Intermolecular central to axial chirality transfer in the self-assembled biphenyl derived bis(amino acid)-oxalamide gelators

Janja Makarević, Zoran Štefanić, Lucija Horvat and Mladen Žinić*

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

General procedure for the preparation of dimethyl esters of 2,2'-biphenyl-oxalylamides 4-7.

To a solution of 2,2'-(3-azidopropyloxy)-biphenyl (1.5 mmol) in MeOH (25 ml), 10% Pd/C (20% w/w) was added and stirred in an H_2 atmosphere at 55 psi for 20 h. The catalyst was filtered off, and the filtrate was evaporated to dryness. The product was dried and used in the next reaction without purification.

To the solution off above diamino product **2** (1.5 mmol) in CH_2Cl_2 (10 ml) selected amino acid oxalamide **3** (3.3 mmol) was added and the reaction mixture was stirred three days at room temperature. The products were purified by preparative TLC (CH_2Cl_2 – MeOH, 200:1.5) to give title product.

Biphenyl-oxalamide **4:** Yield: 70.8%; m.p. 123-124 ^oC; $[\alpha]_D^{RT}$= - 28 (c 1, MeOH- CH_2Cl_2, 9:1); IR (KBr): υ = cm^{-1} 3299, 1748, 1661, 1516; ^1H NMR (300 MHz, $CDCl_3$, δ): 7.93 (2H, d, *J*=8.9, NHLeu), 7.85 (2H, t, *J*=6.1, NHpropyl), 7.30 (2H, dt, *J*=7.8, *J*=1.7, CHbiph), 7.22 (2H, dd, *J*=7.5, *J*=1.7, CHbiph), 7.03 (2H, dt, *J*=7.4; 0.9, CHbiph.), 6.96 (2H, dd, *J*=8.2, *J*=0.9, CHbiph), 4.60 (2H, dt, *J*=8.9, *J*=5.3, CH*), 3.95 (4H, t, *J*=5.8, CH_2Opropyl), 3.72 (6H, s, -OCH_3), 3.20 (4H, q, *J*=6.6, CH_2Npropyl), 1.84 (4H, pent, *J*=6.2, CH_2, propyl), 1.75-1.58 (6H, m, CHγ,Leu and CH_2, β, Leu), 0.94, 0.93 (2x6H, 2d, 2*J*=6.2, CH_3, δ, Leu); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 172.3, 159.9, 159.7, 156.5 (C=O, C(2)biph),, 131.4, 128.9, 121.4, 114.0 (CHbiph), 129.4(Cbiph), 66.7 (CH_2Opropyl), 52.6, 52.2 (CH* and OCH_3), 41.3 (CH_2 , β Leu), 36.8 and 28.9 (CH_2, propyl), 24.9 (CHγ, Leu), 23.0, 21.9 (CH_3 δ, Leu)); HRMS calcd. for $C_{36}H_{50}N_4O_{10}$ [M^+ ,Na^+] 721.3419, found: 721.3411.

Biphenyl-oxalamide **5:** Yield: 70.8 %; m.p. 96-98 ^oC; $[\alpha]_D^{RT}$= - 15 (c1, CH_2Cl_2-MeOH, 9:1); IR (KBr):υ = cm^{-1} 3297, 1742, 1727, 1659, 1519; ^1H NMR (300 MHz, $CDCl_3$, δ): 7.89 (2H, d, *J*=9.4, NHVal), 7.78 (2H, t, *J*=6.1, NHpropyl), 7.31 (2H, dt, *J*=7.8, *J*=1.7, CHbiph), 7.23 (2H, dd, *J*=7.5, *J*=1.7, CHbiph), 7.05 (2H, dt, *J*=7.4; 0.7, CHbiph.), 6.98 (2H, dd, *J*=8.1, *J*=0.6, CHbiph), 4.51 (2H, dd, *J*=9.4, *J*=5.2, CH*), 3.95 (4H, t, *J*=5.8, CH2, propyl), 3.74 (6H, s, -OCH_3), 3.19 (4H, dq, *J*=6.6, *J*=2.0, CH2, propyl), 2.31-2.16 (2H, m, CHβ, Val), 1.83 (4H,

pent, *J*=6.2, CHpropyl) 0.96, 0.94 (2x6H, 2d, 2*J*=6.8, CH_3,γ,Val); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 171.4, 160.0, 159.7 and 156.5 50 (C=O, C(2)biph), 131.4, 129.0, 121.6 and 114.2 (CHbiph), 129.4 (Cbiph), 66.8 (CH_2Opropyl), 57.9 (CH*), 52.4 (OCH_3), 36.7 and 28.8 (CH_2, propyl), 31.4 (CHβ,Val), 19.1, 18.0 (CH_3 γ, Val); HRMS calcd. for $C_{43}H_{46}N_4O_{10}$ [M^+ ,Na+] 693.3106, found: 693.3112.

Biphenyl-oxalamide **6:** Yield: 64%; m.p. 134-135 ^{o}C; $[\alpha]_D^{RT}$= + 18.5 (c1, CH_2Cl_2-MeOH, 9:1); IR (KBr):υ = cm^{-1} 3380, 3290, 1748, 1659; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.96 (2H, d, *J*=8.8, NHPhe), 7.79 (2H, t, *J*=5.9, NHpropyl), 7.35-7.10 (14H, m, CHarom), 7.03 (2H, dt, *J*=7.4; 0.7, CHbiph.), 6.95 (2H, d, *J*=8.1, CHbiph), 4.91-4.81 (2H, m, CH*), 3.91 (4H, t, *J*=5.8, CH_2, propyl), 3.70 (6H, s, OCH_3), 3.22-3.06 (8H, m, CH_2, propyl, CH_2, Phe), 1.80 (4H, pent, *J*=6.1, CH_2, propyl);. ^{13}C NMR (75 MHz, $CDCl_3$, δ):171.0, 159.7, 159.5, 156.6 (C=O, C(2)biph), 135.8 and 129.5 (CHarom), 131.4, 129.4, 128.95, 128. 69, 127.4, 121.6 and 114.2 (Carom), 66.8 (CH_2Opropyl), 53.8 and 52.6 9 (CH*, OCH_3), 38.2, 36.6 and 28.7 (CH_2, propyl and CH_2, β,Phe); HRMS calcd. for $C_{42}H_{46}N_4O_{10}$ [M^+ ,Na^+] 789.3105, found: 789.3098.

