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Strategic stereoselective halogen insertion (F, Cl), a tool to enhance supramolecular properties in polyols

Céline Sperandio,[a] Guilhem Quintard,[b] Jean-Valere Naubron,[c] Michel Giorgi,[c] Mehdi Yemloul,[a] Jean-Luc Parrain,[a] Jean Rodriguez,[a] Adrien Quintard,[a]*

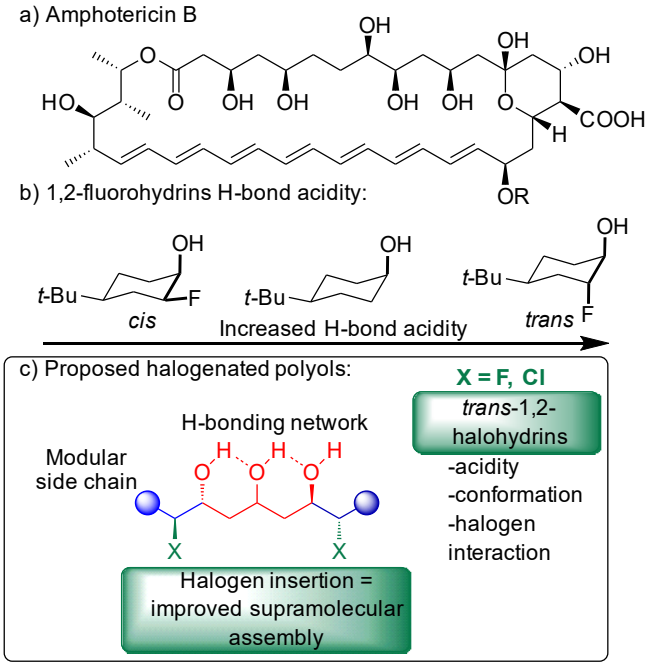
Abstract: In order to improve supramolecular properties of organic structures, chemists continuously need to identify new tools. Herein, we report a full study analyzing the influence of the stereoselective insertion of halogen atoms (F or Cl) over different supramolecular properties. By inserting *anti*-halohydrins in polyols, we considerably strengthened the H-Bonding networks as well as other supramolecular interactions. This behavior resulted in improved anion binding, H-bonding catalysis or organogel properties of the designed polyols opening strong perspectives for applications in other classes of substrates.

Introduction

Organic chemistry has evolved over the last decades to become a pivotal science for understanding and developing physical or biological tools. As a result, to answer the increasing societal demand for more elaborated materials or drugs, organic chemists must continuously invent and understand efficient molecular interactions. In this regard, the development of new engineered molecular or supramolecular entities is crucial to selectively and efficiently create a required chemical, physical or biological function of interest.

Complex aliphatic polyols are known in nature for their ability to selectively coordinate with a wide array of molecules. Through the creation of hydrogen bonding frameworks, polyols bring crucial bioactivities to the impressive amount of natural products possessing this particular motif.[1] For example, the anti-fungal activity of natural amphotericin B is in part due to its ion transportation ability through membrane by supramolecular assembly (Scheme 1.a).[2] To understand and potentially improve polyols properties, researchers have relied on the development of synthetic mimics. It has been shown notably by the group of Kass that in the acyclic series, cooperative effects between the different hydroxyl functions in 1,3-polyols were responsible for enhanced H-bonding properties.[3] As a result, aside from medicinal chemistry, recent studies have shown great expectations by the use of synthetic polyols in anion binding[4,5] or H-bonding catalysis.[6] In addition it was also shown that the hydrogen bonding frameworks created by 1,2-diols could serve as platforms to create promising organic gels for example.[7] However, the limited availability and tunability of synthetic polyols hamper the improvement of the desired properties thus considerably restricting the potential applications.

In this context, we questioned how halogen insertion (F or Cl) would impact the supramolecular properties of acyclic polyols systems.



Scheme 1. Amphotericin B, fluorohydrins acidity and proposed halogenated 1,3,5-triols

In nature, chlorohydrins are central to different natural products possessing impressive bioactivities.[8] However, the exact implication of these chlorine atoms is not always well understood.[9] On the other part, fluorine is interesting given its ability to modulate organic molecules lipophilicity, adjacent functional groups acidity or conformation with poor impact on the steric environment.[10] As a result, it is not surprising that almost 25% of commercial drugs contain at least one fluorine atom. Often relying on fluorinated aromatics or perfluorinated chains, the positive effect of fluorine insertion was also used with success in material sciences.[11a] The electronic modulation and conformational restriction through the so-called “gauche effect” developed in drug design are also useful for the conception of improved catalysts.[11b-c]

Among fluorinated backbones, 1,2-fluorohydrins have found limited applications to enhance supramolecular properties of acyclic alcohols.[12] This is surprising given the ubiquity of

