N-(2-Carboxybenzoyl)-L-Phenylalanylglycine: a Low Molecular-mass Gelling Agent

H. Thijs Stock,[a] Nicholas J. Turner*[a] and Raymond McCague[b]

[a] *Department of Chemistry, University of Exeter, Stocker Road, Exeter, UK EX4 4QD*
[b] *Chiroscience Ltd, Cambridge Science Park, Milton Road, Cambridge, UK CB4 4WE*

N-(2-Carboxybenzoyl)-L-phenylalanylglycine **3a** forms gels with several organic solvents.

Gelation of organic solvents by small molecules has received increasing attention during the last few years. Several organic compounds have been reported to each gelate a specific range of solvents. Small amounts of these gelator molecules can bind considerable amounts of solvent molecules. Gels may have a wide range of possible applications *e.g.* environmentally as hardeners of spilled solvents or medicinally as drug-delivery systems.

Solvent gelation is believed to proceed *via* aggregation of gelator molecules upon formation of a three-dimensional network in which solvent molecules are captured. The gelator network is built-up *via* hydrogen bonding and/or van der Waals interactions. The reported gelator molecules display a wide structural diversity, varying from apolar compounds, such as anthraquinyl linked steroids[1] and anthracyl alkyl ethers,[2] to polar compounds containing long alkyl chains[3] or apolar moieties,[4] to polar compounds without large apolar moieties, *e.g.* β-cyclodextrins,[5] sorbitol derivatives,[6] oligomers of α-amino acids,[7] cyclic depsipeptides[8] and cyclic dipeptides.[9] We here report a new type of polar gelator, which has a low molecular mass (370) and can be obtained in high yield, *via* a facile synthesis.

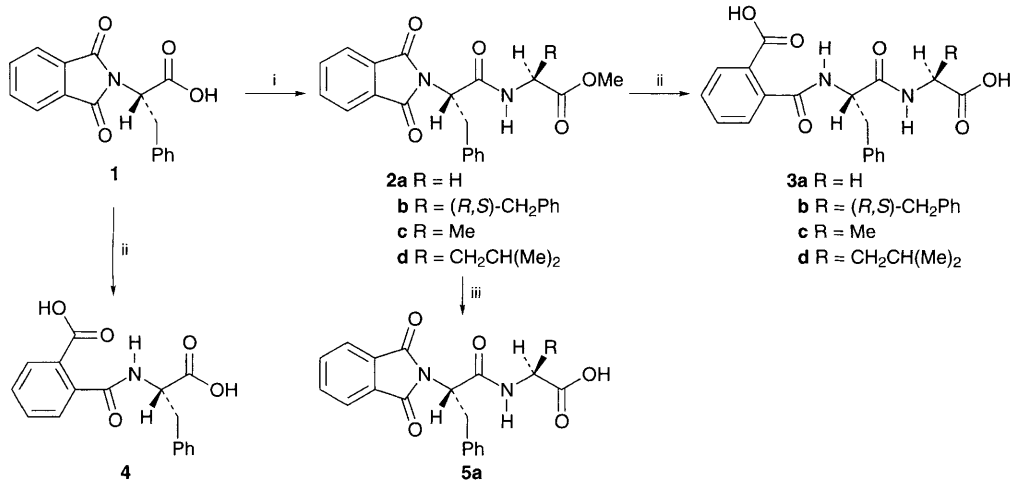
During investigations on the synthesis of oxazolinones derived from *N*-phthalimido-protected dipeptides we found that mild hydrolysis (LiOH, THF, H_2O) of the methyl ester of **2a** was accompanied by partial hydrolysis of the phthalimido protecting group,[10] giving *N*-(2-carboxybenzoyl)-L-phenylalanylglycine **3a** in 81% yield (Scheme 1). Crude **3a** turned out to be able to gelate chloroform. However, after recrystallisation of crude **3a** from ethyl acetate/light petroleum, a white solid was obtained which was insoluble in chloroform and consequently unable to gelate the solvent. From the ^{1}H NMR spectrum of crude **3a** in DMSO-[$^2H_6$], we observed that 1 equiv. of THF was present, whereas the recrystallised material was solvent-free **3a**. When the recrystallised **3a** was boiled in THF until it was totally dissolved and subsequently concentrated and dried *in vacuo*, a 1 : 1 complex of **3a** and THF was again obtained. This complex was again able to gelate chloroform. Apparently, THF is required to make **3a** soluble in chloroform.

