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# Dynamic Evolving Two-Component Supramolecular Gels—Hierarchical Control over Component Selection in Complex Mixtures

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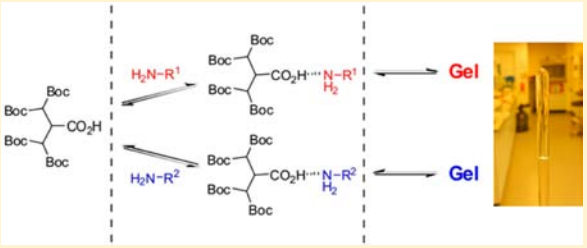
Supporting Information

**ABSTRACT:** We report a two-component acid–amine gelation system which forms instant organogels on simple mixing. We investigate self-assembly using a wide range of different amines and identify the optimum amines for gelation to occur. Using NMR and other spectroscopic methods, we unambiguously determine the stoichiometry of the complex responsible for gelation (1:1) and characterize the noncovalent interactions responsible for gelation. Using Kamlet–Taft parameters we gain a detailed understanding of the role of solvent on gelation. Most importantly, we explore the ability of these multicomponent systems to assemble from complex mixtures, and using NMR can determine which components are preferentially taken up into the immobile "solid-like" fiber network and which components remain mobile in the "liquid-like" solvent phase. In this way, we determine that the component selection process is controlled by the two key steps in hierarchical assembly: (i) acid–base complex formation (as predicted by the p$K_a$ of the amine) and (ii) gel fiber assembly (as predicted by the $T_{gel}$ value). These parameters therefore enable a predictive understanding of the way in which complex mixtures self-organize and assemble and also how the sorted assemblies disassemble on heating. In a key experiment, we demonstrate that these materials are highly responsive and that a preformed gel, exposed to a new component, evolves, adapts, and heals its composition in response to the thermodynamic preferences of the overall system.




## INTRODUCTION

Supramolecular gels are intriguing dynamic materials which contain nanoscale fibrillar architectures that rely on self-assembly for their formation and are highly responsive to stimulus.[1] In recent years, there has been great interest in gaining fundamental understanding of the thermodynamic and kinetic factors which control gelation,[2] as only with a firm grip on these parameters will it be possible to design future soft materials with potential high-tech applications.[3]

One class of gels which are of particular interest are multicomponent systems, in which two (or more) molecular-scale building blocks first have to interact before gelation can take place.[4] Such systems can be based on either noncovalent[5] or covalent[6] interactions to form the active gelator and are highly tunable, as either component can be easily modified in order to change the performance of the gel or introduce additional functionality. Recently, there has been increasing focus on the ability of multicomponent gels to assemble from complex mixtures. For example, by coassembling different units into mixed nanostructures it has been demonstrated that a small amount of one component can influence the properties of the overall assembly.[7] Alternatively to coassembly, there has also been an interest in orthogonal, or selective assembly, based on the molecular recognition pathways programmed into the molecular-scale building blocks. In this way, van Esch and co-workers described the ability of hydrogelators to orthogonally assemble into nanofibers in the presence of self-assembling vesicles.[8] It is also possible to assemble self-sorted multigelator gels, in which self-sorting enables each gelator to establish its own independent fiber network, each of which can, in some cases, be independently thermally addressable or reactive.[9] In multicomponent gels, the concept of component selection is of growing importance, for both noncovalent[10] and covalent[11] multicomponent systems. In component selection certain molecules are selected for incorporation and immobilization into a gel network while others are ignored and left mobile in solution.

In this new paper, we explore component selection within two-component gels in detail. We apply NMR methods which allow easy quantification of assembly processes[12] and use these to gain detailed insight into the driving forces for component selection and gel formation. Importantly, we demonstrate that component selection is a predictable and understandable process and develop ground rules to explain selectivity pathways within these self-assembled materials—in particular focusing on the relative importance of different steps in the hierarchical assembly process. We also demonstrate the key advantage of gel-phase soft materials—their solvated and highly porous nature means they can easily evolve via simple addition of a new solution-phase component to a preformed gel, enabled by the ready diffusion of small molecules within a porous gel

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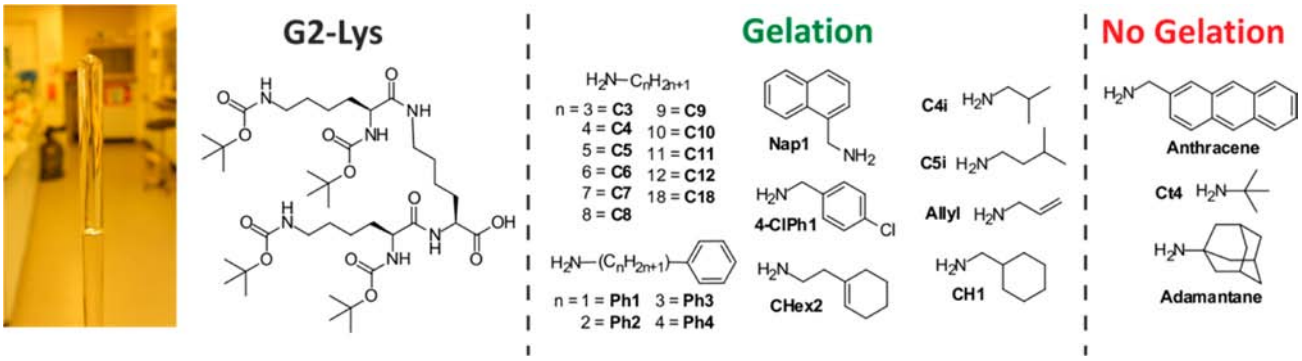


**Figure 1.** Two-component gelation system comprising **G2-Lys** and a primary monoamine selected from the library shown.

matrix and the reversibility of the noncovalent interactions which underpin gelation. We therefore report that these gels therefore report that these gels act as "intelligent", responsive, and healable materials,[13] able to adapt and evolve their structures in response to chemical stimulus.

## RESULTS AND DISCUSSION

**Initial Characterization of Scope of Gelation System.** The gelation system used in this study is related to one previously used by us in a number of reports, in which the key component is **G2-Lys**, a second generation lysine dendron with Boc protecting groups at the periphery and a free carboxylic acid group at the focal point (Figure 1).[10,14] This dendron does not self-assemble in its own right, but we have previously demonstrated that in the presence of diamines, a 2:1 complex is formed in organic solvents such as toluene, which is then capable of hierarchical assembly into a gel-phase material. In this new work, we decided to investigate the performance of these dendrons with monoamines. Surprisingly, we found that organic solutions of monoamines gave rise to instant gelation when mixed with solutions of **G2-Lys**. Instantaneous, in situ gelation remains very rare[15]—most gelators require either heating or sonication in order for solubilization to occur prior to nanofiber assembly. Two-component systems, such as acid–base complexes, are particularly suitable for instantaneous gelation as the complex forms on mixing and can then spontaneously assemble into nanofibers.

