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A new trinuclear Cu(II) complex of inositol as a hydrogelator†

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A trinuclear copper(II) complex with inositol and 2,2′-bipyridine forms a fibrous hydrogel at pH 12.4, the assembly of discrete trinuclear complex molecules to form the metallogel being assisted by H-bonding and inter- and intramolecular π-stacking between the bipyridyls.

In recent years the discovery and design of specific hydrogels and hydrogelators is intended for varied applications from super-absorbant materials to biosensors. The environmentally sensitive hydrogels are considered as promising materials for drug delivery and tissue engineering because of their ability to sense changes in pH, temperature or concentration of metabolite and to release their load as a result of this change.[1,2] Such hydrogels with additional functionalities offer highly specific bio-responsiveness.[3–10] However, finding biodegradable polymers for biological applications is challenging.[11] Here low molecular weight hydrogelators,[12] small molecules capable of gelling aqueous solvents, can be more useful and are finding applications in tissue engineering[13] and controlled drug release.[14,15] Aggregation of these small molecule gelators or formation of supramolecular assemblies is through hydrogen bonds in organogels and through hydrophobic interactions and/or π-stacking in hydrogels.[16–18] These kinds of interactions are found to be important in biomolecules and several sugar based gelators.[19]

Very recently, metallogels are emerging as useful materials for varied applications.[20–22] These are either, coordination polymers, discrete organometallic molecules or metal complexes forming supramolecular assemblies or aggregates through noncovalent interactions,[12,23–24] including metal coordination. The presence of metal ions is also known to modify gel formation, help in chirality control[25] and change certain physical properties. An overview of the role of metal coordination in molecular gelation has been presented by Fages.[26] Though a number of coordination polymer gels have been reported,[27] the interest in low-molecular-weight gelators is for the high potential they have for a wide range of advanced functional nanoscale materials. Self assembly of such materials can be tuned by adding a second component.[28] A series of Ag(I) and Cu(II) complexes of bis-urea ligands form soft tunable metallogels[29] while Au(I) thiolates[30] and trimeric Au(I) pyrazolates[31] form supramolecular pH-responsive hydrogels and phosphorescent organogels, respectively. Hierarchical gelation by organooxotin nanoclusters has also been reported.[32] Iron(II) complexes formed by azobenzene substituted triazoles form photoresponsive gels.[33] Polypyridyl ligands appear to play an important role in the luminescent property of metallogels formed by Re(I) and Pt(II) complexes.[34,35]

A transition metal complex involving a polypyridyl ligand such as 2,2′-bipyridyl and myo-inositol, one of the most abundant natural isomers involved in inositol catabolism, appears to be an interesting candidate as a molecular hydrogelator. Here we report the pH triggered formation of a hydrogel, the first of its kind, formed by a trinuclear copper(II) complex.

Inositol being a hexahydroxy compound, some of its isomers are expected to have chelating ability. However, very few complexes having inositol oxygen coordination are cited in the literature. The *cis*-inositol can readily form complexes where it can bind with one metal ion. The tridentate ax–ax–ax mode is preferred by small metal ions while the ax–eq–ax mode is preferred by large metal ions.[36,37] The myo-inositol uses two adjacent oxygen sites for coordination with the Fe(III) center in myo-inositol oxygenase[38–40] and with Cu(II) in a copper complex catalyzed resolution of D,L-myo-inositol derivatives.[41] It uses the O1, O2 sites to bind with Mg^{2+} and O2, O3 or O5, O6 with divalent Ca.[42,43] Similar coordination has been observed in the complexes formed by lanthanide cations.[44] Thus all oxygen atoms in myo-inositol can participate in coordination, though only two at a time. Though the formation of trinuclear complexes using all six O sites by inositol appears to be obvious, this is not so because inositol being a polyol, the deprotonation of all six –OH groups, under normal pH conditions, as used in most cases, is difficult. Metal coordination, however, can make the protons more acidic, facilitate deprotonation and hence coordination using all oxygen sites at elevated pH. This effect can be more pronounced in the presence of a metal bound to a π-acidic ligand such as 2,2′-bipyridyl.

