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Synthesis and Gelation Behavior of 4′-Propyl-1,1′-bi(cyclohexyl)-4-one 4-Alkoxybenzoylhydrazone

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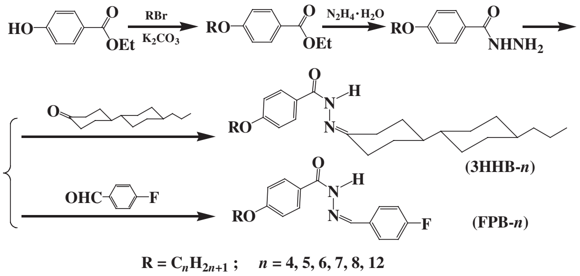
A series of new alkoxybenzoylhydrazones of 4′-propyl-1,1′-bi(cyclohexyl)-4-one were prepared as novel low molecular weight organogelators (LMOGs). Their gelation behaviors in 10 solvents were tested. Some of the compounds could form stable gels in bulk organic solvents and self-assemble into fibrous microstructures in organogel phase. FTIR and ^{1}H NMR spectroscopy studies revealed that hydrogen bonding between the gelator molecules was one of the main driving forces for the formation of the gels.

Low molecular weight organogelators (LMOGs) have been an active research field in materials science and supramolecular chemistry due to their potential applications, involving optoelectronic devices, sensors, nanomaterials,[1] and delivery or modification agents for drugs.[2] Generally, LMOGs can self-assemble into fibrous super-structures driven by multiple and weak non-covalent interactions such as hydrogen bonding, dipole–dipole, van der Waals interaction, π-stacking, and ionic interactions.[3] Hydrogen-bonding interaction is thought to be the major driving force of gelation for amide compounds such as amino acids, peptides, ureas, carbamates, and thioureas. These LMOGs are generally composed of alkyl chains and one amide group (CONH) or two, together with acid moiety, hydroxy moiety, or amino groups to ensure the formation of multiple intermolecular hydrogen bonding between neighboring molecules. On the other hand, cholesterol derivatives are nonhydrogen-bond-based gelators, where van der Waals interaction is responsible for gelation. Some LMOGs consisting of an amide group and a cholesteryl moiety have been developed in recent years.[4] To the best of our knowledge, compounds containing only one amide group reported as LMOGs are few.[5] Herein, a new LMOG with an amide group has been designed and synthesized. The gelator consists of three parts: an alkoxybenzoyl group, a bi(cyclohexyl) moiety, and a hydrazone group functioning as a linker (Scheme 1, **3HHB-*n***). The main ideas behind this design are as follows: (1) benzoylhydrazone moiety bearing an amide group has a strong tendency to form hydrogen bonds; (2) bi(cyclohexyl) moiety, exhibiting specific spatial configuration, is introduced into the structure to enforce van der Waals interaction. The obtained compounds **3HHB-*n*** are able to self-assemble into ordered aggregates in a number of organic liquids and finally gelatinize the liquids. For comparison, analogous compound 4-fluorobenzaldehyde 4-alkoxybenzoylhydrazone (**FPB-*n***, Scheme 1) has also been prepared and studied.

4′-Propyl-1,1′-bi(cyclohexyl)-4-one 4-alkoxybenzoylhydrazone, coded as **3HHB-*n*** ($n = 4$, 5, 6, 7, 8, and 12), was prepared by a condensation reaction between 4′-propyl-1,1′-bi(cyclohexyl)-4-one and 4-alkoxybenzoylhydrazine in absolute ethanol at reflux for 6 h, as shown in Scheme 1, where 4-alkoxybenzoylhydrazine was prepared by a reaction between hydrazine monohydrate and ethyl 4-alkoxybenzoate obtained from etherification of the corresponding bromoalkanes with ethyl p-hydroxybenzoate. **3HHB-*n*** was purified through recrystallization from alcohol to give a purity more than 99% for HPLC measurement with methanol as eluent at 1 mL min^{-1} flow rate. The structures of the intermediates and the products **3HHB-*n*** and **FPB-*n*** were confirmed by ^{1}H NMR and FTIR measurements.



Scheme 1. Synthetic routes of **3HHB-*n*** and **FPB-*n***.