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aliphatic alcohols in biologically active molecules and natural products and might be due to the lack of general understanding on the influence of 1,2-fluorohydrins. Indeed, recent studies aiming at determining the effect of fluorine over the acidity of cyclohexanols indicated a complex behavior.[13] While going from an alcohol to a *trans*-1,2-fluorohydrin increased the acidity, oppositely, going to the *cis*-1,2-fluorohydrin had a negative effect on the acidity (Scheme 1.b).[13] *Given this observation and the biological role of 1,2-chlorohydrins, we wondered about applying anti-1,2-halohydrin insertion as a general tool to improve supramolecular properties in extended 1,3-polyols. We hypothesized that embedding anti-1,2-halohydrins in such backbones would considerably strengthen the crucial H-bonding network (Scheme 1.c). Conformational stabilization and presence of halogen interactions would additionally positively impact the structures with great potential in a broad range of applications.*

This study would bring fundamental knowledge to better appreciate the impact of 1,2-halohydrins over organic molecules supramolecular behavior. In our design, modulation of the lateral chains of such motif would ensure the broad applicability of the approach in a wide range of domains going from organogel formation, catalysis to anion binding.

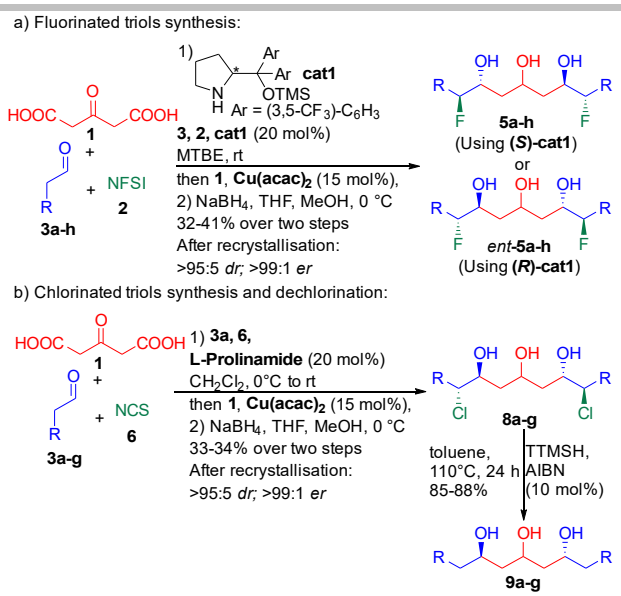
Results and Discussion

Polyols synthesis

Development of new chemical tools for physical applications strongly depends on our ability at rapidly and stereoselectively constructing the required complex molecular objects of interest in the most practical, straightforward and economically reliable manner. Notably, the rapid assembly of acyclic structures possessing multiple controlled stereocenters as in halogenated polyols represents a daunting task. To this endeavor, we recently identified a multi-catalytic sequence enabling the enantioselective direct eco-compatible preparation of halogenated 1,3,5-triols **5** and **8** from a bio-sourced ketodiacid **1** (Scheme 2).[14]

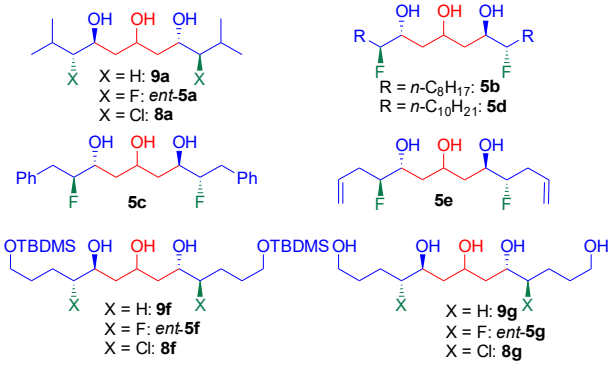
The sequence involves an organocatalyzed enantioselective halogenation of aldehydes **3** followed by a diastereoselective copper-catalyzed bi-directional aldolization reaction. A subsequent reduction of the ketodiol intermediates provides a rapid access to *C2*-symmetric fluorinated or chlorinated triols **5** and **8**. These triols, originally formed as mixtures containing around 80% of the major diasteromers could be efficiently obtained in excellent stereoselectivity through single recrystallization (>95:5 *dr* and >99:1 *er*).[15]

By changing the nature of the starting aldehydes, we have now applied this multicomponent protocol to the simple and straightforward preparation of a family of fluorinated or chlorinated 1,3,5-triols (Scheme 3). The presence of different lateral chains on the halo-triols should ensure the required modulation of the structure to match with the desired supramolecular properties. The availability of both enantiomers of **cat1** enables access with equal efficiency to both enantiomers of **5**, an interesting features to study the influence of the chirality over supramolecular properties. The synthesis is scalable (15 mmol of **1**) and can be performed easily without the requirement of column chromatography given the crystallinity of most of the 1,3,5-triols.



