Cyclo(dipeptide)s as Low-molecular-mass Gelling Agents to Harden Organic Fluids

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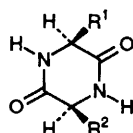
Cyclic dipeptides consisting of diverse amino acids can cause physical gelation in a wide variety of organic fluids, including edible oils, glyceryl esters, alcohols and aromatic molecules; the gelation phenomenon is characterized by minimum gel concentration, FTIR spectroscopy, transmission electron microscopy, and X-ray diffraction.

The disposal of crude oil spills and used cooking oil has been identified as a serious problem with respect to pollution of the environment. Presently there are about twelve groups of small molecule gelling agents[1] which are characterized by both good solubility upon heating (as compared with macromolecular gelling agents[2]) and by inducement of smooth gelation of organic fluids at room temperature of small amounts of them even at low concentrations of the gelling agent. Thus low-molecular-mass gelling agents play an important role in the environment.

We have been studying thermoreversible physical gels, whose behaviour is governed by intermolecular hydrogen bonding and van der Waals interactions. Intermolecular hydrogen bonding is important in building up macromolecule-like aggregates and van der Waals interactions are necessary to juxtapose and interlock the formed aggregates. The most difficult problem for the development of low-molecular-mass gelling agents is how to stabilize the formed gel, in other words, how to prevent the transformation from the metastable gel to a crystalline state. The introduction of long-chain alkyl groups to gelling agents in previous investigations[3] was designed to prevent crystallization. In this communication we report cyclo(dipeptide)s as a new class of gelling agents. The present cyclo(dipeptide)s are, to our knowledge, the lowest-molecular mass and simplest gelling agents so far reported.

We studied the gelation ability of various cyclo(dipeptide)s† with the expectation that (i) cyclo(dipeptide)s have four hydrogen-bonding sites in each molecule to enable formation of a molecular aggregate, (ii) the random alignment of cyclo(dipeptide) consisting of differing amino acids in the aggregate should prevent crystallization and so stabilize the gel state. A typical procedure for studying gel formation ability was to mix a weighed cyclo(dipeptide) with an organic fluid (1 cm³) in a septum-capped test tube and heating until the solid dissolved. The resulting solution was then cooled at 25 °C for 2 h and the onset of gelation studied. Upon formation the gels were stable and the samples can be inverted without any change of shape of the gel.

From our detailed study, it was established that there is no gelation ability for cyclo(glycylglycyl) ($R^1 = R^2 = H$), cyclo[(R)-valyl-(R)-valyl] ($R^1 = R^2 = CHMe_2$), cyclo[(R)-leucyl-(R)-leucyl] ($R^1 = R^2 = CH_2CHMe_2$), cyclo[(R)-phenyl-alanyl-(R)-phenylalanyl] ($R^1 = R^2 = CH_2Ph$), cyclo[(R)-asparaginyl-(R)-phenylalanyl] ($R^1 = CH_2CO_2H$, $R^2 = CH_2Ph$), cyclo[(R)-leucyl-(R)-glutamyl] ($R^1 = CH_2CHMe_2$,

$R^2 = CH_2CH_2CO_2H$), and cyclo[(R)-leucyl-(R)-γ-benzyl-glutamyl] ($R^1 = CH_2CHMe_2$, $R^2 = CH_2CH_2CO_2CH_2Ph$). However, gelation was observed with cyclo[(R)-phenylalanyl-(R)-leucyl] 1, cyclo[glycyl-(R)-γ-ethylglutamyl] 2, cyclo[(R)-valyl-(R)-leucyl] 3, cyclo[(R)-valyl-(R)-γ-ethylglutamyl] 4, cyclo[(R)-valyl-(R)-γ-3,7-dimethyloctylglutamyl] 5, cyclo-[(R)-valyl-(R)-γ-2-ethylhexylglutamyl] 6, cyclo[(R)-leucyl-(R)-γ-ethylglutamyl] 7, cyclo[(R)-β-butylasparaginyl-(R)-phenylalanyl] 8 and cyclo[(R)-β-3,7-dimethyloctylasparag-inyl-(R)-phenylalanyl] 9. Results for gelation with 1–9 several organic fluids are summarized in Table 1. The formed gels are stable even after several months, except for that of glyceryl trioleate with 3 which transforms to a crystalline state after several days. Almost all of the cyclo(dipeptide)s 1–9 can harden soybean oil and glyceryl trioleate even at a low concentration. In general, cyclo(dipeptide)s consisting of differing amino acids (e.g. neutral and acidic) are superior as gelling agents to those containing similar amino acids such as 3, which forms only in chloroform. However, 1 consisting of (R)-phenylalanine and (R)-leucine which are neutral amino acids with quite different structure can form gels at very low concentration (1–5 g for 1 dm³ of organic fluid). From a comparison of 8 with 9, it is clear that the introduction of branched alkyl group into R¹ improves the gelation ability. Branched alkyl groups such as 1,3-dimethyloctyl and 2-ethyl-hexyl are thought to prevent crystallization of the gelling agent.

