A new organogelator effective at both extremes of solvent polarity

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ABSTRACT

A series of aliphatic 2,3,ω-1,ω-diesters have been found capable of forming stable gels from solvents at either end of the usual polarity range, including toluene and cyclohexane at one extreme and water and aqueous ethanol at the other extreme. The low levels of the gelator molecules required [minimum concentration ~1.8–3.2 mg ml^{-1} in optimum cases] is a notable feature in many cases.

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Low molecular weight organogelators (LMOGs or LMWGs), compounds capable of self-assembling to create a three-dimensional network which can then entrap a solvent and create gels, have attracted considerable current interest.[1–4] The self-assembly of low molecular weight gelators to form fibre-like structures, which entangle to form a three-dimensional network resulting in immobilisation of organic fluids gives rise to the phenomenon that is known as gelation. Such molecular self-assembly and network-formation have stimulated much recent research aimed at defining the fundamental structures and driving forces responsible for this fascinating phenomenon, inspired further by their applications in templated materials synthesis,[5] drug delivery,[6] separations[7] and biomimetics[8] to name but a few applications.

Existing organogelators are a diverse group of compounds with little coherence in terms of common structural features. Examples include relatively simple hydroxy-fatty acids, lecithin, a fatty glyceride-type molecule, which also contains a phosphate and ammonium group and a number of hydroxylated steroids. Rather different gelators are based on anthracene and related aromatic cores having lengthy alkyl substituents and various combinations of the foregoing types. However, the presence of long alkyl chains is not necessary, as demonstrated by the viability of various metal carboxylate complexes, some calix[n]arenes, protected sugar and other polyol derivatives and many peptide-like molecules to behave as good organogelators.[1–4] The majority of these, however, can be classified as either non-hydrogen bond-based gelators and hydrogen bond-based gelators. Anthracene, anthraquinone, tetralin and steroid-

based organogelators are well studied and constitute the family of non-hydrogen bond-based gelators, as their aggregation is driven by π–π-stacking and solvophobic effects.[9] Other molecular interactions can be classified into three types: dipole–dipole, van der Waals and hydrogen bonding interactions. The hydrogen bonding interaction(s) generally take place when a hydrogen atom is located between two oxygen atoms, which then align linearly. This strict unidirectional orientation leads the molecules to align in a specific manner, which is the major cause of highly organised supramolecular structures.[10] Although this group of known LMOGs do form a rather diverse range of structures, systematic efforts are now being made to understand this phenomenon so that serious attempts can be made to predict likely LMOG structures.[4,11]

In terms of their structures, gels are easier to recognise than to define, as was pointed out many years ago.[12] It is perhaps remarkable that the single most useful method for determining if a gel has been formed is the 'inversion test', in which a sample tube containing the material is simply inverted. If the material remains in the tube, then it may be a gel. Structural determination in this area is a real challenge, despite the plethora of sophisticated analytical techniques that are now available. Very often, it would appear that the gelator forms lengthy fibres of some kind, whose detailed structure is often difficult to map with any certainty. This of course then precludes any reasoned design of potential gelators and hence, up until recently, most have been discovered serendipitously. This is certainly true in the present case, which we report in this Letter. However, a most significant feature of this new class of LMOGs is their ability to form gels from solvents at the extreme ends of solvent polarity, while being poor at the gelation of medium-polarity solvents.

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Clearly, there are many ways in which gels can be formed and many ranges of concentrations of gelators which are needed to form such a material. However, a very common method is to gently warm a potential gelator until it just dissolves then cools the solution. Speed is not always of relevance as some gels form extremely rapidly, while others can take hours, even days to form completely. Typically, a successful gelator will have just the right solubility characteristics: not too soluble or else no gel will ever form but not too insoluble as there will then be no interactions with the prospective solvent. Such an intermediacy of solubility was exactly what we discovered when trying to crystallise samples of various tetrahydroxy diesters **1**, which we had designed to act as recoverable tartrate surrogates in the Sharpless Asymmetric Epoxidation (SAE) reaction. This proved to be successful and a preliminary report has been published;[13] once this work was completed, we were able to focus on the gelation properties of these compounds, the results of which investigation we report here.


1
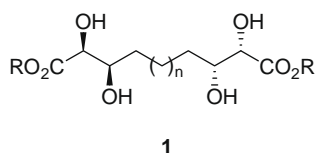
The series of diesters **1** was prepared as single enantiomers, in quantity if required, by a straightforward, two-step sequence consisting of firstly a cross-metathesis reaction between a 1,ω-diene or cycloalkene and 2 equiv of an acrylate and a subsequent double asymmetric dihydroxylation [*bis*-AD] reaction of the resulting *bis*-enoate.[13] We noted that, coincidentally, one of the most effective tartrate surrogates, the diisopropyl diester **1** [$n = 6$; R = ^{i}Pr] also appeared to be an effective organogelator of both toluene and aqueous ethanol. Somewhat surprised by this effect on two solvents with such diverse polarities, we sought to determine the generality of this phenomenon.

Firstly, we chose to retain the six connecting methylene groups between the two dihydroxy-ester functions and to test the effect of variations in the nature of the esterifying group. To this end, we compared the seven diesters **2**.

R = Me, Et, ^{i}Bu, ^{t}Bu, ^{i}Am, cyclohexyl, 3-pentyl

2
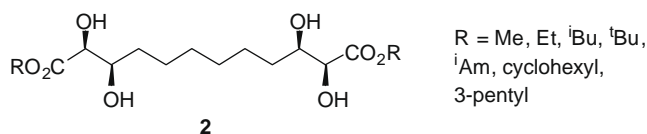
However, none of these were as effective as the di-isopropyl ester **1** [$n = 6$; R = ^{i}Pr]. The methyl and ethyl esters were simply too insoluble in most solvents tested (see below) to be effective LMOGs while the remainder seemed to be too soluble. Gelation was possible in some cases with the *iso*-butyl and 3-pentyl derivatives, but mostly the results were disappointing.