Gel samples were prepared according to the following procedure. A weighed powder sample was mixed with an organic solvent in a sealed test tube and the mixture was heated until the solid dissolved, and the resulting solution was cooled to room temperature in air. Then, the gelation was checked visually. If a test tube containing the solution was inverted and no liquid was observed running down the wall of the tube, it was judged to be a gel. As shown in Table 1, **3HHB-*n*** showed gelation ability in different solvents at a gel concentration of 25 mg mL^{-1}.

Moreover, the obtained gels were stable for a long time at room temperature. Noted that length of alkyl chain of the compounds showed obvious effect on their gelation abilities. The suitable length of alkyl chain of the compounds was in favor of the hydrophile–lypophile balance in different organic liquids. Compared with **3HHB-*n***, **FPB-*n*** exhibited no gelation ability, indicating that bi(cyclohexyl) moiety could help to enforce van der Waals interaction. These results demonstrated that a benzoylhydrazone moiety, a bi(cyclohexyl) group, and a suitable length alkyl chain were essential groups for gelation.

Concentration dependence of 2-propanol gels with **3HHB-6** were also conducted, as shown in Figure 1. The gel to sol transition temperature (T_{gel}) increased with increasing concentration of **3HHB-6** and then remained at 65 °C when the concentration was over 120 mg mL^{-1}. In the lower concentration range (below than 15 mg mL^{-1}), not enough fibrils were formed and the association interactions among fibrils related to the gelator network were not complete.

In order to investigate the aggregation morphology, xerogels of **3HHB-*n*** from ethanol or 2-propanol were obtained through slowly evaporating the solvent in vacuum. The SEM pictures were taken using FEI Quanta 200. Typical SEM images of **3HHB-*n*** xerogels are shown in Figure 2. The SEM images

Table 1. Gelation properties of **3HHB-*n*** and **FPB-7** in organic solvents at a concentration of 25 mg mL^{-1} [a]

Solvents	3HHB-*n*						FPB-7
$n =$	4	5	6	7	8	12	
Methanol	P	P	P	P	P	P	P
Ethanol	P	G	G	G	G	P	P
2-Propanol	P	G	G	G	P	P	P
Hexanol	S	G*	G*	G*	G*	S	P
1,3-Butylene glycol	P	G	P	P	G	G	P
Acetonitrile	P	G	P	P	G	P	P
Benzene	P	P	P	P	P	P	P
Acetone	P	P	P	P	P	P	P
THF	S	S	S	S	S	S	S
$CHCl_3$	S	S	S	S	S	S	P

[a] Note: G: gel, P: precipitate, S: solution, G*: gel at low temperature (−10 °C).

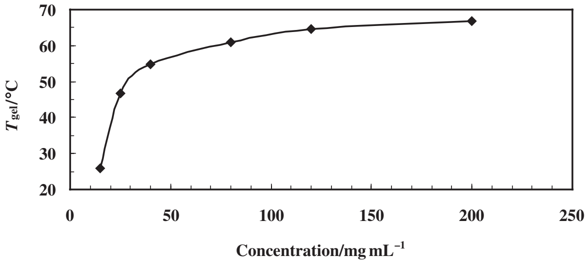


Figure 1. T_{gel} vs. concentration of **3HHB-6** in 2-propanol gels.

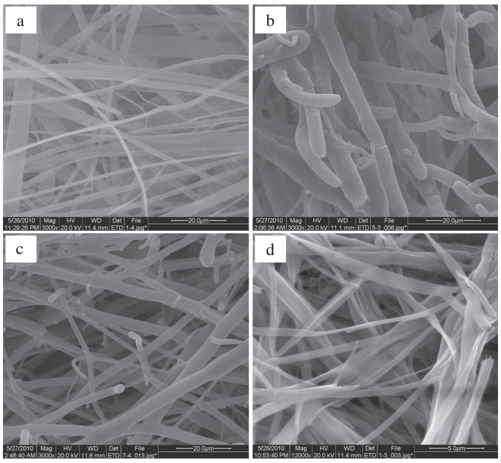


Figure 2. SEM images of xerogels: (a) **3HHB-5** (25 mg mL^{-1}), (b) **3HHB-6** (35 mg mL^{-1}), (c) **3HHB-7** (25 mg mL^{-1}) from 2-propanol, and (d) **3HHB-8** (25 mg mL^{-1}) from ethanol.

demonstrated the presence of a 3D networks composed of intertwined fibers, with the diameters in the range of 1–6 µm and length of about tens of micrometers, in which the flow of the solvent could be prevented, resulting in the formation of a solid-like gel. Similar SEM images were observed from other xerogels.

