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Stereoisomeric bis(phenylglycinol)malonamide gelators: rare examples of gelling *meso*-compounds

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ABSTRACT

Gelation of malonamides was investigated for the first time. Bis(phenylglycinol)malonamide **1**, and methyl-, dimethyl-, ethyl-, diethyl- and isopropylmalonamides **2**, **3**, **4**, **5** and **6**, respectively, exhibited profoundly different gelling properties. Monoalkyl malonamides are efficient organogelators, and their gelling properties strongly depend on their stereochemistry. In contrast, symmetrically substituted dialkymalonamides, that is, (*R,R*)-dimethylmalonamide **3** and (*R,R*)-diethylmalonamide **5** as well as the unsubstituted **1** lack any gelation ability. Methyl derivative (*R,R*)-**2** is an excellent, and its ethyl analogue (*R,R*)-**4** a moderate gelator of toluene, *p*-xylene and tetralin while the isopropyl derivative (*R,R*)-**6** shows only very weak gelation of tetralin and some more polar solvents. *Meso* diastereoisomers (*R,r,S*)-**2** and (*R,s,S*)-**2**, as well as (*R,r,S*)-**4** and (*R,s,S*)-**4**), each possessing a pseudoasymmetric centre represent very rare examples of gelling *meso*-compounds. The racemate **4** (*rac*-**4**) showed more efficient gelation of some solvents than the pure enantiomer (*R,R*)-**4**, while *rac*-**2** failed to gel any of the solvents which were efficiently gelled by (*R,R*)-**2**.

Gelation of liquids by low molecular weight organic gelators represents a highly complex phenomenon comprising many specific non-covalent interactions between gelator molecules and specific solvent effects. Despite considerable recent progress in this field, the phenomenon is still not entirely understood; the reliable prediction of gelation properties considering molecular structure and stereochemistry of a candidate molecule is difficult and even more so, prediction of the solvent that can be gelated. It is generally accepted that well-defined directional attractive interactions, such as hydrogen bonding, aromatic π–π, lipophilic or ionic interactions, are necessary for self-assembly of gelator molecules into fibrous aggregates which then entangle into a 3D gel network.[1] The influence of gelator stereochemistry on gelation properties is well documented; in the majority of cases an enantiomerically pure compound is a better gelator than the racemate although exceptions are reported.[2–5] Among the rather diverse families of chiral gelators, no example could be found where the achiral *meso*-diastereomer was also a gelator. Whenever the *meso*-compounds are tested for gelation they invariably showed lack of any gelation due to a strong tendency for crystallization.[6] To the best of our knowledge, the only exception is the recent report on *meso*-*N*-(Boc-L-valinyl)-*N*-(Boc-D-valinyl)diaminoethane, which showed only very weak gelation of corn oil and decanol.[7]

We have shown that bis(amino acid) or bis(amino alcohol) oxalamides are efficient and versatile gelators of various organic solvents and water (Chart 1).[8] The best gelators within the two families were homochiral oxalamides, while racemic derivatives were less efficient except racemic bis(leucinol) oxalamide which gelled certain solvents much better than the (*R,R*)-enantiomer.[5] As a rule, the *meso*-oxalamides of both families lacked any gelation ability. In contrast to oxalamides, gelation by bis(amino acid)- or bis(amino alcohol)-malonamides (Chart 1) has not been reported until now. A rare example of a supramolecular aggregate formed by malonamides is the formation of microcapsules by bis(phenylalanine)malonamide.[9] However, during the course of our research on metal complexes of methylene-bridged bis(oxazoline) ligands[10] we found that methylmalonamide (*R,R*)-**2**[11] efficiently gelled dichloromethane. This observation prompted us to investigate more closely the gelling properties of (*R,R*)-**2** and its analogs, that is, malonamide **1**, dimethylmalonamide **3**, ethylmalonamide **4**, diethylmalonamide **5** and isopropylmalonamide **6** (Scheme 1).[12]

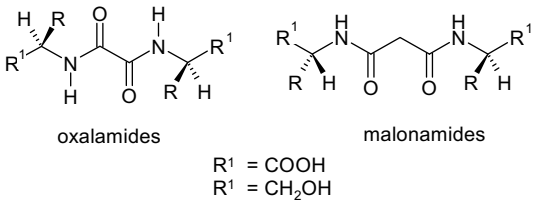

Chart 1.

