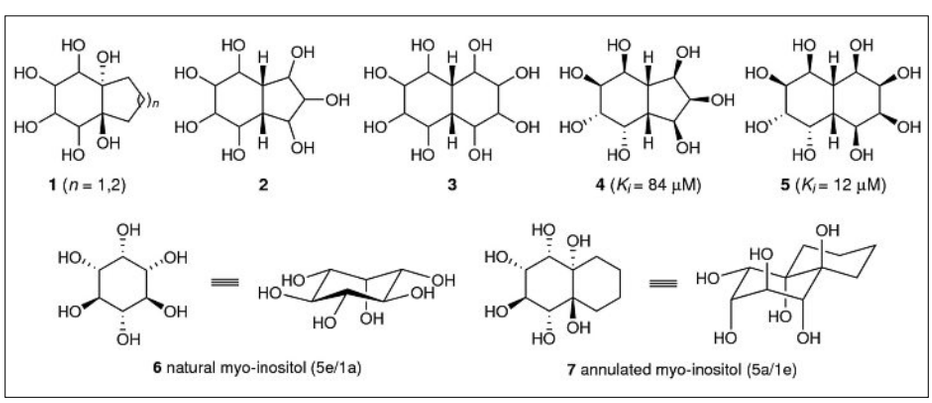


Fig. 1.

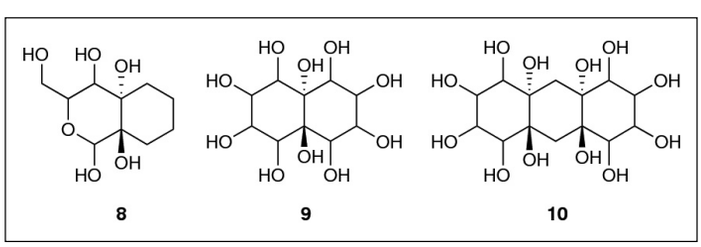


Fig. 2.

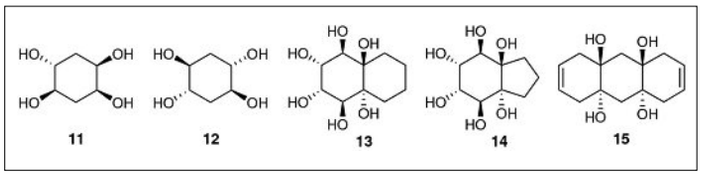


Fig. 3.

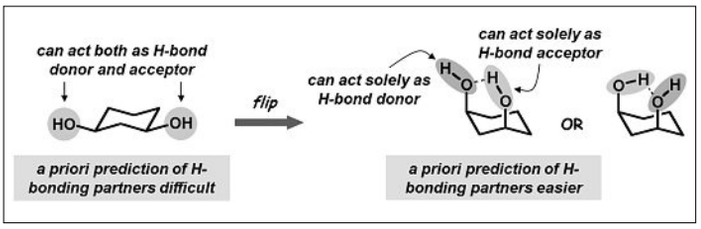


Fig. 4. Formation of intramolecular O–H···O hydrogen bonds between 1,3-syndiaxial hydroxy groups can preordain the positions of intermolecular O–H···O hydrogen bond donors and acceptors in a polyol molecule. This premise has been illustrated here with the two possible conformations of 1,3-cyclohexanediol.

locking of hydroxy groups would lead to a significant alteration in the reactivity pattern and molecular recognition profile of the cyclitol moiety. Much in the way of a corollary, it became evident that conformationally locked polycyclitols would also exhibit O–H···O hydrogen bonding characteristics and self-assembling patterns in the solid state, distinctly different from those observed for their natural congeners. It was our desire to understand the manner in which such spatial locking of the hydroxy groups into axial-rich conformations would express itself in the molecular packing that goaded us to investigate the solid-state supramolecular chemistry of conformationally locked polycyclictols.

