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1,3:2,4-Dibenzylidene-D-sorbitol (DBS) and its derivatives - Efficient, versatile and industrially-relevant low-molecular-weight gelators with over 100 years of history and a bright future

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Dibenzylidene-D-sorbitol (DBS) has been a well-known low-molecular-weight gelator of organic solvents for over 100 years. As such, it constitutes a very early example of a supramolecular gel – a research field which has recently developed into one of intense interest. The ability of DBS to self-assemble into sample-spanning networks in numerous solvents is predicated upon its 'butterfly-like' structure, whereby the benzylidene groups constitute the 'wings' and the sorbitol backbone the 'body' – the two parts representing the molecular recognition motifs underpinning its gelation mechanism, with the nature of solvent playing a key role in controlling the precise assembly mode. This gelator has found widespread applications in areas as diverse as personal care products and polymer nucleation/clarification, and has considerable potential in applications such as dental composites, energy technology and liquid crystalline materials. Some derivatives of DBS have also been reported which offer the potential to expand the scope and range of applications of this family of gelators and endow the nansocale network with additional functionality. This review aims to explain current trends in DBS research, and provide insight into how by combining a long history of application, with modern methods of derivatisation and analysis, the future for this family of gelators is bright, with an increasing number of high-tech applications, from environmental remediation to tissue engineering, being within reach.

Introduction

Gels are colloidal soft materials which demonstrate the continuous flow properties of liquid-phase materials and the rheological properties of solid-phase materials on the analytical time-scale.[1] They are easily recognised materials with a wide range of applications, being used in cosmetics, pharmaceutical preparations, as greases/lubricants and in the food industry. Many commercially-used gels are based on polymers, which are either chemically or physically crosslinked to generate a self-supporting 'solid-like' network.[2] However, in recent years, there has been a surge of academic interest in supramolecular gels, in which small molecules assemble into non-covalent polymers based on hydrogen bonding, van der Waals forces, solvophobic effects, π–π stacking, dipole-dipole interactions, charge-transfer and coordinate bonds.[3] Excitingly, molecular-scale information programmed into the low-molecular-weight gelator (LMWG) molecules is translated into the nanofibres via hierarchical self-assembly, and the fibres tangle with one another to form an extended nanofibrillar network which immobilizes a large volume of solvent under the influence of capillary forces (Fig. 1).[1,3]

Factors such as pH, light, heat, solvent, addition of analyte, reagent or ligand, oxidation/reduction and sonication have been widely used to turn the gelation of potential LMWGs on or off.[1,3] Unlike some of their polymeric counterparts, the assembly of LMWGs is therefore fully dynamic and reversible, giving rise to tuneable and responsive nanostructured soft materials. Consequently, LMWGs have attracted interest for high-tech applications in areas as diverse as catalysis, drug delivery, tissue engineering, light harvesting, nanoelectronics, environmental remediation, and sensing.[4] In the past decade, there has also been increasing interest in multi-component gels, in which several components combine to play an active role in controlling gelation.[5]

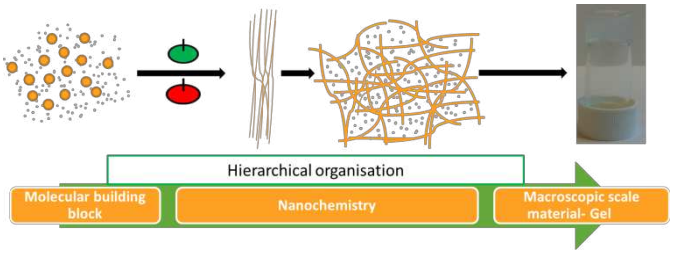

Fig. 1. Bottom-up nanofabrication of self-assembled supramolecular gels controlled by on/off triggers.

Over the past century, a wide range of molecular motifs including peptides, ureas, sugars, steroids and bile acids, lipids, nucleobases, and even simple alkanes have proven their potential as gelators.[1,6] For many years, unprotected sorbitol,

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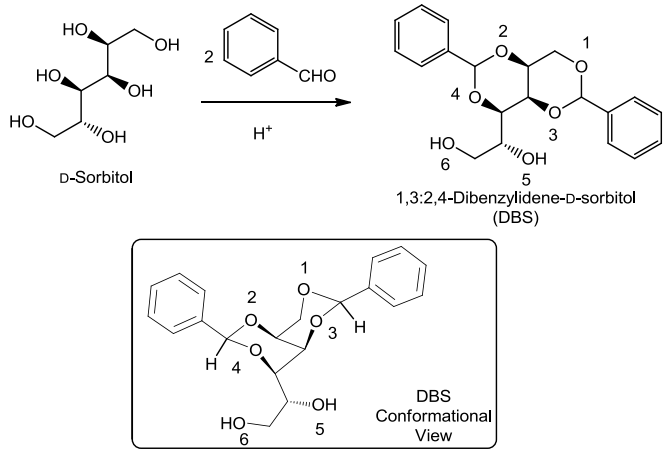
a reduced form of glucose, was well-known to act as a thickener (albeit not formally a gelator) in water, and as a consequence of its rheological properties and sweetness is exploited extensively in the food industry as well as being used for the formulation of cosmetic and other consumer products. Interestingly, one of the first true low-molecular-weight gelators (LMWGs) reported in the scientific literature was itself a protected version of D-sorbitol; 1,3:2,4-dibenzylidene-D-sorbitol (DBS, Scheme 1). This compound was originally synthesised by Meunier in 1891 by condensation of two equivalents of benzaldehyde with sorbitol, and noted to form 'transparent gels' on work-up.[7] Given this early start, and the availability of starting materials, DBS has since witnessed tremendous investigation and has been applied as an efficient gelator of numerous organic solvents. Despite the lengthy history of DBS and its unquestionable utility and importance in industrial chemistry, there is a notable lack of detailed, up-to-date reviews of the topic.[8] Furthermore, recent years have seen a rapid development of fundamental understanding of DBS, combined with its modification to extend the range of its gelation potential and possible applications. As such, this review aims to provide a clear overview of DBS and its derivatives, their gelation performance, and their current and potential applications.



Scheme 1. Conversion of D-sorbitol into 1,3:2,4-dibenzylidene-D-sorbitol (DBS) and a conformational perspective of the molecular structure.

1,3:2,4-Dibenzylidene-D-sorbitol (DBS): A historic overview of the early research

DBS is a chiral low molecular weight amphiphile having a butterfly-shape conformation – it can be considered that the sorbitol backbone is the 'body' and the phenyl rings are the 'wings'. It is a white, crystalline substance derived from the naturally occurring hexose sugar, D-sorbitol, and can be synthesized by a condensation reaction between D-sorbitol and benzaldehyde (Scheme 1). In the earliest report,[7] Meunier reported that the acid-catalysed condensation of D-sorbitol and two equivalents of benzaldehyde yielded a mixture of two isomeric diacetals, each having a unique solubility in boiling water and different melting points, one of which formed a gel while the other did not. This view was supported by Thomas and Sibi, who further investigated DBS organogels and hydrogels in 1926.[9]

Interest in LMWGs (although not named as such at the time) was re-ignited in the 1940s, primarily as a result of the Second World War. This led to the development of LMWG applications relevant to the military such as engine lubricants and greases (based on lithium 12-hydroxystearate in oils),[10] and napalm (originally based on napthenic/palmitic acids in petrol).[11] In those days, long before the availability of NMR for structural determination, a number of studies also explored the reactivity, and hence chemical structure of DBS.

In 1942, Wolfe and co-workers[12] re-investigated DBS and by conversion of the free alcohols into a variety of esters were able to demonstrate that DBS actually existed as a single species rather than being a mixture of isomers as reported earlier. However, it was noted that both the mono- and the tri-substituted benzylidene derivatives of the protected D-sorbitol could be present as by-products (MBS and TBS respectively, Fig. 2) – these were probably also present in the earlier reported syntheses. In order to fully determine the structure of DBS, Wolfe and co-workers carried out a series of derivatisations. Treatment with lead tetra-acetate demonstrated the presence of a glycol group within the DBS structure, indicating it has either 1,2,3,4 or 3,4,5,6 acetal functionalisation patterns. This was supported by reacting DBS with triphenylmethyl chloride, which gave rise to a mono-trityl derivative, confirming the presence of a single primary hydroxyl group in the structure of DBS, and ruling out the 2,3:4,5-diacetal derivative which would have two primary hydroxyl groups. Importantly, by subjecting DBS to acid hydrolysis, they converted six-carbon protected sugar DBS into the dibenzylidene-protected five-carbon sugar L-xylose. The observation of this product rather than five-carbon sugar D-arabinose confirmed the acetal functionalisation pattern of DBS as 1,2,3,4 not 3,4,5,6. However, the precise linkage patterns of the acetal groups could not be confirmed at this stage.

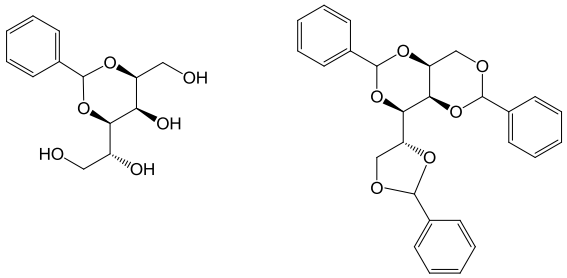


Fig. 2. Structure of (left) 2,4-monobenzylidene-D-sorbitol (MBS) (right) 1,3:2,4:5,6-tribenzylidene-D-sorbitol (TBS).

In 1944, Angyal and Lawler expanded on the work of Wolfe and co-workers by confirming the structure as having a 1,3:2,4 connection pattern. This was achieved by careful hydrolysis of DBS to yield 2,4-monobenzylidene-D-sorbitol.[13] This compound had been previously reported and structurally characterised by Vargha,[14] and has since been shown to form via the rearrangement of an intermediate, less stable, 2,3-monobenzylidene-D-sorbitol with a five-membered ring.[15]

The acetal carbon atoms within the ring structure of DBS are themselves new chiral centres. Given they are formed under thermodynamic control, it is a safe assumption that the bulky phenyl groups occupy the equatorial positions (as shown in Scheme 1). As such, and as noted by Brecknell and co-workers in the 1970s, the structure of DBS can be more fully described as 1,3(*R*):2,4(*S*)-dibenzylidene-D-sorbitol.[16]

DBS and its derivatives: A chronicle of synthetic strategies

Over the past 50 years, the synthesis of DBS has been of increased interest with respect to the variation of reaction media, choice of catalysts, stoichiometric balance of the reagents and product purification procedures. Furthermore, there has been growing interest in creating derivatives of DBS.

In 1973, an early patent from Akazome and co-workers demonstrated a process of preparing DBS in which an aqueous solution of sorbitol and benzaldehyde was dispersed in a large volume of cyclohexane and the reaction was performed at elevated temperature. The azeotropy of cyclohexane and water enabled the reaction to proceed while separating water from the reaction system and hence driving the condensation reaction to completion, to obtain the crude product as a slurry in cyclohexane.[17] However, considerable amounts of MBS and trace amounts of TBS were reported as by-products. The deleterious effects of the MBS on the industrial applications of DBS mean that its removal from the crude product is important, but also complicated and difficult.

Uchiyama improved on the previous method such that practically no MBS was formed. This was achieved by splitting the reaction procedure into two stages.[18] In the first-stage the reactants were heated at 50-70°C. When conversion reached 10-40%, water and an additional amount of acid catalyst were added, and the reaction performed under controlled concentration conditions at room temperature. The product was obtained as an aqueous suspension.

