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The Formation of $CuCl_2$-Specific Metallogels of Pyridyloxalamide Derivatives in Alcohols

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Abstract: Isomeric pyridyloxalamide derivatives **1**–**3**, which differed in the position of the nitrogen atom on the pyridyl ring, showed remarkably different gel-forming aptitudes in the presence of $CuCl_2$ salt in alcohols. Whilst derivatives **1** and **3** formed a soluble complex and a solid precipitate, respectively, ligand **2** generated a remarkably metal- and anion-specific metallogel.

Keywords: amino acids · copper · gels · oxalamides · supramolecular chemistry

Introduction

The controlled assembly of carefully designed small molecules into supramolecular structures has long been envisaged as a powerful approach towards the construction and development of multifunctional materials with new properties.[1] In particular, supramolecular gels that are derived from low-molecular-weight gelators (LMWGs) have recently received increasing attention. Indeed, their unique features and dynamic nature have stimulated numerous curiosity-driven studies, as well as the discovery of potentially innovative and highly technological applications.[2,3]

In this context, metallogels are of particular interest.[4] Metallogels can be obtained by combining small organic molecules with specific metal ions; moreover, they can respond to environmental factors through additional Lewis acid/base interactions and they can possess intriguing spectroscopic features. Indeed, metallogels might provide interesting opportunities in the field of catalysis, molecular recognition, and materials chemistry.

In spite of the many fascinating results that have been obtained to date, great efforts are still being devoted to the study of the subtle structural requirements and molecular motifs that control the behavior of a given compound. Perhaps surprisingly, the features that are required for a certain molecule to act as a gelator are still not fully understood.[5] The gel-forming aptitude of a compound derives from its ability to establish a wide range of non-covalent interactions (such as H-bonding, π–π stacking, van der Waals and hydrophobic forces), which enable the formation of a highly networked soft material. At the same time, such a network of interactions must not produce a too-ordered system, whose fate is then typically precipitation/crystallization. The complexity of such a picture is aggravated by the dynamic nature of gel systems, which often exhibit reversible sol–gel transition upon exposure to external chemical or physical stimuli.

Herein, we report a detailed study on the gelating properties of a series of pyridyloxalamide ligands (**1**–**6**, Scheme 1) in the presence of metal salts. Oxalyl retro-peptide compounds represent a versatile class of molecules that have been previously employed, with considerable success, in the study of gel formation.[6] On the whole, such simple and readily available ligands are able to establish both H-bond-

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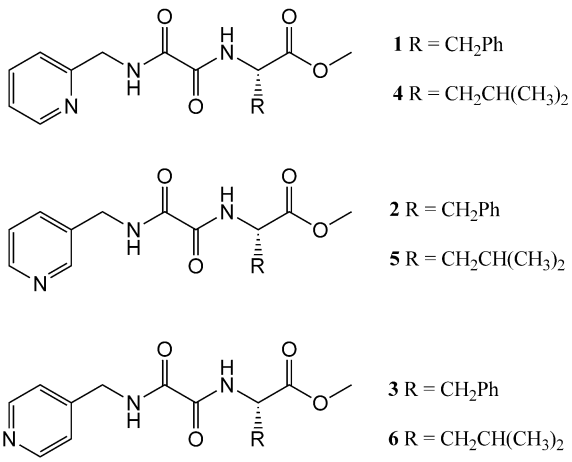

Scheme 1. Chemical structures of pyridyloxalamide derivatives **1**–**6**.

ing and metal coordination. Only a few examples of metal complexes with oxalyl retro-peptide ligands have been described so far and none of these reports were related to the formation of gels.[7] Notably, ligands **1**–**3** (and **4**–**6**) solely differ in the position of the N atom on the pyridine ring. Tiny though such a variation might seem, it clearly has a profound effect on the coordination mode and ability of the ligands. Herein, we show that this feature is responsible for the strikingly different behavior of the three ligands in the presence of $CuCl_2$ in alcohols. In particular, isomer **2** generates a strong gel, whereas, under the same experimental conditions, isomers **1** and **3** form a soluble complex and a solid precipitate, respectively. More importantly, of the many different metal salts that were tested, $CuCl_2$ was the only metal salt that, upon complexation with isomer **2**, generated a stable gel.

