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Reactive organogels based on isoxazole esters: alkali metal ions selected gelation and crystallization

Qingxian Jin,[a] Jing Li,[a,b] Li Zhang,*[b] Shaoming Fang,[a] and Minghua Liu*[b]

A series of simple ester molecules containing isoxazole moiety were found to form instant organogel at room temperature in the presence of NaOH without heating-cooling cycle for conventional supramolecular gels. The gelation process was triggered due to the hydrolysis of isoxazole ester and occurred selectively with Na^+. When LiOH, NaOH and KOH was separately introduced into the methanol solution of isoxazole esters, the solution remained as a solution, transferred to a organogel and a crystal, respectively. With the help of study on phase behavior of corresponding isoxazole acid in the presence of alkai bases, it was revealed that π–π stacking of the isoxazole moiety, the ionic interaction between the carboxylates and Na^+ are the main driving force for the self-assembly and the organogelation. The size of the alkali metal ions will subtly affect the gelation, with the Li^+ and K^+ leading to solution and crystallization, respectively. The results provided an insight into the balances among solution, gelation and crystallization with subtle molecular variations.

Introduction

Over the past decades, research on low molecular weight gels (LMWGs) has witnessed an upsurge, owing to their excellent stimuli responsiveness to the light, ultrasound, mechanical strength and chemical additives[1]. LMWGs, as a kind of soft matter, have potential applications in the fields of sensors[2], light-harvesting systems[3], catalysis[4], biomaterials and optoelectronic devices[5] and chiral nanomaterials[6]. Many organic motifs have been designed to form organogels, including steroids[7], peptides[8], ureas and amides[9], sugars[10], dendrimers[11], and π-conjugated molecules[12]. However, most of these gelator molecules need to synthesized via a tedious procedure. It is always a challenge to find a simple and effective gelator molecules[13].

For a typical supramolecular gel, the gelation process need a heating and cooling cycle. That is, small molecules dispersed in the solvents at room temperature are heated into a transparent solution first. The subsequent cooling process leads the self-assembly of small molecules into nanofibers, nanotapes or nanotubes and then further entangled each other to form a three dimensional networks, to immobilize the solvents[14]. Besides, the sonication[15], chemical additives[16], mixing of the solvents[17] and chemical reaction can some time induce the gelation[18] instantly at room temperature without any heating or cooling. For example, Xu et. al. have developed the enzyme-triggered conversion of the precursor to a hydrogelator resulted in the formation of a hydrogel, pioneered a biomimetic approach for generating soft materials[19]. Yi and co-workers found sonication can effectively trigger gel formation, and the supramolecular gels exhibited different properties as that of heating-cooling caused gels[20]. We have developed an instant gel formed by anti-solvent method[17], in which the uniform hexagonal nanotubes structures can be obtained. By studying these room temperature gels, the gelation process can be understood more thoroughly and their application to the biological system could be more feasible.

On the other hand, understanding the gelation process is also an important issue in the field of designing functional supramolecular gels. It is believed that supramolecular gel is a metastable phase between solution and crystal. Gelation is an aborted crystallization process wherein the gelator molecules form self-assembled fibrillar networks[21]. Furthermore, three-dimensional networks, which formed by hierarchical assembly, can immobilize solvents via capillary force within such 3D networks, resulting in gel formation[22]. In gels, these self-assembled nanostructures can dynamically interact with the solvents. While in crystallization process, the molecules packed perfectly ordered that the solvent cannot react it more. Thus, subtle changes in the structure of gelator, solvents, pH value, addition of metal ions and so on, will adjust the competition between gelation and crystallization[23]. Although there are huge number of papers related to the gelation and the crystallization of molecules, there are still a fewer papers on why certain molecule formed gels or crystals. In this paper, we accidentally found that a series of ester molecules containing isoxazole moiety (Fig. 1) could form instant organogels at room temperature in the presence of NaOH, while they formed crystals in the presence of KOH. In the case of LiOH, the solution remained unchanged. An isoxazolyl ring