In 1985, Machell disclosed a method in which sorbitol was initially mixed with mineral acid, and following this step, an effective amount of an aromatic aldehyde such as benzaldehyde was incrementally ad-mixed into the homogeneous aqueous sorbitol mixture at an appropriate rate to allow a substantially spontaneous reaction to occur.[19]

Murai and co-workers demonstrated a method for making DBS and its derivatives using benzaldehydes (or acetal derivatives of benzaldehydes), D-sorbitol and acid catalyst in a reaction solvent medium comprising a mixture of hydrophobic solvent and a hydrophilic polar organic solvent – the hydrophobic solvent helps precipitate the product while the hydrophilic solvent helps dissolve the reacting species.[20] The reaction was performed under forced agitation conditions in the gel/solid phase. This method was further developed by Kobayashi with the use of long chain amines for the neutralisation step – it is supposed that the surfactant-like characteristics of these bases help control solubility during reaction and work-up.[21]

In the hunt for simpler and more environmentally friendly reaction conditions, Salome and co-workers reported an alternative approach.[22] They used water as the solvent medium and an arylsulfonic acid as catalyst. This allowed them to synthesise DBS and some simple derivatives in good purities (>90%).

Gardlik and Burkes improved on Salome's method by using a C1-C3 aliphatic alcohols as solvent.[23] The DBS was purified by simple washing of the product as a thick paste with the alcohol to remove the mono- and tri-acetal derivatives (MBS and TBS). This method had previously been demonstrated in a patent from Uchiyama in which the percentage purity of crude DBS was increased from 95 to 98% by simple washing with a mixture of aliphatic alcohols.[24] This approach yielded DBS (and meta-substituted halogenated derivatives) largely free of solvent, catalyst impurities or mono and tri-substituted by-products. However, the Gardlik approach uses relatively large amounts of solvent, and as such, Scrivens and Salley patented an approach in which 2-15 wt% (compared to reactants) of a glycol solvent was also present during the reaction.[25] They referred to this solvent as a 'processing agent', and noted that its presence assisted during reaction work-up, which could effectively be condensed down to a single simple washing step.

In 2001, Lever and co-workers reported the addition of surfactant to the reaction as a way of enhancing solubility, which can be particularly important in the formation of simple derivatives of DBS in which the benzylidene groups are functionalised with hydrophobic substituents, because the solubility of these DBS derivatives is significantly lower in polar solvents.[26]

More recently, in 2006, Xie *et al* reported the use of Lewis acid catalysts such as $AlCl_3$, $ZnCl_2$, $SnCl_2$, $Bi(OTf)_3$, $FeCl_3$ and BF_3 either in addition to the Bronsted acid catalysts more typically used, or in replacement for them.[27] It was argued that this lowered the acid-loading during synthesis, enhanced purification, and would limit acid-induced equipment damage when performing reactions on an industrial scale.

Uppara and co-workers recently patented a synthetic method for DBS and its derivatives using ionic liquid as reaction medium and catalyst for the reaction between various benzaldehydes and D-sorbitol.[28] The products were obtained in good yield and high purity without any trace of residual acid or alkaline residues.

When derivatives of DBS are synthesised, this can either be achieved by (i) modification of the aromatic 'wings' (usually during the formation of DBS), or (ii) modification of the free alcohol groups on the sorbitol 'body' (either before or after the acetal-formation reaction). A number of the patents already described in the section above, in addition to synthesising DBS, synthesise simple DBS derivatives with modified aromatic groups by using substituted benzaldehydes during acetal formation.

In 2007, Feng et al reported the synthesis of DBS and numerous new derivatives (Fig. 3).[29] Similar to the method of Gardlik and Burkes,[23] a dual solvent reaction medium (cyclohexane-methanol) and acid catalyst (*p*-TSA.$3H_2O$) were

employed in the syntheses of various derivatives, but a Dean-Stark apparatus was incorporated, thereby circumventing the problem of solvent recycling. The crude products were neutralised by sodium carbonate (Na_2CO_3), sodium chloride (NaCl) and hexadecane/stearyldimethylamine – an approach related to that developed by Kobayashi described above.[21] The products were obtained in very good yields (69-99%).

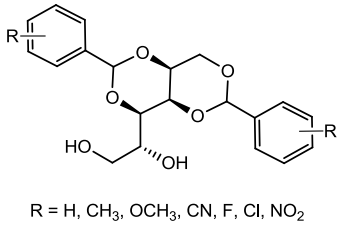
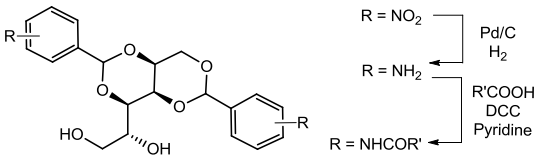


Fig. 3. Chemical structure of DBS derivatives modified on the aromatic 'wings'.

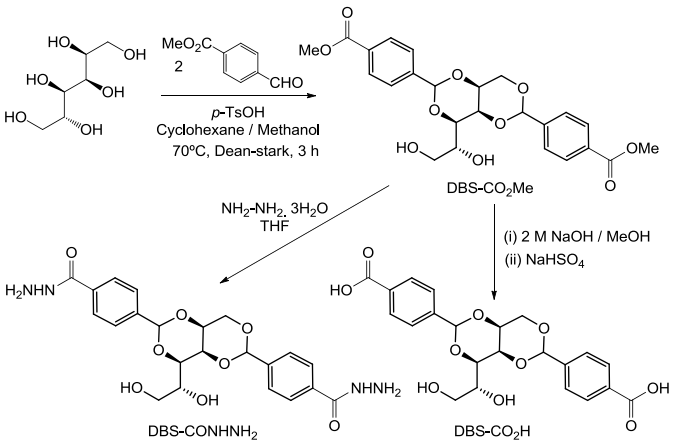
Further elaboration of the aromatic groups on DBS was demonstrated starting from the synthesised nitro derivative. The nitro groups were converted to amines by Pd/C catalysed hydrogenation, and further derivatisation was then achieved by *N*,*N*'-dicyclohexylcarbodiimide (DCC) mediated amide coupling with carboxylic acids to generate DBS-amides (Scheme 2). The reduction of nitro groups to form amines, and their further derivatisation has also been reported by Stan and coworkers.[30]



Scheme 2. Further synthetic modification of aromatic 'wings' of DBS – conversion of nitro groups to yield DBS-amide derivatives.

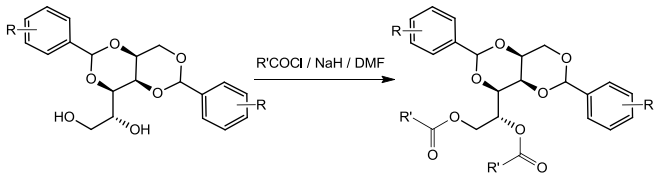
Our own research group has generated some novel derivatives of DBS with modified aromatic 'wings' which significantly expand the potential and scope of DBS derivatives. During these syntheses, we found that washing the crude product of DBS-forming reactions with either warm toluene or cold dichloromethane (dichloromethane works better) is best suited for removing the tri-acetal (TBS) by-product while boiling water removes both the mono-acetal (MBS) and the organic acid catalyst (p-TSA.$3H_2O$). In both cases, little or none of the desired di-acetal is lost (as is commonly found with alcohol washing). With our modified synthetic method, we then reported the syntheses of DBS derivatives functionalised with ester,[31] carboxylic acid[31] and acyl hydrazide[32] groups (Scheme 3).

DBS methyl ester derivative (DBS-CO_2Me) was obtained by condensing D-sorbitol with two equivalents of 4-carboxybenzaldehyde methyl ester in the presence of *p*-TsOH. This was followed by saponification of the methyl ester groups with NaOH to produce the carboxylic acid analogue (DBS-CO_2H). On the other hand, hydrazination of DBS-CO_2Me with hydrazine monohydrate yielded the DBS acyl hydrazide (DBS-$CONHNH_2$). We suggest that the ability of DBS-CO_2H and DBS-$CONHNH_2$ to form highly effective hydrogels opens up significant potential new applications of DBS technology (see below for further discussion).



Scheme 3. Synthesis of DBS hydrogelators, DBS-CO_2H and DBS-$CONHNH_2$ reported by our research group.

In addition to modifying the aromatic wings of DBS, there has been considerable interest in modifying the free alcohol groups on the DBS body. Indeed, this work started in some of the earliest reports from the 1940s in which such derivatisation helped determine the structure of DBS (see above).[12] In general, the primary alcohol (6-OH) is more reactive/nucleophilic than the secondary (5-OH), and hence more easily modified using standard methods such as tosylation, esterification etc. Exemplifying this principle, Feng et al demonstrated how acid chlorides could convert DBS (and its 'wing-modified' derivatives) into mono- or bis-esters, depending on the molar ratio of base and acid chloride used.[29] In the presence of one equivalent, the 6-substituted product was formed, whereas if more acylating reagent was present, the 5,6-disubstituted product resulted (Scheme 4).



Scheme 4. Esterification of the free hydroxyl groups of DBS and derivatives by acylation.

A version of this approach has recently been employed in a patent by Malle and Luukas, who reported esters of DBS in which the modification lies on the primary alcohol of the DBS backbone – the most reactive nucleophilic alcohol group – or on both primary and secondary alcohols.[33] Varieties of esters with a range of alkyl chain lengths were attached (Fig. 4). Furthermore, they reported diesters having tails of different chain lengths – in these cases, the two different acid halides were simultaneously or sequentially reacted with the DBS derivatives. This approach was also used to tether together the primary alcohol units of two DBS molecules in order to form bola-amphiphiles (two-headed amphiphiles) with DBS head groups (Fig. 5).[33] In this case, a diacid chloride was reacted with DBS derivatives as previously discussed. Alternatively, α,ω-dicarboxyl silicone (also known as Tegomer C-Si 2342) was

reacted with the DBS derivative under microwave conditions for about 30 min.

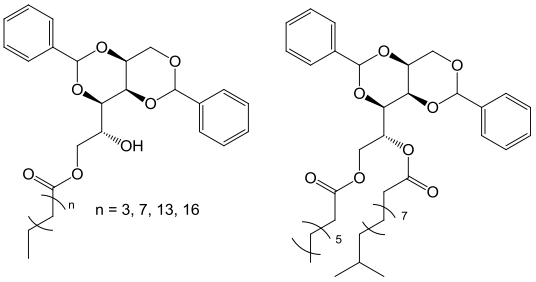


Fig. 4. Examples of DBS derivatives modified with ester groups at the 6-OH or 5-OH and 6-OH positions.

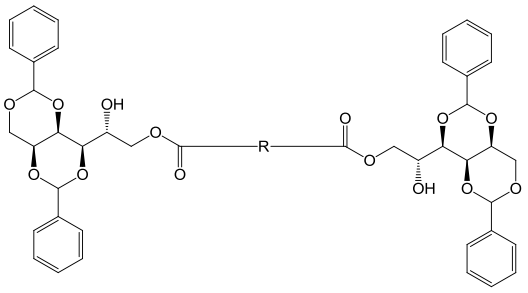
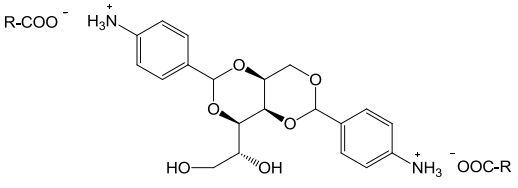


Fig. 5. Generic structure of DBS-based bolaamphiphiles – R can be a wide variety of different linking groups.