Biphenyl-oxalamide **7:** Yield; 70.3%; m.p. 150-12 ^{o}C; $[\alpha]_D^{RT}$= +80.5 (c1, CH_2Cl_2-MeOH, 9:1); IR (KBr):υ =3384, 3278, 3063, 3033, 1748, 1661, 1507 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.41 (2H, d, *J*=7.6, NHPhg), 7.80 (2H, t, *J*=5.9, NHoxal), 7.42-7.31 (10H, m, CHPhg), 7.31-7.18 (4H, m, CHbiph), 7.02 (2H, dt, *J*=7.4, *J*=0.7, CHbiph), 6.93 (2H, *J*=8.2, CHbiph), 5.58 (2H, 2d, *J*=7.9, CH*Phg), 3.90 (4H, t, *J*=5.8, CH_2Npropyl), 3.72 (6H, s, OCH_3), 3.15 (4H, q, *J*=6.4, CH_2,propyl), 1.78 (4H, pent., *J*=6.1, CH_2,propyl); ^{13}C NMR (75 MHz, $CDCl_3$, δ): 170.37, 159.50, 159.44, 156.50 (C=O, C(2)biph), 135.85 (CPhg), 129.47, 129.45 (Cbiph), 131.3, 121.64, 121.60, 114.38, 114.31 (CHbiph), 129.2, 128.9, 127.6 (CHPhg), 66.8 (CH_2N), 56.7 CH*Phg) , 53.1 (OCH_3), 36.6, 28.6 (CH_2, propyl); HRMS calcd. for $C_{40}H_{42}N_4O_{10}$ [M^+ , Na^+] 761.2793, found: 761.2784.

Oxalyl-ether **II**: A solution of **3** (R= i-Bu) (2.020, 8.235 mmol) and ethanolamine (0.750 g 12.279 mmol) in dry CH_2Cl_2 (15 ml) was stirred 20 h at room temperature. The reaction mixture was washed with 1.5 % HCl and 5% $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent was evaporated to give N(2-hidroxyethyl), N'-leucyl methyl ester-oxalamide 1.785 g, 83.3 %. The solution of this product (1.324, 5.087 mmol) and tosyl chloride (1.930 g, 10.123 mmol) in dry pyridine (15 ml) was stirred 4 days at room temperature. The solvent was evaporated and the product was dissolved in CH_2Cl_2 and washed with 1.5 % AcOH and 5% $NaHCO_3$. The organic layer was dried (Na_2SO_4) and the solvent was evaporated. Product was purified by preparative TLC (CH_2Cl_2-EtOH, 100:1.5) to give **II,** 0.587 g, 45.9%; ; ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.86 (2H, s br, NHethyl), 7.76 (2H, d, J=8.9, NHLeu), 4.60 (2H, dt, *J*=5.1, *J*=8.9, CH*), 3.75 (6H, s, OCH_3), 3.70-3.62 (8H, m, CH_2, ethyl), 1.78-1.61 (6H, m, CH_2,β,Leu, CHγ, Leu), 0.95 (12H, d, *J*=6.2, CH_3,δ, Leu) ; ^{13}C NMR (75 MHz, $CDCl_3$, δ):

172.2, 159.8 and 159.4 (C=O), 52.7, 51.4 (CH*, OCH_3), 42.8, 41.7 and 41.5 (CH_2,β,Leu, CH_2,Et), 25.0 (CHγ), 22.9, 21.9 (CH_3,δ, Leu).

2. Gelation experiments

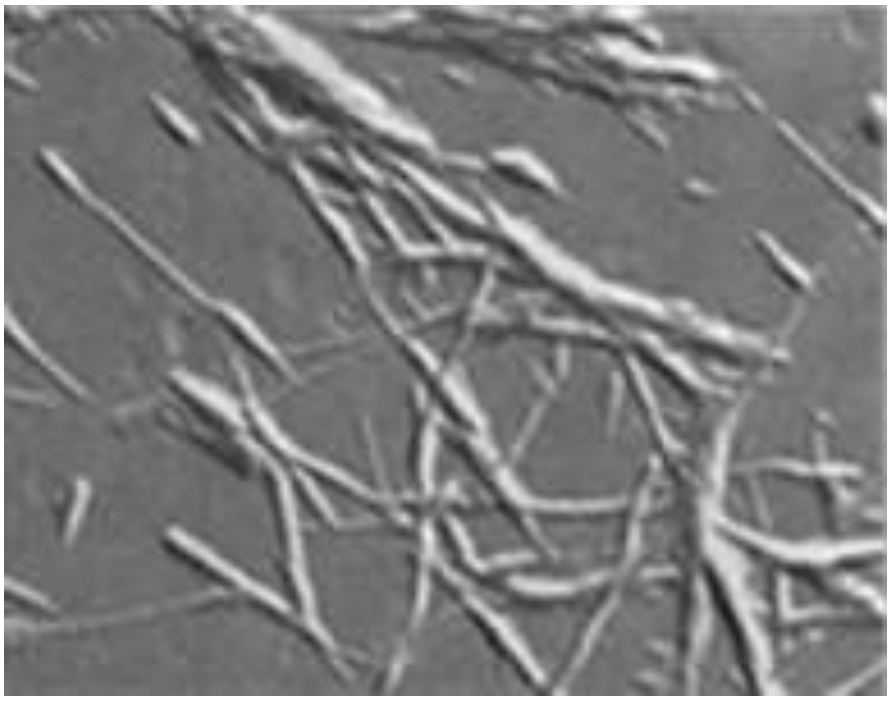
Table 1: Gelator effectiveness (mL of gelled solvent) of biphenyl oxalamides **4** -**7** (10 mg) *****

	4	**5**	**6**	**7**
toluene	gran.	oil	0.05 us	
o-ksilene	0.1 us	0.15 us	gran.	0.1 (1.0 us)
m- xylene	1.0 us	0.1 (0.25 us)	0.1us	0.1 (1.15 us)
p- xylene	1.0 us	0.1 (1.0 us)	gran.	0.1 (1.15 us)
decalin	0.1 (1.55 us)	2.35 us	wax	oil
ethanol	crys.	0.15 (0.25 us)	crys.	gran.
1-propanol	0.05	0.35 (0.55 us)	crys.	crys.
1-butanol	0.4	0.25 (0.9 us)	crys.	crys.
1-pentanol	0.7 (1.8 us)	0.5	crys.	crys.
1-heksanol	1.4 (2.5 us)	0.6 (0.8 us)	crys.	crys.
1-heptanol	1.25 (2.9 us)	0.5 (1.0 us)	crys.	crys.
1-oktanol	6.9 us	0.85	0.5 wax	crys.
±2-oktanol	3.0	0.15 (0.75 us)	crys.	gran.
1-nonanol	3.7 us	0.5 (0.95 us)	0.7 wax	crys.

