Chiral Bis(tyrosinol) and Bis(p-hydroxyphenylglycinol) Oxalamide Gelators. Influence of Aromatic Groups and Hydrogen Bonding on Gelation Properties*

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Enantiomerically pure \( R,R \)-bis(4-hydroxyphenylglycinol) oxalamides 3 and \( S,S \)-bis(tyrosinol) oxalamides 4 were prepared and tested for their gelling properties toward organic solvents, water and aqueous mixtures with polar organic solvents. It was found that oxalamide compounds with aryl substituted phenolic hydroxy groups are efficient organogelators of highly polar solvent systems while the derivatives with free phenolic hydroxy groups tend to crystallize. The revealed different behaviour is explained on the basis of specific hydrogen bonding motifs found in the crystal structures.

INTRODUCTION

There has been considerable recent interest in the development of new organogelators based on low molecular weight compounds. Many potential applications of gels as new »soft« materials are foreseen, for example, designing slow drug delivery systems, development of sensing devices or hardeners of liquid waste materials. In recent years, a number of low molecular weight organic compounds have been reported to be effective gelators of various organic solvents, water and their mixtures. Supramolecular nature of gelation has been widely recognized. Gels are formed by predominantly unidirectional self-assembly of organic molecules and the driving forces involved are ion-ion and dipole-dipole electrostatic interactions, hydrogen bonding, van der Waals interactions, solvophobic and \( \pi-\pi \) stacking interactions. This results in the formation of fibers, tapes or strands, which entangle into a network capable to immobilize large volumes of liquids via surface tension and related forces. In most cases, gels contain less than 5 % (w) of gelator and more than 95 % (w) of solvent. They are thermally reversible systems, and can repeatedly transform their physical state if not changed chemically; by heating they are transformed to a sol and by cooling again to gel.

* Dedicated to Professor Nenad Trinajstić on the occasion of his 65th birthday.

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Despite enhanced research activity in this field during the past 10 years, it is still very difficult to predict gelation properties on the basis of chemical structure. The organogelators reported up to now display a wide structural diversity, including amino acid or peptide derivatives, ureas, sugars, steroids, nucleic acids, aromatic compounds, gemini surfactants, two-component systems, fullerene, calixarene, and porphyrine derivatives, etc.

We have developed a versatile group of bis(amino acid) oxalamide gelators possessing a strongly hydrogen bonding and self-complementary oxalamide unit. It has been shown that some of the prepared compounds show rather rare ambidextrous gelation properties, being capable of forming gels with lipophilic solvents but also with highly polar solvents and water.

As part of a systematic study of the relationship between gelation properties and gelator structure, we have prepared a series of bis(amino alcohol) oxalamide derivatives incorporating valinol, leucinol, phenylglycinol and phenylalaninol (Chart 1). It was found that such derivatives also possess excellent gelling properties, however considerably different from those of the structurally closely related bis(amino acid) oxalamides.

It was found that the gelling properties of the two types of oxalamide gelators investigated are very susceptible to changes of their molecular structure and stereochemistry. Even small structural variations can cancel the gelling ability. The three types of associations are identified as decisive for gelation: the intermolecular hydrogen bonding and also offer the possibilities. Here, we report the preparation of tyrosinol and tyrosinol (Chart 2). It was found that such derivatives also possess excellent gelling properties, however considerably different from those of the structurally closely related bis(amino acid) oxalamides.

RESULTS AND DISCUSSION

Synthesis

The required optically active oxalyl dihydroxy diamides (Chart 2) were prepared according to Scheme 1, starting from previously synthesized amino alcohols, 2-amino-2-(4-benzyloxyphenyl)ethanol (1), 2-amino-3-(4-benzyloxyphenyl)propan-1-ol (2a) and 2-amino-3-(4-methoxophenyl)propan-1-ol (2b) stemming from R-4-hydroxyphenylglycine and S-tyrosine. Amino alcohols 1 and 2 were reacted with diethyl oxalate to give oxalamides 3 and 4. Hydrogenolysis of benzyl group in 3 and 4 gave hydroxy derivatives 3b and 4c. Aliphatic hydroxyl function in 4a was acylated to give acetyl (4d) and benzoyl (4e) derivatives.

\[ \text{Chart 1.} \]

\[ \text{Chart 2.} \]

\[ (R,R)-3a \quad R = Bzl \]
\[ (R,R)-3b \quad R = H \]

\[ (S,S)-4a \quad R = Bzl, R' = H \]
\[ (S,S)-4b \quad R = Me, R' = H \]
\[ (S,S)-4c \quad R = H, R' = H \]
\[ (S,S)-4d \quad R = Bzl, R' = Ac \]
\[ (S,S)-4e \quad R = Bzl, R' = Bz \]
\[ (S,S)-4f \quad R = 1-naphthylmethyl, R' = H \]
\[ (S,S)-4g \quad R = 2-naphthylmethyl, R' = H \]
\[ (S,S)-4h \quad R = 4-biphenylmethyl, R' = H \]
lated. Successful introduction of biphenyl substituent was achieved with 4-bromomethylbiphenyl (84% yield), which was prepared previously by bromination of 4-methyl-biphenyl with NBS in CCl₄ in the presence of dibenzoyl peroxide.