3. Spatial Locking of Hydroxy Groups by Design and its Implication in Engineering Self-assemblies of Polycyclitols

It comes as a natural inference that an axial-rich disposition of the hydroxy groups in a polyhydroxylated molecule should automatically bring the 1,3-*syn* OH functionalities into a geometry favorable for the formation of intramolecular O–H···O hydrogen bonds. However, it is also well-known that a ground-state syndiaxial conformation of hydroxy functionalities is energetically unfavorable for most of the naturally occurring polyols, so that intermolecular O–H···O hydrogen bonds, either to neighboring molecules or solvent, are preferred over the intramolecular ones and observed ubiquitously in the crystal structures of such molecules.[6]

This point was re-iterated in our study of solid-state self-assemblies in two diastereomeric cyclohexane-1,2,4,5-tetrols (**11** and **12,** Fig. 3).[18] It is worth mentioning at this point that intramolecular O–H···O hydrogen bonding has not been observed even in the crystal structure of *epi*-inositol where a 1,3-syndiaxial conformation of hydroxy groups is unavoidable.[6a,19] In comparison, our studies on the crystal structures of the annulated inositols (**7**, **13** and **14**)[20] and the unsaturated tetrol **15**[21] revealed that the formation of intramolecular O–H···O hydrogen bonds between the 1,3-syndiaxial OH groups is an invariant feature of molecular packing in conformationally locked polycyclitols.

This implied in turn that reckoning the possible modes of crystal packing in a conformationally locked polycyclitol should presumably be less involved than other polyols because two hydroxy functionalities, participating in intramolecular H-bonding, would be preordained to function as either a donor or an acceptor (but not both) of intermolecular O–H···O hydrogen bonds in the crystal structure (Fig. 4).

But can locking of hydroxy groups into axial-rich conformations and rendering their spatial positions invariant to crystal packing truly lend predictability to the modes of O–H···O hydrogen bonding in polycyclitols? We sought to test the waters in the solid-state self-assemblies of three polyols **16**–**18** (Fig. 5). Synthesis of the polycyclitols **16**–**18** was carried out from readily available aromatic precursors (tetralin, naphthalene and anthracene respectively) *via* sequential epoxidation and stereoselective acid catalyzed ring opening on their Birch reduction products (see Scheme 1 for a representative example).[22] The polycyclitols **16**–**18** were conceptualized with a common design element in mind, namely that all the hydroxy groups in them would be destined to participate in intramolecular O–H···O hydrogen bonding.

Much like matching congenial partners or a game with LEGO® bricks, the packing patterns in the crystal structures of **16**–**18** can be then conceptualized (in the simplest of the scenarios) essentially from the manner in which one of the intramolecularly H-bonded molecular motifs **22**–**28** (Fig. 6) chooses to be linked to its nearest neighbors through the four possible intermolecular O–H···O hydrogen bonds. This observation not only simplified a qualitative visualization of the various packing patterns in **16**–**18**, but also allowed us to propose, primarily based on steric considerations and crystal packing preferences of polyols from previously reported CSD studies (*vide supra*),[6a,8–10] the packing motifs most likely to converge with the experimental results. Despite its qualitative nature, the O–H···O H-bonding patterns, proposed for **16**–**18**, were found to conform well with those observed experimentally for the tetrols **16** and **18**, and even for the two polymorphic modifications of the hexol **17** (Fig. 7).[22–24]

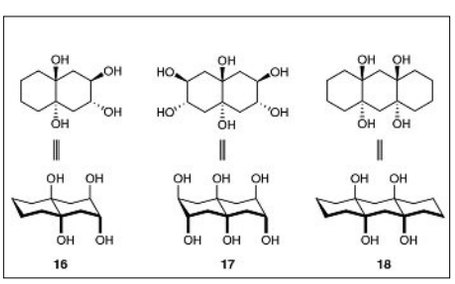


Fig. 5.