[a] Henan Provincial Key Laboratory of Surface & Interface Science, Zhengzhou University of Light Industry, Zhengzhou, Henan 450002, (P.R. China).
[b] Beijing National Laboratory for Molecular Science, CAS Key Laboratory of Colloid Interface and Chemical Thermodynamics, Institute of Chemistry, Chinese Academy of Sciences, Beijing, 100190 (P.R. China),E-mail:liumh@iccas.ac.cn, zhangli@iccas.ac.cn
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was reported to be a key functional moiety for generating molecular assemblies. For instance, a series of isoxazole derivatives exhibited mesomorphic properties[24] and tris-(phenylisoxazolyl)benzenes assembled to form supramolecular gels in organic solvents[25]. The π–π stacking and dipole-dipole interaction were supposed to be the driving force to form fibrillar gel networks. In this study, we further simplified the compounds and provided a sodium selective gelation of compounds containing isoxazole moiety, which may be helpful in the designing of the reactive gels and gave a new insight into the solution, gelation and crystallization.

Results and Discussion

Gelation at the room temperature. The esters contain isoxazole moiety are an important class of heterocycles, largely employed in pharmaceuticals and therapeutics such as insecticidal, antibacterial, antibiotic, antitumour, antifungal, anticancer and antituberculosis[26]. Figure 1 shows the molecular library of isoxazoles. These compounds are dissolved in alcohols such as methanol and ethanol to form a transparent solution. When NaOH was added into methanol solution of the esters, the formation of organogels was triggered as the result of hydrolysis reaction. The gelation process can be verified by the harden of the solution and confirmed by the invert test tube method. After addition of alkali base, LiOH, NaOH and KOH in an equimolar amount, different phase behaviours were found. Firstly, we investigated that the methyl ester derivatives, compound **E1-E4**. Typically, the ester solution remained as clear solution upon addition of LiOH even after 7 days, while the organogels was formed within one hour when NaOH was introduced. The observed gels (Fig. 1c) were robust, opaque and stable for months. The addition of KOH caused the crystallization of **E1-E3** in methanol. As shown in Fig. 1d, the needle shape crystal was found in the **E1**/KOH system. However, compound **E4** was an exception, which did not show any change when three kinds of base were added. This result indicated that the π-π stacking of thiophene and isoxazale moiety contributed to the self-assembly. The thiophene moiety replaced by CH3 decreased the π-π stacking in the ester, which caused the failure in the self-assembly. The transition from solution to gel or crystallization depended on the molecular structure, as shown in Table. 1. The **E2** gave the most rapid reaction time, i.e. 36min was needed to form organogels upon introduction of NaOH and 28min for crystallization in the presence of KOH among **E1-E3**. Secondly, a series esters of 5-(thiophen-2-yl) isoxazole-3-carboxylic acid with different substitute group (**E5-E10**) were synthesized, as shown in Fig. 1. Table 1 shows the response of compound **E1-E10** in methanol solution upon the addition of base. In general speaking, molecules **E5-E10** in methanol exhibited similar response to alkali base with that of compound **E1**, i.e. LiOH kept the solution state, and NaOH, KOH resulted in the formation of gels and precipitation, respectively. The different substitute group caused a slight difference for the gelation time of compound with aliphatic substitute. The gelation time is within 50min. While, the introduction of aromatic ring made the gelation time longer. For **E9**, the time to form gel was 57min, and extended to 24hr for molecule **E10**.

Tab.1 The phase behaviour of methanol solution of compounds E1-E10 in the presence of LiOH; NaOH; KOH.

Compound	LiOH	NaOH(time)	KOH(time)
E1	S	G(43min)	P(33min)
E2	S	G(36min)	P(28min)
E3	S	G(50min)	P(41min)
E4	S	S	S
E5	S	G(30min)	P(20min)
E6	S	G(37min)	P(28min)
E7	S	G(32min)	P(24min)
E8	S	G(43min)	P(35min)
E9	S	G(57min)	P(49min)
E10	S	G(24h)	P(24h)

S: solution; G: gel; P: precipitation; including their gelation time or the time for precipitation.

