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Strategic Stereoselective Halogen (F, Cl) Insertion: 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] and Adrien Quintard*^[a]

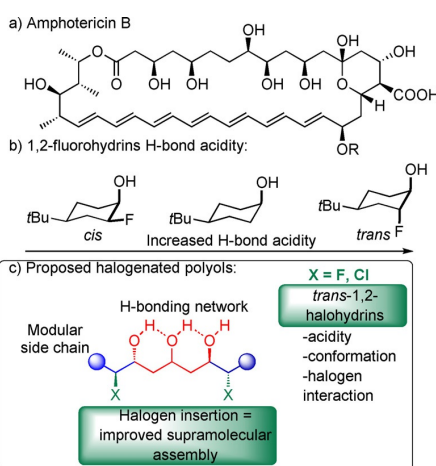
Abstract: To improve the supramolecular properties of organic compounds, chemists continuously need to identify new tools. Herein, the influence of the stereoselective insertion of halogen atoms (F or Cl) on different supramolecular properties is analyzed. Inserting *anti*-halohydrins in polyols

considerably strengthens the H-bonding networks and other supramolecular interactions. This behavior resulted in improved anion binding, H-bonding catalysis, or organogel properties of the designed polyols with 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 and biological tools. As a result, to answer the increasing demand of society for more elaborated materials and 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 H-bonding frameworks, polyols impart crucial bioactivity to the impressive number of natural products having this particular motif.^[1] For example, the antifungal activity of natural amphotericin B (Scheme 1 a) is in part due to its ion-transportation ability through membranes by supramolecular assembly.^[2] To understand and potentially improve polyol properties, researchers have relied on the development of synthetic mimics. It has been shown, notably by Kass et al., that in the acyclic series cooperative effects between the different hydroxyl groups in 1,3-polyols were responsible for en-



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

hanced H-bonding properties.^[3] As a result, aside from medicinal chemistry, recent studies have shown great prospects for the use of synthetic polyols in anion binding^[4,5] and H-bonding catalysis.^[6] In addition it was shown that the H-bonding frameworks created by 1,2-diols could serve as platforms to create promising organic gels.^[7] However, the limited availability and tunability of synthetic polyols hamper the improvement of the desired properties and thus considerably restrict the potential applications. In this context, we questioned how halogen insertion (F or Cl) would affect the supramolecular properties of acyclic polyol systems.

In nature, chlorohydrins are central to different natural products showing impressive bioactivities.^[8] However, the exact implication of these chlorine atoms is not always well understood.^[9] On the other hand, fluorine is interesting given its ability to modulate the lipophilicity of organic molecules, the acidity of adjacent functional groups, or conformation with little

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impact on the steric environment.^[10] As a result, 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 has also been used with success in materials sciences.^[11a] The electronic modulation and conformational restriction through the so-called *gauche* effect developed in drug design are also useful for the design of improved catalysts.^[11b,c]

Among fluorinated backbones, 1,2-fluorohydrins have found only limited applications in enhancing the supramolecular properties of acyclic alcohols.^[12] This is surprising given the ubiquity of aliphatic alcohols in biologically active molecules and natural products and might be due to the lack of general understanding of the influence of 1,2-fluorohydrins. Indeed, recent studies aimed at determining the effect of fluorine on the acidity of cyclohexanols indicated a complex behavior.^[13] Whereas going from an alcohol to a *trans*-1,2-fluorohydrin increased the acidity, going to a *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 the presence of halogen interactions would additionally give the structures great potential in a broad range of applications.

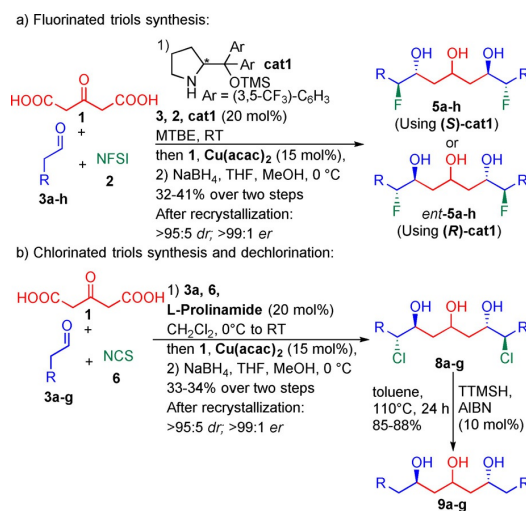
This study provides fundamental knowledge to better understand the impact of 1,2-halohydrins on the supramolecular behavior of organic molecules. In our design, modulation of the lateral chains of such motifs would ensure broad applicability of the approach in a wide range of domains, from organoformation to catalysis and anion binding.

