A four-component organogel based on orthogonal chemical interactions

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A four-component organogel based on orthogonal chemical interactions

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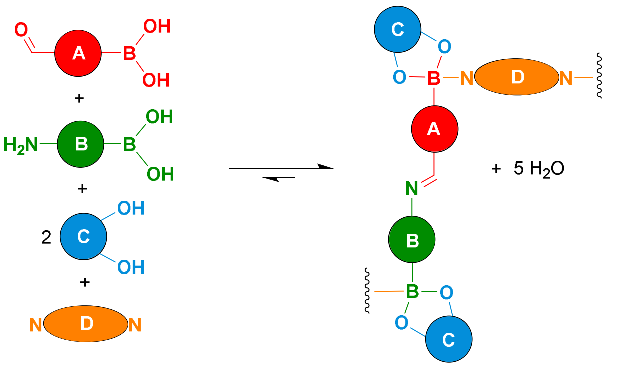
A thermoresponsive organogel was obtained by orthogonal assembly of four compounds using dynamic covalent boronate ester and imine bonds, as well as dative boron-nitrogen bonds. It is shown that the gel state can be disrupted or reinforced by chemicals which undergo exchange reactions with the gel components.

The syntheses and the properties of gels based on mixtures of two or more low molecular weight components have been investigated extensively over the last years.[1] As pointed out in a review article by Hirst and Smith, these multicomponent gels provide "exquisite tunability and controllability".[1b] The gel properties can be altered by structural modifications of the individual building blocks or by variation of the building block ratio. Furthermore, multicomponent gels are typically based on reversible chemical interaction between the gel components. Consequently, they qualify as supramolecular gels,[2] and they are able to respond to changes in temperature or to chemicals which alter the interaction between the gel components.[3,4] While there are numerous reports about two-component gels,[1] there are relatively few studies about gels based on three or more distinct building blocks (solvent not included).[5] Below, we describe a thermoresponsive gel which is formed by orthogonal assembly[6] of four compounds using two different dynamic covalent bonds and dative boron-nitrogen bonds. It is shown that gel formation can be reversed by selective disruption of one of the three interactions.

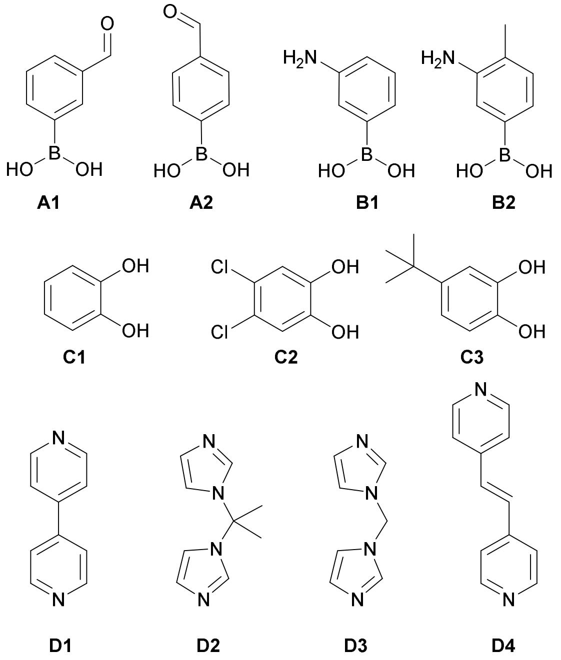
Dative bonds between Lewis acidic boronate esters and N-donor ligands are increasingly being used for the construction of molecular nanostructures and polymeric materials.[7,8] In 2011, we have reported the formation of an organogel by reaction of a triboronate ester with 4,4'-bipyridine in toluene.[9] More recently, the group of Iwasawa has demonstrated the formation of a gel by cross-linking of oligomeric boronic esters with 1,3-diaminopropane.[10] These first reports are evidence that dative B-N bonds can be used for the generation of supramolecular organogels. Several studies have shown that boronate ester linkages can be formed simultaneously with imine bonds.[8,11] These results prompted us to investigate whether it is possible to obtain organogels by simultaneous utilization of boronate esters, imines, and dative B-N bonds. To examine this question, we have performed a small screening using four different types of compounds: arylboronic acids containing a formyl group (**A1**, **A2**), arylboronic acids with a primary amine group (**B1**, **B2**), catechols (**C1**−**C3**), and ditopic N-donor ligands (**D1**−**D4**) (Table 1). Upon condensation, the catechols were expected to react with the boronic acid functions, and the amine groups with the aldehydes. This polycondensation reaction should give a diboronate ester, which could aggregate via dative B-N bonds (Scheme 1). The resulting assembly might induce gelation.