Results and Discussion

Oxalamide derivatives **1**–**3** (and **4**–**6**) were prepared and fully characterized. In general, they displayed similar properties and they all showed the same pattern of hydrogen-bonding interactions in the solid state, in which the NH−C(=O)−C(=O)−NH units dominated.[8] The ligands themselves were not gelators and they were only slightly soluble in polar solvents, such as alcohols and MeCN; their suspensions turned into clear solutions upon heating and slow cooling to room temperature yielded the starting solids.

By looking at the structural features of the three ligands, their interactions with metal cations could be easily anticipated. The pyridine group, which constitutes a classic metal-coordination site, is linked to the oxalamide unit through a short one-carbon spacer group and, depending on their relative positions, they might form a multidentate pattern of donor sites and bind metal cations. Intrigued by the possibility of obtaining metallogels, we tested several common transition-metal cations, such as Ag^{+}, Co^{2+}, Cd^{2+}, Ni^{2+}, Hg^{2+}, Zn^{2+}, and Cu^{2+} (as their chloride salts). When mixed in various solvents with compounds **1**–**3**, under the same preparation conditions, no obvious gelation was observed, except in one case: In the presence of $CuCl_2$, ligand **2** was able to form a gel in MeOH (as low as 0.4 wt%). This gel (Figure 1a) was stable for months, showed no visible deterioration, and the process was reversible. TEM analysis revealed that the gel of **2**/$CuCl_2$ in MeOH consisted of an extended fibrillar network of intertwined fibers with diameters in the range 5–15 nm and lengths of several μm (Figure 1b,c).

Interestingly, this system also displayed a marked anion-specific behavior, a property that has seldom been reported,[5c] because no gelation was observed when other copper(II) salts, that is, copper bromide, nitrate, sulfate, or acetate, were employed instead of $CuCl_2$.

Interested by the specificity of this process, we further investigated this system. We started by varying the ligand (**2**)/$CuCl_2$ ratio and then monitoring the resulting gel stability by measuring the sol–gel transition temperature (T_{gel}). A 2:1 ratio was found to be optimal for gel formation. Indeed, at a ligand/$CuCl_2$ ratio of 2:0.5, $T_{gel}=49\,°C$; T_{gel} increased to 60 °C for a 2:1 ratio, whereas it decreases to 56 and 53 °C at ratios of 1:1 and 1:2, respectively. The addition of larger quantities of $CuCl_2$ (1:>2) completely impeded the gelation process. The **2**/$CuCl_2$ system also formed gels in higher-molecular-weight alcohols, such as EtOH, *n*-propanol, and *n*-butanol (Figure 1a), and in MeOH/water and EtOH/water (1:1 v/v) mixtures, with each solvent giving a differently colored gel materials (see the Supporting Information). No gels were observed in THF, MeCN, DMSO, DMF, and DMSO/water or DMF/water mixtures.