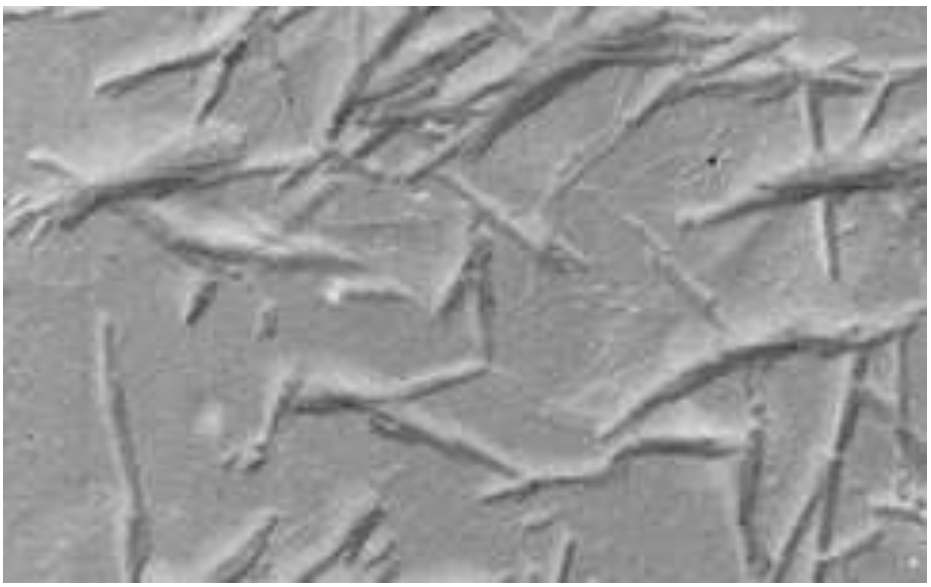
* Nongelling solvents and solvent mixture: H_2O; DMSO/ H_2O; DMF/ H_2O; THF; CH_2Cl_2; CH_3CN; tetralin; Abbreviations: us- ultra sound; crys.- crystallization; gran.-granular gel

3. TEM images

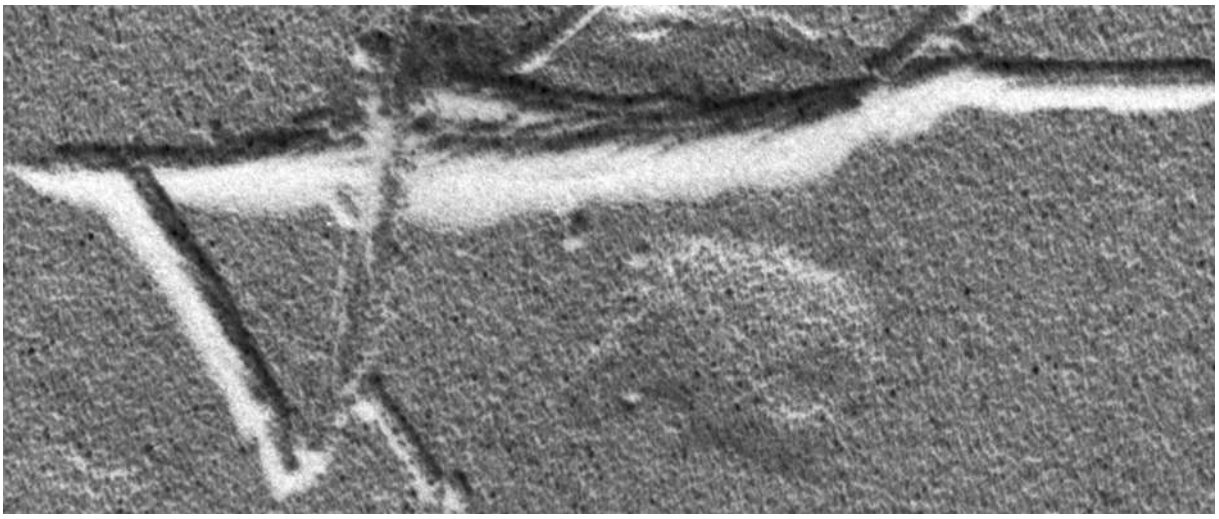
a)



b)



c)



d)

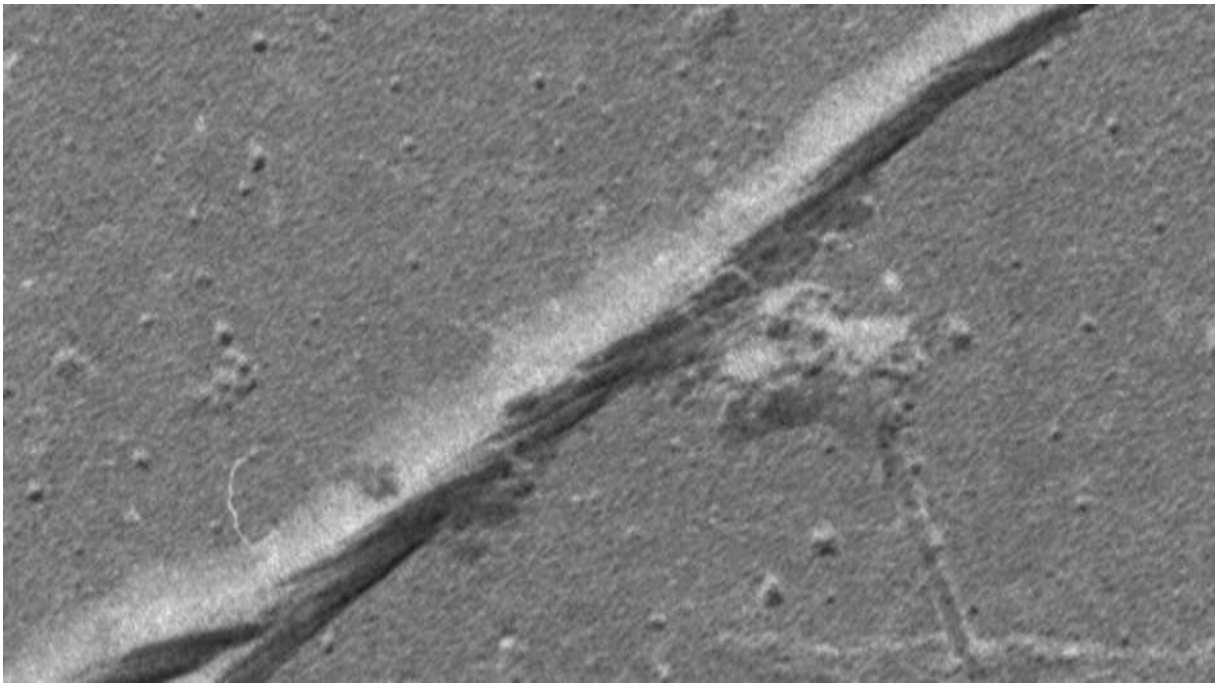


Figure 1 TEM images (Pd shadowed) of (a) (*S*,*S*)-**4** and (b) (*R*,*R*)-**4** 1-octanol gels; (c) and (d) bundles with opposite helicity found in (*S*,*S*)-**4** and (*R*,*R*)-**4** 1-octanol gels, respectively.

