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Hunter's Oligoamide: A Functional C_2-Symmetric Molecule with Unusual Topology for Selective Organic Gel Formation

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We report for the first time the discovery of the gelation properties of Hunter's oligoamide with pendant amino groups, **1**, which possesses structural features different to some conventional gelators. the organogels were studied with infrared spectroscopy, transmission electron microscopy, and differential scanning calorimetry. Remarkably, the effective self-assembly process of this oligoamide to produce stable organogels occurs exclusively in chlorinated solvents.

Introduction

In a fascinating journey from serendipity to rational design, materials made by means of gelation of organic solvents has received increasing attention over the last 10–15 years[1] because of their unique supramolecular architectures and potential applications[2] as functional soft materials in the fabrication of sensors,[3] liquid crystallines,[4] electrophoretic and electrically conductive matrices,[5] templates for cell growth or the growth of sol-gel structures,[6] and in many other industrial fields such as cosmetics, oils, and foods.[1]

These systems, so-called organogels, are thermoreversible, viscoelastic (soft) materials consisting of an organic liquid and a low molecular mass compound (usually <5 wt.-%) self-assembled into gel fibers, often of micrometer-scale lengths and nanometer-scale diameters.[7] Thus, the gel architecture strongly reflects the molecular shape of the unit components. The aggregation of such low molecular mass organic gelators (LMOGs) is driven by multiple, weak interactions such as dipole–dipole, van der Waals (long alkyl, aromatic groups, etc.), and hydrogen-bonding interactions (amide, urea, hydroxy, etc.).[1] It is widely accepted that the entanglement of such microheterogeneous fibrillar phases gives complex nanoscale three-dimensional networks through new "junction zones", which immobilizes large volume of organic liquid in the network compartments primarily by surface tension and capillary forces.[8] Organogels can increase the viscosity of the medium by a factor of 10^{10}, trap up to 10^5 liquid molecules per gelator, and can be sensitive to a variety of stimuli.[9] Generally, the gelled state can be seen as a metastable state between liquid and solid. Thus, this fascinating class of materials are currently considered as leaders of a new field in supramolecular chemistry, a so-called "smart" or "intelligent" approach.[10] Because morphology of the fibrillar network influences the functional properties of these materials, the discovery of new LMOGs with atypical molecular architectures may provide new insight into the gel phenomenon process. There are many foreseeable applications of LMOGs, including waste solvent disposal and more seriously the disposal of chlorinated solvents, which are the most difficult and costly contamination problem for remediation.[11] These solvents are biodegradable in the absence of oxygen, but this biodegradation requires both a food source for the organism and the presence of chlorinated solvent biodegrading organisms. Among others techniques, the use of efficient LMOGs for chlorinated solvents may also help in the development of new strategies to fight the contamination processes by these solvents, which would allow for their easy removal upon gelation.

In this paper we report the discovery of the organogelation ability of C_2-symmetric Hunter's aromatic oligoamide **1**[12a,12b] and the observed chlorinated solvent selectivity (Figure 1). We also report the special conformational and functional features that make **1** an interesting molecular scaffold. As far as we are aware, this is the first report regarding the gelation properties of this compound and the

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study of their stable organogels. In addition, Huc and coworkers have reported oligoamide foldamers that are structurally related to **1** and their molecular recognition properties in the hybridization of helical strands to form stable double helices in solution.[12c]

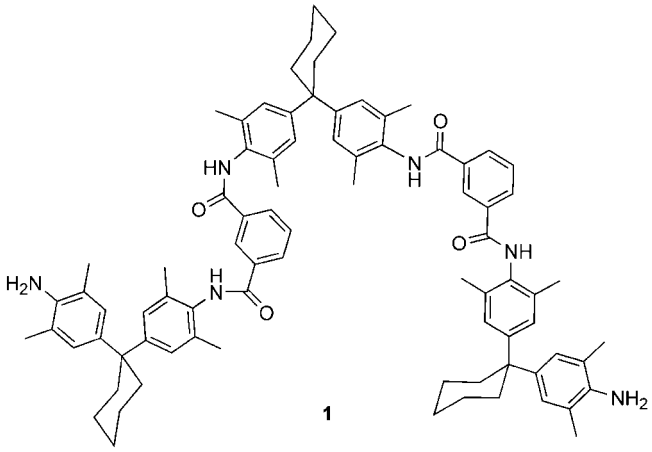


Figure 1. Hunter's oligoamide as a gelator for chlorinated organic solvents.