Results and Discussion

Polyol synthesis

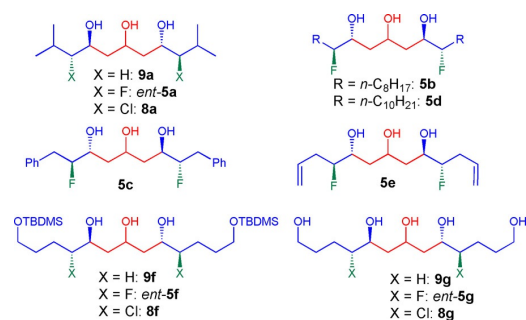
Development of new chemical tools for physical applications strongly depends on our ability to rapidly and stereoselectively construct the required complex molecular objects of interest in the most practical, straightforward, and economically reliable manner. Notably, the rapid assembly of acyclic structures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

The sequence involves an organocatalyzed enantioselective halogenation of aldehydes **3** followed by a diastereoselective copper-catalyzed bidirectional aldolization reaction. Subsequent reduction of the ketodiol intermediates provides rapid access to C_2 -symmetric fluorinated or chlorinated triols **5** and **8**. These triols, originally formed as mixtures containing around 80% of the major diastereomers, could be efficiently obtained in excellent stereoselectivity through single recrystallization (>95:5 *dr* and >99:1 *er*).^[15]



Scheme 2. Multicatalytic route to halogenated 1,3,5-triols. *dr* = diastereomeric ratio, *er* = enantiomeric ratio. acac = acetylacetonate, AIBN = azobisisobutyronitrile, NCS = *N*-chlorosuccinimide, NFSI = *N*-fluorobenzenesulfonamide, TTMSH = tris(trimethylsilyl) hydride, MTBE = *tert*-butyl methyl ether.

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



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

chains on the halotriols 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**, which allows the influence of the chirality on supramolecular properties to be studied. The synthesis is scalable (15 mmol of **1**) and can be performed easily without the need for column chromatography given the crystallinity of most of the 1,3,5-triols. Finally, to fully assess the influence of halogen substitution, radical dechlorination of **8** provided dehalogenated triols **9** in good yields.^[16]

Structure, aggregation, and organogelation of triols

With easy access to a broad range of 1,3,5-triols in hand, we first focused on their structural features in the solid state. 1,3,5-Triols **5a**, **8a**, and **9a** bearing terminal isopropyl groups are crystalline, and their solid structures could be determined by single-crystal XRD (Figure 1).^[17] The three triols have rigid

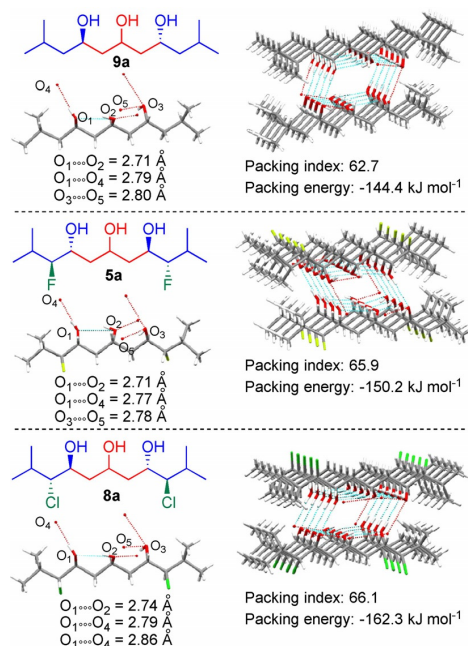


Figure 1. Single-crystal XRD structures and molecular packings of **9a**, **5a**, and **8a**.

bilayer-type motifs and are isostructural with differences in interactions and packings. Remarkably, in **5a** the fluorine atoms are located *trans* to the OH groups without any *gauche* conformation. The preference for *trans* disposition over classical *gauche* stabilization is of utmost importance and in contradiction with common observations on 1,2-fluorohydrins.^[11c,18] This effect can be explained through stabilization of the linear structure by triol H-bonding, which probably minimizes dipole-dipole interactions. The same type of conformation is also observed in parent chlorinated triol **8a**. In **5a** and **8a**, the halogen atoms point outwards from the strong H-bonding network involving two inter- and one intra-alcohol H-bonds. This arrangement creates an infinite 1D chain of H-bonds. Halogen atom insertion (F or Cl) gives a higher packing index thanks to the presence of additional halogen-hydrogen intermolecular interactions.^[19,20] In confirmation of our hypothesis, the *anti*-fluorine *trans*-relationship electronic repulsion increases the strength of intermolecular H-bonding with shorter O–O distances of 2.77 and 2.78 Å for **5a** versus 2.79 and 2.80 Å for **9a**. On the contrary, the larger size of the chlorine atom probably ex-

tends the distance between two molecules by steric repulsion resulting in longer H-bonds in the self-assembly (2.79 and 2.86 Å for the intermolecular H-bonding). This effect is counterbalanced by a number of additional halogen-hydrogen intermolecular interactions, which result in a higher packing index for this chlorinated triol.

DFT calculations in the gas phase also confirmed this stabilized *trans* relationship in the halohydrins (Table 1).^[21] Geometry optimizations and frequency calculations were performed at the DFT level of theory by using the M06-2X functional^[22] as

Table 1. Conformational analysis of 5a and 8a at the M06-2X/6.311 + G(d,p) (ZPE corr.) level of theory.				
Entry	Newman representations		Dihedral angles [°] X-C-C-O, O-C-C-X	Relative energy [kcal mol ⁻¹]
	C3–C4	C8–C9		
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

implemented in Gaussian 09.^[23] For all atoms, the 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 . The NBO 6 program,^[24] which is included in the Gaussian 16 suite of programs, was used to obtain natural bond orbitals (NBOs), atomic net charges, and the energetic evaluation of secondary interactions.