In 2008, Stan and co-workers reported the synthesis and gelation behaviour of cationic organogelators based on 1,3:2,4-di-(*p*-ammoniumbenzylidene)-D-sorbitol (Fig. 6, p-NH_3^+-DBS), counterbalanced by the carboxylate anions of a natural fatty acid; stearic acid (SA), 12-hydroxystearic acid (HSA), *erythro*-9,10-dihydroxystearic acid (DHSA) or *erythro*, erythro-9,10,12,13-tetrahydroxystearic acid (THSA).[34] Although salt formation impaired the inherent gelation ability of *p*-NH_2-DBS, which was reasoned to be due to the disruptive effect of the positive charge on the stacking of the benzylidene groups, the complex with HSA formed stable organogels in some solvents. It was suggested that this could be attributed to the fact that HSA, a natural fatty acid and active component of castor oil, is an active gelator in its own right. These salts can be considered as examples of two-component gelators.[5]



R= $-C_{17}H_{35}$; SA

$-(CH_2)_{10}CH(OH)-(CH_2)_6-CH_3$; HSA

$-(CH_2)_7(CH)(OH)-CH(OH)-(CH_2)_7-CH_3$; DHSA

$-(CH_2)CH(OH)-CH(OH)-CH_2-CH(OH)-CH(OH)-(CH_2)_4-CH_3$; THSA

Fig. 6. Structure of two-component organogelators derived from amine-functionalised D-sorbitol and fatty acids.

In 2009, Stan and co-workers demonstrated the functionalization of both the primary and secondary alcohol groups of the sorbitol backbone with acrylate groups, potentially capable of polymerisation (Fig. 7).[35] This organogelator was synthesized by reacting DBS with 2.5 molar equivalents of 2-isocynanatoethylmethacrylate (IEM) and dibutyltin dilaurate in THF under argon at 60ºC.

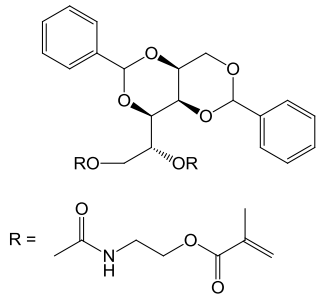
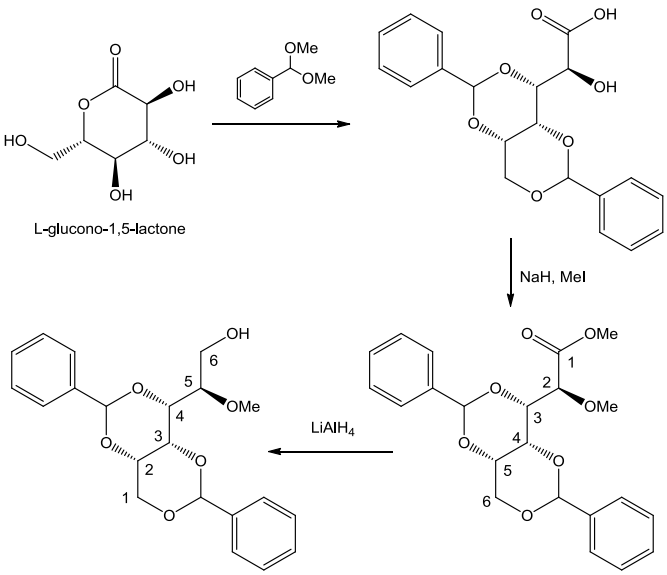


Fig. 7. Chemical structure of IEM-DBS

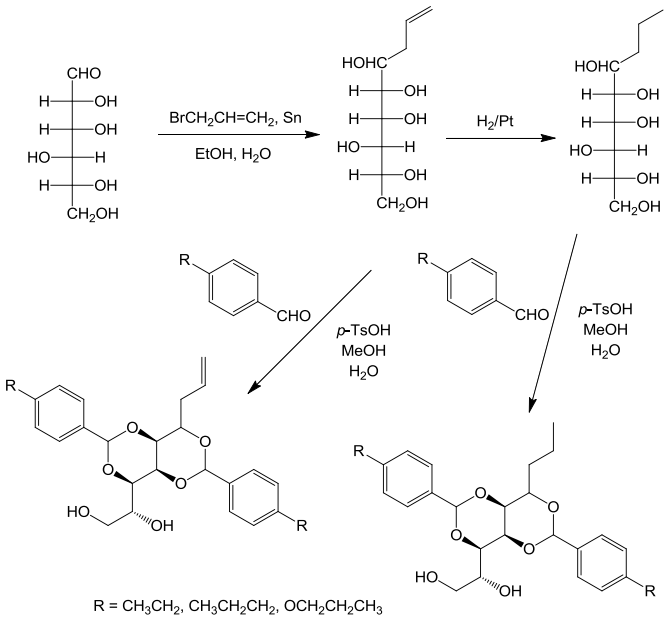
In order to selectively functionalise the 5-position of sorbitol, rather than the more reactive 6-position, it is clear that a more elaborate strategy, such as the use of a protecting group for the 6-OH position, must be employed. Yamasaki and co-workers reported an interesting alternative approach to the 5-methoxy derivative of DBS based on the use of different starting materials.[36] They reacted L-glucono-1,5-lactone with two equivalents of benzaldehyde dimethyl acetal to first yield the intermediate 3,5:4,6-dibenzylidene-L-gluconic acid. This was further reacted with NaH and MeI, and final reduction with $LiAlH_4$ yielded 5-methoxy-1,3:2,4-dibenzylidene-D-sorbitol. (Scheme 5 – note the numbering order of the sugar skeleton changes on reduction of the gluconic acid derivative in the final step).



Scheme 5. Synthesis of DBS derivative functionalised selectively as an ether in the 5-position.

In interesting work, Xie and co-workers demonstrated that not only can the obvious positions of sorbitol be functionalised as described above, but the first carbon atom of the sorbitol skeleton can also be modified (Scheme 6).[37] This is achieved by first generating a modified sorbitol and then carrying out the acetal forming reaction with it. Tin-mediated allylation of

glucose with allylbromide in an aqueous medium was employed to form allyl-sorbitol, which was also subjected to catalytic reduction of the alkene group to yield *n*-propyl sorbitol. Dehydro-condensation of these modified sorbitols with two equivalents of various substituted benzaldehydes then yielded the novel DBS derivatives.



Scheme 6. Synthesis of DBS derivatives modified in the 1-position, starting from glucose.

As described above, syntheses of DBS are well established, and because the compound is of industrial importance, there have been a number of attempts to enhance and optimise the methodology. At heart, however, the synthesis is a relatively straightforward one-step process, and purification can be achieved through simple washing procedures, with no chromatography being required. As such, it can be considered a low cost LMWG and is readily available on multi-kilo scale. Furthermore, DBS is a versatile building block for further modification. The aromatic 'wings' of DBS offer considerable scope for variation, and the free hydroxyl groups of the sorbitol backbone can be readily functionalised. It is also possible to generate more complex derivatives using more extended synthetic procedures. Obviously such derivatisation can impact, either positively or negatively, on gelation. In order to understand the ways in which this can occur, it is vital to fully understand the gelation mechanism of native DBS, as explored in the following section.

Insights into the molecular self-assembly of DBS

Experimental and computational concepts

As outlined in the introduction, for a supramolecular gelation event to occur, a potential gelator must be capable of forming self-complementary non-covalent interactions, with a tendency to form one-dimensional nanostructures called nanofibrils, which bundle together into nanofibres that support a sample-spanning three-dimensional network. However, in the earliest days of supramolecular gels, the detail behind this concept was relatively poorly understood. Indeed, the emergence of modern characterisation techniques for probing the self-assembly of LMWGs in recent decades have completely transformed the ability to study and characterise these fascinating materials.[38]

In an attempt to understand the gelation of DBS, authors have employed both experimental and *in silico* approaches. In essence, the butterfly-like structure of DBS has two potential molecular recognition motifs: (i) hydrogen bonding involving the 'body' of the structure between 5-OH/6-OH groups of one molecule as hydrogen bond donor and the 5-OH/6-OH or the cyclic acetals of another as hydrogen bond acceptor, and (ii) π–π stacking or solvophobic interactions between the aromatic 'wings' of the gelator group of one molecule and those of another. Curiosity to establish the precise structure and mechanism of DBS aggregation has triggered some controversy – some authors propose π–π stacking as the major driving force, others emphasise hydrogen bonding, and some discuss the interplay of both types of interaction.

In early work, Yamasaki and co-workers demonstrated that the polarity of a solvent can have a remarkable effect on the hydrogen bonding, which they suggested was therefore responsible for self-assembly. They explored the impact of different possible hydrogen bonds on DBS self-assembly.[36] In low polarity solvents, intra- and intermolecular H-bonding of DBS was favoured, whilst in high polarity solvents, H-bonding between DBS and the solvent, which does not underpin gel assembly, became favoured and the compound dissolved.

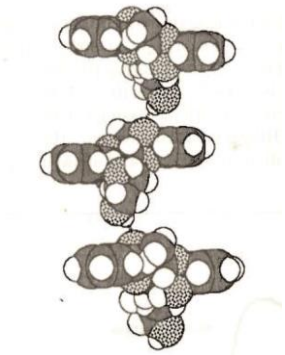


Fig. 8. Qualitative model proposed by Yamasaki and co-workers based on the importance of hydrogen bonds between the 6-OH group and an acetal oxygen atom in organising the ordered stack of DBS molecules. Image reproduced from reference 39 with permission from the Chemical Society of Japan.

In further work, Yamasaki and co-workers selectively converted each of the 5-OH group and the 6-OH group into methoxy groups,[39] and observed that no gelation occurred when the terminal (6-OH group) was protected, while gelation still occurred with the 5-OH group protected. As such, they proposed that 6-OH is critical as a hydrogen bond donor for DBS self-assembly. Yamasaki and co-workers also used IR, UV, and CD spectroscopies to establish that; (i) the 6-OH group is intermolecularly hydrogen-bonded to an acetal oxygen supporting self-assembly, (ii) the 5-OH group either hydrogen-bonds intramolecularly to an acetal oxygen, or intermolecularly to the surrounding solvent and is not involved

in the molecular recognition pathways underpinning gelation, (iii) the phenyl groups are ordered side by side around the aggregate axis, and (iv) helical fibres are formed. This led Yamasaki and co-workers to propose the simple qualitative assembly model shown in Figure 8.

Other researchers went on to demonstrate that if the 6-OH group, instead of being blocked by a methyl group, was functionalised with a hydrogen bond donor moiety, gelation can still occur. This would support the importance of intermolecular hydrogen bond donation from the 6-position of DBS (and its derivatives) in low polarity solvents.[35]

In 1999, Watase et al,[40] investigated the ground state dimerization of DBS molecules, this time in relatively polar alcoholic solvents using fluorescence spectroscopy. It was concluded from this study that the self-assembly of DBS was mediated by π–π stacking of the molecules on top of one another to form a molecular fibre. It was suggested that the 1,3–phenyl ring overlapped that of another molecule, while the 2,4-phenyl ring overlapped that of another molecule within a distance of 0.35 nm – different to the Yamasaki model (Fig. 8). It was further established by the same authors that the stabilization of DBS gel is not only a function of the interplay of the non-covalent interactions but a molecular structural balance that favours the formation of crystals[41] – indeed, the solubility of gelators is known to be of primary importance in controlling their ability to form solvent-compatible yet 'solid-like' gel phase colloidal materials.[42]

In 2003, Wilder and co-workers for the first time used a computational approach – molecular mechanics calculations and molecular dynamics simulations – to determine the configuration of DBS and the intermolecular interactions which underpin its self-assembly.[43] Molecular mechanics analysis of a single DBS molecule produced an energy minimized structure with equatorial, approximately co-planar aromatic rings. However, conformational searches to explore structural variation showed four other energy-minimized structures of DBS, suggesting that the molecular configuration of DBS can potentially switch between several low-energy structures. This provides a significant challenge for modelling, as subtle changes in (e.g.) solvent or derivatisation of DBS may favour or disfavour any of these conformations.

