ORGANIC LETTERS

2004
Vol. 6, No. 10
1547−1550

Diastereomixture and Racemate of *myo*-Inositol Derivatives, Stronger Organogelators than the Corresponding Homochiral Isomers

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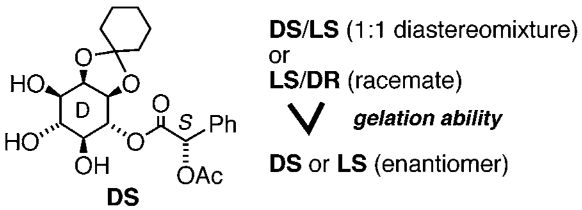
Received February 14, 2004

ABSTRACT



DS

Contrary to the usually accepted phenomena, an optically heterogeneous 1:1 diastereomixture of DS and LS and a racemate of LS and DR obtained, respectively, from a racemic *myo*-inositol derivative and (*S*)- and racemic *O*-acetylmandelic acid formed stronger organogels, especially with aromatic fluids, than those formed from homochiral isomers, DS and LS. One of the plausible reasons for the formation of the stronger diastereomeric gel is shown to be the complementary interaction of two diastereomers.

In the past decade, gels comprising low-molecular weight gelators and organic liquids or water have attracted much attention in the active and promising field of the gel science.[1] Our first unexpected finding that a 1:1 diastereomeric mixture **1DS/LS** of 6-*O*-[(*S*)-*O*-acetyl-mandelates] of DL-1,2-*O*-cyclohexylidene-*myo*-inositol functioned as an efficient organogelator during the total synthesis of a phosphatidylinositol phosphates[2] directed us to investigate the gelation ability of inositol-based gelators in detail.[3] Such a diastereomerically mixed gelator is unprecedented,[4] although the gelation ability of individual diastereomers (epimers),[5] including configurational isomers of the monosaccharide,[6] has been compared. In general, homochiral compounds are recognized to be better gelators than the corresponding racemates[7] or diastereomeric mixtures.[8] The first example of the inositol gelator **4** also needs to be enantiopure.[3] In contrast, racemic fatty acid-appended amino acid amides were reported very recently to gelate larger volumes of some organic liquids

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(1) (a) Terech, P.; Weiss, R. G. *Chem. Rev.* **1997**, *97*, 3133−3160. (b) Esch, J. H. v.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 2263−2266. (c) Abdallah, D. J.; Weiss, R. G. *Adv. Mater.* **2000**, *12*, 1237−1247.

(2) Our latest paper concerning PIPs synthesis: Han, F.; Hayashi, M.; Watanabe, Y. *Chem. Lett.* **2003**, *32*, 724−725.

(3) As an inositol-based gelator, **4** was very recently reported. Hosoda, A.; Nomura, E.; Miyake, Y.; Taniguchi, H. *Chem. Lett.* **2003**, *32*, 1042−1043.

(4) Our group and Hosoda et al. independently reported the same phenomena concerning diastereomeric organogelators: (a) Watanabe, Y.; Miyasou, T.; Hamasaki, Y.; Hayashi, M. 83rd National Meeting of the Chemical Society of Japan, March, 2003, Tokyo; Abstract No. 1, p 381. (b) Hosoda, A.; Nomura, E.; Taniguchi, H. 83rd National Meeting of the Chemical Society of Japan, March, 2003, Tokyo; Abstract No. 1, p 505.

(5) (a) Mukkamala, R.; Weiss, R. G. *J. Chem. Soc., Chem. Commun.* **1995**, 375−376. (b) Vassilev, V. P.; Wood, M. R.; Wong, C.-H. *J. Chem. Soc., Chem. Commun.* **1998**, 1865−1866.

(6) Gronwald, O.; Shinkai, S. *Chem. Eur. J.* **2001**, *7*, 4328−4334.

(7) (a) Luo, X.; Liu, B.; Liang, Y. *Chem. Commun.* **2001**, 1556−1557. (b) Hanabusa, K.; Kobayashi, H.; Suzuki, M.; Kimura, M.; Shirai, H. *Colloid Polym. Sci.* **1998**, *276*, 252−259. (c) Hanabusa, K.; Maesaka, Y.; Kimura, M.; Shirai, H. *Tetrahedron Lett.* **1999**, *40*, 2385−2388. (d) Maitra, U.; Potluri, V. K.; Sangeetha, N. M.; Babu, P.; Raju, A. R. *Tetrahedron: Asymmetry* **2001**, *12*, 477−480.

