ChemComm

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COMMUNICATION

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View Journal

Synthesis of peptoid based small molecular gelators by a multiple component reaction†

Cite this: DOI: 10.1039/c3cc41043a

Received 6th February 2013,
Accepted 7th March 2013

DOI: 10.1039/c3cc41043a

www.rsc.org/chemcomm

Hari P. R. Mangunuru,[a] Hao Yang[b] and Guijun Wang*[a]

We report the synthesis and self-assembling properties of a new class of tripeptoids synthesized by a one-pot Ugi reaction from simple starting materials. Among the focused library of tripeptoids synthesized, several efficient low molecular weight gelators were obtained for aqueous DMSO and ethanol mixtures.

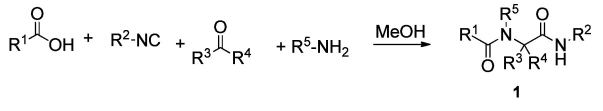
Low molecular weight gelators (LMWGs) are small molecules that can self-assemble in organic solvents or water and form typically fibrous supramolecular architectures that immobilize the solvents.[1–5] The driving forces for supramolecular gelation are non-covalent forces such as hydrogen bonding, hydrophobic interactions, π–π stacking, and van der Waals interactions, *etc.* Because gelation by LMWGs occurs through non-covalent interactions, the process is typically reversible. Small molecule self-assembly has shown great promise as a "bottom up" approach for preparing novel functional materials.[6–12] The three-dimensional networks formed by LMWGs are useful new materials with applications in various fields, including enzyme immobilization and organocatalysis,[6–7] tissue engineering and drug delivery systems.[8–12] Because of these interesting applications, a great deal of effort has been devoted to studying new types of low molecular weight gelators.[13–28] The structures of small molecule gelators encompass a wide range of different functionalities. Several classes of organic compounds have been found to be useful building blocks for the design and synthesis of LMWGs, these include amino acids, sugars, cholesterols, amides, and ureas.[13–28]

Gelators obtained from bio-based starting materials such as amino acids and carbohydrates will in general produce biocompatible materials or degradation products. Peptide based hydrogelators have been extensively studied and have shown great promise in tissue engineering and drug delivery.[29–36] However, peptides are endogenous compounds that are essential for many biological processes, and they suffer from intrinsic problems such as rapid clearance or degradation by proteases. Therefore, peptidomimetic organo/hydrogelators that contain certain structural features of the peptides but can withstand proteolysis will have profound applications in obtaining stimuli responsive advanced materials.

Among peptidomimetics, peptoids have been shown to be able to self-assemble and form fibrous networks[37] and recently a few octa-peptoid–peptide hybrids have been shown to function as hydrogelators.[38] Facile synthesis of simple peptoids that are more resistant to degradation and able to form suitable self-assembled structures will be a valuable endeavor. In this study, we have designed and synthesized a small library of tripeptoids using simple building blocks by Ugi reaction. The multiple component reactions (MCRs) are useful for generating a diverse array of compounds and for analyzing their properties. To the best of our knowledge, so far Ugi reaction has not been used in designing new types of small molecular gelators, though there have been studies using the reaction in the modification of polymer gelators.[39–40]

As shown in Scheme 1, the Ugi reaction is a very efficient reaction involving four components in a one pot reaction, in which an acid, an isocyanide, an aldehyde or ketone and an amine condense into a tripeptoid, **1**.[41] The reactions are carried out under mild conditions and usually give high yields. The tripeptoids obtained are analogous to tripeptides. This is an ideal reaction for exploring the structure diversity and to discover novel scaffolds for drugs or new materials.

For this study, we selected the readily available amines and carboxylic acids (**2**–**10**) as the building blocks for the Ugi reaction, as shown in Fig. 1. In order to simplify product purification, formaldehyde was chosen as the aldehyde component, which can produce a glycine unit in the product. Among the various building blocks, the isocyanide component is the



Scheme 1 Ugi one-pot four component reaction.