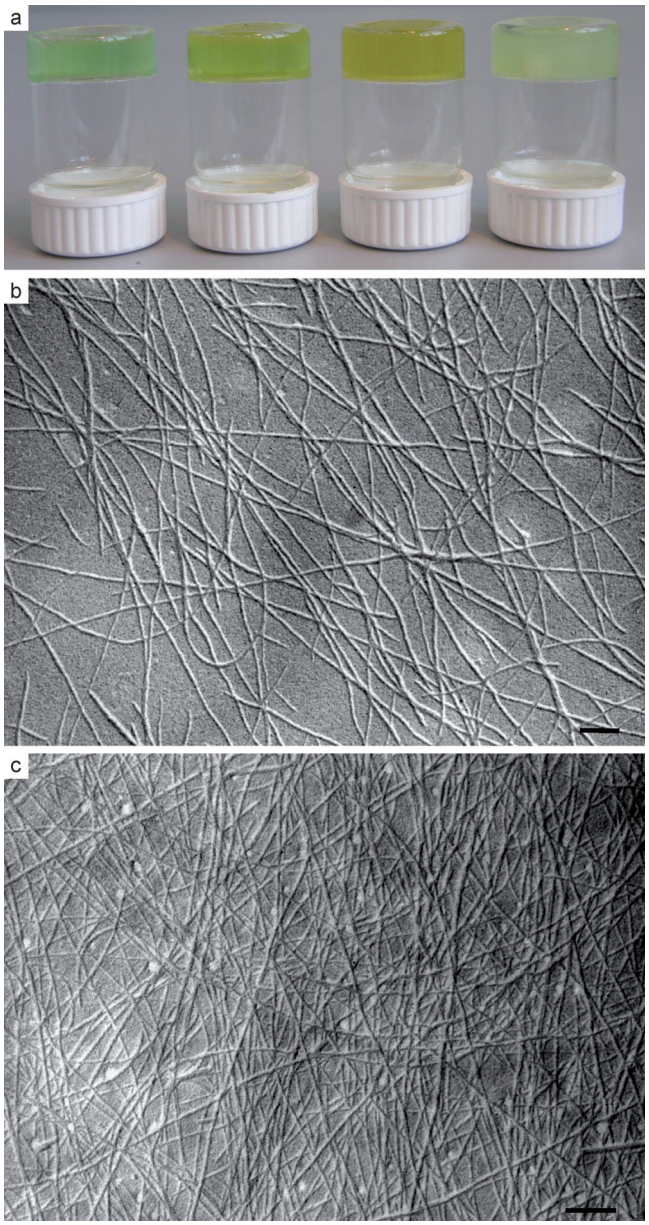

Figure 1. a) Photographs of **2**/$CuCl_2$ gels that were formed in various alcohols (from left to right): MeOH, EtOH, *n*-propanol, and *n*-butanol. TEM images of the **2**/$CuCl_2$ gel in b) MeOH and c) *n*-butanol after staining the sample with Pd (scale bar: 200 nm).

A simple discrimination that was based on the dielectric constant of the solvent seems to indicate that only medium-polarity solvents are gelled. To take into account specific solvent–gelator interactions, Kamlet–Taft solvent parameters can be useful.[9] These parameters have recently been employed to break down specific solvent–solute interactions, which could be responsible for gelation.[10] Regardless of the small data set presented herein, it seems that the α parameter, that is, the hydrogen-bond-donating ability of the solvent, is important, because high α values characterize alcohols in which gelation occurs. However, high β values and low π^* values also seems to be important for the occurrence of gelation.

We also noted that the replacement of the aromatic residues (Phe) with aliphatic ones (Leu), as in derivative **5** (Scheme 1), limited the gel formation to higher-molecular-weight alcohols.[11] This result indicates that aromatic π–π stacking interactions might be important in the overall stabilization of the gel state in more-polar solvents, such as MeOH. Furthermore, the chiral amino acid moiety is a necessary (but not sufficient) feature for gelation, because model systems **7**–**9** (see the Supporting Information), in which the amino acid part is replaced by a NH–CH_2Ph moiety, do not yield any gel material under the same experimental conditions.

The phenomenological description of the behavior of compound **2** as a pro-gelator, under the above-mentioned conditions, includes other aspects. In fact, to form a stable gel in MeOH, pro-gelator **2** not only requires the presence of Cu^{II} (as described above), but also that of Cl^- ions. To demonstrate this fact, we performed a series of experiments that involved mixing ligand **2** with different combinations of metal and organic salts. We started by noting that no gel was formed when ligand **2** was mixed with $CuBr_2$ (L/$CuBr_2$ ratio between 1:4 and 4:1). However, the addition of a source of Cl^- anions, such as tetrabutylammonium chloride (TBACl), to a 2:1 mixture of compound **2** and $CuBr_2$ was able to produce a stable gel when the 2:1:2 (L/Cu^{2+}/Cl^-) proportions were reinstated. It was also possible to perform the experiment in the reverse manner, that is, starting from a gel that was formed from a 2:1 mixture of ligand **2**/$CuCl_2$ and then adding increasing quantities of TBABr. For instance, the addition of six equivalents of TBABr (to a final L/$CuCl_2$/Br^- ratio of 2:1:3) still allowed for the formation of the gel; however, larger quantities did not.[12] Moreover, adding increasing quantities of TBACl (up to a **2**/$CuCl_2$/TBACl ratio of 2:1:9) to the gel did not hamper the gelation process.

These findings clearly highlight three important aspects: First, the presence of chloride is essential for gel formation; second, the detrimental effect that is observed by adding increasing amounts of $CuCl_2$ can be entirely ascribed to the presence of Cu^{II} ions, because the addition of TBACl does not induce any significant effects; this point marks a clear difference compared to other reported systems, in which the destabilization of the gel could be attributed to (inhibiting) HB interactions between the counteranion and the gelator molecule;[13] third, a 2:1 ligand/metal ratio seems to be optimal for the gelation process, which strongly indicates the occurrence of a 2:1 ligand/metal complex as the gelating unit.