(8) (a) Kimura, T.; Yamashita, T.; Koumoto, K.; Shinkai, S. *Tetrahedron Lett.* **1999**, *40*, 6631−6634. (b) Ihara, H.; Sakurai, T.; Yamada, T.; Hashimoto, T.; Takafuji, M.; Sagawa, T.; Hachisako, H. *Langmuir* **2002**, *18*, 7120−7123. (c) Takafuji, M.; Sakurai, T.; Yamada, T.; Hashimoto, T.; Kido, N.; Sagawa, T.; Hachisako, H.; Ihara, H. *Chem. Lett.* **2002**, 548−549.

10.1021/ol049737+ CCC: $27.50

than the homochiral enantiomers.[9] We herein report the formation of stronger organogels by diastereomeric **1DS/LS** and racemic **3LS+DR** rather than enantiomerically pure isomers, suggesting that the diastereomeric and racemic gelators derived from *myo*-inositol may be new promising members of a two-component gelator, which is expected to improve properties of gels with respect to morphology and stability and to gain new functions.[1a,10]

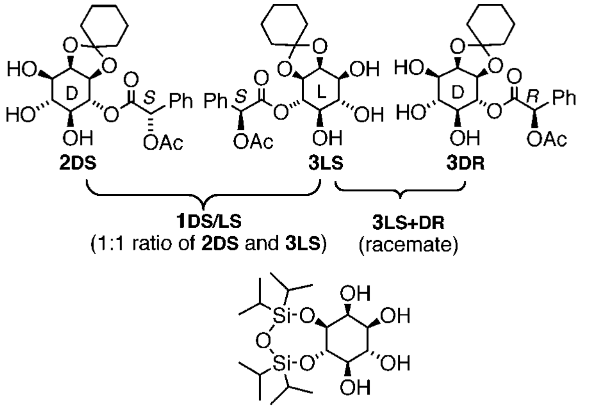

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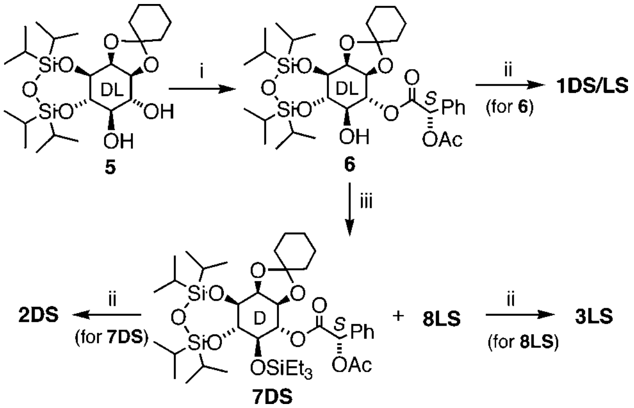
Figure 1. *myo*-Inositol-based gelators.

Racemic diol **5**, derived from *myo*-inositol in two steps, was selectively acylated by the reaction with *O*-acetyl-(*S*)-mandeloyl chloride, and the resultant mandelate **6** was transformed into **1DS/LS** by the removal of the disiloxanyl group (Scheme 1).

Scheme 1. Synthesis of Gelators[a]



[a] Reagents: (i) *O*-acetyl-(*S*)-mandeloyl chloride, Py, CH_2Cl_2 (71%); (ii) TBAF·$3H_2O$, AcOH (**1DS/LS**, 60%; **2DS**, 77%; **3LS**, 45%); (iii) Et_3SiCl, *i*-Pr_2NEt then separation (**7DS**, 29%; **8LS**, 33%).

Table 1. Gelation Ability of Stereoisomeric *myo*-Inositols

	resultant state[a](C_{min})[b]			
	1DS/LS	**3LS+DR**	**2DS**	**3LS**
benzene	SG(1.9)	SG(4.7)	G(11.3)	SG(6.8)
Ph-Me	SG(1.4)	SG(3.2)	SG(4.9)	G(32.7)
Ph-Cl	SG(2.2)	SG(2.4)	G(12.4)	G(11.3)
o-xylene	SG(2.2)	SG(1.7)	G(17.0)	G(21.3)
m-xylene	SG(2.2)	SG(1.6)	G(17.0)	G(34.0)
p-xylene	SG(2.3)	SG(1.8)	G(17.0)	G(48.6)
CH_2Cl_2	G(35.3)	G(10.0)	G(25.0)	S
$CHCl_3$	S	G(26.0)	S	G(24.5)
CCl_4	SG(6.0)	SG(8.7)	G(32.0)	SG(4.4)
AcOEt	G(25.3)	G(11.8)	G(17.0)	G(34.0)
MeCOMe	S	G(65.0)	S	S
MeCOEt	G(49.1)	G(26.0)	G(28.3)	G(42.5)
hexane	I	I	I	I
Et_2O	I	I	I	I
THF	S	S	S	S
MeOH	S	S	S	S
EtOH	S	S	S	S

[a] G = stable gel formed at room temperature; SG = superior gel formed at less than 1 wt % of the gelator; S = soluble; I = insoluble. [b] Critical minimum concentration of each gel (g/L).