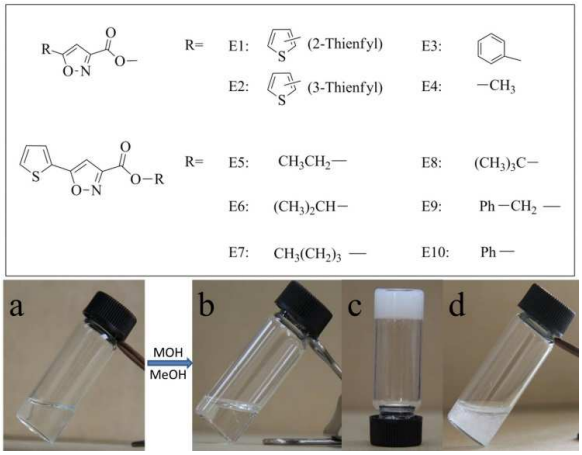


Fig.1 Molecular structures of compounds E1-E10 and the photo images of a) E1 in methanol solution; b) E1/MeOH/LiOH; c) E1/MeOH/NaOH; d) E1/MeOH/KOH.

Fig. 2 shows the scanning electron microscopy (SEM) images of some esters/methanol solution and upon addition of different alkali bases. There is some amorphous punctiform structure cluster together in the **E1**/methanol solution, as shown in Fig. 3a. The similar amorphous structures were found in the

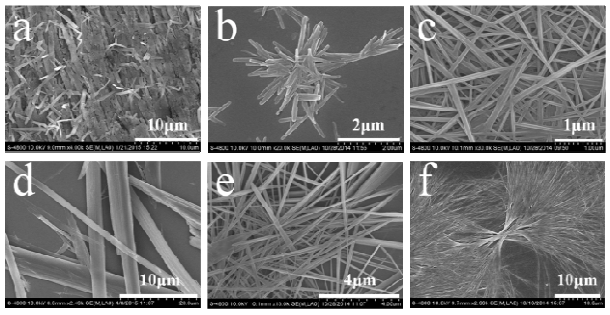


Fig.2 SEM images of: a) E1/MeOH; b) E1/MeOH/LiOH; c) E1/MeOH/NaOH; d) E1/MeOH/KOH; e) E2/MeOH/NaOH; f) E9/MeOH/NaOH.

addition of LiOH, which was consistent with the clear solution microphase state. When NaOH was introduced into **E1**/methanol solution, the nanofiber structures with the width of around 30nm and extended to several micrometers were found. These nanofibers entangled each other to form three dimensional networks, which is the typical morphology of organogels. In the case of addition of KOH, the nanobelt structures with the width of 1μm and the length over 30μm were obtained. The size of nanobelts in either the width or the length is much larger than that nanofibers formed in the presence of NaOH. In addition, there is no effective entanglement of nanorods, which may result in the failure to hold the solvents to form gels. This is the reason for the formation of precipitation instead of organogels in the presence of KOH. We also studied the morphology of **E2**/NaOH and **E9**/NaOH, and entangled nanofiber structures were obtained. The compound **E10** exhibited "broom" morphology in the presence of NaOH.

The state of a 'gel' of **E1**/methanol in the presence of NaOH was supported by evaluating the dynamic rheological properties using a rheometer. Fig. 3 shows the profiles of G' (storage modulus) and G'' (loss modulus) versus the frequency of a **E1**/methanol in the presence of equimolar NaOH. In the range of 0.1–100 rad/s, the existence of pseudo plateaus and G' values much larger than G'' value, confirmed a typical rheological property of gel state[27].

It is well known that the ester can be hydrolyzed in the presence of bases, and then we speculated that corresponding carboxylic acid contributed to the response to alkali bases. We synthesized corresponding acid of **E1** (**H1**) as a reference to test its response to alkali base, as shown in Fig. 4. Similar with **E1**, the solution, gel and precipitation in the **H1**/methanol system was obtained in the presence of LiOH, NaOH and KOH, respectively. But the formation of gel and precipitation exhibited much rapid response than that of **E1**.

In general, the gel formed less than several minutes and depended on the **H1** concentration. Fig. 5 gives the relationship between gelation time and concentration as well as the molar ratio of NaOH/**H1**. When **H1** concentration was below 10mg/mL, **H1** cannot form gel. With the increase of **H1** concentration, the gel formation time decreased to 5s. The molar ratio of NaOH to H1 was also important for the gel

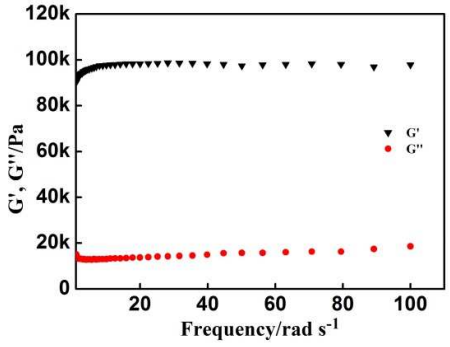


Fig.3 Dynamic rheological properties via a frequency sweep of aE1/methanol in the presence of NaOH system measured using a rheometer.