In the right proportions, of the tested metal salts, $CuCl_2$ was the only single species that was able to form a gel. However, a mixture of ligand **2** with $Cu(NO_3)_2$ (or $CuSO_4$ or $CuBr_2$) and $ZnCl_2$ (or $NiCl_2$) in a **2**/CuX/MCl_2 ratio of 2:1:1 led to the formation of a stable gel in MeOH, which was indistinguishable from that formed by compound **2** and $CuCl_2$. Clearly, this result indicates that the gel formation is indeed a three-component process, in which all three species, that is, ligand **2**, Cu^{II}, and Cl^-, have a specific role and are necessary to obtain the gel state.

The experimental results described so far indicate that compound **2** is a quite specific pro-gelator, in terms of the metal and the anion, despite its simple chemical structure. However, compound **2** is even more remarkable than that. As mentioned, both the metal and the anion have precise roles in the gelation phenomenon. But also, the position of the N atom on the pyridyl ring is crucial. Indeed, it is interesting to note that ligands **1** and **3** do not form gels under the same experimental conditions. More precisely, the reaction of $CuCl_2$ with isomer **1** in MeOH affords a blue solution, whereas the same procedure with isomer **3** yields a light-blue material that instantly precipitates (SI). The position of the N atom on the ring is a tiny, yet determinant structural feature that alone selects the stable state of isomers **1**, **2**, and **3** in the presence of $CuCl_2$ under these experimental conditions.

The different behavior of compounds **1**–**3** likely depends on the coordination ability and denticity of these three compounds. Isomer **1** can hypothetically display various coordination modes. The isolation of the Cu^{II} complex of leucine analogue **4** and its structural characterization by X-ray diffraction show that NNO coordination, which is attained upon the deprotonation of one amide NH group, is preferred (Figure 2). The resulting metal complex has a planar conformation in the pyridyl/oxalyl region, which favors π–π staking in the crystal structure (see the Supporting Information). Weak axial interactions of Cu^{II} ions produce a 2:2 di-

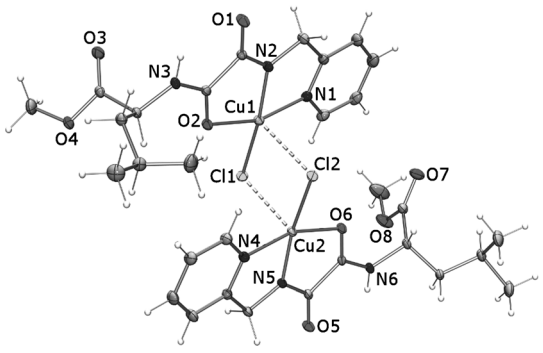

Figure 2. X-ray structure of the Cu^{II} complex with ligand **4**; thermal ellipsoid are shown at 30% probability. Hydrogen atoms are drawn as spheres of arbitrary radii.[14]

meric complex. However, a neutral 1:1 complex is the most likely form of the complex in solution.

Ligands **2** and **3** are multitopic, which means that they can form different kind of complexes with Cu^{II} ions; however, they are certainly not available for tridentate NNO binding to Cu^{II} ions, owing to geometric constrains.[15] In ligand **3**, the coordination mode of the pyridyl group is divergent with respect to both oxalamide NO chelating sites. Moreover, it is practically unencumbered in establishing interactions with metal ions and, thus, it forms stable and insoluble complexes with Cu^{II} salts. Isomer **2**, which has the N atom at position 3 on the pyridyl ring, possesses somewhat intermediate properties. As evidenced above, the ligand/metal stoichiometry that gives the most stable gel is 2:1, which implicates a 2:1 metal complex as being the gelator species. The presence of 2:1 complexes was also detected by MS (ESI) in diluted MeOH solution. Spraying a mixture of ligand **2** (or **5**, see the Supporting Information) and $CuCl_2$ showed the presence of peaks that belonged to the $[(\mathbf{2})_2CuCl]^+$ and $[(\mathbf{2}\text{-H})(\mathbf{2})Cu]^+$ species (see the Supporting Information).

