Pergamon

SCIENCE DIRECT®

Tetrahedron Letters 44 (2003) 3171–3174

TETRAHEDRON LETTERS

New bisamides gelators: relationship between chemical structure and fiber morphology

Rolf Schmidt, Fahuzi B. Adam, Marc Michel, Marc Schmutz, Gero Decher and Philippe J. Mésini*

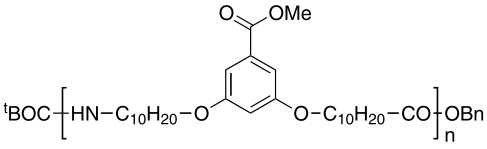
Chemistry of Associating Systems, Institut Charles Sadron, 6 rue Boussingault, 67083 Strasbourg Cedex, France

Received 12 February 2003; revised 17 February 2003; accepted 17 February 2003

Abstract—Different dialkoxybenzoic acid derivatives with identical alkyl chain lengths were synthesized and their properties as organogelators evaluated. Only the compounds bearing amide groups behave like gelators. Their gelation abilities and phase diagrams were described. A structural study was conducted by freeze-fracture electron microscopy and showed that the methyl ester formed platelet-like aggregates whereas the corresponding free acid formed thin fibers in the gel.

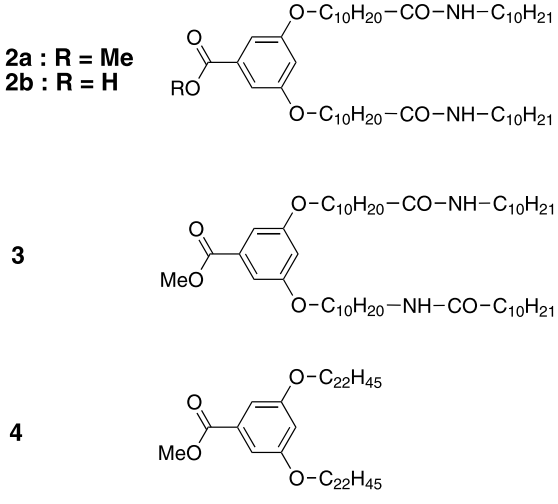
Organogelators[1] are a growing class of low molecular mass molecules that possess the ability to gel solvents at low concentrations (typically a few weight percent). The origin of this behavior is their ability to spontaneously self-assemble into fibrillar aggregate networks that entrap the solvent molecules. As a result, interesting viscoelastic properties can be observed such as a dramatic increase in viscosity (4 to 5 orders of magnitude with respect to the pure solvent), which often leads to the formation of self-supported gels. These materials are widely used as rheomodifying additives, for instance in lubricating greases[2] and gelled fuels.[3] New potential applications in pharmacology,[4] oil-spill recovery[5] or as mesoporous materials[6] are currently under investigation. It is often very hard to predict the gelation properties of a molecule from the chemical structure alone. Structure–activity relationship studies on this type of molecule are required in order to appropriately modify existing gelators or to prepare new ones.

We recently reported that the oligoamides $\mathbf{1_n}$ (Scheme 1) are organogelators of aromatic solvents such as toluene or xylene for $n \geq 3$.[7] Electron microscopy, along with small-angle scattering experiments enabled us to visualize and characterize the gels at a nanometric scale.[8] We prepared shorter analogs of these oligoamides in order to investigate the influence of the different structural elements on their gelation properties. Herein, we report the synthesis of the first analogs in this series (Scheme 2) and present their characteristic gelation behavior. A structural study was conducted by freeze-fracture electron microscopy.



$\mathbf{1_n}$

Scheme 1. Chemical structure of $\mathbf{1_n}$, organogelators for $n \geq 3$.

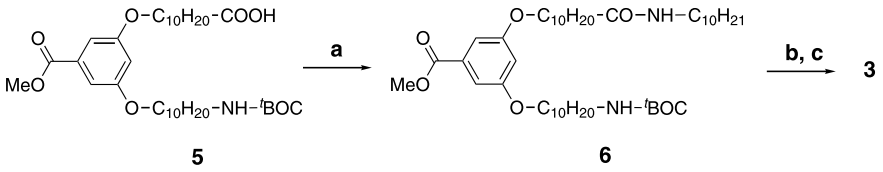


Scheme 2. Synthesized analogs.