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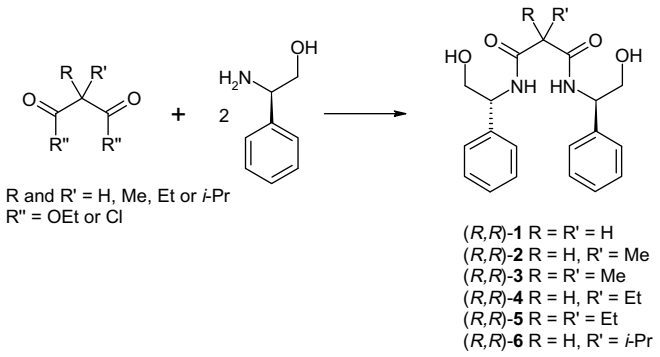


Scheme 1.

All of these compounds were prepared starting from (*R*)-phenylglycinol and thus have (*R,R*)-configuration.

The alkylmalonamides **2**, **4** and **6** are particularly interesting from a stereochemical point of view. When the configurations of the two amino alcohol stereogenic centres are opposite, that is, (*R,S*)- or (*S,R*)-, the α-carbon atom of the malonamide fragment bearing the hydrogen and alkyl substituent becomes a pseudoasymmetric centre. Thus, for **2**, **4** and **6** the enantiomeric, (*R,R*)- and (*S,S*)-isomers, the racemic form and two diastereomeric *meso* forms, (*R,r,S*)- and (*R,s,S*)- each possessing a pseudoasymmetric centre (Chart 2) could be prepared and their gelling properties tested.

In this work, we report on the gelling properties and influence of stereochemistry on the gelation exhibited by novel gelators of the malonamide type and present evidence that a special type of *meso* gelator, (*R,r,S*)-**2** and (*R,s,S*)-**2** possessing pseudoasymmetric centres are able to gel tetralin efficiently.

The methylmalonamide derivatives were prepared from (*R*)-phenylglycinol, (*S*)-phenylglycinol or (*R,S*)-phenylglycinol, giving (*R,R*)-**2**, (*S,S*)-**2**, *rac*-**2** and the corresponding *meso* diastereoisomers (*R,r,S*)-**2** and (*R,s,S*)-**2** (Scheme 1 and Chart 2).[12] Diethyl methylmalonate possessing a prochiral centre, on reaction with the *rac*-phenylglycinol gave a product mixture consisting of the racemic pair (*S,S* and *R,R*), and two *meso* diastereoisomers: (*R,r,S*)-**4** and (*R,s,S*)-**4** as determined by X-ray crystal analysis of separated isomers (a full report on the synthesis, separation and crystal structures will be published elsewhere). The racemate and both *meso* compounds were separated chromatographically. The chromatographic separation of ethylmalonamide isomers **4** required repetitive thin layer chromatography on silica using various solvent mixtures to obtain (*R,r,S*)-**4,** (*R,s,S*)-**4** and *rac*-**4** in pure form. The structures of (*R,r,S*)-**4** (^{1}H NMR, δ_{NH} 8.35 ppm, d, 2H, J = 8.4 Hz) and (*R,s,S*)-**4** (^{1}H NMR, δ_{NH} 8.25 ppm d, 2H, J = 7.9 Hz) were assigned on the basis of the ^{1}H NMR NH chemical shifts and coupling constant similarities with those found in the spectra of (*R,r,S*)-**2** (δ_{NH} 8.30 ppm d, 2H, J = 8.3 Hz) and (*R,s,S*)-**2** (δ_{NH} 8.26 ppm d, 2H, J = 7.8 Hz).[12] However, separation of the stereoisomers of isopropylmalonamides **6** failed.

The gelation behaviour of malonamide compounds **1–6** were tested against water, selected organic solvents and various solvent mixtures (Tables 1 and 2). The results showed striking differences and revealed that gelation depends strongly on the substitution at the α-C atom of the malonamide fragment. Unsubstituted **1** and symmetrically substituted **3** and **5** were unable to gel any of the solvents or solvent mixtures listed. Pure enantiomer (*R,R*)-**2** proved to be a successful gelator of some aromatic solvents, exhibiting excellent gelation of tetralin (53 mL) and moderate gelation of *p*-xylene and toluene (Table 1). Tetralin gel was translucent and stable for a long time at room temperature. Dichloromethane was weakly gelated and the initially formed unstable gel transformed into long crystalline fibres upon ageing at room temperature for 12–15 h. Ethylmalonamide (*R,R*)-**4** exhibited much less efficient gelation of toluene, *p*-xylene and particularly tetralin compared to methylmalonamide (*R,R*)-**2**. The isopropylmalonamide derivative (*R,R*)-**6** demonstrated inferior gelation ability towards the same aromatic solvents compared to monomethyl-(*R,R*)-**2** and monoethylmalonamide (*R,R*)-**4,** exhibiting only very weak gelation of more polar solvents (Table 1). A comparison of the gelation properties reveals that the gelation efficiency expressed as v_{max} towards toluene, *p*-xylene and tetralin depends on the size of the α-carbon substituent and decreases in the order (*R,R*)-**2** > (*R,R*)-**4** > (*R,R*)-**6**.