These calculations showed that **5a** with two *trans*-fluorohydrin moieties is highly favored by more than 7.8 kcal mol⁻¹ through minimized dipole-dipole interactions as compared to the other rotamers having one or two *gauche* fluorohydrin (Table 1, entry 1 versus entries 2–4). Interestingly, in the case of chlorohydrin **8a**, more conformational freedom was calculated,

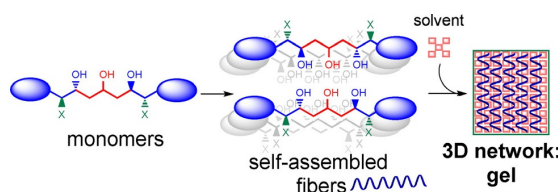
and the most stable conformation features two *trans*-chlorohydrins (Table 1, entry 5). However, one of the two chlorohydrins can rotate to obtain a mixed *trans/cis* conformer of almost equal energy (0.77 kcal mol⁻¹ difference, cf. Table 1, entries 5 and 6). Finally, chlorohydrins with two *cis* relationships are disfavored by more than 3.9 kcal mol⁻¹ (Table 1, entries 7 and 8). More rotational freedom is observed around the central alcohol moiety, which confirms the role of the halogen in conformational rigidification (see Supporting Information). This suggests that the rotational freedom of this central nonhalogenated alcohol allows the structure to adapt to the environment (auto-assembly or anion coordination and catalysis; vide infra).

The single-crystal structures obtained for halogenated triols clearly demonstrate the ability to create strong H-bonding networks and self-assembly of nanostructures, which are two key elements for further applications. Thus, we were curious to see how these changes observed in the solid state would affect other supramolecular properties.

Gels formed by small organic molecules (organogelators) entrapping solvents in high-order 3D networks through fiber self-assembly have recently attracted considerable interest.^[25] For example, these smart materials have found applications in photonics, oil-spill recovery, catalysis, and as self-healing materials.^[25] However, the limited structural variations, which are often based on sensitive acetal and ester functionality, can restrict the potential of these organogelators.

The creation of new gels through fibers formation is closely related to crystallization with subtle differences in the assembly process leading to 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 by innovative low molecular weight organogelator (LMOG) platforms is highly desirable. Given the solid-state structure of synthetic 1,3,5-triols, we hypothesized that, as in 1,2-diol LMOGs,^[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 study and compare the organogelator efficiency of 1,3,5-triols we determined the critical gelation concentration (CGC in wt/vol%), below which the gel scrambles, and the gel transition temperature (T_{gel} in °C), at which the gel starts falling apart, by using the classical vial-inversion method (Table 2).^[27]



Scheme 4. Proposed mechanism of gelation with triols.

Table 2. Influence of the substitution on gelation in selected solvents (see Supporting Information for other solvents) and 0.33% (wt/vol) **5b** image of an *o*-xylene translucent gel.^[a]

Solvent	CGC [%], T_{gel} [°C] ^[b]			
	9a	8a	5a	5b
benzene	NG	NG	1, 50	0.5, 28 ^[d]
toluene	NG	NG	0.66, 59	0.31, 35 ^[d]
<i>o</i> -xylene	NG	2, 38	0.8, 64	0.29, 60 ^[d]
petroleum ^[c]	NG	2, 28	0.36, 78	0.25, 75
CH ₃ CN	NG	NG	NG	1, 53

[a] CGC = critical gelation concentration, in wt/vol%. T_{gel} = gel transition temperature. NG = no gelation observed at 2% (wt/vol). [b] T_{gel} measured at 2% (wt/vol). [c] Drugstore bottle of hydroalkanes (C₁₁–C₁₄), isoalkanes, *n*-alkanes, cycloalkanes with 35% of toluene as the aromatic constituent. [d] Translucent gel.

Comparison of the gelation properties of fluorinated, chlorinated, and nonhalogenated triols revealed totally different behaviors. Nonhalogenated polyol **9a** did not show any gelation at 2% (wt/vol). 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 on the basis of the crystal assembly by the size of the chlorine atom repelling the two polyol layers and decreasing the strength of the fibers. Insertion of fluorine impressively improved the gelation properties of **5a**. In various nonpolar organic media, such as benzene, toluene, and petroleum, a strong gel was obtained with as little as 0.36% (wt/vol) of the organogelator, so that only 10 mg of this particularly small organic molecule (FW = 268) is able to gel 2.75 mL of petroleum. The gels can easily be reversibly generated through successive heating/cooling cycles. In coordinating polar solvents such as CH₃CN and EtOH, no gelation is observed; this indicates that disruption of the H-bonding network breaks down the gel.

To improve the gel properties, we modulated the lateral chains of the fluorinated triols to increase their lipophilicity (see Supporting Information for all the polyols tested). Fluorinated polyol **5b** bearing a linear C₈H₁₇ chain provided materials with lower CGC and was efficient for a broad range of solvents (see Table 2). Notably, even the coordinating EtOH and CH₃CN could form a gel in the presence of only 1–2% (wt/vol) of the fluorinated polyol. The full list of efficient gelation solvents, including diesel, silicon oil, and pump oil (paraffin), can be found in the Supporting Information. Regarding photonic applications,^[7,25] some of these gels are translucent, such as the **5b**/*o*-xylene gel shown in Table 1.

