

A low molecular weight hydro and organogelator derived from an isohexide and sol–gel transcription of the alcogel†

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Heating 2,5-di-*O*-methanesulfonyl-1,4:3,6-dianhydro-D-sorbitol (**1**) in a range of solvents led to the formation of a gel state at low concentrations. **1** was found to gel aromatics, alcohols and water. The structure of **1** in the solid state was solved by single crystal X-ray crystallography; no strong hydrogen bonds or associated solvents were found in the crystal. Electron micrographs revealed the morphology of the gels to be predominantly rod-like. The ethanol alcogel was used to template silica by sol–gel transcription.

Introduction

Organogels are heterogeneous three dimensional networks made up of an organic molecule trapping an organic solvent.¹ Low molecular weight organogelators (LMOGs) that can form gel states at low concentrations are of particular interest due to their low cost, low environmental impact and ease of synthesis. LMOGs are currently finding many applications,¹ including uses in pharmacy,² biomaterials, agriculture and cosmetics.

This paper describes the ability of 2,5-di-*O*-methanesulfonyl-1,4:3,6-dianhydro-D-sorbitol (**1**, Fig. 1) to gel a range of solvents at low concentration and the transcription of the gel structure onto silica. **1** is unusual as it does not contain any aromatic, hydroxyl or long aliphatic functional groups. The structure is compared to that of a conventional sugar-derived organogelator 1,3:2,4-di-*O*-benzylidene-D-sorbitol (DBS, Fig. 1).

The self assembly of LMOGs in a solvent has been shown to lead to a number of gel morphologies.¹ Silica can be grown around these self-organised organics by introducing a silicon alkoxide precursor into the same pot and carrying out a sol–gel process.^{3,4} The inorganic oxide can adopt a morphology transcribed by the gel structure. The use of template directed sol–gel synthesis of organised organogels offers an interesting route to nano- and microstructures.³ The first inorganic structure in this class was formed from sol–gel transcription of a cholesterol-based gelator.⁴ The discovery of templates for silica that communicate *via* hydrogen bonding⁵ and not ionic

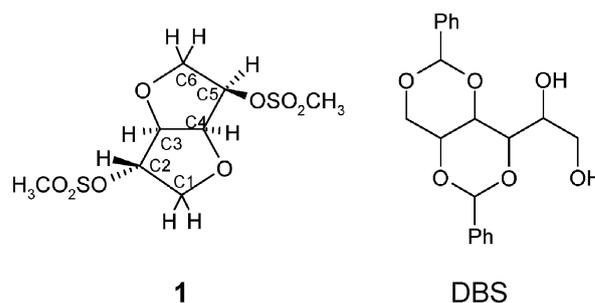


Fig. 1 Comparison of **1** and DBS.

interactions generated renewed interest in organogel templates based on functionalised sugars.^{6,7} The synthesis of molecules containing aromatic and hydrogen-bonding (sugar) functionalities within the same molecule has provided a number of organogelators that could be faithfully transcribed.^{3,4} The promoting effect of benzylamine as a driving force for transcription has been noted in systems relying on hydrogen bonding.⁸ It has been observed that the addition of benzylamine changes the morphology of gels derived from methyl-4,6-*O*-(*p*-nitrobenzylidene)- α -D-glucopyranoside and initiates the sol–gel transcription of silica for an otherwise inactive gelator.

We report the preparation of an organogelator based on a disulfonyl isosorbide. The bicyclic isosorbide and isomannide can be prepared by the dehydration of the parent alditol; the roof-like structure affords distinct environments above and below the ring of the isohexide. This structure makes the isohexides interesting moieties for systematic study as substituents can be positioned in *endo* or *exo* positions.