The authors then investigated dimerisation of DBS using the same computational methodology. With respect to intermolecular interactions, they found that for the initial energy-minimized configuration of DBS, the only interaction in the dimer was the formation of a hydrogen bond between the 6-OH group of one DBS molecule and an acetal oxygen of the other – in agreement with the model proposed by Yamasaki.[36] For the alternative energy-minimized conformations of DBS, it was found that π–π interactions (between phenyl groups in the equatorial position) were also present, in some agreement with the results of Watase.[40] The authors therefore concluded that both H-bonding and π–π interactions must be considered in the mechanism of DBS self-assembly, as well as the degree of fluxionality of DBS. However, it should be noted that these simulations were carried out in a vacuum, and hence did not take explicit solvent effects into account – solvent may well be expected to have

In 2013, Alperstein and Knani[44] used quantum mechanics to determine the molecular configuration of a single molecule and a dimer of DBS, and reported that the energy-minimized conformation of a single DBS molecule had phenyl rings in an almost equatorial position, in close agreement with the results of Wilder.[43] In contrast, however, they found that the 5-OH group pointed towards the 6-OH group with an intramolecular hydrogen bond forming between them. By employing molecular mechanics and molecular dynamics simulations to probe the predominant intra- and intermolecular interactions in DBS as a gelator for polypropylene (an industrially relevant system) they found that the major intermolecular interaction was hydrogen bonding between the O6 and H-O6 groups, with O5/H-O6 and O5/H-O5 interactions also contributing. This agrees with the work from Yamasaki[36] and Wilder[43] about the importance of the 6-OH group, but the proposed destination of the intermolecular hydrogen bond is different. No significant π–π interactions were observed in their simulations, and they argued that the main contribution from phenyl groups was to stiffen the molecular structure. It is noteworthy that the hydrogen bonding interactions were much stronger in the hydrophobic environment of polypropylene, suggesting that the nature of the solvent does indeed affect the intermolecular interactions in DBS fibre formation – this may also be the reason that the π–π interactions were less significant in this simulation.

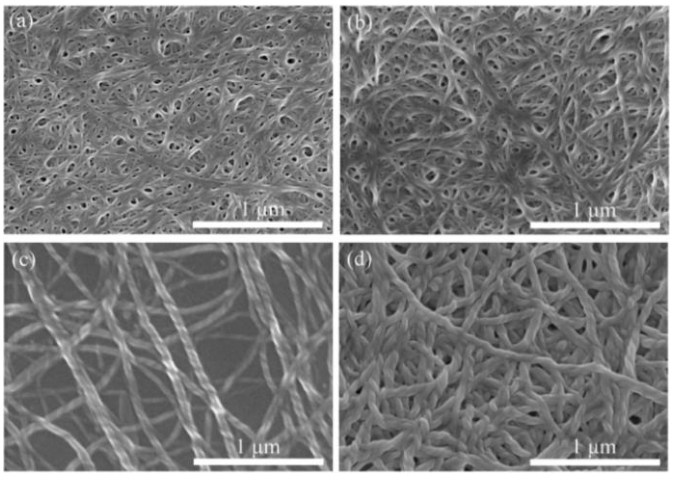


Fig. 9. SEM images of DCDBS xerogels made from (a) DMSO–H_2O (7:3 v/v), (b) ethylene glycol, (c) n-octanol and, (d) o-dichlorobenzene showing solvent control over nanoscale morphology. Figure reproduced from reference 45 with permission from the American Chemical Society.

Song and co-workers used SEM to experimentally demonstrate that the nanofibres of the xerogels of a derivative of DBS; 1,3:2,4-di(3,4-dichlorobenzylidene)-D-sorbitol (DCDBS) exhibited different structures in polar solvents (non-helical fibre aggregates) and non-polar solvents (rope-like helical fibres) (Fig. 9).[45] They also used molecular mechanics to suggest that the gelator molecules adopted a planar-type conformation in polar solvents, causing the molecules to stack on top of each other, with π–π interactions being primarily responsible for self-assembly. They suggested that the π–π

interactions prevent individual molecules bending, leading to the observed non-helical fibres. However, in non-polar solvents, H-bonding between the 6-OH and an acetal oxygen was found to be the driving force responsible for the self-assembly; with the intermolecular interactions having different effects on each side of the molecule, hence twisting the fibres in a helical way to minimize energy. This insight may help reconcile some of the earlier conflicting results, by suggesting different modes of assembly depending on the environment.

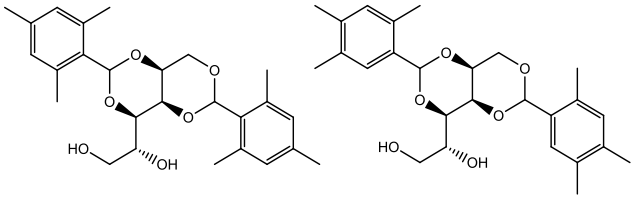


Fig. 10. Chemical structures of (left) 2,4,6-TMDBS and (right) 2,4,5-TMDBS.

Song and co-workers also reported that subtle effects, such as the positioning of the substituents on the aromatic 'wings' of DBS also determines whether it will form gels or not, as demonstrated by 1,3:2,4-di(2,4,6-trimethylbenzylidene)-D-sorbitol (2,4,6-TMDBS) and 1,3:2,4-di(2,4,5-trimethylbenzylidene)-D-sorbitol (2,4,5-TMDBS) (Fig. 10).[46] The former is an efficient organogelator but the latter does not form gels in the solvents tested. This inability of 2,4,5-TMDBS could be attributed to steric effects of the *meta* substituents disrupting the interactions between one molecule of DBS and another during gelation – or alternatively could be due to the substitution inducing conformational changes or slight differences in the overall solubility. This example demonstrates that DBS gelation is held in a subtle balance by various different factors.

Taking all of these experimental and theoretical results in combination, the following factors begin to emerge:

(i) DBS is a relatively fluxional molecule with a number of low-lying energy conformations – the populations of these will be affected by a number of factors, and self-assembly my help favour specific conformations.

(ii) In non-polar solvents, intermolecular hydrogen bonding, predominantly from the 6-OH group, plays a key role in underpinning self-assembly.

(iii) In polar, protic solvents, intermolecular hydrogen bonding becomes less significant, owing to competition for these interactions from the solvent, and π–π stacking and/or solvophobic interactions between the aromatic wings of the gelator become more important.

Clearly, DBS is a versatile and responsive gelator which can, to some extent, adapt to the environment in which it finds itself. This means that as a gelation system it has a relatively broad scope, and clearly synthetic derivatisation, can extend this yet further. In order to probe the structural and solvent effects on gelation in more detail, a number of important and systematic studies have been carried out, as described in the following section.

Systematic studies of solvent effects on DBS gelation

Solvent effects have been of considerable interest in gel-phase materials. In general terms it is often considered that a gelator must be sufficiently soluble for it to be compatible with the solvent, but sufficiently insoluble for self-assembly into a 'solid-like' network to be desirable.[42] Most LMWGs therefore sit on a knife-edge between solubility and precipitation. DBS is somewhat unusual in the breadth of solvents which it can immobilise, and has demonstrated an ability to induce gelation in a range of organic solvents, monomers, polymer melts, oils, liquid crystals, and ionic liquids, providing it with industrial significance as described in more detail later in this review. However, there are fewer studies in which a rational and quantitative approach to understanding solvent effects on its gelation has been attempted.

As early as 1991, in a conference proceeding, rheological analysis was being used to show that the time required for DBS to form stable organogels in esters of diacids such as dimethyl phthalate, dibutyl phthalate, and dibutyl adipate depended significantly on solvent polarity and concentration of DBS.[47] The minimum concentration of DBS required to induce gelation, the gel-sol transition temperature and the mechanical properties of the resulting organogels have all also been reported to depend on solvent polarity.[41,48] In an extension of this early work, Liu and co-workers investigated DBS organogels in liquid paraffin (LP), diisodecyl phthalate (DIDP) and poly (ethylene glycol) (PEG).[49] Interestingly, regardless of the polarity of the solvent, the elastic moduli (*G*') of the resulting gels remained identical, but the phase transition temperature increased significantly with solvent polarity (Fig. 11, right). However, both of these parameters increase with the DBS concentration – as the network becomes more heavily entangled (Fig. 11, left). This suggests that the thermodynamics of nucleation/assembly change with solvent, but the mechanical nature of the network, once assembled, is independent of solvent. This would suggest that solvent primarily affects network growth.

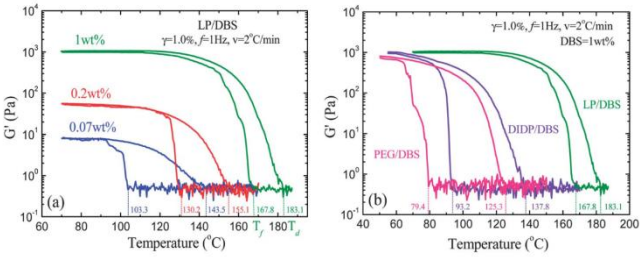


Fig. 11. The dependence of *G*' on the temperature at a heating and cooling rate of 2 °C min^{-1}: (left) LP–DBS gels containing 0.07 wt%, 0.2 wt% and 1 wt% DBS. (right) 1 wt% DBS in LP–DBS, DIDP–DBS and PEG–DBS gel systems, respectively. The strain amplitude and frequency are 1.0% and 1 Hz. Figure reproduced from reference 49 with permission from The Royal Society of Chemistry.

In sharp contrast, however, Santos and co-workers demonstrated that the choice of organic solvent did indeed have significant effects on the rheology of DBS organogels.[50] As shown in Fig. 12, the elastic moduli (*G*') of the organogels of 2% DBS in the tested solvents are in the order: chlorobenzene

> ethylene glycol > glycerol > mineral oil > ethanol. This order seems difficult to rationalise as it does not simply correlate with solvent polarity. It was suggested that including hydrogen bonding effects may help account for this.

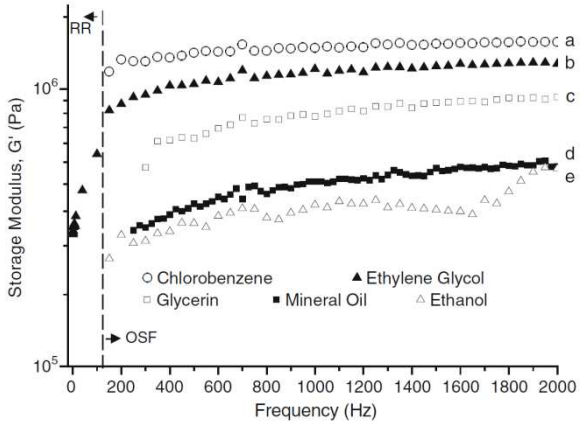


Fig. 12. Storage modulus (*G*') versus frequency for (a) chlorobenzene, (b) ethylene glycol, (c) glycerol, (d) mineral oil, and (e) ethanol containing 2% DBS. The storage modulus (*G*') of ethylene glycol was also measured at lower frequencies using a rotational rheometer (*RR*). Adapted from reference 50. with permission from Springer.