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[a] Department of Chemistry and Biochemistry, Old Dominion University, Norfolk, VA 23529, USA. E-mail: g1wang@odu.edu; Fax: +1 7576834628; Tel: +1 7576833781

[b] School of Medicine at Washington University in St. Louis, Division of Radiological Sciences, St. Louis, Missouri, USA. E-mail: yangh@mir.wustl.edu

† Electronic supplementary information (ESI) available: The experimental procedure and characterization data of compounds **14–26**. See DOI: 10.1039/c3cc41043a

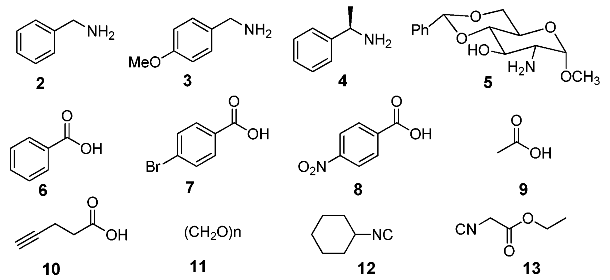

Fig. 1 Structure of the starting materials chosen for the MCR reaction.

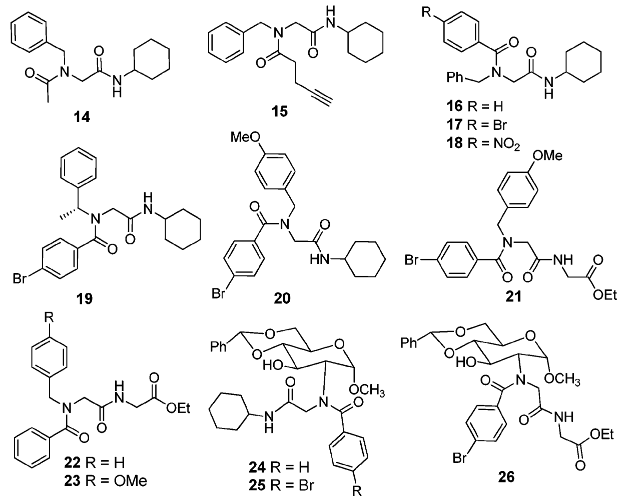

Fig. 2 The structures of peptoids synthesized by a one pot reaction.

least commercially available starting material. We selected cyclohexyl isocyanide **12**, which is based on our finding from previous studies that compounds containing a cyclohexyl group are generally effective gelators.[25] Ethyl 2-isocyanoacetate **13** was selected due to the resulting glycine ester products. Protected glucosamine **5** was also chosen as the amino building block; this can introduce a sugar function into the peptoids. Also in our previous studies, various glucosamine derivatives have shown excellent gelation properties and a broad range of substituents can be tolerated.[24–25]

From these building blocks we synthesized a small library of peptoids as shown in Fig. 2. The gelation properties of these compounds were then tested in several solvents and the results are shown in Table 1.

Only two aliphatic acid derivatives **14** and **15** are synthesized here. The rest of the compounds contain two aromatic groups in their structures, and these will introduce the aryl–aryl interaction, which is an important factor in hydrogelator designs.

From Table 1 we can see that a majority of these compounds were able to form gels in at least one of the tested solvents, several compounds turned out to be efficient gelators for ethanol aqueous solutions and DMSO aqueous solutions. The gels are thermoreversible. The best performing compound is **21**, which forms gels at 0.2 wt% in a DMSO–water (1 : 2) mixture. A general trend for these compounds is that branching or substitutions on the aryl group are generally necessary for gelation. The ethyl glycine series are in general more efficient gelators than the cyclohexyl series. Among the different amines used, *p*-methoxylbenzylamine performed the best, and the protected glucosamine also gave products that are effective gelators; the unsubstituted benzyl group did not perform well. Among the different acids used, aryl acids are in general more efficient than aliphatic acids, and substituted aryl groups performed much better than the unsubstituted analogs.