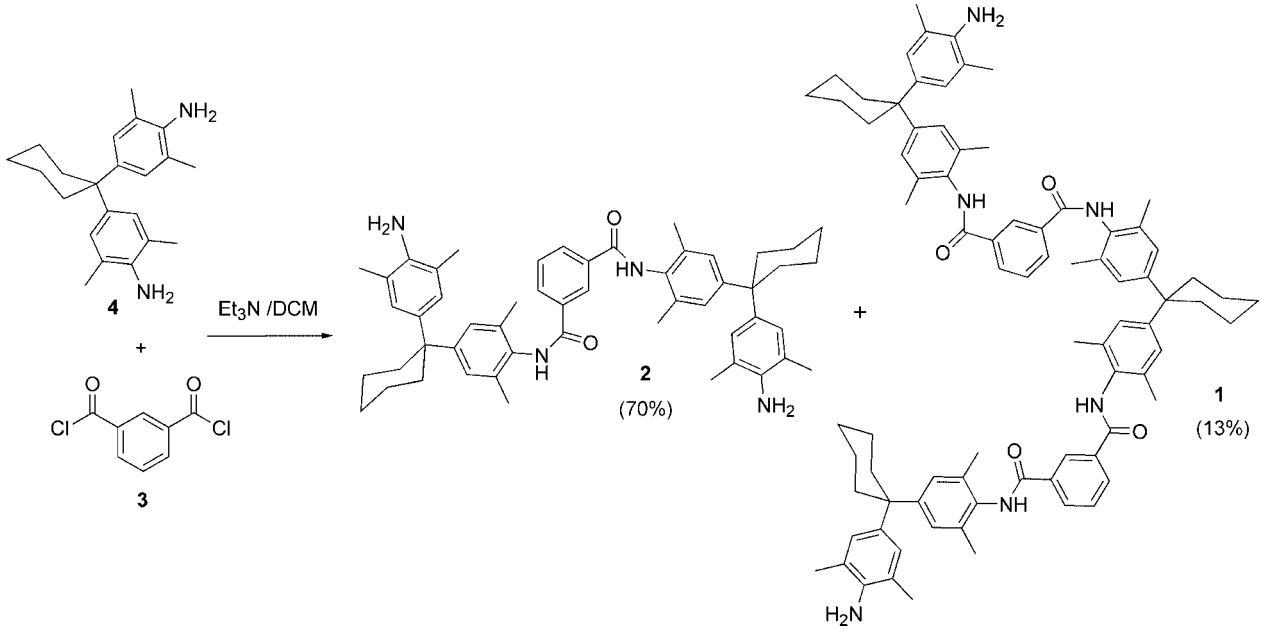
Results and Discussion

Compound **1** was first reported by Hunter and coworkers[12a] as a side product in the coupling reaction between isophthalic dichloride acid and the Hunter's spacer for the synthesis of lineal oligoamides (Scheme 1).

Although the molecular self-recognition properties of these molecules through a zipper motif seem to be driven by hydrogen bonding and edge-to-face aromatic interactions in solution, no clear proof of the dimeric complex formation of **1** could be provided.[12a] On our way to prepare and study functional molecules, we pleasingly observed that oligomer **1** showed organogelating properties with a variety of chlorinated organic solvents. At room temperature, compound **1** was found to be sparingly soluble in chlorinated solvents. Upon heating, the solid fully dissolved in solution and the formation of gel was observed upon cooling. Interestingly, no gelation was observed when shorter units of LMOG **1**, such as bisamide **2**, were used (Scheme 1). In addition to the amide sites, the availability of the free NH_2 groups is mandatory for the self-assembly process that leads to gelation. This was supported experimentally when the amines where acetylated, and despite the presence of amides, gelation did not occur. Others oligoamides have been reported to pose this ability; however, they are structurally very dissimilar to **1**.[12b]