Scheme 1 Synthesis of a supramolecular gel based on dynamic covalent bonds and dative B-N bonds using a 4-component reaction.

The screening was performed as follows: the four different compounds were mixed in the ratio **A**:**B**:**C**:**D** = 1:1:2:1 in toluene ([**A**] = 20 mM). The mixture was heated for 4 h to 120 °C and then it was allowed to cool. Out of the ten different combinations that we have tested, most reactions resulted in the formation of a precipitate (Table 1, entries 1−7). This result was not unexpected because previous studies had shown that the aggregation of polyboronate esters with polytopic N-donor ligands tends to give insoluble (sometimes crystalline) materials.[7d,8a] The use of highly soluble catechol **C3** afforded a viscous liquid (Table 1, entry 8). For two of the combinations, however, we observed the formation of a gel as evidenced by the tube-inversion test (Table 1, entry 9 and 10). Preliminary test revealed that gel formation for **GEL1** could be reversed and re-induced by heating-cooling cycles, whereas **GEL2** was less well behaved (precipitates were observed). Therefore, we focused on **GEL1** for more detailed investigations.

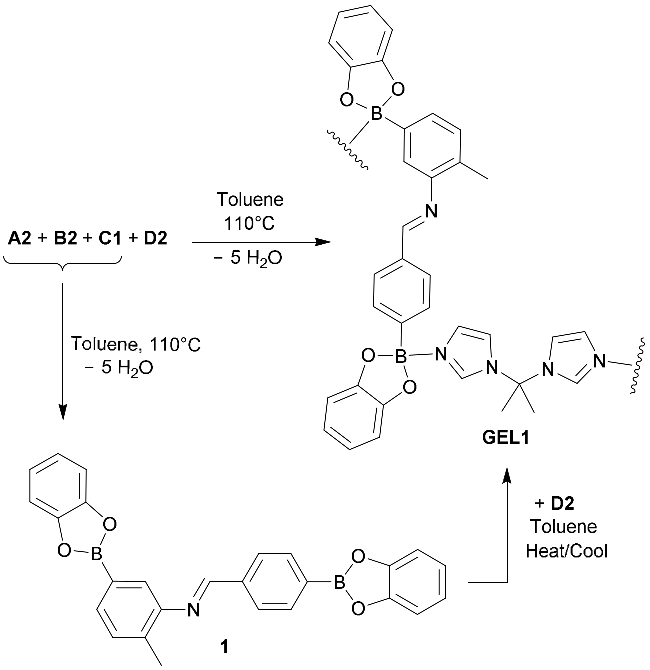
Table 1 The different starting materials used for the 4-component reaction.



Entry	Combination in toluene	Sample state
1	**A1** + **B2** + 2 **C1** + **D2**	Precipitate
2	**A2** + **B1** + 2 **C1** + **D1**	Precipitate
3	**A2** + **B1** + 2 **C1** + **D3**	Precipitate
4	**A2** + **B2** + 2 **C2** + **D2**	Precipitate
5	**A2** + **B2** + 2 **C1** + **D4**	Precipitate
6	**A1** + **B2** + 2 **C2** + **D2**	Precipitate
7	**A2** + **B2** + 2 **C2** + **D1**	Precipitate
8	**A2** + **B2** + 2 **C3** + **D2**	Viscous liquid
9	**A2** + **B2** + 2 **C1** + **D2**	**GEL1**
10	**A2** + **B1** + 2 **C1** + **D2**	**GEL2**

To study the molecular basis for gel formation, we performed a control experiment using only three compounds: **A2**, **B2**, and **C1**. Heating of the three compounds in the ratio 1:1:2 in toluene resulted in the formation of the boronate ester **1**, which could be isolated in 82 % yield (Scheme 2). Addition of the N-donor **D2** to a suspension of **1** in toluene, followed by a heating-cooling cycle, gave a gel which behaved very similarly to the one obtained by a one-step reaction.