Gelation Experiments

Gelation behaviour of the prepared oxalamide compounds was tested against the following solvents or solvent mixtures: water, DMSO–water and DMF–water, EtOH, di-oxane, THF, EtOAc, acetone, CH₂Cl₂, CH₃CN, toluene, and benzene. Due to poor solubility of the prepared derivatives in most of the listed solvents, it was necessary to use a minimal volume of DMSO as a cosolvent. In a typical experiment, measured volumes (100 μl) of the tested solvent were added with a syringe to the weighed amount (10 mg) of the tested gelator in a septum-capped 11 × 133 mm test tube. After each solvent addition, the mixture was heated up to the boiling point, and the resulting solution was then allowed to cool by immersing the test tube into a water bath (20 ± 2 °C). If the formation of a gel was observed, the procedure was repeated until the test tube could be inverted without noticeable flow.

In the case of low or too high solubility, gelation of solvent mixtures was performed. Such gelation experiences resemble a mixed solvent recrystallization. A gelator (10 mg) was dissolved in the measured minimal volume of a solvent where it was highly soluble, measured volumes of another less polar solvent were successively added, and the mixture was heated and cooled as above. The procedure was repeated until the mixture failed to form a gel.

We have observed that the gelling efficiency, expressed as the maximum volume of a solvent that could be gelled by 10 mg of gelator, significantly depends on the diameter (ϕ) of the test tube used. In a narrower tube, a considerably larger volume of solvent could be gelled than in a wider tube. We have performed gelation experiments in tubes of different diameters (ϕ = 4–18 mm) with bis(leucinol) oxalamide (Chart 1) and bis(p-hydroxy-phenylglycinol) oxalamide (3a in Chart 2) in EtOH and toluene, respectively. It was found that 10 mg of leucinol derivative entrapped 5.4 ml of toluene in a 16.3 mm test tube and close to an 8 times larger volume (42.6 ml) in a 4 mm test tube. Similarly, 10 mg of 3a gelled 9 ml of ethanol in the 20 mm test tube and 34.9 ml in the 4.1 mm test tube. The results of these experiments, showing a practically linear dependence of the minimal gelation concentration c (mol dm⁻³) on test tube diameter, are shown in Figures 1a,b.
Due to the observed dependence of gelling efficiency on the test tube diameter, and to allow comparison with other gelators and solvents, the \( V_{\text{max}} \) values shown in Table I were determined using 11x133 mm test tubes for \( V_{\text{max}} < 8.5 \text{ ml} \), 15x160 mm test tubes for \( 8.5-18 \text{ ml} \) and 19x200 mm test tubes for \( V_{\text{max}} >18 \text{ ml} \).

Most of the tested oxalamides formed thermally reversible gels with organic solvents or their mixtures and only 4c also with water but only after rapid cooling to 15 °C. The oxalamides 3b and 4c possessing free phenolic and alkyl OH groups failed to gel (3b) or exhibited only weak gelation (4c) of the solvents and solvent mixtures tested (Table I). It was observed for both derivatives that the initially formed weak gels rapidly transformed to crystals. These observations suggest that the presence of free phenolic and alkyl OH groups in 3b and 4c, capable of providing additional intermolecular hydrogen bonds, make these derivatives prone to crystallization. In contrast, the 4b derivative with methyl instead of benzyl groups on phenolic oxygens of 4a failed to gel any of the tested solvents except toluene. Comparison of the gelation properties of compounds 3a, 4a, 3b, 4c with that of 4b suggests that the presence of benzyl substituents on phenolic oxygens of the former enhance gelation compared to 3b, 4c with free phenolic OH’s, but the presence of methyl (4b) instead of benzyl groups strongly reduces the gelation ability. For derivatives 4d and 4e with both types of OH groups blocked, a strong reduction of gelling property was also observed if compared to 4a. Since the benzyl derivatives 3a and 4a showed improved gelation properties compared to unsubstituted 3b and 4c, it was assumed that the intermolecular aromatic stacking interactions might be responsible for the enhanced gelation. Hence, the derivatives 4f–h bearing larger aromatic substituents were prepared.

The bis(1-naphtyl) derivative 4f is capable of modest gelation of toluene and fails to gel any of the other solvents tested. However, bis(2-naphtyl) derivative 4g and bis(biphenyl) derivative 4h exhibited very efficient gelation of DMSO– and DMF–water mixtures, and weak to moderate gelation of toluene. Compared to unsubstituted 4b, both 4g and 4h are superior gelators, capable to immobilize 8 times larger volumes of DMSO– and DMF–water mixtures. The striking difference of gelation ability observed for 1-naphtyl and 2-naphtyl derivatives 4f and 4g,