Gel formation of oligoamide **1** was determined by a "stable to inversion of the test-tube" method and tested with 19 solvents (Table 1). Gels were not observed in protic (Table 1, Entries 7–9), aprotic polar (Table 1, Entries 10–14), or aprotic apolar solvents (Table 1, Entries 15–19). Nevertheless, complete gel formation occurred with several chlorinated solvents (Table 1, Entries 1–5), with the only exception of 1,1,2,2-tetrachloroethane (Table 1, Entry 6). Thus, gelation with the use of as little as 0.4 wt.-% of **1** in 1,2-dichloroethane was observed within 10 min. Other organogels were obtained with <3.9 wt.-% of **1**.

Chlorinated solvents were suitable organic solvents for the formation of robust, stable, and transparent yellowish-colored gels (Figure 2). All gels displayed good stability over time when stored in sealed glass vials as no change in either the appearance or the melting temperatures were detected after a month, although most of these gels turned opaque or semitransparent at higher concentrations of or-



Scheme 1. Coupling reaction between isophthalic dichloride acid and Hunter's spacer.

Table 1. Physical data for gels of **1** in various organic solvents.

Entry	Solvent	MGC[a] [wt.-%]	Phase[b]	T_{gel}[c] [°C]
1	1,2-dichloroethane	0.4	G	54
2	carbon tetrachloride	3.8	G	62
3	chlorobenzene	2.4	G	58
4	chloroform	1.8	G	45
5	dichloromethane	1.1	G	31
6	1,1,2,2-tetrachloro-ethane	–	S	–
7	2-propanol	–	I	–
8	ethanol	–	P	–
9	water	–	I	–
10	dimethylformamide	–	S	–
11	acetonitrile	–	P	–
12	ethyl acetate	–	S	–
13	acetone	–	S	–
14	tetrahydrofuran	–	S	–
15	*p*-xylene	–	S	–
16	1,4-dioxane	–	S	–
17	toluene	–	I	–
18	*n*-hexane	–	I	–
19	perfluorohexane	–	I	–

[a] MGC is the minimum gelator concentration at which gelation was observed to restrict the flow of the medium. [b] All gels are yellowish in color. Abbreviations: G = stable gel (1 month), S = soluble, I = insoluble, P = precipitate. [c] Determined by the dropping ball method.

ganogelator. The presence of overlapping fibers may promote the formation of microparticles and account for the opacity of the gels. Alternatively, the compacted fibrous character of the sheets in some gels could indicate some confined crystallinity. The interesting observed chlorinated solvent selectivity remains unexplained at this point.

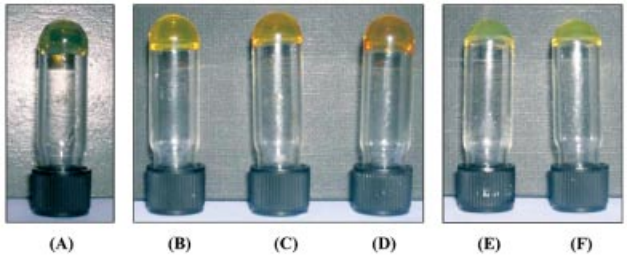


Figure 2. Digital photographs of the organogels prepared at different concentrations of LMOG **1**: (A) 0.4 wt.-% of **1** in 1,2-dichloroethane; (B) 1.0 wt.-% of **1** in 1,2-dichloroethane; (C) 1.5 wt.-% of **1** in 1,2-dichloroethane; (D) 2.0 wt.-% of **1** in 1,2-dichloroethane; (E) 2.5 wt.-% of **1** in dichloromethane; (F) 2.2 wt.-% of **1** in chloroform.