Myo-inositol (H_6ins), when allowed to react with three equivalents of cupric acetate, results in the formation of a trinuclear complex, $[Cu_3(ins)(H_2O)_6]$, at pH 9.8 (C = 15.63, H = 3.35%; calc. for $C_6H_{18}O_{12}Cu_3$: C = 15.23, H = 3.80%). The complex has features of inositol in its FTIR spectrum along with the stretching and bending vibrations of coordinated water. The FAB mass spectrum of the complex has a peak corresponding to the species $[Cu_3(ins)]^+$ at *m/z* 363 (calc. 363) which confirms the trinucleating ability of inositol. Other peaks corresponding to $[Cu(H_5ins)(H_2O)_2]^+$ at 277 (277), $[Cu_2(H_3ins)(H_2O)_2]^+$ at 339 (339), $[Cu_3(ins)(H_2O)_2]^+$ at 399 (399), among others, also support the formation of a trinuclear complex (see ESI†).

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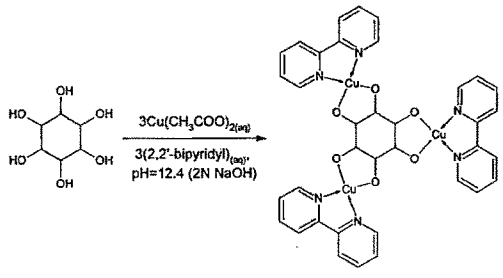
† Electronic supplementary information (ESI) available: Photograph of gel (gel formation test in inverted test tube), IR spectra, TGA, FAB-mass spectrum and the space filling and hydration models of the trinuclear complex. See DOI: 10.1039/b821283j



Scheme 1 Synthesis of the trinuclear Cu(II) complex hydrogelator.

The molecule, being small and sufficiently polar, can easily become aquated rather than forming a gel at all pH values. It also does not form copper hydroxide at higher pH. However, this molecule provides the basic framework for the formation of discrete trinuclear complexes by replacing the water molecules with aromatic ligands. These can be expected to have π-stacking or hydrophobic interactions leading to supramolecular assemblies and provide cavities for entrapping water molecules. Attempts were made to examine the possibility of metallogel formation by substituting water molecules by 2,2′-bipyridine at various pH values.

The reaction of inositol with 3 equivalents of copper and varying amounts of 2,2′-bipyridine (bipy) was carried out. No gel formation was observed with 1 or 2 equivalents of bipy at all pH and varying concentrations. The reaction of 10 ml 2.5% aqueous solution (1.388 mmol) of inositol was carried out with 3 equivalents of $[Cu(bipy)]^{2+}$ complex obtained by reacting 0.831 g (4.163 mmol) of cupric acetate monohydrate and 0.650 g (4.163 mmol) of bipy in 25 ml water (Scheme 1). Subsequently the pH was raised to 12.4 with aqueous sodium hydroxide. The solution was held at 60–70 °C for 30 min and allowed to settle at room temperature. This resulted in the formation of a transparent green gel. The gelation was confirmed by the inverted test tube method (see ESI†).

A similar reaction with higher concentrations resulted in the formation of a thick gel while lower concentrations resulted in the formation of a loose gel suspended in solution.

A xerogel was prepared by drying the gel at 120 °C for 3 h to constant weight. 100 mg of xerogel dissolved in 1.5 ml of water on heating at 60–70 °C and subsequent cooling at RT resulted in the re-formation of the gel. The T_{gel} value determined by the ball-drop method was found to be 46 °C. Scanning electron microscopic (SEM, Fig. 1) analysis of the xerogel indicates the formation of a compact fibrous structure made up of fibrils each having 2–4 μm diameter and > 50 μm length.

The xerogel was thoroughly washed with ethanol to remove any loosely held sodium hydroxide. The dried residue is a

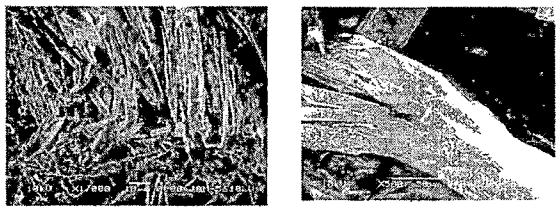


Fig. 1 SEM images of the metallogel.