Scheme 2. Multi-catalytic route to halogenated 1,3,5-triols

Finally, to fully assess the halogen insertion influence, radical dechlorination of **8** provided dehalogenated triols **9** in good yields.[16]



Scheme 3. 1,3,5-triol structures prepared

Triols structures, aggregation and organogelation

With an easy access to a broad range of different 1,3,5-triols, we first focused on the structural feature of these synthetic arrangements in the solid state. Gratifyingly, 1,3,5-triols **5a, 8a** and **9a** possessing terminal isopropyl chains were crystalline and their solid structures could be determined by single crystal X-ray diffraction (Figure 1).[17] The three triols possessing a rigid bilayer type motif are isostructural with differences in interactions and packings. Remarkably, concerning **5a**, it must be pointed out that the fluorine atoms are placed *trans* to the alcohols without any gauche conformation. The preference of *trans*-relation over classical *gauche* stabilization is of utmost importance and in contradiction with 1,2-fluorohydrins common observations.[18,11c] This effect can be explained through the stabilization of the linear structure through the triols H-bonding probably minimizing dipole-dipole interactions. The same type of conformation is also observed in the parent chlorinated triol **8a**. In **5a** and **8a**, the halogen atoms are pointing outside of the strong hydrogen bonding network consisting of two *inter* and one *intra* alcohols hydrogen bond. This

arrangement creates an infinite 1D chain of hydrogen bonds. The halogen atom insertion (F or Cl) gives a higher packing index thanks to the presence of additional halogen-hydrogen intermolecular interactions.[19,20] Confirming our hypothesis, the *anti*-fluorine crucial *trans*-relationship electronic repulsion increases the strength of intermolecular hydrogen bonding with shorter O-O bond distances of 2.77 and 2.78 Å for **5a** *vs* 2.79 and 2.80 Å for **9a**. On the contrary, the larger size of the chlorine atom probably extends the distance between two molecules by steric repulsion resulting in longer H-bonding in the self assembly (2.79 and 2.86 Å for the intermolecular H-bonding). This effect is counterbalanced by the number of additional halogen-hydrogen intermolecular interactions resulting in the higher packing index for this chlorinated triol.

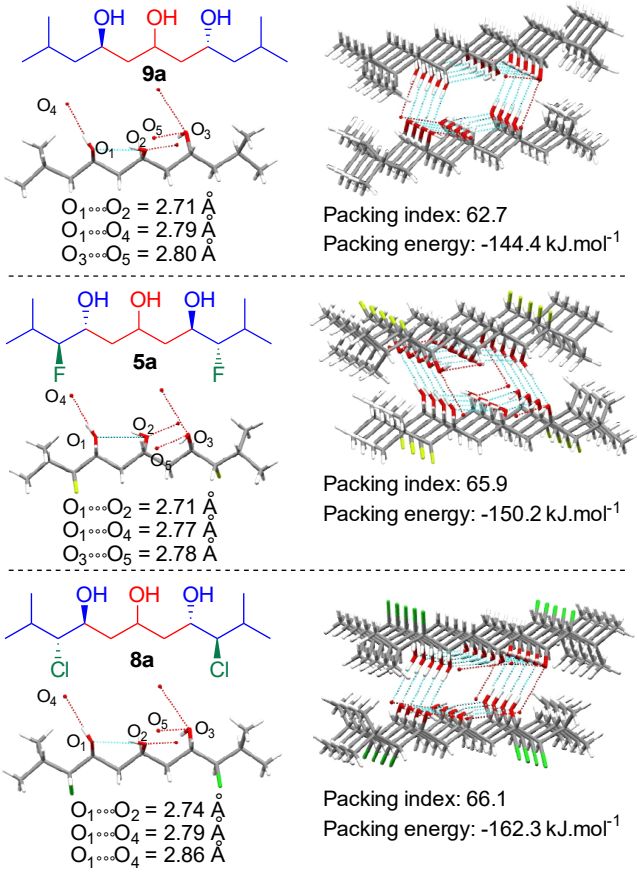


Figure 1. Single crystal X-ray diffraction and molecular packing of **9a**, **5a** and **8a**

As can be seen from these calculations, **5a** with the two *trans*-fluorohydrins is highly favored by more than 7.8 Kcal.mol^{-1} through minimized dipole-dipole interactions as compared to the other rotamers possessing one or two gauche fluorohydrins (entry 1 *vs* entries 2-4).