Additional information was obtained by performing ATR-FTIR studies on ligand **2** and on the corresponding xerogel that was prepared with MeOH. The FTIR spectrum of crystalline ligand **2** showed two vibration bands at 3290 and 1655 cm^{-1}, which were ascribed to the hydrogen-bonded N−H and C=O functionalities of the oxalamide units, respectively (amide A and I bands). The ester carbonyl and amide II bands were located at 1734 and 1521 cm^{-1}, respectively. In particular, the position of the amide II band denoted the participation of the N−H groups in hydrogen-bonding interactions. Upon the addition of $CuCl_2$, the carbonyl stretch and the amide II band were shifted to 1738 and 1509 cm^{-1}, respectively. Moreover, the pyridine C=N band shifted to higher frequencies upon the addition of $CuCl_2$, indicating metal coordination. The oxalamide hydrogen-bonding interactions were still retained in the xerogel state, because no significant shifts in the N−H and amide I bands were observed.

Finally, this above-described gel system can also act as a responsive soft material, that is, it can respond to an external stimulus. A few drops of pyridine were added onto the surface of a previously formed gel in a cylindrical vessel. At the end of a process that took several days, a clear blue solution was obtained, owing the complete disruption of the gel state (see the Supporting Information). Similarly, the addition of a concentrated solution of ammonia in water completely destroyed the gel, thus yielding a transparent solution and a fine greenish blue precipitate (see the Supporting Information).[16] In another experiment, solid ethylenediamine tetra-acetic acid (EDTA), a classic metal chelator, was added onto the surface of the gel and we observed a gradual penetration of the solid material through the gel, which was slowly destroyed (Figure 3).

These simple experiments show that the above-described gel material can respond to the presence of different chemical species through disruption of the gel and the appearance of a liquid phase and/or precipitate. These experiments also further confirmed the nature of the interactions that were responsible for the gel formation. Indeed, the addition of a strong metal chelator (EDTA) or competitor ligands (pyridine, NH_3, or OH^-), which influence the coordination at the Cu^{II} center, all led to the disassembly of the gel.

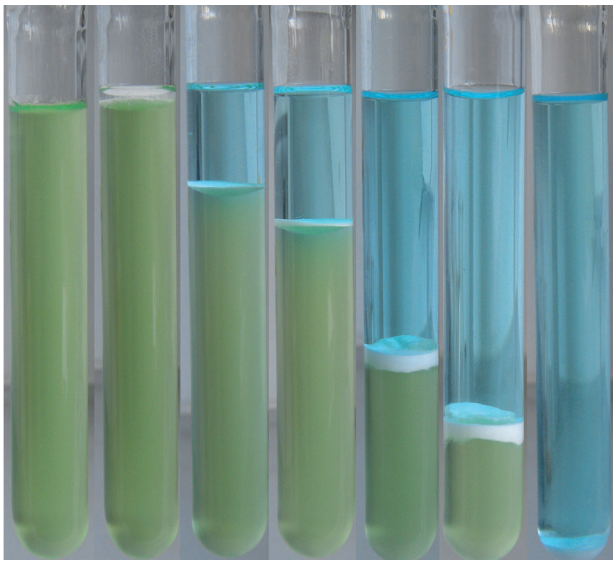

Figure 3. Photographs of the process of gradual disruption of the **2**/$CuCl_2$ gel in MeOH by the addition of EDTA onto the top of the preformed gel material.

Conclusions

This work focused on the properties of isomeric pyridyl-oxalamide derivatives **1**–**3** (**4**–**6**), which only differed in the position of the N atom on the pyridyl ring. This variation had a great influence on the coordination ability of the three ligands and, consequently, induced remarkably different behavior in the presence of $CuCl_2$ salt: Whilst compound **1** formed a stable complex in solution and compound **3** formed an insoluble complex that readily precipitated, isomer **2** generated stable gels under the same experimental conditions. Moreover, the gelation process seemed to be quite specific for Cu^{II}, because tests with several other metals did not lead to any gelation. A detailed phenomenological study also showed that chloride anions (but not Br^-, I^-, or other common anions) were necessary elements for the formation of what could be described as a three-component gel system comprised of a ligand/Cu^{II} (2:1) complex. Finally, this gel system can also act as a responsive soft material, that is, it can respond to external chemical stimuli. For instance, the addition of pyridine, NH_3 (aq), or EDTA onto the top of a preformed gel invariably led to its complete disruption.