<table>
<thead>
<tr>
<th>solvent</th>
<th>3a</th>
<th>3b</th>
<th>4a</th>
<th>4b</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
<th>4g</th>
<th>4h</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)O</td>
<td>ns</td>
<td>A*</td>
<td>ns</td>
<td>ns</td>
<td>7.5*, A*</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>DMSO + H(_2)O</td>
<td>7.90 + 5.40</td>
<td>A*</td>
<td>10.00 + 9.05</td>
<td>cr</td>
<td>0.20 + 2.00</td>
<td>1.35 + 3.15</td>
<td>A*</td>
<td>cr</td>
<td>7.10 + 9.00</td>
<td>12.5 + 6.10 or 0.75 (b)</td>
</tr>
<tr>
<td>DMF + H(_2)O</td>
<td>9.75 + 11.00</td>
<td>cr</td>
<td>2.55 + 4.65</td>
<td>cr</td>
<td>0.20 + 2.25, A*</td>
<td>1.72 + 0.53</td>
<td>A*</td>
<td>cr</td>
<td>6.40 + 10.20</td>
<td>9.00 + 3.35</td>
</tr>
<tr>
<td>EtOH +</td>
<td>10.50</td>
<td>cr</td>
<td>1.40 + 0.10 (b)</td>
<td>cr</td>
<td>0.30</td>
<td>5.25</td>
<td>ns</td>
<td>cr</td>
<td>1.40 + 0.10(b)</td>
<td></td>
</tr>
<tr>
<td>CH(_3)CN +</td>
<td>+b, cr*</td>
<td>cr</td>
<td>ns</td>
<td>cr</td>
<td>1.85, A*</td>
<td>1.65</td>
<td>ng</td>
<td>ns</td>
<td>+b, cr</td>
<td>1.44 + 0.30(b)</td>
</tr>
<tr>
<td>acetone +</td>
<td>A*</td>
<td>ns</td>
<td>+b, s</td>
<td>cr</td>
<td>s</td>
<td>s</td>
<td>+a, cr</td>
<td>ns</td>
<td>0.250 + 0.01(b)</td>
<td>+b, cr</td>
</tr>
<tr>
<td>EtOAc +</td>
<td>A*</td>
<td>ns</td>
<td>+b, s</td>
<td>cr</td>
<td>ns</td>
<td>0.80</td>
<td>+a, cr</td>
<td>cr</td>
<td>+b, cr</td>
<td>+b, cr</td>
</tr>
<tr>
<td>dioxane +</td>
<td>0.55</td>
<td>cr</td>
<td>1.15 + 1.10(a)</td>
<td>cr</td>
<td>+a,cr</td>
<td>cr</td>
<td>0.30</td>
<td>+b, A*</td>
<td>0.45</td>
<td>0.35</td>
</tr>
<tr>
<td>THF +</td>
<td>0.60</td>
<td>ns</td>
<td>2.00 + 2.55(a)</td>
<td>cr</td>
<td>0.55 + 0.25(a)</td>
<td>cr</td>
<td>0.40</td>
<td>cr</td>
<td>+a, cr</td>
<td>cr</td>
</tr>
<tr>
<td>CH(_2)Cl(_2) +</td>
<td>3.35</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
<td>0.35 + 0.01(b)</td>
<td>cr</td>
<td>0.25</td>
<td>3.50</td>
<td>+b, cr</td>
<td>0.30 + 0.05 (b)</td>
</tr>
<tr>
<td>toluene +</td>
<td>3.75</td>
<td>ns</td>
<td>8.90</td>
<td>4.50</td>
<td>ns</td>
<td>1.50</td>
<td>1.50</td>
<td>8.90</td>
<td>+b, cr</td>
<td>4.40 + 0.05 (b)</td>
</tr>
<tr>
<td>other</td>
<td>–</td>
<td>benzene</td>
<td>benzene</td>
<td>3.60</td>
<td>A*</td>
<td>THF–EtOH</td>
<td>0.40 + 0.10</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ng – no gelation; ns – not soluble; s – solution; cr – crystallization; a – hexane; b – DMSO; A*– unstable gel, tends to crystallize; *gelation needs rapid cooling at +15 °C.
respectively, is indicative of structural factors being very important for gelation.

In conclusion, among all the prepared oxalamide derivatives, the best gelling properties exhibited \( p \)-hydroxyphenylglycinol and tyrosinol derivatives possessing aromatic substituents on phenolic oxygens: benzyl derivatives \( 3a \) and \( 4a \), \( \beta \)-naphtyl derivative \( 4g \) and biphenyl derivative \( 4h \). These derivatives are very efficient gelators of the highly polar DMSO–water and DMF–water mixtures; their minimal gelation concentrations are: \( 4.8 \times 10^{-4} \text{ g cm}^{-3}, 3a \) (DMF–water); \( 5.2 \times 10^{-4} \text{ g cm}^{-3}, 4a \) (DMSO–water); \( 6.0 \times 10^{-4} \text{ g cm}^{-3}, 4g \) (DMF–water), and \( 5.4 \times 10^{-4} \text{ g cm}^{-3}, 4h \) (DMSO–water).

**Gel Morphology; TEM and SEM Observations**

Typical gel morphology was observed by electron microscopy. Figure 2 displays TEM images of \( 4c \) and \( 3a \) gels, and SEM micrographs of \( 4c \) hydrogel and crystalline fibers of \( 3b \) formed in the DMF–water system. TEM shows the presence of highly intertwined fibers with diameters in the range of 10–55 nm constituting a dense network of \( 4c \) hydrogel (Figure 2a); SEM imaging of the same gel shows that the network is three-dimensional (Figure 2b). The TEM micrograph of the \( 3a \)–ethanol gel shows that it consists of a much less dense network, formed by fiber bundles of diameters in the range of 100–400 nm.

It is important to note that a gel-like structure consisting of large entangled crystalline fibers can be formed under controlled experimental conditions. If the DMF solution of \( 3b \) in an open vessel is immersed into a larger vessel containing water, very slow water evaporation and mixing with DMF results in the formation of a thin gel layer at the surface. After several days, a non-transparent gel-like system is formed within the whole volume. The cotton-like network is observable under a light microscope; the SEM image of the network (Figure 2d) shows that it consists of crystalline fibers of larger diameters (100–400 nm). This observation indicates that the gel fibers formed at the surface layer may induce crystallization into crystalline fibers of nanometer size. Further investigations aimed to prove this possibility are in progress and the findings could be of interest for the production of organic nano-fibers.