The diastereomeric mixture **1DS/LS** formed excellent organogels with benzene and some other aromatic liquids (Table 1). The minimum concentration of the benzene gel, C_{min}, was 1.9 g/L (0.19 w/v %), which is comparable with the value of a supergelator. Tetrachloromethane was also effective for the gelation, whereas ethereal and alcoholic solvents were not. Some solvents with the carbonyl group gave rather poor results (Table 1).

To compare the gelation ability of **1DS/LS** with each enantiomer, **2DS** and **3LS**, and racemic **3LS+DR**, they were prepared as shown in Scheme 1 and their C_{min} were measured. To our surprise, diastereomeric **1DS/LS** and racemic **3LS+DR** were more efficient for forming gels with various aromatic solvents than the corresponding homochiral **2DS** and **3LS** as shown in Table 1. It should be emphasized that C_{min} for **1DS/LS** and racemic **3LS+DR** are much lower than those for the individual diastereomers, especially in their gels with xylenes. The C_{min} values of the CCl_4 gels of **2DS** and **3LS** were fairly different, 32.0 and 4.4, and the C_{min} of the latter gel was found to be lower than that for the gel of **1DS/LS** (6.0). Interestingly, racemic **3LS+DR** with ethyl acetate formed a gel at the lowest concentration among the four gelators used here.

To investigate the reason the mixed gelator systems, especially with aromatic solvents, provided a higher quality of gels than homochiral derivatives, the ratio of the diaster-

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eomeric components was varied, keeping the concentration constant in benzene and T_{gel} of each mixture and enantiopure diastereomer were measured (Figure 2). The linearity in correlation between T_{gel} and the ratio of the components was observed, and the 1:1 ratio of the diastereomers showed the highest T_{gel} value. In addition to the T_{gel} values of the different ratios of the two diastereomers, their C_{min} measurement showed that, whereas those of nonequivalent mixtures (C_{min} 2−3 g/L) were close to that of **1DS/LS** (Table 1), the latter had the lowest C_{min}. These results suggest a systematic arrangement of an equal amount of the two components. A quite similar correlation was observed in the case of two cholesterol-based gelator components carrying complementary nucleobases, and their 1:1 hydrogen bonded base pair in a gel state was proposed.[11] In an analogous fashion, a 1:1 interaction between **2DS** and **3LS** seems likely in our case, resulting in the formation of a superior organogel. When a gel includes a different amount of the two diastereomers, the gelators are postulated to partly form a superstructure from the 1:1 ratio of **2DS** and **3LS** and a weak one from the remaining enantiomer, resulting in the decrease in the gel quality with respect to T_{gel} and C_{min}. This structural proposal can be supported by SEM analysis.

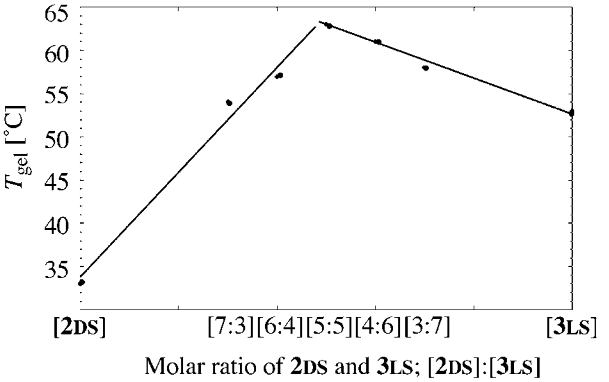
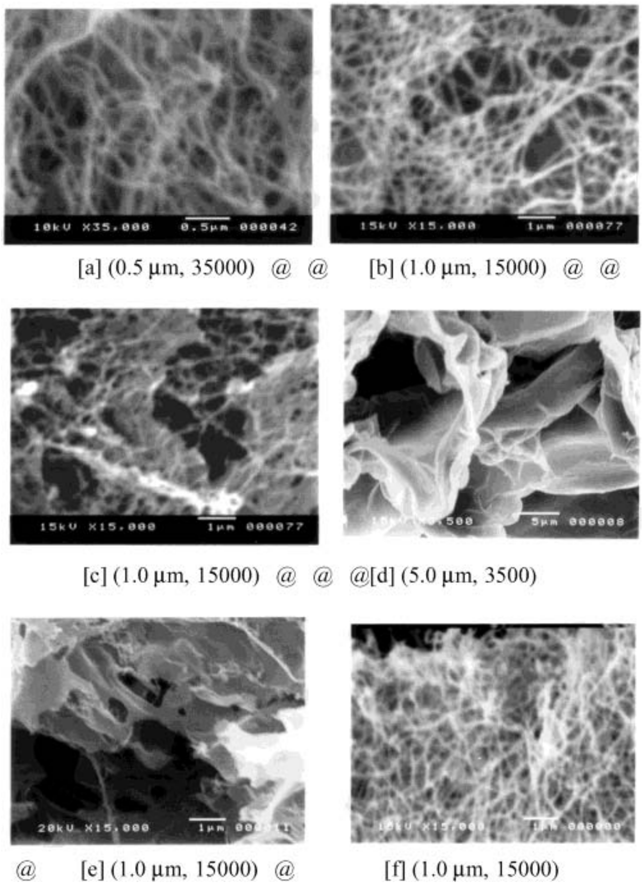