The racemate of methylmalonamide, *rac*-**2**, failed to gel any of the solvents that were gelled by (*R,R*)-**2** (Tables 1 and 2). In contrast, *rac*-**4** exhibited superior gelation of toluene and *p*-xylene

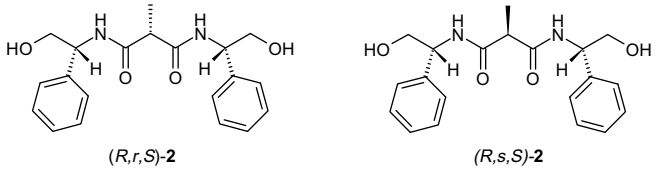


Chart 2.

Table 1
Gelation efficiency of (*R,R*)-methylmalonamide **2**, (*R,R*)-ethylmalonamide **4** and (*R,R*)-isopropylmalonamide **6** towards selected solvents and solvent mixtures expressed as the maximum volume (v_{max}/mL) of solvent gelled by 10 mg of gelator

Solvent	(*R,R*)-**2**	(*R,R*)-**4**	(*R,R*)-**6**
Water	Cryst.	Cryst.	Cryst.
DMSO/H_2O 2:3	Sol.	Cryst.	0.65
DMF/H_2O 1:2	Sol.	Sol.	0.6
EtOH	Sol.	Sol.	0.1
CH_3CN	Cryst.	Cryst.	0.3
THF	Cryst.	0.2[a]	0.2[a]
EtOAc	Cryst.	Cryst.	Cryst.
CH_2Cl_2	3.5	Cryst.	Ins.
Toluene	12	9.2	Ins.
p-Xylene	16	9.0	Cryst.
Decalin	Ins.	Cryst.	Cryst.
Tetralin	53	3.8	2.1

Cryst. = crystals, ins. = insoluble, sol. = solution.
[a] Gelation under ultrasound.

Table 2
Gelation efficiency of *rac*-**2** and *rac*-**4** and *meso* isomers (*R,r,S*)-**2**, (*R,s,S*)-**2** and (*R,r,S*)-**4** towards various solvents and solvent mixtures expressed as the maximum volume (v_{max}/mL) of solvent gelled by 10 mg of gelator

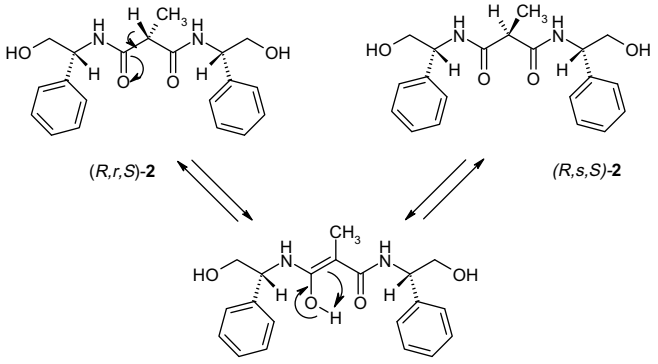
Solvent	*rac*-**2**	*rac*-**4**	(*R,r,S*)-**2**	(*R,s,S*)-**2**	(*R,r,S*)-**4**[a]
Water	Cryst.	Cryst.	Cryst.	Cryst.	Cryst.
DMSO/H_2O 2:3	Sol.	Cryst.	Cryst.	Cryst.	Sol.
DMF/H_2O 1:2	Sol.	Cryst.	Sol.	Cryst.	Sol.
EtOH	Sol.	Cryst.	Sol.	Cryst.	Cryst.
CH_3CN	Cryst.	Cryst.	Cryst.	Cryst.	Cryst.
THF	Cryst.	Sol.	Sol.	Cryst.	Sol.
EtOAc	Cryst.	Cryst.	Cryst.	Ins.	Cryst.
CH_2Cl_2	Cryst.	Cryst.	Ins.	Ins.	Cryst.
Toluene	Cryst.	31.9	Ins	Ins.	Cryst.
p-Xylene	Cryst.	34	Cryst.	Ins.	Cryst.
Decalin	Ins.	Cryst.	Cryst.	Cryst.	Sol.
Tetralin	Sol.	1.0[b]	40	40	0.2[c]