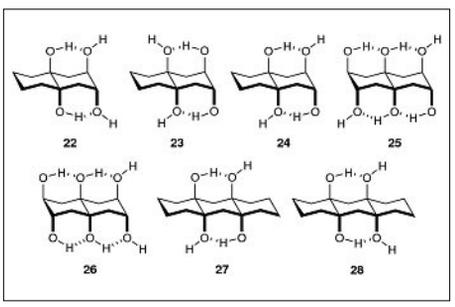
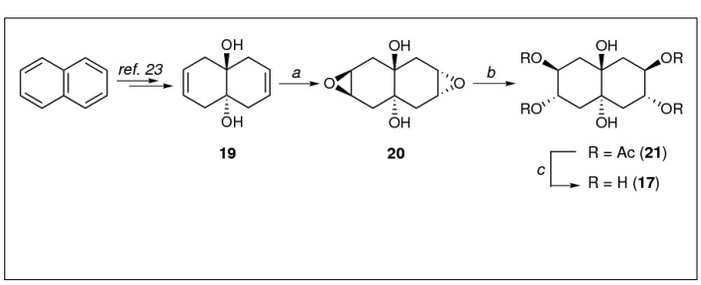


Fig. 6. The conformationally locked, intramolecularly O–H···O hydrogen bonded molecular motifs.



Scheme 1. *Reagents and Conditions*:[22] (a) *m*CPBA, CH_2Cl_2, 0 °C → RT, 3 h, 87%; (b) (i) *p*TSA, moist DCM, RT; (ii) Ac_2O, pyridine, RT, 20 h (65% over two steps); (c) NaOMe, MeOH, 0 °C, 16 h, quant.

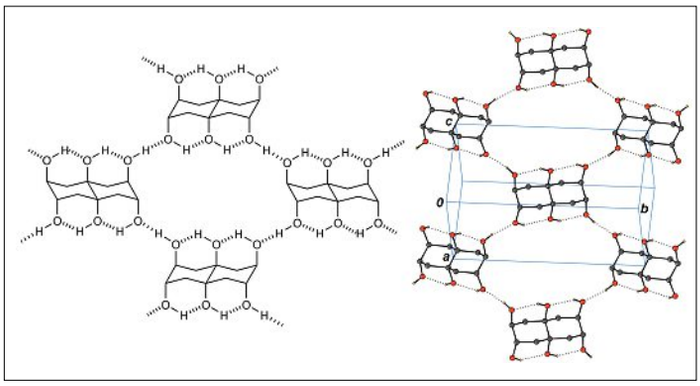


Fig. 7. (*left*) One of the most probable packing modes proposed for the hexol **17** by employing the centrosymmetric motif **25**.[22] That any molecular packing, generated from **25** rather than **26**, would be more likely to be observed in the crystal structure of **17** was an obvious corollary of the conclusions drawn by Brock and Dunitz. A molecule, like **17**, that possesses an inversion symmetry would prefer to crystallize in a centrosymmetric space group[25] and occupy a crystallographic inversion center in such a case.[26] By involving all donor/acceptor oxygens and incorporating infinite chains of O–H···O bonds, the proposed H-bonding pattern also follows the general trend of hydrogen bonding, observed in carbohydrates by Jeffrey.[6a] (*right*) Molecular packing observed experimentally in one of the polymorphs of **17**[27] (*CrystEngComm.* **2007**, *9*, 144 – Reproduced by permission of The Royal Society of Chemistry. Taken from ref. [24].

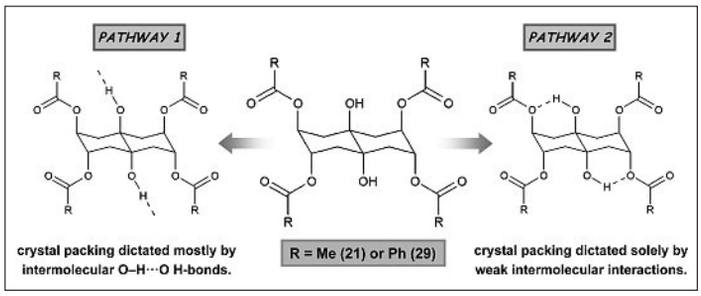


Fig. 8. The two principal and mutually exclusive modes of molecular packing in the tetra-acyl derivatives of the hexol **17**.

