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Liesegang ring formation during the supramolecular hydrogelation of the chiral drug methocarbamol

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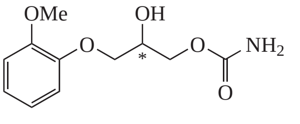
The chiral drug methocarbamol, which is prone to spontaneous resolution, is an effective molecular hydrogelator as both an enantiomer and a racemate; the samples of methocarbamol having an intermediate enantiomeric composition generate clearly visible periodic structures (Liesegang rings) during the gelation process.

Small organic molecules referred to as low molecular weight gelators (LMGs) are capable of self-assembling into spreading networks to form gels with solvents.[1] If LMG self-assembles in aqueous media, the resulting gel is a molecular hydrogel, and this molecule is referred to as a hydrogelator. Chiral LMG could manifest effects caused by its chirality.[2,3] Heterochiral coaggregation of different enantiomers is a more common behaviour of racemic LMG. The two enantiomers of a racemic gelator can spontaneously resolve into gel-forming supramolecular aggregates consisting of a single enantiomer. Brizard *et al.*[2(*d*)] name such cases as conglomerates. Published data[3(*d*),(*e*)] do not contain information on the crystalline phase behaviour of the LMG. In other words, it is unknown whether these low molecular compounds are prone to traditional spontaneous crystallization resolution.[4] Additionally, as both molecular gelation and spontaneous crystallization resolution phenomena are relatively rare, there is a low likelihood that a substance would exhibit both of these properties. We report now one of these rare examples, skeletal muscle relaxant methocarbamol **1** [1-carbamoyloxy-2-hydroxy-3-(2-methoxyphenoxy)propane].



Methocarbamol **1**, MW 241.2

The synthesis of *rac*-**1** was published earlier.[5] We used the same way to obtain both of the methocarbamol enantiomers starting with enantiopure glycerol ethers.[6] An alternative approach to non-racemic **1** is the HPLC resolution of diastereomeric methocarbamol derivatives.[7] Recently, we have disclosed the conglomerate nature of this compound.[6,8] Here we used this property of **1** for obtaining its (*R*)- and (*S*)-enantiomers by entrainment approach.[†] Note that enantiomeric **1** could form clear or slightly opalescent gels in the concentration range of 1–2 wt% [Figure 1(*a*)]. Racemic methocarbamol does not form gels in this concentration region, but at 4–6 wt% heated aqueous *rac*-**1** solutions will form gels after short periods of time in an ice-water bath [Figure 1(*b*)]. The relationship between enantiomeric excess and minimal gelation concentration for **1** is presented in Table 1.

The conglomerate-forming nature of *rac*-**1** may be the reason behind the minimal gelation concentration increase with the ee decrease. The well-known Meyerhoffer rule states that the racemic conglomerates are approximately twice as soluble as pure enantiomers.[9] Thus, the critical gelation concentration for every enantiomer is achieved for a higher general concentration of the racemic substance. The temperature of a gel–solution transition was estimated as $T_{\text{g-s}}$ = 33±3 °C for the hydrogels containing ~3 wt% of both racemic and enantiomeric **1**.

Table 1 Relationship between enantiomeric excess and minimal gelation concentration (MGC, mg of **1** per 100 mg H_2O) for methocarbamol **1**.

ee (%)	0	7.5	29.0	48.0	60.0	95.0	99.5
MGC	4.0	2.3	1.9	1.6	1.5	1.2	1.1

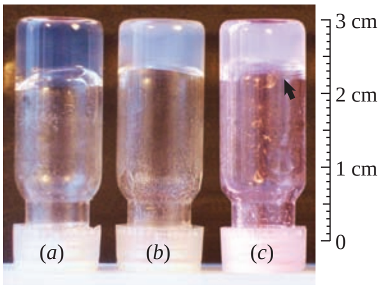


Figure 1 Methocarbamol hydrogels: (*a*) 1.2% (*S*)-**1**, 99.5% ee; (*b*) 4.3% *rac*-**1**; (*c*) 3.3% (*S*)-**1**, 95.0% ee. Arrow points to the area where the rings are formed (see the text).

The gel-forming ability of low molecular API ameliorates their therapeutic characteristics.[10] Methocarbamol is a popular remedy.[11]

In closed glass vials, the hydrogels[‡] formed by **1** could be stored for a long period, but in attempts to prepare their xerogels, the crystals have had time to grow during the vacuum removal of water from the gel samples placed on the mica surface. In the

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[†] Racemic methocarbamol *rac*-**1** (7.28 g) and (*R*)-**1** (0.89 g) were dissolved in 355 ml of water at 50–55 °C. The solution was cooled to 29 °C and seeded with finely pulverized (*R*)-**1** (20 mg). After stirring the mixture for 85 min at 27 °C, precipitated (*R*)-**1** was collected by filtration (2.20 g after drying; 75.5% ee). The extra portion of *rac*-**1** (2.20 g) was then dissolved in the mother liquor at 50–55 °C; the resulting solution was cooled to 29 °C. After addition of (*S*)-**1** (20 mg) as seed crystals to the solution, and stirring the mixture for 65 min at 27 °C, (*S*)-**1** (1.97 g after drying; 72% ee) was collected by filtration. Further resolution was carried out at 27 °C by adding amended amounts of *rac*-**1** to the filtrate in a manner similar to that described above. After a second cycle, 1.87 g of (*R*)-**1** (73.6% ee) and 1.98 g of (*S*)-**1** (76.7% ee) were collected. A high degree of enantiomeric purity of collected scalemic **1** can be achieved by recrystallization. (*R*)-**1**: mp 113–114 °C; $[\alpha]_D^{20}$ –0.8 (*c* 1.0, MeOH), 99.8% ee. (*S*)-**1**: mp 113–114 °C; $[\alpha]_D^{20}$ +0.8 (*c* 1.1, MeOH), 99.5% ee.