Keywords: gels; organogelators; bisamides; electron microscopy.

* Corresponding author. Tel.: +33-(0)388-414-070; fax: +33-(0)388-414-099; e-mail: mesini@ics.u-strasbg.fr

0040-4039/03/$ - see front matter
doi:10.1016/S0040-4039(03)00456-8



Scheme 3. *Reagents and conditions*: (a) EDCI (3 equiv.), $C_{10}H_{21}NH_2$ (1 equiv.), HOBt (0.16 equiv.), NMP, 92%; (b) 4 M HCl in EtOAc; (c) $C_{10}H_{21}COOH$ (1 equiv.), EDCI (2 equiv.), 72%.

All the synthesized analogs contain the dialkoxybenzoic core structure from $\mathbf{1_n}$ and the length of the alkyl chains is identical in all cases. Compounds **2a**, **2b** and **3** possess two amide groups, like the trimer $\mathbf{1_3}$, which is the shortest gelator in the original series.[7] Compounds **2a** and **2b** are symmetrical with respect to the amide group, i.e. the amides are in a parallel orientation. In compound **3**, the orientation of the amides is antiparallel. As a control, we also studied **4**, which possesses no amide groups. Synthesis of the bisamide **2a** was achieved by bis-alkylation of 3,5-dihydroxybenzoic acid methyl ester with 11-bromo-*N*-decylundecanamide. The reaction was carried out under phase transfer catalysis conditions with excess K_2CO_3 and gave **2a**[9] in 58% yield. Compound **4** was prepared under the same conditions using 1-bromodocosane as alkylating agent.[10] Hydrolysis of **2a** (Scheme 2) by LiOH in MeOH gave **2b**.[11] Coupling of acid **5**[12] and decylamine with EDCI as a condensing agent provided amide **6** in good yield (92%) (Scheme 3). Treatment of **6** with a 4 M HCl solution in EtOAc led to the cleavage of the BOC protecting group. The resulting ammonium salt was not purified but immediately coupled with undecanoic acid in the presence of EDCI to provide the final amide **3**[13] (72%).

The gelling abilities of the synthesized molecules were tested with different solvents at a concentration of 3% by weight (Table 1). The samples were heated in sealed vials until dissolution of the solid was complete. The isotropic solutions were then cooled back to room temperature. Depending on the solvent and the substrate, different cases were observed upon cooling: a gel formed (G), the compound was soluble (S) or the compound crystallized (C). In some cases, the compounds were not soluble, even in boiling solvent (I). Compounds **2a**, **2b** and **3** were able to gel the same solvents as the parent gelator $\mathbf{1_3}$, i.e. benzene and toluene. Compound **4** showed no gelation properties under the same conditions. Thus, the presence of amide groups in the molecule is crucial for the gelation process. This result is not as obvious as it may seem as many organogelators without any polar groups or H-donor or acceptor groups at all have been described. This is especially true for the di-*n*-alkoxybenzenes described by Pozzo et al.,[14] that have a chemical structure very similar to **4** but with shorter alkyl chains.

The phase diagrams were established for different gelators in toluene (Fig. 1). We used the dropping ball technique[15] to measure the gel-to-sol transition temperatures. The minimal gel concentrations and the stability of the gels are comparable for all of the compounds studied. Only **3** displays higher gel concentrations and lower transition temperatures than the other gelators. This can partly be explained by the difference in melting points of the pure compounds (**2a**: 104°C, **3**: 90°C): according to the Schröder–van Laar relation,[16] the gel-to-sol transition temperature is related to the melting temperature of the pure gelator.