Cryst. = crystals, ins. = insoluble, sol. = solution.
[a] Same as (*R,s,S*)-**4**.
[b] Unstable gel tending to crystallize.
[c] Mixture of gel and crystals.

compared to pure enantiomer (*R*,*R*)-**4**. *Meso* derivatives (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** showed exclusive gelation of tetralin (v_{max} 40 mL) being slightly less efficient compared to (*R*,*R*)-**2**. Gelation experiments were performed by repeated heating and cooling cycles following each addition of a small measured volume of tested solvent. At the beginning of the gelation experiments the tetralin gels of both *meso* isomers were opaque and became translucent on addition of more solvent. However, the behaviour of (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** in gelation experiments with tetralin appeared different; (*R*,*r*,*S*)-**2** at the beginning of the gelation experiment showed relatively slow gelation giving a weak, partly fluid gel also containing some crystals. Upon further additions of solvent and repeated heating/cooling, it turned into a hard, translucent gel. In contrast, (*R*,*s*,*S*)-**2** from the beginning gave a uniform nonfluid gel. Both gels appeared of limited stability at room temperature tending to crystallize after ageing overnight. Interestingly, an equimolar mixture of (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** was capable of gelling 38 mL of tetralin in total, giving immediately a translucent nonfluid gel which, however, also turned to crystals overnight. The observation that on standing (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** are able to gel equal volumes of tetralin and the fact that their equimolar mixture is able to gel almost an equal volume of the same solvent, indicated their possible interconversion by isomerization at the pseudoasymmetric centre during repeated heating/cooling cycles in the gelation experiments. Such isomerization is possible by keto–enol tautomerism of β-dicarbonyl compounds including malonamides (Scheme 2).[13]

Interconversion of (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** was confirmed by ^{1}H NMR experiments (Fig. 1). Gelation of tetralin with (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** was performed by repeated heating/cooling cycles, and additions of tetralin until v_{max} were reached. The solvent was removed and the remaining solid dissolved in DMSO-d_6, and the spectra were recorded. The ^{1}H NMR spectrum of the solid obtained from the (*R*,*r*,*S*)-**2** tetralin gel showed, in addition to (*R*,*r*,*S*)-**2** (δ_{NH} 8.30 ppm), also the presence of approximately 30% of (*R*,*s*,*S*)-**2** (δ_{NH} 8.26 ppm) (Fig. 1c). In the second case, formation of an almost 1:1 mixture of both isomers was observed (Fig. 1d). Additional evidence of *meso* isomer interconversion at elevated temperatures was provided by variable temperature ^{1}H NMR experiments in DMSO-d_6 (Fig. 2a–f). The results show that isomerization of (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** at 120 °C proceeded at different rates and that the equilibrium point containing about 53% of (*R*,*r*,*S*)-**2** and 47% of (*R*,*s*,*S*)-**2** was reached after four days. Further heating of both samples for six days did not change the ratio, but led to partial decomposition. The NMR results show that (*R*,*r*,*S*)-**2** is thermodynamically more stable than (*R*,*s*,*S*)-**2.** It should be added that no racemization at the amino alcohol chiral centres was observed.

The temperature dependent ^{1}H NMR spectra of (*R*,*R*)-**2** taken in $CDCl_3$ (Fig. 3) show strong upfield shifts of the malonamide NH and OH protons. In the concentration dependent spectra, both the NH



Scheme 2.

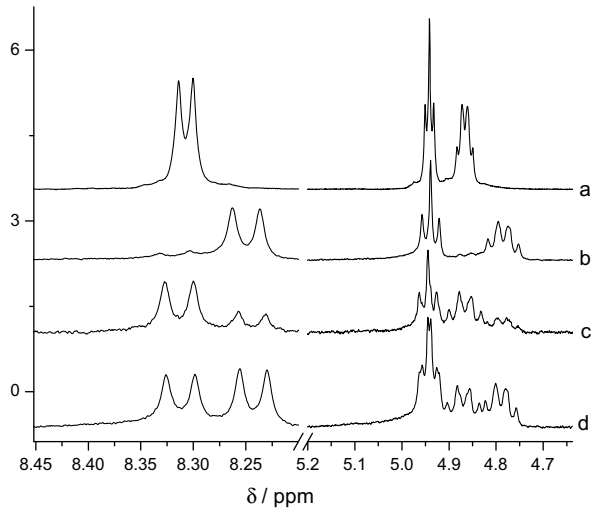


Figure 1. ^{1}H NMR (300 MHz) spectra (NH, OH and *CH regions shown) taken in DMSO-d_6 of: (a) (*R*,*r*,*S*)-**2**; (b) (*R*,*s*,*S*)-**2**; (c) of the solid obtained after gelation with (*R*,*r*,*S*)-**2** and tetralin; (d) of the solid obtained after gelation (*R*,*s*,*S*)-**2** and tetralin.