Despite the increasing number of highly efficient gelation systems that are appearing in the literature, gelation phenomena are not yet fully understood or easily predicted.

The work reported herein presents a simple system that shows remarkable metal- and anion-specific gelation properties and demonstrates how every structural element can be a determinant.

Experimental Section

Material and methods: All of the solvents were purified and dried by using standard procedures and distilled prior to use. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 300 spectrometer. Chemical shifts (in ppm) are referenced to TMS as an internal standard. Optical rotations were measured on an Optical Activity AA-10 Automatic Polarimeter in a cell (path length: 1 dm) at 589 nm; concentrations are given in g/100 mL. Single-reflection attenuated total reflection (SR-ATR) FTIR spectra were recorded at a resolution of 4 cm^{-1} on an ABB Bomem MB102 single beam FTIR spectrometer that was equipped with CsI optics and a DTGS detector for a total of 30 scans by using a horizontal single-reflection ATR diamond prism with a 45° angle of incidence. Each spectrum was recorded as the ratio of the sample spectrum to the spectrum of the empty ATR plate. Mass spectra were recorded on an amaZon ETD ion-trap mass spectrometer (Bruker Daltonik, Bremen, Germany) that was equipped with a standard ESI ion source (nebulizer pressure: 8 psi; drying gas flow rate: 5 L min^{-1}; drying gas temperature: 250 °C; potential on the capillary: −4500 V). The compounds were dissolved in MeOH and injected into the ESI source by using a syringe pump at a flow rate of 65 μL min^{-1}. The mass spectrometer was operated in positive polarity mode. Nitrogen was used as the collision gas.

General procedure for the synthesis of compounds 1–9: A solution of ethyl oxalyl chloride (9 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise into a mixture of the amino acid methyl ester hydrochloride and triethylamine (19.2 mmol) or benzylamine (9 mmol) in dry CH_2Cl_2 (50 mL) over 1 h at 0 °C and the mixture was stirred for 18 h at room temperature. The mixture was washed with water (2×50 mL), a saturated aqueous solution of ammonium chloride (3×50 mL), and water again (2×50 mL). Then, the organic layer was dried over $MgSO_4$ and evaporated to obtain oxamic acid ethyl ester as a colorless oil, which was used in the next step without further purification. Picolylamine (6.5 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP) were added to a solution of oxamic acid ethyl ester (5.42 mmol) in dry CH_2Cl_2 (30 mL). After the mixture was stirred at room temperature for two days, the reaction mixture was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 10:1) to obtain the ligand as a white solid.

***N*-(L-phenylalanine methyl ester)-*N*′-(pyridin-2-ylmethyl)oxalamide (1)**: Yield: 82%; m.p. 134 °C; $[\alpha]_D^{20}=+41$ ($c=1$ in CH_2Cl_2); ^{1}H NMR ([D$_6$]DMSO): $\delta=9.23$ (t, $J=6.0$ Hz, 1H; CH_2NH), 9.03 (d, $J=8.4$ Hz, 1H; CH*NH*CO), 8.49 (d, $J=4.6$ Hz, 1H; C−H$_{aryl}$), 7.76 (t, $J=7.7$ Hz, 1H; C−H$_{aryl}$), 7.25 (m, 7H; C−H$_{Ph}$ and C−H$_{aryl}$), 4.62 (m, 1H; CH_α), 4.42 (d, $J=6.2$ Hz, 2H; CH_2NH), 3.66 (s, 3H; OCH_3), 3.29 ppm (m, 2H; CH_2Ph); ^{13}C NMR ([D$_6$]DMSO): $\delta=35.8$, 44.2, 52.2, 53.7, 121.0, 122.3, 126.6, 128.3, 129.1, 136.7, 137.3, 148.9, 157.2, 159.6, 159.8, 171.1 ppm; IR (KBr): $\tilde{\nu}=3317$, 3284, 1738, 1655, 1508, 1434, 1251 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{21}N_3O_4$: C 58.62, H 6.89, N 13.67; found: C 58.47, H 6.95, N 13.69.

