Formation of Organogel In Situ Based on a Dynamic Imine Bond

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Formation of Organogel in situ Based on a Dynamic Imine Bond

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A simple approach for creating organogel in situ through formation of a reversible imine bond known as a dynamic covalent bond is described. As the condensations of the glutamate-based amine compounds and salicylaldehyde or 2-hydroxy-1-naphthaldehyde in alcohols such as MeOH, EtOH and propanol as well as DMF proceed, gelation occurs in situ depending on the condition. Addition of a small amount of acid and water to a resultant gel induces its collapse due to returning to the corresponding amines and aldehydes. No such a gelation was observed when combining benzaldehyde or naphthaldehyde.

Keywords: Organogelator, dynamic covalent bond, Imine bond

Over the last years the area of the low-molecular-weight gelators (LMWGs) has been extensively investigated because of their promising various technological applications as well as fundamental scientific interests.[1] In general the process of gelation is considered to involve self-assembly of LMWGs triggered by non-covalent interactions such as van der Waals forces, hydrogen bonding, π-π interaction, metal-ligand coordination, hydrophobic effects and charge-transfer (CT) interaction, followed by formation of three-dimensional cross-linked networks that trap a large amount of solvents. In this context we have designed the aromatic LMWGs to develop novel functions.[2]

Compared to dynamic non-covalent interactions as a tool to control the sol-gel transition, dynamic covalent bonds applied for gels have been limited despite of the fact that networks through dynamic covalent bonds are more stable than the corresponding non-covalent cross-linking ones. Dynamic covalent bonds are characterized by reversible reactions of making and breaking bonds under relatively mild conditions.[3] Some of the most commonly used dynamic covalent bonds in the gelatinous system encompass boronate ester bonds,[4] imine bonds,[5] acylhydrazone bonds[6], disulfide bonds[7] and so on. The most relevant strategies involve polymer networks crosslinked by dynamic covalent bonds.[8] On the contrary, to our best knowledge, a few studies on dynamic covalent bonds applied for discrete gelators have reported. For example guanosine hydrazide-based supramolecular hydrogels employing reversible hydrazine bonds have been reported.[9] Disulfide dynamic chemistry has been applied for cyclic peptide-derived hydrogels by formation of the disulfide bond[10] and for peptide gelator by cleavage of the disulfide bond.[11] The reaction of the trishydrazide and the aldehyde in situ afforded an acylhydrazone gelator.[12] Although an imine bond as the dynamic covalent bond has also been utilized to construct discrete gelators, in most cases it is applied to the choresterol-appended aromatic gelators.[13,14]

Regarding design of various gelators it has been suggested that combination of a glutamate-based structure (L) and an aromatic group enhances the ability of gelation. From this point of view it has occurred to my mind that the imine bond is utilized to connect these versatile units in the aim of creation of the gel in situ based on a dynamic covalent bond.

Thus, here we report the gel production in situ in terms of formation of the imine bond between two components by mixing them up.

We have chosen the L-glutamate skeleton as the core segment of organogelators because it is known to be effective for intermolecular hydrogen bonding.[15,16] We employed four kinds of L-glutamate moieties (Glu-Gly, Glu-Ala, Glu-Val, Glu-Phe) to which two long alkyl chains were introduced (Chart 1).

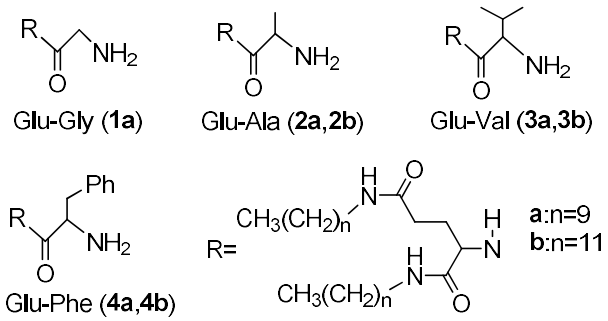


Chart 1.

At first the gelation behaviors of the glutamate-based compounds **1a**–**4a** were examined in some solvents (Table 1).