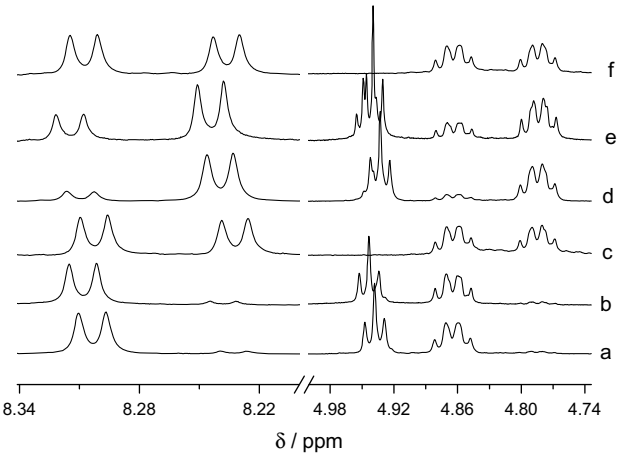


Figure 2. Variable temperature ^{1}H NMR (600 MHz) spectra (DMSO-d_6) of (*R*,*r*,*S*)-**2** (a = 1 h, b = 25 h, c = 96 h) and (*R*,*s*,*S*)-**2** (d = 1 h, e = 25 h, f = 96 h) heated at 120 °C in DMSO-d_6.

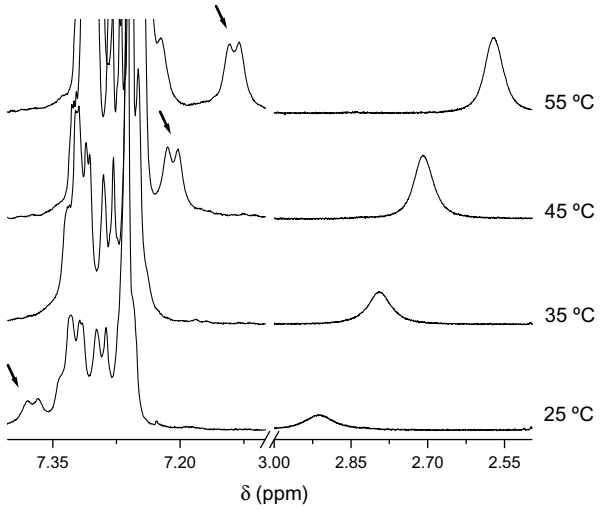


Figure 3. Temperature dependent ^{1}H NMR (300 MHz) spectra of (*R*,*R*)-**2** ($CDCl_3$) showing upfield shifts of the amide NH (indicated by arrows) and OH protons with increasing temperature.

and OH protons are shifted downfield with increasing concentration of (*R*,*R*)-**2**. These observations show that both the NH and OH protons are involved in intermolecular hydrogen bonding which stabilize the gel aggregates in $CDCl_3$.

Transmission electronic microscopy (TEM) investigation of the gels was used to reveal possible differences in gel morphologies. Table 1 shows that (*R*,*R*)-**2** is capable of only moderate gelation of CH_2Cl_2 (v_{max} 3.5 mL) and very efficient gelation of tetralin (v_{max} 53 mL). The TEM image of the (*R*,*R*)-**2** gel (in CH_2Cl_2) shows simultaneous presence of straight thin fibres with diameters of 20–40 nm and also very thick fibre bundles of 100–400 nm diameters (Fig. 4a). A similar morphology was observed in (*R*,*R*)-**2** toluene and *p*-xylene gels (not shown). In contrast, the TEM image of the (*R*,*R*)-**2** tetralin gel showed the presence of many tiny fibres with almost uniform diameters of about 20 nm (Fig. 4b). This striking difference in gel morphologies of less efficiently gelled CH_2Cl_2, toluene and *p*-xylene on one hand and very efficiently gelled tetralin by (*R*,*R*)-**2** is in accord with earlier observations for other types of gelators.[5] The formation of many tiny gel fibres of efficiently gelled solvent allows construction of a 'larger' network, which is able to immobilize more solvent. In contrast, in the less efficiently gelled solvent, many thick fibre bundles are present, which can form a 'smaller' network which is able to immobilize less solvent.

