Self-Assembly Hot Paper

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A Supramolecular Gel from a Quadruple Zwitterion that Responds to Both Acid and Base**

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The development of smart materials that exhibit changes in their physicochemical properties in response to external stimuli is of current interest for various applications. For example, responsive polymeric gels have been well exploited for biomedical applications, drug delivery, actuators, sensor technology, etc.[1] But owing to the covalent nature of their cross-linked network this approach is limited. Such materials are often brittle, they may contain structural defects resulting from the polymerization process, and the materials cannot self-heal.[2] In contrast, in nature, the self-assembly of small building blocks is ubiquitously used for constructing complex superstructures.[3] Accordingly, tailor-made strategies for designing well-defined and organized artificial nano-architectures using self-assembly have evolved in recent years.[4] In this respect supramolecular gels are an intriguing new class of nanomaterials.[5] Owing to the dynamic and reversible interactions that hold the gel network, these viscoelastic materials are endowed with inherent responsive properties that are usually lacking in traditional covalently cross-linked polymeric gels. Their properties can be modulated by variation of temperature[6] or solvent composition, since these changes directly affect the strength of the noncovalent interactions within the gel network. Furthermore, when the gelators possess functionalities that respond to external stimuli such as light, pH value, redox processes, ionic species, host–guest interactions, etc. the gels become responsive to an external stimulus.[7]

In general, there are two possibilities to form a supramolecular gel. One can either start from a polymer that is cross-linked by additional supramolecular interactions between the polymer chains[8] or one can rely on the self-assembly of small low-molecular-weight organic molecules.[9] The latter approach is more challenging because it requires very stable noncovalent interactions between the individual small building blocks to ensure a sufficient degree of polymerization needed to form a gel. For example, H-bonded supramolecular gels are only stable in nonpolar organic media,[10] owing to the limited strength of H bonds in polar and especially protic solvents.[11] However, stable H-bonded gels in such solvents can be obtained in combination with solvophobic interactions.[12] Also the very stable metal–ligand interaction or electrostatic interactions have been used for gel formation in polar solvents. Yet, examples for gel formation driven by ionic interactions are limited so far to those formed between two oppositely charged multivalent polymeric strands.[13]

Herein, we now report the novel quadruple zwitterionic molecule **1** (Scheme 1), built from a tetrahedral pentaerythritol core, which forms thermoreversible, transparent gels in DMSO.[14] The aggregation and the gelation of **1** are driven solely by the formation of ion-paired dimers between the self-complementary zwitterionic units,[15] which form extremely strong dimers even in polar solvents ($K_{dim} > 10^{10}\,M^{-1}$ in DMSO and $K_{dim} > 10^{2}\,M^{-1}$ in pure water, respectively).[16,17] Furthermore, since the guanidiniocarbonyl pyrrole cation has pK_a value of approximately 6–7, ion-pair formation with the carboxylate ($pK_a \approx 3$–5) can occur only in a narrow and specific range around neutral pH. This provides a simple way of turning the aggregation on or off by either protonation or deprotonation of the zwitterion.[18] The gels in DMSO, therefore, exhibit dual pH dependence; they transform into sols by the addition of either acid or base. Furthermore, these pH-triggered gel–sol transitions are completely reversible; by neutralizing the excess acid or base, the original gels are restored (Scheme 1). Although there are several examples of pH-responsive gels in the literature, to our knowledge, this is the first example of a supramolecular gel that displays such bidirectional, reversible pH-switchable properties.

The synthesis of the quadruple zwitterion **1** was accomplished by employing an alkyne–azide click reaction as a key step (for details see Scheme S1 in the Supporting Information). The four arms in **1** are oriented in a tetrahedral fashion around the pentaerythritol core and since they are reasonably flexible, the formation of both intra- and intermolecular ion-paired dimers between the four zwitterions is feasible. Concentration-dependent ^{1}H NMR experiments confirmed that in [D$_6$]DMSO even at low concentrations (0.5 mM), the zwitterions in **1** are already ion-paired as indicated by the expected characteristic shift changes of the guanidinium amide NH for example (Figure S8 in the Supporting Information).[15] Two-dimensional diffusion-ordered NMR (DOSY)[19] measurements for **1** at 1 mM revealed a diffusion coefficient of $D = 8.6 \times 10^{-11}\,m^2 s^{-1}$. When this value was used