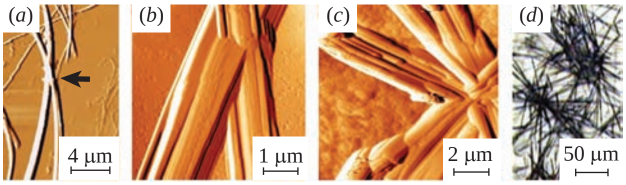

Figure 2 (*a*)–(*c*) Atomic-force and (*d*) optical microphotographs of the vacuum-dry hydrogels formed by (*a*), (*b*), (*d*) enantiomeric and (*c*) racemic methocarbamol. Picture (*b*) corresponds to scaled-up fragment marked in (*a*).

xerogels of enantiopure methocarbamol, it is possible to detect very elongated crystal wiskers [Figure 2(*a*)] forming net-like structures owing to the intergrowth of crystals through one another [Figure 2(*b*)]. However, the multibranch crystalline aggregates growing from the mutual centre [Figure 2(*c*)] are the more frequent patterns for the *rac*- and *scal*-**1** xerogels.

A striking feature of the hydrogels derived from an intermediate enantiomeric purity **1** lies in the fact that the stable periodic structures in the shape of concentric ellipses arise on the gel surface [Figures 1(*c*) and 3].

The structures in Figure 3 in outward appearance resemble the ubiquitous and the most known periodic structures, the Liesegang rings. This phenomenon was first noted by the German chemist Rafael Liesegang in 1896.[12] As time passed, scientists became cognizant of the widespread occurrence of Liesegang-like phenomena not only in chemistry but also in biology, geology and even astronomy.[13] Gels are usual media for Liesegang rings.[12,14] However, information on any periodic structures accompanying the immediate process of supramolecular gelation is not available.

It is probable that the unique combination of the supramolecular gelation ability of **1** and its tendency to spontaneous resolution during association opens up possibilities for Liesegang rings appearance. It is evident from Figure 2(*d*) that the crystals resulting from the hydrogels during their dehydration form star-like crystalline aggregates growing from the common origins. Atomic-force microscopy shows [Figure 2(*a*)–(*c*)] that **1** is prone to form the beams of elongated crystalline arms that are divergent from a common origin during early crystal growth. Figure 3(*d*)–(*f*) demonstrates that the tendency toward the formation of radial strands (fibrils) is characteristic of the Liesegang rings within the methocarbamol gel. If we assume that the habit of the macroscopic crystalline aggregates has much in common with the habit of the gel-forming fibrils, it would appear reasonable that the tendency to homochiral crystal formation acts at the preceding stage of the homochiral supramolecular associate formation as well.

A bundle of homochiral fibrils, growing in radial directions, consumes one of the enantiomers from the solution. At some time the concentration of this enantiomer in a growth region would become below the critical one, followed by stopping the homochiral bundle growth. Simultaneously, around the periphery of every homochiral region, the prerequisites arose to another enantiomer associate formation. In this zone, a developed surface having a great excess energy exists, and there is an increased concentration (through partial bonding of the water molecules by the already formed fibrils) of the as yet unused enantiomer. The growth decelerating of the one kind of the hydrogel and the simultaneous beginning of another kind of gel growth would lead to change in the gel density, and, as a consequence, to appearance of the first ring of the periodic structure. In the sequel, as the homochiral fibrils of the opposite enantiomer would grow and the enantiomer concentration would decrease, the situation recurs, and the next ring appears.

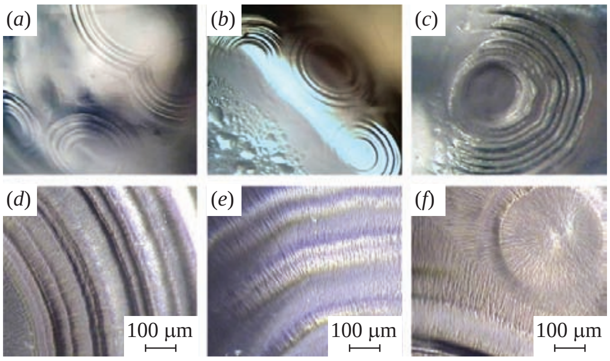

Figure 3 Periodic structures (concentric ellipses) on the surface of the hydrogel derived from an intermediate enantiomeric purity (95% ee, 3.4 wt%) methocarbamol: (*a*)–(*c*) magnification $\sim 30^{\times}$.

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[‡] The typical procedure for hydrogel formation is illustrated by the sample of intermediate enantiomeric composition. (*S*)-Methocarbamol (13 mg, 95% ee) and twice-distilled water (380 mg) were placed in a 2 ml vial. The stoppered vial was placed in a hot water bath (70–80 °C) and agitated until the solid was completely dissolved. The solution was rapidly transferred to an ice-water bath and kept there motionless for 1–5 min.

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