At the same time, a number of studies already described above were exploring DBS gelation in terms of solvent polarity and struggling to come to definite conclusions.[36,39,46] It was clear that a more integrated approach than simple consideration of solvent polarity would be needed to fully comprehend DBS gelation. As such, the understanding of solvent effects on DBS assembly was put onto a more quantitative footing by the landmark research of Raghavan and co-workers, who published a powerful predictive gelation model for DBS in a wide range of organic solvents.[51] By fitting practically-obtained data from the gelation of DBS at given temperatures and concentrations, into 'Hansen space', which is designed using Hansen solubility parameters (HSPs)[52] they could generate a 3-D colour co-ordinated maps (Fig. 13) of gelation performance. Hansen space takes account of solvent polarity, but also the ability to accept and donate hydrogen bonds. These parameters had previously been used to model the performance of other low molecular weight gelators.[53]
Using this approach, it became possible to predict the region of Hansen space where DBS will remain soluble (S), form gels slowly (SG), form gels instantly (IG) or remain insoluble (I) (the blue, green, red and yellow regions respectively in Fig. 15). The distance (R_o) from the centre of the sphere effectively determines the degree of compatibility between gelator and solvent, which informs both the speed of gelation and the mechanical properties of the resulting gels. As R_o increases, DBS-solvent compatibility decreases while speed of gelation and mechanical properties increase, up to a point when the gelator ultimately becomes insoluble. This is in agreement with the simple qualitative solubility-driven model of self-assembly and gelation, in which sufficient insolubility to nucleate gel fibres, and sufficient compatibility of the fibres with the solvent, are both essential characteristics. The authors also considered the effect of DBS concentration on the Hansen space treatment, and as would be expected, found that the insolubility region became increasingly dominant as the concentration of DBS increased. This study provides an excellent, potentially predictive insight into the gelation performance of DBS. It should be possible to extend this approach to other DBS derivatives relatively simply.

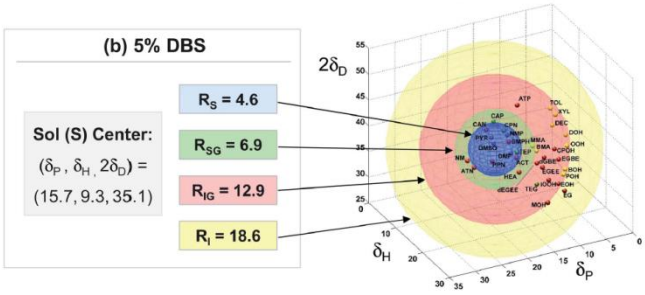


Fig. 13. Gelation results for 5% DBS in various solvents, plotted in 3-D Hansen space. The axes represent the three Hansen solubility parameters (δ_D = dispersive, δ_P = polar, and δ_H = hydrogen-bonding interactions). Each solvent is represented as a color-coded point on the plot. The results show a pattern of concentric spheres, i.e., the central sol (S) sphere in blue, followed in order by spheres corresponding to slow gel (SG) in green, instant gel (IG) in red, and insoluble (I) in yellow. The co-ordinates for the centre of the S sphere and the radii of each sphere are indicated. Adapted from reference 51 with permission from The Royal Society of Chemistry.

Rogers and co-workers also considered all possible solvent parameters in some detail, and went on to demonstrate the importance of a solvent's hydrogen bond acceptor/donor character in determining whether DBS will form a solution, transparent or an opaque gel – properties which are all connected strongly to gelator solubility.[54] They found that individual HSPs, especially the hydrogen bonding HSP (δ_h), strongly influence the physical properties of the DBS organogel – much more so than solvent polarity. It is also noteworthy that unlike their polymer gel counterparts, the appearance of DBS organogels is dependent on both the distance between the HSPs for DBS and the HSPs of the solvent, and the directionality of Hansen distance (R_{ij}) – a solvent with a larger δ_h than that of DBS will yield a transparent gel while a solvent with a lower δ_h yields an opaque gel.

The by-products of DBS synthesis also have the capability to induce gelation. Watase and co-workers proposed with the use of fluorescence spectroscopy that the 5,6-O-bezylidene groups of TBS interacted with the 1,3- and 2,4-benzylidene groups, thereby disrupting their π–π stacking. As a result of this interaction, organogels of TBS are less stable than those of DBS.[40]

Hydrogels from sorbitol derivatives

Even though, as described above, numerous derivatives of DBS that can gel organic solvents have been reported, there was no report of an optimised DBS-based hydrogelator until we reported for the first time that DBS acid (DBS-CO_2H)[31] and DBS-acylhydrazide (DBS-$CONHNH_2$)[32] form stable hydrogels. Clearly modifying the periphery of the aromatic 'wings' with more hydrophilic groups encourages the solubility of the gelator in water, and we suggest this shifts it in Hansen space from being in the insoluble region into one of the gel-forming areas.

DBS-CO_2H (Scheme 3) is a pH-switchable hydrogel which undergoes deprotonation under basic pH condition to form a homogeneous solution (deprotonation of the carboxylic acid means it becomes highly solvated, and hence dissolves).[31] However, on acidification, protonation of the carboxylic acid lowers the solubility such that self-assembly into nanofibrillar gel-phase aggregates is encouraged. It is important to control the kinetics of the pH change in order to obtain an effective homogeneous gel, and this can be achieved using the slow hydrolysis of glucono-δ-lactone (GdL) – an excellent method developed by Adams and co-workers to turn on a variety of pH-responsive carboxylic acid gels.[55]

Replacing the carboxylic acid with a related acyl hydrazide functional group in DBS-$CONHNH_2$ (Scheme 3) removed pH dependence.[32] As such, this modified DBS demonstrated exceptional ability to form stable hydrogels across a wide range of pH values (2 – 11.5). It was suggested that acyl hydrazides may offer an effective general approach to pH-stable gelation in place of a wide range of pH-sensitive carboxylic acid functionalised gels, which are common within the LMWG literature.[56]

These new hydrogelators will hopefully provide better insight into understanding the packing mechanisms of DBS in water, in which, as a hydrogen bonding solvent, solvophobic effects and aromatic-aromatic interactions are expected to play a more dominant role in providing the driving force for DBS assembly. Furthermore, these derivatives importantly allow extension of DBS applications into aqueous environments such as drug delivery systems, tissue engineering, food formulation, separation science, and sensing, and as such, we reason they could transform the potential applications of DBS-based gels.

There have also been reports of monobenzylidenesorbitol (MBS) derivatives, which have suggested they can effectively gel water (as well as other organic solvents).[57] This is presumably as a consequence of their increased hydrophilicity compared with DBS which provides them with greater solubility in this medium (a factor that limits the ability of simple unfunctionalised DBS to act as a good hydrogelator).

DBS gels formed in a polymeric medium

Instead of using simple solvents for gel formation, it is also possible to use a liquid phase which is more functional in nature – in the case of DBS, polymer melts have been quite widely investigated as the self-assembled network can potentially enhance the mechanical properties of the polymer, which has industrial applications (see below). Gels using polymer matrices including but not limited to isotactic polypropylene (iPP),[58] poly(propyleneglycol) (PPG),[59] poly(ethyleneglycol) (PEG),[60] poly(dimethylsiloxane) (PDMS),[59b] poly(propyleneoxide) (PPO),[59b] poly(methylmethacrylate) (PMMA),[59b] silicone fluids,[61] copolymers and triblock polymers,[62] have all been reported. Further to using polymers as neat solvents themselves, it is possible to cast polymes from organic co-solvents in the presence of DBS, in order to integrate a self-assembled nanofibrillar DBS network into the resulting materials.

In large part, the polymeric melt phase effectively behaves just like a solvent. For example, the nanofibrils of PEG/DBS gel systems were 10-70 nm in diameter with a primary nanofibrillar diameter of 10 nm; identical to those of gels of DBS in low-molar-mass organic solvents.[63] It has been reported that using PEG derivatives with a pendant methoxy group at one end tends to enhance the speed of gelation.[63] Capping one end of PEG as a methyl ether clearly lowers its hydrogen bond potential and will affect its solvent-like parameters.

As commonly found in simple organic solvents (and described above), the speed of gelation, elastic modulus (*G*') and sol-gel/gel-sol transition temperature of polymer/DBS gel systems then increase with increasing DBS concentration, up to a saturation value. In PPG, this saturation in rheological performance was observed at about 3% wt/vol.[59c] Gelation in polymer matrices is also particularly time-dependent, requiring a certain period of time to attain equilibrium, depending on the concentration of DBS.[59c]

The molecular weight of the polymer can also affect the stability of the gel as exhibited by PPG – the higher the molecular weight of the polymer, the less DBS was required for onset of gelation.[64] It was suggested that the solubility of DBS decreased significantly as the molecular weight of PPG was increased and that this was responsible for the observed behaviour. Once again this demonstrates the dominant role played by solubility in controlling gelation.

Nanofibrillar morphologies formed from DBS melts

If solid DBS is allowed to melt, and then cooled from the melt, nanofibrillar morphologies result. These indicate that this molecule has an inherent willingness to crystallise with a one-dimensional aspect to its architectural organisation. Exemplifying this, Mercurio and Spontak reported the spherulitic texture observed by polarised light microscopy, attributed to a nanofibrillar network, after melting DBS at 225ºC and cooling at a controlled rate of 10ºC/min.[59a] Similar observations were made by Lai and Wu, who also went on to use SEM to characterise the aggregated nanofibres, which had diameters ranging from 100 nm to 1 μm.[59c]

Applications of DBS and derivatives: Highly patented supramolecular gelators

DBS has a long history of industrial use, and as such, has attracted a very large number of patents, which have seen it employed in a wide range of different industrial sectors. Furthermore, as gel chemists increasingly consider high-tech applications for these responsive self-assembled materials,[4] DBS and its derivatives are well-placed for potential future use, given the long history of precedent – studies to expand the scope of DBS applications are underway.

Cosmetic and healthcare products.

DBS has long been employed in the formulation of cosmetics due to its ability to gel the cosmetic condiments, thereby imparting the product with the desired thickness, adhesion, strength, and consistency – indeed the use of DBS in this industry is widespread.

About 35 years ago, in the development of DBS technology, Roeh[65] patented DBS-mediated gelation of glycols with acidic aluminium anti-perspirant salts. DBS was used to give a clear solid antiperspirant composition, with suitable stick hardness and adhesion. However, it was noticed that these formulations were not stable over time, did not have adequate shelf life, and deteriorated at elevated temperatures.[66] These drawbacks could be attributed to the instability of the 10-membered acetal ring of DBS in acidic media. Therefore, several patents were developed in which less reactive solvents were used and stabilizing agents were added into the DBS gel. Schamper *et al* described the use of alcohols which would be less reactive in the presence of acidic antiperspirant salts and the addition of a gel stabilizer such as zinc acetate.[66] This formulation was an improvement over the earlier versions as it retarded degradation of the gel sticks and enhanced stability at elevated temperatures.[67] Agents such as guanidines,[68] polypropylene glycol ethers of fatty alcohols,[69] *N*-(2-hydroxyethyl) fatty acid amides, zinc and magnesium acetate,[70] silicone elastomers,[71] and amino acid salts,[72] have also been used to stabilize deodorants containing DBS gels in the past decades – demonstrating the vitality of this area of industrial research and the significant market for these products.