The TEM image of (*R*,*r*,*S*)-**2** tetralin gel shows the presence of curved fibre bundles with diameters between 10 and 50 nm (Fig. 4c). The TEM image of (*R*,*s*,*S*)-**2** tetralin gel shows the presence of fibre bundles with diameters between 20 and 120 nm; the structure of bundles consisting of many tiny intertwined fibres can be clearly seen in Figure 4d. The TEMs of both gels were taken with the gel samples prepared at $1/2v_{max}$ concentration with only one heating/cooling step. Nevertheless, formation of a small amount of (*R*,*r*,*S*)-**2** in the (*R*,*s*,*S*)-**2** gel cannot be excluded which in turn may explain the formation of the fibre bundles in the latter gel.

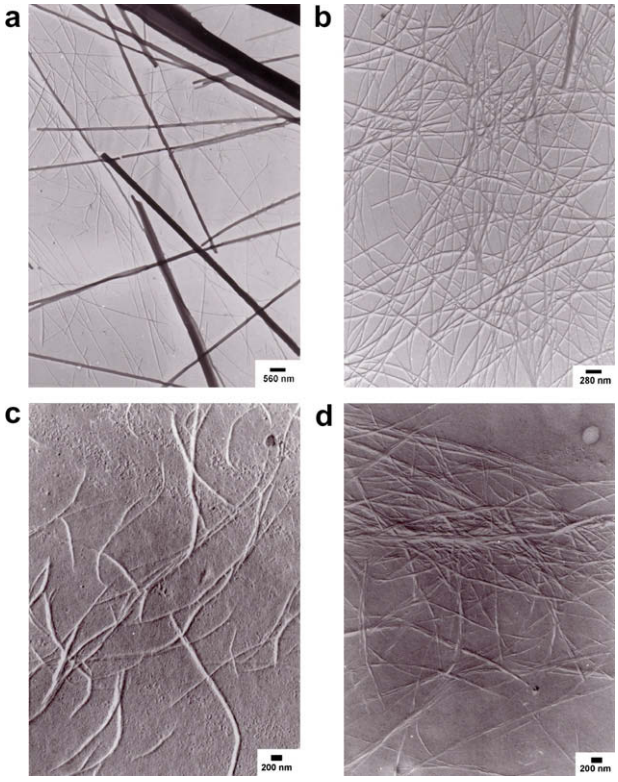


Figure 4. TEM images of gels of (a) (*R*,*R*)-**2** in CH_2Cl_2, (b) (*R*,*R*)-**2** in tetralin, (c) (*R*,*r*,*S*)-**2** in tetralin and (d) (*R*,*s*,*S*)-**2** in tetralin (Pd shadowing).

In conclusion, we have reported on the gelation properties of a new type of gelators of bis(aminoalcohol)malonamide structure. We have also shown that their gelation properties depend strongly on the substitution at the α-C position of the malonamide fragment: unsubstituted **1**, and symmetrically disubstituted dimethylmalonamide **3** and diethylmalonamide **5** lack any gelation ability in contrast to unsymmetrically substituted alkylmalonamides **2**, **4** and **6**. Among the latter, the optically active methylmalonamide (*R*,*R*)-**2** moderately gelled toluene and *p*-xylene and gelled tetralin very efficiently. The optically inactive *meso* isomers (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** possessing pseudoasymmetric centres showed exclusive and very efficient gelation of tetralin; however, the gels that formed were stable for a limited amount of time usually turning to crystals within 24 h at room temperature. Nevertheless, (*R*,*r*,*S*)-**2** and (*R*,*s*,*S*)-**2** represent very rare examples of gelling *meso* compounds. Further studies aimed towards revealing the self-assembly motifs of such gelators and particularly how their stereochemistry influences the self-assembly and gelation properties are underway.

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12. *Selected data for malonamide derivatives*: Compound (*R*,*R*)-**1**: mp 148–149 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): 8.47 (d, J = 8.1 Hz, 2H, 2 × NH), 7.36–7.20 (m, 10H, 2 × Ph), 4.93 (t, 2H, J = 5.5 Hz, 2 × OH), 4.85 (m, 2H, 2 × *CH) 3.57 (octet, 4H, J = 5.5 Hz, 2 × CH_2OH), 3.22 (s, 2H, CO–CH_2–CO). ^{13}C NMR (DMSO-d_6, 75.5 MHz): 167.09 (CO), 141.35 (C-1′), 128.52, 127.32, 127.23 (C-2′, C-3′ and C-4′), 65.11 (CH_2OH), 55.44 (*CH), 43.87 (CO–CH_2–CO). IR (KBr) ν_{max}/cm^{-1}: 3378, 3264, 1653,1627, 1551. Elemental Anal. calcd for $C_{19}H_{22}N_2O_4$ (342.395): C, 66.65; H, 6.48; N, 8.18. Found: C, 66.39; H, 6.30; N, 8.12.