***N*-(L-phenylalanine methyl ester)-*N*′-(pyridin-3-ylmethyl)oxalamide (2)**: Yield: 80%; m.p. 195 °C; $[\alpha]_D^{20}=+35$ ($c=1$ in CH_2Cl_2); ^{1}H NMR ([D$_6$]DMSO): $\delta=9.36$ (t, $J=6.3$ Hz, 1H; CH_2NH), 9.00 (d, $J=8.4$ Hz, 1H; CH*NH*CO), 8.46 (m, 2H; C−H$_{aryl}$), 7.63 (d, $J=7.8$ Hz, 1H; C−H$_{aryl}$), 7.35 (dd, 1H, $J=7.7$ and 4.8 Hz; C−H$_{aryl}$), 7.23 (m, 5H; C−H$_{Ph}$), 4.59 (m, 1H; CH_α), 4.31 (d, $J=6.3$ Hz, 2H; CH_2NH), 3.64 (s, 3H; OCH_3), 3.12 ppm (m, 2H; CH_2Ph); ^{13}C NMR ([D$_6$]DMSO): $\delta=35.8$, 40.1, 52.1, 53.6, 123.5, 126.6, 128.2, 129.0, 134.1, 135.2, 137.2, 148.3, 148.9, 159.6, 159.8, 171.0 ppm; IR (KBr): $\tilde{\nu}=3290$, 1734, 1655, 1522, 1435, 1257 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{21}N_3O_4$: C 58.62, H 6.89, N 13.67; found: C 58.49, H 6.97, N 13.55.

***N*-(L-phenylalanine methyl ester)-*N*′-(pyridin-4-ylmethyl)oxalamide (3)**: Yield: 87%; m.p. 157 °C; $[\alpha]_D^{20}=+35$ ($c=1$ in CH_2Cl_2); ^{1}H NMR ([D$_6$]DMSO): $\delta=9.39$ (t, $J=6.4$ Hz, 1H; CH_2NH), 9.01 (d, $J=8.4$ Hz, 1H; CH*NH*CO), 8.49 (d, $J=5.9$ Hz, 2H; C−H$_{aryl}$), 7.24 (m, 7H; C−H$_{Ph}$ and C−H$_{aryl}$), 4.61 (m, 1H; CH_α), 4.32 (d, $J=6.4$ Hz, 2H; CH_2NH), 3.65 (s, 3H; OCH_3), 3.13 ppm (m, 2H; CH_2Ph); ^{13}C NMR ([D$_6$]DMSO): $\delta=$ 35.8, 41.5, 52.2, 53.7, 122.1, 126.6, 128.2, 129.1, 137.2, 147.4, 149.5, 159.7, 159.8, 171.0 ppm; IR (KBr): $\tilde{\nu}=3303$, 1729, 1656, 1521, 1414, 1280 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{21}N_3O_4$: C 58.62, H 6.89, N 13.67; found: C 58.72, H 6.90, N 13.67.

***N*-(L-leucine methyl ester)-*N*′-(pyridin-2-ylmethyl)oxalamide (4)**: Yield: 80%; m.p. 119 °C; $[\alpha]_D^{20}=-14$ ($c=1$ in CH_2Cl_2); ^{1}H NMR ([D$_6$]DMSO): $\delta=9.29$ (t, $J=5.9$ Hz, 1H; CH_2NH), 9.06 (d, $J=8.3$ Hz, 1H; CH*NH*CO), 8.51 (d, $J=3.7$ Hz, 1H; C−H$_{aryl}$), 7.78 (t, $J=7.6$ Hz, 1H; C−H$_{aryl}$), 7.28 (d, $J=7.6$ Hz, 2H; C−H$_{aryl}$), 4.47 (d, $J=6.1$ Hz, 2H; CH_2NH), 4.39 (m, 1H; CH_α), 3.64 (s, 3H; OCH_3), 1.74 (m, 3H; CH_γ and $CH_{2\beta}$), 0.89 and 0.86 ppm (2×d, $J=5.9$ Hz, 6H; CH(CH_3)$_2$); ^{13}C NMR ([D$_6$]DMSO): $\delta=$ 21.0, 22.8, 24.3, 38.9, 44.2, 50.5, 52.0, 121.1, 122.2, 136.9, 148.8, 157.2, 159.7, 160.1, 171.9 ppm; IR (KBr): $\tilde{\nu}=3288$, 3152, 1749, 1654, 1523, 1395, 1149 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{21}N_3O_4$: C 58.62, H 6.89, N 13.67; found: C 59.02, H 6.89, N 13.67.

