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Intermolecular central to axial chirality transfer in the self-assembled biphenyl containing amino acid–oxalamide gelators†

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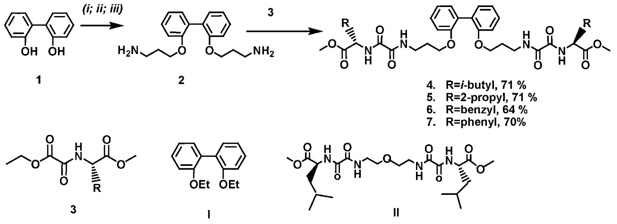
Chiral amino acid and biphenyl incorporating oxalamide gelators 4–7 with large, 9 bond distance between chiral centres and biphenyl units have been studied. CD investigation of 4-octanol gel and the crystal structure of *rac*-4 reveal that efficient central to axial chirality transfer occurs by intermolecular interactions in gel and solid state assemblies.

Chirality has a profound influence on gelation of various liquids by chiral low molecular weight organic molecules.[1] For example, the racemic forms are generally weaker gelators than the corresponding pure enantiomers although the exceptions are also known.[2] Importantly, it was shown that in gels as well as in other kinds of supramolecular polymers the efficient chirality transfer from the molecular to the supramolecular level may occur by the self-assembly of chiral monomers into helical aggregates.[3] Aggeli and Meijer have shown that in gels such chirality transfer occurs by a multistep hierarchical pathway.[4]

The majority of chiral gelators studied to date possess central chirality while axially chiral gelators are rare.[5,6] To the best of our knowledge, gelators combining central and axial chirality in the same molecule were not studied to date. Here, we report on the investigation of oxalamide gelators **4–7** (Scheme 1) containing a conformationally flexible proatropoisomeric 2,2′-biphenyl unit at large, 9 bond distance to amino acid chiral centres in the 2,2′-arms. It is well known that the intramolecular central to axial chirality transfer occurs in cyclic and acyclic 2,2′-disubstituted biphenyls possessing short, usually 3–4 bond distance between chiral centres and biphenyl units.[7] We provide the circular dichroism (CD) and crystal structure evidence that central to axial chirality transfer occurs in the (*S*,*S*)-**4** or (*R*,*R*)-**4** gel and solid state aggregates despite the large intramolecular distance between biphenyl units and chiral centres. We also show that in the latter systems the chirality transfer is enabled by the self-assembly and that it occurs through intermolecular interactions in the aggregates with chiral centres and biphenyl units of neighbouring molecules located in the close proximity.



Scheme 1 Synthesis and yields of gelators **4–7**: (i) $BrCH_2CH_2CH_2Br$, base; (ii) NaN_3; (iii) H_2, 10% Pd/C. Structures of model biphenyl (**I**) and bis(LeuOMe) dioxalamide (**II**) derivatives.

Gelators **4–7** have been synthesized starting from 2,2′-dihydroxybiphenyl **1** which in reaction with 1,3-dibromopropylene and subsequent reaction with sodium azide and hydrogenation gave the 2,2′-di(*O*-propylamine)-biphenyl, **2**. Reaction of ethyl chloroformate with methyl ester of selected amino acid gave the ethyl formamide **3** which in reaction with **2** gave derivatives **4–7** (Scheme 1, ESI†, synthetic procedures).

Gelation tests revealed moderate gelling properties of Val and Leu derivatives **4** and **5** while **6** and **7** containing aromatic amino acids Phe and Phg (phenyl glycine) showed poor gelation of the tested solvents (ESI†, Table S1). The former showed moderate gelation of aromatic solvents and a series of *n*-alcohols with and without application of ultrasound. The application of sonication is reported to increase gelling ability in some cases most probably by destructing non-productive gelator aggregation and enabling productive assembly into fibrous aggregates.[8] In our case the use of ultrasound resulted in higher gelation efficiency reflected in the larger volume of solvent gelled per weight of the gelator. TEM investigation of the gels formed by (*S*,*S*)-**4** and its enantiomer (*R*,*R*)-**4** with 1-octanol shows the presence of fiber bundles composed of thinner fibers of 15–25 nm diameters. Closer examination of TEM images revealed that the bundles present in (*S*,*S*)-**4** and (*R*,*R*)-**4** gels possess left and right helicity, respectively (ESI†, Fig. S1a–d).

