A Small Molecular Gelling Agent for Organic Liquids: N-Benzyloxycarbonyl-L-alanine 4-Hexadecanoyl-2-nitrophenyl Ester

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N-Benzyloxycarbonyl-L-alanine 4-hexadecanoyl-2-nitrophenyl ester can form thermoreversible hard gels at less than 1% by mass in methanol or cyclohexane; TEM (transmission electron micrograph) and SEM (scanning electron micrograph) of gels reveal rod-like fibres and huge aggregates with branched structure, which are mainly assembled by hydrogen bonding between N–H and C=O of the urethane bond.

It is known that some small molecules form huge polymer-like aggregates and cause physical gelation for which weak interactions are involved in establishing the network.[1] In the course of the preparation of amphiphilic amino acid derivatives, we discovered serendipitously the gelling phenomena of methanol or cyclohexane in the presence of a small amount (less than 1% by weight) of N-benzyloxycarbonyl-L-alanine 4-hexadecanoyl-2-nitrophenyl ester.†

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† N-Benzyloxycarbonyl-L-alanine 4-hexadecanoyl-2-nitrophenyl ester was prepared from N-benzyloxycarbonyl-L-alanine and 4-hexadecanoyl-2-nitrophenol[2] using N,N'-dicyclohexylcarbodiimide as the coupling reagent in ethyl acetate. The filtrate after the removal of dicyclohexylurea was evaporated and the resulting residue was dissolved in hot methanol. After cooling, the gel formed was filtered with suction and dried (yield 83%). Pale-yellow matter, m.p. 84–86 °C, satisfactory C, H and N analyses were obtained.

The TEM of a gel formed by the L-alanine ester in methanol (Fig. 1), negatively stained by osmic acid, shows a rod-like molecular fibre juxtaposed by several extended slender filaments whose diameter is *ca.* 30–40 nm. The SEM, which can reflect the large scale structure of the aggregate as compared with the TEM, of the gel in methanol is shown in Fig. 2. It reveals a huge aggregate which is three-dimensional and interlocking. Considering the size of the smallest diameter (*ca.* 10 000 nm) of the huge aggregate in Fig. 2, it can be assumed that the gathering of numerous rod-like fibres observed in the TEM forms the intertwined huge aggregate to immobilize the isotropic liquid.

The FTIR spectrum of the L-alanine ester gel in cyclohexane is characterized by bands at 3300 and 1700 cm^{-1} which are assigned to N–H and C=O stretching vibrations of the urethane bond for intermolecular hydrogen bonding. It should be mentioned here that the FTIR spectrum of the
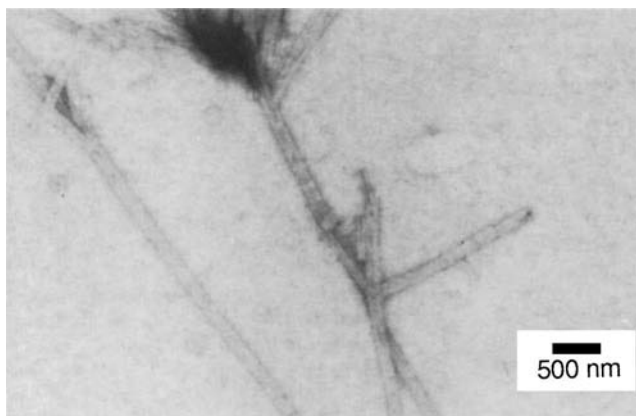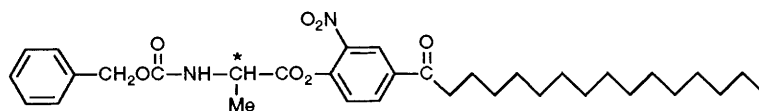
Fig. 1 Transmission electron micrograph of loose gel from the L-alanine ester in methanol (1 g dm^{-3}), negatively stained by osmic acid
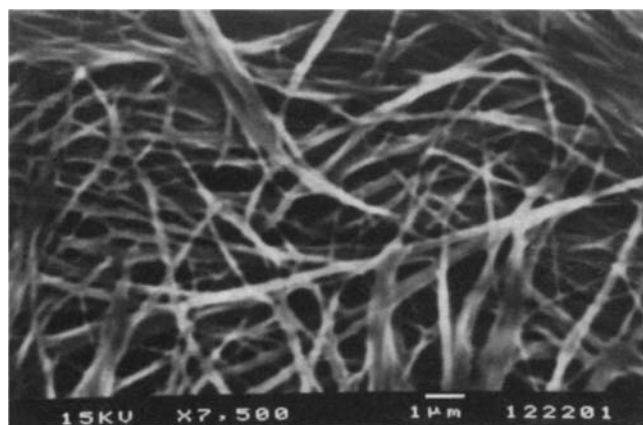