**Spectroscopic Investigations**

In the FTIR spectrum of the \( 5.87 \times 10^{-2} \text{ mol dm}^{-3} \) THF solution of \( 3a \), the \( v_{\text{NH}} \) and amide I bands appear at \( 3397 \text{ cm}^{-1} \) and \( 1681 \text{ cm}^{-1} \), respectively. The positions of these bands are characteristic of non-hydrogen bonded oxalamide units. In the amide II region, two shoulders could be detected, at \( 1511 \text{ cm}^{-1} \) and \( 1500 \text{ cm}^{-1} \), partly overlapped by the broad THF band at \( 1459 \text{ cm}^{-1} \). However, in the THF gel spectrum at a \( 2.62 \times 10^{-2} \text{ mol dm}^{-3} \) concentration of \( 3a \), two \( v_{\text{NH}} \) bands are present: the one at \( 3397 \text{ cm}^{-1} \) of free, non-hydrogen bonded NH’s and the one at \( 3292 \text{ cm}^{-1} \), being characteristic of hydrogen bonded NH’s. Also the two amide I bands (free at \( 1681 \text{ cm}^{-1} \) and hydrogen bonded at \( 1654 \text{ cm}^{-1} \)) and two amide II bands (at \( 1511 \text{ cm}^{-1} \) and \( 1500 \text{ cm}^{-1} \)) can be observed. Similar positions of the free and associated \( v_{\text{NH}} \) and amide I bands can be found also in the spectra of \( 4d \)–toulene and \( 4c \)–dioxane gels. The spectra of gels show clear temperature dependence. Figure 3 illustrates the changes ob-

![Figure 2.](image-url)
served in the spectra of 4d–toulene gel in the temperature range of 25–90 °C; with temperature increase, the intensities of hydrogen bonded NH and amide I bands decreased while those of free, non-hydrogen bonded functionalities appearing at higher wave numbers increased. These observations clearly show that oxalamide functionalities are involved in intermolecular hydrogen bonding that stabilizes gel fibers.

The temperature dependent 1H NMR spectra of 3a–THF, 4a–dioxane/cyclohexane and 4h–DMSO/water gels show significant upfield shifts of NH protons with increasing temperature. Such upfield shifts are interpreted by dissociation of intermolecularly hydrogen bonded aggregates involving oxalamide units (Figure 4). The NH temperature coefficients Δδ/ΔT of 5.3 × 10⁻³, 3.4 × 10⁻³ and 2.8 × 10⁻³ ppm K⁻¹ have been determined for 4h, 3a and 4a gels; the values show the highest temperature induced shifts of NH protons of 4h gel formed in the DMSO/water system, which is capable to strongly compete with intermolecular oxalamide hydrogen bonding. Smaller coefficients were obtained for 3a and 4a gels containing more lipophilic and less competitive solvents. Surprisingly, a very small coefficient was determined for 3a OH protons (Δδ/ΔT = 0.7 × 10⁻³ ppm K⁻¹); this can be interpreted either by the absence of intermolecular OH......OH hydrogen bonding in the aggregates or by only a slight chemical shift difference of hydroxyl protons involved in OH......OH and OH......O–THF hydrogen bonding.

In the temperature dependent spectra of 3a–THF and 4a–dioxane-d₈/cyclohexane-d₁₂ gels, the signals of aromatic protons are only slightly shifted upfield. These observations are inconclusive since in the case of intermolecular aromatic stacking interactions in the aggregates, aromatic protons should be significantly shifted downfield by disaggregation.

In conclusion, both the temperature-induced changes in FTIR and 1H NMR spectra of selected gels clearly point...
to intermolecular hydrogen bonding between oxalamide units in the aggregates constituting gel fibers in highly polar DMSO–water as well as in the lipophilic solvent mixtures. These observation are in accord with those previously found for the structurally closely related bis(amino acid) and bis(aminoalcohol) oxalamide gelators.\textsuperscript{17,18}

**Molecular and Crystal Structure of 3b**

Among the crystal structures of $N,N'$-bis(amino acid) oxalamides\textsuperscript{17,18} and their derivatives there is a single example of a three-dimensional hydrogen bonded 3b $\gamma$-network: (R,R)-3b oxalamide reveals an entirely different system of hydrogen bonds. According to experience in crystal engineering of using oxalamide, carboxyl, hydroxy or amide groups as synthons, there are preferences for hydrogen bonding.\textsuperscript{21} One-dimensional $\alpha$-network though is created via oxalamide groups whereas terminal donor and acceptor groups participate in hydrogen bonding completing a two-dimensional $\beta$-network.\textsuperscript{17,21} However, a three-dimensional $\gamma$-network can be obtained by inserting additional donor/acceptor groups in-between the oxalamide bridge and the termini of a molecule. Thus, the additional synthon participates in the formation of the three-dimensional network. Introducing PhOH groups on both sides of the oxalamide bridge, two additional OH groups contribute to hydrogen bonding. Intensive hydrogen bonding stabilized the crystal lattice and very good quality crystals were obtained. In contrast to other oxalamide derivatives studied, which involve a one-dimensional hydrogen bonded ‘ladder’ pattern acting between oxalamide groups, the $p$-hydroxyphenyl analogue 3a does not reveal such a pattern. Instead, the N1H of oxalamide, both terminal hydroxy groups and one of tyrosyl moiety exchange donor and acceptor functions: N1H $\rightarrow$ O21H $\rightarrow$ O2H $\rightarrow$ O31H $\rightarrow$ O11, and O3H $\rightarrow$ O1. Thus, hydrogen bonds act between oxalamide and terminal hydroxy groups, between terminal hydroxy groups, between hydroxy groups of PhOH moieties and oxalamide carboxyl groups, and finally between hydroxy groups of PhOH and the terminal ones. (Table II, Figure 5). It is interesting that one of oxalamide amide groups (N11H) does not participate in intermolecular hydrogen bonds, the closest neighbour is O3 at 3.470 Å but the angle is not favourable for hydrogen bonding (less than 90°). However, the typical intramolecular N–H–O hydrogen bonds, including both N1H and N11H, form pseudo-C$_2$ rings like in all crystal structures of oxalamide derivatives solved.