The fact that gelation can be induced upon addition of the bisimidazole **D2** to **1** suggests that dative B-N bonds are responsible for network formation. The ability of **1** to bind imidazole-type N-donors was confirmed by isothermal titration calorimetry (ITC) experiments in chloroform with **1** and the model compound N-methylimidazole. The data could be fitted to a 1:2 binding model assuming two identical and independent binding sites (see ESI). The resulting association constants are $K_{a1} = 4.4(\pm0.7) \times 10^3$ M^{-1} and $K_{a2} = 1.1(\pm0.2) \times 10^3$ M^{-1}. NMR titration experiments in $CDCl_3$ showed that the complexation of N-methylimidazole is fast on the NMR time scale. Plotting the changes in chemical shifts vs. concentration resulted in binding isotherms, which could be nicely fitted using the association constants obtained by ITC (see ESI).† Taken together, these results are good evidence that the chemistry outlined in Scheme 2 is indeed responsible for gel formation.



Scheme 2 Synthesis of **GEL1** by a direct 4-component reaction or by a two-step process involving the intermediate **1**.

We then explored the gelation properties of the **1**/**D2** mixture in different solvents (Table 2). We chose non-protic, medium-to-low polarity solvents because highly polar solvents were expected to interfere with the dative B-N bonds, and protic solvents might disrupt the ester linkage. Apolar solvents such as hexane were likewise omitted because the starting materials are not sufficiently soluble. Toluene and CCl_4 gave gels with low critical gel concentrations (CGC) – as low as to 0.065 percent in weight for toluene.†† Xylenes were tested as well and showed that the relative position of both methyl groups have strong influence on the gel properties, with *o*-xylene giving a more robust gel compared to *m*-xylene. No gelation was observed with THF, presumably because it is already too polar to allow efficient B-N bond formation. Interestingly, both chlorobenzene and 1,2,4-trichlorobenzene gave gels, but neither 1,2- nor 1,3-dichlorobenzene resulted in gelation. These results show that the system is very sensitive to the nature of the solvent.

With 1.0 wt % of the gel components, the sol-gel temperature was estimated with the tube inversion test. The corresponding values are listed in Table 2. In *m*-xylene, solubilization was already observed at 45 °C. In the less polar CCl_4, on the other hand, gel disruption was only observed when reaching the boiling point of the solvent.

Scanning electron microscopy images of the xerogels obtained by air-drying samples of **GEL1** in all gelating solvents were taken to investigate the gel morphology. The results revealed the coexistence of spherical aggregates along with a variable amount of fibrous structures in all cases (ESI, Figure S10−S16).

Wide-angle X-ray scattering (WAXS) measurements of the **GEL1** xerogel from toluene revealed a mainly amorphous material, while the xerogel sample from *p*-xylene showed a slightly higher degree of crystallinity (ESI, Figure S17). The scattering peaks appear at the same angles for both samples, indicating that the molecular packing of the crystalline part of the xerogel is similar. Due to the low crystallinity of the samples, we have not attempted to derive more detailed structural information from the WAXS patterns.

Finally, we tried to prepare a gel by omitting one out of the four compounds **A2**, **B2**, **C1**, or **D2**. None of these reactions gave a gel, indicating that all four compounds are required.

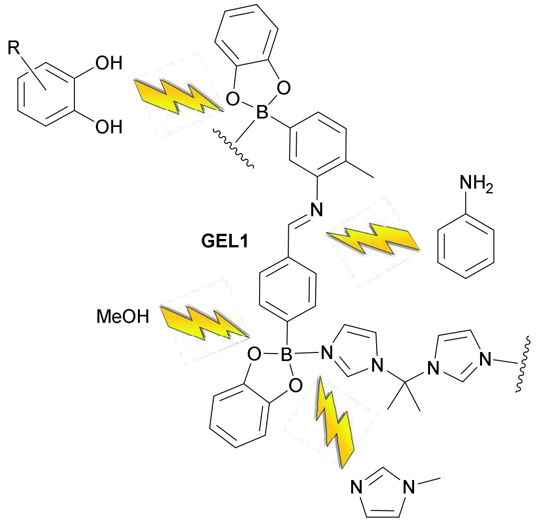
Table 2 Gelation tests with a mixture of **1** and **D2** in different solvents