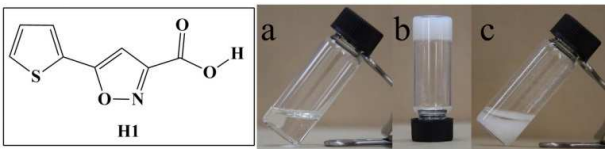


Fig.4 Chemical structure of H1 and the picture of a) H1/MeOH /LiOH; b) H1/MeOH /NaOH; c) H1/MeOH/KOH.

formation. Keeping the concentration of H1 at 11mg/mL, the least NaOH needed to gel methanol is 1 mol ratio to H1. With the increase of NaOH concentration, the gelation time decreased from 120s to about 5s. Keeping **H1** concentration at 19.5mg/mL (0.1mmol), the least NaOH needed to gelation methanol is still 1 mol ratio to **H1**. Further increasing the NaOH concentration, there is no obvious effect on the gel formation, as the time for gelation is similar, i.e. about 5s. This result indicated that entire transition of COOH to COO^- is necessary for the organogels formation.

This NaOH induced organogel formation was not only occurred in methanol, but in other alkyl alcohol, such as ethanol, propanol, butanol and pentanol. The CGC (critical gelation concentration) of **H1**/NaOH in ethanol, propanol, butanol and pentanol were lower than that of in methanol. The 5mg/ml of **H1** can form organogels in other four alcohols. As for the alcohols with longer alkyl chains, the organogels cannot be formed by this method because that NaOH cannot be dissolved in them.

According to the results mentioned above, we speculated that the size of alkali metal ions played a key role in the gel formation. In order to further verify this, the response of **H1**/methanol solution on alkali metal ions was evaluated, as shown in Fig. 6. The organogel of **H1**/NaOH was destroyed and precipitation appeared when KOH was introduced, while it kept constant after addition of LiOH. And **H1**/LiOH can form gels while NaOH was introduced and precipitation in the presence of KOH. On contrary, the addition of NaOH or LiOH cannot change the phase behaviour of **H1**/KOH system. That is to say, the **H1**/KOH was still in precipitation either in the presence of NaOH or LiOH. This result indicates that the crystal state of **H1**/K^+ is more stable than the state of solution and organogels in the presence of Li^+ and Na^+.

In order to get insight on the hydrolysis of esters, FT-IR spectrum of compound **E1** and that of in the presence of alkali bases were monitored, as shown in Fig. 7A. A strong vibration band was observed at 1731cm^{-1} for molecule **E1**, which can be ascribed to the C=O vibration of ester group. The peak at 1242cm^{-1} and 1135$cm^{-1}$was ascribed to the C-O stretching

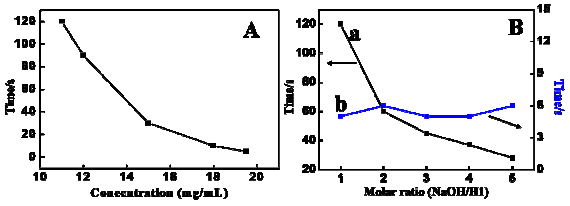


Fig.5 A): Dependence of gelation time on concentration of H1; B): Dependence of gelation time on the ratio of NaOH to H1 a) concentration of H1 at 11mg/mL; b) concentration of H1 at 19.5mg/mL(0.1mmol).

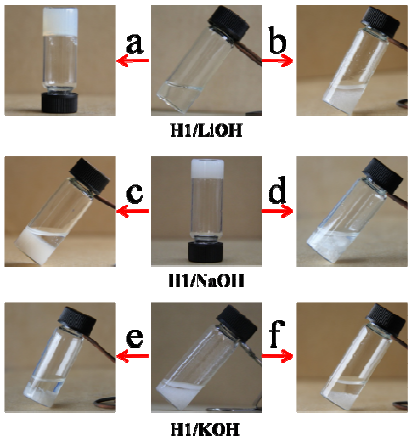


Fig.6 Selective gelation: the phase transition of the primary Sol/Gel/Precipitation while introduced another two alkali base, the molar ratio of them are 1/1, the dosage is 0.5mL. a) MeOH/NaOH; b) MeOH/KOH; c) MeOH/LiOH; d) MeOH/KOH/; e) MeOH/NaOH; f) MeOH/LiOH.