The thermal properties of the gels were examined by differential scanning calorimetry (DSC) and determination of their gel-melting temperatures (T_{gel}), where T_{gel} is defined as the organogel destroyed temperature and determined by the dropping ball method.[14] The values of T_{gel} for the gels increased with the concentration of LMOG **1** (Figure 3) and were in good agreement with a sharp transition peak in the DSC thermograms.[13] In addition, the gels made from **1** were found to be fully thermoreversible; thus, by raising the temperature above the T_{gel} point induced the gel-sol phase transition, and the solutions changed back to the organogels upon cooling at room temperature. Such a cycle can be repeated many times without affecting the gelation ability of **1**.

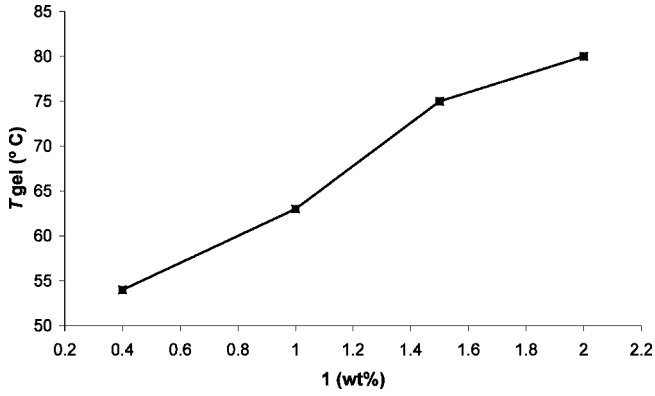


Figure 3. Gel melting temperatures as determined with the dropping ball method for gels in 1,2-dichloroethane at different concentrations of **1**.

To gain visual insight into the microscopic morphology of the gels and the aggregation mode of this organogelator, we recorded transmission electron micrographs (TEM) of the gels (Figure 4).

In every case, compound **1** self-assembled into nanoscale fibrous structures with regular fiber diameters of ca. 80–110 nm. This assembly creates a closely packed three-dimensional network structure by entanglement of such nanofibers, which trap solvent molecules into its interstices. The 3D network consists of different polyhedral units fused to each other, which leads to a porous arrangement with average inner diameters of ca. 500–550 nm for the cavities. Interestingly, an enlargement of the pictures reveals that each of the walls of these cavities is constructed from well-grown and entangled nanofibers and forms a much denser network. The notable regular shape must arise from a strong anisotropic growth process, which indicates well-ordered molecular packing.

It is clear from the results of the electronic micrographs that a change in the solvent and/or the concentration has a considerable effect on the morphology of the fibers (Figure 4).[13] For instance, the denser intertwined fibrous structure of the gels in 1,2-dichloroethane with respect to the gels in dichloromethane seems to reflect the increased thermal stability and intermolecular cohesiveness of the former, as determined by the T_{gel} measurements (vide supra). In addition to hydrogen bonding and edge-to-face interactions, the special conformational arrangement of **1** may provide an unusual topology that surely plays a key role in both the self-assembling process and the morphology of the gels, which will be the focus of our upcoming studies.

In order to understand the precise roles of the CO- and NH- residues in **1** in the gelation process, FTIR studies were carried out[13] in which only slight differences between

