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Novel resorcinarene-based pH-triggered gelator

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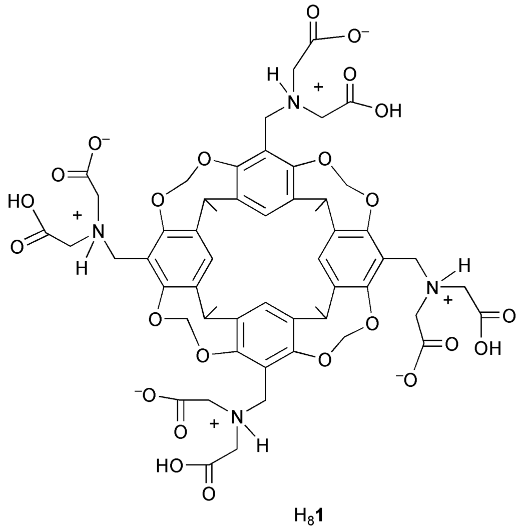
Iminodiacetate resorc[4]arene is shown to produce gels that are pH-reversible. The gels formed are clear and stable to inversion. (The gels are not stable above a certain temperature, which varies with concentration.) When the pH of an iminodiacetate resorc[4]arene solution (concentration >7.6 mM) is lowered to below 2.5, which is near one of the K_a values of the molecule, the dissolved molecules aggregate and cause gelation of water. ^1H NMR showed that at the pH of gelation a change occurs in the chemical environment of the iminodiacetate group. Scanning electron microscopy showed that the gel is composed of long strands that interweave and create a molecular mesh.

Calixarene and resorcinarene molecules are of great interest in the field of host–guest chemistry.[1] In connection with that field we have been studying various derivatives of resorc[4]arene molecules.[2] One compound of interest, **1**, has four phenyl rings bound into a cup shaped molecule with four iminodiacetate moieties along its upper rim. While studying the ability of **1** to complex metal ions we observed that under certain pH conditions and concentrations, **1** is capable of forming a gel in water. Gels comprise an important class of materials used for various purposes such as separations, drug delivery systems and as biomaterials.[3] Molecular gelators of water are rare[4,5] and those that form from pH changes are very rare.[6] Compound **1** is a new member of a unique class of gelators.

A gel is a colloidal material composed of gelator molecules and solvent. The gelator molecules are arranged in such a way that they form a mesh that traps solvent in the interstitial spaces. Gels can be classified as either chemical or physical. Chemical gels form a molecular mesh by covalent bonds, whereas physical gels form as a result of non-covalent interactions.[5] The majority of physical gels are made from polymeric molecules, but non-polymeric molecules can also self-assemble to form aggregates that gelate solvent. Many non-polymeric physical gels have been discovered recently that are capable of forming gels in various organic solvents.[3,7] However, non-polymeric physical gels that form from aqueous solutions are uncommon. Self-assembly into a molecular mesh commonly requires hydrogen bonding, and in aqueous solutions, potential sites are usually out-competed for by water.



H_8**1**

Gel formation typically occurs when dissolved molecules slowly assemble and form a molecular mesh. Most gels are formed by techniques similar to crystallization procedures[5] such as heating a solution of gelator to dissolve it and, then allowing the solution to cool. Also, in some cases, gelation is achieved by the use of a cosolvent. Compound **1** is different; the change in solubility is achieved by lowering the pH of an aqueous solution of **1**. **1** is a pH-triggered gelator.[8]

Compound **1** readily dissolves in neutral or basic aqueous solutions.† However, when the pH of a solution of **1** is lowered from neutral with HCl(*aq*) to below 2.5, compound **1** causes water to become a transparent gel and stable to inversion. The minimum concentration of **1** required for gelation is 7.6 mM or 1.7% by weight. (Most gels are typically <2 wt% compound.)[3] At the minimum concentration of **1**, gelation takes as long as 15 min, whereas at relatively high concentrations the process is nearly instantaneous. When below the minimum concentrations of **1** are used, compound **1** slowly precipitates as the pH is lowered. Once the gel is formed it can be redissolved by raising the pH. The resulting solution can then be gelled again by lowering the pH to below 2.5.‡ This can be repeated any number of times until the minimum concentration is exceeded, thus the gelation of **1** is pH-reversible.

SEM pictures reveal that the gel is composed of fibers that form a random network as they interlace and crossover (Fig. 1).§ The fibers ranged in width from 1 to 2 μm, with an indeterminable length. Compound **1** has a 2 nm width across its upper rim, so thousands of molecules span the diameter of one fiber.