We therefore chose to return to the series of *iso*-propyl esters **3** and compared the effect of varying the chain length; the results obtained are collected in Table 1.

a) n = 3
b) n = 4
c) n = 5
d) n = 6
e) n = 8

3
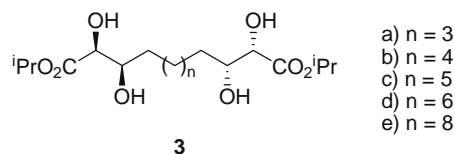
In all cases, a simple inversion test was used to confirm gelation: a weighed sample of the potential LMOG was warmed with the given solvent until dissolution after which the solution was slowly cooled in a simple sample tube. If gelation appeared to have taken place, the tube was inverted; if the solution remained in place, then gelation had occurred.[12]

We were delighted to find that the initial observations were both confirmed and considerably extended. At one extreme of the solvent polarity spectrum, all the diesters **3** proved highly capable of forming organogels with toluene, although the example with the eight methylene connection, **3d**, turned out to be marginally the best. Its MGC of just over 3 mg per gram of toluene is quite remarkable and places it in the 'supergelator' class.[14] Very similar levels of this and the two-methylene lower homologue **3c** allowed the formation of stable gels from cyclohexane. These compounds were also capable of forming gels from slightly more polar mixed solvents. For example, a 10:1 hexane–chloroform mixture forms stable gels but requires slightly enhanced levels of the diesters **3** to achieve this. Also notable is a feature common to many of the foregoing methyl and ethyl esters **2** and related structures, that of insufficient solubility in relatively non-polar solvent systems. No doubt, many other mixtures of similar overall polarity would be transformed into gels by similar levels of these diesters, especially compound **3d**. It may also be significant that gelation was unaffected by the fact that a mixed solvent was used. In a separate study, diester **3d** has been found to be the first example of a purely organic and non-fluorinated gelator which is capable of forming stable gels from a number of perfluorocarbons.[15]

In general, however, solvents of intermediate polarity were not suitable for gel formation using the diesters **3**. Thus, in tetrahydrofuran, acetonitrile and ethyl acetate, the diesters **3** proved to be too soluble for gel formation. Of this group, only dichloromethane proved capable of exhibiting successful gelation. Curiously, the lower carbon analogues **3a–d** were required in much higher amounts but which decreased with increasing chain length until the final example, **3e**, in which case the gelator level was almost equivalent to the spectacular ones observed during toluene gelation.

Even more remarkably, many of the diesters **3** were also highly capable of gelating very polar solvents at the opposite extreme of the spectrum. Thus, while the shortest and longest diesters studied, **3a** and **3e**, were essentially insoluble in water, the other three were highly effective as LMOGs. Once again, the best in terms of low quantity was found to be diester **3d**, which was able to form a stable aqueous gel at a very low MGC value of 1.7 mg ml^{-1}. Such behaviour was not confined to the pure liquid: diester **3d** formed gels with equal alacrity with both lager and wine, as did some

Table 1
Minimum gel concentration [MGC] in mg ml^{-1}

LMOG	Toluene	*c*-C$_6$H$_{12}$	Hex/CHCl$_3$[a] 10:1	CH$_2$Cl$_2$	H$_2$O	Lager[b]	Wine[c]
3a	10.3	–	ppt[d]	ppt[d]	ppt[d]	–	ppt[d]
3b	4.9	–	3.9	94.4	12.6	–	12.4
3c	3.4	4.0	5.4	53.3	5.5	5.7	5.6
3d	3.2	4.0	5.3	33.8	1.7	1.8	1.7
3e	3.8	–	4.1	7.1	ppt[d]	–	1.8

[a] Hex = hexanes.
[b] Grolsch or Stella Artois.
[c] A 2005 13.5% French Merlot.
[d] The LMOG precipitated upon cooling.

other members of the group (Table 1). These were not frivolous experiments; the fact that gelation occurred at much the same low levels with these highly complex aqueous solutions as it did with pure water suggests that the gelation mechanism and the associated structures must be quite robust, certainly in terms of competing hydrogen bonding and potential structural disruption by the diversity of compounds present in such complex mixtures. Perhaps not surprisingly given their static nature, all the foregoing gels proved to be stable over periods of many months, given protection from solvent evaporation.

In common with many other LMOGs, the present examples are capable of forming gels at quite remarkably low ratios to the bulk molecules. For example, the lowest value found for toluene, 3.2 mg ml^{-1} of diester **3d**, equates to a little fewer than 1200 molecules of solvent to every LMOG molecule. The equivalent values for water and aqueous solutions are even more impressive: at the optimum value, over 13,000 water molecules enter into gel formation for each molecule of gelators. It seems entirely obvious that the mechanism of gelation and the structures thus formed must be held together by extensive arrays of hydrogen bonds. There is also a tantalising stereochemical feature associated with the present gelator molecules: while the chiral, non-racemic examples **3** with either *d* or *l* stereochemistry are very effective as LMOGs, the corresponding *meso* forms and their racemates are nothing like as effective or are completely ineffective. We continue to try and define and interpret these features in more detail and intend to report the results elsewhere, once complete, for what we would propose could be referred to as an 'omnigelator', in view of the ability to form gels across the solvent polarity extremes.[16]

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