The ability of **G2-Lys** to form gels was then tested with a library of different primary amines (Figure 1) using **G2-Lys** (10 mM) mixed with amine (10 mM) in toluene (0.5 mL). For gelation testing, all samples were heated to form a solution and left to cool at ambient temperature (21 °C) overnight, before being checked to see if gelation had occurred. Although many of these gels formed instantaneously in situ under ambient conditions, we always applied a heat–cool cycle to the gels we studied in detail. This is because the kinetics of gelation were often faster than the kinetics of mixing and as such, it proved difficult to make homogeneous reproducible gels by simple mixing. Small air bubbles would sometimes form in the samples, which made quantitative NMR work in particular, effectively impossible, as such inhomogeneities had a significant adverse impact on the quality of spectra.

In general, it was found that shorter unbranched alkyl amines were able to form gels with **G2-Lys** (from **C3** to **C8**), while longer chain lengths (**C9** to **C18**) did not form gels unless cooled to a low temperature (−20 °C). Branched alkyl, cyclic alkyl, and allyl amines were found to form gels unless the alkyl units became particularly bulky—such as *tert*-butyl or adamantane groups. Aromatic amines could induce gelation, as long as the amine was not directly conjugated with the aromatic ring, or if the aromatic ring system becomes too large, such as in the case of anthracene. We suggest that larger, more bulky amines are unable to support gelation as they hinder effective packing within the nanoscale fibers. A more comprehensive list of amines tested is given in the Supporting Information.

**Determination of Stoichiometry of the Two-Component Gelation System.** In order to determine the stoichiometry of the complex responsible for gelation we initially monitored the $T_{gel}$ values of gels formed with different ratios of **G2-Lys** to hexylamine (**C6**) using the reproducible and simple tube-inversion method.[16] The experiment was carried out with constant concentrations of **G2-Lys** (either 2 mM or 10 mM) and **C6** was then added at varying concentrations. Below a certain amount of amine (0.2 equiv for 10 mM dendron, 0.5 equiv for 2 mM dendron), a self-supporting gel was not observed. However, on increasing the amount of amine present, the $T_{gel}$ value was observed to increase up to the addition of 1 equiv of **C6**, and then, as additional amine was added, no significant further increase in thermal stability was observed (Figure 2A). All of the $T_{gel}$ data in this paper were reproduced on multiple samples and shown to be highly reproducible, particularly in the "plateau region", allowing us to estimate errors as ±1 °C. This is strongly suggestive of a 1:1 acid–base complex being responsible for gelation.

We then employed NMR methods to precisely quantify what is mobile in the "liquid-like" phase and visible by NMR and, hence, indirectly determine what is immobilized (on the NMR time scale) in the "solid-like" fibers and not visible in the NMR spectrum due to line broadening.[12] NMR samples containing **G2-Lys** (10 mM) and varying concentrations of **C6** were heated and allowed to cool. The integration of **G2-Lys** and **C6** peaks in each case were compared to a mobile internal standard (diphenylmethane, 10 mM). The results clearly showed that at a 1:1 ratio of **G2-Lys**:**C6** (both 10 mM), both of these molecules are barely visible in the spectrum (8% of **G2-Lys**, 4% of **C6**), meaning they are both almost entirely fixed in the gel network. If an excess of either component was present, all of the excess was visible in solution, indicating it remained mobile and uncomplexed (i.e., not taken into the gel network). As such, we suggest that this novel NMR approach is the best way to unambiguously characterize the molecular-scale composition of multicomponent self-assembled gels as a 1:1 complex.

FEG-SEM performed on the xerogel of **G2-Lys**:**C6** indicated that, as expected, this system formed a nanoscale fibrillar


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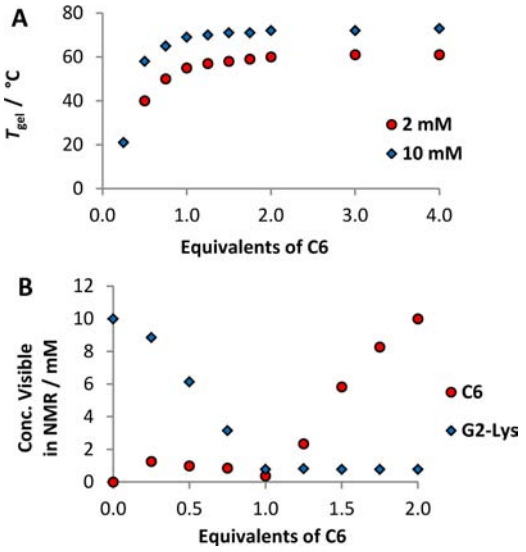


**Figure 2.** (A) Variation of $T_{gel}$ with number of equivalents of amine added showing saturation at 1:1 stoichiometry—data only shown for systems above the MGC. (B) NMR quantification of composition of mobile phase at different ratios of **G2-Lys**:**C6** showing the presence of a 1:1 complex immobilized in the fiber network.

network (see Supporting Information). Performing FEG-SEM on a gel with a 1:2 ratio of **G2-Lys**:**C6** showed a gel with an identical morphology to that made with the 1:1 ratio, further evidence that excess **C6** is not involved and does not affect the assembly of the gel network.

**Characterization of Non-Covalent Interactions Responsible for Gelation.** In order to identify the noncovalent interactions responsible for gelation of the 1:1 complex, we performed ATR-FTIR and variable temperature NMR (VT-NMR) on the gel formed by a 1:1 mixture of **G2-Lys** and **C8** (10 mM). The ATR-FTIR spectrum of the dried two-component xerogel was compared to the spectrum of powdered **G2-Lys** dried from solution. The spectrum of **G2-Lys** powder showed a carbamate C═O stretch at 1690 $cm^{-1}$, amide C═O at 1658 $cm^{-1}$, and NH stretch at 3308 $cm^{-1}$. In the xerogel spectrum, the carbamate C═O stretch was shifted slightly to 1685 $cm^{-1}$, the amide C═O was shifted more significantly to 1646 $cm^{-1}$, and the NH stretch to 3320 $cm^{-1}$. This suggests that the addition of amine induces a change associated with gelation in which both carbamate and especially the amide groups become more involved in hydrogen bond interactions. We did not observe bands (1650−1550 $cm^{-1}$) characteristic of a carboxylate group, and it is therefore doubtful whether full proton transfer takes place between the carboxylic acid of **G2-Lys** and the amine group of **C8**. Proton transfer may be partial or not occur, with a neutral hydrogen bond being formed instead. A neutral hydrogen bond is supported by theoretical studies which suggest that in low dielectric conditions (e.g., toluene) acid−amine interactions can occur without full proton transfer.[17]

The VT-NMR study of the gel showed the NH peaks of the amide and carbamate groups appearing and shifting upfield as the temperature of the sample was increased, consistent with the increased molecular mobility on gel disassembly and the loss of intermolecular hydrogen bonds between the CONH groups on **G2-Lys**. The amide peaks showed larger total shifts ($\Delta\delta_{NH}$ = 0.469 and 0.405) than the carbamate ($\Delta\delta_{NH}$ = 0.302), again indicating that the amide groups are more important to the hydrogen bonding network which underpins gelation.