Given the excellent performance of fluorinated triols as LMOGs, and to understand the effects causing gelation, we studied in further detail the properties and structures of these gels. First, the gel properties obtained by the vial inversion method were confirmed by rheological measurements (Figure 2a–c and Supporting Information). The strength of fluorinated

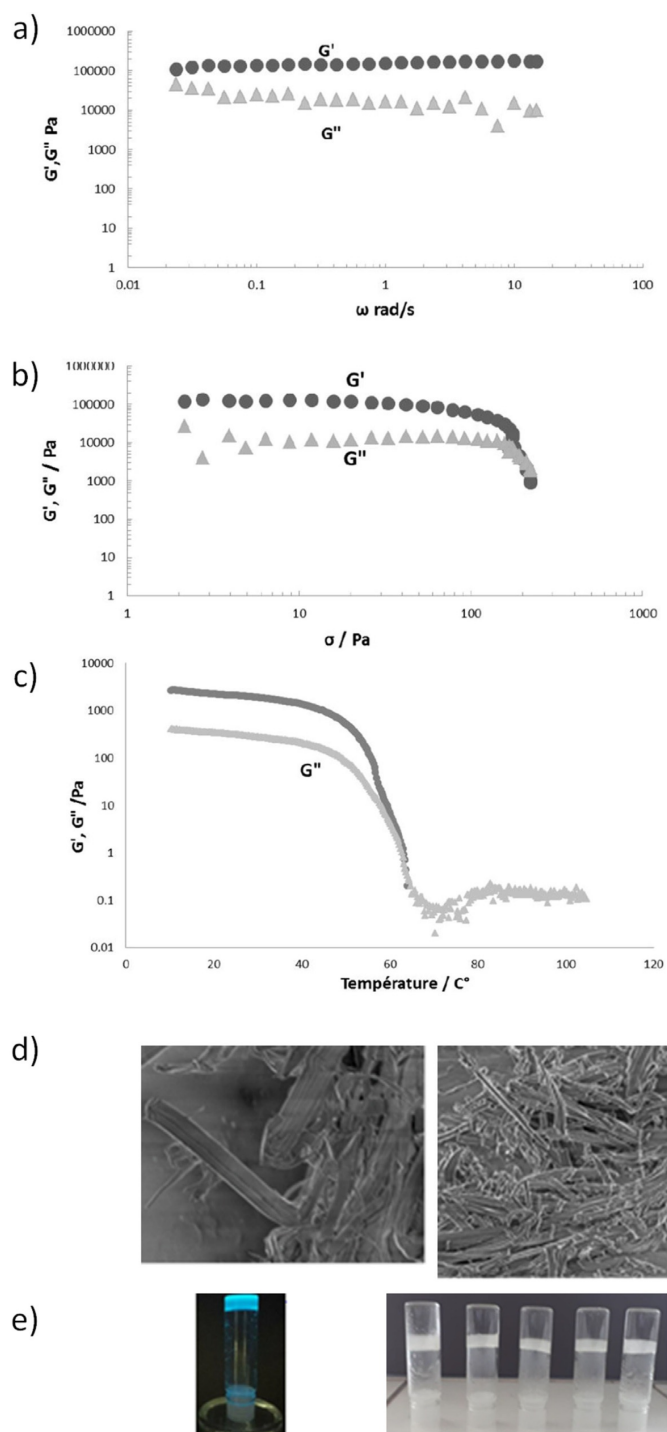


Figure 2. Gel properties. a) Frequency sweep of 4% (wt/vol) **5b** in petroleum. b) Stress sweep of 4% (wt/vol) of **5b** in petroleum. c) Temperature dependence of 2% (wt/vol) **5a** in *o*-xylene. d) SEM image of **5b** and **5a** xerogels [2% (wt/vol) in petroleum]. e) Images of gels. Left: UV-irradiated 0.4% (wt/vol) **5b** in toluene doped with 0.2% (wt/vol) pyrene; right: stability of 2% (wt/vol) **5b** gel of petroleum in the presence of aqueous solutions: 3.5% NaCl; pH 1; pH 4; pH 8; pH 14.

nated triol gels such as **5b** in petroleum favorably compares to literature data.^[7] In confirmation of the gel behavior, the elastic modulus G' is larger 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 molecules (Figure 2a). Monitoring G' and G'' as a function of the stress amplitude (Figure 2b) indicated that the **5b**-based gel was resistant up to at least 100 Pa of applied stress.

The values of T_{gel} obtained by the vial-inversion method (Table 2) can be correlated with the rheological properties (G' and G'') as a function of the temperature for gel **5a** in *o*-xylene, which shows a destructuring gel at a temperature around 62 °C (Figure 2c). Xerogels were obtained by evaporation of the solvent of different gels and analyzed by SEM. This confirmed the gelation process through the formation of large fibers, as in the xerogel obtained from **5a** or **5b**/petroleum gel (Figure 2d and Supporting Information).

Doping a **5b** gel of petroleum with 0.2% (wt/vol) of pyrene resulted in a strongly UV fluorescent gel, which opens perspectives for applications to other doped fluorinated gels (Figure 2e, left).

Considering the structure of the fluorinated polyols, the great advantage of the organogels created from **5b** is their high stability in the presence of a broad range of aqueous solutions. Going from pH 1 (HCl solution) to pH 14 (NaOH solution) or in the presence of 3.5% NaCl solution, all the gels kept their resistance (Figure 2e, 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 base-sensitive functions (esters, amides, acetals).^[7,25]

Analysis of the fluorinated triols and the related gels by NMR spectroscopy and vibrational circular dichroism (see Supporting Information for details) seemed 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 XRD of **5a**. All these observations suggest that the fibers are exclusively formed by H-bonds and hydrophobic interactions. Fluorine insertion positively affects gelation through different means. First, a stronger H-bond framework, which increases the strength of the supramolecular assembly, is created by the electronegative fluorine atom. The presence of the hydrophobic fluorine atoms, which point outside of the fibers and are able to create additional interactions with the solvent, also strengthens 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 causing a weaker supramolecular assembly.

