Small Depsipeptides as Solvent Gelators

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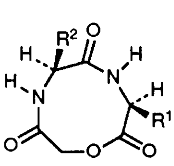
The formation of very thermostable gels with several solvents is reported for two cyclic depsipeptides of comparatively low molecular mass.

During investigations of the synthesis and complexing properties of cyclic depsipeptides of the type shown (**1**–**4**),[1] we met with an unexpected phenomenon. Compound **1**, cyclo[CH_2-CO-L-Leucyl-L-Leucine], is able to gelate the solvents diethyl ether, methylene chloride, ethyl acetate, acetonitrile and acetone. This is unanticipated and as far as we are aware only one article has appeared in the field of the cyclic (depsi)peptides in which the gelation of solvents is even mentioned specifically. The catalytic hydrocyanation of benzaldehyde is catalysed by the six-membered diketopiperazine cyclo[(*R*)-

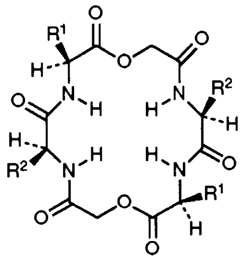
Table 1 Gelation ratio and T_{gel} of the five solvents that can be gelated by **1**

	Mol ratio **1** : solvent	T_{gel}/°C
CH_2Cl_2	1 : 167	>60
MeCN	1 : 429	>90
Et_2O	1 : 315	>37
EtOAc	1 : 110	—[a]
Acetone	1 : 364	>85

[a] Not determined, this gel is not uniform.

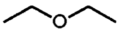
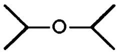
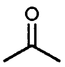
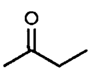
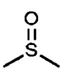
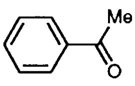
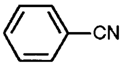
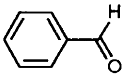
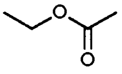
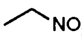
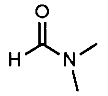


1; $R^1 = R^2 = CH_2CHMe_2$
2; $R^1 = R^2 = H$



3; $R^1 = R^2 = CHMe_2$
4; $R^1 = CHMe_2$, $R^2 = CH_2CHMe_2$

Table 2 Solvents that can be gelated and some structurally similar solvents that are not gelated by **1**

Gelation	No gelation
	
	  
MeCN	 
	 $MeNO_2$ 
CH_2Cl_2	EtOH $CHCl_3$ CCl_4 CS_2 Hexane

Phe-(*R*)-His], which gelates the solvent toluene.[2] Recently the aggregation of cyclic peptides in solution through a hydrogen bond interaction between amide linkages has been described.[3,4] This, however, does not lead to gelation.

Until recently, the gelation of solvents seemed to be the province of macromolecules, surfactants and other compounds containing long alkyl chains. However, cholesterol-based gelators[5] are now known, a menthyl-derived gelator has been described,[6] and even gelation induced by calixarenes[7] and cyclodextrins[8] has been reported. A common feature of these systems is that they are only able to gelate relatively apolar solvents like hexane, cyclohexane and pentanol. Our system gelates both a polar (MeCN) and an apolar (Et_2O) solvent but not hexane, cyclohexane or pentanol. The low molecular mass of **1**, 284, along with the lack of functional groups like aryl rings or alkyl chains that might in a logical fashion lead to multiple interactions between the gelator and solvent, make our gelator a special case.

A typical procedure for preparation of a gel is as follows: 10 mg of compound **1** is dissolved in a drop of methanol in a test tube. The solvent under investigation is slowly added from a Pasteur pipette whereupon virtually instantaneous gelation occurs. Immediately after the gel is formed, it contracts a little and expels a little solvent (syneresis). The best solvent is diethyl ether; 10 mg of **1** can gelate *ca.* 1 g of this solvent. This gel is very stable (months) and resists gravitational flow. The test tube can be inverted (for weeks) without change of shape of the gel. For further results see Table 1.

We do not know whether the small amount of methanol has any other role than bringing **1** into solution (it is not freely soluble in the solvents that are gelated). Preparing a gel from acetone alone fails because **1** does not dissolve in acetone. Heating or sonication failed to bring **1** into solution. Instead of methanol other solvents that dissolve **1** can be used, *i.e.* water or dimethyl sulfoxide (DMSO). Gelation of, *e.g.*, acetone is again observed.