The internal gel structures were investigated by freeze-fracture electron microscopy (Fig. 2), according to the procedure described previously.[7] The gels obtained from **2a** and **3** (Figs. 2a and 2b) exhibit similar structures in the gel: platelet-like aggregates with varying width (150–180 nm) and length (up to several μm) throughout the sample. Slight structural differences can be observed between **2a** and **3**: inside the **2a** platelets, smaller fibrils can be distinguished (Fig. 2a, arrow). The structures from gels of **3** show no individual fibrils, but

Table 1. Gelation test for 3% by weight of **1**–**4** in various solvents

Solvent	$\mathbf{1_3}$–$\mathbf{1_4}$	2a	2b	3	4
$CHCl_3$	S	S	S	S	S
Hexane	I	I	I	I	I
MeOH	C	C	C	C	C
Benzene	G	G	G	G	S
Toluene	G	G	G	G	S
p-Xylene	G	G	G	G	S

S, soluble; C, recrystallizes; I, insoluble; G, gel (see text).

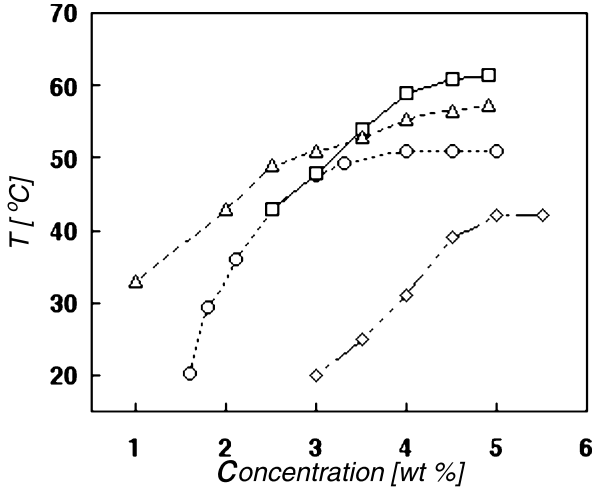


Figure 1. Gel-to-sol transition temperatures in toluene: ○, $\mathbf{1_3}$; □, **2a**; △, **2b**; ◇, **3**.

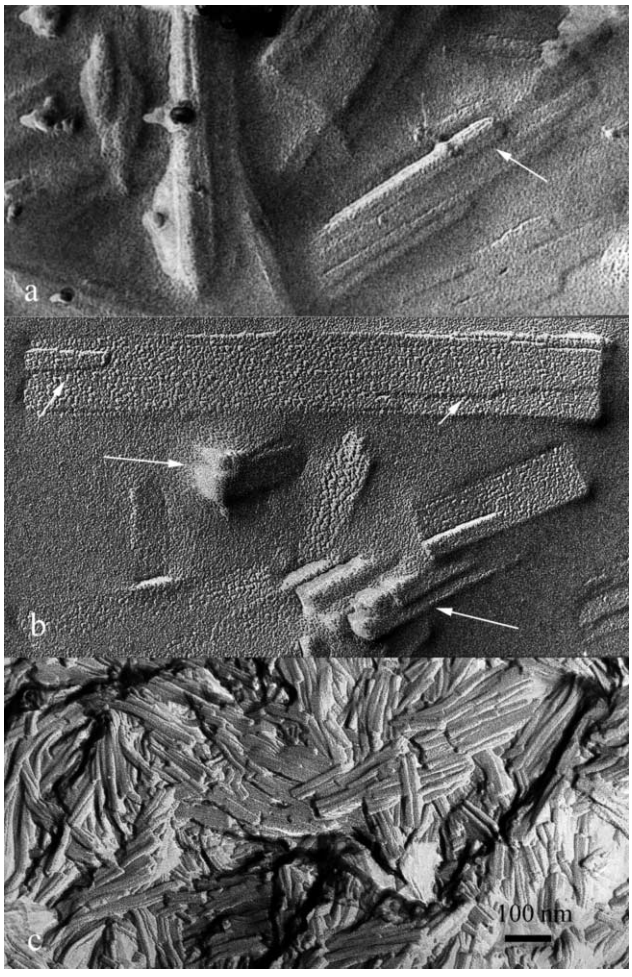


Figure 2. Freeze fracture of 3% by weight gels in toluene. (a) **2a**; large fibers made of thinner fibrils (arrow). (b) **3**; large rectangular structures. Short arrows: lamellar inner structure. Long arrows: fibers pointing out of the fracture plane. (c) **2b**; the observed fibers are 17 nm wide and several μm long.

