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Chirality-directed organogel formation

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New low molecular mass enantiopure organogelators (1*R*,4*R*)-**1**, (*S*)-**2**, (*R*)-**3** and (*R*)-**4** were found; racemates (*R*,*S*)-**3** and (*R*,*S*)-**4** have only a moderate gelating power, whereas (*R*,*S*)-**1** and (*R*,*S*)-**2** do not show gelating properties at all.

Van't Hoff[1] was captivated by an interesting experiment of Wallerant:[2(a)] during the cooling of the melts of malonic acid diamide in the presence of (+) or (–)-tartaric acids, helical crystallization with the opposite senses of helicity was observed, whereas the racemic acid did not produce such an effect.[2(b)] This observation was further developed in the whole science of a unique state of matter, a cholesteric mesophase. The chirality-directed formation of a cholesteric mesophase from an achiral nematic mesophase is a sensitive test for conglomerate formation.[3]

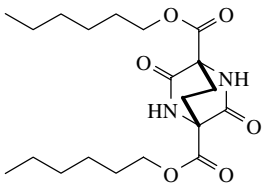
Another mesophase, namely, gels formed by low molecular mass organic compounds, have attracted a lot of attention recently due to their ubiquity and important applications,[4] such as the binding of oil in oil/water mixtures,[4(b)] the use as biocompatible soft materials,[4(c)] pH-sensitive fluorescent probes,[4(d)] and other interesting properties, more often associated with covalent polymeric assemblies.[5] Note that such gels also show the effects of chiral recognition: they often consist of helically twisted fibers with the sence of helicity determined by the relative configuration of a gelator, whereas racemates form regular crystals.[6] These facts may be explained by a higher kinetic stability of an enantiomeric mesophase due to difficulties of a rearrangement to enantiomeric crystals.[6]

Here we describe new chiral amidic organogelators: diketopiperazine (1*R*,4*R*)-(–)-**1a**[7] and compounds (*S*)-(–)-**2a**, (*R*)-(+)-**3a**, (±)-**3b**, (*R*)-(+)-**4a** in the series of amidoalcohols **2**–**13** (Figure 1,† Table 1). These systems are of interest as promising chiral stimuli-responsive gels.[8]

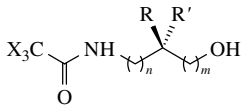
Compounds **1a**–**4a** and **4b** reversibly gelate organic solvents (Table 1) on heating at reflux to dissolution and cooling to room temperature at minimum concentrations of 0.003–0.5 mol dm^{-3}. Figure 2 shows the formation of linear micrometre-sized aggregates of organogelators **1a** and **2a** visualised by the atomic force microscopy (AFM) of their xerogels (dried gels)† obtained from methylcyclopentane or cyclohexane. The visual appearance of a typical gel of compound (*R*)-(+)-**3a** is shown in Figure 3.

Note that racemates **1b** and **2b**, as well as compounds **5**–**10**, do not form stable gels in a variety of organic solvents. Compounds **2b** and **10**, on cooling their solutions in light petroleum (bp 70–100 °C), give a mixture of a solid phase and a gel at 50–55 °C; however, the gel disappears at 20 °C. The behaviour of racemates **3b** and **4b** is different: they also have a moderate gelating ability.

Under the hypothesis of enantioselective precipitation, we attempted to resolve the enantiomers of **3b** to form an optically active gel. However, unsuccessfully: in a solution of **3b** (1.2 g) in cyclohexane (240 ml) at 35 °C, the seed of **3a** (20 mg) in cyclohexane (1 ml) was added. The mixture was kept at 20 °C for 16 h. The gel precipitate was separated and evaporated under a reduced pressure with the volume of the solvent in the cooling trap equal to 34 ml. For 0.337 g of dry residue $[\alpha]_D$ +1.06 (*c* 6.74, MeOH). The mother liquor was evaporated, and the residue was identified as pure racemate **3b**.



