Synthesis and Characterization of Low Molecular Weight Organogelators Derived from Amide Derivatives of *N*-acetylglycine

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Summary: Six new *N*-acetylglycine amides and bisamides were prepared by reacting *N*-acetylglycine with different isocyanates including, hexamethylene diisocyanate, bis(4-isocyanatophenyl)methane, toluene 2,4-diisocyanate, 1,3-bis(2-isocyanatopropan-2-yl)benzene, phenyl isocyanate and 2-naphthyl isocyanate to furnish amides **1**-**6**. The gelation ability of compounds (**1-6**) was investigated using fourteen different solvents including polar, non-polar organic solvents. Only compound **1** solidified toluene. Characterization of compounds (**1-6**) was done using spectroscopic methods, ESI-MS, FTIR, ^{1}H- and ^{13}C-NMR. The morphology of toluene organogel (as xerogel) was determined through scanning electron microscopy (SEM).

Key words: Low Molecular Weight Organogels, Supramolecular self-assemblies, *N*-acetylglycine, Isocyanates, Amides.

Introduction

Gels are fascinating soft materials making themselves a profitable product with a variety of applications ranging from cosmetics to electronics [1-5]. Low Molecular Weight Gels (LMWGs) are derived from supramolecular self-assemblies of small molecules due to non-covalent interactions like, metal ligand interaction, van der Wall forces, H-bonding, π–π interaction and other hydrophobic interactions etc among small molecules. The functional moieties considered as building blocks for supramolecular assemblies are amides, esters, carbamates, ureas etc. to furnish H-bonding along with aromatic systems to provide π–π interaction or long hydrocarbon chains resulting into hydrophobic interactions [6]. All these interactions collectively form cavities to uptake solvent to form gels. The advantages of Low Molecular Weight Gels are; response to stimuli, reversibility, ordered structures, controllable assembly and easy modification.

Naturally occurring compounds are also proved to be potential gelators for water, organic solvents and ionic liquids. The naturally occurring classes of compounds are extensively used for gelator formation including amino acids, peptides, sugars, lipids, nucleobases, terpenes etc [7]. Among these, amino acid is the most studied class [8-10]. Low Molecular Weight Supramolecular self assembled gels generated from amino acids find applications in environmental remediation [11]. Self-assembled gels as smart materials for pollutant removal *via* gelling spilled oil [12], dye absorption from water [13], heavy metal removal from water [14] and used as lubricants [15].

The paper deals with the design, synthesis, characterization and gelation studies of simplest α-amino acid (Glycine) derivatives. N-Acetyl Glycine is reacted with different aliphatic and aromatic isocyanates to furnish mono and bis-amides (**1-6**). The gelation behavior of all prepared compounds (**1-6**) is investigated in fourteen solvents although only amide **1** gelled toluene to form sheet like supramolecular structure.

Experimental

General

All reactions were performed in glassware, which is over dried (150 °C). The Chemicals *N*-acetylglycine and isocyanates were purchased from Sigma-Aldrich, Chemie and MERCK. All the chemicals were accessible at greatest commercial grade and no need to purify further for use. The solvents needed in synthesizing our desired product were distilled as per requirement. M-N ALUGRAM Silica gel / UV 254 sheets were used for thin layer chromatography. Iodine vapors and UV light were prior for concluding visualization. Infrared spectra were recorded at room temperature on SHIMADZU

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FTIR Spectrophotometer. NMR spectra were reported on Bruker AM instrument operating at 700 MHz (^{1}H) and 175 MHz (^{13}C). Chemical shifts recorded in ppm, coupling constant J are resulted in Hz. The following terms are abbreviated as: br = broad signal, q = quartet, m = multiplet or unresolved, s = singlet, d = doublet, t = triplet. Mass spectra were reported on high resolution mass spectrometry-electro spray ionization positive mode (HRMS-ESI$^+$). SEM was recorded using JEOL-JSM-6380.

General procedure of amide synthesis

To a 250 ml conical flask, *N*-acetylglycine (0.177 g, 1 mmol) was suspended in toluene (5.3 ml), heated the solution and stirred until it was clear and then a solution of isocyanate or diisocyanate (0.16 ml, 1 mmol) in chloroform (5.7 ml) was added drop wise and refluxed for 2 hrs after addition of 3-4 drops of triethylamine and then cooled to room temperature (25 °C). The product obtained as white suspension, solvent evaporated on Rota vapor.