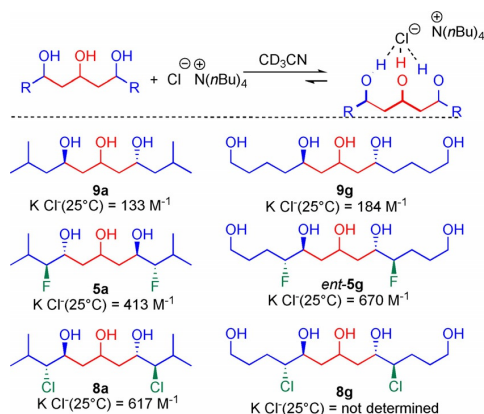
Thus, halogen insertion, notably of fluorine atoms, affects drastically the organogelation properties of triols. The small, easily prepared, stereodefined, and highly stable fluorinated triols allow strong gelation of a broad range of organic solvents and led us to study other possible supramolecular 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, and catalysts.^[28] To further probe the influence of halogen insertion on 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 ¹H NMR titration experiments in CD₃CN. The addition of tetrabutylammonium chloride (TBACl) to polyols resulted in large downfield shifts of the hydroxyl hydrogen atoms. In addition, the binding of fluorinated polyols could also be easily monitored by ¹⁹F NMR. Association constants from triplicate experiments were obtained by fitting these spectroscopic data to 1:1 binding isotherm models with the Thordarson method.^[29] When nonhalogenated polyol **9a** or **9g** was used, and in accordance with the results of Kass et al., relatively weak Cl⁻ binding was observed (Scheme 5, 133 or 184 M⁻¹, respectively).^[3] In contrast, fluorine insertion considerably improved the anion binding by a factor of 3.1–3.6 in **5a** and *ent*-**5g**. A relatively large Cl⁻ binding constant of 413 M⁻¹ for the simple acyclic polyol **5a** was observed. Interestingly, addition of terminal free alcohol to *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 to give binding constant of 617 M⁻¹ clearly demonstrated the positive impact of chlorine insertion.^[30] Given the presence of chlorohydrins in numerous highly bioactive molecules, this observation should have implications for the understanding of their biological mode of action and for drug design.



Scheme 5. Cl⁻ anion-binding properties of different 1,3,5-triols in CD₃CN (average of triplicate experiments).

Table 3. Calculated properties of polyol-TBACl structures and DFT modeling of the structure of **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.

To shed light on the mechanism behind the observed binding improvement by halogen insertion, these values were correlated with DFT calculations (Table 3). First, calculations of the different enthalpies of formation of polyol-TBACl complexes confirmed the impact of halogen insertion (Table 3). Formation of the TBACl complex was less favored for **9a** ($\Delta H = -8.36$ kcal mol⁻¹), whereas fluorine or chlorine insertion in **5a** and **8a** improved the affinity ($\Delta H = -11.25$ and -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 halogen atoms (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 O–Cl distance is less modified depending on the substitution and ranges from 3.20 for **9a** to 3.21 Å for **8a** (Table 3). The higher affinity observed for halogenated polyols directly arises 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 allow the acidity of the alcohols to be efficiently increased.

Given the impressive effect of halogen insertion on anion binding, we also checked the ability of the halogenated polyols to act as H-bond-donor catalysts. Even though those properties are closely linked, the binding mode of polyols is different in the two applications. Indeed, it was previously described by Kass et al. that 1,3-polyols bind anions with three alcohol hydrogen atoms, whereas the acidity necessary for H-bonding catalysis results from a cooperative effect between the alcohol groups through intramolecular H-bonds.^[31] This intramolecular

network significantly increases the pK_a of the most acidic alcohol group, which is subsequently able to activate a suitable electrophile such as a nitroolefin. DFT calculations confirmed this type of activation for fluorinated polyol **5c**, in which only one H-bond was found to be established (Figure 3).

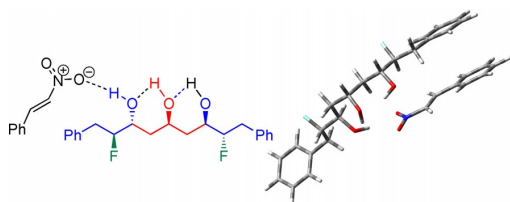


Figure 3. DFT calculated structure of nitrostyrene-**5c** in $CDCl_3$.

To evaluate the catalytic activity of our triols we chose the Friedel–Crafts addition of *N*-methyl indole (**11**) to 2-nitrostyrene **12** (Figure 4).^[32] Halogen insertion positively affected the catalytic ability of polyols. Threefold rate acceleration was observed for fluorinated **5a** compared with nonhalogenated polyol **9a**. Both fluorinated and chlorinated polyols provided the same type of catalytic profile in this transformation.^[33]

Simple modulation of the fluorinated polyols by incorporating phenyl substituents on the lateral chains considerably increased the reaction rate. With **5c**, a reaction rate comparable to that of binol phosphoric acid derivative **10** was observed but with a compound having a much lower pK_a value. This indicates a cooperative effect of the lateral chain, possibly through π interactions with the substrates, which opens broad perspectives for improvement of these structures for catalysis through further modulation of the side chain.