The ^{1}H NMR spectrum of **3a**, in DMSO-[$^2H_6$], showed a downfield shift of both amide protons (to 8.69 ppm for the phenylalanyl proton, and 8.13 ppm for the glycinyl proton) as compared to the amide protons in **2a**, indicating that both amide protons of **3a** are involved in hydrogen bonding. The downfield shift of the proton *ortho* to the carboxyl group in the ring-opened phthalimido residue of **3a** (to 7.81 ppm) and the upfield shift of the proton *ortho* to the amide group in the ring-opened phthalimido residue of **3a** (to 7.08 ppm) indicates that this carboxyl group acts as a hydrogen bond acceptor and this amide group as a hydrogen bond donor. Unfortunately, the ^{1}H NMR spectrum of **3a** as a gel in $CDCl_3$ did not give us information on the type of hydrogen bonding since all the signals were extremely broad.

The 1 : 1 complex of **3a** and THF was also able to gelate methylene chloride, methylene bromide, toluene and benzene. Complex **3a**·THF did not form gels with carbon tetrachloride, cyclohexane, diethyl ether and water, in which it was (partially) insoluble and in THF, acetonitrile, nitromethane, ethyl acetate, acetone, dimethylsulfoxide, ethanol, and methanol, in which it was totally soluble.

In a typical gelation experiment a large excess of solvent was added to a weighed amount of **3a**·THF in a test tube. The mixture was heated until boiling and was then allowed to cool to room temperature. In those cases when a gel was formed (which generally happened within several minutes) the test tube was allowed to stand for 15 min. at room temperature. Thereafter the excess solvent was carefully decanted from the gel by slowly inverting the test tube. The test tube plus gel were weighed to determine the amount of gelated solvent. Chloroform was gelated most effectively by **3a**·THF. As little as 10.7 mg of **3a**·THF gelated 1.49 g of chloroform, showing that 1 molecule of complexed **3a** binds 520 molecules of chloroform. The quantitative results are summarised in Table 1.

We also performed gelation experiments with several solvent mixtures. Complex **3a**·THF was able to gelate a 1 : 1 mixture (molar ratio) of chloroform and methylene chloride. The molar gelation ratio (460) of this mixture was between the molar gelation ratios of each separate solvent. This is not generally so, since **3a**·THF did not form gels in 1 : 1 mixtures of chloroform and toluene and chloroform and benzene. Additionally, **3a**·THF did not form gels in 1 : 1 mixtures of chloroform and diethyl ether and chloroform and THF.



Scheme 1 *Reagents and conditions*: i, $H_2NCHRCO_2Me$, DCC, CH_2Cl_2, room temp., 17 h; ii, LiOH, THF/H_2O (1 : 1), room temp., 1 h; iii, BBr_3, CH_2Cl_2, room temp., 5 h

All gels could be kept for several weeks in a septum-capped tube, without noticeable deformation of the gel. However, when a gel was kept in an open tube, the solvent slowly evaporated within several days leaving behind uncomplexed **3a** as a white powder.

The gelling capacities of the gelator molecules reported in the literature generally are very susceptible to small changes in their molecular structures.[1–9] Small variations often lead to total loss of the gelling capacity. In order to determine the effect of changes in the molecular structure of **3a** with respect to the gelating capacity we synthesised several analogues (Scheme 1). Compounds **3b** (as a mixture of diastereoisomers), **3c** and **3d** were synthesised analogously to **3a**, compound **4**[10b] was prepared *via* ring opening (LiOH, THF, H_2O) of phthalimide **1**[11] and compound **5a** was prepared from methyl ester **2a** *via* demethylation with BBr_3, by which method the phthalimido group was unaffected. Neither of the analogous compounds **3b–d**, **4** and **5** formed a gel in chloroform or toluene. Except for **3d**, all these compounds were insoluble in chloroform and toluene.