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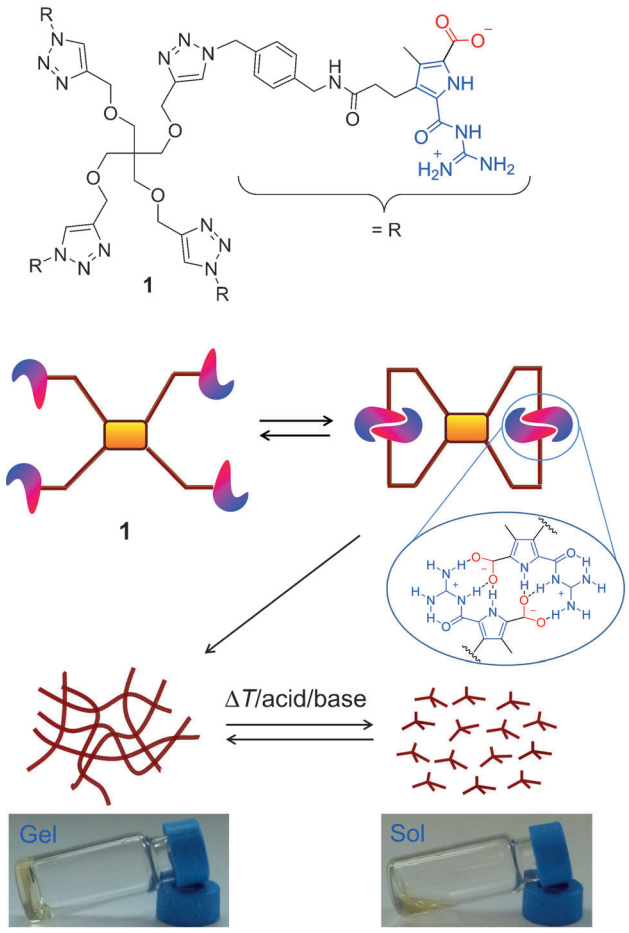

Scheme 1. Self-assembly of quadruple zwitterion **1** leads to a multi-responsive supramolecular gel in DMSO. The self-assembly and hence the gel formation can be switched not only by temperature but also by the addition of either acid or base.

in the Einstein–Stokes equation (see the Supporting Information), a hydrodynamic diameter of $d(H) = 2.6$ nm was calculated. This value corresponds well with the size of a single molecule of **1** (extended length ca. 2.8 nm), as obtained from molecular modeling studies (see the Supporting Information). Accordingly, the protonated form **1**·4 H^+, which is not capable of forming any kind of ion pairs (neither intra- nor intermolecularly) and always exists in solution as single molecules, exhibited an almost identical diffusion coefficient ($D = 7.7 \times 10^{-11}$ $m^2 s^{-1}$). These observations, therefore, unambiguously suggest that **1** at low concentrations mainly exists in the form of a monomer, with two pairs of intramolecular ion pairs among the four zwitterionic arms (Scheme 1). With increasing concentration (from 1 to 25 mM), new peaks appeared in the ^{1}H NMR spectra (Figure S8), indicating the formation of higher-order aggregates from **1**. DOSY spectra recorded at a higher concentration (25 mM), gave a diffusion coefficient of 1.9×10^{-12} $m^2 s^{-1}$, which is significantly lower (ca. 45 fold) than that observed at 1 mM. Such a drastic decrease in the diffusion coefficient is typically associated with the formation of extended intermolecular polymeric species.[20] Dynamic light scattering (DLS) studies performed on DMSO solutions of **1** also demonstrated the increase in size with increasing concentration (Table S3 in the Supporting Information).