Results and discussion

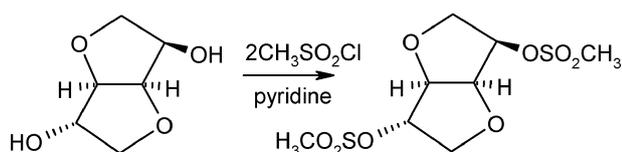
Synthesis and organogel discovery

The synthesis of **1** from isosorbide is illustrated in Scheme 1. Aromatic, hydroxyl and N-containing functionalities are known to aid gelation and assist the transcription of silica onto the gel.^{3,6} Following this convention we attempted to

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† Electronic supplementary information (ESI) available: Tables of additional sol to gel and gel to sol experiments and selected bond distances and angles of **1**. CCDC reference number 646818. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/b814274b



Scheme 1 Conversion of isosorbide into **1**.

prepare a new organogelator by introducing amine and aromatic functionalities into isosorbide. The reaction mixture from the attempted substitution of the sulfonyl groups of **1** with benzylamine in *n*-butanol set into a gel on cooling.

Initially this was thought to be due to the successful synthesis of the target benzylamine derivative, but NMR spectra exhibited only the resonances assigned to benzylamine and **1**. All attempts to isolate the amino isosorbide resulted in the recovery of **1**. These findings led us to suggest that the organogelator was the bis-methanesulfonyl derivative of isosorbide **1** working in synergy with benzylamine.⁸ To test this 1% wt/v **1** and benzylamine were added to ethanol and the mixture stirred at 70 °C for 2 h. Under these conditions there was no conversion to the amino sugar. The flask was removed from the heat and left to cool slowly; on cooling a stable gel was formed. A control experiment was carried out in which 1% wt/v **1** was added to ethanol in the absence of benzylamine and the mixture was stirred at 70 °C for 2 h, unexpectedly this mixture also formed a stable gel on cooling. Further control

experiments in which gelation of ethanol was attempted with isosorbide (with or without benzylamine) resulted in no gel formation. This led to the conclusion that the gelator was **1**, to our knowledge this is the first LMOG to be based on an isohexide backbone.

A range of other sulfonyl derivatives of isosorbide and isomannide were tested as potential organogelators including *endo*-5-*O*-methanesulfonyl-1,4:3,6-dianhydro-D-sorbitol, 2,5-di-*O*-propylsulfonyl-1,4:3,6-dianhydro-D-sorbitol, 2,5-di-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-sorbitol, *endo*-5-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-sorbitol, 2,5-di-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-mannitol and 2-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-mannitol; no gels were formed. Introduction of an aryl group or lengthening of the alkyl chain were detrimental to the ability of the isohexide derivatives to gel solvents. No gels based on the isomannide skeleton were discovered.

Further gel tests

Sol to gel tests. Initial screening of **1** at 0.5, 1 and 2% wt/v with a range of solvents was carried out (Table 1). Gels that were stable to inversion were found to form in ethanol, methanol, benzene, 2-propanol, toluene, 1-butanol and water (Fig. 2). Further gelation studies were carried out with percentages (wt/v) of **1** ranging from 0.1–2.0 wt% at intervals of 0.1% for ethanol, methanol, benzene, 2-propanol, toluene, 1-butanol and water. Additional details of gel tests are

Table 1 Sol to gel testing of **1** in a range of solvents

Solvent	Temperature of oil bath/°C	Gelator (%)	Time taken to gel/min	Condition on cooling to RT ^a	Condition after 24 h ^a
Dichloromethane	37	0.5, 1, 2	—	S	S
1,2-Dichloroethane	78	0.5, 1, 2	—	S	S
Chloroform	66	0.5, 1, 2	—	S	S
Acetonitrile	77	0.5, 1, 2	—	S	S
Acetone	53	0.5, 1, 2	—	S	S
Pyridine	110	0.5, 1, 2	—	S	S
Tetrahydrofuran	62	0.5, 1, 2	—	S	S
Ethyl acetate	71	0.5, 1, 2	—	S	P
Water	95	0.5	—	S	C
		1	10.21	GN	GN
		2	8.57	GI	GI
Methanol	61	0.5	—	S	C
		1	9.58	GI	GI
		2	6.29	GI	GI
Ethanol	70	0.5	7.22	GI	GI
		1	3.01	GI	GI
		2	—	SS	SS
2-Propanol	78	0.5	6.20	GN	GI
		1	4.42	GI	GI
		2	—	SS	SS
1-Butanol	112	0.5	—	S	P
		1	7.12	GI	GI
		2	—	SS	GI
Toluene	107	0.5	12.30	S	GN
		1	10.20	GN	GI
		2	—	SS	GI
Benzene	76	0.5	—	GN	GN
		1	7.50	GI	GI
		2	6.20	GI	GI

^a Gel can invert (GI), gel cannot invert (GN), partially soluble (P), **1** crystallised (C), solution (S), saturated solution (SS), laboratory temperature 17 °C, **1** is not soluble in diethyl ether, *n*-hexane or petroleum ether.