To promote gel formation we typically start with a neutral solution of **1** and add HCl(*aq*) to it and to dissolve the gel we add NaOH(*aq*). We tested several other acids (H_2SO_4, H_2NO_3) and bases (KOH, RbOH, NH_4OH, K_2CO_3) to determine if the Cl^- or Na^+ ions had any specific effect on gelation. As with HCl and NaOH, these other compounds promoted gel formation and dissolution. However, we did observe that transition metal ions affected the gelating ability of **1**. When either Fe^{2+} or Co^{2+} (2 equivalents) were present, higher than normal concentrations of **1** were needed to induce gelation. When Cu^{2+} was present, gelation could not be induced even at pH's around zero and concentrations of **1** that were 5 times the minimum. In fact, when $CuCl_2$ is added to a sample of gel, the gel rapidly dissolves into a fluid. This change in gelation is presumably due to metal ion coordinating to the iminodiacetate ligand and thereby altering the K_a of the ligand.[8] Of the three ions (Cu^{2+}, Fe^{2+} and Co^{2+}) Cu^{2+} has the strongest interaction with the iminodiacetate. (K_f of the Cu^{2+} iminodiacetate complex is 4.3×10^{10}, compared to 6×10^5 and 9.3×10^6 for Fe^{2+} and Co^{2+} respectively.)[8] This might explain why Cu^{2+} has the most pronounced effect on gelation.

Although the gel forms independent of temperature, we observed that temperature does have an effect on the stability of the gel. For example an 11.00 mM gel begins to sweat at 50 °C when the temperature increases from 20–70 °C (2° C min^{-1}),

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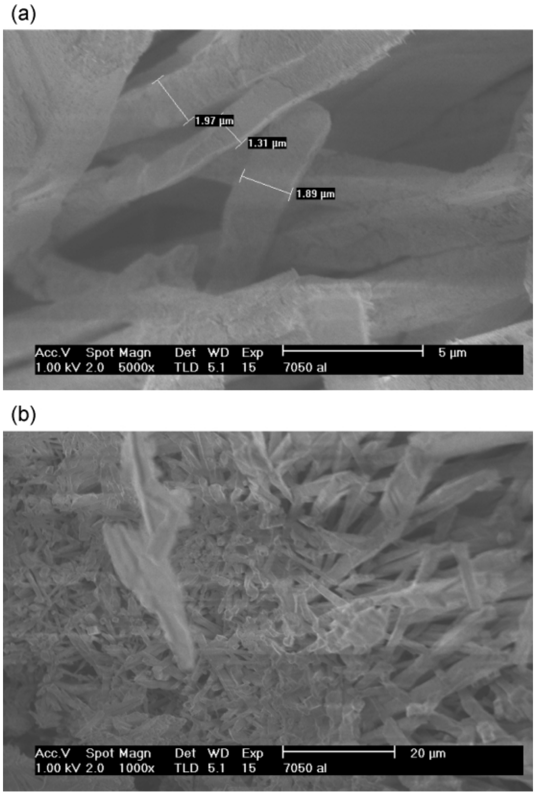
(a)



(b)

Fig. 1 SEM pictures of gel at 5000× (a) and 1000× (b) showing the fibers.

and then over a small temperature range, from 61–62 °C, it collapses. The gel separates into a powdery white precipitate of **1** and an aqueous solution. After cooling, the white precipitate can be re-dissolved in a neutral environment and re-gelled. The temperature where the gel becomes unstable depends on the concentration of the gel. More concentrated gels are stable to higher temperatures.

To help understand the mechanism of gelation we invoked gelation of **1** in D_2O by adding small amounts of DCl and observing the NMR chemical shifts of **1**. At pHs above 2.5, the chemical shifts of **1** are (δ, D_2O, HDO reference): 7.43 ($\mathrm{C_6}H$), 5.83 (outer $\mathrm{OC}H_2\mathrm{O}$), 4.79 ($\mathrm{C}H\mathrm{CH_3}$), 4.00 (inner $\mathrm{OC}H_2\mathrm{O}$), 3.23 (benzyl $\mathrm{C}H_2$), 2.85 ($\mathrm{C}H_2\mathrm{CO_2}$), 1.67 ($\mathrm{CHC}H_3$). After gelation has commenced and at a pH below 2.5, the chemical shifts are: 7.73 ($\mathrm{C_6}H$), 5.82 (outer $\mathrm{OC}H_2\mathrm{O}$), 4.85 ($\mathrm{C}H\mathrm{CH_3}$), 4.31 (benzyl $\mathrm{C}H_2$), 4.15 (inner $\mathrm{OC}H_2\mathrm{O}$), 3.88 ($\mathrm{C}H_2\mathrm{CO_2H}$), 1.75 ($\mathrm{CHC}H_3$). Two peaks shift significantly, they are the acetyl methylene and benzyl methylene resonances. Both of these groups are along the upper rim of the molecule and next to the nitrogen and carboxylate groups. Presumably, the addition of a proton to one of the acetates results in a shift of electron density toward that proton and away from the methylenes resulting in a downfield shift in the signal.