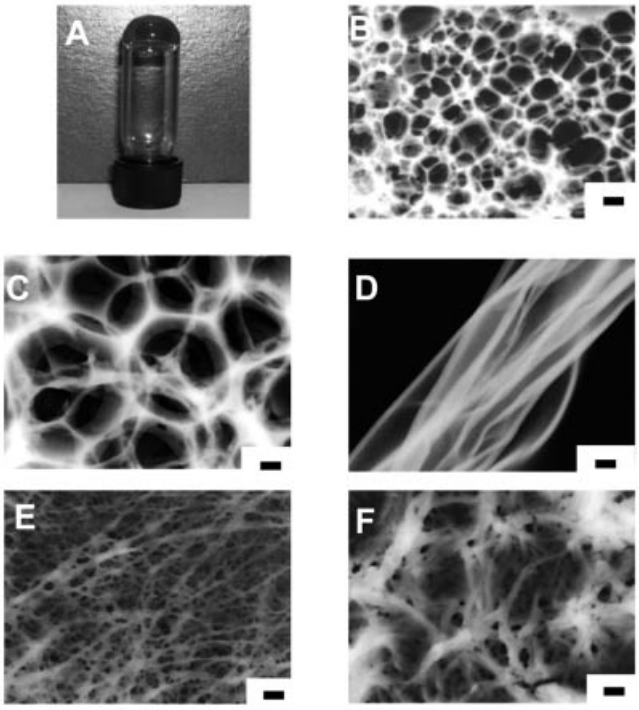


Figure 4. A: Digital photograph of the gel of **1** (0.63 wt.-%) in 1,2-dichloroethane. B and C: Negative TEM images of the gel formed from **1** (0.63 wt.-%) in 1,2-dichloroethane (scale bar 1 μm and 200 nm for B and C, respectively). D: Enlargement of the previous image (scale bar 200 nm). E: Negative TEM image of the gel formed from **1** (2.5 wt.-%) in CH_2Cl_2 (scale bar 200 nm). F: Negative TEM image of the gel formed from **1** (2.0 wt.-%) in 1,2-dichloroethane (scale bar 500 nm).

the solid and the gel phase could be detected. In the latter, stretching vibration bands for the NH moiety were observed at ca. $\tilde{\nu}$ = 3276 cm^{-1} in the IR spectrum, whereas the signals originating from the CO moieties all fell between $\tilde{\nu}$ = 1649 and 1509 cm^{-1}. The absorption bands assignable to amide-I and amide-II were located at ca. $\tilde{\nu}$ = 1649 cm^{-1} and ca. $\tilde{\nu}$ = 1509 cm^{-1}, respectively. These results indicate that the gelator molecules undergo intermolecular hydrogen bonding through the amide groups in the nanofibers as well, which is one of the driving forces necessary to promote the efficient organization of **1** into aggregates and fibers. Thus, although chlorinated solvents promote perpetuation of the superstructure, solvents capable of hydrogen bonding *suppress* gelation in this system by disallowing the self-assembly process.

Even though we do not have conclusive data regarding the gelation mechanism of oligoamide **1**, the results described in this paper point out the general significance of gelator–solvent interactions[15] in the gelation phenomenon. In the zipper dimerization model already proposed by Hunter and coworkers,[12a] hydrogen bonding and edge-to-face aromatic interactions are the main driving forces for aggregate unit formation. Nonetheless, unambiguous proof of such a zipper motif dimerization has not been obtained so far, and this will direct our future work.

Conclusions

In conclusion, we have reported for the first time the gelation ability of oligoamide **1**, and we have studied the physical properties of their stable organogels by using the various data acquired with FTIR, TEM images, and DSC. With the unexpected finding that the gelation ability of **1** is efficiently controlled by specific molecular recognition, studies are underway in our laboratories to gain additional information on the assembled structure of **1** by X-ray diffraction measurements, and the results will be reported in due course. In addition, the rational design and solid-phase synthesis of new LMOGs based on this polyamide core to be used for understanding the observed solvent-selectivity and for fine-tuning the range of solvents to be gelled with precise control of the morphology is also under investigation.

Experimental Section

General Remarks: ^1H and ^{13}C NMR spectra were obtained with a Bruker Advance400 instrument. IR spectra were obtained with a Bruker IFS 66 instrument with ATR accessories or with a Bruker IFS 28/55 instrument by using KBr pellets at room temperature. Melting point was measured with a Büchi Melting Point B-540 apparatus and is uncorrected. Chromatographic purifications were conducted by column chromatography with the use of 0.063–0.2 mm silica gel obtained from Fluka or by chromatotron plates coated with gypsum-containing silica gel PF_{254} from Merck. TLC analysis was facilitated by the use of UV light (254 nm) with fluorescent-indicating plates (silica gel on aluminum, Sigma). Solvents used were dried by standard distillation procedures[16] or were of p.a. grade and purchased from Aldrich. Commercially available reagents were used without further purification. All solvents and reagents were ACS reagent grade or better and were used as received or purified in an appropriate manner.