Figure 2. Plots of T_{gel} against various molar ratios of **2DS** and **3LS** in benzene. T_{gel} measurement: 1 wt % of two components in benzene.

Thus, the xerogel prepared from homochiral **2DS** or **3LS** gel with lower quality was shown to have a sheetlike structure (Figures 3d and 3e), suggesting clearly that such a sheet structure is less interactive and forms a morphologically weaker gel. On the other hand, high-quality diastereomeric and racemic gels, **1DS/LS** and **3LS+DR**, respectively, provided SEM pictures showing a complex fibrous network system, indicating a superstructure (Figures 3a and 3f).[12] The benzene gels of different ratios of **2DS** and **3LS** provided the SEM pictures of their xerogels, including partially fibrous and sheetlike parts (Figures 3b and 3c). The complementary interaction could be one of the reasons for the superior gelation in that particular case. Although a similar interaction is also likely in the case of enantiomers, other possibilities still cannot be ruled out. Detailed investigations are being done to address this issue.



[a] (0.5 μm, 35000) @ @ [b] (1.0 μm, 15000) @ @

[c] (1.0 μm, 15000) @ @ @[d] (5.0 μm, 3500)

@ [e] (1.0 μm, 15000) @ [f] (1.0 μm, 15000)

Figure 3. SEM pictures of xerogels prepared from 1 wt % benzene gels containing (a) 5:5, (b) 4:6, and (c) 3:7 of **2DS** and **3LS**, (d) **3LS**, (e) **2DS**, and (f) **3LS+DR** (racemate). The bar in each picture indicates a scale, and its length is shown in parentheses, in which magnification is also recorded.

As part of our efforts in the structural elucidation of the inositol-based organogels, we observed that an L-3-*O*-[(*S*)-acetylmandeloyl]inositol analogue, a regioisomer of **3LS**, did not form a benzene gel. In addition, *O*-acylation and *O*-silylation of polyol derivatives of *myo*-inositol are known to take place selectively at the 3-position,[13] indicating that the 3-OH group is most interactive with other molecules. These results suggest that the 3-OH plays a key role for intermolecular hydrogen bondings to form a gel network. The FT-IR spectra of the benzene gel of **1DS/LS** showed a moderate intensity of a broad band around 3384 cm^{-1} due to intermolecular hydrogen bonds. Although the comprehensive work of Shinkai's group on the sugar-based gel system has suggested the importance of a one-dimensional hydrogen-bonded feature to form a good gel,[6,14] further

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[11] Snip, E.; Koumoto, K.; Shinkai, S. *Tetrahedron* **2002**, *58*, 8863−8874.

[12] Luboradzki, R.; Gronwald, O.; Ikeda, A.; Shinkai, S. *Chem. Lett.* **2000**, 1148−1149.

[13] Han, F.; Hayashi, M.; Watanabe, Y. *Tetrahedron* **2003**, *59*, 7703−7711.

detailed study is necessary to disclose the molecular assembly system of the present inositol-based gel.

In conclusion, we have shown novel hybrid inositol gelators, and these optically heterogeneous composites of diastereomers or enantiomers were found to be better gelators than the corresponding homochiral ones in certain cases. Although inositols are structurally similar to glycopyranoses, the former provides access to enantiomeric (D-, L-, and racemic forms), diastereomeric (pure and mixed), and meso derivatives much more easily than the latter. Such variations are important for probing the effect of chirality on the gelation process. That there are nine isomeric inositols (hexahydroxycyclohexanes) and a variety of derivatives that can be prepared by the known protection−deprotection chemistry projects inositol derivatives as prospective candidates for developing promising gelators. In addition, the structural diversity of inositols offers tools for investigating the finer details of the gelation process at the molecular level.

Acknowledgment. This work was supported by The Naito Foundation. We also thank Venture Business Laboratory and Advanced Instrumentation Center for Chemical Analysis, Ehime University, for NMR and elemental analyses.

Supporting Information Available: Detailed experimental procedures for the preparation of gelators of the inositol derivatives used here and their characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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