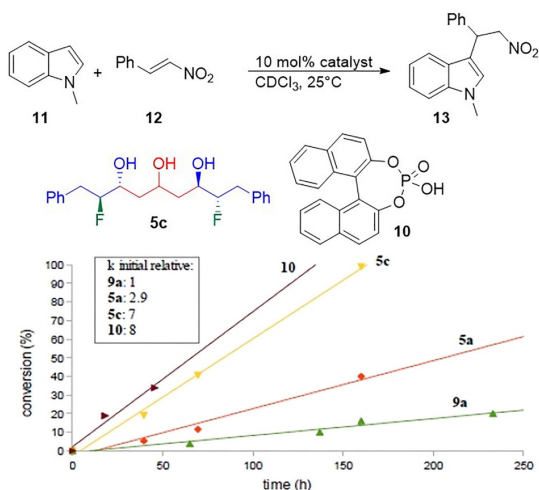


Figure 4. Organocatalyzed addition of *N*-methylindole to 2-nitrostyrene. Reaction performed with 0.1 mmol of **12** and 0.25 mmol of **11** in 0.2 mL of solvent. Conversions determined by comparing ratios of starting material and product by 1H NMR spectroscopy. Note: product **13** was obtained as a racemate on using **5c**.

Conclusion

Selective introduction of halogen atoms (F or Cl) strongly affected different supramolecular properties of 1,3,5-triols, a central motif widely found in nature. By increasing the strength of the polyol H-bonding networks, halogen insertion considerably improved their anion-binding and H-bonding catalytic abilities. Moreover, the strength of fibers created by self-assembly is significantly increased, and this results in robust organogelation properties towards different solvents. This is a particularly interesting feature for such unusually small molecules that are easily available from simple commercially available materials. Hence, this work should help in the design of future anion binders, catalysts, and innovative organogelators with enhanced properties. In addition, these observations should also help in designing new drugs. Finally, the modularity and the efficiency of our synthetic approach should allow the herein-observed properties of 1,3,5-triols to be considerably enhanced through cooperative action of the lateral chains, for example, with aromatic rings.

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Conflict of interest

A patent on the organogelating properties of fluorinated 1,3,5-triols has been submitted by Céline Sperandio, Jean Rodriguez and Adrien Quintard. Patent declaration. EP18305732. Submitted 15 June 2018.

Keywords: chlorine · fluorine · gels · alcohols · supramolecular chemistry

- [1] A. M. P. Koskinen, K. Karisalmi, *Chem. Soc. Rev.* **2005**, *34*, 677.
- [2] a) K. Yamashita, V. Janout, E. M. Bernard, D. Armstrong, S. L. Regen, *J. Am. Chem. Soc.* **1995**, *117*, 6249, and references therein; b) K. A. Murgalia, R. S. Chorghade, B. R. Kim, X. X. Tang, V. S. Shah, A. S. Grillo, P. N. Daniels, A. G. Cioffi, P. H. Karp, L. Zhu, M. J. Welsh, M. D. Burke, *Nature* **2019**, *567*, 405.
- [3] a) A. Shokri, J. Schmidt, X.-B. Wang, S. R. Kass, *J. Am. Chem. Soc.* **2012**, *134*, 16944; b) A. Shokri, J. Schmidt, X.-B. Wang, S. R. Kass, *J. Am. Chem. Soc.* **2012**, *134*, 2094; c) A. Shokri, A. Abedin, A. Fattahi, S. R. Kass, *J. Am. Chem. Soc.* **2012**, *134*, 10646; d) A. Shokri, Y. Wang, G. A. O'Doherty, X.-B. Wang, S. R. Kass, *J. Am. Chem. Soc.* **2013**, *135*, 17919.
- [4] In the cyclic series where strong organizational bias exists, several polyols based notably on catechols, or rigid tripodal cyclohexanes have been developed, see: a) D. K. Smith, *Org. Biomol. Chem.* **2003**, *1*, 3874; b) S.-I. Kondo, Y. Kobayashi, M. Unno, *Tetrahedron Lett.* **2010**, *51*, 2512; c) M. Samet, M. Danesh-Yazdi, A. Fattahi, S. R. Kass, *J. Org. Chem.* **2015**, *80*, 1130.
- [5] a) A. Shokri, X.-B. Wang, Y. Wang, G. A. O'Doherty, S. R. Kass, *J. Phys. Chem. A* **2016**, *120*, 1661; b) A. Shokri, X.-B. Wang, S. R. Kass, *J. Am. Chem. Soc.* **2013**, *135*, 9525; c) N. Busschaert, J. Jaramillo-Garcia, M. E. Light, J. Herniman, G. J. Langley, P. A. Gale, *RSC Adv.* **2014**, *4*, 5389.