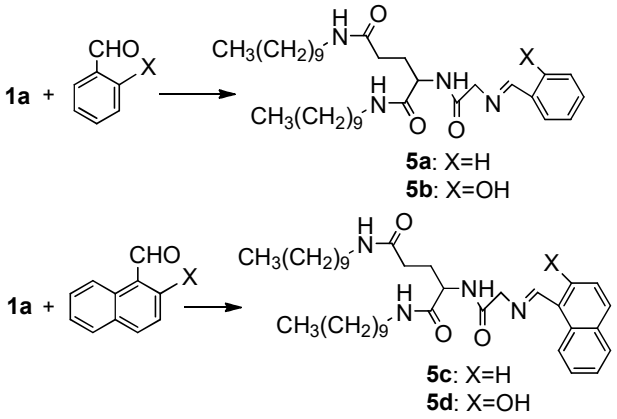
Table 1 Gelation properties of glutamate-based compounds (**1a–4a**) in some solvents[a]

	1a	2a	3a	4a
n-Hexane, Cyclohexane	PG	G(1.0)	G(0.8-1.0)	G(3.0)
Benzene, Toluene	G(0.8-1.0)	G(0.6)	PG	PG
EtOH, MeOH	S	S	S	S
1-Propanol, DMF	S	S	S	S

[a]G:gel, PG:partial gel, S:soluble.
The values given in parentheses are the minumun concentration (wt %) (CGC) to achieve gelation.

When the solvent is partially gelated, it is indicated by 'PG' meaning a partial gel. Although all compounds exhibit tendency to gelate hexanes and aromatic solvents, they show good solubilities in alcohols examined here

resulting in no gelation. It is commonly accepted that the aromatic component and the hydroxy group in the molecular structure could induce its ability to gelate organic solvents.[17] It can be envisioned that the imine products from **1a**–**4a** and aromatic aldehydes might gelate alcohols. Thus, combinations of **1a** and four kinds of aldehydes (benzaldehyde, salicylaldehyde, naphthaldehyde, 2-hydroxy-1-naphthaldehyde) were chosen to prepare the imine products (**5a**–**d**) in order to explore this possibility as shown in Scheme 1.



Scheme 1. Preparation of imine compounds (**5a-d**).

The capability of **5a**–**d** to form organogel was first investigated in some solvents as summarized in Table 2.

Table 2 Gelation properties of imine compounds (**5a-d**) in aromatic solvents, alcohols and DMF[a]

	5a	5b	5c	5d
Benzene, Toluene	G(1.0-2.0)	G(0.1-0.2)	G(0.8)	G(0.1-0.4)
EtOH, MeOH	P	G(2.0-3.0)	P	P
1-Propanol	P	S	P	S
DMF	S	G(7.0)	P	PG

[a]G:gel, PG:partial gel, S:soluble, P:precipitate.
The values given in parentheses are the minumun concentration (wt %) (CGC) to achieve gelation.

As expected from the result of the precursor **1a**, and **5a**–**d** exhibit gelation in benzene and toluene.

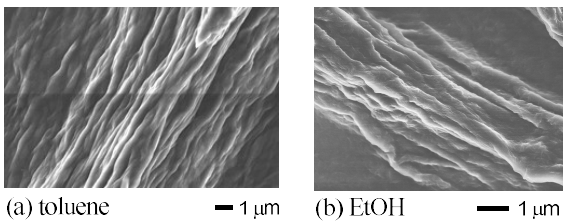


Figure 1. SEM images of gels from **5b** in toluene (a) and EtOH (b).

It has been also found out that **5b** can gelate EtOH, MeOH and DMF. The SEM images of the gels from **5b** in toluene and EtOH are shown in Figure 1. A developed network of fibers is observed for both gels.