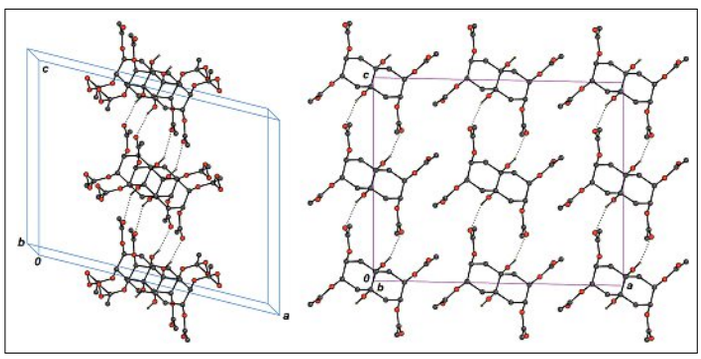


Fig. 9. Molecular packing in the α (*left*) and β (*right*) forms of the tetraacetate **21**. Note that in both polymorphs, the crystal packing is dictated by intermolecular O–H···O hydrogen bonds, which link the molecules into tapes along the *c* axis (*Chem. Commun.* **2009**, 5981 – Reproduced by permission of The Royal Society of Chemistry. Taken from ref. [28].

4. Recognizing the Built-in Chemodifferentiation of Hydroxy Groups as means of Disabling the Peripheral O–H···O Hydrogen Bond Donors

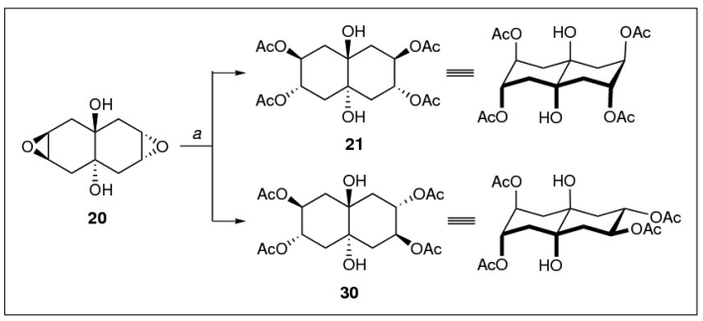
In the foregoing study, it is apparent that the simplistic nature of supramolecular assembly in **17** is characterized and effected by the end-to-end co-operative intramolecular O–H···O–H hydrogen bonding chain on both faces of the molecule. This observation led us to examine, much in the way of intellectual curiosity at the outset, the consequences of disabling the peripheral O–H···O H-bond donors, in the form of the secondary hydroxy groups, in the hexol **17**. To this end, the built-in chemodifferentiation between the hydroxy groups in **17** was exploited to protect the secondary hydroxy moieties selectively as their acyl derivatives. The acetyl and benzoyl protecting groups were selected for this purpose on grounds of the ease in their introduction (even in a sterically encumbered position), purification and the well-documented crystallizability of the esters thus obtained. Inherent in this substrate design was the expectation that the presence of the two tertiary hydroxy groups as the sole O–H···O hydrogen bond donors in the hexol **17** would trigger the supramolecular assembly of the two tetra-acyl derivatives of **17**, namely the tetra-acetate **21** and the tetrabenzoate **29**, to evolve along two mutually exclusive pathways (Fig. 8).

The pathway 1 follows the hierarchy of the strength of the non-covalent interactions available in **21** or **29**, and opts for a crystal packing dictated mostly by intermolecular O–H···O H-bonds, employing the lesser accessible tertiary hydroxy groups (Fig. 8). The pathway 2, on the other hand, relegates the central OH moieties to function as intramolecular O–H···O H-bond donors to ester oxygens and settles for a self-assembly dictated solely by weaker intermolecular interactions, involving the alkyl/aryl groups of the ester moieties (Fig. 8). It is to be noted that while proposing the two modes of O–H···O hydrogen bonding, it was assumed that either of the two C_{2h} symmetric tetra-acyl derivatives (**21** and **29**) will occupy a crystallographic inversion center in its experimentally observed crystal structure.[26]

Irrespective of the crystallization conditions employed, a pure sample of the tetraacetate **21** was found to crystallize exclusively along pathway 1, *albeit* in two enantiotropic polymorphic modifications,[27] one obtainable at room temperature (α form) and the other at –20 °C (β form) (Fig. 9).[28] Behaving much like a temperature-guided molecular switch, the tetraacetate **21** could shift reversibly between the α and β forms in response to changes in the ambient temperature. Thus, the α form converted at –4 °C to the denser β form, which displayed an unusual kinetic stability till 67 °C and transformed back to the α form beyond this temperature.