Table 1 Conformational analysis of **5a** and **8a** at M06-2X/6.311+G(d,p) (ZPE corr.) level of theory

Entry	Newman representations C3-C4	C8-C9	Dihedral angles (°) X-C-C-O & O-C-C-X	Relative energy (Kcal.mol^{-1})
1			-178 & -173	0
2			-52 & -51	+7.84
3			95 & -173	+10,95
4			-52 & 56	+11.47
5			-175 & -175	0
6			-59 & -171	+0.77
7			-58 & 90	+3.91
8			-58 & -59	+4.70

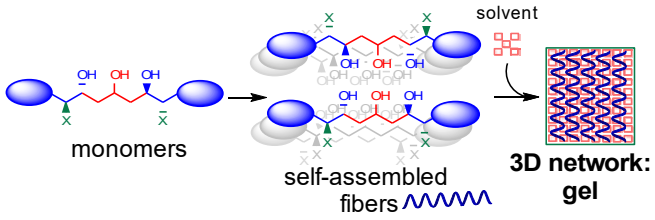
DFT calculations also confirmed in the gas phase this stabilized *trans*-relationship in the halohydrins (Table 1).[21] Geometry optimizations and frequencies calculations were performed at the DFT level of theory by using the M06-2X functional[22] as implemented in the Gaussian 09.[23] For all the atoms, all-electron standard 6-311+G(d,p) basis set was employed. For each optimized stationary point vibrational analysis was performed to establish its nature as a minimum or saddle point, and zero-point vibrational energy (ZPE) corrections were included in all relative energies (ΔE). NBO 6 program,[24] which is included in Gaussian16 suite of programs, was used to obtain natural bond orbitals (NBOs), atomic net charges and the energetic evaluation of secondary interactions.

Interestingly, in the case of chlorohydrin **8a**, more conformational freedom is calculated and the most stable conformation features two *trans*-chlorohydrins (entry 5). However, one of the two chlorohydrin can rotate to obtain a mixed *trans*/*cis* conformer of almost equal energy (0.77 Kcal.mol^{-1} difference, compare entries 5 and 6). Finally, chlorohydrins with two *cis* relationships are disfavored by more than 3.9 Kcal.mol^{-1} (entries 7 and 8). More rotational freedom is observed around the central alcohol, confirming the role of the halogen in conformational rigidification (see SI). This suggests that the rotational freedom of this central non-halogenated alcohol allows to adapt the structure to the

environment (auto-assembly or anion coordination and catalysis) (vide infra).

The single crystal X-ray diffraction obtained for halogenated triols clearly demonstrate the ability to create strong H-bonding networks as well as self-assembly nano-structures, two key elements for further applications. Thus, we were curious to see how these changes observed in the solid state would impact other supramolecular properties.

Gels created by small organic molecules (organogelators) entrapping solvents in high order 3D networks through fibers self-assembly have recently gained considerable interests.[25] For example, the potential of these smart materials found applications in photonics, oil spill recovery, catalysis or as self-healing materials for example.[25] However, the limited structural variations often based on sensitive acetals and esters functions can restrict the potential of these organogelators.



Scheme 4. Proposed mechanism of gelation with X-triols

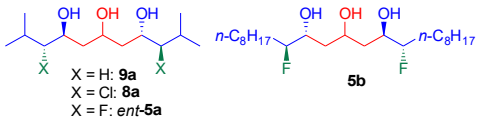
The creation of new gels through fibers formation is closely related to crystallization with subtle differences in the assembly process conducting to the solvent trapping.[26] However, the rational *de novo* design of improved organogelators still represents a daunting challenge. As a result, the discovery of new tools to enhance gelation of innovative LMOG (Low Molecular Weight Organogelators) platforms is highly desirable. Given the solid-state structure of synthetic 1,3,5-triols, we hypothesized that as in 1,2-diol LMOG's,[7] the central polyols would create the expected H-bonding networks while introducing two external aliphatic chains would stabilize the gel through van der Waals interactions with the solvent (Scheme 4). Given the supposed stronger H-bonding network, halogen preorganization and hydrophobicity, stronger supramolecular networks and as a result higher gel efficiency should be obtained through selective halogen insertion.

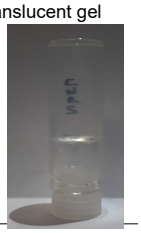
To determine and compare the organogelator efficiency of 1,3,5-triols we determined several parameters such as Critical Gelation Concentration (CGC in wt/v%) below which the gel scrambles and Gel Transition Temperature (Tgel in T°C) at which the gel starts falling apart by using the classical vial inversion method (Table 2).[27]

Comparison of the gelation properties of fluorinated, chlorinated and non-halogenated triols indicated totally different behaviors. The non-halogenated polyol **9a** did not provide any gelation at 2 wt/v%. On the contrary, a relatively weak gel was observed with chlorinated polyol **8a** in *o*-xylene or petroleum. The weak gelation property can be explained based on the crystal assembly by the size of the chlorine atom repelling the two polyols layer and decreasing the fibers strength. Gratifyingly, insertion of fluorine impressively improved the gelation properties of **5a**. In various non-polar organic media such as benzene, toluene or petroleum, a strong gel is obtained using as low as 0.36 wt/v% of the organogelator meaning that only 10 mg of this particularly small organic molecule (FW = 268) is able to gel 2.75 mL of petroleum. The gel materials obtained can be reversibly generated easily through successive heating-cooling cycles. Using coordinating polar solvents such as CH_3CN or EtOH, no gelation is observed indicating that disruption of the H-bonding network breaks down the gel.