(1*R*,4*R*)-(–)-**1a**[a]



	R	R′	X	*n*	*m*
(*S*)-(–)-**2a**[a]	Me	H	F	0	1
(*R*)-(+)-**3a**[a]	H	Et	F	0	1
(*R*)-(+)-**4a**[a]	H	Pr^i	F	0	1
(*R*)-(+)-**5a**	H	Et	H	0	1
(*S*)-(–)-**6a**	H	CO_2Me	F	0	1
(*R*)-(–)-**7a**[a]	Me	H	F	1	0
8	H	H	F	1	0
9	H	H	F	2	0
10	Me	Me	F	0	1
11	CH_2OH	CH_2OH	F	0	1
12	CH_2OH	Me	F	0	1
13	CH_2OH	Et	F	0	1

[a]Racemates: (±)-**1b**, (±)-**2b**, (±)-**3b**, (±)-**4b**, (±)-**7b**.

Figure 1 Compounds studied as possible gelators.

Table 1 Gelating power of compounds **1**–**4**: (+) gel, (±) unstable gel, (–) no gel, (n.d.) no data. Numbers indicate the minimum concentration for the gelation, in 10^{-3} mol dm^{-3}.

Compound	Light petroleum	Cyclohexane	C_6H_6	C_6F_6	2,3,4-Trimethylpentane	$CHCl_3$	Et_2O	CCl_4
1a[a]	–	3	–	n.d.	n.d.	–	n.d.	n.d.
2a[a]	6	3	18	18	18	100	–	12
3a[b]	3	3	30	12	6	–	100	12
3b	±(120)	30	±(30)	±(30)	30	–	–	60
4a	±(30)	10	15	50	25	>200	–	50
4b	±(50)	–	–	–	–	–	–	100

[a]**1b** and **2b** do not form gels. [b]Forms a gel at room temperature in heptane–ethyl acetate, 7:1(v/v); at –18 °C, the gel is destroyed.

Thus, we found that optically pure low molecular mass enantiopure amidoalcohols are organogelators, whereas the corresponding racemates are not, either not forming gels, or forming unstable gels in the narrow range of organic liquids.

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† **1a** and **1b** were described previously.[7]

(*S*)-(–)-**2a** was obtained by the reaction of (*S*)-(–)-alaninol with CF_3CO_2Et in MeCN, yield 100%, mp 80 °C (MeCN) [lit.,[10] mp 80–81 °C (C_6H_6)], $[\alpha]_D^{20}$ –14.1 (*c* 0.7, MeOH), [lit.,[10] $[\alpha]_D^{20}$ –15.3 (*c* 4.0, EtOH)]. ^{1}H NMR ($CDCl_3$) δ: 1.25 (d, 3H, Me, ^3J 6.8 Hz), 3.67 (m, 2H, CH_2, AB-part of ABX-spectrum, $\Delta\nu$ 56.0 Hz, $^2J_{ab}$ –11.2 Hz, $^3J_{ax}$ 6.8 Hz, $^3J_{bx}$ 5.2 Hz), 4.11 (qdd, 1H, HC, $^3J_{HCMe} = {}^3J_{HCCH_a}$ = 6.8 Hz, $^3J_{HCCH_b}$ 5.2 Hz), 6.92 (br. s, 1H, NH).

(±)-**2b**: yield 100%, mp 48–50 °C.

(*R*)-(+)-**3a**: yield 100%, mp 74–77 °C, $[\alpha]_D^{20}$ +14.8 (*c* 3.6, MeOH). ^{1}H NMR (C_6D_6) δ: 0.63 (t, 3H, Me, ^3J 7.5 Hz), 1.13 (m, CH_2Me), 1.20 (br. s, 1H, OH), 2.97 (m, 2H, CH_2O, AB-part of ABX-spectrum, $\Delta\nu$ 31.7 Hz, $^2J_{ab}$ –10.8 Hz, $^3J_{ax}$ 4.5 Hz, $^3J_{bx}$ 3.4 Hz), 3.58 (m, 1H, CH), 5.42 (br. s, 1H, NH).