Compound (*R,r,S*)-**2**: mp 166–167 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): 8.30 (d, 2H, J = 8.3 Hz, 2 × NH), 7.32–7.24 (10H, 2 × Ph), 4.94 (t, 2H, J = 5.6 Hz, 2 × OH), 4.86 (q, 2H, J = 4.9 Hz, 2 × *CH), 3.60–3.56 (m, 4H, 2 × CH_2OH), 3.35 (q, 1H, J = 7.0 Hz, CHCH$_3$), 1.21 (d, 3H, J = 7.1 Hz, CH$_3$). ^{13}C NMR (DMSO-d_6, 75.5 MHz): 170.15 (CO), 140.89 (C-1′), 128.07 and 126.77 (C-2′, C-3′ and C-4′), 64.53 (CH$_2$OH), 54.85 (*CH), 46.71 (CHCH$_3$), 15.35 (CH$_3$). IR (KBr) ν_{max}/cm^{-1}: 3351, 3305, 1669, 1539. HRMS calcd for $C_{20}H_{24}N_2O_4$ 357.1809 [M+H]$^+$, found 357.1976, Δ = 4.2 ppm.

Compound (*R,s,S*)-**2**: mp 196–198 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): 8.26 (d, 2H, J = 7.8 Hz, 2 × NH), 7.33–7.12 (m,10H, 2 × Ph), 4.94 (t, 2H, J = 5.6 Hz, 2 × OH), 4.81 (m, 2H, 2 × *CH), 3.62–3.47 (m, 4H, 2 × CH_2OH), 3,43 (q, 1H, J = 7.0 Hz, CHCH$_3$), 1.17 (d, 3H, J = 7.0 Hz, CH$_3$). ^{13}C NMR (DMSO-d_6, 75.5 MHz): 169.69 (CO), 141.33 (C-1′), 128.43, 127.28, 127.08 (C-2′, C-3′ and C-4′), 65.31 (CH$_2$OH), 55.64 (*CH), 46.75 (CHCH$_3$), 14.77 (CH$_3$). IR (KBr) ν_{max}/cm^{-1}: 3357, 3331, 3248, 1671, 1636, 1548, 1519.

Compound (*R,R*)-**3**: mp 127–128 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): 7.87 (d, 2H, J = 8.0 Hz, 2 × NH), 7.26–7.18 (m, 10H, 2 × Ph), 4.93–4.86 (m, 4H, 2 × OH and 2 × *CH), 3.60 (dd as t, 4H, J = 6.1 Hz, 2 × CH_2OH), 1.36 (s, 6H, CO–C–CH$_3$). ^{13}C NMR (DMSO-d_6, 75.5 MHz): 173.28 (CO), 141.42 (C-1′), 128.49, 127.21, 127.14 (C-2′, C-3′ and C-4′), 64.91 (CH$_2$OH), 55.78 (*CH), 49.93 (CO–C–CO), 24.27 (CH$_3$). IR (KBr) ν_{max}/cm^{-1}: 3427, 3379, 3321, 1650, 1632, 1541, 1523. HRMS calcd for $C_{21}H_{26}N_2O_4$ 371.1965 [M+H]$^+$, found 371.1967, Δ = 0.81 ppm.

Compound (*R,R*)-**4**: mp 160–162 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): 8.43 (d, J = 8.0 Hz, 2H, 2 × NH), 7.31–7.19 (m, 10H, 2 × Ph), 5.00 (t, 2H, J = 4.9 Hz, 2 × OH), 4.89–4.79 (m, 2H, 2 × *CH), 3.61–3.57 (m, 4H, 2 × CH_2OH), 3.19 (dd as t, 1H, J = 7.4 Hz, CHCH$_2$CH$_3$), 1.72 (pent., 2H, J = 7.3 Hz, CH_2CH$_3$), 0.78 (t, 3H, J = 7.3 Hz, CH$_2$CH_3). ^{13}C NMR (DMSO-d_6, 75.5 MHz): 169.15 (CO), 141.09 (C-1′), 128.01, 126.72 (C-2′, C-3′ and C-4′), 64.55 (CH$_2$OH), 54.45 (CO–C–CO), 54.88 (*CH), 23.48 (CH_2CH$_3$), 11.75 (CH$_2$CH_3). IR (KBr) ν_{max}/cm^{-1}: 3309, 3289, 1666, 1640, 1549, 1531. HRMS calcd for $C_{21}H_{26}N_2O_4$ 371.1965 [M+H]$^+$, found 371.1968, Δ = 0.51 ppm.