- [6] a) Y. Huang, A. K. Unni, A. N. Thadani, V. H. Rawal, *Nature* **2003**, *424*, 146; b) O. Coulembier, D. P. Sanders, A. Nelson, A. N. Hollenbeck, H. W. Horn, J. E. Rice, M. Fujiwara, P. Dubois, J. L. Hedrick, *Angew. Chem. Int. Ed.* **2009**, *48*, 5170; *Angew. Chem.* **2009**, *121*, 5272; c) M. Samet, S. R. Kass, *J. Org. Chem.* **2015**, *80*, 7727; and Ref. [3b,c].
- [7] For notable examples of organogels notably based on 1,2-diols scaffolds, see: a) N. Amanokura, K. Yoza, H. Shinmori, S. Shinkai, D. N. Reinhoudt, *J. Chem. Soc. Perkin Trans. 2* **1998**, 2585; b) J. H. Jung, M. Amaike, S. Shinkai, *Chem. Commun.* **2000**, 2343; c) O. Gronwald, S. Shinkai, *Chem. Eur. J.* **2001**, *7*, 4328; d) A. Friggeri, O. Gronwald, K. J. C. van Bommel, S. Shinkai, D. N. Reinhoudt, *J. Am. Chem. Soc.* **2002**, *124*, 10754; e) S. R. Jadhav, P. K. Vemula, R. Kumar, S. R. Raghavan, G. John, *Angew. Chem. Int. Ed.* **2010**, *49*, 7695; *Angew. Chem.* **2010**, *122*, 7861; f) A. Vidyasagar, K. Handore, K. M. Sureshan, *Angew. Chem. Int. Ed.* **2011**, *50*, 8021; *Angew. Chem.* **2011**, *123*, 8171; g) S. Nandi, H.-J. Altenbach, B. Jakob, K. Lange, R. Ihizane, M. P. Schneider, *Org. Lett.* **2011**, *13*, 1980; h) A. Prathap, K. M. Sureshan, *Chem. Commun.* **2012**, 48, 5250; i) Rajkama, D. Chatterjee, A. Paul, S. Banerjee, S. Yadav, *Chem. Commun.* **2014**, 50, 12131; j) A. M. Vibhute, V. Muvvala, K. M. Sureshan, *Angew. Chem. Int. Ed.* **2016**, *55*, 7782; *Angew. Chem.* **2016**, *128*, 7913; k) A. Prathap, K. M. Sureshan, *Angew. Chem. Int. Ed.* **2017**, *56*, 9405; *Angew. Chem.* **2017**, *129*, 9533.
- [8] a) M. T. Cabrita, C. Vale, A. P. Rauter, *Mar. Drugs* **2010**, *8*, 2301; b) G. W. Gribble, *Mar. Drugs* **2015**, *13*, 4044; c) B. Gál, C. Bucher, N. Z. Burns, *Mar. Drugs* **2016**, *14*, 206.
- [9] a) C. Nilewski, R. W. Geisser, M.-O. Ebert, E. M. Carreira, *J. Am. Chem. Soc.* **2009**, *131*, 15866; b) A. M. Bailey, S. Wolfrum, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 639; *Angew. Chem.* **2016**, *128*, 649; c) S. Fischer, N. Huwyler, S. Wolfrum, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 2555; *Angew. Chem.* **2016**, *128*, 2601. For another example of chlorinated bioisostere synthesis, see: d) S. Krautwald, C. Nilewski, M. Mori, K. Shiomi, S. Omura, E. M. Carreira, *Angew. Chem. Int. Ed.* **2016**, *55*, 4049; *Angew. Chem.* **2016**, *128*, 4117.
- [10] a) K. Muller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320; c) D. O'Hagan, *Chem. Soc. Rev.* **2008**, *37*, 308; d) J. Wang, M. Sánchez-Roselló, J. L. Aceña, C. del Pozo, A. E. Sorochinsky, S. Fustero, V. A. Soloshonok, H. Liu, *Chem. Soc. Rev.* **2014**, *43*, 2432; e) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015**, *58*, 8315.
- [11] a) R. Berger, G. Resnati, P. Metrangolo, E. Weber, J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496; b) L. E. Zimmer, C. Sparr, R. Gilmour, *Angew. Chem. Int. Ed.* **2011**, *50*, 11860; *Angew. Chem.* **2011**, *123*, 12062; c) M. Aufferio, R. Gilmour, *Acc. Chem. Res.* **2018**, *51*, 1701. After the initial submission of this manuscript, Gilmour et al. recently published a study on the reactivity of polyfluorinated polyols prepared in more than ten steps: d) P. Bentler, K. Bergander, C. G. Daniliuc, C. Mück-Lichtenfeld, R. P. Jundt, A. K. H. Hirsch, R. Gilmour, *Angew. Chem. Int. Ed.* **2019**, *58*, 10990; *Angew. Chem.* **2019**, *131*, 11106.
- [12] For examples in drug design, see: a) J. Fried, E. F. Sabo, *J. Am. Chem. Soc.* **1954**, *76*, 1455; b) A. G. Myers, J. K. Barbay, B. Zhong, *J. Am. Chem. Soc.* **2001**, *123*, 7207; c) T. J. Graham, R. F. Lambert, K. Ploessl, H. F. Kung, A. G. Doyle, *J. Am. Chem. Soc.* **2014**, *136*, 5291.
- [13] a) J. Graton, Z. Wang, A.-M. Brossard, D. G. Monteiro, J.-Y. Le Questel, B. Linclau, *Angew. Chem. Int. Ed.* **2012**, *51*, 6176; *Angew. Chem.* **2012**, *124*, 6280; b) J. Graton, G. Compain, F. Besseau, E. Bogdan, J. M. Watts, L. Mtashobya, Z. Wang, A. Weymouth-Wilson, N. Galland, J.-Y. Le Questel, B. Linclau, *Chem. Eur. J.* **2017**, *23*, 2811.
- [14] a) A. Quintard, J. Rodriguez, *ACS Catal.* **2017**, *7*, 5513; b) A. Quintard, C. Sperandio, J. Rodriguez, *Org. Lett.* **2018**, *20*, 5274; c) A. Ricucci, J. Rodriguez, A. Quintard, *Eur. J. Org. Chem.* **2018**, 3697; d) J. Rodriguez, A. Quintard, *Chimia* **2018**, *72*, 580.
