RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

Journal Name

RSCPublishing

COMMUNICATION

Unique polymeric gel by thiol-alkyne click chemistry

Cite this: DOI: 10.1039/x0xx00000x

Mutyala Naidu Ganivada, Pawan Kumar and Raja Shunmugam*

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

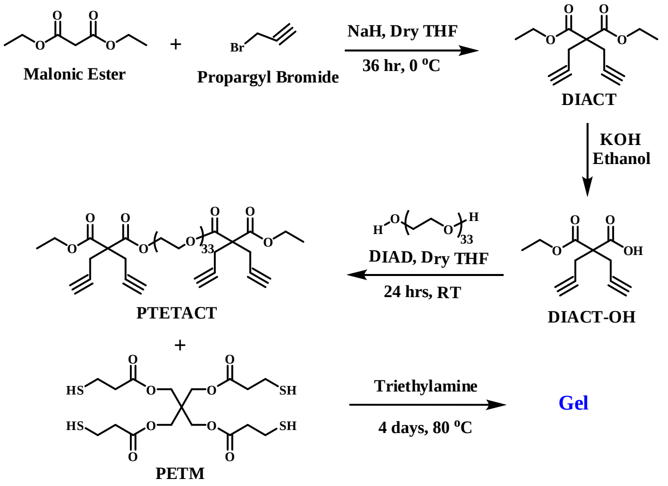
www.rsc.org/

Poly(ethylene glycol) functionalized with tetra-acetylene (PTETACT) and pentaerythritol (3-mercaptopropionic acid) (PETM) are cross-linked by a thiol-yne reaction to create robust, tuneable networks. A new class of unique gels is produced by gelations in various organic solvents as well as water. This is the first report of creating 3 D gel networks by thiol-alkyne reaction in the presence of triethylamine under moderate temperature.

Gels can be classified in two types: either by the bonds present in the network or by the nature of the liquid component used for gelation. The gel shall be called as a hydrogel if the liquid component is water[1,2] or an organogel in the case of organic liquid component.[3,4] Similarly, based on the nature of the bond involved in the gelation process, a gel can be classified. A physical gel is held by physical forces of attraction for example either by van der Waals force or hydrogen bonds.[5,6,7] However the chemical gels are held by covalent bonds.[8,9] This report explores the possibility of making unique organo/chemical-gel without using metal catalyst but by simple thiol-alkyne click chemistry.

Organogel is a solid material in which a liquid organic phase entrapped in a three-dimensionally cross-linked network. These gels are finding vast applications including electronics, medical, sports and household.[10,11,12,13] Synthesis of this type of organogels can be achieved by following two strategies; either by using high molecular weight polymers as basic material or by using low molecular weight polymers in combination with a chain extender. Presently, there are few methods to make a variety of organogels, which are well documented in the literature.[14] But the problem associated with these gels is the removal metal catalyst or other cross-linker that has been used to generate the gel network. Recently, one type of chemistry that is emerging as a potential candidate for making chemical gels, without the use of a catalyst, is thiol-ene chemistry.

Thiol-ene click chemistry has emerged remarkably in popularity over the past few years due to its numerous advantages. This Michael addition reaction is highly efficient and applicable to a wide variety of functional groups.[15] Due to high nucleophilicity of the sulfhydryl moiety, thiol-ene coupling proceeds under physiological conditions.[16,17] The advantage of the thioether linkage is very stable under physiological conditions and resists a strong basic or acidic environment. In the literature, thiol-ene reaction of multifunctional thiols with multifunctional enes is well documented in detail for the preparation of chemical gels with different types of functionality.[18] For example, gels that are useful in medical applications,[19,20,21] low gas permeable membrane, dental and optical applications to mention few.[22,23] However, thol-yne reactions to make 3D network is not explored in detail. Particularly, thiol-yne reactions without catalyst or UV light but in presence of simple amine and moderate temperature are so far not explored in the literature.



Scheme 1. Schematic representation of Synthesis polymeric gel.

In this communication, we report poly(ethylene glycol) functionalized with tetra-acetylene (**PTETACT**) and pentaerythritol (3-mercaptopropionic acid) (**PETM**) are forming an interesting 3 D network in presence of triethylamine under moderate temperature. The electron density on the ene (or yne) moiety is directly related to the thiol-ene free radical reaction rate.[24] Hence, we have predicted that the thiol-yne reaction between **PTETACT** and **PTEM** would generate an interesting 3 D network due to the enriched electron density associated with **PTETACT**.