The use of DBS derivatives in formulating other personal care products has also been reported. For example, Malle and Luukas have recently patented a library of DBS esters (for synthesis, see Figs. 4 and 5) which demonstrated tremendous ability as thickeners for lipophilic media. Lipstick sticks made with these esters exhibited better properties such as transparency, flexibility, good adhesion to supports, good coverage, stability, glossiness and strength when compared with more conventional waxy lipsticks.[33] Similarly, DBS has recently been used as oil-soluble thickener in oil-in-water emulsions – currently finding application in products as diverse as milky lotion, cream, foundation, sunscreen and makeup base.[73]

In terms of healthcare, Furuishi and co-workers patented a pharmaceutical formulation containing an organogel, a fatty acid ester and a glycerolglycerin fatty acid ester that incorporates non-narcotic analgesics like tramadol for external applications.[74] The use of DBS with 30% ethanol as a gel presented good skin permeability, together with high drug release, leading to efficient transdermal absorbable pharmaceutical compositions.

In a recent study, instead of applying DBS as an organogel, we reported the use of our novel DBS-$CONHNH_2$ derivative as a hydrogel in order to formulate active pharmaceutical ingredients (APIs) with analgesic (pain-killing) applications – specifically ibuprofen, naproxen and mesalazine (Fig. 14).[75] It was found that mixing solids of the gelator with the API followed by sonication in water and heating/cooling gave rise to the formation of a stable two-component gel. Using spectroscopic methods it was demonstrated that there were directed interactions between the amine-like groups on DBS-$CONHNH_2$ and the carboxylic acid groups on the API. The effect of the API on the macroscopic properties of the gel network (e.g. T_{gel}, rheology etc.) was dependent on the log*P* of the API – as this partition coefficient impacts on the solubility of the overall two-component system. Importantly, release of the API from the gel depended on the pH of the receiving solution, and it was shown that for naproxen, 100% of the drug was released at pH8 (intestinal pH), but much less was released at lower pH values. This has direct relevance because naproxen can cause problems such as stomach ulceration – this type of gel formulation may assist stomach transit and limit side effects.

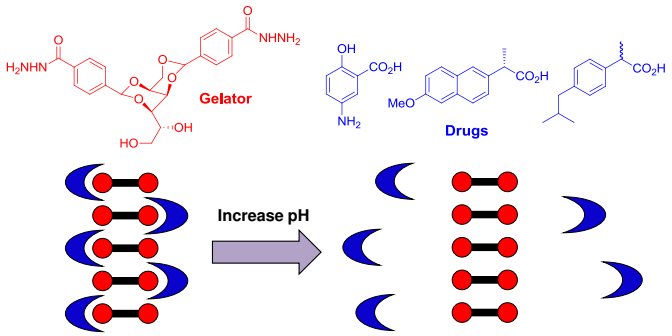


Fig. 14. DBS-hydrazide gelator and anti-inflammatory painkiller drugs which could be formulated into a gel and released at pH8. Figure reproduced from reference 75 with permission from The Royal Society of Chemistry.

Very recently, in a clever application of DBS technology, pseudoephedrine, a highly effective over-the-counter decongestant, has been formulated within DBS which acts as a controlled release formulation.[76] There is a significant problem with over-the-counter pseudoephedrine because it is used for the illicit synthesis of methamphetamine (crystal meth). By formulating pseudoephedrine within a gel it becomes much more difficult to use as a precursor for methamphetamine synthesis, as it is not possible to easily remove pure pseudoephedrine – the process is time-consuming and tedious. However, if pseudoephedrine is not removed from the gel, the reducing conditions for its conversion to methamphetamine lead to breakdown of DBS, wasting reductant and contaminating product. It is argued that this formulation may allow continued use of pseudoephedrine as an over-the-counter medication.

Applications of DBS and its derivatives in healthcare are not limited to drug delivery systems but have also been explored in analytical clinical laboratories. Graper and co-workers demonstrated that the use of DBS, a blood compatible and shear-sensitive gel, can facilitate the separation of serum from the cellular portion of blood.[77] In their patent, a block copolymer was gelled by DBS in the bottom of a tube and a blood sample was added on top. The thermo-reversible, shear-sensitive properties of the obtained gel enabled the formation of a viscous liquid when centrifuged, with the gel being

capable of recovering and reforming once centrifugation was complete. At this point, the formation of a solid gel barrier helped separate the solid and the liquid constituents of blood according to their densities.

Polymers with embedded DBS networks for enhanced performance

The importance of combining low molecular weight gelators with polymeric systems has recently been reviewed by us.[78] DBS-based compounds are an excellent industrially applied example of this concept, widely used as nucleating and clarifying agents in plastic or thermoplastic materials – indeed this is one of the primary industrial applications of DBS and its derivatives.[79] Importantly, the presence of DBS (or DBS derivatives) shortens processing times, improves mechanical properties and reduces the 'haze' in these materials.[80] DBS acts as a nucleating agent, by dissolving in the molten polymer and homogeneously dispersing in the polymer matrix, then on cooling forms a thermoreversible nanofibrillar network within the polymer, resulting in faster and more organized crystal growth of the polymer matrix, hence leading to the desired properties.[81] There have been a large number of developments of this technology, selected significant examples are described in more detail below.

Titus and co-workers[82] patented a polyolefin composition with improved clarity, highly desirable in certain plastic products such as syringes, made by injection moulding. The polyolefin composition contained fluorinated DBS as a clarifying agent, which contributed to the improved clarity, resistance to shrinkage and heat deterioration, without loss of mechanical and chemical properties. Furthermore, these fluorinated DBS derivatives increased the temperature of polymer crystallisation and allowed the moulds to be opened more rapidly, speeding up processing and leading to cost savings. Other patents have proven the ability of DBS and derivatives to improve transparency and reduce moulding shrinkage of polyolefins making them suitable for packaging, containers for cosmetics, transparent doors and electrical component parts.[83]

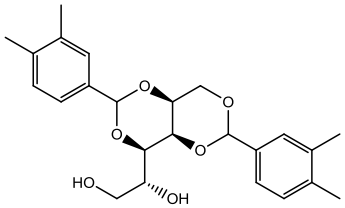


Fig. 15. Chemical structure of Millard®3988 (1,3;2,4-di(3,4-dimethylbenzylidene) sorbitol).

Despite its efficiency as a nucleating/clarifying agent of polyolefins, DBS is not suitable for food packaging due to the transfer of taste and odour to the food. On researching this problem, Rekers found that substitution on the aromatic rings to make bis-dialkylbenzylidene sorbitols is crucial for the performance of this type of compound as clarifying agents and can also overcome the organoleptic (taste/odour) problems associated with the native (unsubstituted) DBS.[84] As a result, the commercial product sold under the trade name Millard®3988 (1,3;2,4-bis(3,4-dimethylbenzylidene)sorbitol, Fig. 15) led to compositions with suitable taste and odour transfer properties for food packaging. The allylated version of DBS prepared by Xie et al[37] (see Scheme 6 for synthesis) was also found to exhibit improved organoleptic properties.

Simultaneous use of DBS as a nucleating agent, and poly(ethylene glycol) (PEG) as a plasticizer, in order to improve the rate of crystallization of poly(lactic acid) (PLA) has been reported by You and co-workers.[85] Due to the presence of the DBS nanofibrils that acted as heterogeneous nucleating sites for crystallization, it was possible to observe a crystallization peak after cooling, even at very high cooling rates (40˚C/ min) – therefore enabling very rapid polymer processing. The influence of DBS self-assembly on the liquid-liquid phase separation and crystallization of ultrahigh molecular weight polyethylene (UHMWPE)/ liquid paraffin (LP) blends was also studied and it was confirmed that DBS nanofibrils can be an effective heterogeneous nucleating agent and accelerate the crystallization of UHMWPE.[86] Furthermore, the competition between the liquid-liquid phase separation and crystallization of UHMWPE can be controlled by the amount of DBS used.

In addition to simply modifying the kinetics of polymer crystallisation, DBS gel networks can also play a more active role in directing the structure of polymeric materials. Indeed, the 3D fibrillar networks of DBS organogels can be used as self-assembled templates for the polymerization of a monomer, inducing its crystal orientation (Fig. 16). Furthermore, if the nanostructured scaffold is removed, a nanoporous polymer matrix is generated, which may be suitable for a variety of applications – this approach is well known for a range of LMWGs.[78,87]

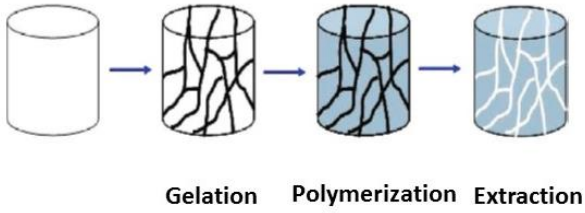


Fig. 16. Schematic representation of (from left to right) (i) a homogeneous solution containing DBS molecules, (ii) the formation of DBS nanofibrils in a gel, (iii) polymerisation within the DBS organogel, and (iv) nano-porous polymers after extraction of the DBS organogel. Image reproduced from reference 89 with permission from The American Chemical Society.

Lai and Tseng demonstrated the polymerization of styrene using DBS as a template.[88] DBS nanofibrils were formed in styrene followed by the free-radical polymerization of the monomer in the presence of a chemical cross-linker, divinyl benzene. The obtained material remained transparent and homogeneous and it was proved that the DBS fibrils remained intact in the final product, showing that the thermal polymerization process did not affect the DBS network. Subsequently, a nanoporous polymer was successfully obtained by solvent-mediated extraction of the DBS, suggesting the feasibility of using DBS as a template. The

concentration of DBS influenced the crystallization and the morphology of the resulting polymer. In 2009, Lai and co-workers carried out BET analysis of the nano-imprinted polystyrene which showed that the specific surface area (3.1 m^2/g) of their template polymer was about six times greater than that of the untemplated counterpart.[89]

In a similar manner, Lai et al demonstrated that the gelation of DBS in methyl (methacrylate) (MMA), a hydrophilic monomer, takes a longer time to attain equilibrium than in hydrophobic styrene due to hydrogen bonding interactions between DBS and the MMA monomer phase.[90] As a result of this, the average pore diameter of the resulting porous material was larger than the diameter of the nanofibres of the gel. Lai also applied this approach to the formation of structured and porous poly(lactic acid).[91]

In order to orient polymer crystallisation, DBS derivative 1,3:2,4-di(3,4-dimethylbenzylidene)-D-sorbitol was used in polypropylene (PP).[92] It was reported that the polymer had a better orientation when 0.4% (instead of 1%) of the DBS-based gelator was used. This was attributed to the fact that a lower concentration of gelator produced longer fibres which could be more effectively aligned and organized, leading to a good orientation of the polymer chains.

Mitchell and co-workers reported that DBS could direct the crystallisation of poly-(ε-caprolactone).[93] Specifically, applying modest shear forces caused the DBS to form highly extended nanostructures which furthermore adopted a preferred alignment with respect to the flow field and were reasoned to be controlling polymer crystallisation on cooling and allowing greater control over directionality. These authors then went on to show that chloro-substituted DBS was significantly more effective at directing this effect than unsubstituted DBS – an effect that they attributed to the lower solubility of the former compound.[94] It was also demonstrated that the presence of DBS could impact on the fibre dimensions and crystallinity of electrospun fibres of poly-(ε-caprolactone).[95] Although in these studies the DBS was not removed from the polymer, there is clear potential to generate polymeric systems with aligned porosity in this way.