It was however possible to goad **21** into crystallizing along the pathway 2 through preferential inhibition of pathway 1 in presence of a '*tailor-made*' additive[29] – namely, a diastereomeric tetraacetate **30**, obtained serendipitously *en route* to **21** *via* an apparent breakdown of the Fürst-Plattner rule (Scheme 2).[30,31] As a matter of fact, our rationale behind employing **30** as a nucleation inhibitor to access the elusive third polymorphic modification of **21** (the γ form) had more to do with the observed uncanny similarity between the crystal packing of **30** and the two dimorphs of **21**, rather than the diastereomeric relationship between **21** and **30** (Fig. 10, left). Crystal structure of the γ form confirmed our expectations – with the hydroxy groups engaged in intramolecular O–H···O hydrogen bonding, the tetraacetate molecules in the γ form were held in place solely *via* the weaker C–H···O hydrogen bonds (Fig. 10, right).[31]

With increased sequestering of the central hydroxy groups by the peripheral benzoate moieties in the tetrabenzoate **29**, crystal packing in **29** preferred to follow exclusively pathway 2 as expected. Similar to the γ form of the tetraacetate **21**, the hydroxy groups participated in intramolecular O–H···O hydrogen bonding, while intermolecular C–H···O hydrogen bonds linked the molecules in the crystal structure of **29** (Fig. 11).[32]



Scheme 2. *Reagents and Conditions*:[31] (a) (i) 10% v/v AcOH (*aq.*), RT, 48 h; (ii) Ac_2O, DMAP, RT, 10 h [**21** : **30** = 9 : 1; yields over two steps: 44% (**21**) and 5% (**30**)].

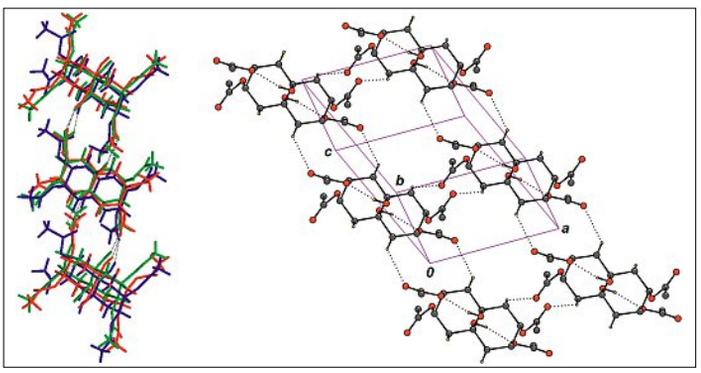


Fig. 10. (*left*) Molecular overlay diagram of packing in **30** (blue) and the α (red) and β (green) forms of **21**. (*right*) Crystal packing in the γ form of **21** [Reprinted from *Tetrahedron* **2009**, *65*, 9713 with permission from Elsevier][31]

5. Extending the Concept of Conformational Locking to the Study of Non-covalent Interactions Involving 'Organic Fluorine'

Having successfully exploited the *trans*-decalin scaffold to predictably bring hydroxy groups into a geometry congenial for intramolecular O–H···O hydrogen bonding, it came as a natural extrapolation that the concept of conformation locking can be employed as a simple, but effective, maneuver to enforce propinquity (a 1,3-syndiaxial relationship) between a fluro and a hydroxy group, and thus evaluate unambiguously the capability of 'organic fluorine' to serve as an acceptor for O–H···F hydrogen bonding. This proposition had a particular contemporary relevance on account of the wide ranging practical applications of organofluorine compounds[33] and the on-going controversy that resides over the ability of organic fluorine to function as a hydrogen bond acceptor.[34] We believed that a minor tweak in the synthetic stratagem, leading to **17** and **18**,[22] should allow introduction of a fluorohydrin moiety in the *trans*-decalin framework and afford access to a novel class of molecular probes, capable of bringing clarity to the role of fluorine in a self-assembly.