In Fig. 1 are shown transmission electron micrographs (Hitachi H700) of a chloroform gel formed by 3 and a toluene gel formed by 9. Numerous juxtaposed and intertwined fibres are formed by entanglement of long slender aggregates with widths of 30–70 nm in the case of the gel with 3. The FTIR spectrum of the chloroform gel of 3 is characterized by broad bands at 3320 and 1640 cm⁻¹ assigned to N–H and C=O hydrogen-bonding stretching vibrations, whereas the corresponding homogeneous solution containing 3 at less than the minimum gel concentration affords bands at 3400 and 1690 cm⁻¹ indicative of non-hydrogen-bonding stretching vibra-

1 R¹ = CH₂Ph, R² = CH₂CHMe₂
2 R¹ = H, R² = CH₂CH₂CO₂Et
3 R¹ = CHMe₂, R² = CH₂CHMe₂
4 R¹ = CHMe₂, R² = CH₂CH₂CO₂Et
5 R¹ = CHMe₂, R² = CH₂CH₂CO₂CH₂CH₂CHMeCH₂CH₂CH₂CHMe₂
6 R¹ = CHMe₂, R² = CH₂CH₂CO₂CH₂CHEtCH₂CH₂CH₂Me
7 R¹ = CH₂CHMe₂, R² = CH₂CH₂CO₂CH₂Me
8 R¹ = CH₂CO₂CH₂CH₂CH₂Me, R² = CH₂Ph
9 R¹ = CH₂CO₂CH₂CH₂CHMeCH₂CH₂CH₂CHMe₂, R² = CH₂Ph

Table 1 Minimum gel concentration of cyclo(dipeptide)s necessary for gelation at 25 °C

Organic fluid	Minimum gel concentration/ g dm⁻³ (gelator/organic fluid)								
	1	2	3	4	5	6	7	8	9
Soybean oil	1	3	a	5	14	20	5	5	13
Glyceryl tricaprylate	2	4	a	21	a	14	10	a	15
Glyceryl trioleate	2	3	a	23ᵇ	19	20	9	a	15
Ethanol	a	a	a	a	a	a	a	a	28
Acetone	c	a	d	a	a	a	a	d	27
Ethyl acetate	c	a	a	a	a	a	a	d	23
Chloroform	c	c	16	a	a	a	a	a	a
Tetrachloromethane	d	d	d	d	6	c	c	c	c
Benzene	c	c	a	d	d	9	6	c	10
Toluene	5	c	c	2	25	9	2	c	3
Methoxybenzene	3	11	a	a	a	a	7	5	a
Chlorobenzene	3	10	a	11	a	15	10	4	11
Nitrobenzene	3	10	a	a	a	a	a	7	a

ᵃ Crystallization. ᵇ The formed gel was transformed into crystals after several days. ᶜ Highly viscous fluid was obtained. ᵈ Almost insoluble.

tions; the long slender aggregates are built up by intermolecular hydrogen bonds between N–H and C=O of amide bonds of cyclo(dipeptide).