In an alternative approach to polymer/LMWG combination, we reported the self-assembly of a supramolecular pH-activated DBS-CO_2H hydrogel within a photo-polymerisable synthetic polymer hydrogel.[96] By photopatterning the overall material using a mask in the presence of GdL as pH activator, we were able to obtain multi-domain gel-phase materials, in which those regions exposed to UV irradiation contained the photo-activated polymer gel along with the pH-activated DBS-CO_2H supramolecular gel, while those areas covered by the mask only contained the supramolecular gel (Fig. 17A-C). Dyes showed differential diffusion rates through the different domains of this gel (Fig. 17D-F), with diffusion either being controlled by the network density of the polymer hydrogel, or specific interactions with the supramolecular DBS-CO_2H hydrogel. Such multi-domain polymer/supramolecular gel materials might have applications in controlled drug formulation and release. Furthermore, they may be useful for tissue engineering, with the tissue growth responding to the different rheological properties and chemical functionality of different gel domains.

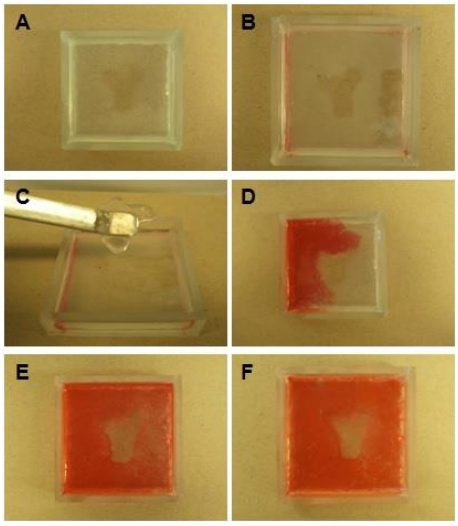


Fig. 17. A) Patterned multi-domain gel consisting of non-hybrid region (more translucent) and hybrid dual-network Y-shaped region (less translucent). B) The non-hybrid domain is easily deformed, whilst C) the hybrid region is robust. D-F) Diffusion of Direct Red 80 dye at 60s, 3h and 24h – there is only minimal diffusion into hybrid region. Image reproduced from reference 96 with permission from Wiley-VCH.

DBS offers a low cost method for the modification of various polymer matrices. Obviously, there is significant further scope for the active templating of polymer matrices with DBS and its derivatives in which the nanoscale network introduces activity or function to the overall system rather than simply modifying kinetics and structure. This approach to modifying well-established polymeric materials with a smart self-assembled nanoscale network offers potential for future high-tech applications, a number of which are currently being explored for DBS and other self-assembled gel-phase materials.[78,87]

Dental composite

Dental composites can be obtained by photopolymerization of several dimethacrylate monomers, such as bisphenol-A-glycidyl dimethacrylate (bis-GMA) and urethane dimethacrylate (UDMA). However, polymeric dental composites are vulnerable to shrinkage and incomplete vinyl conversion that can lead to the presence of free monomers or unbound species and cause oral health problems.

Wilder and co-workers designed a dental composite consisting of DBS, photopolymerisable ethoxylated bisphenol A (EBPADMA) and zirconium-modified amorphous calcium phosphate (Zr-ACP) suitable for assisting the remineralisation of teeth.[97] Clearly this application is related to the other examples of DBS-modified polymers outlined in the section above, but given the specificity of use, we have separated it out for the purposes of this review. In addition to increasing the monomer conversion rate (by increasing viscosity, limiting radical termination and enhancing free radical propagation), the introduction of DBS into dental composites enhanced strength and reduced shrinkage. However, the incorporation of DBS also retarded the desirable leaching of calcium and

phosphate ions from the Zr-ACP. It is nonetheless clear that DBS-modified polymers have significant potential for application in this area.

Stan and co-workers used DBS, 1,3:2,4-bis-O-(p-methoxybenzylidene)-D-sorbitol (MeO-DBS – modified on the aromatic 'wings') and 1,3:2,4-bis-O-benzylidene-5,6-biscarbonylamino-ethylmethacrylate-D-sorbitol (IEM-DBS; modified at both 5-OH and 6-OH positions, Fig. 8) to gelate bis-GMA and UDMA.[35,98] They verified that regardless of the type of DBS derivative, 2 wt% of organogelator contributed to increased vinyl conversion. Furthermore, in the presence of IEM-DBS (2 wt%) the samples revealed a compact structure, most likely due to the additional methacrylic groups that contribute to better compatibility with the polymer matrix. It should, however, be noted that as described in the synthesis section, IEM-DBS was synthesised using an organotin reagent – in our view, this is a significant concern with respect to applications in dentistry due to the known toxicity profile of such reagents.

Adhesives

In the late 1960s, adhesive sticks (sometimes referred to as 'crayons'), represented a major step forwards in adhesive technology.[99] In these materials, a polymer with adhesive properties is formulated into a gel stick, which on rubbing, breaks down to release the active monomer/polymer onto the surface, causing adhesion. Perhaps the most famous amongst these glue-sticks is the 'Pritt stick' which as its gelation agent contains stearic acid derived LMWGs.[100]

In 1974, a patent from Nippon Synthetic reported the use of DBS as an alternative gelation agent for formulation of such products.[101] In the patent, it was noted that the DBS used also contained other derivatives such as MBS and TBS. The adhesion system was based on polymers such as partially hydrolysed poly(vinylacetate) and the solvent medium was a mixture of water and a water-miscible organic solvent. The authors noted that using a DBS-based gelation system had significant advantages in terms of the hardness of their adhesive stick and its performance – adding greater stability in hot and humid climates compared with stearic acid derived products. A modified version of these DBS derived glue-sticks was later reported, incorporating different solvents in order to enhance the safety profile.[102] Adhesive sticks have also been developed based on DBS gels using different polymer-forming technology – such as polyester formation.[103] Stick-type technology has also been developed using DBS gels as the carrier for the related applications of priming surfaces prior to adhesion,[104] and the application of solvent to surfaces to remove adhered products.[105]

These applications demonstrate the way in which DBS can be simply incorporated in products to enhance their rheology and formulation. In this way, these applications are related in principle to the use of DBS in cosmetic and personal care applications described above.

Gel electrolytes for future energy technologies

The examples in the sections above are all established technologies. However, there are a number of developing potential applications of DBS derivatives described in the following sections.

The development of gel electrolytes has been of great interest in the past decades due to the inherent drawbacks with the use of liquid and solid electrolytes in energy capture and storage technology – areas of vital technological importance in a world increasingly short of energy, with a significant energy storage problem and filled with mobile devices. Liquid electrolytes use volatile organic solvents which may lead to leakage and volatilization problems, while solid electrolytes present much lower conductivity when compared to their liquid counterparts. Gels offer a potential solution to this dichotomy.

In early work on dye-sensitised solar cells (DSSCs), Grätzel and co-workers demonstrated that DBS and its derivatives were suitable for immobilisation of the electrolyte. In particular, methyl-substituted DBS (MDBS) and dimethyl-substituted DBS (DMDBS), were optimal to solidify the polar organic solvents, (e.g. 3-methoxypropionitrile) frequently used in DSSCs.[106] DMDBS proved to have a higher T_{gel} value and viscoelastic behaviour than MDBS, making it the optimal gelator for these electrolyte systems. The quasi-solid-state dye-sensitized solar cells yielded identical overall solar energy conversion efficiency using a DMDBS gel electrolyte as they did for a liquid electrolyte. This indicates that the gel-based electrolyte exhibits good conductivity and also has excellent thermal stability, at relatively low cost.

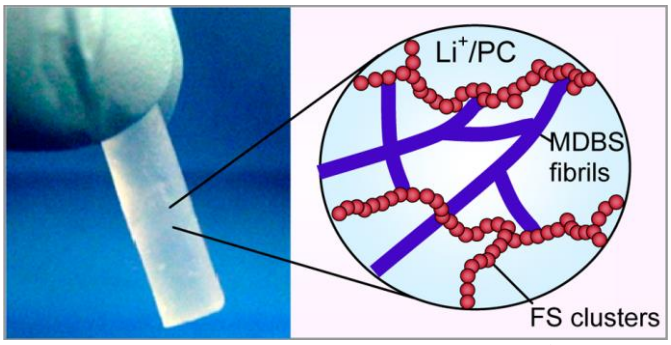


Fig. 18. Schematic depicting the synergistic interaction between FS in Li^+/PC electrolyte and MDBS and the resulting free-standing gel. Adapted from reference 107 with permission from The American Chemical Society.

In terms of battery technology, Raghavan and co-workers demonstrated the combination of a DBS derivative; 1,3;2,4-bis(4'-methylbenzylidene)sorbitol (MDBS), with nano-particulate fumed silica (FS), suspended in propylene carbonate (PC) containing lithium perchlorate ($LiClO_4$) as a source of lithium ions for lithium-ion batteries.[107] It is worth noting that FS did not itself form a gel in the mentioned solvent, but helped rigidify the resulting organogel via non-covalent cross-linking between the silanol (Si-OH) groups of FS and the free hydroxyl groups of MDBS. This produced a robust 'solid-like' electrolyte with high 'liquid-like' ionic conductivity, and an electrochemical stability window and good interfacial

stability against Li ions (Fig. 18). This clearly demonstrates how the solid-like/liquid-like properties of gel phase materials can be harnessed within this application.

Lai and Chen prepared gel electrolytes comprising various concentrations of DBS in poly(ethylene glycol) (PEG) containing iodide-based redox couples.[108] The molecular weight and the end groups of the PEG influenced the ionic mobility and hence conductivity of the hybrid organogels – demonstrating how the liquid-like phase of the electrolyte gel can be used to tune performance. The addition of more DBS to PEG increased the thermal stability and led to better dissolution of the electrolyte ions. As such, it was possible to obtain similar high conductivity for these electrolyte gels as for liquid electrolytes. When used in dye-sensitized solar cells, PEG-based electrolytes having inactive methyl end groups achieved the highest energy conversion efficiency among the tested cells. The efficiency of the DSSC containing the gel electrolyte remained basically the same over a one-month period, implying that the materials and devices were relatively stable

The application of DBS organogel-based electrolytes in a more biological setting is also being explored. Such devices are not being used for energy creation or storage, but rather in biosensors. In 1997, a method of incorporating a microscale gel membrane based on DBS (in 2-nitrophenyloctylether) as an interface between two immiscible electrolyte solutions was first reported and used as an amperometric ion sensor.[109] This approach to device fabrication has since been used with the enzyme glucose oxidase in order to create a biosensor for glucose.[110]

So far, most uses of DBS have relied simply on its rheological, gel-like properties. It seems likely, however, that in the future, DBS (and derivatives of it) have more to offer in terms of introducing additional activity/function into gel electrolytes in order to achieve simple advances such as higher efficiency and capacity, as well as innovative and new multi-functional energy storage or sensory devices. Furthermore, the ability of gels to bridge between hard and soft materials, being compatible with both biological tissue[111] and electrode surfaces[4e] means there is significant potential to use these types of materials in a biological setting at the rapidly developing and all-important interface between electronic and biological systems.

Liquid-Crystal Gels

The use of LMWGs to immobilize liquid crystals and the associated properties of these hybrid materials has attracted significant scientific attention owing to the potential of a nanoscale gel network to impact on liquid crystal properties such as switching times and voltages.[112] Furthermore, the liquid crystal organisation is also able to impact upon the nanoscale morphology of the gel.