The viscosity of the DMSO solutions of the quadruple zwitterion **1** was found to be strongly concentration dependent. Although in the concentration range of 1–15 mM, the increase in viscosity with concentration was rather gradual, a much sharper increment was observed above 15 mM (Figure 1 a). This trend in the viscosity profile is quite typical of

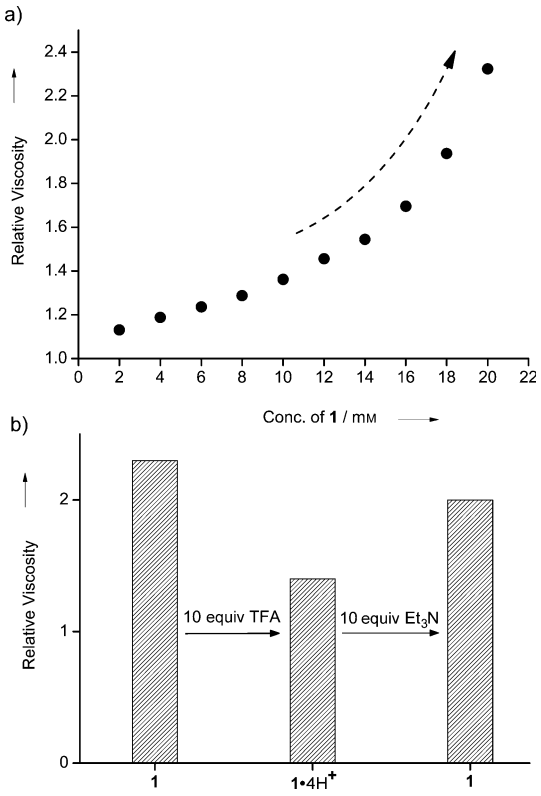

Figure 1. a) Plot of relative viscosity against the concentration of **1** in DMSO and b) variation in relative viscosity of a 20 mM solution of **1** in DMSO upon sequential addition of trifluoroacetic acid (TFA) and base.

the formation of higher-order aggregates such as oligomers and polymers.[21] A further increase in the concentration (20 mM $< c <$ 40 mM) led to a drastic increase in the viscosity and the viscosity values for the corresponding samples could no longer be measured. The first macroscopic hint of gelation was observed with a 40 mM sample. It appeared like a weak gel, which subsequently transformed into stronger gels at higher concentrations (45 to 50 mM). The gels were transparent and demonstrated excellent thermoreversibility; they could be turned into sols by heating while the hot sols could be converted back to the gels upon cooling to room temperature (Figure 2), and this cycle could be repeated several times. The gels were thermally quite robust; for example, the 50 mM gel melted to sol only at 100 °C (T_{gel}). Also, the gels kept in sealed vials were found to be stable for more than a month, thus suggesting a reasonable long-term stability.

The strong pH dependence of the zwitterionic dimer formation provides an efficient way of tuning the gel proper-

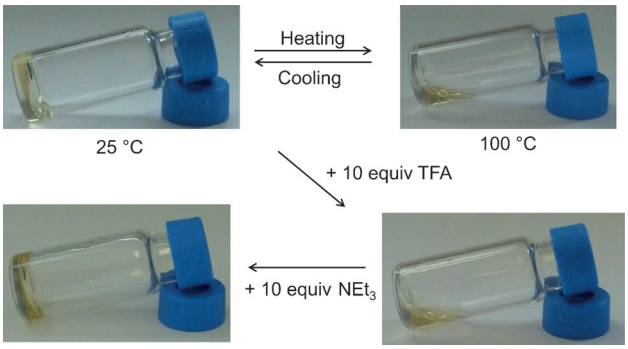

Figure 2. Reversible gel–sol transitions of a gel of **1** in DMSO upon heating/cooling and by the addition of acid and base ([**1**] = 50 mM).

ties. Therefore, the gel–sol transition was also induced by adding TFA (10 equiv) or Et_3N (10 equiv). These pH-triggered gel–sol transitions were completely reversible as the sols with the excess of acid or base were converted back to the gels simply by neutralizing with appropriate amounts of base or acid. The different ways of triggering the gel–sol transition are depicted in Figure 2. Thus, the DMSO gel of the quadruple zwitterion **1** is a multiresponsive supramolecular gel that responds to three different external stimuli: temperature, acid, and base. To our knowledge this is the first single-component supramolecular gel that responds to both the addition of acid or base. Any other pH-responsive organic gelator reported to date can only be switched in one direction by the addition of either acid or base.

The reversible switching of the aggregates of **1** by varying the pH value was also demonstrated by viscosity and DLS measurements. For example, upon the addition of TFA (10 equiv), the 20 mM sample exhibited an appreciable drop in viscosity. The initial viscosity, however, was restored[22] by subsequently adding Et_3N (10 equiv; Figure 1b). In a similar way, the aggregates (ca. 16.4 nm) observed in DLS (see Figure S10 in the Supporting Information) for the 20 mM sample were converted to smaller particles with sizes of approximately 3 nm upon the addition of acid (10 equiv of HCl). Larger aggregates with similar sizes (ca. 14.9 nm) could be reformed by adding Et_3N (10 equiv; see Table S3 in the Supporting Information).