The PhOH groups are trans-oriented with respect to the oxalamide bridge. Hence, the intramolecular $\pi$–$\pi$ interactions are not feasible. However, there are CH–$\pi$ interactions between one of the methylene groups and the aromatic ring operated by 1–$x$, 1/2+$y$, 1–$z$ with the hydrogen to centroid (of the aromatic ring) separation distance of 2.966 Å. There are also CH–$\pi$ interactions with the corner to centroid separation distances of 2.978 and 3.001 Å of two neighbouring aromatic rings of molecules related by a screw two-fold axis and a translation.

**CONCLUSIONS**

We present evidence that $p$-hydroxyphenylglycinol and tyrosinol derivatives possessing aromatic substituents on phenolic oxygens, such as benzyl derivatives 3a and 4a, $\beta$-napthyl derivative 4g and biphenyl derivative 4h, are efficient gelators of highly polar DMSO– or DMF–water mixtures and moderate gelators of lipophilic solvents CH$_2$Cl$_2$ and toluene. Compared to 3b and 4c possessing free phenolic OH groups, the former molecules are much more efficient gelators capable of immobilizing up to 8

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**TABLE II. Hydrogen bond geometry of the three-dimensional $\gamma$-network**

<table>
<thead>
<tr>
<th>D–H $\rightarrow$ A</th>
<th>D–H</th>
<th>H$^+$–A</th>
<th>D$^+$–A</th>
<th>$\angle$ D–H–A $^\circ$</th>
<th>Symmetry operation</th>
</tr>
</thead>
<tbody>
<tr>
<td>N1–H1 $\rightarrow$ O11</td>
<td>0.86</td>
<td>2.33</td>
<td>2.715(3)</td>
<td>107</td>
<td>$x$, $y$, $z$</td>
</tr>
<tr>
<td>N1–H2 $\rightarrow$ O21</td>
<td>0.86</td>
<td>2.07</td>
<td>2.853(3)</td>
<td>152</td>
<td>1+$x$, $y$, $z$</td>
</tr>
<tr>
<td>O2–H2 $\rightarrow$ O31</td>
<td>0.82</td>
<td>2.10</td>
<td>2.900(3)</td>
<td>165</td>
<td>–$x$, 1/2+$y$, –$z$</td>
</tr>
<tr>
<td>O3–H3 $\rightarrow$ O1</td>
<td>0.82</td>
<td>1.89</td>
<td>2.708(3)</td>
<td>179</td>
<td>–$x$, 1/2+$y$, 1–$z$</td>
</tr>
<tr>
<td>N11–H11 $\rightarrow$ O1</td>
<td>0.86</td>
<td>2.26</td>
<td>2.648(3)</td>
<td>108</td>
<td>$x$, $y$, $z$</td>
</tr>
<tr>
<td>O21–H21 $\rightarrow$ O2</td>
<td>0.82</td>
<td>1.94</td>
<td>2.737(4)</td>
<td>164</td>
<td>–1+$x$, –1+$y$, $z$</td>
</tr>
<tr>
<td>O31–H31 $\rightarrow$ O11</td>
<td>0.82</td>
<td>1.87</td>
<td>2.674(3)</td>
<td>167</td>
<td>–$x$, 1/2+$y$, –$z$</td>
</tr>
</tbody>
</table>

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**Chart 3.**
times larger volumes of solvents. However, compound 4b with methyl substituents on phenolic OH groups failed to gel any of the tested solvents and solvent mixtures except toluene. This observation suggests that aromatic substituents on phenolic oxygens play an important role in gelation; however, no spectroscopic evidence was found for intermolecular aromatic stacking interactions in the aggregates. Spectroscopic investigations showed that intermolecular hydrogen bonding between oxalamide units stabilizes gel aggregates in highly polar and in lipophilic solvent systems. It was observed that 3b with free phenolic OH groups have a strong tendency to crystallization or initially form unstable gels that rapidly turn to crystals. The determined molecular and crystal structure of 3b provides explanation of such behaviour. In contrast to all previously determined molecular structures of bis(aminocacid) and bis(aminocacid) oxalamide gelators,17,19 which show cis-arrangement of substituents on asymmetric carbons, the trans-arrangement of p-hydroxyphenyl substituents was found for 3b. Also in contrast to β-hydrogen bonded network found in the crystal structures of bis(aminocacid) and bis(aminocacid) oxalamide gelators, 3b formed a three dimensional γ-network lacking the intermolecular oxalamide-oxalamide pairing. The

Figure 5. The molecular structure (a) and the three-dimensional γ-network (b) found in the crystal of 3b.
latter, however, presents the basic motif in all the previously determined crystal structures, being responsible for unidirectional self-assembly into fibrous aggregates.\(^{1,19}\)  

Apparently, the presence of additional hydrogen bonding functionalities (phenolic OH's) in 3b led to a complete change of the intermolecular hydrogen bonding pattern. The molecular structure of 3b with trans-oriented phenolic units was formed to ensure formation of the maximal number of intermolecular hydrogen bonds. As a consequence, the formation of the three-dimensional \(\gamma\)-network with altogether 10 intermolecular hydrogen bonds led to crystallization. It should be noted that the tyrosinol derivative 4c, differing from 3b only in having more flexible \(p\)-hydroxybenzyl instead \(p\)-hydroxyphenyl substituents on asymmetric carbons, still retained weak gelation ability. The latter represents a remarkable illustration how very subtle structural differences could have a decisive influence on gelation properties.