Compound (*R,r,S*)-**4**: mp 163–168 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): 8.35 (d, 2H, J = 8.1 Hz, 2 × NH), 7.35–7.21 (m, 10 H, 2 × Ph), 4.94 (t, 2H, J = 5.4 Hz 2 × OH), 4.87 (dd, 2H, J = 5.8; 13.6 Hz, 2 × *CH), 3.62–3.54 (m, 4H, 2 × CH_2OH), 3.15 (t, 1H, J = 7.5 Hz, CHCH$_2$CH$_3$), 1.74 (pent. 2H, J = 7.4 Hz, CH_2CH$_3$), 0.77 (t, 3H, J = 7.4 Hz, CH$_3$). IR (KBr) ν_{max}/cm^{-1}: 3354, 3305, 1670, 1550, 1540.

Compound (*R,s,S*)-**4**: mp 185–190 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): 8.25 (d, 2H, J = 7.9 Hz, 2 × NH), 7.32–7.20 (m, 10 H, 2 × Ph), 4.92 (t, 2H, J = 5.4 Hz, 2 × OH), 4.84–4.79 (m, 2H, 2 × *CH), 3.58–3.50 (m, 4H, 2 × CH_2OH), 3.18 (t, 1H, J = 7.5 Hz, CHCH$_2$CH$_3$), 1.73 (pent. 2H, J = 7.5 Hz, CH_2CH$_3$), 0.83 (t, 3H, J = 7.4 Hz, CH$_3$). IR (KBr) ν_{max}/cm^{-1}: 3411,3319, 3259, 1650, 1558, 1539.

Compound (*R,R*)-**5**: mp 163–164 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): 8.82 (d, 2H, J = 8.0 Hz, 2 × NH), 7.31–7.19 (m, 10H, 2 × Ph), 4.95–4.90 (m, 4H, 2 × OH and 2 × *CH), 3.61–3.57 (m, 4H, 2 × CH_2OH), 1.91+1.87 (2q, 4H, J = 7.0 Hz, 2 × CH_2CH$_3$), 0.64 (t, 6H, J = 7.0 Hz, 2 × CH$_2$CH_3). ^{13}C NMR (DMSO-d_6, 75.5 MHz): 172.43 (CO), 141.20 (C-1′), 127.96, 126.79 and 126.65 (C-2′, C-3′ and C-4′), 64.48 (CH$_2$OH), 57.47 (*CH), 55.20 (CO–C–CO), 29.16 (CH_2CH$_3$), 9.11 (CH$_2$CH_3). IR (KBr) ν_{max}/cm^{-1}: 3339, 3306, 3212, 3152, 1658, 1612, 1528. Elemental Anal. calcd for $C_{23}H_{30}N_2O_4$ (398.503): C. 69.32; H, 7.59; N, 7.03. Found: C, 69.13; H, 7.47; N, 7.12.

Compound (*R,R*)-**6**: mp 211–213 °C, ^{1}H NMR (DMSO-d_6, 300 MHz): 8.35 (dd, 2H, J = 7.8; 19.4 Hz, 2 × NH), 7.31–7.20 (m, 10 H, 2 × Ph), 4.95 (m, 2H, 2 × OH), 4.90– 4.78 (m, 2H, 2 × *CH), 3.64–3.53 (m, 4H, 2 × CH_2OH), 2.90 (d, 1H, J = 10.2 Hz, CO–CH–CO), 2.25–2.13 (m, 1H, CH(CH$_3$)$_2$), 0.82 (dd, 6H, J = 6.5; 12.3 Hz, CH(CH_3)$_2$). ^{13}C NMR (DMSO-d_6, 75.5 MHz): 169.06 and 168.82 (CO), 141.09 and 141.04 (C-1′), 128.02, 127.95, 127.92, 126.79, 126.71 and 126.62 (C-3′, C-2′ and C-4′), 64.53 (CH$_2$OH), 61.09 (CO–CH–CO), 54.78 (*CH), 30.00 (CH(CH$_3$)$_2$), 20.43 and 20.32 (CH(CH_3)$_2$). IR (KBr) ν_{max}/cm^{-1}: 3304,1666, 1553, 1540. HRMS calcd for $C_{22}H_{28}N_2O_4$ 385.2122 [M+H]$^+$, found 385.2114, Δ = 2.08 ppm.

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