Synthesis of N^1,$N^{1'}$-[4,4′-(cyclohexane-1,1-diyl)bis(2,6-dimethyl-4,1-phenylene)]bis(N^3-{4-[1-(4-amino-3,5-dimethylphenyl)cyclohexyl]-2,6-dimethylphenyl}isophthalamide) (1): The synthesis of LMOG **1** was carried out by the reported procedure.[12a] The purity of **1** was verified by NMR spectroscopy, thin-layer chromatography, elemental analyses, mass spectroscopy, and melting point (m.p. 242–243 °C, ref.[12a] 243 °C). All the experimental data of the isolated products were coincident with those previously reported.[12a] Oligomer **1** was isolated in 13% yield upon purification by radial chromatography.

Gelation Test: A weighted amount of LMOG **1** and the appropriate solvent (1 mL) were placed in a screw-capped glass vial (5 cm length and 1 cm diameter) and heated with a heat-gun until the solid was completely dissolved (isotropic solution). The resulting clear solution was cooled to room temperature and left for 1 h, after which time the state of the solution was monitored visually by turning the test vial upside down. The material was classified as "gel" if it did not exhibit gravitational flow.

Estimation of Gel-to-Sol Phase Transition Temperature (T_{gel}): Gelation temperatures were determined by the dropping ball method.[14] A glass ball (275 mg) was placed on top of the gel and the tube sealed. The sample was placed in a stirred thermostatted oil bath. The temperature was raised at a rate of ca. 2 °C min^{-1} while the position of the glass ball was observed and the temperature simul-

taneously monitored with the aid of thermocouple in one of the vials. Here, the melting point of a particular sample (T_{gel}) was defined as the temperature at which the glass ball begins to fall down. The experimental error of T_{gel} was less than 1 °C.

Transmission Electron Microscopy (TEM): The TEM images were obtained as follows: the polymeric gel suspension (0.3–0.5 μL) was allowed to adsorb for 3–5 min onto copper grids (300 mesh) coated with both formvar and silicon monoxide. A Teflon sheet was used to remove the excess solvent by slight contact with the sample (×2), which allowed the formation of a thinner film on the grid. The specimens were finally dried at low pressure ($>10^{-5}$ Torr) before taking the electronic pictures. The relatively large size of the polymer pieces made negative staining unnecessary for visualization. Samples were observed with a Jeol JEM 1010 transmission electron microscope operating at a voltage of 90 kV. In studying the specimens, we first searched for patches of the gel to be sure that the observed structures originate from the gel. Micrographs were taken from structures at the periphery of the gel patches because here the fibers are deposited in a layer thin enough to be observed by transmission electron microscopy.

Differential Scanning Calorimetry (DSC): A given amount of gel was placed in a preweighed pan, which was sealed and weighed on a six-decimal plate balance. Heating and cooling scans were measured with a Pyris Diamond DSC (Perkin–Elmer) instrument at a scan rate of 5 °C min^{-1}. After the measurements, the pan was weighed again to check for possible leakage.

FTIR Spectra of Gel Samples: IR spectra of gels were obtained by depositing the gel on a NaCl disk and recording the spectrum directly and operating at 8 cm^{-1} resolution with 40 scans. No correction was made for the solvent. Stretching vibration bands for the NH group were observed at ca. $\tilde{\nu}$ = 3276 cm^{-1}, and the amide group represents two IR bands, amide I in the ca. 1649 cm^{-1} region and amide II in the ca. 1509 cm^{-1} region. In addition to hydrogen bonding, for which the amide functions are crucial, dipolar and aromatic interactions may also play significant roles in promoting the efficient organization of **1** into aggregates and fibers.

Supporting Information (see also the footnote on the first page of this article): MALDI-TOF spectrum, DSC thermogram, FTIR spectra, and TEM pictures.

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