In order to improve these gel properties, we modulated the lateral chains of the fluorinated triols notably by increasing their lipophilicity (see supporting information for all the polyols tested). Satisfyingly, fluorinated polyol **5b** possessing the linear C_8H_{17} chain provided materials with a lowering CGC and efficient for a broad range of solvents (see Table 2). Notably, even the more difficult coordinating EtOH and CH_3CN could form a gel in the presence of only 1-2 wt/v% of the fluorinated polyol. The full list of efficient gelation solvents including diesel, silicon oil, pump oil (parrafin) can be found in the supporting information. Of interest for photonic applications,[7,25] some of these gels are translucent as for **5b** o-xylene gel shown in Table 1.

Table 2. Influence of the substitution on gelation in selected solvents (see SI for other solvents) and 0.33 wt/v% **5b** image of an o-xylene translucent gel





Solvent	CGC in wt/v%, Tgel (°C)[a]			
	9a	**8a**	**5a**	**5b**
Benzene	NG	NG	1%, 50°C	0.5%, 28°C[c]
Toluene	NG	NG	0.66%, 59°C	0.31%, 35°C[c]
o-xylene	NG	2%, 38°C	0.8%, 64°C	0.29%, 60°C[c]
Petroleum[b]	**NG**	2%, 28°C	0.36%, 78°C	0.25%, 75°C
CH_3CN	NG	NG	NG	1%, 53°C

CGC = Critical Gel Concentration. Tgel = Gel transition temperature. NG = No gelation observed at 2 wt/v%. [a]: Tgel measured at 2 wt/v%. [b]: drugstore bottle of hydroalkanes (C11-C14), *iso*-alkanes, *n*-alkanes, cycloalkanes with 35% of toluene as the aromatic constituent. [c]: Translucent gel.

Given the excellent performance of fluorinated triols as LMOG's, and to understand the effects behind gelation, we decided to further study in detail the properties and structures of these gels. First of all, the gel properties obtained by the vial inversion method were confirmed by rheology (Figure 2 a,b,c and supporting information). The strength of fluorinated triol gels such as **5b** in petroleum favorably compares to literature data.[7] Confirming the gel behavior, the elastic modulus G' is higher than the viscosity modulus G". The excellent elastic modulus G' of 110 000-170 000 Pa indicates an impressively high resistance for such simple low molecular weight molecule (Figure 2.a). Monitoring G' and G" as a function of the stress amplitude

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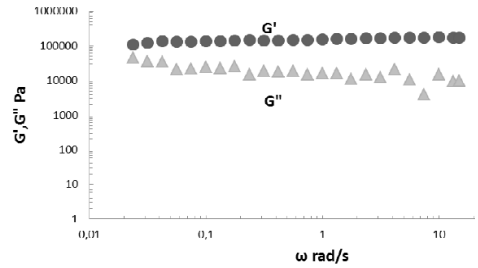
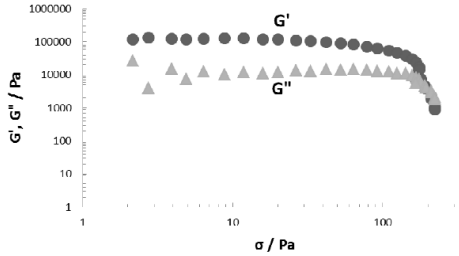
(Figure 2.b) indicated that **5b** gel was resistant until at least 100 Pa of applied stress.

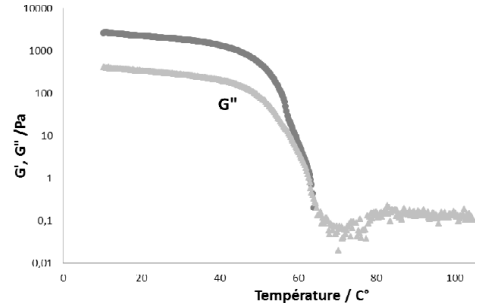
a)



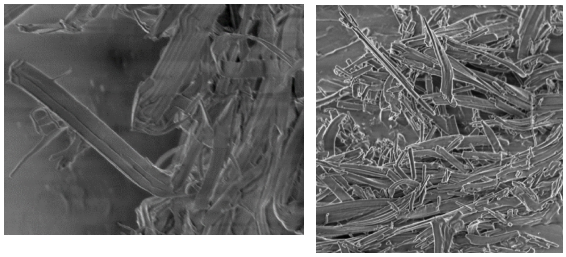
b)



c)



d)



e)

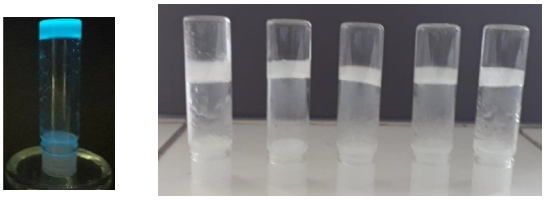


Figure 2. Gel properties. a) Frequency sweep of 4 wt/v% of **5b** in petroleum. b) Stress sweep of 4 wt/v% of **5b** in petroleum. c) T°C dependence of 2 wt/v% of **5a** in *o*-xylene. d) SEM image of **5b a**nd **5a** xerogels (2 wt/v% in petroleum). e) Gel images for, left: UV irradiated **5b** 0.4 wt/v% in toluene doped with 0.2 wt/v% of pyrene; right: stability of 2 wt/v% **5b** gel of petroleum in the presence of water solutions: 3.5% NaCl; pH = 1 ; pH = 4; pH = 8; pH = 14.