Compound 1: State: White solid. Yield: 98%. M.P: 108-110°C. ESI-MS: $[M + H]^+$ at *m/z* 314.38 ($C_{14}H_{26}N_4O_4$). FTIR (KBr, ν, cm^{-1}): 3342 (N–H, amide), 2941-2866 (CH_2, stretch), 1697 (C=O, amide), 1463 (CH_2, bend), 1348 (CH_3, bend), 1265-1004 (C-N). ^{1}H-NMR (700 MHz, DMSO-d$_6$) δ ppm: δ 9.57 (s, NH, 4H), 3.7 (s, H-2, 4H), 2.1 (s, H-5, CH_3x 2), 1.3 (4H, m, H-6' & 7'), 1.4 (4H, m, H-5' & 8'), 3.1 (4H, t, *J* = 6.3 Hz, H-4' & 9').^{13}C-NMR (700 MHz, DMSO-d$_6$) δ ppm: 171.9 (C-4), 170.0 (C-1), 51.5 (C-2/2'/7'), 29.8 (C-3'/6'), 26.4 (C-4'/5'), 22.6 (C-5).

Compound 2: The product was purified by column chromatography (Chloroform-MeOH 9.5:0.5). State: White solid. Yield: 99%. M.P: 183-185°C. ESI-MS: $[M + H]^+$ at *m/z* 396.44 ($C_{21}H_{24}N_4O_4$). FTIR (KBr, ν, cm^{-1}): 3334 (N–H, amide), 2947-2850 (CH_2, stretch), 1707 (C=O, amide), 1600-1533 (C=C, Aromatic), 1440 (CH_2, bend), 1411-1317 (CH_3, bend), 1240-1022 (C-N), 848-678 (C-H, Aromatic). ^{1}H-NMR (700 MHz, DMSO-d$_6$) δ ppm: 9.5 (s, N-H, 4H), 7.3 (d, *J*=8.0 Hz, H-3'/7', 4H), 7.1 (d, *J*=8.0 Hz, H-3'/7', 4H), 3.7 (s, H-8', 2H), 3.6 (s, H-2, 4H), 2.5 (s, H-5, CH_3x 2). ^{13}C-NMR (700 MHz, DMSO-d$_6$) δ ppm: 171.9 (C-4), 171.0 (C-1), 154.4 (C-2'), 137.5 (C-4'/6'), 135.9 (C-'5), 129.3 (C-3'/7'), 118.7 (C-'), 42.3 (C-8'), 41.2 (C-2), 22.6 (C-5).

Compound 3: State: White solid. Yield: 98%. M.P: 162°C. ESI-MS: $[M + H]^+$ at *m/z* 324.34 ($C_{15}H_{20}N_4O_4$). FTIR (KBr, ν, cm^{-1}): 3265 (N–H, amide), 2958-2852(CH_2, stretch), 1693 (C=O, amide), 1606 (C=C, Aromatic), 1543 (CH_2, bend), 1450 (CH_3, bend), 1249-1068 (C-N), 877-723 (C-H, Aromatic). ^{1}H-NMR(700 MHz, DMSO-d$_6$) δ ppm: 9.9 (s, NH-3, 2H), 8.8 (s, H-7', 1H), 7.4 (s, NH-1', 2H), 7.1 (1H, d, *J* = 8.0 Hz , H-3'), 7.0 (1H, d, *J* = 8.0 Hz, H-4'), 3.6 (s, H-2, 4H), 2.5 (s, H-8', CH_3), 2.1 (s, H-5, CH_3x 2).^{13}C-NMR (700 MHz, DMSO-d$_6$) δ ppm: 171.9 (C-4), 171.0 (C-1), 155.1 (C6'), 154.4 (C2'), 134.2 (C-5'), 137.6 (C-4'), 136.9 (C-5'), 130.7 (C-3'), 115.3 (C-7'), 42.1 (C-), 17.5 (C-5).

Compound 4: State: White solid. Yield: 98%. M.P: 162°C. ESI-MS: $[M + H]^+$ at *m/z* 390.48 ($C_{20}H_{30}N_4O_4$). FTIR (KBr, ν, cm^{-1}): 3323 (N–H, amide), 2976 (CH_2, stretch), 1708 (C=O, amide), 1535 (C=C, Aromatic), 1450 (CH_2, bend), 1371 (CH_3, bend), 1265-1097 (C-N), 788-634 (C-H, Aromatic). ^{1}H-NMR (700 MHz, DMSO-d$_6$) δ ppm: 7.5 (s, NH), 7.3(s, H-4', 1H), 7.1 (m, H-6'/7'/8', 3H), 3.4 (s, H-2, 4H)., 2.5(s, H-5, CH_3x 2), 1.5(s, H-9', CH_3 x 4). ^{13}C-NMR (700 MHz, DMSO-d$_6$) δ ppm: 155.4, 148.0, 127.8, 122.8, 121.6, 54.9, 51.1, 32.9, 30.6, 30.1.