vibration. The apparent peak at 1405cm-1, can ascribe to the thiophene group. After addition of NaOH and KOH, the peak at 1731cm-1, 1242cm-1, 1135cm-1 disappeared entirely. Combined with new vibration bands appeared at 1613cm^{-1} or 1615cm^{-1} and 1345cm^{-1}, which are typical vibrations of C=O and C-O in carboxylate, indicating that the ester was hydrolysed to form carboxylate[28]. The FI-IR spectrum of **E1**/NaOH (**E1**/KOH) was same with that of **H1**/NaOH (**H1**/KOH), as shown in Fig. 7B, further supported that the **E1** was completely hydrolysed to form carboxylate in the presence of NaOH (KOH). In the case of LiOH, the C=O vibration shifted to 1728cm^{-1} and appearance of band at 1641cm^{-1} suggested that hydrolysis of **E1** was not completed.

Fig. 7B shows the IR spectra of **H1** upon addition of KOH, NaOH and LiOH. **H1** exhibited strong vibration bands at 1714cm^{-1} and 1276cm^{-1}, which can be ascribed to the cyclic dimeric hydrogen bonded COOH[29] and C-O respectively. After addition of bases (LiOH, NaOH, KOH), the bands at 1714cm^{-1} and 1276cm^{-1} disappeared, following with a broad peak observed at 1639cm^{-1}, 1356cm^{-1} in LiOH, 1612cm^{-1}, 1348cm^{-1} in NaOH, and 1615cm^{-1}, 1346cm^{-1} in KOH. These new peaks suggested the existence of COO^-, indicating that the COOH was completely transferred to COO^-. Previous paper reported that the binary of sodium carboxylate and carboxylic acid contributed to the organogelation[30]. In this context, considering that the entire disappearance of C=O vibration of COOH and the least amount of NaOH to compound H1 to gelify methanol was equimolar, the gelling species is likely to arise from the base-assisted deprotonation of the carboxylic acid.

The X-ray diffraction spectroscopy was further used to investigate the molecular packing of the powder of **E1** in the presence of KOH and xerogel of **E1**/NaOH(Fig. 8).The X-ray diffraction profile of the **E1**/KOH showed a series of peaks corresponding to distances of 1.96, 0.98, 0.76, 0.66, 0.56nm and so on, with a ratio of1: $1/\sqrt{4}$: $1/\sqrt{7}$: $1/\sqrt{9}$: $1/\sqrt{12}$: $1/\sqrt{16}$ …, a character of hexagonal column packing of the molecules[31]. The structure parameter of a = 2.27nm and c=1.19nm was calculated according to XRD profiles. By comparison, in the X-ray diffraction profile of xerogel of **E1**/NaOH, the more amorphous structure was obtained. Both the intensity and number of peak decreased. The d-spacing of 1.83 (110), 1.23 (200), 1.06 (210) and 0.92 (220) show the formation of BCC phase with the structure parameters of a=2.46nm. The XRD patterns of **E1** in the presence of KOH was obvious different from in the presence of NaOH, indicating that the molecular packing of **E1** can be adjusted by the alkali base.

H-bonding has been found to be a main driven force for most of LMWGs. However, in the present work, π-π stacking between aromatic rings, electrostatic and ion-dipole interactions between sodium carboxylates contributed strongly to stabilization of the aggregates in organogels, as shown in Scheme 1a. The monomeric unit of sodium carboxylates further packed to forma BCC structure. As for KOH, we speculated that it can coordinate with N-atom in the isoxazole moiety (Scheme 1b) as the result of its ion diameter is a bit larger than that of sodium. This monomeric unit packed into columns as basic structural units. The different packing mode between sodium carboxylate and potassium carboxylate may result in the gelation and crystallization. In the case of LiOH, the ester cannot be hydrolysed completely (Fig. 7A, curve b), which may be one reason of preserving solution state. But the most plausible reason is that the lithium ion possesses relative strong polarization ability due to its smaller ion radius, then the lithium carboxylate exhibits both character of ionic compound and covalent compound. This caused the electrostatic interaction between lithium carboxylate was not enough to provide its self-assembly in alcohol.