Accordingly, three fluorinated polycyclitols **31**–**33** (Fig. 12) were crafted with the specific intent of investigating the capability of covalently bonded fluorine to engage itself in C(sp^3)–F···H–X(sp^3) (X = O and/or C) H-bonding, in presence of its isostere, the hydroxyl group.[35,36] Conformationally locked with well-defined spatial disposition of functional groups, all the three fluorinated polycyclitols **31**–**33** bore a fluorohydrin moiety, embedded in a rigid *trans*-decalin framework. In **31** and **33**, it was conceived that the presence of a hydroxyl donor in a favorable 1,3-syndiaxial relationship to a fluoro group on one side and a hydroxyl group on the other would allow an unambiguous comparison between the two isosteric functionalities (C–OH and C–F) to serve as acceptors for intramolecular hydrogen bonds (O–H···O and purported O–H···F respectively). The difluorodiol **32** was sought to serve as a control to assess the change in the C—F···H—X interactions (if any) which might be observed upon incorporating the peripheral secondary hydroxyl groups in **33**.

As indicated above, the synthetic strategy leading to the three fluorinated polycyclitols **31**–**33** was chalked out quite in

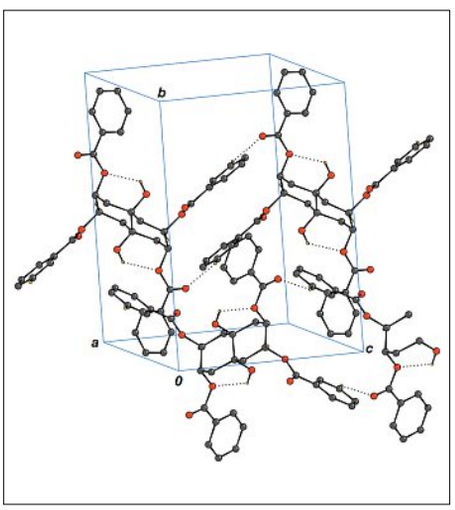


Fig. 11. Molecular packing in the tetrabenzoate **29** (*Acta Crystallogr., Sect. C: Cryst. Struct. Commun.* **2010**, *C66*, o59 – Reproduced by permission of the International Union of Crystallography.[32]

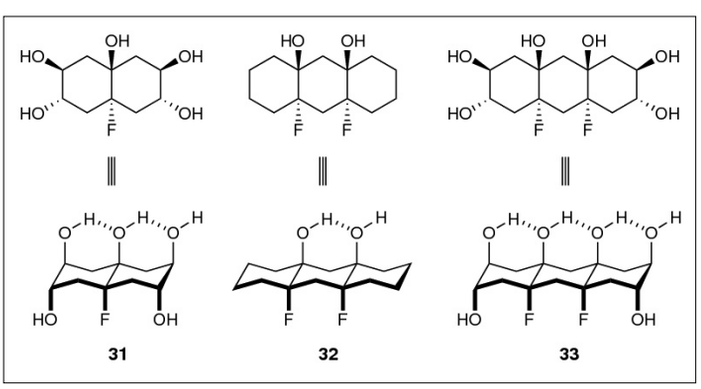
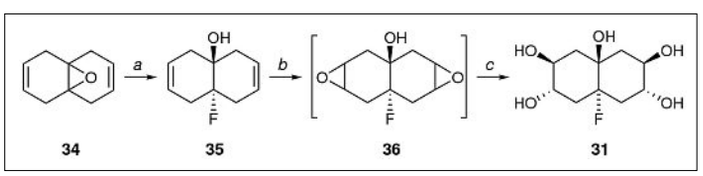


Fig. 12.



Scheme 3. *Reagents and Conditions*:[36] (a) pyridine poly(hydrogen fluoride), THF, RT, 12 h, 97%; (b) *m*CPBA (2.1 equiv.), CH_2Cl_2, RT, 1 h, 78% (overall); (c) 10% AcOH (aq.), THF, 50–60 °C, 3 days, 75% after re-crystallization from 1:3 methanol-ethyl acetate.

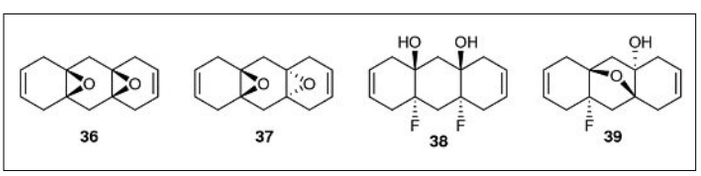


Fig. 13.