The significance of the gelation pH of 2.5 is further understood by comparing it to one of the pK_a's of the molecule. We determined by a pH titration that **1** has a pK_a value of 2.2 (22 °C), this value corresponds to the protonation of one of the carboxylates. (This value is close to one of the pK_a's of *N*-benzyliminodiacetic acid, a very similar molecule, which has a pK_a value of 2.30 at 25 °C.)[8] Below a pH of 2.5, the amino groups and a significant number of the carboxylates of **1** are protonated, while one of the carboxylates from each arm of **1** is still negatively charged. When the amines and one of the carboxylates are protonated, **1** has no net charge, which would decrease its interaction with water and decrease its solubility. Also, with an additional hydrogen bonding site, bonding between molecules of **1** should be favorable. The combination of lower solvent interactions and the increased possibility for interactions between molecules of **1** could promote the formation of aggregates.[9] These aggregates could then be responsible for the observed gelation.

In summary, compound **1** is a resorcinarene with four iminodiacetate moieties along its upper rim. Under certain conditions, **1** self-assembles into aggregates that trap solvent and gelate water. Aggregation and gelation occur as the pH of the solution is brought below 2.5. The gel is composed of fibers, which form a mesh. The gel can be dissolved by raising pH and reformed again by lowering the pH. Future research will involve using the structural unit of **1** to develop new gelators that form gels at other pHs.

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Notes and references

† To synthesize **1**, 500 mg Ba**1**[2a] is dissolved in 10 mL of 1M HCl, after which 500 mg K_2SO_4 is added and $BaSO_4$ precipitated. The solution is brought to neutral pH using K_2CO_3 and the precipitate is removed by decanting. The pH is lowered again to 2.0 and the K^+ salt of **1** precipitates. This precipitate is isolated and washed with 1 M HCl. If the solution of **1** is very concentrated, then the product will gelate instead of precipitate.

‡ Gelation has also been observed by starting at low pH and adding small amounts of base. However, due to the difficulty of changing pHs below pH = 1, it is easiest to promote gelation by starting at a pH above 3.0 and adding acid.

§ SEM pictures were obtained at low voltage (1.00 kV) on a Philips XL 30 S-FEG instrument and were done without metallic coating. The sample was prepared by lypholization of the gel.

1 (*a*) C. D. Gutsche, *Calixerenes*, (v.1, ed J. F. Stoddart) Royal Society of Chemistry, Cambridge, 1989; (*b*) V. Böhmer, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 713.

2 (*a*) O. Fox, J. Leung, J. Hunter, N. Dalley and R. Harrison, *Inorg. Chem.*, 2000, **39**, 783; (*b*) O. Fox, N. Dalley and R. Harrison, *J. Inclusion Phenom. Molec. Recognit. Chem.*, 1999, **33**, 403.

3 See these and references therein: (*a*) R. Lyon and W. Atkins, *J. Am. Chem Soc.*, 2001, **123**, 4408; (*b*) B. Simmons, C. Taylor, F. Landis, V. John, G. McPherson, D. Schwartz and R. Moore, *J. Am. Chem. Soc.*, 2001, **123**, 2414; (*c*) P. Terech and R. Weiss, *Chem. Rev.*, 1997, **97**, 3133.

4 (*a*) J. Makarević, M. Jokić, B. Perić, V. Tomiśić, B. Kojić-Prodić and M. Žinić, *Chem. Eur. J.*, 2001, **7**, 3328; (*b*) C. Marmillon, F. Gauffre, T. Gulik-Kryzwicki, C. Loup, A.-M. Caminade, J.-P. Majoral, J.-P. Vors and E. Rump, *Angew. Chem., Int. Ed.*, 2001, **40**, 2626; (*c*) U. Maitra, S. Mukhopadhyay, A. Sarkar, P. Rao and S. Indi, *Angew. Chem., Int. Ed.*, 2001, **40**, 2281; (*d*) L. Estroff and A. Hamilton, *Angew. Chem., Int. Ed. Engl.*, 2000, **39**, 3447.

5 F. Menger and K. Caran, *J. Am. Chem. Soc.*, 2000, **122**, 11679.

6 A. Aggeli, M. Bell N. Boden, J. Keen, P. Knowles, T. McLeish, M. Pitkeathly and S. Radford, *Nature (London)*, 1997, **386**, 259.

7 Compound **1** is similar in structure to a calixerene-based gelator: M. Aoki, K. Murata and S. Shinkai, *Chem. Lett.*, 1991, 1715.

8 L. Sillen and A. Martell, *Stability Constants of Metal Ion Complexes*, Supplement No. 1, The Chemical Society, London, 1971.

9 For a discussion of the effects of pH on self assembly see: K. Aoki, M. Nakagawa and K. Ichimura, *J. Am. Chem. Soc.*, 2000, **122**, 10997.