4. Electronic absorption, CD, FTIR and ^{1}H-NMR spectra

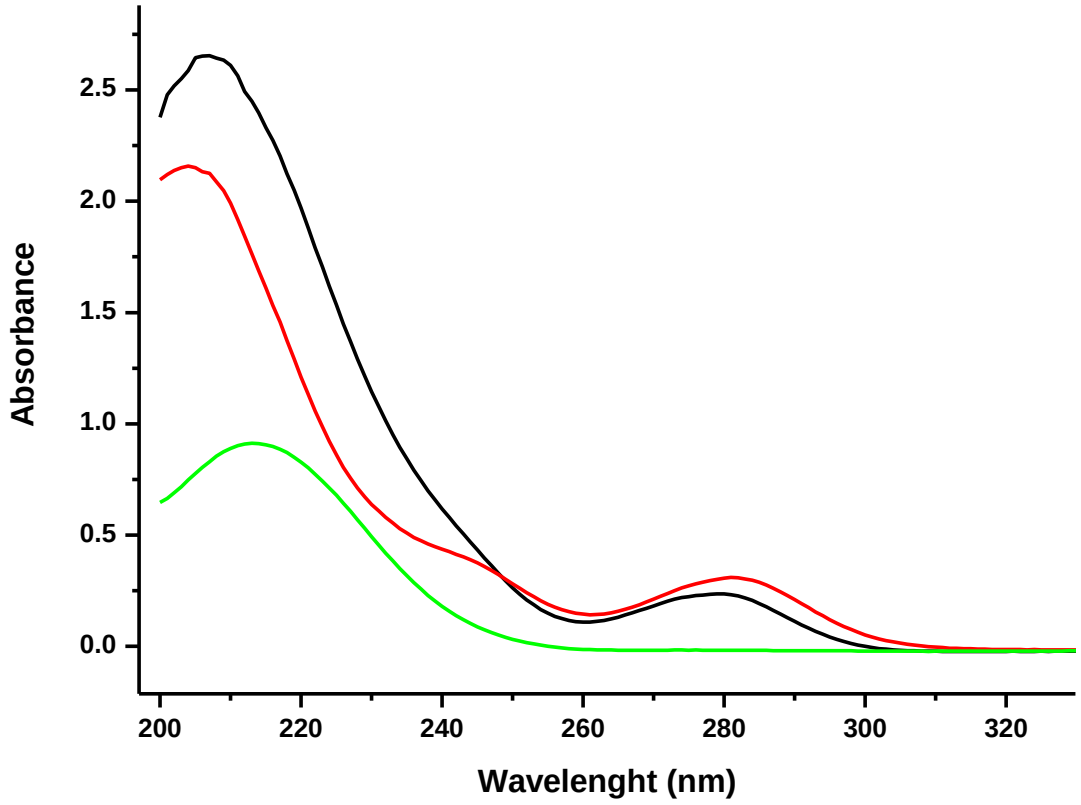
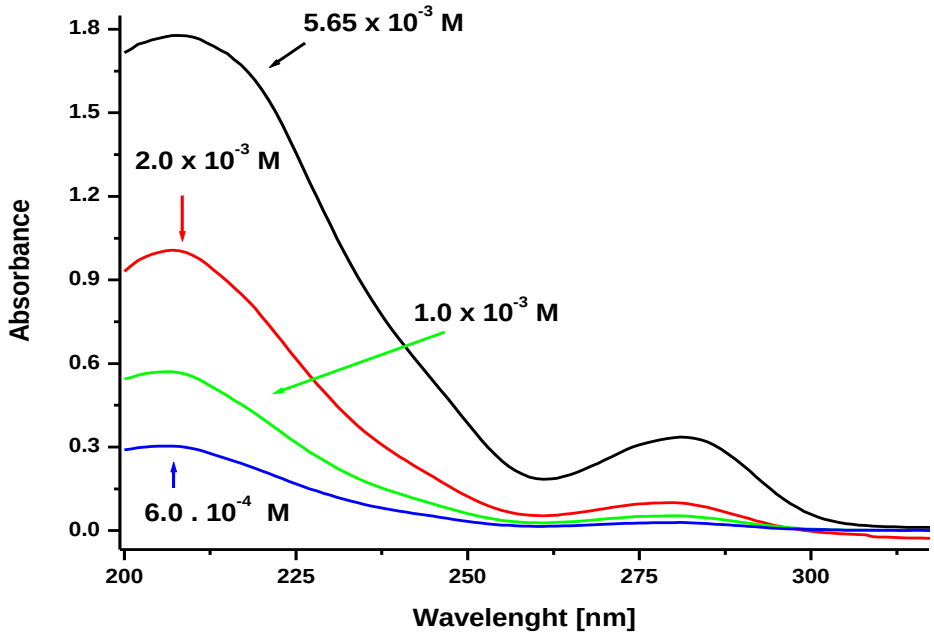


Figure 2 Electronic absorption spectra of (*S*,*S*)-**4** 1-octanol gel (black, c = 5.0 x 10^{-4} M), 2,2-diethoxybiphenyl **I** (red, c = 5.7 x 10^{-4} M) and dioxalamide derivative **II** (green, c = 5.0 x 10^{-4} M).