The main objective of this study is to develop an effective method to prepare polymeric gels using thiol-alkyne click chemistry, which has, so far, not been much explored. Towards this goal, **PTETACT** and **PETM** were used in the formation of polymeric gels as shown in **Scheme 1**. **PTETACT** was first synthesised in three steps **(Scheme 1)** using simple reaction conditions. **DIACT** was prepared by treating propargyl bromide with the malonic ester in presence of sodium hydride. The crude product was purified first by column chromatography, which gave **DIACT** as a colourless crystal with 90% yield. The formation of product was confirmed by ^{1}H NMR (**Figure S1**), ^{13}C NMR (**Figure S2**), MASS and FT-IR spectroscopy. Selective mono ester hydrolysis of **DIACT** produced **DIACT-OH** as colourless crystal with 90% yield. In ^{1}H NMR spectroscopy (**Figure S3**), the appearance of new signal at δ 8.35 ppm, which was responsible for carboxylic acid protons, confirmed the formation of the **DIACT-OH**. It was further confirmed by the ^{13}C NMR (**Figure S4**), MASS and FT-IR spectroscopy.

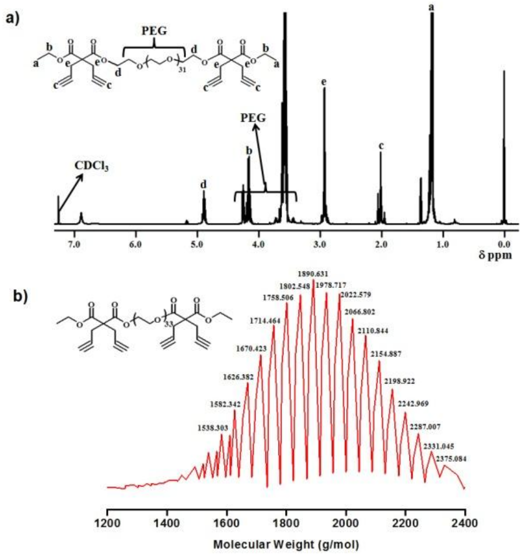


Figure 1. a) ^{1}H NMR spectroscopy and b) MALDI data of **PTETACT.**

Finally to prepare **PTETACT,** the efficient Mitsunobu coupling reaction was employed.[25] Coupling reaction between poly(ethylene glycol) (PEG-OH) (M.W. = 1450 g / mol) (**Figure S5**) and excess of **DIACT-OH** in the presence of Ph_3P and DIAD produced **PTETACT**. The formation of product was confirmed by the ^{1}H NMR spectroscopy and MALDI-TOF as shown in **Figure 1**. The measured m/z values in MALDI analysis was agreeing with the desired structure.

After the successful synthesis of **PTETACT**, it's click chemistry reaction with pentaerythritol (3-mercaptopropionic acid) (**PETM**) was explored. But in the literature, most of the thiol and acetylene click reactions were performed under the UV light. However, in our experiments, the click reaction was performed, for the first time, in presence of triethylamime (TEA) under moderate heating conditions which produced interesting gel (**Scheme 1**). In a typical reaction, the click reaction of **PTETACT** with **PETM** was performed in presence of triethylamime (TEA) at 80 °C temperature for 4 days. Formation of the gel was first characterized by FT-IR spectroscopy and later confirmed by rheology experiment. The thermogravimetric analysis study under N_2 condition confirmed thermal stability of polymeric gel upto 320 °C (**Figure S6**).

Figure 2 shows the FT-IR spectra of the **PTETACT**, **PETM** and Gel (PTETACT:PETM)(1:3) before and after cross-linking. It was clearly evident from the FT-IR of the freeze-dried gels that the S-H peak of free thiol at 2568 cm^{-1} observed in **PETM** was completely absent in Gel. This was clearly responsible for a successful click event where a C-S-C linkage was formed between **PETM** and **PTETACT** (Figure 3). From the FT-IR spectroscopy, it was confirmed that the thiol-alkyne reaction did produce the expected gel.