In summary, these spectroscopic studies demonstrated that intermolecular hydrogen bonds between the CONH groups of **G2-Lys** are responsible for the assembly of the 1:1 acid−base complex into fibrillar architectures.

**Solvent Effects on Gelation.** Given the importance of solvent in gelation, we investigated the effect of solvent on gels formed from a 1:1 mixture of **G2-Lys** and **C6** (both 10 mM). The thermal stability of the gels in each solvent were determined. We also noted whether gels were transparent, translucent, or opaque in each solvent (see Supporting Information for full data)—in general terms, opaque gels are associated with lower solubility and/or larger aggregates being present. We then attempted to correlate gelation performance and thermal behavior with a variety of solvent parameters.[18]

Bulk solvent parameters such as dielectric constant ($\varepsilon$) had little correlation to the gel performance. The normalized Dimroth−Reichardt parameter ($E_T^N$) indicated that, as the solvent parameter increased, gel thermal stability gradually decreased, suggesting gelation was preferred in lower polarity solvents—however, a number of solvents which might be predicted to support gelation according to this parameter did not do so. Similarly, the Hildebrand solubility parameter ($\delta_0$) only showed a poor correlation with gel performance. The Hansen parameters,[19] which subdivide solvent interactions into different types ($\delta_d$ = dispersion interactions, $\delta_p$ = dipole−dipole interactions, and $\delta_h$ = hydrogen bond interactions) provided a somewhat better predictive correlation, but the correlation remained far from perfect. The Hansen parameters do not differentiate between hydrogen bond donor and acceptor effects, and we therefore employed Kamlet−Taft parameters,[20] which are able to do this. There are three Kamlet−Taft parameters describing different properties of a solvent ($\alpha$ = hydrogen bond donating ability, $\beta$ = hydrogen bond accepting ability, and $\pi^*$ = polarizability). Gels would only form in solvents for which $\alpha$ = 0.00 (except for acetonitrile, $\alpha$ = 0.19), and it can therefore be proposed that hydrogen bond donor solvents strongly inhibit gelation—in agreement with the primary noncovalent interaction which underpins fiber assembly being amide−amide hydrogen bonds. The $T_{gel}$ values of the gels were plotted against the $\beta$ and $\pi^*$ values for each solvent (Figure 3); however, individually, these parameters did not give a good correlation with thermal stability. However, linear combination of these parameters gave rise to a good correlation (Figure 3), with a 1:1 weighting giving the best fit.[20]

We therefore suggest that the ability of solvents to support gelation is (i) primarily dependent on the solvent not being a hydrogen bond donor ($\alpha$)[18i−k] but is then further tuned by (ii) the ability of the solvent to accept hydrogen bonds ($\beta$) and its general polarity/polarizability ($\pi^*$). If these values are too high (e.g., in THF, DMF, chloroform, etc.) then the gelator will become too soluble to assemble and will instead dissolve, while if they are too low (e.g., hexane), the gelator will be too insoluble to form gel networks within the solvent phase. However, it should be noted that although this was the best approach to predict gelation in these systems, it was not perfect (e.g., acetonitrile supports gelation even though $\alpha \neq 0$).

**Effect of Amine on Gelation.** Alkyl amines from **C3** to **C8** had been found to support gelation. The effect of chain length on gel stability was therefore investigated by measuring the $T_{gel}$ values of gels made with **G2-Lys** and amines **C3** to **C8** (1:1 mixture) over a concentration range of 2 to 10 mM. The


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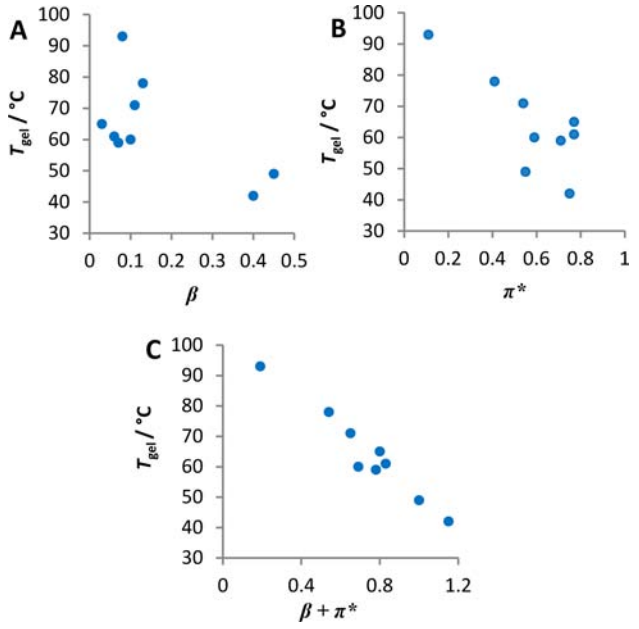


**Figure 3.** Correlation of $T_{gel}$ with Kamet–Taft parameters (A) $\beta$, (B) $\pi^*$, and (C) 1:1 linear combination of $\beta$ and $\pi^*$.

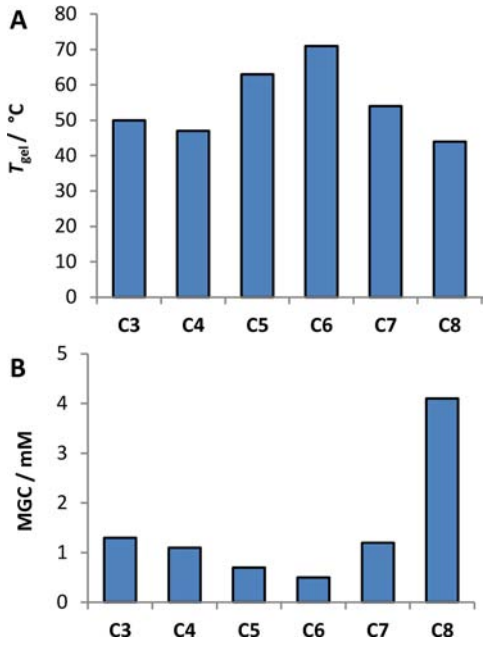


**Figure 4.** (A) Thermal stabilities ($T_{gel}$ values) of **G2-Lys:Cn** (10 mM) gels in toluene and (B) minimal gelation concentrations (MGC values) for these complexes.

thermal stability of the gels increased to a maximum for **C6** (Figure 4). Furthermore, the minimum gelation concentration (MGC) was at its lowest for **C6**, and as the chain length increased, significantly more of the complex was required to support a gel (Figure 4).