(a)



(b)

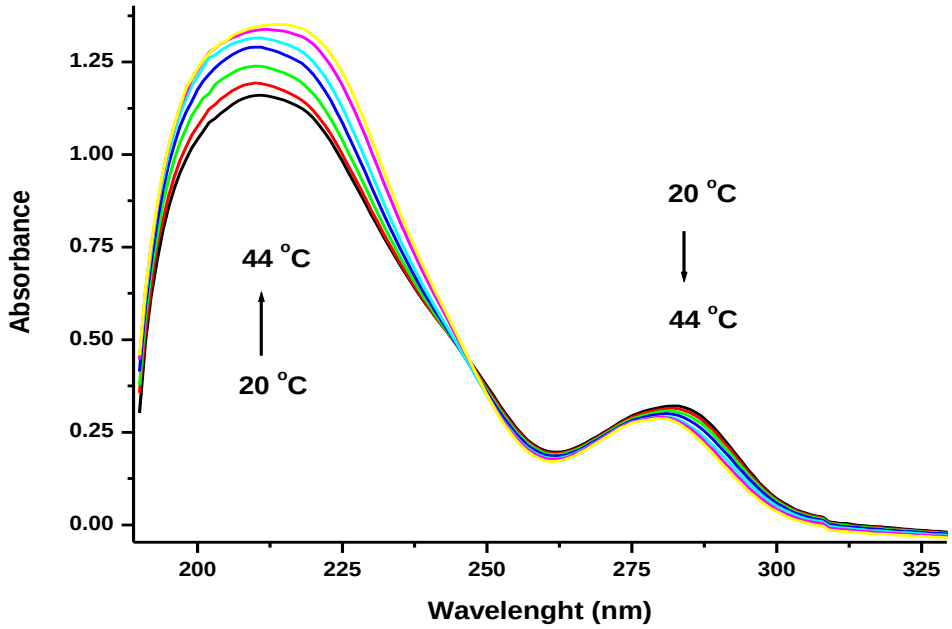
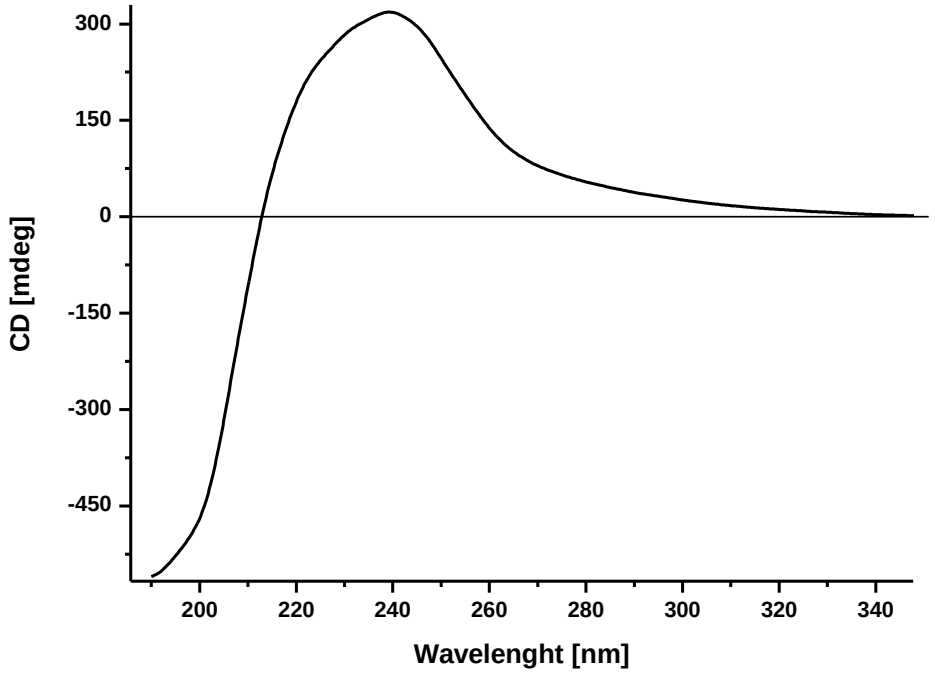


Figure 3 Concentration (a) and temperature (b) dependent UV spectra of **(*S*,*S*)-4** in 1-octanol.

a)



b)

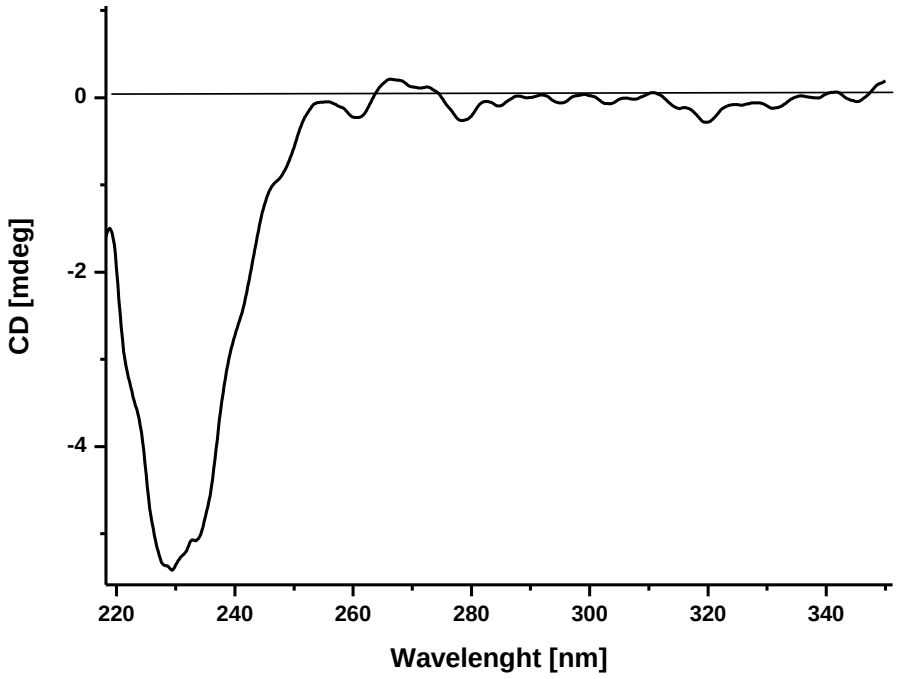


Figure 4 (a) Positive differential scattering effect at 240 nm in the CD spectrum of LeuMeO-oxalamide **II**) decaline gel (c = 8.1 x 10^{-3} M; (b) CD spectrum of (*S*,*S*)-**4** ethanol solution.