Here the formation of gel in situ can be defined as the follows: as the gelator, i.e. the imine compound is produced little by little, gelation of solvent gradually progresses and finally completes with stable gel. In order to realize this gelation process effectively the most suitable condition using **1a** and salicylaldehyde in EtOH has been carefully examined. Considering the minimum concentration to gelate EtOH by the product **5b**, solutions of three different concentrations of **1a** (100 mg, 200 mg, 300 mg) in 5 mL of EtOH were prepared and their appearances in terms of gelation were observed by addition of 1.2 mol equivalent of salicylaldehyde. In the case of the solution of **1a** (100 mg, 0.2 mmol) no change was observed even after completion of addition of salicylaldehyde followed by stirring for 30 min. On the other hand when the solution of **1a** (200 mg, 0.4 mmol) was employed, partial gelation was only seen in the course of addition of salicylaldehyde. Thorough gelation of EtOH accompanied with no spinning of a stirring bar was confirmed for the solution of **1a** (300 mg, 0.6 mmol) in 3 min. In 2 min the reaction mixture started to gelate. The pictures in time course of this reaction are shown in Figure 2.

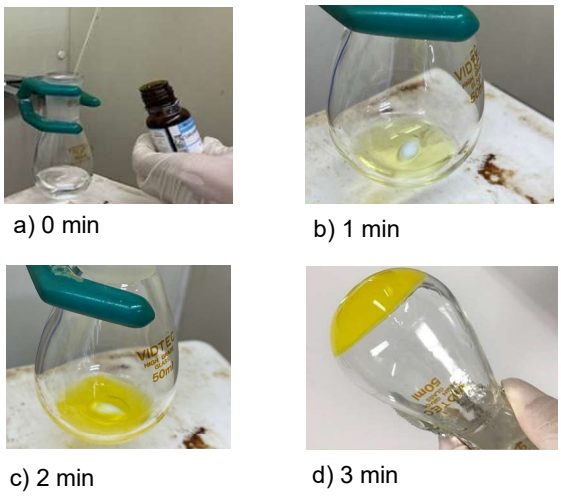
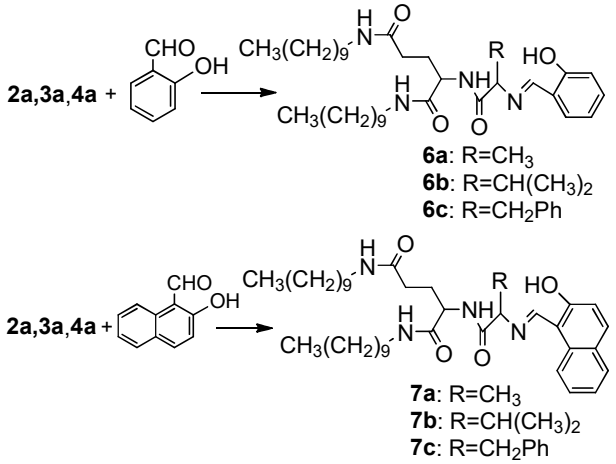


Figure 2. Time course of gel formation in situ from **1a** and salicylaldehyde in EtOH.

These results strongly suggest that EtOH can be gelated by the imine product **5b** as its concentration increases. Neither of the components can gelate the solvent alone but in just mixing them at room temperature to form the imine compound a gel is yielded. It should be emphasized that this system is very simple and unique because the reaction between two components proceeds smoothly at room temperature by just mixing them up without any catalysts to give the gelator. The similar condition has applied to the reaction between **1a** and benzaldehyde, naphthaldehyde, 2-hydroxy-1-naphthaldehyde, to produce **5a**, **5c**, **5d**, respectively. These reaction products predictably gave a precipitate, not a gel in

EtOH. Furthermore, gelation of DMF in situ was observed for the reaction of **1a** and 2-hydroxy-1-naphthaldehyde.

Taking this result into account a hydroxy group in the compound is playing an important role for its ability for gelation. Thus, we have prepared the imine compounds **6a**–**c** and **7a**–**c** from **2a**, **3a** and **4a**, respectively, as shown in Scheme 2.



Scheme 2. Preparation of imine compounds (**6a-c**, **7a-c**).

Gelation properties of the imine compounds **6** and **7** in alcohols and DMF have been examined as summarized in Table 3.