It is well known that hydrogen bonding is one of the driving forces for the self-assembly of organogel in organic solvents. As powerful tools for investigating hydrogen-bonding interaction, FTIR and ^{1}H NMR spectroscopy were utilized. Figure 3 shows FT-IR spectra of **3HHB-6** powder (a) and its xerogel from 2-propanol (b). It could be seen from Figure 3 that the IR spectrum of xerogel was similar to that of the KBr pellet of **3HHB-6** powder, suggesting that the pattern of hydrogen bonding in the gel was close to that in the crystal. Figure 4 shows a set of partial ^{1}H NMR spectra of **3HHB-6** in $CDCl_3$ at different concentrations. The result from the concentration-dependent test of the ^{1}H NMR signal of N–H bond is also in support of the involvement of the group in the formation of gel network structures. With reference to Figure 4, the signal of N–H shifted to higher field (from 8.78 to 8.66 ppm) along with decreasing the concentration from 0.1 to 0.01 M, evidence of disruption of the hydrogen bonds, in which the amide proton was involved.

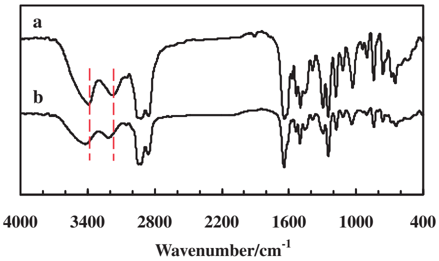


Figure 3. FT-IR spectra of (a) crystal and (b) xerogel of **3HHB-6** from 2-propanol (35 mg mL^{-1}).

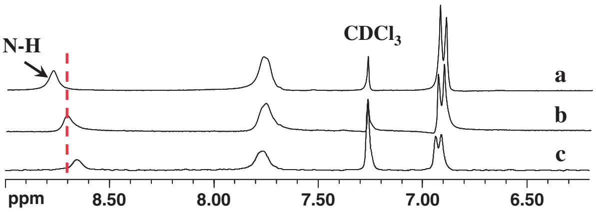


Figure 4. ^{1}H NMR spectra of **3HHB-6** in $CDCl_3$ at different concentrations (300 MHz): (a) 10^{-1}, (b) 5×10^{-2}, and (c) 10^{-2} M.

In conclusion, the present results provided a novel kind of a low molecular weight organogelator with a benzoylhydrazone moiety and a bi(cyclohexyl) group. These compounds could self-assemble into ordered aggregates of fiber structure and construct 3D networks, in which hydrogen bonding and van der Waals interaction played important roles.

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References

1 M. Llusar, C. Sanchez, *Chem. Mater.* **2008**, *20*, 782; N. W. Fadnavis, A. Deshpande, *Curr. Org. Chem.* **2002**, *6*, 393; I. Sato, K. Kadowaki, H. Urabe, J. H. Jung, Y. Ono, S. Shinkai, K. Soai, *Tetrahedron Lett.* **2003**, *44*, 721; K. Hanabusa, K. Hiratsuka, M. Kimura, H. Shirai, *Chem. Mater.* **1999**, *11*, 649.
2 A. Vintiloiu, J.-C. Leroux, *J. Controlled Release* **2008**, *125*, 179; L. Kang, X. Y. Liu, P. D. Sawant, P. C. Ho, Y. W. Chan, S. Y. Chan, *J. Controlled Release* **2005**, *106*, 88; N. M. Sangeetha, U. Maitra, *Chem. Soc. Rev.* **2005**, *34*, 821.
3 O. Gronwald, E. Snip, S. Shinkai, *Curr. Opin. Colloid Interface Sci.* **2002**, *7*, 148; P. Terech, R. G. Weiss, *Chem. Rev.* **1997**, *97*, 3133.
4 S. Malik, S. Kawano, N. Fujita, S. Shinkai, *Tetrahedron* **2007**, *63*, 7326.
5 A. Vintiloiu, M. Lafleur, G. Bastiat, J.-C. Leroux, *Pharm. Res.* **2008**, *25*, 845; F. Plourde, A. Motulsky, A.-C. Couffin-Hoarau, D. Hoarau, H. Ong, J.-C. Leroux, *J. Controlled Release* **2005**, *108*, 433; K. Hanabusa, K. Okui, K. Karaki, M. Kimura, H. Shirai, *J. Colloid Interface Sci.* **1997**, *195*, 86.