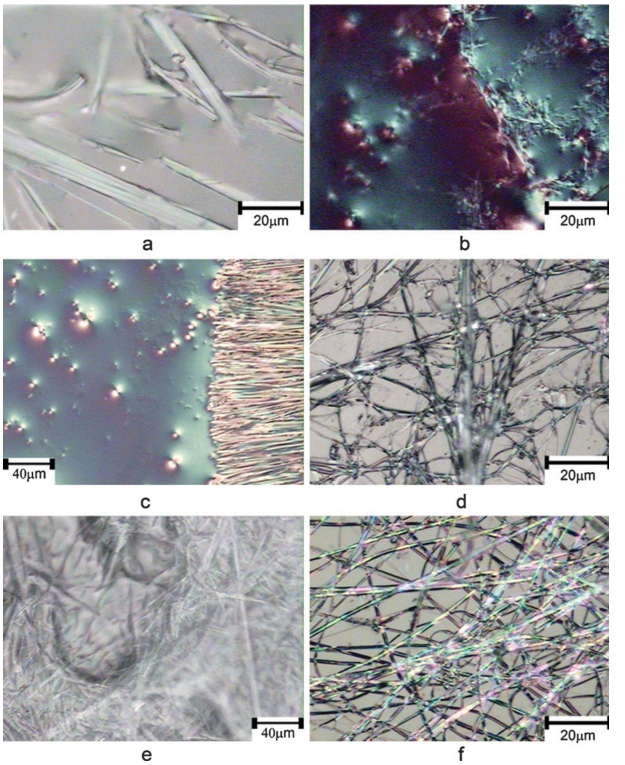

Fig. 3 Optical micrographs of the gels formed by compounds **18** (a), **26** (b) and **21** (c–f); a–d solvent DMSO : H_2O (1 : 2), e and f solvent EtOH : H_2O (1 : 2).

Fig. 3 shows the optical micrographs of several gels. Compound **18** formed a gel in DMSO aqueous mixture at 2 wt%, which is not a very efficient gelator, and the gel exhibited rod- or sheet-like morphology (Fig. 3a). Compound **26** formed a gel in DMSO–H_2O (1 : 2) at 0.66 wt%, which is a more efficient gelator, and the gels formed narrower fibrous networks (Fig. 3b). Compound **21** is the most efficient gelator identified in this study, interestingly the self-assembled structures in both DMSO–H_2O and EtOH–H_2O appeared as very long and uniform fibrous assemblies. The DMSO–H_2O gel on the edge appeared to form a cluster of aligned fibers bundled together during the drying process while in the middle of the sample showed more separated fibers (Fig. 3c and d). The EtOH–H_2O gel showed more uniform fibrous structures with an average diameter of 0.5 μm and over 300 μm in length (Fig. 3e and f). The morphology study indicated that there is a certain correlation between the gelation efficiency and the fibrous assemblies.

In summary, we have designed and synthesized a series of low molecular weight peptoids by a one-pot Ugi reaction and obtained several effective organo/hydrogelators. These compounds represent a new class of organo/hydrogelators and can have

Table 1 Gelation test results for the library compounds

Compound	Hexane	Water	EtOH	EtOH : H_2O (1 : 1)	EtOH : H_2O (1 : 2)	DMSO : H_2O (1 : 1)	DMSO : H_2O (1 : 2)
14	I	P	S	S	P	S	P
15	P	S	P	P	G 20.0	G 20.0	G 20.0
16	I	I	P	P	P	P	P
17	I	P	S	G 20.0	P	G10.0	G 5.0
18	I	P	P	G 20.0	P	G 20.0	G 10.0
19	S	P	S	P	P	G 20.0	P
20	P	P	P	G 10.0	P	G 5.0	G 6.6
21	I	S	G 20.0	G 5.0	G 2.8	G 2.5	G 2.0
22	S	S	P	P	P	S	P
23	I	S	S	P	P	P	G 20.0
24	P	I	G 20.0	P	G 20.0	P	P
25	P	I	G 20.0	G 20.0	G 20.0	G 20.0	P
26	I	P	I	G 20.0	G 10.0	G 10.0	G 6.6

G, gel at room temperature, the numbers are the corresponding minimum gelation concentrations (MGCs) in mg mL^{-1}; I, insoluble; P, precipitating; S, soluble at $\sim$20 mg mL^{-1}; the ratios for mixed solvents are volume : volume ratios.

potential applications in medicinal and materials chemistry. Using MCRs to discover low molecular weight gelators is a valid approach and will rapidly generate structures with diversity. Also the resulting peptoid gels would be more resistant to peptidases and this feature may be necessary for certain applications. These initial structure gelation properties from the focused small library can help us to design more efficient gelators and also to better understand the tripeptoid properties in aqueous solutions.

This work was supported by a grant from NSF CHE 1153129. We also thank Dr Patrick Hatcher and Susan Hatcher at COSMIC of ODU for their help with Mass spectrometry and NMR access.

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