Compound 5: State: Yellow solid. Yield: 40%. M.P: 42°C. ESI-MS: $[M + H]^+$ at *m/z* 192.21 ($C_{10}H_{12}N_2O_2$). FTIR (KBr, ν, cm^{-1}): 3302 (N–H, amide), 2953 (CH_2, stretch), 1710 (C=O, amide), 1606 (C=C, Aromatic), 1537 (CH_2, bend), 1444 (CH_3, bend), 1317-1070 (C-N), 902-690 (C-H, Aromatic). ^{1}H-NMR (700 MHz, DMSO-d$_6$) δ ppm: 9.6 ((s, NH-3, 2H), 7.4 (d, *J* = 7.0 Hz, H-3'/7', 2H), 7.2 (t, *J* = 7.0 Hz, H-4'/6', 2H), 6.9 (t, *J* = 7.0 Hz, H-5', 1H), 3.6 (s, H-2, 2H), 2.5 (s, H-5, CH_3). ^{13}C-NMR (700 MHz, DMSO-d$_6$) δ ppm: 170.9 (C-4), 169.1 (C-1), 154.4 (C2'), 139.6 (C-4'/6'), 129.2 (C-6'), 122.8 (C-3'/7'), 42.3 (C-), 22.6 (C-5).

Compound 6: State: White solid. Yield: 98%. M.P: 117°C. ESI-MS: $[M + H]^+$ at *m/z* 242.11 ($C_{14}H_{14}N_2O_2$). FTIR (KBr, ν, cm^{-1}): 3286 (N–H, amide), 2954 (CH_2, stretch), 1697 (C=O, amide), 1593 (C=C, Aromatic), 1436 (CH_2, bend), 1394 (CH_3, bend), 1273-1053 (C-N), 773-640 (C-H, Aromatic). ^{1}H-NMR (700 MHz, DMSO-d$_6$) δ ppm: 9.5 (s, NH-3, 1H), 8.1 (s, NH-2', 1H), 8.08 (s, H-3', 1H), 8.07 (d, *J* = 7.0 Hz, H-7', 1H), 7.9 (d, *J* = 7.0 Hz, H-5', 1H), 7.7 (d, *J* = 7.0 Hz, H-10', 1H), 7.6 (d, *J* = 7.0 Hz, H-4', 1H), 7.54 (t, *J* = 7.0 Hz, H-9', 1H), 7.51 (t, *J* = 7.0 Hz, H-8', 1H), 3.7 (s, H-2, 2H), 1.8 (s, H-5, CH_3). ^{13}C-NMR (700 MHz, DMSO-d$_6$) δ ppm: 171.9 (C-4), 171.0 (C-1), 155 (C2'/11'), 134.2 (C-5'), 134.1 (C-6'), 128.5 (C-7'), 126.4 (C-9'),

126.2 (C-10'), 126.0 (C-8'), 125.3 (C-4'), 123.1 (C-3'), 42.3 (C-), 22.7 (C-5).

Results and Discussions

Keeping in view the gelation behavior of α-amino acid, we have carried out present studies to investigate the potential of *N*-acetylglycine, the least studied α-amino acid, as organogelator by providing aromatic and aliphatic spacer. The spacers introduced to promote gelation applying ALS or A(LS)2 strategy [16]. It is a well-known that amide bonds also play significant role in inducing gelation [17] through hydrogen bonding in the presence of hydrophobic interaction furnished using long alkyl chain or benzene ring etc. The gelation occurs when a balance between hydrophobic part and hydrophilic part is established. Aromatic groups like phenyl, naphthyl etc. are also found to be responsible for gelation through π–π stacking. Hence the present studies shows that aliphatic long chains have comparatively better potential of gelating organic solvents (Table-1).

Table-1: Degree of Gelation ability for compound 1-6 in 2.0mL of solvent inspected per heating-cooling process.