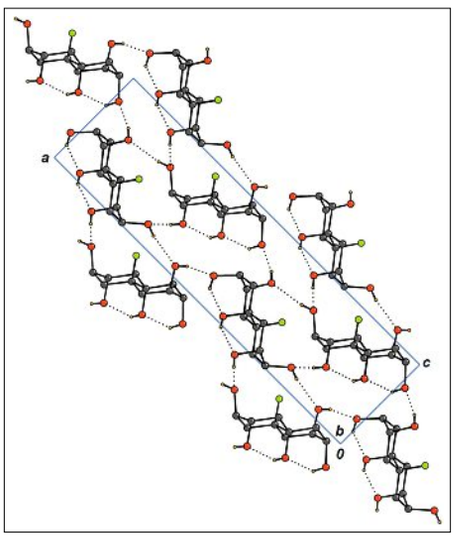


Fig. 14. Molecular packing in the monofluoropentol **31**. The dotted lines indicate the O–H···O hydrogen bonds [Reprinted from *Eur. J. Org. Chem.* **2010**, 3387–3394 with permission from John Wiley and Sons].[36]

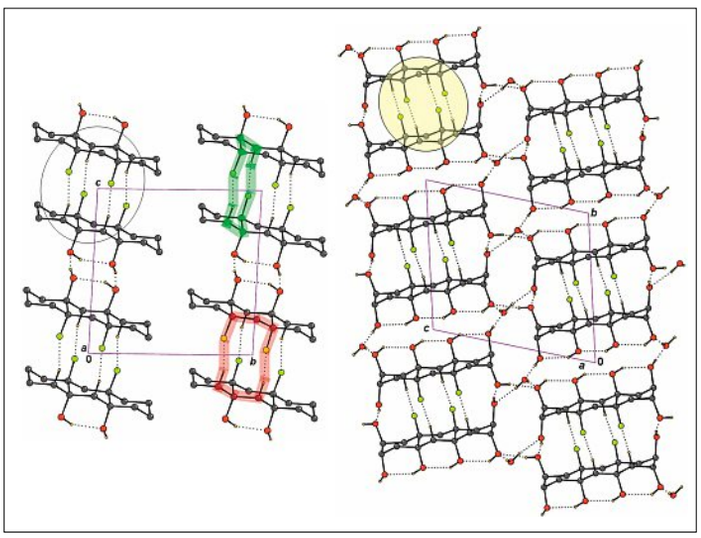


Fig. 15. (*left*) Molecular packing in the difluorodiol **32**, showing how four intermolecular C—H···F hydrogen bonds forms a part of a $R^2_2(10)$ H-bonding motif (encircled). This centrosymmetric supramolecular recognition unit is observed even in the molecular packing in the difluorohexol **33** (*right*) [Reprinted from *Eur. J. Org. Chem.* **2010**, 3387–3394 with permission from John Wiley and Sons].[36]

analogy to that followed for the preparation of the polycyclitols **17** and **18**.[22] As a representative example, synthesis of the monofluoropentol **31** commenced with pyridine-poly(hydrogen fluoride) mediated ring opening of the epoxide **34**,[37] obtained from isotetralin *via* regioselective electrophilic epoxidation.[23c] Treatment of the resulting *trans*-fluorohydrin **35** with *m*CPBA, followed by mild acid mediated ring opening in the diastereomeric mixture of diepoxides (**36**) thus obtained,[38] furnished the desired monofluoropentol **31** as the sole product (Scheme 3).[39] The stereochemical convergence, occurring during the formation of **31** from **36**, conformed to our earlier observations in the synthesis of **16**–**18**,[22] and could be anticipated on the basis of the conformational rigidity of the *trans*-decalin framework and the Fürst-Plattner rule.[30]