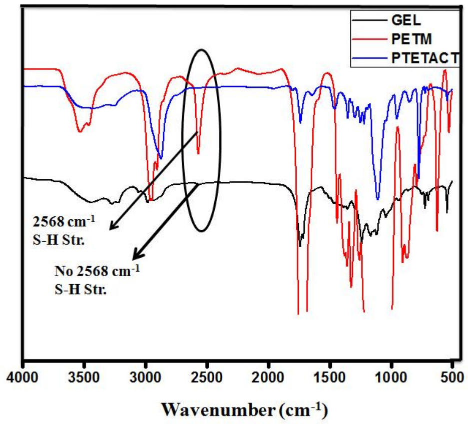


Figure 2. FT-IR spectra of **PTETACT, PETM** and GEL (PTETACT:PETM)(1:3).

The gel formation was first observed by the vial inversion experiment (**Figure 4a**). To find out the best feed ratio of **PETM** and **PTETACT** to get the strong gel, different combinations of the mol ratios of **PTETACT** and **PETM** were tried. It was very interesting to note that a 1:3 molar ratios of **PTETAC**T and **PETM** gave the strongest gel. If the ratio was not 1:3, then different type of gels like, weak, very weak or liquid gels were observed (**Table S1**). This prompted us to propose the mechanism as shown in the **Figure 3a**. To measure the mechanical strength of the gels produced with various feed ratios, rheology experiments were performed using a steel parallel plate with 40 mm diameter at 25 °C with 1.0 mm Gap spacing for all gel samples. Measurements of storage modulus (G') and loss modulus (G'') versus % strain of gel materials were first performed to understand their mechanical strength.

The greater value of G' than G'' over the measured frequency range for the gel obtained from 1:3 molar ratios of **PTETACT** and **PETM**, demonstrated the maximum mechanical behaviour for a typical cross-linked 3D network (**Figure 4d**). As expected, the differences in G' and G'' for the weaker gels were not much as shown in **Figure S7 and S8**.

After standardizing the conditions for the strong gel formation, swelling capacity of the gel was explored. Swelling ratio was monitored for 24 hour with interval of time (**Table S2 and S3**). From the given experimental conditions, it was observed that the swelling did occur in organic solvents such as DMSO, DMF, DCM, chloroform and water within an hour (**Figure 4b**). The maximum swelling occurred in DCM, followed by chloroform. We believed that by increasing the PEG content, the swelling in water would improve a lot. It was very interesting to note that the gel never showed swelling behaviour in toluene and hexane.

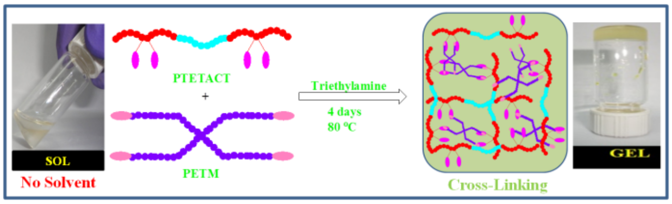


Figure 3. Cartoon representation of possible mechanism of cross-linking gel.

Finally, microstructures of both organogels as well as hydrogels were studied with scanning electron microscopy (SEM).

In general, all gels showed a continuous gel structure under the SEM. It was clearly evident from the SEM studies that a large number of porous structures could be seen in the case of organogels (**Figure 4c**). This was quite obvious since the microporous gels were obtained using polymers cross-linked at the chain ends. The maximum as well as uniform porous were observed in the case of gels swollen in DCM and $CHCl_3$ solvents (**Figure S9b** and **S9c**). The porous structure also observed in the case of gels swollen in $CHCl_3$ and DMF (**Figure S9c** and **S9d**). Interestingly the morphology totally changed in the case of gels swollen in DMSO solvent. Instead of porous structure, a fibre like morphology (**Figure S9e**) was observed in the case of gels swollen in DMSO. Surprisingly, there was a uniform pattern observed in the case of hydrogels (**Figure S9f**). Since the swelling was not that effective in the case of H_2O, the pores observed were not too large. More importantly, it was very interesting to note that the gels kept in toluene and hexane never swollen so their morphology of the surface as well as interior never changed at all.