Fig. 2 Gels formed using the LMOG 1.

included in the supplementary data.† Water based gels which were stable to inversion were formed at a weight per volume percentage of 2.0%, partial gels were observed in water at concentrations ranging from 0.9–1.9 wt%. Methanol gels stable to inversion were formed at 0.8–2.0 wt%. Ethanol formed a stable gel at 0.5–1.2 wt%. In 2-propanol, stable gels were formed at concentrations from 0.6–1.0 wt%. 1-Butanol gelled in the concentration range 0.8–1.3 wt%. In toluene the gelation range was found to be 1.2–1.8 wt%. Stable gels were formed in benzene at concentrations from 0.7–2.0 wt%. 2-Propanol, 1-butanol and toluene showed the tendency to form stable gels over a larger concentration range when left for 24 h. In all the successful solvents the time taken for the gel to form on cooling increased as the concentration of gelator was decreased.

Gel to sol testing. Tests evaluating the thermal reversibility of the stable gels were carried out by placing the gels into an oil bath at room temperature and increasing the temperature until the isotropic phase was observed. All gels transformed into isotropic liquids at elevated temperature, the gel state was

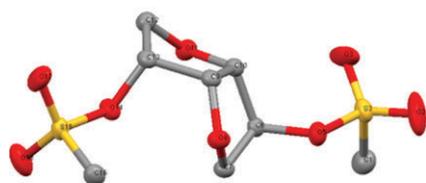


Fig. 3 View of the structure of 1. Thermal ellipsoids are at 30% probability and H's are removed for clarity.

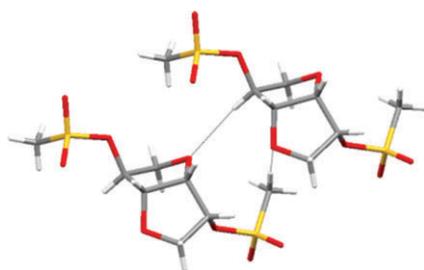


Fig. 4 Short contacts in the crystal of 1, C(6)–H(6A)···O(8) 3.381(3) Å, 162°; C(16)–H(16C)···O(11) 3.444(3) Å, 162°.

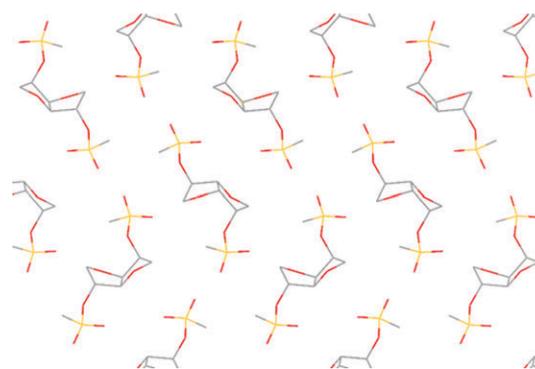


Fig. 5 Packing of 1 viewed along the *a* axis.

found to reform on the cooling of the liquid. Full details are supplied as supplementary data.†

The structure of 1 by X-ray crystallography

Crystals of 1 were grown from ethanol–propan-2-one; the structure was solved by single crystal X-ray crystallography (Fig. 3, Cambridge database CCDC = 646818).† The intramolecular forces most commonly invoked to explain the gelation of sugar derivatives are hydrogen bonds;^{6,7} however, the packing of 1 in the crystalline state contains no strong hydrogen bonds. Analysis of the geometry using PLATON⁹ reveals two possible C–H···O bonds as short contacts with angles of 162° (Fig. 4). This introduces the possibility that the gel contains intramolecular attractions between ring oxygens and acidic hydrogens. The packing in the solid state viewed along the *a* axis is represented by Fig. 5.