**EXPERIMENTAL**

Reagents were purchased from Aldrich or Fluka and were used without further purification. All solvents were purified and dried according to standard procedures. Thin-layer chromatography (t.l.c.) was performed on Merck Kieselgel HF\(_{254}\) plastic sheets and spots were made visible using a UV lamp (254 nm) or \(I\_2\) vapours. Preparative t.l.c. was performed on silica gel (type 60 F\(_{254}\), Merck), the plates were dried according to standard procedures. Thin-layer chromatography (t.l.c.) was performed on Merck Kieselgel 60 F\(_{254}\) in capillary tubes and were not corrected. Optical rotations were measured on an Optical Activity AA-10 Automatic Polarimeter and were not corrected. Optical rotations were recorded on Extrell FTMS 2001-DD Fourier Transform Mass Spectrometer electron impact, ionizing voltage 70 eV.

**General Procedure for the Preparation of Oxalyl-dihydroxy-diamides 3a, 4a and 4b**

The appropriate amino alcohol 1, 2a or 2b (4 mmol) was suspended in toluene (10–20 ml), and diethyl oxalate (2 mmol) was added under vigorous stirring. The reaction mixture was refluxed under vigorous stirring for 1 hour. Very soon in the heating to reflux period, the solution was formed, which quickly transformed to a dense gelatinous mass. After cooling to room temperature, the mixture was diluted with methanol (15–25 ml) until the gelatinous mass was destroyed, and the crystalline product was obtained, which was separated by filtration.

\[
\text{(R,R), N,N'-Bis[1-[(4-benzyloxy)phenyl]-2-hydroxy-ethylenediamide (3a)}
\]

From 1: 75 %; \(R_F\) ca. 0.45 (CH\(_2\)Cl\(_2\):MeOH 19:1); m.p. 230–232 °C (from DMSO–MeOH); \([\alpha]_D^{20}\) = −111 (c = 1.0 g/100 ml, DMSO); IR (KBr) \(\nu_{\text{max}}/\text{cm}^{-1}\): 3355, 3270, 1648, 1610, 1584, 1508; \(^1\)H NMR (DMSO–d\(_6\)) \(\delta/\text{ppm}\): 8.95 (d, 2H, J = 8.5 Hz, NH), 7.41–7.28 (m, 10H, (CH\(_2\))PhH) 7.24 (d, 4H, J = 8.5 Hz, OPhH–2'), 6.91 (d, 4H, J = 8.5 Hz, OPhH–3'), 5.04 (s, 4H, OCH\(_2\)(Ph)), 4.90 (br s, 2H, OH), 4.85–4.78 (m, 2H, \(\delta/\text{ppm}\): 8.31 (d, 2H, J = 9.0 Hz, NH), 7.40–7.11 (m, 10H, –(CH\(_2\))–PhH), 7.06 (d, 4H, J = 8.5 Hz, OPhH–2'), 6.81 (s, 4H, OCH\(_2\)(Ph)), 3.90 (m, 2H, *CH), 3.37 (m, 4H, CH\(_2\)(OH)), 2.77 and 2.64 (dd, 2H, J = 5.0 Hz, J = 14.0 Hz, *CH(Ha)Hb); \(^1\)C NMR (DMSO–d\(_6\)) \(\delta/\text{ppm}\): 159.83 (CO), 157.26 (1C, O(CH\(_2\))–Ph, 137.26 (1C, O(CH\(_2\))–Ph), 132.65 (OPhC–1'), 128.52, 127.90, 127.81 (5CH, O(CH\(_2\))–Ph), 114.57 (OPhC–3'), 69.27 (OCH\(_2\)(Ph)), 64.10 (CH\(_2\)(OH)), 55.28 (*CH).

Anal. Calcd. for C\(_{32}\)H\(_{32}\)N\(_2\)O\(_6\) \(\times\) H \(_2\)O (M = 558.61): C 68.80, H 6.13, N 5.01 %; found: C 68.60, H 6.07, N 5.12 %.

\[
\text{(R,R), N,N'-Bis[1-[(4-benzyloxy)benzy]-2-hydroxy-ethylenediamide (4a)}
\]

From 2a: 74 %; \(R_F\) ca. 0.35 (CH\(_2\)Cl\(_2\):MeOH 19:1); m.p. 210–212 °C (from DMSO–MeOH); \([\alpha]_D^{20}\) = −45 (c = 1 g/100 ml, DMSO); IR (KBr) \(\nu_{\text{max}}/\text{cm}^{-1}\): 3365, 3270, 1650, 1610, 1582, 1508; \(^1\)H NMR (DMSO–d\(_6\)) \(\delta/\text{ppm}\): 8.34 (d, 2H, J = 9.0 Hz, NH), 7.40–7.11 (m, 10H, –(CH\(_2\))–PhH), 7.06 (d, 4H, J = 8.5 Hz, OPhH–2'), 6.86 (d, 4H, J = 8.5 Hz, OPH–3'), 4.99 (s, 4H, –OCH\(_2\)(Ph)), 4.90 (br s, 2H, OH), 3.90 (m, 2H, *CH), 3.77 (m, 4H, CH\(_2\)(OH)), 2.77 and 2.64 (dd, 2H, J = 5.0 Hz, J = 14.0 Hz, *CH(Ha)Hb), 2.39 (s, 4H, –CH\(_2\)-(Ph)); \(^1\)C NMR (DMSO–d\(_6\)) \(\delta/\text{ppm}\): 159.64 (CO), 156.85 (OPhC–4'), 137.29 (1C, O(CH\(_2\))–Ph, 131.04 (OPhC–1'), 128.52, 127.90, 127.81 (5CH, O(CH\(_2\))–Ph), 114.54 (OPhC–3'), 69.25 (OCH\(_2\)(Ph)), 62.29 (CH\(_2\)(OH)), 53.30 (*CH), 35.35 (–(*CH)CH\(_2\)–).