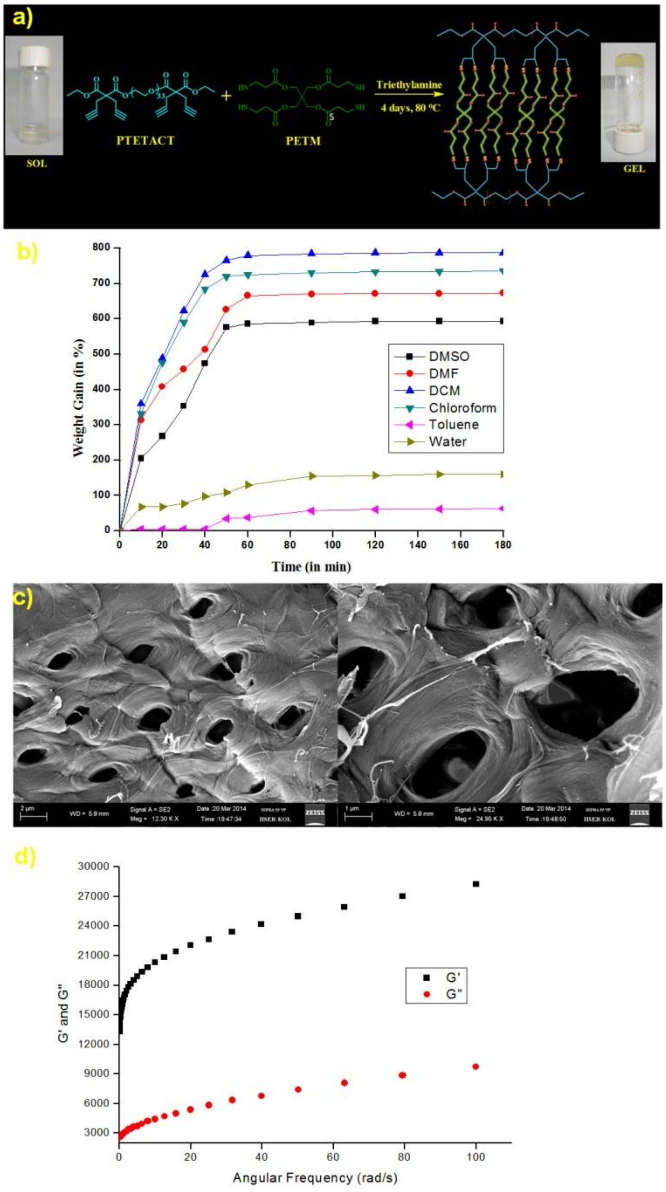


Figure 4. a) Cartoon representation of the 3 D networking; b) swelling efficiency of gel in different solvents; c) SEM image of swollen gel under cryo conditions; d) rheology of the gel swollen in DCM solvent.

In conclusion, thiol-yne reaction of **PTETACT** and **PETM** is proved to be an efficient way for creating **chemical** gels. It is important to note that the reaction is not inhibited by metal catalyst or other curators since the method is not depending on the use of any heavy metal catalyst. FT-IR spectroscopy analysis of the cross-linked thiol-yne gel network demonstrates that the reaction between thiol and yne in this particular system is extremely efficient. The triple bond conversion of the thiol-yne networks are all identical to the maximum possible conversion calculated from the thiol to yne feed-ratio. It is interesting to note that a 1:3 molar ratios of **PTETACT** and **PETM** produce the strongest gel which is confirmed by rheology data. The highest swelling is observed in DCM. The SEM image of the swollen gel in DCM shows uniform pores present in the gel. We believe that increase in PEG content would increase the hydrogel capabilities. The non-swelling property of the gel in hexane and toluene has prompted us to envisage the gel's application in removing chlorinated solvents from hydrocarbon solvents.

GMN thanks UGC for the research fellowship and RS thanks DST, New Delhi for Ramanujan Fellowship and IISER-Kolkata for the infrastructure. Mr. Kashinath from Carl Zeiss India, is acknowledged for the help in capturing quality SEM pictures.