Electron micrographs of a dried organogel

SEMs of dried ethanol alcogels were obtained. The sample was prepared by allowing an ethanol gel to dry in air. The SEM revealed the material had self assembled into straight highly anisotropic structures. The nano- and microstructures were predominantly rod-like (Fig. 6) with some belts and tubes also evident.

Transcription by a sol–gel process

The transcription of silica onto the organogel structure was affected by the adsorption of silica onto the surface of the structure by a sol–gel method. A silicon alkoxide precursor, tetraethylorthosilicate (TEOS), water and a base catalyst (benzylamine) were added to the organogel mixture of 1, benzylamine and ethanol. The combination of 1, benzylamine and ethanol formed a structured gel. The silica, water and benzylamine form colloidal silica *via* hydrolysis and condensation of the silicon alkoxide (TEOS). Once these silica particles are formed they are attracted to the surface of the organogel.

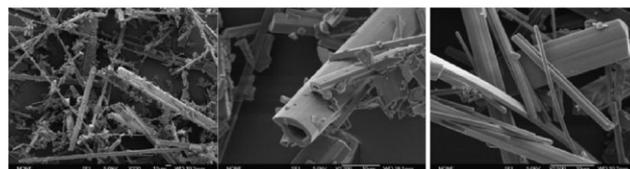


Fig. 6 SEM images of the dried alcogel, 10 μm and 1 μm.

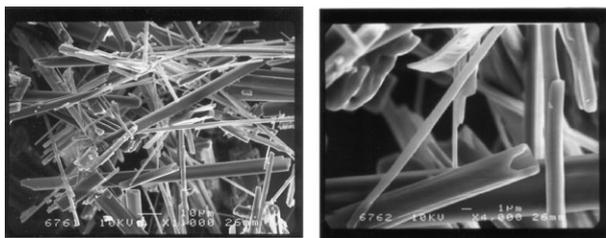


Fig. 7 SEM images of silica, templated on a **1** alcogel, with the organics removed, 10 μm .

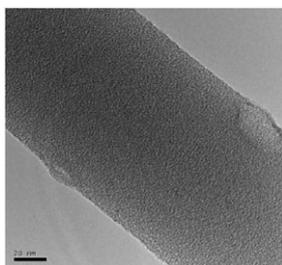


Fig. 8 TEM of a single silica tube, 20 nm.

Hydrolysis and condensation continues until a uniform silica skin is formed around the organogel, thus freezing in the organogel structure. Scanning electron micrographs were taken once the organogel template had been washed out (Fig. 7). The image at lower magnification reveals that the structure of the silica is highly elongated and one dimensional ordering has been achieved. There is a large variation in the length, width and shape, consistent with the variety observed in the dried alcogel. The structure of a single tube was analysed by transmission electron microscopy (TEM), the resultant structure appears to be porous in nature (Fig. 8).

Experimental

General

Scanning electron micrographs were imaged on a Jeol 6400 SEM (samples were dried in air), transmission electron micrographs (TEM) were imaged on a FIB200 TEM (samples dried under vacuum). The NMR spectra were obtained using a Bruker Advance DPX 300 spectrometer, with chemical shifts reported on CDCl_3 solutions relative to a standard reference of tetramethylsilane.

Preparation of 2,5-di-*O*-methanesulfonyl-1,4:3,6-dianhydro-D-sorbitol (**1**)

Isosorbide (24.10 g, 0.165 mol, Lancaster) was slowly added to pyridine (120 mL) cooled in an ice-salt water bath. When completely dissolved, methanesulfonyl chloride (31 mL, 0.40 mol) was added dropwise over 30 min. On the addition of the methanesulfonyl chloride, the colourless mixture turned through dark yellow to brown. The solution was stirred at room temperature ($\sim 15^\circ\text{C}$) for 20 h. The resulting slush was heated to 55°C and water (250 mL) was added. A white solid precipitated. The mixture was heated to reflux for 2 h and once cooled the white solid collected and

dried *in vacuo*. The compound was recrystallised from ethanol. Yield 39.99 g, 0.132 mol, 80%.