The great stability of the gel is reflected in its gel-melting temperature T_{gel}. Every gel has a temperature above which it disintegrates and loses all structure. A very simple test for the determination of T_{gel} has been developed by Takahashi *et al.*[9] A small steel ball is placed on top of the gel in a test tube, which is slowly heated in a thermostatted waterbath. At T_{gel} the ball falls to the bottom of the test tube. The temperatures determined in this way usually range up to about 55 °C. Every time we tried to perform this test, it failed; in our case, when the gel is heated above the boiling point of the solvent, the solvent evaporates and the gel slowly shrinks without losing structure (with macromolecules this is the typical behaviour of xerogels). In the case of acetone, the solvent begins to evaporate only at 85 °C (the boiling point of acetone is 57 °C!).

The gel displayed no birefringency and a total absence of gelation is found in the presence of salts like NaCl and $Zn(NO_3)_2$.

Structural analogues of the solvents that can be gelated often fail to gelate. For instance, whereas acetone can be gelated neither butan-2-one nor DMSO can be gelated; further examples are given in Table 2.

That this fine balance is the result of differing steric interactions between **1** and the solvents seems unlikely since the structural diversity among the gelated solvents is great. If the structure of butan-2-one is for some reason too large, then why is it possible to gelate ethyl acetate? If this lack of gelation is the result of differing polarity of the solvents, then this should be reflected in the solvent parameters which are known for most solvents.

The dielectric constants of the gelated solvents show no logical connection; these range in ε from 5–36, whereas the solvents that cannot be gelated sometimes have very similar ε-values. The difference in ε for acetone and butan-2-one (20.7 and 18.5 respectively[10]) is not very large. Furthermore, the large variation in ε is not satisfying. A similar unsatisfactory pattern emerged on examination of the Dimroth ET_{30} solvent parameter.[11]

From NMR-studies we were acquainted with the Gutmann donating number[12] (DN, Gutmann donicity). There is a linear relationship between the DN of a solvent and the ^{23}Na chemical shift in that solvent.[13] The DN describes the ability of the solvent to solvate ions. Also with this parameter there is no absolute correlation with gelating properties; the solvents that can dissolve **1** all have a DN of about 30 and the solvents that can be gelated all have rather similar donicities (14–20). The solvents that cannot dissolve **1** have low donor numbers; however, CH_2Cl_2, which has a DN of 1 but still can be gelated, is an exception.

The gelating properties of **1** have been investigated most extensively. The nine-membered ring compound **2**, devoid of side chains and amorphous, is not effective as a gelator. The 18-membered ring compound **3** is a good gelator of water (T_{gel} > 65 °C), if first dissolved in a drop of DMSO. Surprisingly, the structurally related ring compound **4**, which is the most crystalline of the series **1–4**, exhibits no tendency to gelate any solvent.

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References

1 W. H. Kruizinga, R. Kingma, L. Leegstra, E. Rokaszewski, G. Gruppen and R. M. Kellogg, *J. Chem. Soc., Chem. Commun.*, 1990, 1647.
2 H. Danda, H. Nishikawa and K. Otaka, *J. Org. Chem.*, 1991, **56**, 6740.
3 T. Shimizu, Y. Tanaka and K. Tsuda, *Int. J. Pept. Protein Res.*, 1986, **27**, 554.
4 H. Miyake, Y. Kojima, T. Yamashita and A. Ohsuka, *Bull. Chem. Soc. Jpn.*, 1992, **65**, 917.
5 Y. Lin, B. Kachar and R. G. Weiss, *J. Am. Chem. Soc.*, 1989, **111**, 5542.
6 J. C de Jong, PhD Thesis, Groningen, 1991.
7 M. Aoki, K. Murata and S. Shinkai, *Chem. Lett.*, 1991, 1715.
8 C. de Rango, P. Charpin, J. Navaza, N. Keller, I. Nicolis, F. Villain and A. W. Coleman, *J. Am. Chem. Soc.*, 1992, **114**, 5475.
9 A. Takahashi, M. Sakai and T. Kato, *Polym. J.*, 1980, **12**, 335.
10 *Handbook of Chemistry and Physics*, CRC Press, Boca Raton, Florida, 56th edn., 1984.
11 C. Reichart, *Solvents and Solvent Effects in Organic Chemistry*, VCH Verlag, Weinheim, 2nd edn., 1988.
12 For a list of about 200 Donor Numbers see: Y. Marcus, *J. Solution Chem.*, 1984, **13**, 599.
13 R. H. Ehrlich, E. Roach and A. I. Popov, *J. Am. Chem. Soc.*, 1970, **92**, 4989.