Notes and references

Polymer Research Centre, Department of Chemical Sciences,
Indian Institute of Science Education and Research Kolkata.
E-mail: sraja@iiserkol.ac.in

Electronic Supplementary Information (ESI) available: Supporting information includes synthetic procedure, TGA and additional analytical data. This material is available free of charge via the Internet at DOI: 10.1039/c000000x/

1) R. E.Webber and C. Creton, *Macromolecule*, 2007, **40**, 2919-2927.
2) M. P. Lutolf, *Nat. Mater.*, 2009, **8**, 451-453.
3) E. A. Wilder, C. K. Hall, S. A. Khan and R. J. Spontak, *Langmuir*, 2003, **19**, 6004-6013.
4) M. Watase, Y. Nakatani and H. Itagaki, *J. Phys. Chem. B*, 1999, **103**, 2366-2373.
5) E. A. Appel, J. del Barrio, X. J. Loh and O. A. Scherman, *Chem. Soc. Rev.*, 2012, **41**, 6195-6214.
6) M. Djabourov and P. Papon, *Polymer*, 1983, **24**, 537-542.
7) R. Shunmugam, C. E. Smith and G. N. Tew, *J. Polym. Sci., Part A: Polym. Chem.*, 2007, **45**, 2601–2608.
8) C. D. Pritchard, T. M. O'Shea, D. J. Siegwart, E. Calo, D. G. Anderson, F. M. Reynolds, J. A. Thomas, J. R. Slotkin, E. J. Woodard, and R. Langer, *Biomaterials*, 2011, **32**, 587–597.
9) Y. Okumura and K. Ito, *Adv. Mater.*, 2001, **13**, 485-487.
10) S. S. Babu, K. K. Kartha and A. Ajayaghosh, *J. Phys. Chem. Lett.*, 2010, **1**, 3413–3424.
11) M. N. Ganivada, V. N. Rao, H. Dinda, P. Kumar, J. D. Sarma and R. Shunmugam, *Macromolecules*, 2014, **47**, 2703−2711.
12) K. R. Kamath and K. Park, *Adv. Drug Delivery Rev.*, 1993, **11**, 59-84.
13) J. Steed, *Chem. Commun.*, 2011, **47**, 1379−1383.
14) K. Zhang, M. A. Lackey, J. Cui and G. N. Tew, *J. Am. Chem. Soc.*, 2011, **133**, 4140–4148.
15) A.Gress, A. Volkel and H. Schlaad, *Macromolecules*, 2007, **40**, 7928–7933.
16) A. Dondoni, *Angew. Chem., Int. Ed.*, 2008, **47**, 8995–8997.
17) C. E. Hoyle, T. Y. Lee and T. Roper, *J. Polym. Sci., Part A: Polym. Chem.*, 2004, **42**, 5301–5338.
18) R. T. C. Cleophas, M. Riool, H. C. Q. V. Ufford, S. A. J. Zaat, J. A. W. Kruijtzer, and R. M. J. Liskamp, *ACS Macro Lett.* 2014, **3**, 477-480.
19) A. Song, A. A. Rane and K. L. Christman, *Acta Biomater.*, 2012, **8**, 41−50.

20) N. M. Matsumoto, D. C. Gonezalez-Toro, R. T. Chacko, H. D. Maynard and S. Thayumanavan, *Polym. Chem.*, 2013, **4**, 2464–2469.
21) A. A. Aimetti, A. J. Machen and K. S. Anseth, *Biomaterials*, 2009, **30**, 6048−6054.
22) T. Ono, T. Sugimoto, S. Shinkai and K. Sada, *Nat. Mater.*, 2007, 6, 429−433.
23) Y. Zhou, N. Sharma, P. Deshmukh, R. K. Lakhman, M. Jain and R. M. Kasi, *J. Am. Chem. Soc.*, **2012, 134**, 1630-1641.
24) H. Kim, J. V. Olsson, J. L. Hedrick and R.M. Waymouth, *ACS Macro Lett.*, 2012, **1**, 845−847.
25) K. Zhang, J. Cui, M. Lackey and G. N. Tew, *Macromolecules*, 2010, **43**, 10246-10252.
26) S. G. Roy, U. Haldar and P. De, *ACS Appl. Mater. Interfaces*, 2014, **6**, 4233−424.

TOC Content:

Unique polymeric gel by thiol-alkyne click chemistry

Mutyala Naidu Ganivada, Pawan Kumar and Raja Shunmugam*