Table 3 Gelation properties of imine compounds (**6**,**7**) in alcohols and DMF[a]

	6a	6b	6c	7a	7b	7c
EtOH	I	P	P	P	G(3.0)	G(2.0)
1-Propanol	I	P	G(2.0)	S	S	G(3.0)
DMF	S	G(1.0)	G(3.0)	S	S	G(4.0)

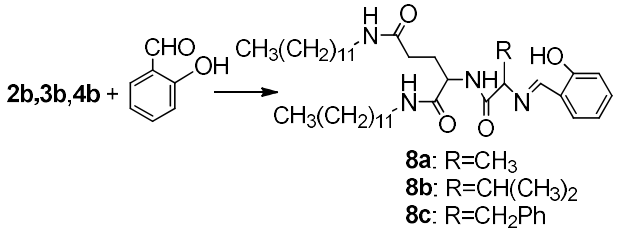
[a]G:gel, I:insoluble, S:soluble, P:precipitate.
The values given in parentheses are the minumun concentration (wt %) (CGC) to achieve gelation.

In terms of gelation properties depending on the structure of the amino acid residue some interesting characteristics have been indicated. Although EtOH can be gelated by **5b** (Glu-Gly), no EtOH gelation can be observed for **6a** (Glu-Ala), **6b** (Glu-Val) and **6c** (Glu-Phe). These results suggest that the alkyl groups (R) might contribute to poor solubilities in EtOH, resulting in no gelation. On the contrary gels in EtOH were produced by the corresponding naphthyl compounds **7b** and **7c**, meaning that some π-π interactions work effectively for building a fiber structure from the individual molecules. Especially, the compound **7c** having a phenyl group in addition to a naphthyl group shows an excellent ability for gelating solvents as shown in Table 3. Such an effect was confirmed for **6c**, because it exhibits gelation in 1-propanol and DMF.

Based on these gelation properties we have examined gel formation in EtOH to combine 2-hydroxy-1-naphthaldehyde with **3a** and **4a**, respectively. After some trials we have finally reached the condition suitable for completion of gelation of EtOH in situ. In the case of **7b** it is found out that gelation in situ needs a higher concentration than expected from its CGC value. No complete gelation was observed until the final concentration of the solution reached ca. 8.0 wt %. For the gelation of EtOH by **7c** it required ca. 6.0 wt %. The minimum concentrations to achieve gelation of EtOH by **7b** and **7c** shown in Table 2 were basically obtained by cooling down the appropriate solution to room temperature after the gelators were dissolved in EtOH by heating. On the contrary gelation in situ is carried out at room temperature. Thus, it can be considered that formation of the gel needs a higher concentration. Gelation in a similar way has been confirmed for the reactions of 2-hydroxy-1-naphthaldehyde with **4a** in 1-propanol and DMF, respectively.

In the course of our research on organogelators it has been suggested that the length of the alkyl chains in the compound plays an important role in terms of gelation properties. Thus, we have designed some compounds having the C12 alkyl chains. Three kinds of L-glutamate moieties (Glu-Ala, Glu-Val, Clu-Phe) carrying two long alkyl chains (C12) **2b**–**4b** were prepared (Chart 1). In order to know the effect of the length of the alkyl chain on gelation we have conducted a test similar to that as described in Table 1. No major difference was confirmed between C10 and C12 in the compounds, however, the compounds **3b** and **4b** exhibit gelation in benzene and toluene contrast to PG by the corresponding compounds **3a** and **4a**. This indicates that a longer alkyl chain could enhance gelation ability in apolar solvents such as benzene and toluene.

Syntheses of the imine compounds **8a**–**c** using **2b**–**4b** and salicylaldehyde were carried out in the purpose of gelation in situ (Scheme 3).



Scheme 3. Preparation of imine compounds (**8a-c**).

Before examination of gelation in situ we have clarified gelation properties of **8a**–**c** in EtOH and 1-propanol as shown in Table 4. Interestingly all products exhibit gelation in EtOH. On the other hand 1-propanol can be gelated by **8b** and **8c**. Obviously a longer alkyl chain seems to contribute formation of gel at least in EtOH and 1-propanol. Although the exact reason of this effect is not clear, the interaction among alkyl chains based on van der Waals forces probably works in these solvents.

These results imply extension of a possibility to produce the gel in situ. As a matter of facts gradual

formation of gel was observed in the reaction of **2b** and salicylaldehyde in EtOH as the reaction proceeded because the product **8a** can gelate this solvent.