- [15] These molecules have four acyclic stereogenic centers created in distinct steps. This results in the possible formation of multiple stereoisomers. From the crude reaction mixture, it is difficult to determine the exact *dr* and *ee* of the reaction, but according to ¹⁹F NMR spectroscopy the desired adducts are formed with about 80% of the major diastereomer, and this stereoselectivity is increased through purification.
- [16] a) S. D. Halperin, R. Britton, *Org. Biomol. Chem.* **2013**, *11*, 1702. Alternatively, nonhalogenated 1,3,5-triols could also be accessed by a reductive coupling we recently developed: b) A. Quintard, J. Rodriguez, *Org. Lett.* **2019**, *21*, 453.
- [17] CCDC 1879983, 1879890, and 1879889 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.
- [18] For studies related to fluorohydrin conformations, see: a) D. A. Dixon, B. E. Smart, *J. Phys. Chem.* **1991**, *95*, 1609; b) R. J. Abraham, E. J. Chambers, W. A. Thomas, *J. Chem. Soc. Perkin Trans. 2* **1994**, 949; c) C. R. S. Briggs, M. J. Allen, D. O'Hagan, D. J. Tozer, A. M. Z. Slawin, A. E. Goeta, J. A. K. Howard, *Org. Biomol. Chem.* **2004**, *2*, 732.
- [19] P. A. Champagne, J. Desroches, J.-F. Paquin, *Synthesis* **2015**, 47, 306.
- [20] a) A. Gavezzotti, *Acc. Chem. Res.* **1994**, *27*, 309; b) A. Gavezzotti, G. Filippini, *J. Phys. Chem.* **1994**, *98*, 4831.
- [21] See the Supporting Information for details.
- [22] Y. Zhao, D. G. Truhlar, *Theor. Chem. Acc.* **2008**, *120*, 215.
- [23] Gaussian 09, Revision A.1, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Menucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, Gaussian, Inc., Wallingford CT, **2009**.
- [24] NBO 6.0, E. D. Glendening, J. K. Badenhoop, A. E. Reed, J. E. Carpenter, J. A. Bohmann, C. M. Morales, C. R. Landis, F. Weinhold, Theoretical Chemistry Institute, University of Wisconsin, Madison, WI, **2013**, <http://nb06.chem.wisc.edu/>.
- [25] For reviews, see: a) A. R. Hirst, B. Escuder, J. F. Miravet, D. K. Smith, *Angew. Chem. Int. Ed.* **2008**, *47*, 8002; *Angew. Chem.* **2008**, *120*, 8122; b) G. O. Lloyd, J. W. Steed, *Nat. Chem.* **2009**, *1*, 437; c) B. Escuder, F. Rodriguez-Llansola, J. F. Miravet, *New J. Chem.* **2010**, *34*, 1044; d) D. Díaz, D. Kühbeck, R. J. Koopmans, *Chem. Soc. Rev.* **2011**, *40*, 427; e) L. E. Buerkle, S. J. Rowan, *Chem. Soc. Rev.* **2012**, *41*, 6089; f) C. D. Jones, J. W. Steed, *Chem. Soc. Rev.* **2016**, *45*, 6546; g) B. O. Okesola, D. K. Smith, *Chem. Soc. Rev.* **2016**, *45*, 4226; h) W. Fang, Y. Zhang, J. Wu, C. Liu, H. Zhu, T. Tu, *Chem. Asian J.* **2018**, *13*, 712.
- [26] a) A. R. Hirst, D. K. Smith, J. P. Harrington, *Chem. Eur. J.* **2005**, *11*, 6552; b) P. Dastidar, *Chem. Soc. Rev.* **2008**, *37*, 2699; c) D. J. Adams, K. Morris, L. Chen, L. C. Serpell, J. Basca, G. M. Day, *Soft Matter* **2010**, *6*, 4144; d) A. Vidyasagar, K. M. Sureshan, *Angew. Chem. Int. Ed.* **2015**, *54*, 12078; *Angew. Chem.* **2015**, *127*, 12246; e) M. Liu, G. Ouyang, D. Niu, Y. Sang, *Org. Chem. Front.* **2018**, *5*, 2885.
- [27] See reference [7] and the Supporting Information for details.
- [28] For a recent review, see: N. Busschaert, C. Caltagirone, W. V. Rossom, P. A. Gale, *Chem. Rev.* **2015**, *115*, 8038.
- [29] For the tool used, see: <http://supramolecular.org> and a) P. Thordarson, *Chem. Soc. Rev.* **2011**, *40*, 1305; b) D. Brynn Hibbert, P. Thordarson, *Chem. Commun.* **2016**, 52, 12792.
- [30] Unfortunately, in the case of chlorohydrin **8g**, anion binding could not be determined accurately due to lower stability.
- [31] See reference [3]. We also confirmed this catalyst geometry by DFT calculations; see the Supporting Information for details.
- [32] See: R. P. Herrera, V. Sgarzani, L. Bernard, A. Ricci, *Angew. Chem. Int. Ed.* **2005**, *44*, 6576; *Angew. Chem.* **2005**, *117*, 6734, and references [3] and [5b].
- [33] On diluting the reaction mixture by a factor of two, the same increase in the reaction rate was observed with fluorinated triol. This rules out a possible rate increase through aggregate formation. See Supporting Information for details.