(±)-**3b**: yield 100%, mp 59–61 °C.

(*R*)-(+)-**4a**: yield 100%, mp 85–86 °C, $[\alpha]_D^{20}$ +7.01 (*c* 13.5, MeOH). ^{1}H NMR ($CDCl_3$) δ: 0.96 (d, 3H, A-Me, ^3J 6.8 Hz), 1.00 (d, 3H, B-Me, ^3J 6.8 Hz), 1.96 (d hept, 1H, CH, ^3J 6.8 Hz), 3.70–3.85 (m, 3H, $HCCH_2$), 6.62 (br. s, 1H, NH).

(±)-**4b**: yield 100%, mp 64–65 °C.

(*R*)-(+)-**5** was obtained from (*R*)-(+)-2-aminobutan-1-ol and AcOMe in MeOH, yield 55%, liquid, $[\alpha]_D^{20}$ +9.43 (*c* 1.4, MeOH). ^{1}H NMR ($CDCl_3$) δ: 0.94 (t, 3H, *Me*CH_2, ^3J 7.5 Hz), 1.54 (m, 2H, C*H*$_2$Me), 2.00 (s, 3H, MeCO), 2.36 (br. s, 1H, OH), 3.60 (m, 2H, CH_2O, AB-part of ABX-spectrum, $\Delta\nu$ 31.7 Hz, $^2J_{ab}$ –11.1 Hz, $^3J_{ax}$ 5.5 Hz, $^3J_{bx}$ 3.7 Hz), 3.83 (m, 1H, CH), 6.00 (br. s, 1H, NH).

(*S*)-(–)-**6** was obtained from (*S*)-(–)-serine methyl ester, yield 100%, oily liquid, $[\alpha]_D^{20}$ –27.2 (*c* 4.4, MeOH). ^{1}H NMR ($CDCl_3$) δ: 3.2 (br. s, 1H, OH), 3.80 (s, 3H, Me), 4.00 (m, 2H, CH_2O, AB-part of ABX-spectrum, $\Delta\nu$ 33.0 Hz, $^2J_{ab}$ –11.5 Hz, $^3J_{ax}$ 3.2 Hz, $^3J_{bx}$ 3.4 Hz), 4.66 (m, 1H, CH), 7.60 (br. s, 1H, NH).

(*R*)-(–)-**7a** was obtained by the reaction of (*R*)-(–)-1-aminopropan-2-ol with CF_3CO_2Et, yield 100%, mp 33–35 °C, $[\alpha]_D^{20}$ –25.7 (*c* 7.2, MeOH). ^{1}H NMR ($CDCl_3$) δ: 1.07 (d, 3H, Me, ^3J 6.2 Hz), 3.36 (m, 2H, CH_2N, AB-part of ABX-spectrum, $\Delta\nu$ 154.8 Hz, $^2J_{ab}$ –13.8 Hz, $^3J_{ax}$ 6.6 Hz, $^3J_{bx}$ 3.3 Hz), 3.98 (m, 1H, CH), 7.11 (br. s, 1H, NH).

(±)-**7b** was obtained analogously, mp 60–62 °C ($CHCl_3$).

8 was described previously without characteristics,[11] obtained by the reaction of 2-aminoethanol with CF_3CO_2Et in MeCN, yield 100%, mp 33–35 °C (sealed capillary). ^{1}H NMR ($CDCl_3$) δ: 1.55 (br. s, 1H, OH), 3.55 (dt, 2H, CH_2N, $^3J_{HCNH} = {}^3J_{HCCH}$ = 5.0 Hz), 3.82 (t, 2H, CH_2O, ^3J 5.0 Hz), 6.53 (br. s, 1H, NH).