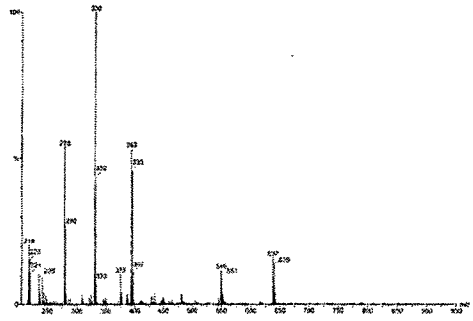


Fig. 2 ESI-MS of the complex $[Cu_3(ins)(bipy)_3]$.

single compound (complex) which forms a gel on addition of water at pH 12.4. Thermogravimetric analysis of the complex indicates the presence of nine water molecules in hydrogen bonded or coordinated form. The first water molecule is lost at 141 °C (1.18%), three subsequent weight losses between 141–165 °C (17.11%), 165–221 °C (30.43%) and 221–368 °C (9.78%) correspond to a total of three bipy and eight water molecules (see ESI†).

The ESI-MS analysis of the trinuclear complex (Fig. 2) has the base peak at m/z = 330 corresponding to $[Cu_3(ins)(bipy)_3(H_2O)_9]^{3+}$ along with $[Cu_3(ins)(bipy)_3(H_2O)_9 + 3H]^{3+}$ at m/z 332 and $[Cu_3(ins)(bipy)_3 + 3H]^{3+}$ at m/z 278 as major peaks and $[Cu(bipy)]^{2+}$ (219), $[Cu(bipy)_2]^{+}$ (375), $[Cu(ins)(bipy)]^{+}$ (393) and $[Cu(ins)(bipy)_2]^{+}$ (549) as minor peaks with lower abundance. This confirms that the residue is a trinuclear complex with formula $[Cu_3(ins)(bipy)_3(H_2O)_9]$.

The FTIR spectrum (KBr) of the complex was compared with inositol and bipy. It shows all the major bands of both inositol and bipy. The C–H stretching in alkane (inositol) at 2903 cm^{-1} is shifted to 2854 cm^{-1} in the complex, which confirms the coordination of inositol. The characteristic C–C multiple bond stretching and the ring C–N vibrations in bipy, observed at 1579, 1557, 1453 and 1416 cm^{-1}, are split and shifted in the complex at 1664, 1600, 1562, 1445 and 1406 cm^{-1}. The latter two overlap with the absorptions in inositol. These and the strong characteristic absorptions at 1250, 1029, 895 and 776 cm^{-1} confirm the presence and coordination of the bipy while the absorptions at 1111, 731 and 657 cm^{-1} confirm the presence of inositol (see ESI†).

Unlike the xerogel, the complex does not form a gel on adding water; instead the gel is formed on addition of 1.5 ml water of pH 12.4 to 100 mg of complex. Thus, both bipy as well as the hydroxyl ion seem to have important roles in the gel formation. In the electronic spectrum of $[Cu(bipy)]^{2+}$, an absorption maximum is observed at 675 nm corresponding to the ligand field transition, while this is shifted to 657 nm in the spectrum of the solution containing inositol–Cu–bipy (1 : 3 : 3) at natural pH, corresponding to the increase in the ligand field. At pH 12.4, the absorption maximum is observed at 665 nm. Thus the coordination of inositol is evident. The absorption at ~248 nm is found to shift gradually to higher energy, at ~236 nm, with increase in pH, while the intensity of absorption at 300 and 310 nm decreases. The absorption at 300 nm shifts to 297 nm as the pH approaches 12.4. The small shifts in the energy of transitions within coordinated bipy can

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be due to a very small change in the strength of Cu(II) to bipy π-interactions, which can be brought about by axial coordination of hydroxyl ion resulting in the change in energy of metal orbitals.

Geometry optimization of the complex $[Cu_3(ins)(bipy)_3]$ using Universal Force Field indicates the presence of intramolecular π-stacking. The optimization up to the first layer of solvation with water indicates the presence of both intra- and intermolecular π-stacking between coordinated bipy and formation of large voids (see ESI†).

As the hydroxyl ions are essential for gel formation, they must be forming intermolecular –OH bridges between the trinuclear complex molecules through axial coordination and also probably through H-bonding with inositol. A close examination of the sugar-based hydrogelators reported earlier[45] reveals that the sugars with one axial OH can have more H-bonds and close-packing with π-stacking between the phenyl substituents making them better gelators. Myo-inositol has striking similarity, with one axial –OH, thus there can be similar H-bonding and orientational effects. It appears that the fibrous super-structure is formed due to the presence of axial coordination and H-bonding by –OH, and the π-stacked bipy are helping in the formation of hydrophobic cavities that can hold water molecules to form a gel. Thus, the complex $[Cu_3(ins)(bipy)_3]$ is the first discrete trinuclear complex of its type with gel forming ability. We are further exploring the magnetic and other physical properties of this and similar systems.

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