have a lamellar internal organization parallel to the fracture plane, as pointed out by short arrows in Figure 2b. Furthermore, they diffract electron beams (data not shown), which clearly indicates their crystallinity, in fact they can be identified as nanomonocrystals. It is well known for many organogelators that the formation of fibrils in the gel is directly related to crystallization during gelation. This has been shown, for instance, by the identity of the WAXS spectra of the powder and the gels.[17] The parallel or antiparallel orientation of the amide groups might explain the different morphologies of **2a** and **3**, since it influences the packing of the molecules. This can be related to the strong odd–even effects observed for other amide-based gelators.[18]

The morphology of gels of compound **2b** stands in sharp contrast to the morphologies described above. Throughout the sample, fibers with constant width (17 nm) and variable length (several μm) were observed. The only difference between **2a** and **2b** is the functional group on the aromatic ring: **2a** is a methyl ester while **2b** is the corresponding free acid. This functional group plays a key role in the aggregation process: the presence of the acid group prevents the lateral packing of fibrils into larger objects as for **2a** and limits agreggation to one dimensional fibers. This is another example of the fact that a small change in the chemical structure can lead to drastically different internal gel structures.[1] While the parallel/antiparallel orientation of the amide groups in the alkyl chains leads to minor differences of the internal gel structure, we identified the functional group on the aromatic ring to be the most important factor that governs aggregation extent and directionality of the gel-constituting aggregates. The synthesis and evaluation of extended ester analogues is under investigation.

Acknowledgements

This work was supported by a MESR fellowship (R.S.). Dr. P. Schultz is deeply thanked for the use of the cryofracturing apparatus developed by Dr. J.-C. Homo at the IGBMC UMR 7104, Illkirch, France

References

1. (a) Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133–3159; (b) Van Esch, J. H.; Feringa, B. L. *Angew. Chem. Int. Ed.* **2000**, *39*, 2263–2266.
2. (a) Vold, M. J.; Vold, R. D. *J. Colloid Sci.* **1950**, *62*, 1–19; (b) Hotten, B. W.; Birdsall, D. H. *J. Colloid Sci.* **1952**, *7*, 284–294.
3. (a) Mysels, K. J. *Ind. Eng. Chem.* **1949**, *41*, 1435–1438; (b) Whitaker, G. C. *Kirk-Othmer Encycl. Chem. Technol., 2nd ed.* **1965**, *7*, 272–287.
4. (a) Murdan, S.; Gregoriadis, G.; Florence, A. T. *Eur. J. Pharm. Sci.* **1999**, *8*, 177–186; (b) Murdan, S.; Gregoriadis, G.; Florence, A. T. *Int. J. Pharm.* **1999**, *180*, 211–214.
5. Bhattacharya, S.; Krishnan Ghosh, Y. *J. Chem. Soc., Chem. Commun.* **2001**, 185–186.
6. (a) Jung, J. H.; Ono, Y.; Hanabusa, K.; Shinkai, S. *J. Am. Chem. Soc.* **2000**, *122*, 5008–5009; (b) Jung, J. H.; Amaike, M.; Nakashima, K.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1938–1943; (c) Kobayashi, S.; Hanabusa, K.; Suzuki, M.; Kimura, M.; Shirai, H. *Chem. Lett.* **1999**, 1077–1078; (d) Kubo, W.; Murakoshi, K.; Kitamura, T.; Yoshida, S.; Haruki, M.; Hanabusa, K.; Shirai, H.; Wada, Y.; Yanagida, S. *J. Phys. Chem. B* **2001**, *105*, 12809–12815; (e) Ono, Y.; Nakashima, K.; Sano, M.; Kanekiyo, Y.; Inoue, K.; Hojo, J.; Shinkai, S. *J. Chem. Soc., Chem. Commun.* **1998**, 1477–1478; (f) Ono, Y.; Nakashima, K.; Sano, M.; Hojo, J.; Shinkai, S. *J. Mater. Chem.* **2001**, *11*, 2412–2419.
7. Schmidt, R.; Schmutz, M.; Michel, M.; Decher, G.; Mésini, P. *Langmuir* **2002**, *18*, 5668–5672.
8. Schmidt, R.; Schmutz, M.; Mathis, A.; Decher, G.; Rawiso, M.; Mésini, P. *Langmuir* **2002**, *18*, 7167–7173.
9. Mp 102–104°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.14 (m, 2H, C2-**H**, C6-**H**), 6.62 (t, 1H, $J=2.2$ Hz, C4-**H**), 5.48 (wide s, 2H, N**H**), 3.95 (t, 4H, $J=6.5$ Hz, ArOCH_2), 3.88 (s, 3H, $COOCH_3$), 3.22 (q, 4H, $J=6.5$