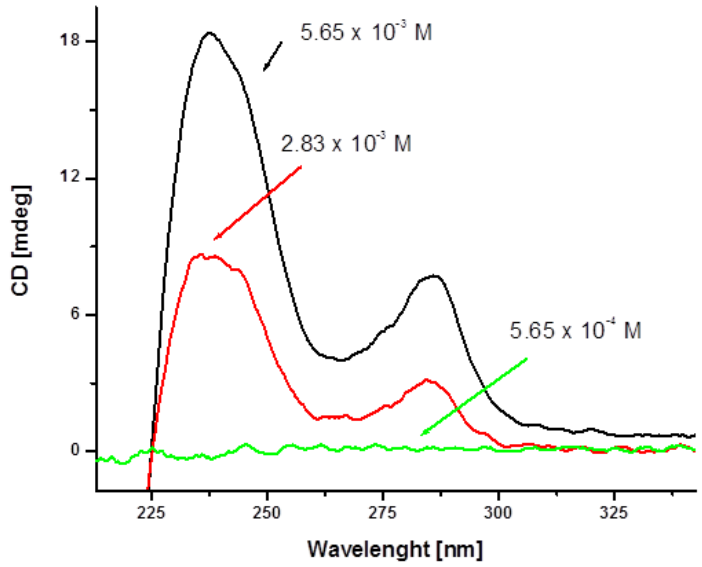


Figure 5 Concentration dependent CD spectra (225 -325 nm region) of (*S,S*)-**4** in 1-octanol-gel. *MGC* (minimal gelation concentration) is 2.0 x 10^{-3}.

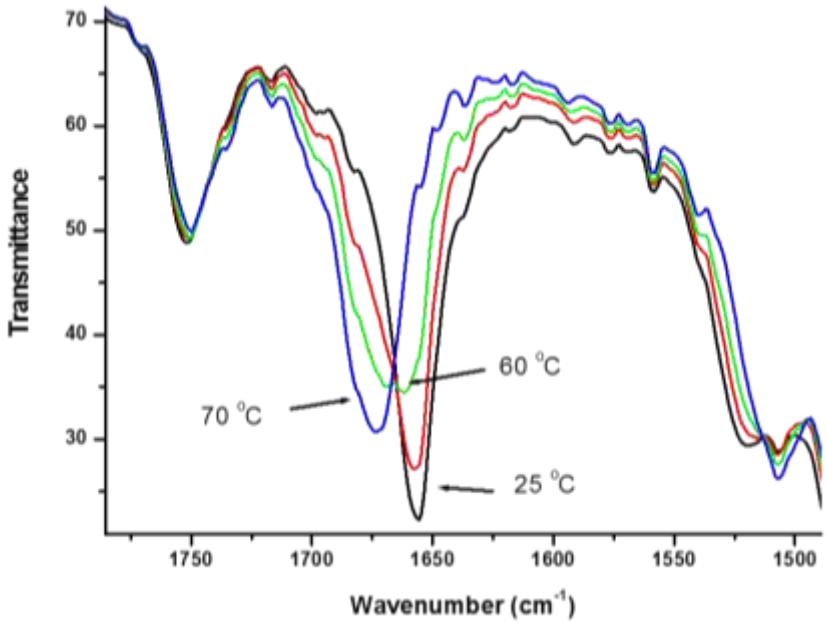


Figure 6 Temperature dependent FTIR spectra (amide I region) of (*S,S*)-**4** (c = 4.2 x 10^{-2} M) 1-octanol gel showing shifts of amide I band toward higher wave numbers with temperature increase due to disaggregation of the oxalamide- oxalamide hydrogen bonded gelator molecules.