Anal. Calcd. for C\(_{32}\)H\(_{32}\)N\(_2\)O\(_6\) (M = 568.65): C 71.81, H 6.38, N 4.93 %; found: C 71.68, H 6.14, N 5.11 %.

\[
\text{(S,S), N,N'-Bis[2-hydroxy-1-(4-methoxybenzyl)ethyl]-ethylenediamide (4b)}
\]

From 2b: 62 %; \(R_F\) ca. 0.37 (CH\(_2\)Cl\(_2\):MeOH 19:1); m.p. 205–206 °C (from MeOH); \([\alpha]_D^{20}\) = −58 (c = 1 g/100 ml, DMSO); IR (KBr) \(\nu_{\text{max}}/\text{cm}^{-1}\): 3360, 3280, 1640, 1608, 1576, 1500; \(^1\)H NMR (DMSO–d\(_6\)) \(\delta/\text{ppm}\): 8.31 (d, 2H, J = 9.0 Hz, NH), 7.04 (d, 4H, J = 8.5 Hz, OPhH–2'), 6.77 (d, 4H, J = 8.5 Hz, OPhH–3'), 4.86 (br s, 2H, OH), 3.89–3.73 (m, 2H, *CH), 3.68 (s, 6H, OCH\(_3\)), 3.61–3.36 (m, 4H, (HO)CH\(_2\)), 2.76 and 2.63 (dd, 2H, J = 5.3, 14.0 Hz, (HO)–CH\(_2\)(Ph)) and dd, 2H, J = 8.5, 14.0 Hz, (HO)–CH\(_2\)(Ph)), \(^1\)C NMR (DMSO–d\(_6\)) \(\delta/\text{ppm}\): 159.64 (CO), 157.70 (OPhC–4'), 130.75 (OPhC–1'),

130.07 (OPhC–2’), 113.69 (OPhC–3’), 62.32 (CH2OH), 55.03 (CH2(OH)); IR (KBr): 3449, 3381, 3293, 1654, 1508; 1H NMR (DMSO-

General Procedure for the Preparation of Oxalyl-dihydroxy-diamides 3b and 4c

To a solution of the benzyloxy compound 3a or 4a (1 mmol) in methanol (55 ml), 10 % palladium on activated carbon (40 mg) was added and stirred in an H2 atmosphere at 104 hPa at 40 °C for 2 h. The catalyst was filtered off and the filtrate was evaporated to dryness. The residue was triturated with dichloromethane–methanol (10:1) and diethyl ether to give the crystalline product 3b or 4b.

(R,R) N,N'-Bis[2-hydroxy-1-(4-hydroxybenzyl)ethyl]-ethanediamide (3b)

From 3a: 93 %; Rf ca. 0.69 (CH2Cl2:MeOH 7:3); m.p. 244–245 °C (from H2O); [α]D 20 = −132 (c = 1.0 g/100 ml, MeOH); IR (KBr) ν max/cm–1: 3441, 3372, 3298, 3237, 1670, 1650, 1617, 1511; 1H NMR (DMSO-d6) δ/ppm: 9.27 (s, 2H, OH–(Ph)), 8.82 (d, 2H, J = 8.6 Hz, NH), 7.09 (d, 4H, J = 8.3 Hz, OPh–2’), 6.64 (d, 4H, J = 8.3 Hz, OPh–3’), 4.88 (t, 2H, J = 5.6 Hz, CH2OH), 4.73 (dd, 2H, J = 7.6; 13.0 Hz, *CH), 3.64–3.49 (m, 4H, CH2(OH)), 2.68 and 2.57 (dd, 2H, J = 7.5; 11.1 Hz, OPhH–2’), 6.86 (d, 4H, J = 8.1 Hz, OPhH–3’), 4.99 (s, 4H, OCH2(Ph)), 4.18–4.10 (m, 2H, *CH), 4.06 and 3.96 (dd, 2H, J = 4.2; 11.1 Hz, (HO)CHa(Hb)), 2.72–2.70 (m, 4H, (CH2)CH), 1.93 (s, 6H, CH3); 13C NMR (DMSO-d6) δ/ppm: 170.27 (CO, acetyl), 159.67 (CO, oxalyl), 156.92 (OPhC–4’), 131.75 (1C, (OCH2)Ph), 131.01 (OPhC–1’), 129.98 (OPhC–2’), 128.42, 127.81, 126.79 (SCH, (OCH2)Ph), 114.55 (OPhC–3’), 69.21 (**(CH)CH2O), 64.76 (OCH2(Ph)), 49.98 (**CH), 35.25 (**(CH2)CH2), 20.61 (CH3).

Anal. Calcd. for C22H28N2O6 (M+ = 416.46): C 63.44, H 5.85, N 5.98 %; found: C 63.62, H 5.85, N 5.97 %.