9 was described previously,[10] obtained by the reaction of 3-aminopropanol with CF_3CO_2Et. ^{1}H NMR ($CDCl_3$) δ: 1.8 (quint., 2H, CCH_2C, ^3J 5.8 Hz), 3.51 (q, 2H, CH_2N, $^3J_{HCNH} = {}^3J_{HCCH}$ = 5.8 Hz), 3.78 (t, 2H, CH_2O, ^3J 5.8 Hz), 7.54 (br. s, 1H, NH).

10 was obtained by the reaction of 2-amino-2-methylpropan-1-ol with CF_3CO_2Et, yield 86%, mp 94–98 °C (MeCN). ^{1}H NMR ($CDCl_3$) δ: 1.40 (s, 6H, 2Me), 2.73 (br. s, 1H, OH), 3.65 (s, 2H, CH_2), 6.46 (br. s, 1H, NH).

11: yield 100%, mp 92–93 °C (MeCN). ^{1}H NMR ([$^2H_6$]acetone) δ: 3.85 (s, 6H, $3CH_2$), 4.53 (br. s, 3H, 3OH), 7.55 (br. s, 1H, NH).

12: yield 100%, mp 112–114 °C. ^{1}H NMR ([$^2H_6$]acetone) δ: 1.33 (s, 3H, Me), 3.74 (m, 4H, $2CH_2O$, AB spectrum, $\Delta\nu$ 19.0 Hz, $^2J_{ab}$ –11.1 Hz), 7.58 (br. s, 1H, NH).

13: yield 100%, mp 77–78 °C. ^{1}H NMR ([$^2H_6$]acetone) δ: 0.88 (t, 3H, Me, ^3J 7.60 Hz), 1.84 (q, 2H, C*H*$_2$Me, ^3J 7.60 Hz), 2.78 (br. s, 2H, 2OH), 3.73 (m, 4H, $2CH_2O$, AB spectrum, $\Delta\nu$ 43.2 Hz, $^2J_{ab}$ –10.8 Hz), 7.40 (br. s, 1H, NH).

AFM sample preparation. Hot solutions of the gelators were sandwiched between two glass plates (1×1 cm) by capillary forces and left to cool to room temperature, the solvents slowly evaporated at atmospheric pressure. The top cover was removed when the surface became opaque. AFM was done with a Smena microscope (ND MDT, Zelenograd) in a half-contact mode at a rate of 1.2 scan s^{-1}, cantelever NSG 11 (type B, radius 10 nm).

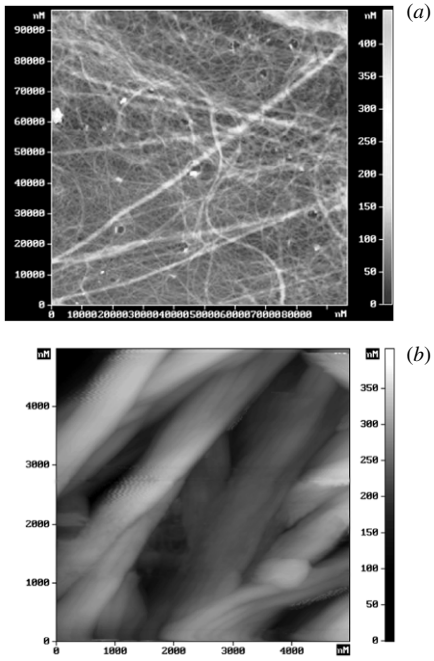

Figure 2 AFM micrographs of the xerogels of (*a*) **1a** from methylcyclopentane (90×90 μm) and (*b*) **3a** from cyclohexane (5×5 μm). Scale to the right depicts the depth of the scan (nm) by brightness of the picture.

Figure 3 Gel of (*R*)-(+)-**3a** in cyclohexane (a penicillin flask is turned upside down).

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