***N*-(L-leucine methyl ester)-*N*′-(pyridin-3-ylmethyl)oxalamide (5)**: Yield: 78%; m.p. 151 °C; $[\alpha]_D^{20}=-15$ ($c=1$ in CH_2Cl_2); ^{1}H NMR ([D$_6$]DMSO): $\delta=9.44$ (t, $J=6.1$ Hz, 1H; CH_2NH), 9.04 (d, $J=8.3$ Hz, 1H; CH*NH*CO), 8.51 (s, 1H; C−H$_{aryl}$), 8.47 (d, $J=4.4$ Hz, 1H; C−H$_{aryl}$), 7.69 (d, $J=7.7$ Hz, 1H; C−H$_{aryl}$), 7.36 (dd, $J=7.7$ and 4.9 Hz, 1H; C−H$_{aryl}$), 4.39 (m, 1H; CH_α), 4.35 (d, $J=6.3$ Hz, 2H; CH_2NH), 3.63 (s, 3H; OCH_3), 1.68 (m, 3H; CH_γ and $CH_{2\beta}$), 0.88 and 0.84 ppm (2×d, $J=5.7$ Hz, 6H; CH(CH_3)$_2$); ^{13}C NMR ([D$_6$]DMSO): $\delta=21.0$, 22.8, 24.3, 38.9, 40.2, 50.5, 52.1, 123.5, 134.1, 135.4, 148.3, 149.0, 159.8, 160.1, 171.9 ppm; IR (KBr): $\tilde{\nu}=$ 3293, 1750, 1652, 1522, 1425, 1205 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{21}N_3O_4$: C 58.62, H 6.89, N 13.67; found: C 58.75, H 6.80, N 13.70.

***N*-(L-leucine methyl ester)-*N*′-(pyridin-4-ylmethyl)oxalamide (6)**: Yield: 90%; m.p. 115 °C; $[\alpha]_D^{20}=-15$ ($c=1$ in CH_2Cl_2); ^{1}H NMR ([D$_6$]DMSO): $\delta=9.46$ (t, $J=6.3$ Hz, 1H; CH_2NH), 9.05 (d, $J=8.3$ Hz, 1H; CH*NH*CO), 8.50 (d, $J=5.7$ Hz, 2H; C−H$_{aryl}$), 7.25 (d, $J=5.7$ Hz, 2H; C−H$_{aryl}$), 4.41 (m, 1H; CH_α), 4.36 (d, $J=6.5$ Hz, 2H; CH_2NH), 3.64 (s, 3H; OCH_3), 1.68 (m, 3H; CH_γ and $CH_{2\beta}$), 0.88 and 0.86 ppm (2×d, $J=6.0$ Hz, 6H; CH(CH_3)$_2$); ^{13}C NMR ([D$_6$]DMSO): $\delta=21.0$, 22.8, 24.3, 38.9, 41.5, 50.6, 52.1, 122.2, 147.4, 149.6, 159.9, 160.0, 171.9 ppm; IR (KBr): $\tilde{\nu}=3292$, 1748, 1650, 1522, 1210, 1155 cm^{-1}; elemental analysis calcd (%) for $C_{15}H_{21}N_3O_4$: C 58.62, H 6.89, N 13.67; found: C 59.15, H 6.79, N 13.70.

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[11] Ligands **4** and **6** do not form gels under any of the tested conditions.

[12] The addition of a further six equivalents (final L/$CuCl_2$:Br^- ratio, 2:1:6) caused the volume of the gelated MeOH to decrease to about half and the addition of a total of 18 equivalents of TBABr (final L/$CuCl_2$:Br^-, 2:1:9) decreased the volume of the gelated solvent to approximately one fifth.

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[16] Furthermore, the gel formation was inhibited by premixing a few drops of pyridine or NH_3 (aq.) with the ligand (**2**) in MeOH before the addition of $CuCl_2$. Also, the addition of pure water onto the top of a preformed gel had no effect on its stability; indeed, the gel remained stable and the only detectable change was in its color, which gradually changed from green to bluish, thus acquiring the characteristic appearance of the gel that was formed in a MeOH/water (1:1) mixture (see the Supporting Information).

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