To a suspension of bis(tyrosinol) oxalyl amide 4d (403–414 °C) the catalyst was added and stirred in an H2 atmosphere at 104 °C for 5 h. After cooling to room temperature, the precipitate was filtrated off and washed thoroughly with water (5x5 ml) to remove inorganic salts. The undissolved material was air-dried, giving crystalline products 4d–4h.

General Procedure for the Preparation of Oxalyl-dihydroxy-diamides 4f–4h

To a suspension of bistyrosinol oxalyl amide 4e (1 mmol) in acetonitrile (20 ml), K2CO3 (6 mmol) and the corresponding 1- or 2-bromomethylnaphtalenes or 4-bromomethylbiphenyl (1.1 mmol) were added. The mixture was heated to reflux for 5 h. After cooling to room temperature, the precipitate was filtered off and washed thoroughly with water (5 x 5 ml) to remove inorganic salts. The undissolved material was air-dried, giving crystalline products 4f, 4g or 4h.

D2O exchangeable, NH), 7.99–7.38 (m, 14H, 1-naphthyl), 7.09 (d, 4H, J = 7.6 Hz, OPh–2'), 6.94 (d, 4H, J = 7.6 Hz, OPh–3'), 5.39 (s, 4H, OCH2(Ph)), 4.86 (br s, 2H, D2O exchangeable, OH), 3.92 (m, 6H, CH2OH), 3.45 (m, 2H, *CH), 2.82 and 2.68 (dd, 2H, J = 5.0, 14.0 Hz, (HO)CH(Ph) and dd, 2H, J = 8.6, 14.0 Hz, (HO)(CHa)Hb), 13C NMR (DSMO-d6) δ/ppm: 159.49 (CO), 156.80 (OPhC–4'), 130.97 (OPhC–1'), 127.98 (OPh–2'), 134.83, 132.77, 132.51, 129.77, 127.71, 127.55, 126.23, 126.14, 126.03 and 125.64 (3C and 7CH, 1-naphtyl), 114.59 (OPh–3'), 67.82 (OCH2(Ph)), 62.29 (CH3OH), 53.30 (*CH), 35.35 (*CH2(Ph)).

Compound 4f was analyzed as diacetyl derivative. Anal. Calcd. for C50H48N2O8 (M = 761.836); C 73.62, H 5.95, N 3.48 %. found: C 73.68, H 6.24, N 3.54 %.

(S,S) N,N'-Bis[2-hydroxy-1-{4-(1-naphthylmethoxy)benzyl}ethyl]ethanediamide (4g)

From 2-bromomethylnaphtalene: 73 %; From 4-bromomethylbiphenyl (S,S) N,N' -Bis(2-hydroxy-1-{4-(2-naphtylmethoxy)benzyl}ethyl)ethanediamide (4f)

(S,S) N,N'-Bis[2-hydroxy-1-{4-(1-naphthylmethoxy) benzyl}ethyl]ethanediamide (4f)

From 4-bromomethylbiphenyl: 81 %; Rf ca. 0.45 (CH2Cl2; MeOH 9:1); m.p. 186–188 °C; [α]D20 = –26 (c = 0.5 g/100 ml, THF); IR (KBr) νmax/cm–1: 3387, 3300, 1656, 1613, 1579, 1506; 1H NMR (DSMO-d6) δ/ppm: 8.35 (d, 2H, J = 9.0 Hz, D2O exchangeable, NH), 7.99–7.38 (m, 14H, 1-naphthyl), 7.09 (d, 4H, J = 7.6 Hz, OPh–2'), 6.94 (d, 4H, J = 7.6 Hz, OPh–3'), 5.39 (s, 4H, OCH2(Ph)), 4.86 (br s, 2H, D2O exchangeable, OH), 3.92 (m, 6H, CH2OH), 3.45 (m, 2H, *CH), 2.82 and 2.68 (dd, 2H, J = 5.0, 14.0 Hz, (HO)CH(Ph) and dd, 2H, J = 8.6, 14.0 Hz, (HO)(CHa)Hb), 13C NMR (DSMO-d6) δ/ppm: 159.49 (CO), 156.80 (OPhC–4'), 130.97 (OPhC–1'), 127.98 (OPh–2'), 134.83, 132.77, 132.51, 129.77, 127.71, 127.55, 126.23, 126.14, 126.03 and 125.64 (3C and 7CH, 1-naphtyl), 114.59 (OPh–3'), 67.82 (OCH2(Ph)), 62.29 (CH3OH), 53.30 (*CH), 35.35 (*CH2(Ph)).

Compound 4g was analyzed as diacetyl derivative. Anal. Calcd. for C50H48N2O8 (M = 761.836); C 73.62, H 5.95, N 3.48 %; found: C 73.68, H 6.24, N 3.54 %.

REFERENCES


SAŽETAK

Kiralni bis(tirozinol) i bis(\(p\)-hidroksifenilglicinol) oksalamidni gelatori. Utjecaj aromatičkih skupina i vodikovih veza na svojstva geliranja

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Pripravljeni su enantiomerno čisti \(R,R\)-bis(\(4\)-hidroksifenilglicinol) oksalamidi 3 i \(S,S\)-bis(tirozinol) oksalamidi 4 te su ispitana njihova svojstva geliranja organskih otapala, vode i vodenih smjesa s polarnim organskim otapalima. Nađeno je da su oksalamidni spojevi s fenolnim hidroksilnim skupinama supstituiranim arilom djelotvorni organogelatori jako polarnih sustava otapala dok derivati sa slobodnim fenolnim hidroksilnim skupinama teže kristalizaciji. Ustanovljena razlika u ponašanju objašnjena je na temelju specifičnih vodikovih veza nađenih u kristalnoj strukturi.