Preparation of the THF complexes of these compounds did not significantly affect their solubility in chloroform and toluene and did not result in formation of gels. The ^1H NMR of **3d** in DMSO-[$^2H_6$] showed very sharp peaks, and the chemical shifts were in accordance with the chemical shifts of **3a** in DMSO-[$^2H_6$]. However, the ^1H NMR of **3d** in $CDCl_3$ showed broad peaks, although it was completely soluble and did not form a gel in this solvent. In $CDCl_3$ the C–H protons of the peptide chain both shifted 0.3 ppm downfield, one of the two benzylic protons shifted 0.1 ppm downfield, and the other benzylic proton shifted 0.4 ppm downfield. The protons of the isoleucinyl side chain shifted 0.1 ppm upfield. This might suggest different conformations of **3d** in DMSO-[$^2H_6$] and in $CDCl_3$. The sharp signals in DMSO-[$^2H_6$] indicate that in this solvent **3d** has a well defined conformation, probably with intramolecular hydrogen bonds. The broad peaks in $CDCl_3$ indicate that **3d**, although not able to form a gel, does form an aggregate *via* intermolecular hydrogen bonds. It is unclear why formation of an aggregate of **3a** in chloroform results in formation of a gel, while the aggregate of **3d** does not form a gel.

Table 1 Molar gelation ratio of **3a**·THF with several solvents

Solvent	Molar ratio
$CHCl_3$	520
CH_2Cl_2	250
toluene	77
benzene	76
CH_2Br_2	44
$CHCl_3/CH_2Cl_2$ 1 : 1 (molar ratio)	460

We are grateful to the BBSRC and Chiroscience Ltd for financial support.

Received, 20th June 1995; Com. 5/03974F

References

1 Y.-C. Lin and R. G. Weiss, *Macromolecules*, 1987, **20**, 414; Y.-C. Lin, B. Kachar and R. G. Weiss, *J. Am. Chem. Soc.*, 1989, **111**, 5542; R. Mukkamala and R. G. Weiss, *J. Chem. Soc., Chem. Commun.*, 1995, 375.

2 T. Brotin, R. Utermöhlen, F. Fages, H. Bouas-Laurent and J.-P. Desvergne, *J. Chem. Soc., Chem. Commun.*, 1991, 416.

3 K. Hanabusa, K. Okui, K. Karaki, T. Koyama and H. Shirai, *J. Chem. Soc., Chem. Commun.*, 1992, 1371; K. Hanabusa, J. Tange, Y. Taguchi, T. Koyama and H. Shirai, *J. Chem. Soc., Chem. Commun.*, 1993, 390; K. Hanabusa, T. Miki, Y. Taguchi, T. Koyama and H. Shirai, *J. Chem. Soc., Chem. Commun.*, 1993, 1382; M. Aoki, K. Murata and S. Shinkai, *Chem. Lett.*, 1991, 1715; M. Aoli, K. Nakashima, H. Kawabata, S. Tsutsui and S. Shinkai, *J. Chem. Soc., Perkin Trans. 2*, 1993, 347; T. Tachibana, T. Mori and K. Hori, *Bull. Chem. Soc. Jpn.*, 1980, **53**, 1714; R. Scartazzini and P. L. Luisi, *J. Phys. Chem.*, 1988, **92**, 829; J.-I. Fukasawa and H. Tsutsumi, *J. Colloid Interface Sci.*, 1991, **143**, 69.

4 T. D. James, K. Murata, T. Harada, K. Ueda and S. Shinkai, *Chem. Lett.*, 1994, 273; C. de Jong, Ph.D. Thesis, Groningen, 1991.

5 C. de Rango, P. Charpin, J. Navaza, N. Keller, I. Nicolis, F. Villain and A. W. Coleman, *J. Am. Chem. Soc.*, 1992, **114**, 5475.

6 S. Yamamoto, *J. Soc. Chem., Ind. Japan*, 1943, **46**, 279 (*Chem. Abstr.*, 1952, **46**, 7047); S. Yamasaki and H. Tsutsumi, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 2053.

7 K. Hanabusa, Y. Naka, T. Koyama and H. Shirai, *J. Chem. Soc., Chem. Commun.*, 1994, 2683.

8 E. J. de Vries and R. M. Kellogg, *J. Chem. Soc., Chem. Commun.*, 1993, 238.

9 K. Hanabusa, Y. Matsumoto, T. Miki, T. Koyama and H. Shirai, *J. Chem. Soc., Chem. Commun.*, 1994, 1401.

10 Ring opening of phthalimido protecting groups under alkaline aqueous conditions has been described previously: (*a*) A. McKenzie and N. Walker, *J. Chem. Soc.*, 1928, 646; (*b*) T. Yamashita, *Bull. Chem. Soc. Jpn.*, 1972, **45**, 195.

11 J. P. Greenstein and M. Winitz, *Chemistry of the Amino Acids*, Wiley, New York, vol. 2, 1961, 902.