S/no	Solvents	MGCmol l^{-1}	1	2	3	4	5	6
1	Water	2×10^{-4}	I	I	I	I	I	ppt
2	Methanol	2×10^{-4}	S_{RT}	S_H	S_H	S_{RT}	S_H	S_H
3	Ethanol	2×10^{-4}	S_{RT}	S_H	S_H	S_{RT}	S_H	S_H
4	Acetonitrile	2×10^{-4}	ppt	ppt	S_H	Ppt	S_H	S_H
5	EtOAc	2×10^{-4}	S_H	ppt	ppt	S_H	ppt	ppt
6	Chloroform	2×10^{-4}	S_H	I	ppt	S_{RT}	ppt	ppt
7	Toluene	2×10^{-4}	OG	I	I	S_{RT}	S_H	S_H
8	*n*-Hexane	2×10^{-4}	I	I	I	S_H	I	I
9	DMSO	2×10^{-4}	S_{RT}	S_{RT}	S_H	S_{RT}	S_{RT}	S_{RT}
10	Paraffin oil	2×10^{-4}	I	I	I	S_H	I	I
11	Xylene	2×10^{-4}	I	I	I	S_{RT}	S_H	ppt
12	Petrol	2×10^{-4}	I	I	I	S_H	I	I
13	Diesel	2×10^{-4}	I	I	I	Ppt	I	I

Abbreviations: S_H =soluble on heating, I =insoluble, OG =Opaque gel, MGC = minimum gelation concentration, S_{RT} = Soluble at room temperature, ppt = Precipitates, The Gelation ability tested with reverse test tube method, test tube containing gel inverted for more than 10 min at room temperature, the gel was not broken.

We have synthesized compound 1-6 by assembling the mixture of commercially available *N*-acetylglysine and different isocyanates with a high reaction yield. These reactions were single-pot synthetic procedures and can be performed on large-scale. The reaction yields are excellent up to 98% (Scheme-1).

The confirmation of the formation of compounds 1-6 was done by FTIR and ^{1}H-NMR spectroscopy. In IR spectrum of all compounds carbonyl of amide was displayed around 1710-1693 cm^{-1} due to delocalization of nitrogen lone pair on carbonyl while NH functionality of amide appeared at 3342-3265 cm^{-1}. The formation of compounds 1-6 was further confirmed through High Resolution Mass Spectrometry-Electron Spray Ionization (HRMS-ESI$^+$) exhibiting molecular ion peaks (M^+) at *m/z* 314.38, 396.44, 324.34, 390.48, 192.21 and 242.11 corresponding to molecular formula $C_{14}H_{26}N_4O_4$, $C_{21}H_{24}N_4O_4$, $C_{15}H_{20}N_4O_4$, $C_{20}H_{30}N_4O_4$, $C_{10}H_{12}N_2O_2$, and $C_{14}H_{14}N_2O_2$ respectively. The ^{1}H-NMR spectra of 1-6 displayed some common signals in all compounds i.e. a four proton singlet around δ 9.5 ascribed to -NH of amides, a six proton singlet around δ 1.8 attributed to methyl group of acetyl moiety, another singlet of four proton around δ 3.7 due to glycine methylene beside respective signals of each compound (*vide experimental*).

The capability of gelator system (compounds 1-6) for gelation was examined for 13 different solvents. For this, Heating-cooling processes at concentrations 2×10^{-4} mol l^{-1} of the gelator system were tested (Table-1).

The gelation ability of all derivatives was tested in 13 solvents in (Table-1). It demonstrates that compound 1 was adept to gel in aromatic solvent i.e. toluene. It is in accoradance with the previously reported gels of bisurea derivative obtained from methyl ester of glycine on reaction with hexamethylene diisocyanate. This shows that there is a fix cavity formation by hexyl spacer which may be $\leq$5.8 A^0, as toluene molecule domain is 5.8 A^0 [18]. In contrast other aromatic, hydrocarbons, oil, water or halogenated solvents inspected, no gelation occurred. The schematic representation of compound 1 gelation is given in Fig. 1, showing factors responsible for entrapping solvent.