Circular dichroism (CD) was employed to monitor the effect of the achiral amine on the assembly of the chiral **G2-Lys**. A solvent mixture of methylcyclohexane:dioxane (95:5) was chosen as it produced transparent gels, with equivalent thermal stability trends to those in toluene, and importantly was transparent in the required spectroscopic window. CD bands for these gel systems (10 mM) were observed at ca. 220 nm—indicative of chiral organization of the amide chromophores. Variable temperature (VT) CD studies demonstrated that the CD bands disappeared on heating and hence correspond to thermally responsive self-assembled nanostructures. The CD spectra observed for samples made with **C3** to **C7** were similar, but for **C8** a much lower intensity CD band was observed (see Supporting Information). This is consistent with the observation that for **C8** the gelation ability is significantly diminished—it is the longest chain length for which room temperature gels are still observed.

We then used VT NMR studies to provide further insight into the effect of amine. Samples containing **G2-Lys** and amine (both 10 mM) were slowly heated and NMR spectra recorded every 5 °C. We used diphenylmethane as an internal standard to quantify the mobile material within the sample. On increasing the temperature, an increasing amount of gelator was observed within the mobile phase as the gel fibers begin to disassemble. We have previously employed this type of study to gain insight into single-component gelation systems.[12c] This study allows a number of parameters to be experimentally determined: (i) the temperature at which all the gelator network is broken down and is visible in solution ($T_{100\%}$) and (ii) the percentage of the gelator complex invisible (i.e., within the fibers) at the $T_{gel}$ value ([Insol]@$T_{gel}$).

In each case the $T_{gel}$ value is in reasonable agreement with $T_{100\%}$ (Table 1) indicating that what is observed macroscopically on breakdown of the gel ($T_{gel}$) reflects what is happening at the molecular scale in terms of fiber disassembly ($T_{100\%}$). The $T_{gel}$ measurements are slightly lower than the corresponding $T_{100\%}$ values as they represent the point at which the gel network is no longer stable to inversion (but some fibers may still exist), whereas $T_{100\%}$ is the temperature at which the entire network is disbanded. The [Insol]@$T_{gel}$ of each sample was compared with the MGC values. This former value indicates how much of the network is intact at $T_{gel}$, i.e., how much network is needed to ensure the sample can support itself against gravity. The molecular-scale parameter is in some agreement with the trend in macroscopically observed MGC values, with **C6** requiring the least material to form an effective gel. It should be noted that there is a difference between the exact values for each sample because they are measuring subtly different things. The MGC is the minimum *total* concentration of gelator required to form a gel stable to inversion at room temperature, whereas [Insol]@$T_{gel}$ is the concentration of gelator "invisible" in the sample (i.e., only in the fibers) at its $T_{gel}$ value.

**Table 1. Correlation between Macroscopic Observations of Gels ($T_{gel}$ and MGC Values) and NMR Molecular-Scale Parameters ($T_{100\%}$ and [Insol]@$T_{gel}$**

| | macroscopic observations | | molecular-scale parameters from NMR | |
|---|---|---|---|---|
| amine | $T_{gel}$, °C | MGC, mM | $T_{100\%}$, °C | [Insol]@$T_{gel}$, mM |
| **C4** | 47 | 1.1 | 55 | 3.6 |
| **C5** | 63 | 0.7 | 64 | 1.2 |
| **C6** | 71 | 0.5 | 73 | 0.2 |
| **C7** | 54 | 1.2 | 56 | 0.6 |
| **C8** | 44 | 4.1 | 49 | 2.8 |

We then applied a van't Hoff treatment to the VT NMR data and treated the disassembly of gel fibers as a solubilization process.[12c,d] Data were collected in the range of 25–65 °C, and


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the assumption was made that $\Delta H$ and $\Delta S$ were temperature independent. Given that NMR provides a direct measure of '"solubility", this approach allows thermodynamic parameters associated with gelation/dissolution to be extracted.

As can be seen from Table 2, gelation (which is the inverse of the dissolution process) is enthalpically favorable and entropically disfavored as would be expected for the assembly of ordered fibers through hydrogen bond interactions. There is a clear enthalpy−entropy compensation type effect[21]—i.e., if gelation is more enthalpically favorable (stronger interactions between molecular scale building blocks) then it also becomes more entropically disfavored (a higher degree of organization). The precise balance between these enthalpic and entropic terms leads to the overall favorabilty of gel formation ($-\Delta G_{diss}$, Table 2), which as expected reflects the $T_{gel}$ values for gelation (Table 1) and reaches a maximum for **C6**. This sample forms the most enthalpically favored *and* best organized gel, but the favorable enthalpy offsets the unfavorable entropy most effectively among this family of gelators.

**Table 2. Thermodynamic Parameters Extracted from the van't Hoff Treatment of VT NMR Data in the Temperature Range 25−65°C, Assuming that $\Delta H$ and $\Delta S$ Are Temperature Independent**

| amine | $-\Delta H_{diss}$, kJ mol$^{-1}$ | $-\Delta S_{diss}$, J mol$^{-1}$ K$^{-1}$ | $-\Delta G_{diss}$, kJ mol$^{-1}$ |
|---|---|---|---|
| **C4** | −85.9 | −226 | −18.4 |
| **C5** | −78.2 | −192 | −20.7 |
| **C6** | −90.5 | −226 | −22.9 |
| **C7** | −63.6 | −155 | −17.3 |
| **C8** | −67.6 | −172 | −16.3 |

We then investigated gels formed from aromatic amines, focusing on gels incorporating different aliphatic spacer chain lengths between the benzene ring and the amine group. The $T_{gel}$ values of these gels (in toluene) were measured (see Supporting Information). The gels made with **Ph1** and **Ph3** have similar thermal stabilities, while the gels formed with **Ph2** were much stronger and those with **Ph4** weaker (see Supporting Information). CD spectroscopy in methylcyclohexane:dioxane (95:5, see Supporting Information) indicated that all of these gels show an absorbance band at around 220 nm (due to chiral of organization of amide and carbamate groups). None of the samples showed any other absorbance at higher wavelengths, which might have suggested chirally organized $\pi-\pi$ interactions. The gel formed with **Ph2** has the most pronounced CD signal, followed by **Ph1** and **Ph4**, but **Ph3** has a weak signal. These data were hard to fully correlate with the $T_{gel}$ data, but the sample formed with **Ph2**—the most stable gel—also has the largest CD signal. Unfortunately, the very high thermal stability of the **Ph2** system made it impossible to perform VT NMR studies in order to investigate the thermodynamic parameters for this class of gelator. FEG-SEM analysis indicated that all of these systems assembled into one-dimensional nanostructures (see Supporting Information), with **Ph2** forming the most well-defined morphology of highly organized fibrillar aggregates. This is likely the cause of the difference in thermal stability.

**Amine Selectivity—Studying Assembly from Mixtures of Different Components.** One of the most intriguing aspects of gel-phase materials is that they are highly dynamic and responsive. This is particularly true for multicomponent gels such as these, in which the individual components can each be varied and controlled independently. In order to investigate this, we decided to explore whether self-assembly from complex mixtures occurred in predictable ways to achieve the directed formation of gel nanostructures wth a degree of self-organization based on the "information" programmed in at the molecular scale. For these studies, we selected amines which supported gels and that, importantly, could be differentiated by NMR spectroscopy and then explored the gelation of **G2-Lys** in the presence of multicomponent amine mixtures.

To illustrate the general approach, consider the assembly of gels from **G2-Lys** with a mixture of **C6** and **Ph1**. Dendron **G2-Lys** formed more stable gels with **C6** ($T_{gel}$ = 71 °C, 10 mM) than with **Ph1** ($T_{gel}$ = 57 °C, 10 mM). The concentration dependent thermal stabilities of each gelation system individually were compared with the $T_{gel}$ values for a mixture of **G2-Lys**, **C6**, and **Ph1** (1:1:1, all 10 mM). As illustrated in Figure 5A, the $T_{gel}$ values for the three-component system

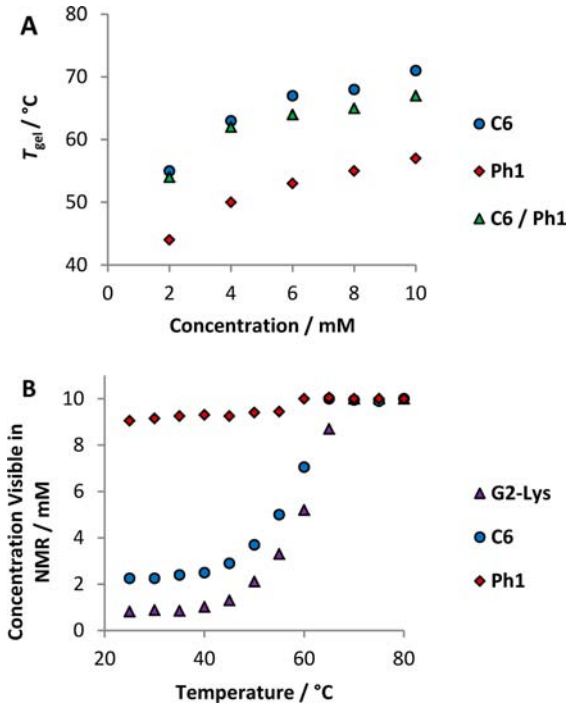


**Figure 5.** (A) $T_{gel}$ values for **G2-Lys** in the presence of 1 equiv of **C6** or **Ph1** or 1 equiv of both amines. (B) VT NMR quantification of the mobile components in a 1:1:1 mixture of **G2-Lys**, **C6**, and **Ph1** (all 10 mM).

almost directly mapped onto those for **C6** and were significantly higher than those for **Ph1**. This initial experiment therefore suggests that far more **C6** is incorporated into the gel network than **Ph1**.

VT-NMR was an extremely powerful technique which provided a more accurate insight into the selective uptake of **C6** over **Ph1**. We suggest this is the only method that can effectively quantify which components of a complex mixture are in different locations within a gel-type material, hence giving direct insight into self-organization on the molecular scale. A gel with **G2-Lys**, **C6**, and **Ph1** (all 10 mM) was formed in toluene-$d_8$ in an NMR tube with a heat−cool cycle. Any amine not incorporated into the gel will be visible by NMR, as will any **G2-Lys**. The amines could readily be distinguished by their


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$CH_2NH_2$ protons. The amine which is preferentially incorporated into the "solid-like" gelator network will only become visible at higher temperatures as the gel breaks down.

The spectra at 25 °C clearly showed that the majority of **C6** (77.5%) is incorporated into the gel network, while the vast majority of **Ph1** (91.5%) is mobile in solution at room temperature (Figure, 5B). Not all of **Ph1** is visible in the spectrum at 25 °C, and its peak is broadened compared to its appearance at higher temperature, indicating that a small amount of **Ph1** (8.5%) is incorporated into the network and that some of the excess **Ph1** in solution is in exchange with the amine in the network (the likely cause of peak broadening). Nonetheless, these NMR results clearly indicate that **G2-Lys** (which is itself 92% immobilized) demonstrates a strong component selection effect in favor of **C6** over **Ph1**. On heating, the **C6** and **G2-Lys** both became mobile in solution at a temperature corresponding to the $T_{gel}$ value as the gel was broken down (Figure 5B).

A xerogel made using a 1:1:1 mix of **G2-Lys**, **C6**, and **Ph1** (all 10 mM) was analyzed by FEG-SEM and the morphology of this sample compared to those of xerogels made with **G2-Lys** and either **C6** or **Ph1** alone. The xerogel made with **C6** showed a network of fibers with a width of roughly 100 nm, while the xerogel made with **Ph1** showed a network of thinner, straighter fibers. As is usual in gels, these fiber dimensions do not correspond to individual molecular-width fibers, but rather bundles of such objects into nanofibers. The images of the sample made with both amines showed some characteristics from each but was more similar to that of the **C6** containing sample, but with slightly thinner and straighter fibers (Figure 6).

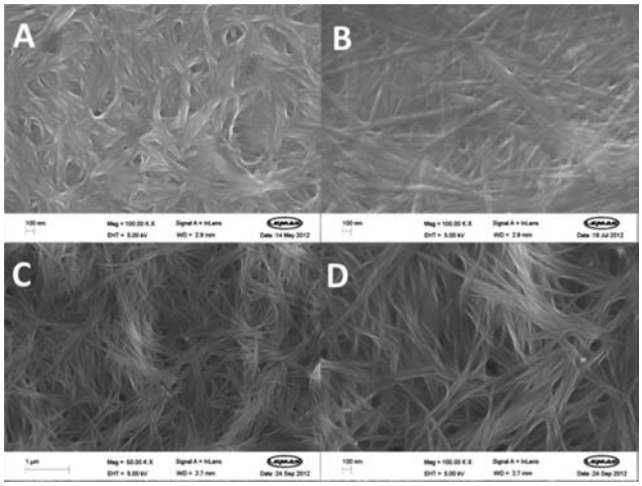


**Figure 6.** SEM images of xerogels formed from **G2-Lys** with A, **C6**; B, **Ph1**; and C and D, **C6** and **Ph1**. All images are shown on similar scales, short scale bar = 100 nm, long scale bar = 1 $\mu$m.

In summary, **G2-Lys** appears to strongly select **C6** over **Ph1** when given a choice in a dynamic mixture—an impressive result, demonstrating the selective uptake of one amine component over another. The resulting gel had properties that were more similar to a gel formed with only **G2-Lys** and **C6** but was still slightly influenced by the relatively small amount of **Ph1** present.

There are, however, different possible reasons for this component selection effect. The formation of these gels is a multistep hierarchical process (Figure 7), and there are various

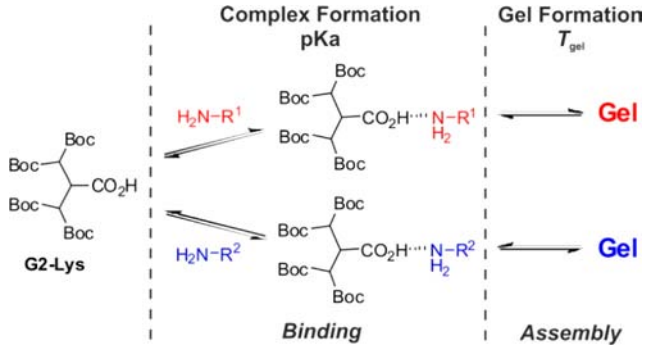


**Figure 7.** Two-step hierarchical process for gel formation. Acid base formation (step (i)) depends on the p$K_a$ value of the amine, while assembly of the resulting complex into fibers (step (ii)) will be reported on by the $T_{gel}$ value of the gel. Component selection may depend on either, or both, of these steps.

**Table 3. pKa Values of Different Amines and $T_{gel}$ Values for Their Gels Formed with G2-Lys (10 mM)[a]**

| | p$K_a$ | $T_{gel}$ |
|---|---|---|
| CHex2 | 10.94 (±0.1) | 54 |
| C6 | 10.69 (±0.1) | 71 |
| Ph1 | 9.06 (±0.1) | 57 |
| Nap1 | 9.06 (±0.3) | 73 |
| Cl-Ph1 | 8.85 (±0.1) | 61 |

[a]These values indicate the propensity of the amines towards step (i) and step (ii) of hierarchical assembly.

points at which the selectivity could originate: (i) acid–base interaction to form the two-component complex (binding) and (ii) hydrogen bond mediated assembly of the complex into nanoscale fibers (assembly). Amine **C6** has a higher p$K_a$ than **Ph1** (Table 3), which will mean it preferentially complexes to **G2-Lys** (favoring step (i)). However, amine **C6** also forms a more thermally stable gel with **G2-Lys** than **Ph1**, indicative of the fact that it is better able to assemble into nanoscale fibers (favoring step (ii)). It is therefore unclear which factor plays the dominant role in enabling the selectivity in this case. We therefore went on to explore selectivity using a range of different amines in order to determine whether complex formation (p$K_a$) (i) or gel stability ($T_{gel}$) (ii) was the dominant driving force in selective assembly from complex mixtures in this system.

**Amine Selectivity—Uncovering the Mechanism.** Amines with a range of p$K_a$ values, which produced varying $T_{gel}$ parameters, and were distinguishable by $^1$H NMR were chosen. It is clear from Table 3 that these two parameters do not directly correlate with one another. For example, **CHex2** is the most basic amine and is best placed to form an acid–base complex with **G2-Lys**, yet this system is the least able to assemble into a thermally stable gel. Conversely **Nap1** is a relatively nonbasic amine, yet the complex which forms assembles into the most thermally stable gel. As such, this selection of amines is perfect for dissecting at which hierarchical mechanistic step component selection takes places.

Different amine mixtures were investigated, and in each case, the same $T_{gel}$ and VT-NMR experiments as described previously were carried out—the results are tabulated (all original graphs and data can be found in the Supporting Information). Initially, we studied **G2-Lys** with **C6** and considered the effect of competitor amines (Table 4). The


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**Table 4. $T_{gel}$ Values for G2-Lys (10 mM) in the Presence of Amines As Listed (all 10 mM) in Toluene-$d_8$ and the Percent Incorporation of Each Amine into the Fibrillar Gel Network at 25 °C, As Determined by VT NMR Methods**

| amine 1 (10 mM) | amine 2 (10 mM) | $T_{gel}$ | % amine 1 in fibers | % amine 2 in fibers |
|---|---|---|---|---|
| **C6** | | 71 | 90% | |
| **C6** | CHex2 | 66 | 50% | 22% |
| **C6** | Ph1 | 67 | 77.5% | 9.5% |
| **C6** | Nap1 | 67 | 79.5% | 13% |
| **C6** | 4Cl-Ph1 | 69 | 73% | 10% |

**C6** amine combines good acid−base complexation (high p$K_a$ value) with effective assembly into gel nanofibers (high $T_{gel}$ value). The presence of the other amines had a minimal effect on the thermal stability of these gels. Furthermore, VT NMR indicated that, in all cases, **C6** was the major amine component in the fibers.

It is not surprising that **C6** can out-compete **Ph1** and **4-ClPh1** as these amines have *both* lower p$K_a$ values and form gels with lower $T_{gel}$ values. However, it is noteworthy that **C6** is selected in preference to **Nap1**. Both these amines give rise to gels with similar $T_{gel}$ values, and we therefore conclude that the higher p$K_a$ of **C6** must drive its preferential uptake into the gel network. This might suggest that the p$K_a$ (step (i), binding) is more significant than $T_{gel}$ (step (ii), assembly). However, the **C6** amine is also able to out-compete **CHex2**, even though the latter amine has a higher p$K_a$ value and should more easily form an acid−base complex. This indicates that the stability of the overall gel also helps direct the assembly process and can lead to component selection. It is, however, notable that the high p$K_a$ of **CHex2** does lead to more disruption of the **C6** gel and that this high p$K_a$ amine is better incorporated into the gel fibers than the amines with lower p$K_a$ values.

We then considered the effect of competitor amines on the gel formed from **G2-Lys** and **Nap1** (Table 5). This amine

**Table 5. $T_{gel}$ Values for G2-Lys (10 mM) in the Presence of Amines As Listed (all 10 mM) in Toluene-$d_8$ and the Percent Incorporation of Each Amine into the Fibrillar Gel Network at 25 °C, As Determined by VT NMR Methods**

| amine 1 (10 mM) | competitor amines (10 mM) | $T_{gel}$ | % amine 1 in fibers | % amine 2 in fibers |
|---|---|---|---|---|
| **Nap1** | | 73 | 90% | |
| **Nap1** | CHex2 | 67 | 45% | 50% |
| **Nap1** | C6 | 67 | 13% | 79.5% |
| **Nap1** | Ph1 | 67 | 76.5% | 23.5% |
| **Nap1** | 4Cl-Ph1 | 70 | 86% | 11% |

forms very thermally stable gels (i.e., effective fiber assembly, step (ii)), even though it has a low p$K_a$ value and is less able to form the initial acid−base complex (step (i)). Interestingly, **Nap1** was selected in strong preference to **Ph1** and **4Cl-Ph1**. These three amines have similar p$K_a$ values, and this demonstrates that $T_{gel}$ (i.e., gel stability) can provide a strong driving force for component selection. Notably, component selection was more marked against **4Cl-Ph1**, which has the lowest p$K_a$ value—indicating that minor p$K_a$ differences assist the $T_{gel}$-driven component selection. Conversely, when in competition with more basic amines (**C6** and **CHex2**), **Nap1** is no longer favorably selected into the gel network. The amine **C6** is strongly preferred to **Nap1** as it has both high p$K_a$ and high $T_{gel}$. When **Nap1** and **CHex2**—which has high p$K_a$ but low $T_{gel}$—are mixed they are taken into the gel in similar proportions (Figure 8). This indicates a balance between the