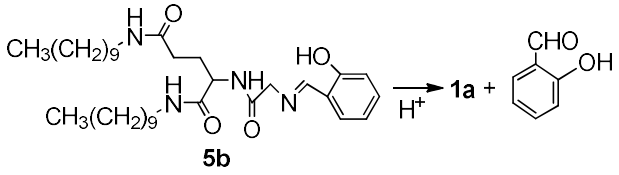
Table 4 Gelation properties of imine compounds (**8a-c**) in EtOH and 1-propanol[a]

	8a	**8b**	**8c**
EtOH	G(2.0)	G(1.0)	G(0.8)
1-Propanol	S	G(2.0)	G(1.0)

[a]S:soluble, G:gel.
The values given in parentheses are the minumun concentration (wt %) (CGC) to achieve gelation.

The similar formation of gel in situ was seen for the reaction of **3b** and **4b** in EtOH and 1-propanol. Such a gelation in situ also requires a higher concentration as compared with that described in Table 4.

Finally we have examined possibility of collapse of the gel in terms of characteristics of the imine bond. It is well known the imine bond can be easily dissociated by the acid. To the EtOH gel (3.0 wt %) by **5b** (20 mg) was added a small amount of trifluoroacetic acid and water, then a collapse of the gel was observed. It has confirmed that this collapse is due to a cleavage of the imine bond resulting in reproduction of the starting materials (Scheme 4). An extensive research concerning such a reversibility is now under progress.



Scheme 4. Decomposition of the imine compound (**5b**).

In summary gel formation in situ which means that the gel is gradually formed and eventually the whole solvent is solidified in the course of the reaction between amino compounds and aldehydes in appropriate solvents can be successively achieved. Combination of two starting materials (amines and aldehydes) and solvent is critical. It should be noted that formation of gel by mixing up two compounds without any additives in the solvent can be applied to some practical usages.

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Supporting Information for characterization of new compounds is available on http://dx.doi.org/10.1246/cl.

References and Notes

1 a) J. H. Jung, S. Shinkai, T. Shimizu, *Chem. Record* **2003**, *3*, 212; b) L. A. Estroff, A. D. Hamilton, *Chem. Rev*. **2004**, *104*, 1201;c) N. M. Sangeetha, U. Maitra, *Chem. Soc. Rev*. **2005**, *34*, 821; d) T. Ishi–I, S. Shinkai, *Top. Curr. Chem.* **2005**, *258*, 119; e) M. George, R. G. Weiss, *Acc. Chem. Res*. **2006**, *39*, 489; f) C. Wang, D. Zhang, J. Xiang, D. Zhu, *Langmuir* **2007**, *23*, 9195; g) P. Dastidar, *Chem. Soc. Rev*. **2008**, *37*, 2699; h) D. K. Smith, *Chem. Soc. Rev*. **2009**, *38*, 684; i) M.-O. M. Piepenbrock, G. O. Lloyd, N. Clarke, J. W. Steed, *Chem. Rev*. **2010**, *110*, 1960; j) A. Dawn, T. Shiraki, S. Haraguchi, S. Tamaru, S. Shinkai, *Chem. Asian J*. **2011**, *6*, 266; k) S. S. Bau, V. K. Praveen, A. Ajayaghosh, *Chem. Rev*. **2014**, *114*, 1973.

2 a) A. Tsuge, R. Matsushita, K. Sakura, T. Moriguchi, K. Araki, *Chem. Lett*. **2012**, 485; b) A. Tsuge, D. Yakeya, T. Moriguchi, D. Kaneko, T. Kawahara, K. Araki, *Chem. Lett*. **2013**, *42*, 263; c) A. Tsuge, T. Fujiwara, D. Yakeya, H. Kawasaki, T. Moriguchi, K. Araki, *Tetrahedron* **2015**, *71*, 9429; d) D. Yakeya, N. Kitou, S. Kinugawa, T. Moriguchi, A. Tsuge, *Tetrahedron* **2017**, *73*, 3973; e) D. Yakeya, T. Moriguchi, A. Tsuge, *Tetrahedron Lett.* **2018**, *59*, 712; f) A. Tsuge, S. Matsumoto, D. Hashimura, K. Araki, *Tetrahedron Lett.* **2020**, *61*, Article 151501.