Found C 31.81, H 4.36. Calcd for $\text{C}_8\text{H}_{14}\text{O}_8\text{S}_2$: C 31.78, H 4.67%. Mp $144\text{--}146^\circ\text{C}$; m/z 325.0 ($\text{M} + \text{Na}^+$); $^1\text{H-NMR}$ (500 MHz, CDCl_3): δ : 3.08 (s, 3H, SCH_3), 3.13 (s, 3H, SCH_3'), 3.88 (dd, 1H, $^2J_{\text{H}_6, \text{H}_6'} = 10.1$ Hz, $^3J_{\text{H}_6, \text{H}_5} = 5.8$ Hz, H-6), 4.01 (dd, 1H, $^2J_{\text{H}_6, \text{H}_6'} = 10.1$ Hz, $^3J_{\text{H}_6', \text{H}_5} = 6.1$ Hz, H-6'), 4.08 (dd, 1H, $^2J_{\text{H}_1, \text{H}_1'} = 11.2$ Hz, $^3J_{\text{H}_1, \text{H}_2} = 3.5$ Hz, H-1), 4.23 (m, 1H, $^2J_{\text{H}_1, \text{H}_1'} = 11.2$ Hz, H-1'), 4.71 (m, 1H, H-3), 4.89 (m, 1H, H-4), 5.11 (m, 1H, H-2), 5.15 (m, 1H, H-5). $^{13}\text{C-NMR}$ (500 MHz, CDCl_3): δ : 38.67 (SCH_3), 38.73 (SCH_3'), 70.48 (C6), 73.49 (C1), 78.24 (C5), 80.56 (C4), 80.21 (C2), 85.92 (C3).

The NMR assignments were made from 2D spectra and aided by comparison with published spectra.¹⁰

Other isohexide derivatives

endo-5-*O*-Methanesulfonyl-1,4:3,6-dianhydro-D-sorbitol and 2,5-di-*O*-propylsulfonyl-1,4:3,6-dianhydro-D-sorbitol were prepared using the above method by varying the ratio of isohexide : sulfonyl chloride.

2,5-Di-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-sorbitol, *endo*-5-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-sorbitol, 2,5-di-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-mannitol and 2-*O*-*p*-toluenesulfonyl-1,4:3,6-dianhydro-D-mannitol were prepared by a published method;¹⁰ mono- and disubstituted isohexides were prepared by varying the ratio of isohexide : sulfonyl chloride.

Gel tests

The required quantity of **1** (Table 1) was stirred into the solvent in a glass vial. The vial was closed (apart from two small holes in the cap) and placed in an oil bath at the appropriate temperature; once a homogeneous solution was obtained the vial was removed from the heat and the stirring ceased. The phase behaviour was monitored as the solution cooled.

Sol-gel transcription of silica from a 1% w/v organogel

1 (0.0300 g, 0.099 mmol) was dissolved in benzylamine (0.0319 g, 0.298 mmol), water (0.04 mL) and ethanol (3 mL). The mixture was stirred and heated to 70°C . After 2 h TEOS (0.16 g, 0.99 mmol) was added. After a further 1 h a further aliquot of benzylamine (0.0400 g, 0.373 mmol) was added. After 1 min the heater and stirrer were switched off and the sample was left to cool slowly. On cooling a gel was formed which was stable to inversion. The gel was left to age for over a week.

Conclusions

1 gels a range of alcoholic and aromatic solvents as well as water. The structure in the solid state analysed by single crystal X-ray crystallography did not contain any strong hydrogen bonds. The nano- and microstructures observed by electron microscopy form as a result of the roof-like structure of **1** which encourages molecular stacking reinforced by intramolecular interactions. Due to the absence of long alkyl chains to increase van der Waals forces and aromatics to encourage π - π interactions the gelation is finely balanced and

small changes to the structure disrupt gel formation. Thermochemical characterisation may provide further insight into the gel state. In particular DSC measurements and AFM data could provide essential information to allow the elucidation of the gelation mechanism in these systems. Organogels of **1** can be used to template silica by a sol-gel process and the resultant silica contains a similar variety of micro- and nanostructures to the parent alcogel.

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