Slow evaporation of the gels gave translucent films *i.e.* xerogels, not crystals. The X-ray diffraction patterns of the xerogel from the tetrachloromethane gel of **5** are characterized by four sharp reflections of 19.3, 9.7, 6.4 and 4.9 Å which are almost exactly in the ratio 4 : 3 : 2 : 1. This means the xerogel displays a layered structure as the interlayer distance corresponding to the (100) plane is 19.3 Å.

Combining the FTIR and X-ray diffraction data, it can be deduced that the aggregate responsible for gel formation is an assembly of hydrogen-bonded molecular ladders. It may be assumed that ladder-like aggregates are initially formed from numerous molecules by intermolecular hydrogen bonding, then they are juxtaposed and grow as the large slender aggregates observed in Fig. 1. The (100) plane of the layered

structure as determined by X-ray diffraction is the distance between close-neighbouring ladders. The aggregates are intertwined and interlocked by defects of hydrogen bonding and/or the van der Waals interactions between the R^1 and R^2 groups, and this results in the immobilization of the organic fluids. It is important to note that the random alignment of R^1 and R^2 in aggregates will enhance the stability of formed gel. Such stability was found only in cyclo(dipeptide)s consisting of differing amino acids, and was not observed in any cyclo-(homodipeptide) which easily precipitated crystals in organic fluids. We can conclude that the main driving forces for gel formation of cyclo(dipeptide) are (*i*) the presence of the intermolecular hydrogen bonds which lead to aggregation and (*ii*) random alignment of each molecule which prevents crystallization.
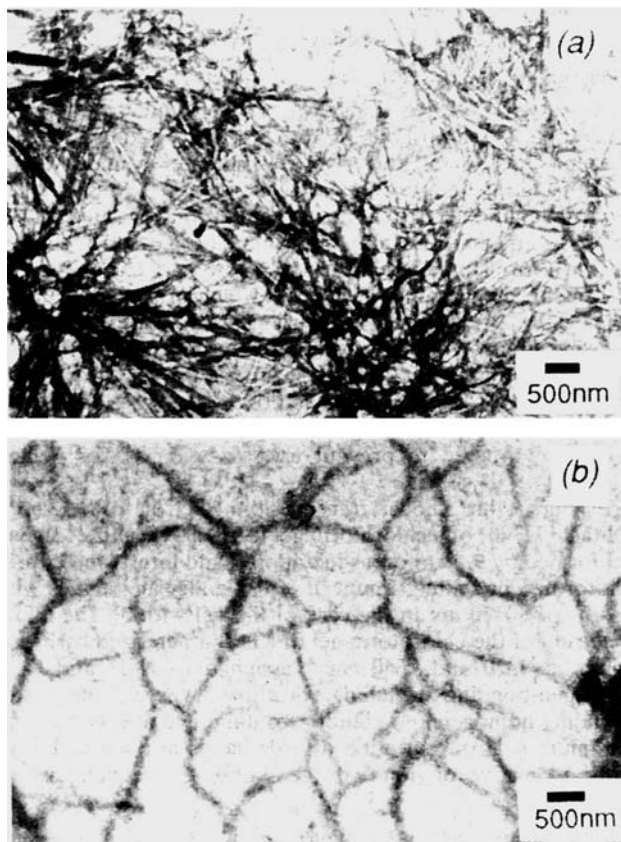
Fig. 1 Electron micrographs negatively stained by osmic acid: (*a*); a chloroform gel formed by **3**, (*b*); a toluene gel formed by **9**

Footnote

† Cyclo(dipeptide)s were usually prepared by cyclization of dipeptide ethyl esters, refluxed in 1,3,5-trimethylbenzene, which were obtained by catalytic hydrogenation of the corresponding *N*-benzyloxycarbonyldipeptide ethyl ether with 10% Pd–C. **5** and **6** were prepared by the transesterification of **4** in 3,7-dimethyloctanol and 2-ethylhexanol. **8** and **9** were synthesized by the esterification of cyclo[(*R*)-asparaginyl-(*R*)-phenylalanyl] which was prepared by heating the commercially available artificial sweetener Aspartame (Wako). Satisfactory C, H, and N analytical data within ±0.4% were obtained for all cyclo(dipeptide)s after recrystallization.

References

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3 See the reference of Brotin *et al.* and the three last refs. of ref. 1.