Gels are viscoelastic soft solid-like materials that simultaneously store and dissipate energy.[9a,23] The viscoelasticity is characterized by two dynamic moduli: the storage modulus G' and the loss modulus G''. We performed dynamic rheology to investigate the viscoelastic behavior of the DMSO gels of **1**. Two kinds of experiments were performed: frequency sweep at a constant strain and strain sweep at a constant frequency. The frequency sweep experiments at a low, constant value of strain (0.1 %) were analyzed first. Both the 45 and 50 mM gels exhibited higher values of G' than G'' in the whole frequency range (the frequency sweep experiment for the 50 mM gel is shown in Figure 3a) as is typically observed for soft solid-like materials such as gels.[7h] Expectedly, the absolute value of the storage modulus (G') was higher for the 50 mM gel than for the 45 mM gel (Table 1). The stiffness/rigidity values of the gels, that is, the ratio of the two dynamic moduli (G'/G''), were

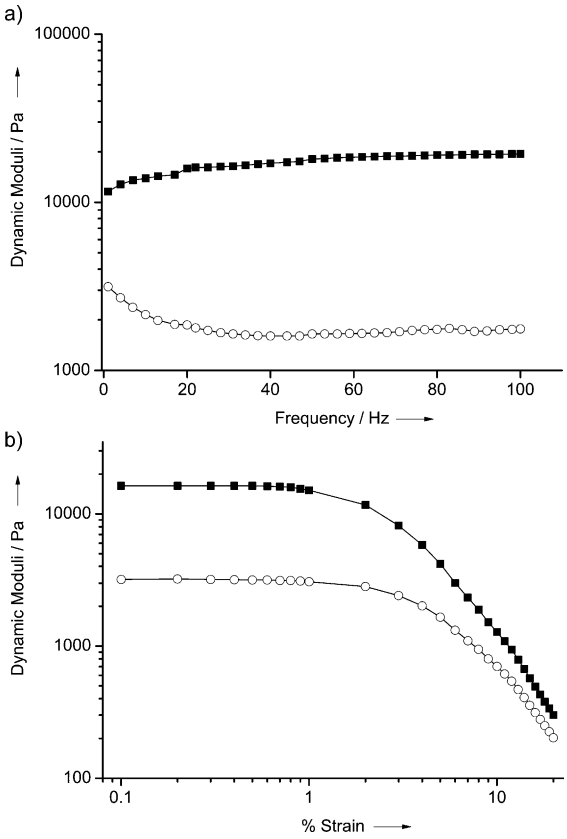

Figure 3. Dynamic rheology of a gel of **1** (50 mM) in DMSO; a) frequency sweep at 0.1 % constant strain; b) strain sweep at a constant frequency of 5 Hz. G':—■—; G'':—○—.

Table 1: Dynamic rheology of the gels of the quadruple zwitterion **1** in DMSO. The G' and G'' values were obtained from frequency sweep experiments performed at a fixed strain of 0.1 %. The values are at $f = 20$ and 10 Hz for the 50 mM and 45 mM gels, respectively. The critical strain values shown were obtained from strain sweep experiments at a fixed frequency of 5.0 Hz.

Conc. of gel [mM]	Storage modulus (G' [Pa])	Loss modulus (G'' [Pa])	Stiffness (G'/G'')	Critical strain [%]
50	15900	1900	8.3	3
45	12800	1720	7.8	2

found to be 7–8 (Table 1). The response of the DMSO gels under an ascending strain ramp was also analyzed by keeping the frequency at a constant value of 5 Hz. Typically, above a threshold value (yield stress, σ^*)[7h] of the imposed oscillatory deformation/stress, the gel structure breaks down and it starts to flow. In strain sweep experiments, the gels of **1** exhibited a plateau regime at lower values of the applied strain (0.1–1.0 %) where G' and G'' remained almost constant. A pronounced drop in G' and G'' was observed at 2–3 % of strain (Table 1), thereby indicating the onset of flowing behavior in the gels (the strain sweep plot for the 50 mM gel is shown in Figure 3b). In terms of the mechanical properties, that is, the storage modulus G', the stiffness (G'/G''), and the critical strain amplitude, the DMSO gels of **1** compare fairly well with other low-molecular-weight gels reported.[23,24]