A synthetic route, similar to the one engendering **31** from the epoxide **34**, led us to obtain the difluorodiol **32** and the difluorohexol **33** from the *syn*-diepoxide **36** (conveniently prepared, along with its *anti*-diastereomer **37**, from 1,4,5,8,9,10-hexahydroanthracene[22,40]) *via* the common intermediate **38**.[36,41] Unlike the *syn*-diepoxide **36**, which underwent bis-fluorination in pyridine poly(hydrogen fluoride) with complete regio- and streocontrol to furnish the unsaturated difluorohexol **38** as the sole product,[36] its sibling **37** afforded the tetracyclic monofluoroalcohol **39** (Fig. 13) as the major component of the product mixture *via* a tandem HF-mediated epoxide ring opening and transannular oxacyclization.[42]

While the presence of intramolecular O–H···O hydrogen bonds between the 1,3-syndiaxial hydroxy groups was expectedly an easily discernible feature of molecular packing in **31**–**33**, no O–H···F interactions, either intra- or inter, could be gleaned in the crystal structures of **31**–**33**. As expected from any polyhydroxylated molecule, the solid-state self-assembly of all the three fluorinated polycyclitols **31**–**33** strove to maximize the O–H···O H-bonds possible. Indeed, the extensive O–H···O hydrogen bonding network in **31**–**33** involved all the donor oxygen atoms and was the sole interaction controlling the molecular packing in the monofluoropentol **31**, wherein short H···F contacts resulted merely from the compressive forces generated by the intricate O–H···O H-bonding network (Fig. 14).

However, the crystal structures of the difluorinated polyols **32** and **33** presented an interesting adjustment to fulfill the principle of maximum hydrogen bonding.[7] Despite the presence of stronger O–H···O H-bonds, C–H···F hydrogen bonds were observed – not just in effect, but as the constituent interactions of a conserved three-dimensional centrosymmetric supramolecular recognition unit as well (Fig. 15). It is pertinent to mention at this point that the clustering of fluoroalkyl substituents, as noted in the crystal structures of **32** and **33**, has been observed even in aggregates of fluorinated peptides and other fluorine based materials, and has been suggested to lend increased stability to the supramolecular assembly.[43] In the self-assemblies of the difluorinated polycyclitols **32** and **33**, this enhanced stability might be contributed by the antiparallel arrangement of the C–F dipoles in the common centrosymmetric C–H···F recognition unit.

6. Summary and Outlook

In hindsight, we have successfully demonstrated that a *trans*-decalin derived scaffold can be employed as a versatile platform to design and craft diverse molecular entities with desired functional attributes. For the study of non-covalent interactions, one may utilize this rigid carbocyclic scaffold not just to lock functional groups into spatial positions that will remain unaffected by crystal packing, but bring, as 'matchmakers', potential hydrogen bonding partners into a favorable intramolecular interaction geometry as well. In the case of polycyclitols, this tactic – namely, maximize the possible intramolecular O–H···O hydrogen bonds in order to minimize the number of intermolecular O–H···O hydrogen bonds needed to be considered – can viewed upon as a viable *modus operandi* for 'scaffold based crystal engineering'. It is equally feasible to exploit the in-built chemodifferentiation between the central and peripheral functional groups on a *trans*-decalin framework to sequester or completely disable an activated hydrogen-bond donor, and allow the crystal packing to be dictated by weaker interactions alone. Indeed, there is much room for extending our findings towards the study of hydrogen bonding and self-assembling preferences in molecules having not only hydroxyl, but also other functional groups (such as NH_2, COOH and halogens) as well.

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[38] The lack of stereoselectivity in the epoxidation of **35** contrasts the stereoselection that leads to the *anti*-diepoxide **20** as the sole product during the epoxidation of the diol **19**. Formation of a H-bonded complex between two molecules of mCPBA and the *trans*-hydroxy groups in **19** might account for the stereoselective formation of **20** (see ref. [22]).

[39] Our attempts to isolate the monofluoropentol **31** from the reaction mixture *via* its peracetylation and subsequent transesterification of the purified tetraacetate derivative were repeatedly unsuccessful. Formation of a (*trans*, *anti*, *trans*, *anti*, *trans*)-perhydro-2,3,4a,6,7,8a-naphthalenehexol during these endeavors was explained and proven on the basis of a base induced fluoride displacement in the initially formed **31**, followed by a preferential anti-Fürst-Plattner opening by OH^- in the epoxytetrol intermediate. For details, see: G. Mehta, S. Sen, *J. Org. Chem.* **2010**, *75*, 8287.

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