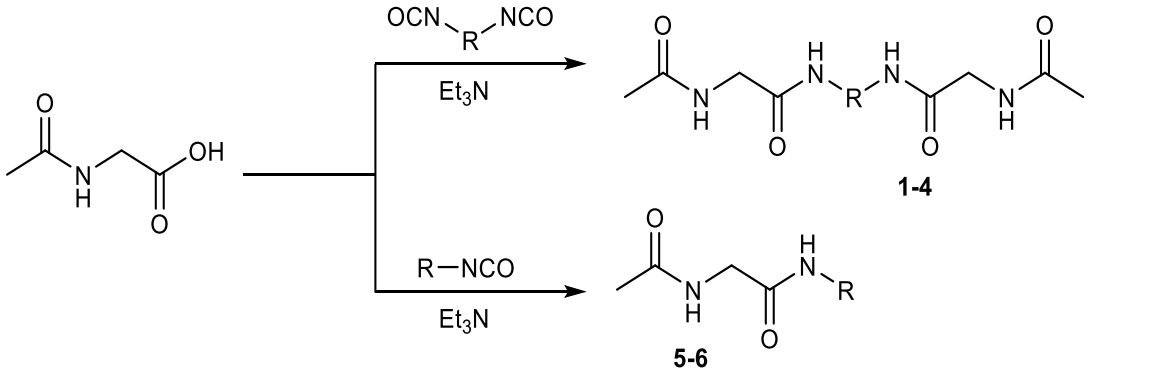
As, only compound 1 has shown the gelation ability in toluene. At 4 °C milky white gel was obtained (Fig. 2a). In all other solvents compound 1 and compounds 2-6 were either insoluble or lead to precipitation (Table-1).

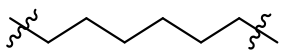
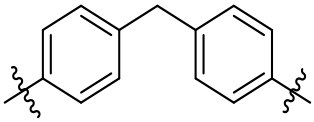
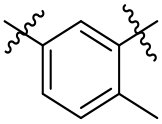
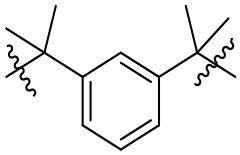
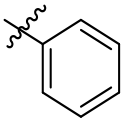
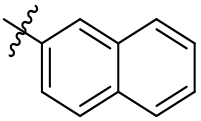
Though the organogel were produced by cooling down up to 0 °C. Finally this approach empowers the gel formation from isotropic solution of *N*-acetylglycine derivative 1 and solvent (toluene). The constancy and stability of two gels were investigated after 24 h after removing from refrigerator by inversion of the vials for 30 min at room temperature. The stability of organogels was long lasting as it was kept at room temperature for couple of months but it remained in same condition.

As it was evident that the toluene gel is thermally reversible (gel on cooling and sol on

heating is obtained), the sol-gel transition temperature of the gel was investigated by ball dropping method. It was converted into sol at 45 °C.

The morphology of the organogel was studied using (SEM) in xerogel form. The SEM indicated presence of sheets stacked over one and other. These sheets can be attributed to the formation of lamella due to H-bonding. Very small pores can be seen in magnified structure.