We investigated the morphology of the samples by microscopy (FESEM or AFM). Field emission scanning electron microscopy (FESEM) was employed to examine the morphology of the dried DMSO gels (xerogels) of **1** (50 mM). The images recorded for the xerogels obtained by drying either under ambient conditions (Figure 4a) or

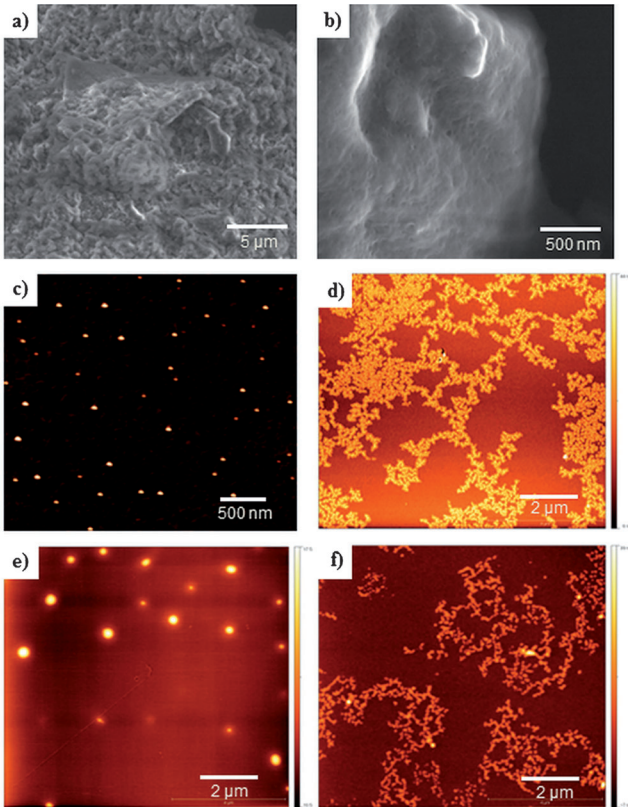

Figure 4. a, b) FESEM images of DMSO gels of **1** and c–f) AFM images of DMSO solutions of **1**; c) 0.1 mM, *z* scale 10 nm d) 5 mM, *z* scale 40 nm, e) 5 mM + TFA (20 equiv), *z* scale 10 nm, and f) 5 mM + TFA (20 equiv) + Et_3N (20 equiv), *z* scale 40 nm.

under vacuum (Figure 4b) revealed a dense entangled network of fibers (see also Figure S13 in the Supporting Information). The fibers were also found to form bundles in some places. Such morphological features are typically observed for an interconnected gel network and originate from a hierarchical self-assembly process in which the molecular building blocks initially form one-dimensional fibers that further undergo cross-linking to generate a sample spanning network. DMSO solutions of **1** at different concentrations were also spin-coated on mica surface and analyzed by tapping-mode AFM. At lower concentrations (0.1 mM), the formation of soft vesicles (Figure 4c) was observed, which were transformed into larger nanostructures at higher concentrations (1–20 mM, see Figure S14 in the Supporting Information). The switching of the aggregate morphology upon changing the protonation state was also observed in the AFM images. For example, the nanoaggregates of a 5 mM sample (Figure 4d) disappeared upon the addition of TFA (20 equiv; Figure 4e) but reappeared once the acid was neutralized with Et_3N (20 equiv; Figure 4f).

In conclusion, we report the aggregation and gelation behavior of a quadruple zwitterionic molecule **1** in DMSO. The novel feature of the gelation of this low-molecular-weight gelator is that it is solely driven by the H-bond assisted formation of ion-paired dimers between the zwitterionic moieties, thereby allowing gel formation in a polar solvent like DMSO. Furthermore, the strong pH dependence of the dimer formation allows to switch the gelation by changing the protonation state; the gels undergo completely reversible gel–sol transitions in the presence of both acid and base. Thus, we believe that the quadruple zwitterion introduces an interesting new type of nonpolymeric building block in the existing library of gelators; this building block might be of interest for further development of functional soft materials.

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