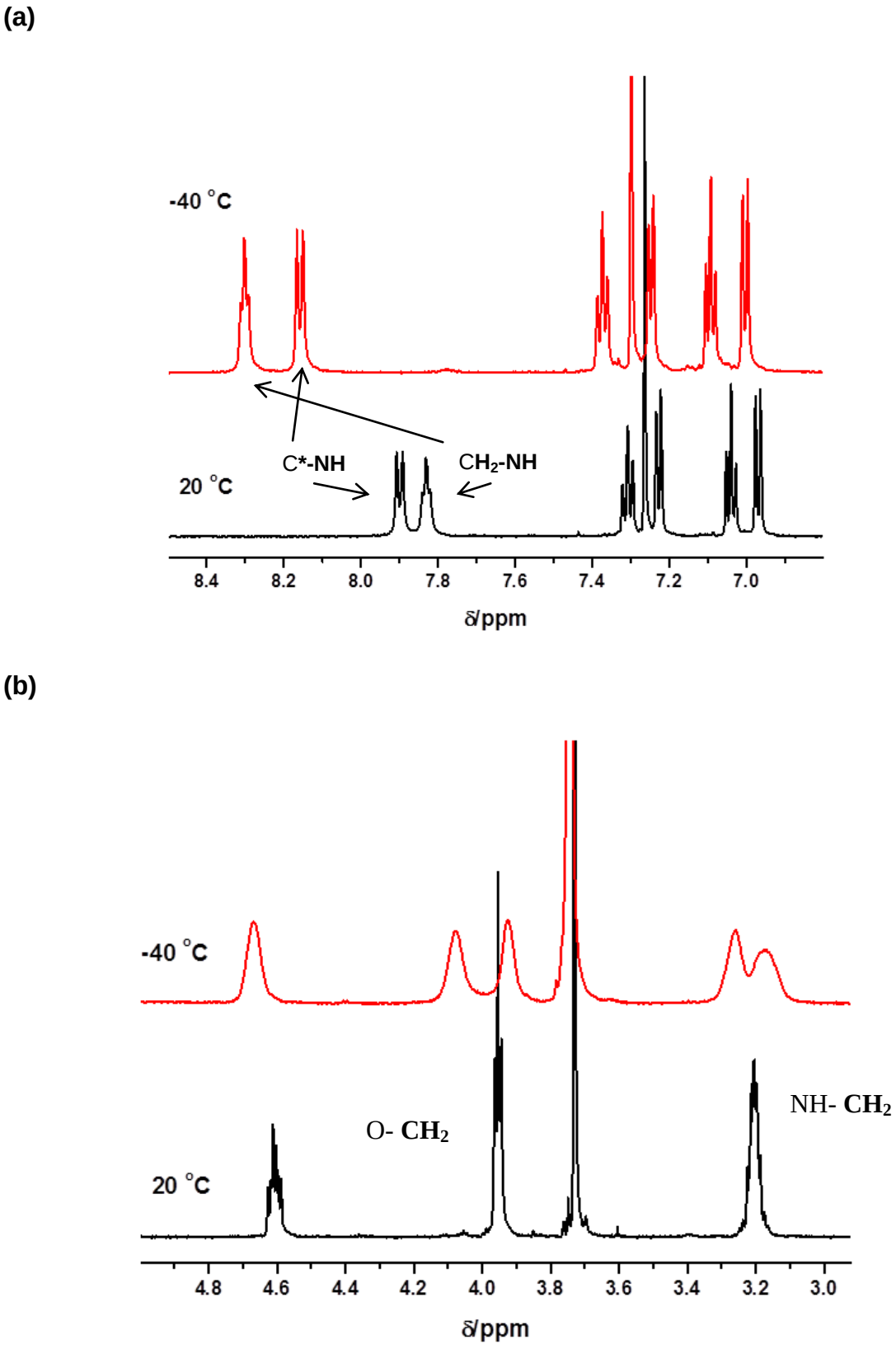


Figure 7 ^{1}H-NMR spectra of (*S*,*S*)-**4** taken in $CDCl_3$ at 20 and -40 ^{o}C. (a) Downfield shifts of oxalamide NH signals at -40 ^{o}C (red). (b) Splitting of NH- **CH_2** (δ 3.2 ppm, at 20 ^{o}C) and O- **CH_2** (δ 3.9 ppm, at 20 ^{o}C) resonances at -40 ^{o}C (red).

5. X-ray Crystallographic Analysis

Masurement

Single crystal X-ray diffraction data of the crystals were collected on Agilent Xcalibur Nova single crystall diffractometer with micro focus X-ray tube and Ruby CCD detector using CuKα (λ = 1.5418 Å) radiation. The crystal structure was solved by direct methods using SHELXS-97 and refined by full-matrix least-squares SHELXL-97.[1] All non-hydrogen atoms were refined anisotropically and hydrogen atoms were included as their calculated positions.

(1) Sheldrick, G. M. (2008). *Acta Cryst.* **A64**, 112-122.

Crystal data for *rac*.-4

$C_{36}H_{50}N_4O_{10}$, M = 698.80, monoclinic, a = 14.7898 (17), b = 33.377 (3), c = 10.1506 (12) Å, β = 123.924 (17)°, V = 4157.8 (8) Å3, T = 293 K, space group $C2/c$, Z = 4, 8062 reflections measured, 2265 unique (Rint = 0.050), 1472 reflections with $I > 2\sigma(I)$. PLATON-SQUEEZE[2] routine was used to eliminate the contribution of disordered solvent. The final R_1 and wR_2 after modifying 0.056 and 0.138 for ($I > 2\sigma(I)$), 0.093 and 0.158 (all data). **CCDC-871767**.

(2) Spek, A.L. (2009). *Acta Cryst.* **D65**, 148-155.

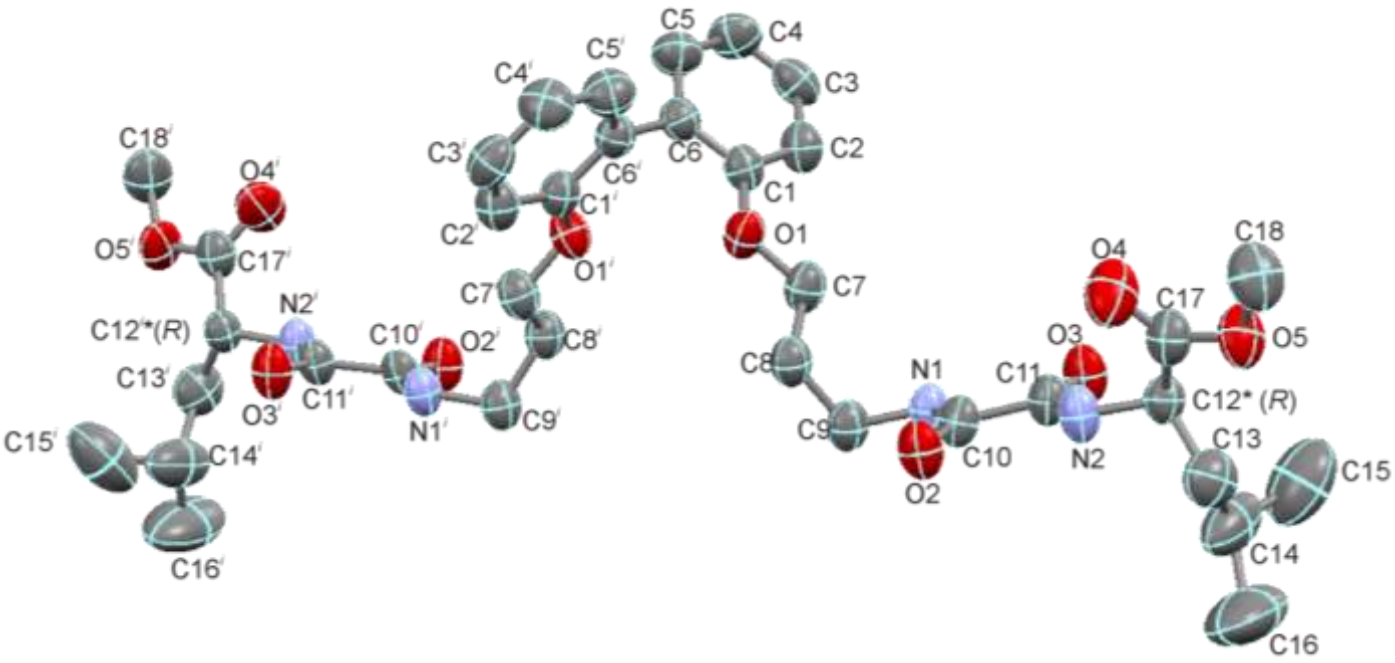


Figure 8. Thermal ellipsoid model of rac.-**4**. The molecule lies on the twofold symmetry axis in the space group $C2/c$ and the atoms generated by this symmetry operation ($-x$, y,½ $-z$) are denoted by superscript i. Atoms C12 and C12^i are of R chirality. The ellipsoids of non-hydrogen atoms are drawn at the 50 % probability level.

