Salts of 4-Substituted Dipicolinic Acid Derivatives − Very Low Molecular Mass Gelators of Aqueous DMSO

Walter M. Müller,[a] Ute Müller,[a] Gudrun Mieden-Gundert,[a] Fritz Vögtle,*[a] Marion Lescanne,[b] Karine Heuzé,[c] Anthony D'Aléo,[c] and Frédéric Fages*[c]

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This study reports on the gelation behaviour of a well-known family of dipicolinic acid derivatives that lack any long aliphatic chain as substituent. The mechanism of gelation is likely to arise from the base-assisted deprotonation of the carboxylic functionality which leads to the formation of the monodeprotonated ligand as the key gelling species. The gels of aqueous DMSO are remarkably thermally resistant and stable over long periods.

Introduction

The creation of organic superstructures from the solution-phase, spontaneous self-assembly of small molecular components is a fascinating approach in materials chemistry.[1−4] In this respect, low molecular mass gelators are a promising class of molecules for the generation of novel organic networks consisting of fibre-like supramolecular objects.[5−7] The de novo design of molecular systems programmed to gelate a given fluid remains a major challenge. The most reliable approach so far is based on the covalent grafting of long aliphatic side-chain substituents to functional motifs prone to propagate one-directional H-bond interactions.[8] Elongated molecules containing urea[9] or amide groups[10] are among the archetypal examples of gelators obtained in this way. Long-chain moieties are believed to fine-tune solvophobic interactions and to frustrate three-dimensional crystal growth. Indeed, systems prone to experience marked one-dimensional interactions in the crystal state have been found to act as efficient gelators.[11] Besides, examples of low molecular mass gelators lacking long aliphatic fragments are so far much less classical and the behaviour of this class of molecules remains intriguing with respect to self-assembly and gelation phenomena.[5,12−14] It is therefore challenging to identify novel prototype structures that might offer further synthetic opportunities as versatile building-blocks for the generation of gelators endowed with functional features. Cholesterol derivatives[15,16] and methyl 4,6-*O*-benzylidene monosaccharides[17] are remarkable examples of such systems.

Here we report on the gelation ability in water/DMSO mixtures of a series of simple derivatives of 2,6-pyridinedicarboxylic acid that lack large aliphatic groups. Unsubstituted 2,6-pyridinedicarboxylic acid (dipicolinic acid, dipicH2) and its metal complexes have been the subject of extensive investigation.[18] Some of us have been involved in the use of pyridinedicarboxylic acids as molecular building blocks for the generation of knot-shaped supramolecular species.[9] Although several derivatives of dipicH2 have already been described, their organogelation properties have not been reported so far. Interestingly, recent work by Gourdon et al.[18] mentioned the pH-controlled thickening of highly concentrated water solutions (0.5 m) of dipicH2. We decided to examine closely the behaviour of dipicH2 (**1**) and some of its 4-substituted derivatives (**2**−**8**; Figure 1) in aqueous organic solvents at low concentration.[20]

Results and Discussion

Compounds **1**−**7** are readily soluble in DMSO at room temperature and were investigated at a concentration of 50 mM, whereas the poorly soluble 4-chloro-derivative **8** was examined at 10 mM. For all compounds, instantaneous partial gelation was induced by addition of two equivalents of aqueous NaOH into the test tube (water content 5%). After heating to ensure homogenization and cooling down to room temperature, the whole liquid volume was observed to be gelled within a few minutes (Table 1).

[a] Kekulé-Institut für Organische Chemie und Biochemie,
Gerhard-Domagk-Str. 1, 53121 Bonn, Germany
Fax: (internat.) +49-228/735-662
E-mail: voegtle@uni-bonn.de
[b] CRPP, UPR 6441 CNRS,
115 Avenue du Docteur Albert Schweitzer,
33600 Pessac, France
[c] LCOO, UMR 5802 CNRS, University Bordeaux 1,
33405 Talence Cedex, France
Fax: (internat.) +33-556/846-994
E-mail: f.fages@lcoo.u-bordeaux.fr

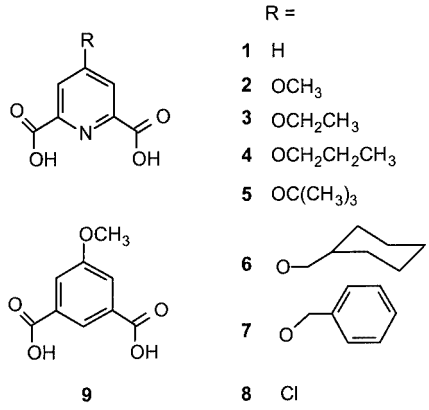

Figure 1. Constitutional formulae of the compounds **1**−**9** investigated in this study

Table 1. Gelation properties of 4-substituted dipicolinic acid derivatives in aqueous DMSO[a]

Compound	95% DMSO	90% DMSO
1	g (100)	p
2	g (> 150)	g (> 150)
3	g (50)	g (> 150)
4	g (30)	p
5	g (120)	p
6	g (90)	p
7	g (60)	p
8	g (100)[b]	g (> 150)[c]

[a] Gels were prepared in 1 mL of the solvent system and in the presence of 2 molar equivalents of NaOH. The concentration is 50 mM except for compounds **8**. g: gel, p: precipitate. In parentheses: gel-to-sol transition temperature (°C). [b] Concentration: 10 mM. [c] Concentration: 20 mM.