In a key patent, Kato and co-workers used DBS, amongst other gelators, in order to form liquid crystal gel devices.[113] They noted that immobilisation of a liquid crystal phase was desirable in terms of speed of response. This was traditionally done within a polymerisable phase, but the use of LMWGs for immobilisation made the device fabrication process much simpler and only used small amounts of additive. It should be noted, however, that Kato and co-workers expressed a preference for gelators which possessed a mesogen within their structure, and DBS was not their preferred embodiment of the invention.

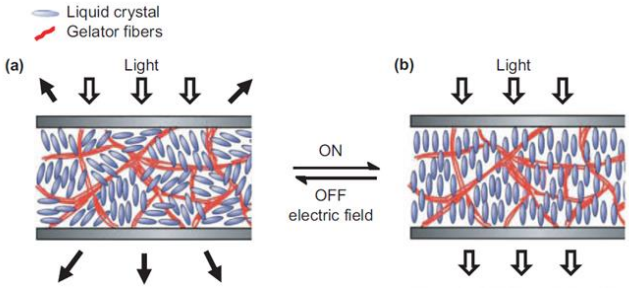


Fig. 19. Schematic representation of the orientation of liquid crystal molecules in the presence of DBS nanofibrils, when an electric field is applied. Adapted from reference 114a with permission from Wiley-VCH.

Jansen and co-workers demonstrated that DBS could be used to gel liquid crystals in order to obtain a thermo-reversible and electro-responsive hybrid soft material having electro-optical characteristics appropriate for use in projection systems.[114] The development of a white light-scattering film constituted by a commercial liquid crystal, LC-E7 combined with DBS, caused the orientation of the liquid crystal molecules in the direction of the electric field when an alternating current electric field was applied, leading to the alignment of the molecules and consequently transmission of light (Fig. 19). The gel plays a key role in controlling the phase diagram of these materials to provide the desired electro-optical properties.

Interestingly, it has been noted that when confined on the microscale, the nanoscale network morphology of DBS-derivatives can be modified, simply by the dimensions of the confining space.[115] It is to be expected that this observation will be of importance in applications where such gel-phase materials are applied in optical or electronic device technology.

The compatibility of DBS with a variety of different solvents and other systems suggests it has significant potential for further development in optical applications. Of key importance is the transparency of these materials (which relates to the solubility of the gelator and its ability to form a nanoscale, non-light-scattering network). Also important is the rheology and dynamics of the gel network which will impact on the potential of switchable and responsive optical materials.

Environmental remediation

The use of DBS and its derivatives for selective gelation of oil from an aqueous admixture, as a potential oil-spill remediation technology has been known since 1985.[116] It is interesting to note that the use of gels in this way has been an area of some activity amongst academic scientists working on gels of late,[117] but the earlier patent is not usually cited. In the original

patent,[116] the ability of DBS and its derivatives to solidify some organic liquids was exploited to entrap an oily layer in the presence of seawater. For instance, when a layer of kerosene on the surface of seawater was treated by spraying with a mixture of hydrophilic solvents such as *N*-methyl-2-pyrrolidone (NMP) and hydrophobic solvents such as liquid palm oil containing 5% DBS and polyoxyethylene lauryl alcohol ether (1%) for 10 minutes. Interestingly, DBS rapidly and selectively gelled the oil layer within 10 min, leading to the recovery of 100% of the kerosene with only 1% water content. It should be noted that NMP has since been reported to cause cancer, although it does rapidly biodegrade and has low toxicity to aquatic life. Other additives may be preferable. The use of 6 wt% of 1,3:2,4-di(p-methylbenzylidene)-D-sorbitol in another composition enabled 95% of recovery of gasoline in seawater with only 0.3% of water content. The immobilised oil was scooped off the surface of the seawater using a net having 2 mm x 2 mm mesh opening and easily recovered by either dilution or distillation. These results, together with the high hardness of the gels make this approach a potentially powerful and simple technology for reclaiming spilled oil from water.

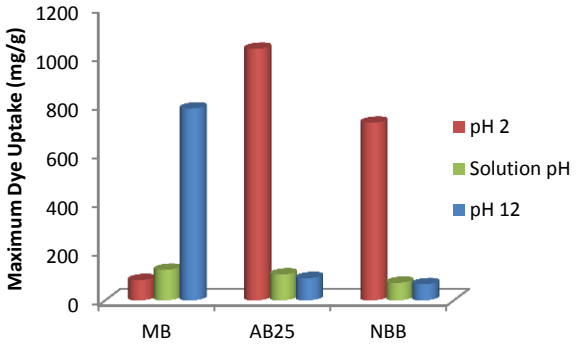


Fig. 20. Maximum dye adsorption of three dyes, methylene blue (MB), acid blue 25 (AB25) and naphthol blue black (NBB) by DBS-$CONHNH_2$ under different conditions of pH. Figure reproduced from reference 32 with permission from The Royal Society of Chemistry.

With a different type of environmental remediation in mind, we recently developed a pH-independent hydrogel based on DBS-$CONHNH_2$ (Scheme 3).[32] Hydrogels have real potential for environmental application, as the primary solvent in the biosphere is water. In this case, the hydrogel has initially been studied for the removal of pollutant dyes from water samples. Hydrogels are well-suited to this kind of 'water purification' application as they are highly porous, compatible with water, and the filtration network of the gel matrix has a high surface area (as a consequence of its nanoscale structuring) – this maximises potential interactions with the pollutant. DBS-$CONHNH_2$ formed gels across a wide pH range, making it stand out amongst other low molecular weight hydrogelators that have demonstrated significant ability in sequestering dyes from water but often require acidic conditions in order for gelation to occur.[118] The pre-formed hydrogel adsorbed pollutant dyes to very high loading levels (ca. 1000 mg/g). The degree of uptake of different pollutant dyes from water depended on their protonation states (Fig. 20). This made it possible to promote pH-mediated adsorption and desorption of dyes from the hydrogel, resulting in not only the removal of pollutants from water, but also the recyclability and reusability of the gel.[32] It is clear that modified gel fibres may, in this way, be able to play significant active roles in the removal of a wide range of different pollutants from water at low cost, using a fundamentally simple technology that is already widely applied and considered to be benign.

Other applications

Besides the described applications it is also possible to find DBS and its derivatives in many other formulations such as fluid detergents with enhanced rheological properties,[119] air-treating gels capable of controlled release of fragrance,[120] black crayons with improved stability,[121] distillation membranes with improved hardness, stiffness and ductility,[122] and even wood stain.[123] It is clear that DBS has had significant impact on industrial development, and will continue to do so in the future.

Conclusions and Outlook

Acetal-protected D-sorbitol DBS (1,3:2,4-dibenzylidene-D-sorbitol) is a highly versatile self-assembling system which has remarkably been known for well-over 100 years and found many applications. As such, it can be considered one of the best examples of nanotechnology – long before the field, or even the terminology, had been considered or defined.

DBS is synthesized via an acid-catalysed dehydration-condensation reaction, with MDBS and TDBS as by-products which can be easily removed by washing. As such, DBS is a readily-synthesised and low cost bulk material which can be considered for high-tonnage applications, and as such, has high industrial relevance. Furthermore, over 100 derivatives of DBS have been reported to date – in some cases, functionalisation of DBS can significantly expand the scope of self-assembly of these materials into other solvents, such as enabling the formation of true hydrogels in the case of modification of the aromatic 'wings' with an acid or acyl hydrazide group.

With the advent of modern analytical tools, the self-assembly of DBS-based gelators in organic solvents has been shown to proceed via the interplay of non-covalent interactions, predominantly hydrogen bonding and π–π stacking, provided by synergistic contributions from both the sugar backbone and the aromatic 'wings' of the butterfly-like amphiphile respectively, with the contributions of these depending on the solvent environment. The nature of the solvent determines the speed of gelation, geometry of the resulting fibres, the thermal and the rheological properties of the resulting gels. Indeed, solubility parameters clearly play a key role in determining the gelation scope of DBS. We suggest that this understanding will enable a much greater degree of *ab initio* gelator design in the future.

The synthetic simplicity and generally benign nature of DBS-based gelators have made them suitable for numerous industrial applications, and hence they are highly patented LMWGs. It is fair to say that in many cases where nanostructuring is desirable, DBS has been one of the 'go-to' systems for industrial chemists. As such, this simple molecule, with a remarkable nanoscale performance is a significant component in a surprisingly wide range of technologies, demonstrating that the application of low molecular weight gelators is already well-advanced (perhaps more so than some academic researchers may think).

Having reviewed this area, we believe that the key for the future will lie in harnessing DBS derivatives in which the derivatisation endows additional functionality onto the self-assembled materials, hence opening up high-tech applications and ensuring that nanostructuring brings multiple advantages to bear in addition to simple rheological performance. In this way, we believe that DBS is a powerful platform technology in nanomaterials science, on which the next generation of smart, multi-functional nanostructured materials can be assembled.

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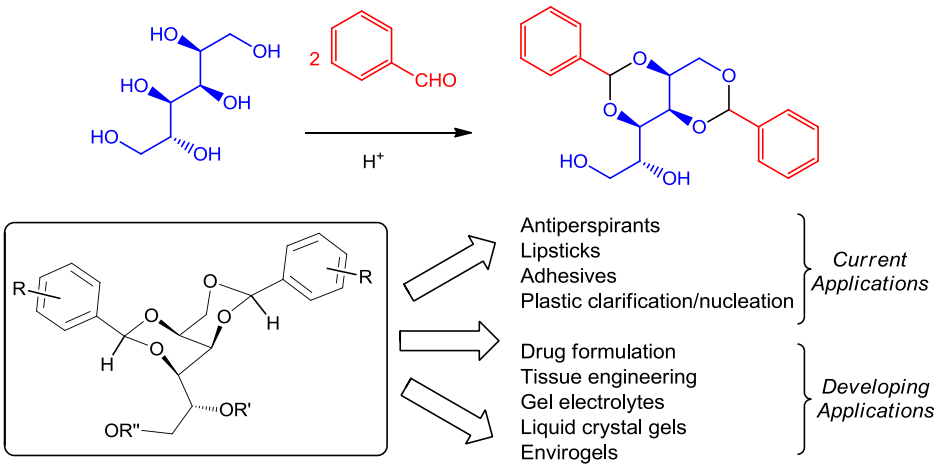
Journal Name

ARTICLE

1,3:2,4-Dibenzylidene-D-sorbitol (DBS) and its derivatives - Efficient, versatile and industrially-relevant low molecular weight gelators with over 100 years of history and a bright future

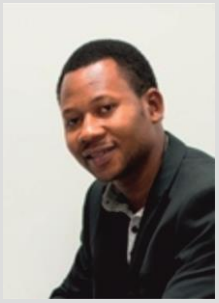
Graphical Abstract:

From its origins in the late 19th century, DBS has become an efficient, versatile, low-molecular-weight gelator which has seen a wide-range of industrial applications. In recent years, greater understanding of its self-assembly and the creation of new derivatives are expanding the scope of this fascinating family of gel-phase materials.



Professor David K. Smith carried out his DPhil at University of Oxford with Prof. Paul Beer and was then Royal Society European Research Fellow with Prof. Francois Diederich at ETH Zurich. In 1999, he was appointed Lecturer in York, and in 2006 promoted to a Professorship. His research focusses on applying fundamental understanding of supramolecular science and self-assembly to nanomaterials and nanomedicine. He has received the RSC Corday Morgan Award for

research excellence (2012), a Higher Education Academy National Teaching Fellowship (2013) and was recognised as one of the RSC's Diverse 175 Faces of Chemistry (2014).



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