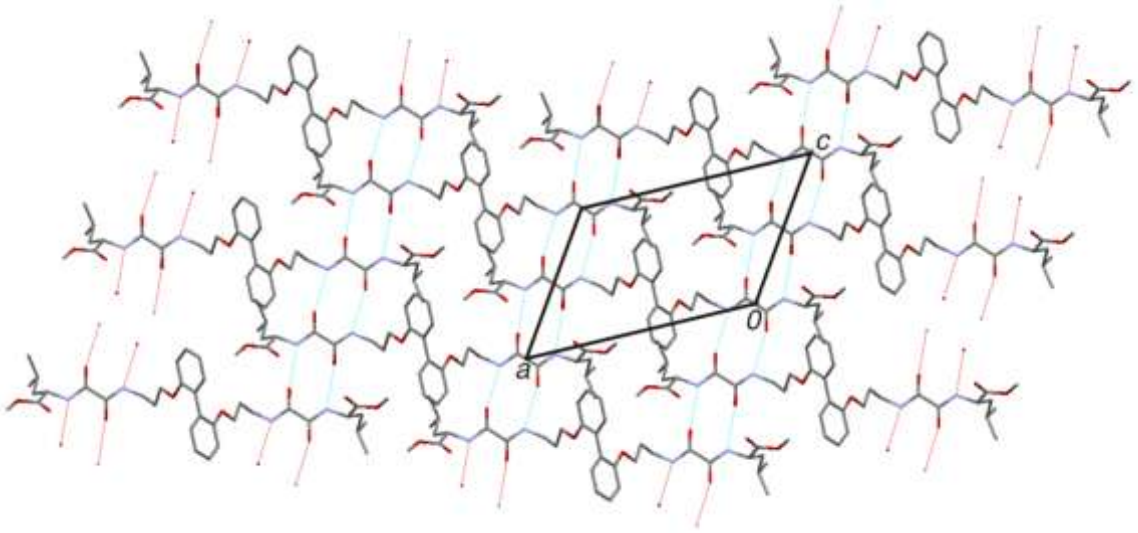


Figure 9. The view down the crystallographic *b* axis in the crystal structure of *rac*.-**4** reveals the formation of two-dimnesional hydrogen bonded network composed entirely of molecules of the single chirality. The hydrogen bonds are formed between the oxalamide units and each molecule makes contact with four neighbouring molecules.

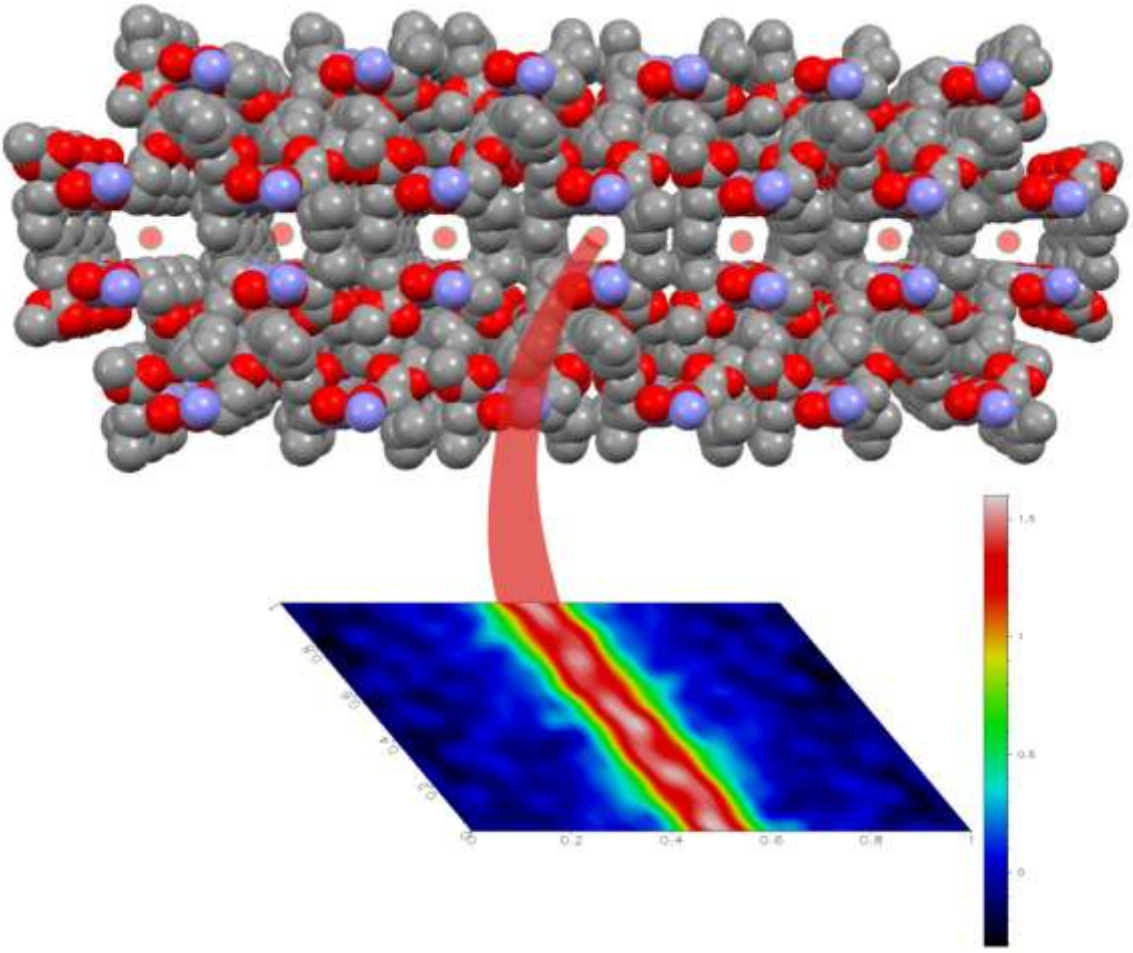


Figure 10. At the top the space-filling representation of the packing in the structure of *rac*.-**4** is shown. The red dots denote the centres of channels occupied presumably by disordered solvent molecules. At the bottom the cross section (*x*, ½, *z*) through *Fo*-*Fc* map of electron density is depicted. Almost constant electron density running along *c* axis is visible.

6. Molecular modelling

Sybyl of Tripos Inc. molecular modelling software was used. The (*S*,*aR*,*S*)-**4** conformation similar to that of (*S*,*aS*,*S*)-**4** as found in the crystal structure of *rac*.-**4** was generated by inverting axial chirality of the biphenyl. Then oxalamide-oxalamide hydrogen bonded (*S*,*aR*,*S*)-**4** dimer was generated by docking procedure preserving the same distance of NH…O=C< hydrogen bonds as found in the (*S*,*aS*,*S*)-**4** crystal structure dimer. The comparison of (*S*,*aS*,*S*)-**4** dimer and generated (*S*,*aR*,*S*)-**4** dimer shows steric repulsion between one phenyl and Leu methyl ester group in the latter one which is clearly absent in the former. The results suggest that formation of (*S*,*aR*,*S*)-**4** aggregates of similar structure to those of (*S*,*aS*,*S*)-**4** is less favoured due to steric repulsion between (*aR*)-biphenyl and Leu methyl ester groups.