The 4-methoxy and 4-chloro derivatives are observed to be the most efficient gelators. Indeed, compound **8** forms a stable gel at a concentration of 5×10^{-3} M (1 mg·mL^{-1}) at room temperature. Furthermore, the gels obtained with **2** and **8** display unusual high gel-to-sol transition temperatures. With **2** at a concentration of 10 mg·mL^{-1}, the transition temperature exceeds 150 °C. The gels were observed to be thermoreversible, transparent, and stable over long periods (several months). The gel-to-sol phase transition was observed not to be sharp, and to occur over a broad temperature range (20 to 30 °C). The presence of water is necessary not only for gelation but also for solubilization to be observed. Indeed evaporation of methanolic solutions of compounds **1**−**8** to dryness in the presence of 2 molar equivalents of NaOH afforded solid samples which, after extensive drying, were found to be insoluble in anhydrous DMSO. No gelation could be observed under these conditions, although the gelation property was restored when a minute amount of water was added to the dried solid samples prior to addition of DMSO. Stable, but opaque, gels of **2** were obtained when the water content was increased up to 25%. At higher water content, the gel-to-sol transition temperature was observed to increase as exemplified by the case of compound **3** (Table 1). In contrast, dipicH2 (**1**) and compounds **4**−**7** were not observed to gel at high water content. Dioxane, propylene carbonate, or DMF were investigated as solvents in the presence of water. Only the 4-chloro derivative **8** was found to gelate 95% DMF at a concentration of 30 mM.

Critical to gelation within this series of compounds is the presence of a base in the medium. Indeed, gelation is not observed when the neutral diacid species are dissolved in aqueous DMSO, but takes place in the presence of NaOH (from one molar equivalent to an excess). When KOH or RbOH were used as a base with **2**, gelation was still effective, but the gels were observed to be less stable than those obtained with NaOH. In contrast, gel formation did not occur with LiOH, NH_4OH or tetra(*n*-butyl)ammonium hydroxide. Furthermore, the isophthalic derivative **9** — lacking the nitrogen atom but otherwise an analogue of pyridine **2** — failed to gelate aqueous DMSO under the same conditions. The special behaviour of the dipicolinic acid derivatives is believed to arise from the known ability of the deprotonated species to form a chelate in which the monocharged sodium cation is surrounded by the nitrogen and two oxygen atoms, as seen from the crystallographic data obtained by Gourdon on dipicH2.[8] Furthermore, these literature results underline the role of the sodium monocarboxylate salt of compound **1** as a key species in the self-assembly process, along with the participation of both nondeprotonated diacid species and water molecules, to form mixed supramolecular structures. Despite the basic conditions used in this study (at least two molar equivalent of NaOH), total deprotonation of the diacid derivatives may not be effective within the fibre-like assemblies; reprotonation reactions during fibre formation have already been observed for a related compound.[21] Electrostatic interactions and hydrogen bonds are thus believed to account to some extent for the formation of extended structures in which dipicolinic acid species self-assemble with the help of bridging water molecules. In this respect, the situation is somewhat reminiscent of the behaviour of sugar-based gelators whose gelation ability is reinforced by hydrogen-bond formation and metal coordination.[22] The critical influence of water on the organogel stability has recently been the subject of investigation.[23] X-ray structure analysis of some of the free acid derivatives shows the presence of hydrogen-bound water molecules in the crystal.[20] In particular, the heteroatom at the 4-position can act as a hydrogen acceptor site, which could explain the gelation efficiency of both the chloro and the nonbulky methoxy derivatives. The fact that increasing the water amount leads to precipitation for compounds **4**−**7** and to an enhanced gelation ability for compounds **2**, **3**, **8** indicates that hydrophobic interactions are also of primary importance.

Electron micrographs[23] of gels of **2** in aqueous DMSO (Figure 2) show the presence of thin, straight fibres that are tens of micrometers long and weakly interconnected. Remarkably, the regular shape (average diameter 90 nm) and untwisted morphology of the fibres are consistent with a high degree of crystallinity within the aggregates, resulting from a well-ordered molecular packing process. In agree-

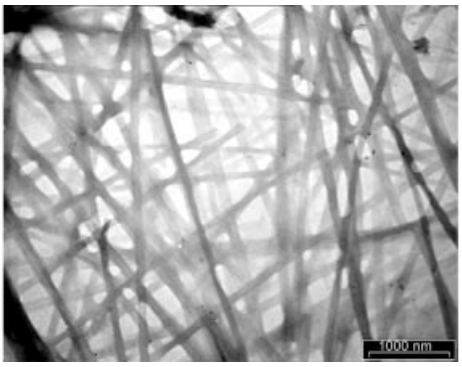

Figure 2. Electron micrograph of a gel of **2** in 95% DMSO (10 mg/mL, bar = 1000 nm)

ment with these observations and with the thermal behaviour of the gel (vide supra), preliminary rheological measurements indicate that the aqueous DMSO gels behave as jellies,[24] pointing to the occurrence of rather weak junctions between fibres.[25]

This study reports on the gelation behaviour of a well-known family of dipicolinic acid derivatives that lack any long aliphatic chain. The mechanism of gelation is likely to arise from the base-assisted deprotonation of the carboxylic functionality, leading to the formation of the sodium chelate of the monodeprotonated ligand as the key gelling species. These findings may become the basis for the design of molecular systems incorporating two or more covalently linked dipicH2 units and displaying unique self-assembling and gelation properties.

Acknowledgments

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