Fig. 2 Scanning electron micrograph of a dried gel from the L-alanine ester in methanol (1 g dm^{-3}), shaded by gold
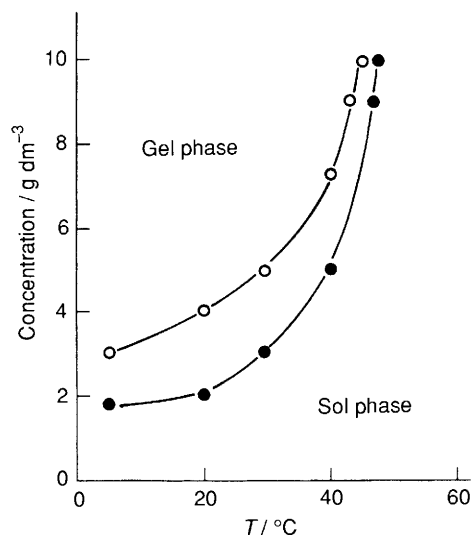

Fig. 3 Sol–gel phase diagram; the minimum gel concentration of the L-alanine ester vs. temperature in methanol ($\circ$) and cyclohexane ($\bullet$)

L-alanine ester in chloroform or carbon tetrachloride which is a homogeneous solution shows N–H and C=O stretching vibrations at 3450 and 1780 cm^{-1} for non-hydrogen bonding, but not hydrogen bonding. Surprisingly, hydrogen bonding is confirmed for the L-alanine ester gel in methanol a polar protic solvent. These results suggest that the intermolecular hydrogen bonding between N–H and C=O of the urethane bond is essential for gelation.

In Fig. 3 the minimum concentration of the L-alanine ester necessary for gelation is plotted vs. temperature. The sol–gel process depends on temperature, since the minimum concentrations necessary to form the gel decrease with decreasing the temperature. Using the sol–gel phase diagram, the thermodynamic parameters can be calculated from the following equations:[3] $\Delta G = RT\ln C$, $\Delta H = -RT^2(\mathrm{d}\ln C/\mathrm{d}T)$, $\Delta S = \Delta H/T - \Delta G/T$, where C is the minimum gel concentration expressed as unit mol fraction. The thermodynamic parameters for the sol to gel transition are: ΔH (25 °C) = -22.6 kJ mol^{-1}, ΔS (25 °C) = -7.1 J K^{-1} mol^{-1} for

methanol, and ΔH (25 °C) = -24.7 kJ mol^{-1}, ΔS (25 °C) = -9.6 J K^{-1} mol^{-1} for cyclohexane. These parameters indicate that the enthalpic contribution compensates for the undesirable entropic change. In other words, the enthalpic contribution is substantially important for the gel formation. Considering that the ΔH of hydrogen bonding is -15.5 kJ mol^{-1} for N-methylacetamide in cyclohexane,[4] the interaction that makes ΔH negative might arise from not only hydrogen bonding between N–H and C=O of the urethane bond but also from other interactions. In particular, the dipole–dipole interaction of NO$_2$ and C=O, and the hydrophobic interaction of the long hydrocarbon chain should be significant for gelation, since the structurally related molecules without NO$_2$ at the 2-position, C=O at the 4-position, or a long hydrocarbon chain can no longer act as gelling agents.

To study the chiral structure of the aggregate in a loose gel (0.1% by mass), circular dichroism (CD) spectra were measured for the L-alanine and D-alanine ester in cyclohexane. The CD spectrum for the L-alanine ester at 25 °C reveals a strong negative peak due to the nitrophenylene unit; $[\theta]_{294} = -6.65 \times 10^4$. In contrast, the spectrum for the D-alanine ester at 25 °C is characterized by a positive peak; $[\theta]_{292} = +6.71 \times 10^4$. These strong CD peaks disappear at 50 °C as the loose gel is transformed to an isotropic solution. In addition, a racemic D,L-alanine ester which is not a gel-forming agent does not show a CD spectrum. As such a much-enhanced CD is derived from exciton coupling among the organized chromophore,[5] the observed CD data indicate that the component molecules in the aggregate are cooperatively organized in cyclohexane. The original chirality of the alanine ester is also essential for the formation of a suitable aggregate for gelation.

In conclusion, N-benzyloxycarbonyl-L-alanine 4-hexadecanoyl-2-nitrophenyl ester can form thermoreversible gels in methanol or cyclohexane. The formation of gels depends upon the concentration of the gelling agent, its structure, and the temperature. The TEM and SEM suggest that the intertwined huge threads may be formed by the gathering of numerous rod-like molecular fibres juxtaposed by several slender filaments. The hydrogen bonding interaction between N–H

and C=O of the urethane bond, the dipole–dipole interaction of NO_2 and C=O, and the hydrophobic interaction of the long hydrocarbon chain are the driving force for gelation.

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