Hz, C**H**$_2$NHCO), 2.14 (t, 4H, $J=7.5$ Hz, C**H**$_2$CONH), 1.75 (p, 4H, $J=6.5$ Hz, ArOCH$_2$C**H**$_2$), 1.60 (p, 4H, $J=6.6$ Hz, C**H**$_2$CH$_2$CONH), 1.28 (m, 56H), 0.86 (t, 6H, $J=6.7$ Hz, C**H**$_3$); ^{13}C (50 MHz, $CDCl_3$): δ (ppm) 173.0, 167.0, 160.1, 131.8, 107.6, 106.6, 68.3, 52.1, 39.5, 36.9, 31.9, 29.3, 26.9, 22.6, 14.1; IR (KBr) ν_{max} 3312, 2919, 2851, 1708, 1636, 1536, 1469, 1434, 1357, 1302, 1239 cm^{-1}. HRMS (FAB+) 815.6978 (M−H+, calcd for $C_{50}H_{90}N_2O_6$: 815.6877).

10. Mp 84.5–86.5°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.16 (dd, 2H, $J=6$ Hz, $J=2$ Hz, C2-**H**, C6-**H**), 6.63 (t, 1H, $J=2$ Hz, C4-**H**), 3.95 (t, 4H, $J=6.3$ Hz, ArOC**H**$_2$), 3.90 (s, 3H, COOC**H**$_3$), 1.78 (m, 4H, ArOCH$_2$C**H**$_2$), 1.56–1.20 (m, 76 H), 0.86 (t, 6H, $J=6.4$ Hz, C**H**$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 171.1, 160.2, 130.8, 106.5, 68.3, 32.1, 29.6, 29.5, 29.3, 27.1, 15.3; IR (KBr) ν_{max} 2921, 2925, 2853, 1725, 1602, 1472, 1444, 1322, 1237, 1167 cm^{-1}. Anal. calcd for $C_{52}H_{96}O_4$: C, 79.53; H, 12.32; O, 8.15. Found: C, 79.37; H, 12.19; O, 8.13.
11. Mp 92–93°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.20 (dd, 2H, $J=6$ Hz, $J=2$ Hz, C2-**H**, C6-**H**), 6.60 (t, 1H, $J=2.2$ Hz, C4-**H**), 5.62 (s large, 2H, N**H**), 3.93 (t, 4H, $J=6.5$ Hz, ArOC**H**$_2$), 3.24 (q, 4H, $J=6.4$ Hz, C**H**$_2$NHCO), 2.19 (t, 4H, $J=7.3$ Hz, C**H**$_2$CONH), 1.75–1.24 (m, 64 H), 0.86 (t, 6H, $J=6.7$ Hz, C**H**$_3$); ^{13}C (50 MHz, $CDCl_3$): δ (ppm) 173.5, 170.1, 159.9, 132.4, 109.4, 106.3, 70.9, 43.1, 36.7, 31.8, 29.2, 26.8, 25.8, 23.1, 15.2; IR (KBr) ν_{max} 3308, 2920, 2850, 1699, 1639, 1559, 1467, 1305 cm^{-1}. Anal. calcd for $C_{49}H_{88}N_2O_6$: C, 73.45; H, 11.07; N, 3.50. Found: C, 73.38; H, 11.48; N, 3.40.
12. (a) Schmidt, R.; Decher, G.; Mesini, P. *Tetrahedron Lett*. **1999**, *40*, 1677–1680; (b) Schmidt, R.; Decher, G.; Muller, P.; Mesini, P. *Polym. Mater. Sci. Eng*. **1999**, *80*, 93–94.