Solvent	Gelation	CGC [wt %]	CGC [mM]	$T_{\text{sol-gel}}$[a] [°C]
Tetrahydrofuran	No	-	-	-
Toluene	Yes	0.065	0.9	75
Nitrobenzene	No	-	-	-
Chlorobenzene	Yes	0.25	4.6	60
1,2-Dichlorobenzene	No	-	-	-
1,3-Dichlorobenzene	No	-	-	-
1,2,4-Trichlorobenzene	Yes	0.1	2.4	55
Carbon tetrachloride	Yes	0.2	5.2	77[b]
Chloroform	No	-	-	-
Mesitylene	No	-	-	-
o-Xylene	Yes	0.1	1.4	90
m-Xylene	Yes	1.0	14.2	45
p-Xylene	Yes	0.25	3.6	65

[a] $T_{\text{sol-gel}}$ for 1.0 wt % of **GEL1**. [b] The gel was only broken in boiling CCl_4.

An attractive feature of a supramolecular gel based on orthogonal interactions is the possibility to selectively disrupt these interactions by chemical or physical means. As outlined above, heating of **GEL1** in toluene above 75 °C results in its solubilization. It is likely that temperature affects the weakest links of the assembly, that is the dative B-N bonds. We have also studied the disassembly of **GEL1** by chemical stimuli.[3] In these experiments, we have placed an excess of the corresponding chemical in pure form on top of a 1.0 wt % gel in toluene. The following compounds were found to disrupt the gel state: methanol, N-methylimidazole, dichlorocatechol (**C2**), and aniline. Importantly, these chemicals appear to be selective stimuli, since they disturb mainly one of the three reversible interactions of the assembly (Scheme 3). The selectivity was substantiated by a series of control experiments (see ESI). The addition of aniline, for example, results in a transimination reaction as shown by a model reaction of **1** with aniline. The dative B-N bond, on the other hand, is less disturbed by aniline as evidenced by competition experiments using a simple boronate ester in combination with N-methylimidazole (a substitute for **D2**) and aniline. The addition of methanol or dichlorocatechol to a solution of **1** in $CDCl_3$ resulted in partial liberation of catechol. In the gel state, the trans-esterification with **C2** leads to the formation of an insoluble precipitate (similar to what was observed in 4-component reactions involving **C2**; see Table 1).

Addition of 4-*t*-butylcatechol (**C3**) to **GEL1** in toluene followed by a heating-cooling cycle resulted in a modified gel **GEL1-C3**, which exhibited an increased mechanical resistance compared to its precursor **GEL1**. This was evidenced by putting a metallic sphere on freshly prepared samples of **GEL1** and **GEL1-C3**. After 2 minutes, the sphere had sunken into **GEL1**, while it was still on top of **GEL1-C3** (ESI, Figure S18). This result was unexpected, since a boronate ester with the more electron-rich catechol **C3** (obtained by catechol exchange) should form slightly weaker B-N bonds.[12] When **GEL1** was treated with normal catechol **C1** instead of **C3**, an increased mechanical resistance of the resulting gel was not observed. These results are further evidence that minor structural modifications can have a large impact on the gel properties. Importantly, the results show that one can use exchange reactions via dynamic covalent chemistry to reinforce the mechanical properties of a multicomponent gel such as **GEL1**.



Scheme 3 The gel state of **GEL1** can be disrupted of reinforced by addition of chemicals.

To summarize: we have reported a thermoresponsive organogel which is based on four different low molecular weight compounds. In solution, three of the compounds undergo a polycondensation reaction to give an imine-linked diboronate ester (**1**). The latter aggregates with the fourth component (**D2**) via dative B-N bonds, thereby inducing gel formation. A unique feature of the system is the presence of three types of dynamic interactions between the gel components: dynamic covalent imine and boronate ester bonds, as well as dative B-N bonds. These interactions are largely orthogonal to each other.††† It is thus possible to selectively address them with physical or chemical stimuli, resulting in rupture or reinforcement of the gel state.

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Notes and references

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† A direct fit of the NMR titration data did not provide reliable results (see ESI).

†† Despite the low CGC values, the gels are rather soft. Rheology measurements were therefore not performed.

††† They are not perfectly independent: imines and boronate esters are both hydrolysed by water, and imines are potential N-donors for dative B-N bonds.

Electronic Supplementary Information (ESI) available. See DOI: 10.1039/c000000x/

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Graphic for the TOC: