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Enantioselective Component Selection in Multicomponent Supramolecular Gels

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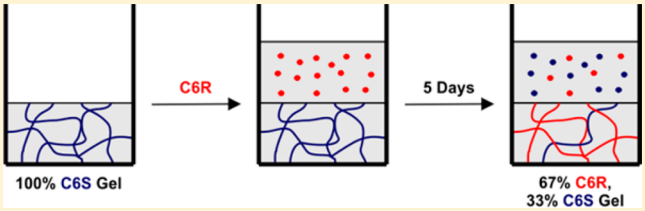
Supporting Information

ABSTRACT: We investigate a two-component acid–amine gelation system in which chirality plays a vital role. A carboxylic acid based on a second generation L-lysine dendron interacts with chiral amines and subsequently assembles into supramolecular gel fibers. The chirality of the amine controls the assembly of the resulting diastereomeric complexes, even if this chirality is relatively "poor quality". Importantly, the selective incorporation of one enantiomer of an amine over the other into the gel network has been demonstrated, with the *R* amine that forms complexes which assemble into the most stable gel being primarily selected for incorporation. Thermodynamic control has been proven by forming a gel exclusively with an *S* amine, allowing the *R* enantiomer to diffuse through the gel network, and displacing it from the "solidlike" fibers, demonstrating that these gels adapt and evolve in response to chemical stimuli to which they are exposed. Excess amine, which remains unincorporated within the solidlike gel fiber network, can diffuse out and be reacted with an isocyanate, allowing us to quantify the enantioselectivity of component selection but also demonstrating how gels can act as selective reservoirs of potential reagents, releasing them on demand to undergo further reactions; hence, component-selective gel assembly can be coupled with controlled reactivity.



INTRODUCTION

Supramolecular gels are soft materials with self-assembled nanoscale fibrillar architectures which are being explored for a wide range of different applications, from formulation science through to high-tech multifunctional materials.[1] Recently there has been particular focus on multicomponent gels, in which several different molecular-scale building blocks participate in gel formation.[2] These gels often rely on a complex forming between different components before gelation can take place.[3] In multicomponent gels, complex/gelator formation and/or fiber self-assembly can sometimes drive a "component selection" event. When this occurs, certain molecules are selected from a mixture because their favored self-assembly thermodynamically drives the evolution of the mixed molecular library.[4] Furthermore, gelators programmed with different molecular-scale information may be able to independently self-sort into their own nanoscale networks.[5] Understanding how self-assembly operates within complex systems such as these is of fundamental importance in understanding how noncovalent chemistry can effectively program the emergence of order from chaos.[6] Furthermore, these complex, yet well-organized, multicomponent gels are particularly interesting, because the presence of multiple molecular-scale species offers the possibility of introducing multifunctionality to these materials.

Chiral gels have been of particular interest, as the chiral information programmed in at the molecular-scale can be translated through to the nanoscale assembly of chiral architectures and ultimately have an impact on the macroscopic performance of the gel.[7] There have been a number of studies in which mixtures of enantiomers have been investigated, and in general terms, mixing enantiomeric gelators suppresses gelation.[8] In some cases, if homochiral recognition is preferred, the enantiomers can self-sort to form their own chirally sorted nanostructures.[5,9] In rare cases, the two enantiomers interact preferentially with each other to form a complex which is an even better gelator than either individual enantiomer.[10] In general terms, however, rules about chiral selectivity in gelation are still emerging. It has been demonstrated, for example, that enantiopure gelators can express their chiral assembly preferences on an achiral analogue in a "sergeants and soldiers" type manner.[11] An achiral gelator has even been shown to undergo a mirror symmetry breaking event upon gelation, leading to spontaneous amplification of chirality.[12] Furthermore, there have been several reports in which chiral gels respond in an enantioselective manner to chiral analytes (and solvents) with changes in properties signaling the recognition event.[13] There have also been several examples in which a chiral compound can be induced to form a gel if it complexes with one guest enantiomer but a precipitate when bound to the other.[14]

We have recently been working on a simple and highly effective organogelation system composed of two components (e.g., Figure 1) in a 1:1 ratio: (i) a chiral second generation dendron based on L-lysine (**G2-Lys**) with a carboxylic acid at

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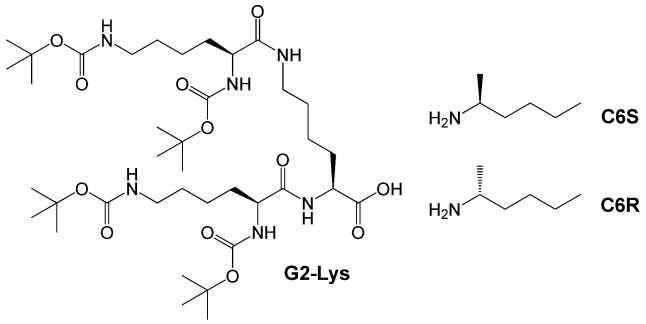

Figure 1. Chiral gelation system of **G2-Lys** and **C6R/S**.

the focal point, and (ii) a primary amine.[15] These two soluble components can form instant gels on mixing, and we recently demonstrated how **G2-Lys**, if challenged with mixtures of different amines, would select those which had the highest pK_a values and/or which formed the complexes best able to self-assemble into nanoscale fibers. These systems were shown to be adaptive and responsive to chemical stimuli. We therefore reasoned that if chiral **G2-Lys** was challenged with enantiomeric amines, we may observe interesting enantioselective uptake effects. This would potentially leave one enantiomer unincorporated within the gel and available for further reaction, enabling gel-mediated enantioselective derivatization.

RESULTS AND DISCUSSION

Gelation with Different Enantiomers. In our previous work,[15] hexylamine was one of the most effective amines for inducing gelation, and we therefore chose chiral amines **C6R/S** to study enantioselection. Compound **G2-Lys** was tested with each enantiomer individually in a 1:1 mixture (both 10 mM) in toluene (0.5 mL). For reproducibility of mixing kinetics, all gels formed in this paper were made using a heat−cool cycle. Both enantiomers were able to induce gelation when mixed with **G2-Lys**. Interestingly, however, the enantiomers produced gels with markedly different T_{gel} values.[16] The gel formed with **C6R** was more thermally stable (80 °C) than that formed with **C6S** (67 °C), an intriguing result, given that in this complex (mass of over 900 Da), the orientation of just one methyl group has such a pronounced effect on gel stability, a significant impact of relatively low quality chiral information upon the assembly of these complexes.

Mixtures of **G2-Lys** with each enantiomer were investigated using circular dichroism (CD) spectroscopy in a 95:5 mixture of methylcyclohexane/dioxane (Figure 2); the thermal characteristics of the gels in this solvent mix were analogous to those in toluene. The CD spectrum recorded for **G2-Lys** with **C6R** shows a negative Cotton effect band, while that made with **C6S** produces a different spectrum, with a simpler, less intense, broad negative CD band. The peak maximum at 220 nm corresponds to absorbance of the peptides within **G2-Lys**; hydrogen bond interactions between these groups are primarily responsible for gel fiber assembly here.[17] It should be noted that although **C6R** and **C6S** are enantiomeric, they produce gels with a diastereomeric relationship, because **G2-Lys** has the same chirality in each complex. CD clearly demonstrates different chiral organization which, as expected for diastereomeric samples, are not mirror images. Interestingly, the CD signature with **C6R** is similar to that previously observed with hexylamine (which formed good gels),[15] whereas the CD signature with **C6S** is similar to that previously observed with

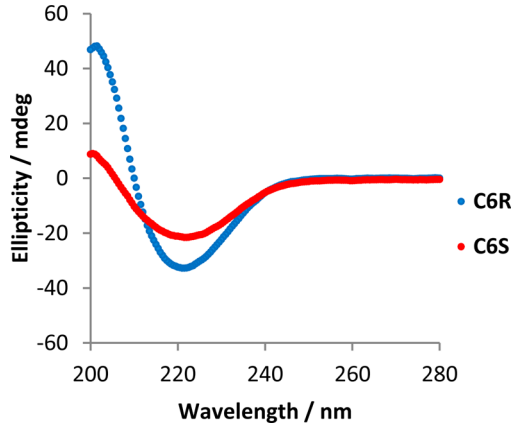

Figure 2. CD spectra of **G2-Lys** in the presence of **C6R** and **C6S**, in methylcyclohexane/dioxane (95:5).

octylamine (which formed less effective gels).[15] This therefore suggests that the nanoscale chiral organization of **G2-Lys** can be optimized with **C6R** (and hexylamine) but not with **C6S** (and octylamine).

To gain further insight into the structure of the gels formed with the different amine enantiomers, dried xerogels were formed under ambient conditions and analyzed by FEG-SEM and TEM. The images produced (see Supporting Information) indicated that the different amine chiralities gave rise to quite different nanoscale morphologies, with **C6R** giving rise to very small diameter poorly defined fibers, and **C6S** yielding significantly larger and better defined nanofibers. The smaller fibers associated with **C6R** will constitute a network with a larger number of contact points and greater degree of entanglement, supportive of the higher T_{gel} value.[18] Crucially, the different morphologies, must result from differing amine chirality leading to diastereomeric complexes with differing assembly modes.

Gelation Using Mixtures of Enantiomeric Amines in Overall 1:1 Stoichiometry with G2-Lys. We then went on to explore how gels made with mixtures of enantiomeric amines would behave, and how the ratio of **C6R** to **C6S** would control this. In all of these initial experiments, the concentration of **G2-Lys** was held at 10 mM and the total amine concentration was also 10 mM (i.e., one stoichiometric equivalent). This ensures that all of the amine should be bound by **G2-Lys** in these experiments.

A series of gels with a 1:1 mix of **G2-Lys** (10 mM) and varying ratios of **C6R/S** (10 mM in total) were formed and their T_{gel} values measured. Overall the T_{gel} values show that the thermal stability decreases as an increasing amount of **C6S** is present and incorporated into the network (Figure 3A). It takes ca. 20% of **C6S** before the gel is significantly disrupted and stability starts decreasing. Similarly it takes ca. 20% of **C6R** being incorporated into the gel network before the thermal stability of the gel increases. It therefore appears that the complex present in the majority can direct the thermal stability of the gel. To investigate whether this change in thermal stability was linked to a change in chiral organization, the same mixtures of **G2-Lys** with varying ratios of **C6R** and **C6S** were analyzed by CD spectroscopy in 95:5 methylcyclohexane:dioxane. Surprisingly, the spectra from samples with 0−90% **C6S** are very similar. Only when the sample is made with entirely **C6S** did we see a significant change in the CD spectrum (Figure 3B).

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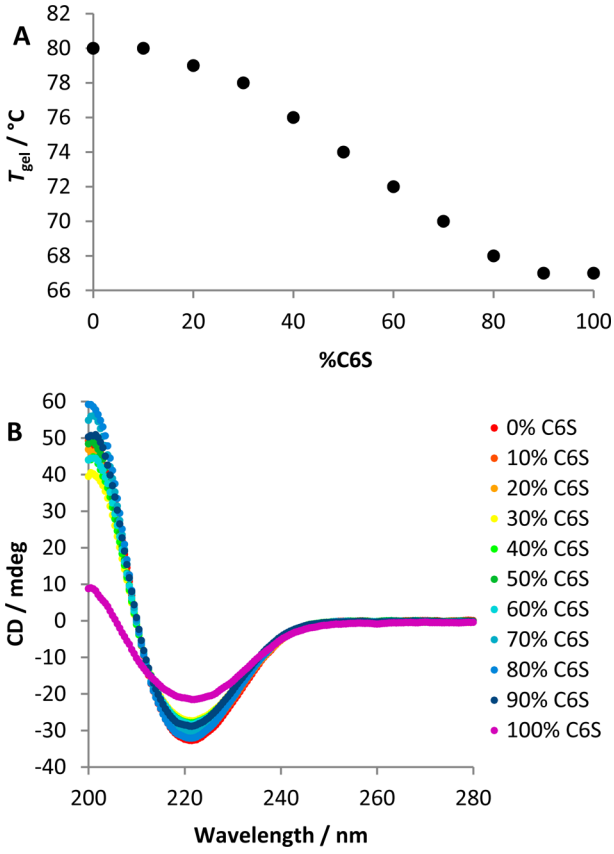

Figure 3. A: Effect of mixing enantiomers on macroscopic thermal stability of the gel. [**G2Lys**] = 10 mM, [**C6R**] + [**C6S**] = 10 mM. B: Effect of mixing enantiomers on the nanoscale chiral organization of the gel as recorded in the CD spectrum [**G2Lys**] = 0.625 mM, [**C6R**] + [**C6S**] = 0.625 mM..

We propose that the reason for the different responses of thermal stability (macroscopic) and CD intensity (nanoscale chirality) lies in the fact that the thermal stability depends on the packing of the whole acid−amine complex, whereas the CD signal corresponds only to the **G2-Lys** component. The presence of the "wrong" amine therefore impacts the thermal stability, because this depends on the overall packing of the complex. However, the CD only directly reports on the chiral nanoenvironment experienced by **G2-Lys** and would suggest that **C6S** can only change the chiral environment experienced by **G2-Lys** when it is present in very large amounts. This indicates that **G2-Lys** is better suited to achieve its optimal nanoscale chiral assembly mode with **C6R** rather than with **C6S**. As such, the assembly of the two-component complex into the gel (T_{gel}) and the chiral nanoenvironment experienced by **G2-Lys** (CD) are not directly correlated. Similar non-correlations have been observed previously by Maitra and co-workers,[19] highlighting the complex and hierarchical nature of gel formation.

We wanted to confirm whether these mixtures produced a single network (a coassembly) made with **G2-Lys** and both **C6R** and **C6S**, rather than two separate networks, each made from a different diastereomeric complex. This was first probed using differential scanning calorimetry (DSC). In self-sorting gels, where two separate networks are formed, two separate thermal transitions can sometimes be observed.[5f] Toluene gels (10 mM) were placed in a DSC pan and analyzed, but the gels gave either a very small signal or no signal at all, as only a relatively small part of the sample is the gelator. 1,2,3,4-Tetrahydronaphthalene was thus used as a solvent; it is chemically very similar to toluene but with a much higher boiling point, and 50 mM gels could now be analyzed. These more concentrated samples produced more easily detectable heat changes.

Three samples were measured, using **G2-Lys** and either **C6R**, **C6S**, or a 50/50 mixture of both (Table 1). The calorimetry

Table 1. DSC Data for G2-Lys (50 mM) with C6R (50 mM) or C6S (50 mM) or both C6R and CSR (25 mM of each)

%C6R	%C6S	endotherm peak max/°C	exotherm peak max/°C
100	0	104	93
50	50	95	81
0	100	85	65

traces recorded were still of low quality but did show reproducible endo/exotherm peaks for each gel, representative of a phase transition (the exotherms for gel formation were more reproducible than the endotherms for gel breakdown). As expected, the gel formed with **C6R** had thermal transitions at temperatures higher than that formed with **C6S** and well separated from it. When a gel with a 50:50 mixture of **C6R** and **C6S** was analyzed, it showed a single transition, in agreement with a mixed coassembled network being present rather than two separate, independently melting networks. This transition occurs at temperatures intermediate between those for the gels formed with either **C6R** or **C6S** individually. Neither the endotherm nor exotherm of this mixed sample were any broader than those of the other samples, further supporting the conclusion that a coassembled network is formed. Coassembly of the different systems into a single network was broadly supported by the FEG-SEM images of the xerogel formed from the mixed gel which shows a single network similar to both the xerogels made with **C6R** or **C6S** (see Supporting Information)

Further examination of these gels was then conducted using VT-NMR experiments. Three samples were measured, using **G2-Lys** (10 mM) and either **C6R** (10 mM), **C6S** (10 mM), or a mixture of both (5 mM of each). All of these samples also contained diphenylmethane (10 mM) as a mobile internal standard. If molecules are immobile in the "solidlike" fiber network, they will not be observed by NMR, whereas if they are in the mobile "liquidlike" phase, they will have quantifiable resonances.[15,20] The temperature of the sample was increased, and ^{1}H NMR spectra were recorded at 5 °C intervals. The concentration of mobile **G2-Lys** at each temperature was plotted as a way of following dissolution of the gel network (see Supporting Information). This allowed us to quantify $T_{100\%}$ (the temperature at which all the gelator is mobile and "visible" in the ^{1}H NMR). The $T_{100\%}$ and T_{gel} values are similar for each sample, with the $T_{100\%}$ values being slightly higher in each case, as this represents the temperature at which the gelator network is completely disbanded on the molecular scale, whereas T_{gel} is the point at which the macroscopic gel network can no longer support itself against the force of gravity. Importantly, the molecular scale data from this NMR experiment is in full agreement with the macroscopic observations, indicating that the thermal stability of the 50/50 gel was intermediate between that containing 100% **C6R** and that with 100% **C6S**.

The thermodynamic parameters associated with the gel−sol transition, ΔH_{diss}, and ΔS_{diss} values could also be found using the van't Hoff method plotting ln[Sol] against $1/T$.[15,22] Both

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values for the sample made with **C6R** are larger than those for the gel made with **C6S**. This would suggest that the **C6R** gel, with a larger entropic gain upon dissolution is likely a highly organized, more rigid, and closely packed structure. The larger endothermic change upon dissolution of this **C6R** network indicates that this network is better stabilized by hydrogen bonding interactions, again indicative of a more closely packed structure. The **C6S** sample is less well organized and less able to take advantage of hydrogen bonding. Interestingly, the gel produced with a mixture of **C6R** and **C6S** has much lower ΔH_{diss} and ΔS_{diss} values than for either of the gels with individual enantiomers. We suggest that this is due to the network having to accommodate both **C6R** and **C6S** into the fibers and the diastereomeric complexes formed being unable to pack as efficiently into overall supramolecular aggregates. At first, it might therefore seem surprising that the gel based on the **C6R/S** mixture is not also thermally less stable than either of the gels made with individual enantiomers given it has a smaller ΔH_{diss}. However, the fact that it has a T_{gel} value between those of the gels formed with either **C6R** or **C6S** alone is a result of the balance between ΔH_{diss} and ΔS_{diss}. The entropic cost of gelating 50/50 **C6R** and **C6S** drops very significantly, and therefore even though the enthalpy of gelation is lower, the relative lack of order within the mixed coassembled gel more than compensates for it in thermodyamic terms.

Table 2. Comparison of Molecular ($T_{100\%}$) and Materials (T_{gel}) Properties for Gels Formed with Enantiomeric Amines C6R/S and the Thermodynamic Parameters Associated with the Gel−Sol Transition

C6R/%	C6S/%	T_{gel}/°C	$T_{100\%}$/°C	ΔH_{diss}/kJ mol^{-1}	ΔS_{diss}/J mol^{-1} K^{-1}
100	0	80	83	78.3	181
50	50	74	77	45.4	91
0	100	67	69	66.9	157

In summary, the chirality of the amine mixed with **G2-Lys** has a significant effect on the assembly of the resulting complexes and a pronounced effect on the gel that is produced. The chirality of the amine profoundly affects the molecular-scale assembly of complexes in solution (CD, NMR), the nanoscale morphology of fibrous network formed (FEG-SEM and TEM), and ultimately the macroscopic stability of the material produced (T_{gel}). Furthermore, when a gel is formed from a mixture of **G2-Lys** and **C6R/S** with varying ratios of enantiomers, a coassembled network appears to be formed rather than individual self-sorted assemblies.

Component Selection Experiments. In all of the systems described above, there was stoichiometric equivalence between acid (**G2-Lys**) and total amine (**C6R/S**), meaning that all of the amine should be bound in each case. An alternative experimental approach would provide **G2-Lys** with a choice between different amines, a "component selection experiment".[4,15] To the best of our knowledge, this has not previously been performed with regard to chiral selection within gels.

We therefore made gels made with a 1:1:1 mixture of **G2-Lys**, **C6R**, and **C6S** at concentrations ranging from 2 to 10 mM, and the T_{gel} values were measured. In each experiment, **G2-Lys** effectively has a choice between the two amines; it could bind all of one enantiomer, all of the other, or any ratio in between. The T_{gel} values were compared to those of gels formed with **G2-Lys** and **C6R** or **C6S** only (Figure 4). The gels

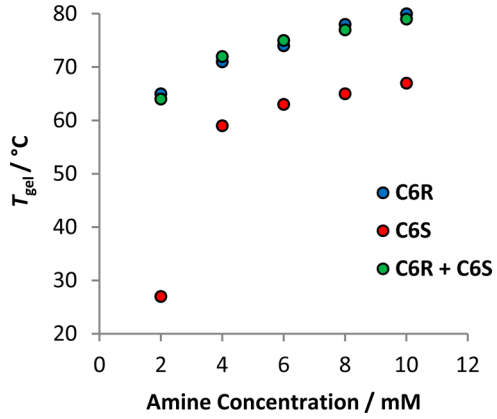

Figure 4. T_{gel} values measured for **G2-Lys** (1 equiv) with **C6R** (1 equiv), **C6S** (1 equiv), or **C6R** and **C6S** (1 equiv of each).

made from a mixture of both enantiomers had T_{gel} values almost identical to the more stable gels formed with only the **C6R** enantiomer. This gives a strong indication that **G2-Lys** has selected to assemble its gel network primarily with **C6R** rather than **C6S**, which we would propose remains unselected, and mobile in solution (see below). Interestingly, we know from the analysis of the 1:0.5:0.5 mixture described above, in which **G2-Lys** is effectively forced by stoichiometry to interact with 50% of each of the amines, that the T_{gel} value was only 74 °C (10 mM). As such, we can be confident that in the 1:1:1 component selection system, we are indeed seeing significant enantioselectivity, with T_{gel} being 79 °C, much closer to the value for 100% **C6R** (80 °C) than for the gel in which 50% each of **C6R** and **C6S** have been taken up (74 °C).

The xerogel produced from the 1:1:1 mixture of **G2-Lys**, **C6R**, and **C6S** was imaged by FEG-SEM (see Supporting Information). The images show a sample with a very ill-defined morphology. No distinct fibers are easily visible, similar to the SEM images seen with **C6R** alone. However, given the limitations of FEG-SEM for these very narrow nanofibers, we also made use of small-angle X-ray scattering experiments (SAXS) to probe the morphology further. SAXS data for the solvated gels showed the gels made with **C6R** and **C6S** had different cylinder form factors of 4 and 3 nm, respectively. The component selecting 1:1:1 gel had a cylinder form factor of 4 nm, the same as the gel made with only **C6R**. In addition, the 1:1:1 xerogel had Bragg peaks which were more similar to the gel formed with **C6R** alone than with **C6S** (see Supporting Information).

Further analysis of the gel with a 1:1:1 mixture of **G2-Lys**, **C6R**, and **C6S** was performed using VT-NMR in toluene-d_8 (all components 10 mM). The concentration of **G2-Lys** visible in solution at each point was used to determine ΔH_{diss} and ΔS_{diss}. The gel has ΔH_{diss} = 56.0 kJ mol^{-1} and ΔS_{diss} = 122 J mol^{-1} K^{-1} These values are lower than for **G2-Lys** made with either single enantiomer but higher than for the 1:0.5:0.5 mixture. This suggests that when **G2-Lys** has a choice between **C6R** and **C6S**, it is not identical to the gel formed with **C6R**, but neither is it anywhere near a 50:50 mix of enantiomers. It should also be noted that the additional equivalent of amine present in the gel will be in dynamic exchange with the amine bound to the solidlike fibers, which might be expected to decrease the thermodynamic stability and order of the gel.

We wanted to use NMR methods to directly quantify the amount of each amine free in solution (and by inference that

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immobilized in the solidlike fibers), as we hoped to determine the enantioselectivity of this self-assembling system. We attempted to do this using a chiral shift reagent approach but were unable to get sufficient peak separation between the diastereomers formed from **C6R** and **C6S** in the liquidlike phase. This led us to consider alternative approaches.

We decided to use a chiral derivatization reagent to probe these component-selecting chiral gels further. Gels are fascinating media for organic reactions. They are solvated and porous; hence, reagents and catalysts can be diffused in and out of them very simply.[21] In this case, we hoped to use the gelation event to facilitate enantiomer separation by preferentially immobilizing one enantiomer into the gel nanofibers, allowing the mobile enantiomer to diffuse out of the gel and react with a chiral substrate. We reasoned this would allow us to infer how much of each enantiomer was immobilized within the gel.

We formed the 1:1:1 gel with **G2-Lys**, **C6R**, and **C6S** in toluene (0.5 mL). After gelation, a further amount of toluene (0.5 mL) was gently pipetted on top of the gel and the sample was left for 24 h to allow any amine not included in the solidlike gel network to diffuse throughout the entire volume of toluene. The supernatant solvent was removed using a pipet and placed in a round-bottom flask, and an excess of (*S*)-methylbenzyl isocyanate was added to derivatize all of the chiral amine that had diffused into the toluene. This converts the amine enantiomers into two diastereoisomeric ureas (Figure 5), which, it was hoped, could be distinguished and quantified by ^{1}H NMR.

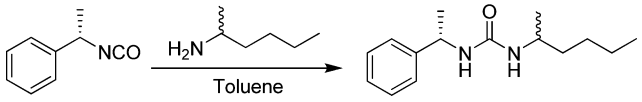

Figure 5. Reaction between **C6R**/**S** and (*S*)-methylbenzyl isocyanate, giving rise to diastereoisomeric products.

After reaction, the solvent was evaporated and reaction success determined by NMR and MS analysis. The solid was redissolved in $CDCl_3$, analyzed by ^{1}H NMR, and compared to samples prepared using the same method but with either **C6R** or **C6S** alone. The difference in chemical shift between the peaks of the CH_3CH protons (originally on the amine) of each diastereomeric urea was 0.085 ppm. There was also a measurable difference in the chemical shift of the peak of the terminal CH_3CH_2 group of each diastereomer ($\Delta\delta$ = 0.072 ppm). Therefore, upon analysis of the mixed gel, the resonances associated with both diastereomers were easily resolved and the relative amounts of each could be simply quantified (Figure 6). Of all the urea, 20% was derived from **C6R** and 80% from **C6S**. This would indicate that the solidlike gelator fiber network is formed from the inverse composition (80% **C6R** and 20% **C6S**). This result demonstrates unambiguously that there is indeed selective uptake of the **C6R** enantiomer that forms the most stable gel network into the gel fibers by **G2-Lys**. We suggest that gels of this type may be of interest for applications in chiral resolution and enantioselective reaction pathways, especially given that they can select between relatively low quality chiral information.

Self-assembly of these multicomponent gel nanofibers occurs in several hierarchical steps, with the initial key steps being (i) formation of acid–base complexes and (ii) unidirectional self-assembly of these complexes (Figure 7).[15] We wanted to

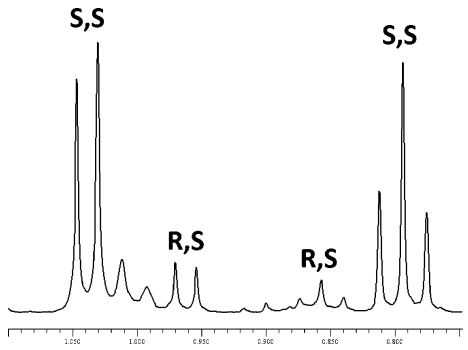

Figure 6. NMR spectra of diasteromeric mixture arising from reaction of **C6R**/**S** mixture diffused out of gel made with **G2-Lys** after reaction with (*S*)-methylbenzyl isocyanate.

determine whether the apparent selectivity of **G2-Lys** for the *R* amine was associated with the initial formation of the acid–base complex (step i) or self-assembly of the diastereomeric complexes into gel fibers (step ii).

To examine the acid–base formation step, NMR titration experiments were carried out in which the concentration of either **C6R** or **C6S** remained constant while the concentration of **G2-Lys** was increased. This titration was carried out in a solvent ($CDCl_3$) which did not support self-assembly of the complexes and therefore effectively isolated the initial complexation event (step i).

The change in chemical shift of the CH peak of **C6R** or **C6S** as the concentration of **G2-Lys** increases was almost identical (Figure 8). To quantify binding, stability constants were fitted using WinEQNMR2[22] and a 1:1 binding model. With **C6R**, log K = 4.30, and with **C6S** log K = 4.37 (±15%), clearly showing that, within error, the stability constant of the complex is the same in each case. Acid–base complex formation (step i) is therefore not responsible for the selective uptake of one amine enantiomer, and step ii must be more important.

We used infrared (IR) spectroscopy to probe this further. We measured IR spectra of gels formed in toluene from **G2-Lys** (10 mM) with **C6R** (10 mM) or **C6S** (10 mM). The IR spectra were almost identical, reflecting the fact that both diastereomeric complexes give rise to gelation. However, there was a reproducible difference in the IR absorbance associated with the N–H (amide) stretch (ca. 3300 cm^{-1}), with the N–H peak being clearly split in two in the presence of **C6R** (see Supporting Information for data). This reflects that the chirality of the amine has a direct effect on the self-assembly of **G2-Lys**, which is underpinned by intramolecular amide–amide hydrogen bond interactions. Furthermore, when we measured the IR spectrum of the gel formed from **G2-Lys** (10 mM) with both **C6R** and **C6S** (both 10 mM), the N–H stretch was identical to that observed for **C6R** alone (see Supporting Information). We can therefore conclude that the selective uptake of one amine enantiomer is driven by preferential self-assembly of the complex formed with **C6R** rather than that with **C6S** (step ii). We suggest that the steric influence of the methyl group attached to the chiral center on **C6R**/**C6S** has a significant influence on the way these complexes can pack, with **C6R** enabling better interaction between **G2-Lys** peptides, while **C6S** compromises **G2-Lys** assembly and enforces a chiral adjustment.

We then wanted to prove that this component selection was a true thermodynamic preference, not simply the result of a kinetically trapped gel forming on cooling the sample. Kinetic

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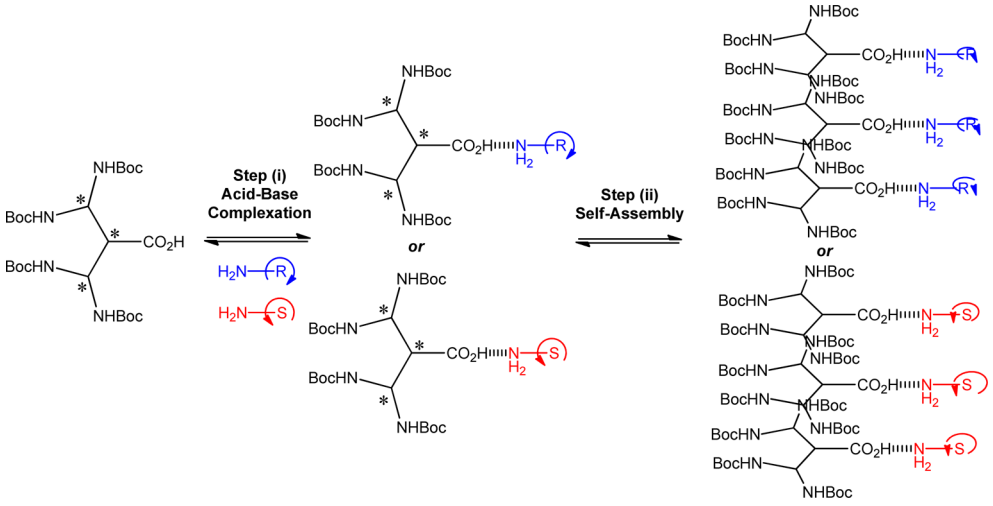

Figure 7. Schematic of self-assembly showing step i: acid–base formation, and step ii: self-assembly of the complexes formed.

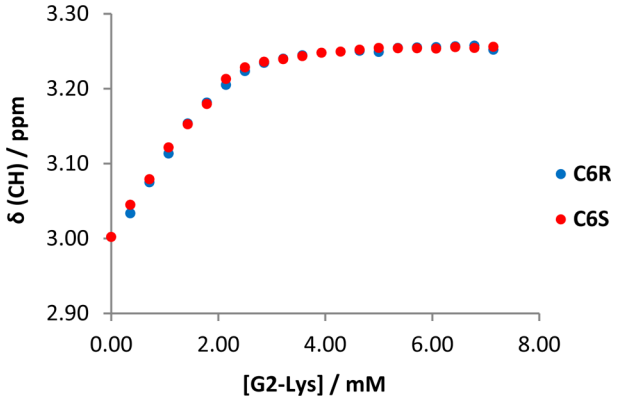

Figure 8. NMR titration of **G2-Lys** with **C6R** or **C6S** (2.0 mM) in $CDCl_3$, indicating how the CH proton at the chiral center of the amine is perturbed on addition of the carboxylic acid.

trapping could occur if, as the sample was cooled, the network with **G2-Lys** and **C6R** preferentially formed simply because it has the higher T_{gel} value; in other words, on reaching the temperature at which the network with **C6S** could actually start to form, all of the **G2-Lys** would already have been "used" in forming a network with **C6R**. To test the reversibility of component selection and gel-assembly, a gel with **G2-Lys** and **C6S** was preformed and a solution of **C6R** pipetted onto the gel and allowed to diffuse into the sample for 5 days (Figure 9). If the system is kinetically trapped, it should not change. The proportion of each amine in the network was calculated by derivatizing the excess solution-phase amine with (*S*)-methylbenzyl isocyanate as already described. After equilibration, an excess of **C6S** was found in solution; clearly it has been

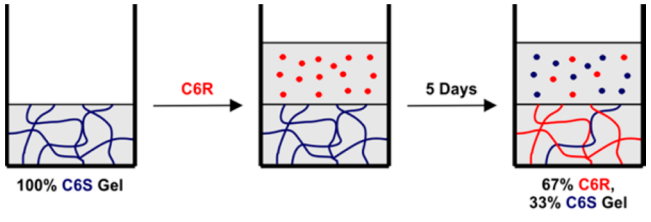

Figure 9. Schematic of thermodynamically controlled gel evolution on addition of **C6R** to a gel made from **G2-Lys** and **C6S**.

displaced from the gel network by **C6R**. In the solution phase only 33% of the amine is **C6R** and 67% is **C6S**. Therefore, the gelator network is 67% **C6R** and 33% **C6S**, demonstrating that the preference for **C6R** is primarily thermodynamic and that these gels are responsive, adapting and evolving their compositions in response to chemical stimulus. The selective uptake of **C6R** is slightly lower than observed for the gel formed directly from the 1:1:1 mixture with a heat–cool cycle (80% **C6R**, 20% **C6S**). We suggest that for the gel formed by displacement the network needs to reorganize to accommodate the new amine, slightly lowering selectivity.

In summary, when a 1:1:1 mixture of **G2-Lys**, **C6R**, and **C6S** is used to form a gel, the resulting gelator network is mainly composed of **G2-Lys** and **C6R**, while most of the **C6S** is left in the liquidlike phase: enantioselective component selection. Most importantly, this combination of experimental approaches allows us to directly connect macroscopic performance (T_{gel}) with the molecular level behavior (NMR). We have also clearly demonstrated that these gels are adaptive and responsive to changes in their external environment.

Fascinatingly, the ability of chiral gels to induce differential uptake and reactivity in a mixture of enantiomeric amines demonstrates how chirality can be simply passed on from one source to another, with the gel matrix acting to preferentially remove one enantiomer from the system. Porous gels are thus fascinating media in which chiral information may be transferred and/or amplified.[23] Such a mechanism may have been relevant in prebiotic evolution of homochiral systems; it has often been noted that the interior of a cell is a gel-like matrix, and it has been suggested that simple gels may have played a prebiotic role before the evolution of membranes.[24]

Probing Component Selection with a Range of Amines. We then applied these techniques to mixtures of other chiral amines (Figure 10). In each case, we used the chirality of **G2-Lys** to select between enantiomeric amines. This was rapidly tested using T_{gel} evaluation and the reaction of excess amine with (*S*)-methyl isocyanate combined with NMR characterization. We took care to choose amines which gave rise to diastereomeric products with (*S*)-methyl isocyanate having good solubilities and distinguishable NMR peaks; for examples of amines where this was not possible, see the Supporting Information. We hoped to determine the following:

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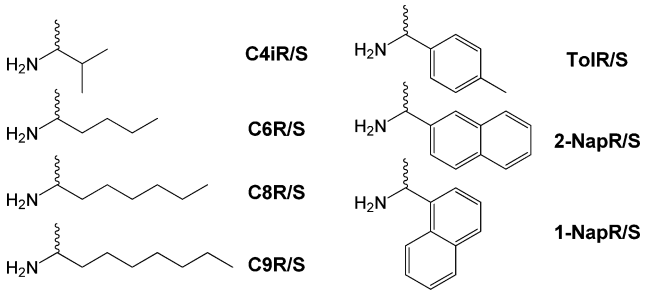

Figure 10. Selection of amines used successfully in component selection experiments.

(a) if molecular-level chiral selectivity is a general rule in these systems;
(b) if the sense of chiral preference for *R* enantiomeric amines is retained;
(c) if macroscopic thermal performance can be rationalized in terms of molecular level chiral selectivity.

Initially, we tested chiral aliphatic amines, which have a methyl group adjacent to the primary amine as the source of chirality. The NMR derivatization experiment indicated that **C4iR**, **C8R**, and **C9R** are selected by **G2-Lys** in preference to **C4iS**, **C8S**, and **C9S**, respectively (Table 3). As such, we note

Table 3. Quantification of % Amine Incorporation in Fibers and Enantiomeric Excess (ee) of Uptake into Fibers Using Molecular-Scale Derivatization (NMR) and Macroscopic-Scale Analysis of T_{gel} Data

	molecular scale			macroscopic behavior			
amine	%*R* in fibers	%*S* in fibers	ee (%)	T_{gel} (*R*)	T_{gel} (*R*/*S*)	T_{gel} (*S*)	$T_{gel\ obs}$
C4i	68	32	36	54	48	37	50
C6	80	20	60	80	74	67	79
C8	83	17	66	70	60	54	64
C9	79	21	58	61	52	46	54
Tol	68	32	36	60	54	53	59
1-Nap	62	38	24	79	71	54	74
2-Nap	54	46	8	57	53	53	58

that the chiral selectivity in all of these systems matches that for **C6R/S** in which the *R* enantiomer is preferred because the resulting complex better assembles into gel fibers.

The chiral preference observed by the derivatization approach was also reflected in the thermal stability of the mixed gels. First, it should be noted that for all of these amines, the *R* enantiomer forms a gel more thermally stable than that of the *S* enantiomer (as for **C6R/S**, Table 3). Furthermore, the 1:0.5:0.5 gels, in which **G2-Lys** is forced to interact with both enantiomers equally (i.e., 50% *R*, 50% *S*) had T_{gel} values ($T_{gel}(R/S)$) somewhere in between the *R* and *S* extremes. Considering the T_{gel} values for the component selection 1:1:1 experiment ($T_{gel\ obs}$), in which **G2-Lys** has a choice of which amine to interact with, it is evident that, in all cases, these $T_{gel\ obs}$ values lie between those for the 50/50 mixture and those for 100% *R* (Table 3). As such, these macroscopic observations are in agreement with the molecular scale information which indicates preferential incorporation of *R* amines into the gel. As such, we propose that the molecular-scale chiral information, enantioselected by **G2-Lys**, is being read through into the macroscopic performance of the gel.

We then tested some chiral primary amines with pendant aromatic groups, **TolR/S**, **1-NapR/S**, and **2-NapR/S**. Similarly to the aliphatic amines, the *R* enantiomer was preferentially taken into the gel over the *S* version, and the thermal stability reflected this chiral preference (Table 3). However, in all cases, the degree of chiral selectivity was somewhat lower than observed for aliphatic amines and had all but disappeared for **2-NapR/S**. We propose that the greater steric hindrance of the aromatic groups may hinder the chiral directing preference of **G2-Lys** during self-assembly.

CONCLUSIONS

We have demonstrated that the chirality of the amine used to form a gel with **G2-Lys** has a large bearing on the assembly of the resulting diastereomeric complexes into self-assembled gel networks. This has been investigated most thoroughly using **C6R/S** but has also been observed using a range of other amines, all of which have what would otherwise be regarded as poor quality chiral centers. This demonstrates the remarkable and powerful effect of chirality on gelation of these systems. Importantly, the selective incorporation of one enantiomer of an amine over the other into the gel network has been demonstrated, and in all cases, the *R* amine that forms the most stable gel network is primarily selected for incorporation into the gel. The thermodynamic control over this process has been proven by forming a gel exclusively with **C6S** and then allowing **C6R** to diffuse through the sample and displace **C6S** from the solidlike nanofibers. This forms a new nanoscale network and shows that these gels can adapt and evolve in response to chemical stimuli to which they are exposed. Finally, it has been demonstrated that excess amine, which remains unincorporated within the gel network, can diffuse out and selectively react with a chiral isocyanate. This allowed us to quantify the enantioselectivity of component selection within these gels but also illustrates how gels can act as selective reservoirs of potential reagents, releasing them on demand to yield (in this case) one enantiomer (of amine) in preference to another. We suggest that the lessons learned in this research may go on to be applied in enantioseparation, asymmetric synthesis, or the development of hydrogels which can play active roles in prebiotic reaction pathways.

ASSOCIATED CONTENT

Supporting Information

Full details of amine gelation studies including T_{gel} data for all amines at different enantiomeric ratios, FEG-SEM imaging, VT-NMR data, IR data, and full data from selectivity studies including NMR spectra of diastereomeric products. 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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