Compound #	R
1	
2	
3	
4	
5	
6	

Scheme-1: Synthesis of *N*-acetylglycine-based amide derivatives **1-6.**

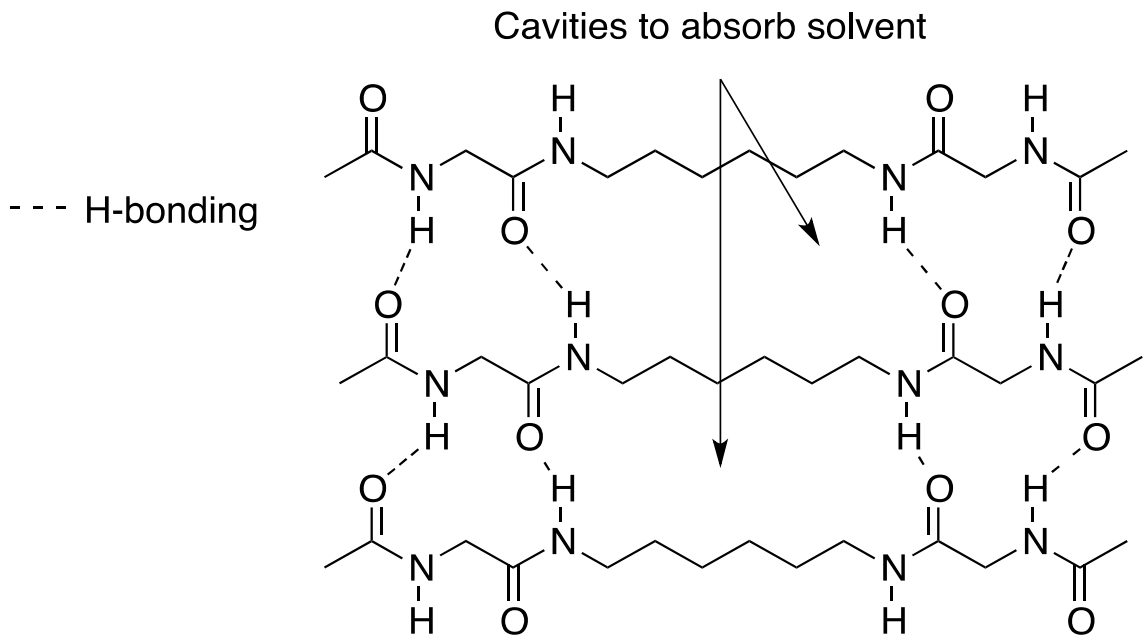


Fig. 1: Proposed schematic representation for gelation in compound **1.**

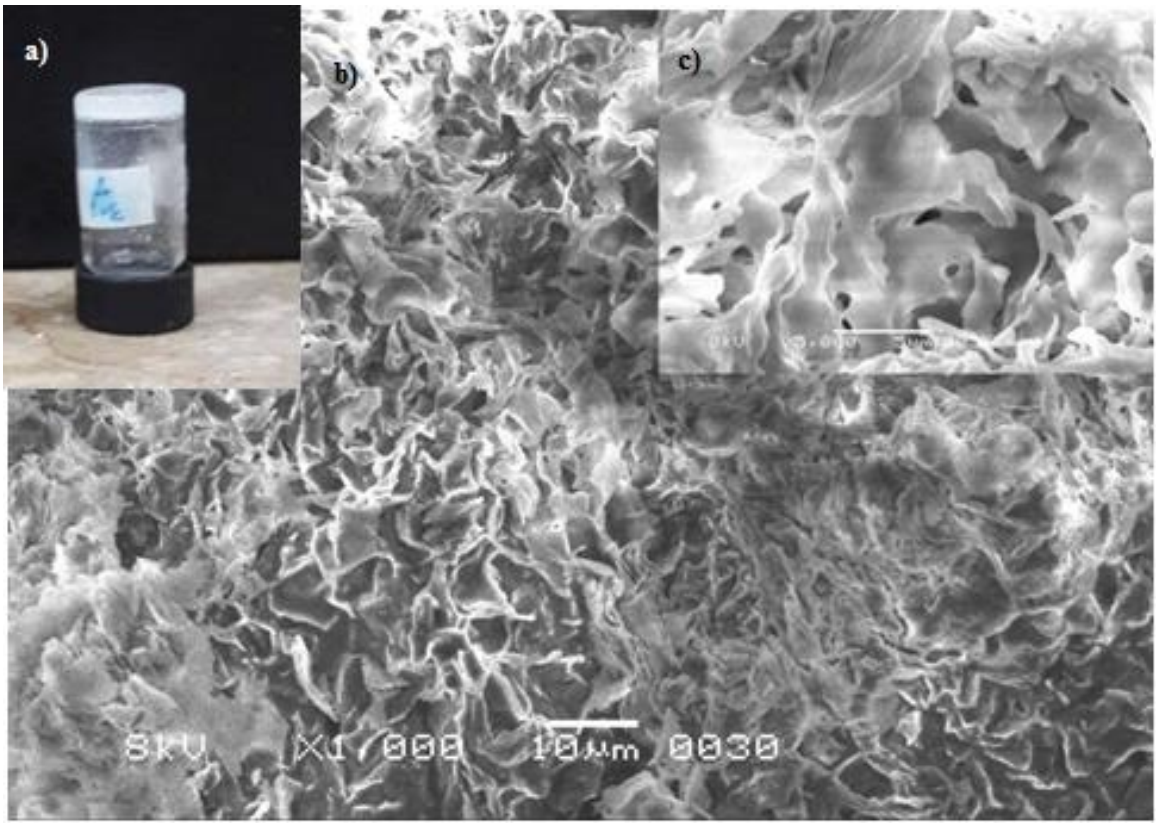


Fig. 2: Compound 1: a) wet gel b) SEM images of xerogel in toluene at 2 wt % c) 5000x magnified image of xerogel.

Conclusion

In short, six new amide derivatives of *N*-acetylglycine were synthesized to investigate their gelation ability. Since only one compound containing aliphatic spacer group is solidified in toluene. The toluene organogels is thermally reversible and stable at room temperature for months.

Acknowledgements

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