It is interesting to point out that the values of Tgel obtained by the vial inversion method in table 2 can be correlated to the rheological properties (G' and G") as a function of the temperature for gel **5a** in *o*-xylene showing a destructuring gel at a temperature around 62 °C (Figure 2.c). Xerogels were obtained from the evaporation of the solvent of different gels and analyzed by Scanning Electron Microscopy (SEM). This confirmed the gelation process through the formation of large fibers as in xerogel obtained from **5a** or **5b** petroleum gel (Figure 2.d and supporting information).

Of interest, doping a **5b** gel of petroleum with 0.2 wt/v% of pyrene resulted in a strongly UV fluorescent gel, opening perspectives for applications to other doped fluorinated gels (Figure 2.e, left).

Given the structure of the fluorinated polyols, the great advantage of the organogels created from **5b** are they high stability in the presence of a broad range of aqueous solutions. Going from pH = 1 (HCl solution) to pH = 14 (NaOH solution) solution or in the presence of 3.5% NaCl solution all the gels kept their resistance (Figure 2.e, right). This behavior is of importance in a context of water cleaning of industrial leaks and in contrast to most organogelators based on acid or basic sensitive functions (esters, amides, acetals...).[7,25]

NMR and VCD analysis of the fluorinated triols and the related gels (see SI ford details) seem to indicate that the spatial arrangement observed in the fibers within the gel is closely related to the spatial arrangement observed in the solid state by single crystal X-ray diffraction of **5a**. All these observations suggests that the fibers are exclusively formed by hydrogen bonds and hydrophobic interactions. Fluorine insertion positively impact gelation through different manners. First of all, a stronger H-bond framework is created by the electronegative fluorine, increasing the strength of the supramolecular assembly. The presence of the hydrophobic fluorine atoms pointing outside of the fibers and able to create additional interactions with the solvent also strengthen the fibers (higher packing). In the case of chlorinated triols, these increased interactions are counterbalanced by the larger size of the chlorine atom and the higher conformational freedom arguing for a weaker supramolecular assembly.

As can be seen from this section, halogen insertion notably of fluorine atoms, affects drastically the organogelation properties of triols. The small and easy to prepare stereodefined and highly stable fluorinated triols, allow for a strong gelation of a broad range of organic solvents and lead us to study other possible supramolecular interactions.

H-bonding properties and anion binding

Anion binding is a fundamental process in chemistry with implications in fields ranging from the understanding and modulation of anion centered biological processes to the engineering of sensors, materials or catalysts.[28] To further probe the influence of halogen insertion over H-bonding properties and molecular recognition phenomenon, we subsequently focused on the anion binding ability of polyols.

This anion binding behavior was first determined by ^{1}H NMR titration experiments in CD_3CN. The addition of tetrabutylammonium chloride (TBACl) to polyols resulted in large downfield shifts of the hydroxyl hydrogens. In addition, the binding of fluorinated polyols could also be easily monitored by ^{19}F NMR. Association constants from triplicate experiments were obtained by fitting these spectroscopic data to 1 : 1 binding

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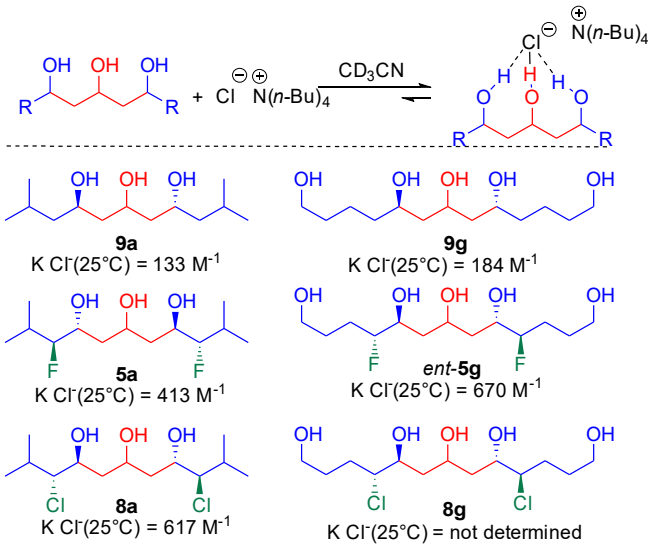
isotherm models, using the Thordarson method.[29] When a non-halogenated polyol **9a** or **9g** is used and in accordance with Kass results, relatively weak Cl^- binding is observed (Scheme 5: 133 or 184 M^{-1}, respectively).[3] In contrast, fluorine insertion considerably improved the anion binding by a factor of 3.1 to 3.6 in **5a** and *ent*-**5g**. A relatively important Cl^- binding constant of 413 M^{-1} for the simple acyclic polyol **5a** was observed. Interestingly, addition of terminal free alcohol in *ent*-**5g** further increased the anion binding to 670 M^{-1}.