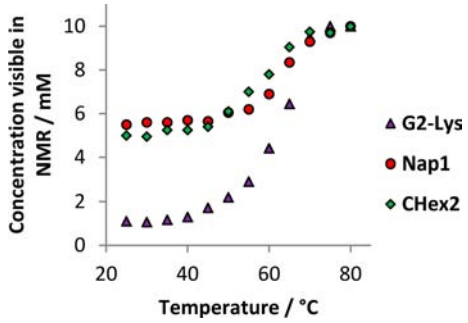


**Figure 8.** VT NMR quantification of the mobile components in a 1:1:1 mixture of **G2-Lys**, **Nap1**, and **CHex2** (all 10 mM).

two steps in self-assembly, with **Nap1** being preferred in terms of fiber assembly ($T_{gel}$) and **CHex2** being favored in terms of initial complex formation (p$K_a$).

Taken together, we argue that these results clearly demonstrate that component selection depends on both the ability of the system to form an acid−base complex as predicted by the p$K_a$ value (step (i)) and the ability to assemble into fibers as predicted by $T_{gel}$ (step (ii)) (Table 6). When both

**Table 6. Summary of the Influence of pKa and $T_{gel}$ on Component Selection for Gelation with G2-Lys and Mixtures of Amines[a]**

| amine 1 | p$K_a$ | $T_{gel}$ | amine 2 | p$K_a$ | $T_{gel}$ | outcome |
|---|---|---|---|---|---|---|
| **C6** | ○ | ○ | **Ph1** | × | × | amine 1 selected |
| **C6** | ○ | ○ | **4-ClPh1** | × | × | amine 1 selected |
| **C6** | ○ | ○ | **Nap1** | × | ○ | amine 1 selected |
| **C6** | ○ | ○ | **CHex2** | ○ | × | amine 1 selected |
| **Nap1** | × | ○ | **Ph1** | × | × | amine 1 selected |
| **Nap1** | × | ○ | **4-ClPh1** | × | × | amine 1 selected |
| **Nap1** | × | ○ | **CHex2** | ○ | × | no selection |

[a]Circles indicate higher pKa and/or $T_{gel}$ values, and crosses indicate lower values.

steps prefer the same component then that component will be strongly selected. When, on balance, a component is preferred by one step, then the component will still be selected. However, if the amines are each favored by one of the factors, then both will be incorporated into the network to significant extents.

Interestingly, in many cases, it was not possible to distinguish by NMR between the melting of different networks associated with each individual amine component. However, in some of the mixtures where there was a large difference in $T_{gel}$ values between the two individual components, it was possible to use the NMR approach to detect sequential disassembly. For example, consider the mixture of **Nap1** and **CHex2** with the dendron, in which each amine was taken into the network in similar proportions, but for different reasons ($T_{gel}$ vs p$K_a$). It was quite clear that **CHex2** became visible in the NMR before **Nap1** (Figure 8). This is in agreement with the relative $T_{gel}$ values of the two individual gels, which had quite a large difference of 19 °C, with **CHex2** forming a less thermally stable gel than **Nap1**. It is impossible to say for certain whether the fibers in this system are completely mixed or completely sorted, as the NMR method only reports on the mobility of individual


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molecules, not the actual thermal parameters of gel networks, but the observation of different thermal sensitivities of the individual components is consistent with the conclusion that some regions of the gel, perhaps certain fibers, have higher **CHex2** composition and are therefore more thermally sensitive—this may suggest a degree of self-sorting.

**Amine Selectivity—Complex Multi-Component Mixtures.** We then went on to try and apply these component selection rules in more complex multicomponent mixtures. We initially probed the assembly of **Nap1** in more detail to see whether **G2-Lys** could select this amine in a dominant manner from a more complex mixture of amines (**Nap1**, **Ph1**, and **4-ClPh1**, all 10 mM). All of these amines have similar p$K_a$ values, but **Nap1** produces the highest $T_{gel}$ value with **G2-Lys** and has the greatest ability to form a fibrous network. In this case, the $T_{gel}$ of the mixture was depressed to 64 °C—however, this thermal stability value is still greater than for all of these gels individually except the **G2-Lys** and **Nap1** combination (Table 3). We then applied VT NMR methods to determine the relative composition of the gel (Table 7), and this indicated

**Table 7. $T_{gel}$ Values for G2-Lys (10 mM) in the Presence of Complex Mixtures of Amines (all 10 mM) in Toluene-$d_8$ and the Percent Incorporation of Each Amine into the Fibrillar Gel Network at 25°C, As Determined by VT NMR Methods**

| amines in mixture (all 10 mM) | $T_{gel}$ | % amine in fibers |
|---|---|---|
| **Nap1** | 64 | 57.5% |
| **Ph1** | | 16.5% |
| **4-ClPh1** | | 9% |
| | | |
| **Nap1** | 64 | 24.5% |
| **CHex2** | | 51% |
| **Ph1** | | 23.5% |
| **4-ClPh1** | | 10% |
| | | |
| **C6** | 63 | 48.5% |
| **CHex2** | | 31% |
| **Ph1** | | 18% |
| **4-ClPh1** | | 11.5% |

that at 25 °C, significantly more **Nap1** is immobilized than the other amines. It is therefore evident that **Nap1** is being preferentially taken into the gel network, driven by its higher $T_{gel}$ value and preference to assemble into fibers. However, the component selection effect is not as strong as when **Nap1** was mixed with these amines individually (Table 5).

We then included **CHex2** in the mixtures in order to explore the effect of an amine with a higher p$K_a$ value. The $T_{gel}$ of the mixture was again depressed to 64 °C, but in this case, VT NMR methods indicated that **Nap1** is no longer the major component of the gel fibers (Table 7). The dominant amine being immobilized in this case was **CHex2**, with 51% being taken into the fibrillar network. Furthermore, the preference for **Nap1** over **Ph1** was clearly also being depressed, with similar amounts of each amine being immobilized. As for the individual mixture of **Nap1** and **CHex2**, the more basic amine (**CHex2**) is able to compete against the better assembling **Nap1**. Notably, however, this effect has become more marked in this more complex multicomponent mixture. As such, we suggest that in more complex mixtures, p$K_a$ differences, which drive acid−base complexation prior to gel assembly, become more important, hence controlling component selection. This is likely because the $T_{gel}$ of a gel with one amine is less relevant as more complex coassembly gels are produced. FEGSEM imaging of this complex mixture (see Supporting Information) indicated an indistinct fibrillar morphology, in contrast to the morphologies of the gels made from a single amine component—suggesting that the directed assembly of these amines becomes less effective.