13. Mp 83–84°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.14–7.13 (m, 2H, C2-**H**, C6-**H**), 6.61 (t, 1H, $J=2.4$ Hz, C4-**H**), 5.56 (s large, 2H, N**H**), 3.94 (t, 4H, $J=6.5$ Hz, ArOC**H**$_2$), 3.88 (s, 3H, COOC**H**$_3$), 3.21 (q, 4H, $J=6.6$ Hz, C**H**$_2$NHCO), 2.13 (t, 4H, $J=7.6$ Hz, C**H**$_2$CONH), 1.75 (p, 4H, $J=6.7$ Hz, ArOCH$_2$C**H**$_2$), 1.60 (p, 4H, $J=6.9$ Hz, C**H**$_2$CH$_2$CONH), 1.43 (p, 4H, $J=6.7$ Hz, C**H**$_2$CH$_2$NHCO), 1.28–1.24 (m, 52H), 0.86 (t, 6H, $J=6.4$ Hz, C**H**$_3$); ^{13}C NMR (50 MHz, $CDCl_3$): δ (ppm) 173.0, 167.0, 160.1, 131.8, 107.6, 106.5, 68.3, 52.1, 39.5, 36.9, 31.9, 29.7, 29.5, 29.3, 26.9, 25.9, 25.8, 22.6, 14.1; IR (KBr) ν_{max} 3305, 2925, 2855, 1730, 1639, 1546, 1458, 1326, 1239, 1168, 1121 cm^{-1}; Mass (FAB+) calcd for $C_{50}H_{90}N_2O_6$: 814.7; found: m/z 815.7 (MH$^+$). Anal. calcd for $C_{50}H_{90}N_2O_6$: C, 73.66; H, 11.13; N, 3.44. Found: C, 73.45; H, 10.92; N, 3.40.
14. Clavier, G.; Mistry, M.; Fages, F.; Pozzo, J. L. *Tetrahedron Lett*. **1999**, *40*, 9021–9024.
15. Tan, H.; Moet, A.; Hiltner, A.; Baer, E. *Macromolecules* **1983**, *16*, 28–34.
16. (a) Atkins, P. W. *Physical Chemistry*; 6th ed.; Oxford University Press: Oxford, 1998; (b) Moore, W. J. *Physical Chemistry*; 5th ed.; Oxford University Press: Oxford, 1972.
17. (a) Terech, P.; Rodriguez, V.; Barnes, J. D.; McKenna, G. B. *Langmuir* **1994**, *10*, 3406–3418; (b) Garner, C. H.; Terech, P.; Allegraud, J. J.; Mistrot, B.; Nguyen, P.; deGeyer, A.; Rivera, D. *J. Chem. Soc., Faraday Trans*. **1998**, *94*, 2173–2179; (c) Abdallah, D. J.; Sirchio, S. A.; Weiss, R. G. *Langmuir* **2000**, *16*, 7558–7561.
18. (a) Jung, J. H.; Ono, Y.; Shinkai, S. *Chem. Lett*. **2000**, 636–637; (b) Jung, J. H.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **2000**, 2393–2398; (c) Schneider, J.; Messerschmidt, C.; Schulz, A.; Gnade, M.; Schade, B.; Luger, P.; Bombicz, P.; Hubert, V.; Fuhrhop, J.-H. *Langmuir* **2000**, *16*, 8575–8584; (d) Tomioka, K.; Sumiyoshi, T.; Narui, S.; Nagaoka, Y.; Iida, A.; Miwa, Y.; Taga, T.; Nakano, M.; Handa, T. *J. Am. Chem. Soc*. **2001**, *123*, 11817–11818.