There are also some works about the alkali metal ions responsive gel- sol transition reported previously, in which most of gelators or pregelators contained a well-known host

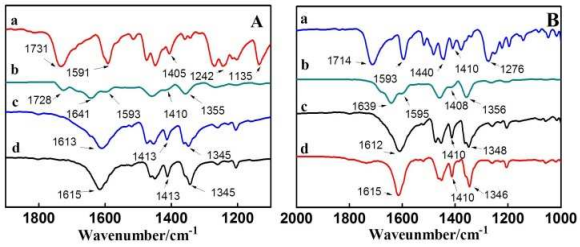


Fig.7(A) The FTIR spectra for ester E1, a) and in the presence of b) LiOH, c) NaOH, d) KOH; (B) FT-IR spectra of H1, a) and in the presence of b) LiOH, c) NaOH, d) KOH.

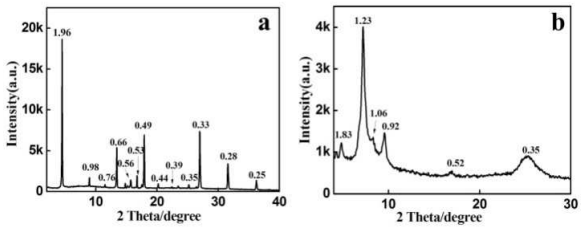
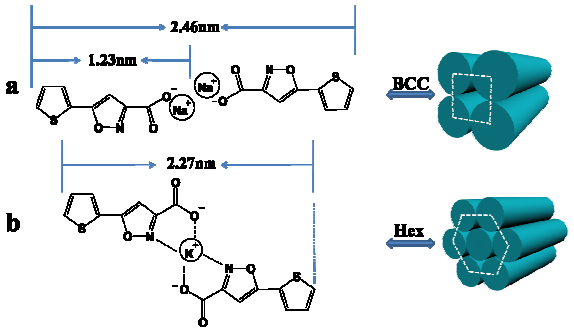


Fig.8 XRD profile of a) E1/KOH system and b) E1/NaOH system.



Scheme1.The different packing mode for H1 in the presence of a) NaOH and b) KOH.

moiety such as crown or calix[4]pyrrole[32]. The host-guest interactions attributed to the responsiveness. In this study, although isoxazole did not provide a suitable cavity for the alkali metal ions, it seemed that the sodium cation offered the optimum size and charge distribution necessary for an effective interaction with the isoxazole carboxylate as compared to lithium or potassium cations. Isoxazolyl ring was reported to have a fairly large dipole moment, directed to the nitrogen atom along the N=C bond [33], thus the intermolecular local dipole–dipole interactions attributed to self-assembling of compounds containing isoxazole moiety. Further, the large dipole moment in isoxazole caused the relative strong binding ability of N atom and can coordinate with metal ions. Therefore, when the alkali metal ions were introduced to the system, the intermolecular dipole-dipole interactions and metal-ligand interactions will be adjusted by the size of metal ions, which led to the difference phase behaviour in the presence of Li^+, Na^+ and K^+, respectively.

Conclusions

In summary, we newly developed a sodium-selected organogelation system at room temperature based on a series of simple esters containing isoxazole moiety. We have shown that different LiOH, NaOH and KOH can lead the methanol solution of isoxazole into solution, gel and precipitation, respectively, where the size of the alkali ions played an important role. It has been revealed that the gel formation was due to the hydrolysis of isoxazole esters into the corresponding carboxylates and their interaction with the alkali metal ions. The π–π stacking of the aromatic rings and the matched interactions between the carboxylate and Na^+ played an important role in the gel formation. This work provided a new insight into the balances among solution, gelation and crystallization with subtle molecular variations and new clues for the design of simple molecular gelators.

Acknowledgements

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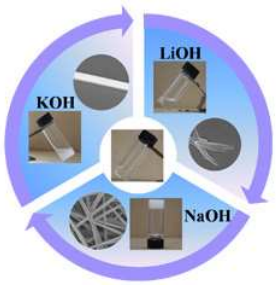

A methanol solution of a series of simple esters exhibited response to alkali base, which formed solution, organogels and crystals, respectively, when LiOH, NaOH and KOH was separately introduced.