Finally we probed the ability of **G2-Lys** (10 mM) to select **C6** from a mixture of four different amines (**C6**, **Ph1**, **4-ClPh1**, and **CHex2**, all 10 mM). In this case, the $T_{gel}$ of the mixture was depressed to 63 °C. VT NMR methods indicated (Table 7) that at 25 °C, **C6** is the major immobilized component, followed by **CHex2**, **Ph1**, and **4-ClPh1**. Remarkably, therefore, **C6** is still preferentially taken into the gel—indeed the complex five-component mixture behaves very similarly to the simpler mixtures. We suggest that as **C6** has both a high p$K_a$ and a high $T_{gel}$, this amine remains able to dominate component selection, even in complex mixtures. We used FEGSEM (see Supporting Information) to probe this complex mixture. This illustrated that the gel resulting from this complex mixture maintains a well-defined one-dimensional fibrillar nanostructure. It is difficult to say unambiguously whether the morphology is most similar to any individual gel system, but it is clear that the highly complex nature of the mixture does not significantly suppress self-assembly of well-organized nanostructures.

The work with these complex multicomponent systems therefore supports our hypothesis that both hierarchical steps in the self-assembly process are vital and that p$K_a$ and $T_{gel}$ values, when combined, act as accurate predictors of component selection in this case. It is interesting to note that the factors controlling these complex mixtures (i.e., p$K_a$ and aggregation) are similar to those which have long been used in separation science for the fractional crystallization of salts, an observation which serves to highlight the oft-noted similarity between gelation and crystallization processes.[1] However, unlike most crystals, gels are highly porous, dynamic, and potentially responsive materials. We therefore decided to explore the extent to which these complex materials could respond to chemical stimuli by evolving their compositions and to establish whether these processes were determined by the thermodynamic driving forces elucidated above.

**Dynamic Component Selection—Evolution of Multi-Component Gels.** All of the studies above had been performed by setting up mixtures and then heating and cooling the sample to form a homogeneous gel. We were concerned that component selection might be driven simply by the preferential formation of the network with the highest $T_{gel}$ during slow cooling, leading to removal of much of the **G2-Lys** from the solution phase and hence kinetically trapping the most thermally stable network. As such, we wanted to demonstrate that gelation in these systems was a truly dynamic process and that gel mixtures could evolve over time under ambient conditions and respond to the individual components which are present.

A gel was therefore made using the normal heating and cooling approach in an NMR tube with a 10 mM concentration of **G2-Lys** and **Ph1**. A solution with an equal amount of **Nap1** was then pipetted on to the top of the gel, after it had formed, and the whole sample was left for 48 h to allow diffusion and equilibration. The sample was then analyzed by $^1$H NMR. Pleasingly, of the amine that was incorporated into the gel network 63% was **Nap1** and only 37% was **Ph1**. This clearly indicates that **Nap1** can displace **Ph1** from the gel network


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under ambient room temperature conditions and that the gel network is not kinetically trapped, or irreversible. Indeed, the composition of the gel fibers can respond in a dynamic way to chemical stimulus. We propose that this process is driven by the fact that **Nap1** forms a gel with a higher $T_{gel}$ value than **Ph1**—i.e., the gel assembly (step (ii)) is more thermodynamically stable. The gel was left for a further 5 days and was analyzed again by NMR. The percentage of the immobilized amine in the gelator network had changed further to 71% **Nap1** and 29% **Ph1**. An equal amount of **C6** was then pipetted onto the top of the gel, and the sample was left for a further 5 days. When analyzed by $^1$H NMR the fibrillar gel network consisted of 67% **C6**, 27% **Nap1**, and only 6% **Ph1**—driven by the higher p$K_a$ of **C6** over **Nap1** which favors its incorporation into the gel network. This clearly shows that these gels evolve over time in a dynamic sense and that selectivity seen in these gels is indeed due to thermodynamic preferences for specific hierarchical assembly processes which are able to express themselves in the dynamic gel environment. NMR is an ideal approach for probing these composition changes on the molecular scale.

The ability of gels to evolve and respond to chemical stimuli provided by their environment, and as in this case, change their composition, is one of the most fascinating aspects of multicomponent gels. This may give rise to a variety of applications in which highly solvated gel matrices act as chemo-responsive soft materials systems or have self-healing characteristics[13] when key components are added, allowing them, as in this case, to repair their chemical composition which can lead to adaption and change in their performance and properties.

## CONCLUSIONS

It has been demonstrated that **G2-Lys** can form complexes with monoamines and that, in some cases, this complex forms gels in organic solvents. The range of amines able to do this, the solvents that can support gelation, and the noncovalent forces that underpin this process have all been investigated, and gelation has been well-characterized. The fact that both **G2-Lys** and the amine are soluble until mixing and that gelation occurs spontaneously makes these systems of interest as relatively rare in situ gelators.

Selection of a specific amine as one component of a multicomponent mixture can be achieved. The reasons behind this have been investigated, and the use of NMR methods has allowed us to dissect the roles of two key steps in the hierarchical assembly process:

Step (i): complex formation (as predicted by amine p$K_a$)

Step (ii): fiber assembly (as predicted by $T_{gel}$ value)

It has been found that both of these steps play a role in component selection (Table 7). When one or both of these steps are preferred for one of the amines, then that will be selected as a favored component. However, if the amines are each preferred for different steps or if the amines behave similarly in both steps, then both will be incorporated into the network. Interestingly, in such cases, the system which is less thermally stable becomes mobile first as the gel is heated, suggestive of different regions of the material having different thermal responses and perhaps indicating some self-sorting. These assembly rules have then been used to predict the performance of more complex multicomponent mixtures.

Finally it has been demonstrated that these gel systems can evolve in the presence of added solution phase components and reorganize their gel networks such that they become more thermodynamically stable. This paper therefore gives, for the first time, a complete thermodynamic rationale for the assembly of these two-component gels from complex mixtures. In ongoing work, we are exploring kinetic aspects of assembly in these complex mixed materials and how these interface with the thermodynamic control. We note that these materials are highly chemo-responsive and have the potential to evolve over time. We suggest this feature may have applications in the development of evolvable, stimulus-responsive self-healing soft materials.

## ASSOCIATED CONTENT

### Supporting Information

Materials and methods, full details of amine gelation studies, FEGSEM imaging, FTIR spectra, VTNMR data, gelation data in all solvents, and full data from selectivity studies including variable concentration $T_{gel}$ studies and variable temperature NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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