3 a) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Che. Int. Ed*. **2002**, *41*, 898; b) B. A. R. Hunta, S. Otto, Chem. Commun. 2011, 47, 847; c) E. Moulin, G. Cormos, N. Giuseppone, *Chem. Soc. Rev*. **2012**, *41*, 1031; d) J. W. Li, P. Nowak, S. Otto, *J. Am. Chem. Soc.* **2013**, *135*, 9222; e) D. Beaudoin, T. Maris, J. D. Wuest, *Nat. Chem*. **2013**, 5, 830; f) A. Herrmann, *Chem. Soc. Rev*. **2014**, *43*, 1899.

4 a) V. Yesilyurt, M. J. Webber, E. A. Appel, C. Godwin, R. Langer, D. G. Anderson, *Adv. Mater.* **2016**, *28*, 86; b) W. L. A. Brooks, B. S. Sumerlin, *Chem. Rev*. **2016**, *116*, 1375.

5 a) C. B. Minkenberg, L. Florusse, R. Eelkema, G. J. M. Koper, J. H. van Esch, *J. Am. Chem. Soc.* **2009**, *131*, 11274; b) M. E. Belowich, J. F. Stoddart, *Chem. Soc. Rev*. **2012**, *41*, 2003; c) K. Lv, L. Qin, X. Wang, L. Zhang, M. Liu, *Phys. Chem. Chem. Phys*. **2013**, *15*, 20197; d) K. Lv, L. Zhang, M. Liu, *Langmuir* **2014**, *30*, 9295.

6 a) R. Eelkema, J. H. van Esch, *Org. Biomol. Chem*. **2014**, *12*, 6292; b) Y. Feng, C. Xiaodong, D. Jie, W. Gang, C. Xiaofeng, *ACS Appl. Mater. Interfaces*, **2015**, *7*, 24023.

7 a) K. Sada, M. Takeuchi, N. Fujita, M. Murata, S. Shinkai, *Chem. Soc. Rev*. **2007**, *36*, 415; b) L. J. Prins, P. Scrimin, *Angew. Chem. Int. Ed*. **2009**, *48*, 2288.

8 D. E. Apostolides, C. S. Patrickios, *Polym. Int*. **2018**, *67*, 627.

9 N. Sreenivasachary, J. M. Lehn, *Proc. Natl. Sci. U. S. A.* **2005**, *102*, 5938.

10 J. W. Li, J. M. A. Carnall, M. C. A. Stuart, S. Otto, *Angew. Chem. Int. Ed*. **2011**, *50*, 8384.

11 C. Ren, Z. Song, W. Zheng, X. Chen, L. Wang, D. Kong, Z. Yang, *Chem. Commun*. **2011**, *47*, 1619.

12 J. Boekhoven, J. M. Poolman, C. Maity, F. Li, L. van der Mee, C. B. Minkenberg, E. Mendes, J. H. van Esh, R. Eelkema, *Nat. Chem.* **2013**, *5*, 433.

13 G. T. Wang, J. B. Lin, X. K. Jiang, Z. T. Li, *Langmuir*, **2009**, *25*, 8414.

14 a) H. Bunzen, Nonappa, E. Kalenius, S. Hietala, E. Kolehmainen. *Chem. Eur. J*. **2013**, *19*, 12978; b) L. Zang, H. Shang, D. Wei, S. Jiang, *Sens. Actuators B* **2013**, *185*, 389.

15 H. Ihara, H. Hachisako, C. Hirayama, K. Yamada, *J. Chem. Soc., Chem. Commun*. **1992**, 1244.

16 P. Duan, Y. Li, L. Li, J. Deng, M. Liu, *J. Phys. Chem. B* **2011**, *115*, 3322.

17 S. S. Bub, V. K. Praveen, A. Ajayaghosh, *Chem. Rev.* **2014**, *114*, 1973.

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Graphical Abstract

Textual Information

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Graphical Information