The presence of chlorine atoms in **8a** was even more impressive. In this case, an increase by a factor of 4.6 giving 617 M^{-1} binding constant clearly demonstrated the positive impact of chlorine insertion.[30] Given the presence of chlorohydrins in numerous highly bioactive molecules, this observation should find relevant implications in the understanding of their biological mode of action and in drug design.

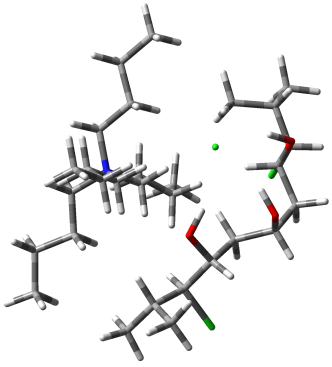


Scheme 5. Cl^- anion binding properties of different 1,3,5-triols in CD_3CN (average of triplicate experiments).

In order to shed light on the mechanism behind the observed binding improvement by halogen insertion, these values were correlated with DFT calculations (Table 3).

First of all, calculations of the different enthalpies of polyol•TBACl complexes formation confirmed the halogen insertion impact (Table 3). Formation of the TBACl complex was less favored for **9a** (ΔH = -8.36 Kcal.mol^{-1}), while fluorine or chlorine insertion in **5a** and **8a** improved the affinity (ΔH = -11.25 or -16.67 Kcal.mol^{-1}, Table 3). This higher affinity of halogenated polyols clearly arises from the increased acidity resulting from the presence of F or Cl atoms. This is reflected in the distance between the different oxygen atoms and the chlorine anion. Most notably, the distance between Cl^- and the two oxygen atoms adjacent to the halogens (C4-O and C8-O) are much shorter. This distance varies for C4-O from 3.17 Å for **9a** to 3.13 Å for **8a** and for C8-O from 3.34 Å for **9a** to 3.27 Å for **8a**. On the contrary, the central oxygen-Cl distance is less modified depending on the substitution ranging from 3.20 Å for **9a** to 3.21 Å for **8a** (Table 3). The higher affinity observed for halogenated polyols is directly arising from the appropriate geometry of the halohydrin. Indeed, as in the solid state, the dihedral angles ranging between 169.4° and 177.1° for X-CH-CH-O allows to efficiently increase the acidity of the alcohols.

Table 3. Calculated properties of polyol•TBACl structures and DFT modeling of **8a**•TBACl structure



8a•TBACl

	ΔH (Kcal.mol^{-1}) [a]	O(C4-O)-Cl (Å)[b]	O(C6-O)-Cl (Å)[b]	O(C8-O)-Cl (Å)[b]
9a	-8.36	3.17	3.20	3.34
5a	-11.25	3.15	3.22	3.28
8a	-16.67	3.13	3.21	3.27

[a] Calculated enthalpy of formation of the polyol•TBACl complexes. [b]Calculated distance.

With this impressive effect of halogen insertion over anion binding, we also checked the ability of the halogenated polyols as H-bond donor catalysts. Even though those properties are closely linked, the binding mode of polyols is different in both applications. Indeed, it was previously described by Kass that 1,3-polyols bind anions with three hydrogen of alcohols, while on the contrary, the acidity necessary for H-bonding catalysis results from a cooperative effect between the alcohol functions by intramolecular hydrogen bonds.[31] This intramolecular network significantly increases the pKa of the most acidic alcohol function, subsequently able to activate a suitable electrophile such as nitroolefins. DFT calculations confirmed this type of activation using fluorinated polyol **5c** in which only one H-bond was found to be established (Figure 3).

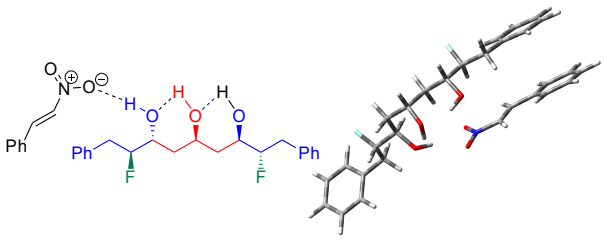


Figure 3. DFT calculated structure of nitrostyrene ⊂ **5c** in $CDCl_3$

To evaluate the catalytic activity of our triols we choose the Friedel-Crafts addition of *N*-methyl indole (**11**) to 2-nitrostyrene **13** (Figure 4).[32] Once again, halogen insertion positively impacted the catalytic ability of polyols. Three times rate acceleration were observed for fluorinated **5a** as compared to non-halogenated polyol **9a** (entries 1-3). It must be pointed out that both fluorinated and chlorinated polyols provided the same type of catalytic profiles in this transformation.[33]

Of interest, preliminary simple modulation of the fluorinated polyols by incorporating phenyl substituents on the lateral chains considerably increased the reaction rate. Using **5c**, a reaction rate comparable to binol phosphoric acid derivative **10** was observed albeit using a molecule with much lower pKa! This indicates a cooperative effect of the lateral chain possibly through π-interactions with the substrates opening broad perspectives for the improvement of these structures for catalysis through further modulation of the side chain.

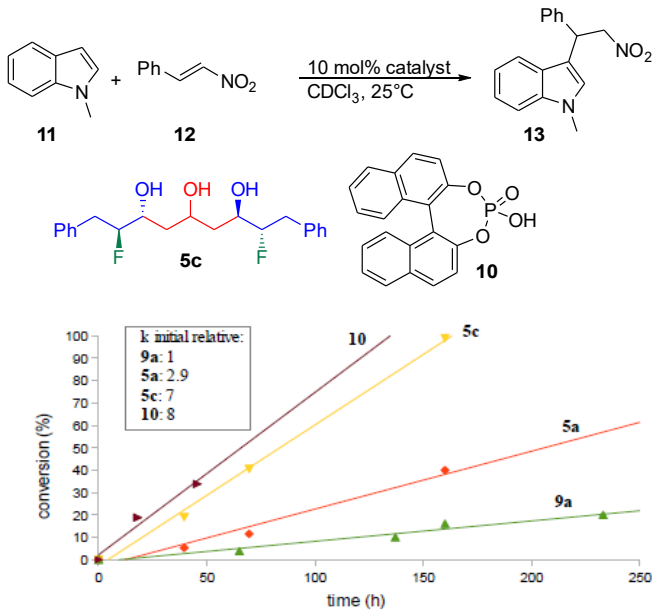


Figure 4. Organocatalyzed addition of N-methyl indole to 2-nitrostyrene. Reaction run using 0.1 mmol of **12**, 0.25 mmol of **11** in 0.2 mL of solvent. Conversions determined by comparing starting material and product ratios by ^{1}H NMR. Note: The product **13** was obtained as a racemate using **5c**.

Conclusions

The present study shows that the selective introduction of halogen atoms (F or Cl), strongly affected different supramolecular properties of synthetic 1,3,5-triol structures, a central motif widely found in nature. By increasing the strength of the polyol hydrogen bonding networks, halogen insertion considerably improved their anion binding properties as well as their H-bonding catalytic abilities. Moreover, the strength of fibers created by self-assembly is significantly increased, resulting in robust organogelation properties towards different solvents. This constitutes a particularly interesting feature for such unusually small molecules easily available from simple commercially available materials.

As a result, it should help in the design of future anion binders, catalysts or innovative organogelators with enhanced properties. In addition, these observations should also help understanding and designing new drugs. Finally, the modularity and the efficiency of our synthetic approach should allow to considerably enhance the current observed properties of 1,3,5-triols through cooperative action of the lateral chains such as with extended aromatic rings.

Experimental Section

See supporting information for details on polyols preparation, X-Ray single crystal analysis, organogel formation and analysis, anion binding and catalysis.

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Keywords: • supramolecular • fluorine • chlorine • halogenohydrins • polyols

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[33] Diluting the reaction by a factor of two, the same reaction rate increase is observed using fluorinated triol. This rules out possible rate increase through aggregate formation. See SI for details.

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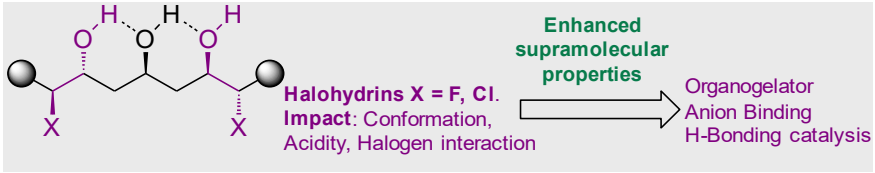

Anti-1,2-halohydrins provide new tools to enhance supramolecular properties in natural product looking 1,3,5-triols. Increase in the polyol H-bonding strength as well as additional Van der Waals interactions improve the resulting 3D association behavior. This results in enhanced organic gels, anion binding or H-bond donor catalysis.

*Céline Sperandio, Guilhem Quintard, Jean-Valere Naubron, Michel Giorgi, Mehdi Yemloul, Jean-Luc Parrain, Jean Rodriguez, Adrien Quintard,**

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Strategic stereoselective halogen insertion (F, Cl), a tool to enhance supramolecular properties in polyols