The observed CD spectrum of (*S*,*S*)-**4** 1-octanol gel shows the presence of a positive Cotton effect at 281 nm (Fig. 2a) corresponding to a biphenyl absorption band (ESI†, Fig. S2, electronic absorption spectra of (*S*,*S*)-**4** 1-octanol gel, and ethanol solutions of **I** and **II**). A positive CD signal at 241 nm corresponds to the shoulder at the close wavelength appearing in the absorption spectra of (*S*,*S*)-**4** and 2,2′-diethoxybiphenyl derivative **I** (ESI†, Fig. S2.). The latter absorption could be ascribed to the

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biphenyl A band appearing between 240 and 250 nm.[9] It is well documented that the sign of the Cotton effect corresponding to the biphenyl A band is related to the twist of the biphenyl system: the positive effect corresponds to *M* twist and the negative one to *P* twist of biphenyl.[10,11] However, in the gel CD spectra of some dioxalamide gelators lacking any biphenyl group a strong positive signal close to 240 nm possessing a characteristic tail could be observed (ESI†, Fig. S3a). The latter may originate from the circular differential scattering effect which is also observed in the CD spectra of macromolecules with sizes larger than $\lambda/20$ nm.[12] Hence, a strong positive signal at 241 nm in the CD spectrum of (*S*,*S*)-**4** 1-octanol gel may be the consequence of the differential scattering effect. Recent experimental and theoretical study of chiral 2,2′-(2-butoxy)-biphenyls showed the appearance of a positive–negative–positive sequence of Cotton effects at around 280, 240 and 210 nm, respectively, for the (*aS*)-biphenyl atropisomer and the opposite sequence for the (*aR*)-isomer.[13] Based on the presence of the positive Cotton effect at 281 nm in the CD spectrum of (*S*,*S*)-**4** 1-octanol gel (Fig. 1a) the (*aS*)-configuration could be ascribed to the biphenyl of assembled gelator molecules; the expected negative ($\sim$240 nm) and positive ($\sim$210 nm) Cotton effects of (*aS*)-biphenyl are masked by strong differential scattering of opposite sign at 240 nm and the opposite signed strong effect at 212 nm (Fig. 1a) corresponding to overlapped electronic absorptions of biphenyl (208 nm) and oxalamide (212 nm) (ESI†, Fig. S2).[14] In the CD spectrum of (*S*,*S*)-**4** ethanol solution (ESI†, Fig. S3b) the positive signals at 241 and 281 nm observed in the gel spectrum are absent. This together with the observed increase of the CD signals with increasing (*S*,*S*)-**4** concentration (ESI†, Fig. S4) and their decrease with increasing temperature (Fig. 1a) points to their aggregation origin. CD spectra of (*S*,*S*)-**4** and (*R*,*R*)-**4** 1-octanol gels (Fig. 1b) are in the mirror image relationship showing that for the gelators of opposite central chirality also the opposite axial chirality of biphenyl units is induced by gelation. The latter results taken together consistently support the conclusion that central to axial chirality transfer is the consequence of gelator self-assembly.

Temperature dependent FTIR and ^{1}H-NMR investigations of (*S*,*S*)-**4** 1-octanol gel and its $CDCl_3$ solution show strong tendency of intermolecular hydrogen bonding by oxalamide units in both systems (ESI†, Fig. S5 and S6a). In the ^{1}H-NMR spectrum at -40 °C the appearance of doubled CH_2–O and CH_2N methylene resonances is in accord with formation and slow interconversion of (*S*,*aS*,*S*)- and (*S*,*aR*,*S*)-**4** diastereoisomers (ESI†, Fig. S6b).

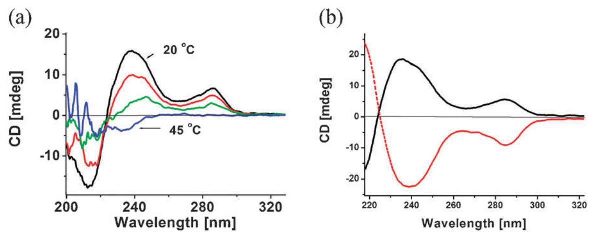

Fig. 1 (a) Temperature dependent CD spectra of (*S*,*S*)-**4** 1-octanol gel (temp. range 20–45 °C) and (b) the mirror image relationship of (*S*,*S*)-**4** and (*R*,*R*)-**4** 1-octanol gel CD spectra.

Crystal structure of *rac*-**4** crystallized from the DMF : dichloromethane 5 : 1 mixture provides the evidence of central to axial chirality transfer that occurred also in the solid state. The structure is composed of the homochiral (*S*,*aS*,*S*)-**4** and (*R*,*aR*,*R*)-**4** bands assembled by hydrogen bonds between oxalamide units in the direction of *c* axes (Fig. 2 and ESI†, Fig. S7–S9). Formation of separated homo-chiral bands represents the example of the self-sorting process during the crystallization.[1a,15] It starts with the fast interconverting (*S*,*aS*,*S*)-, (*S*,*aR*,*S*)- and (*R*,*aR*,*R*)-, (*R*,*aS*,*S*)-diastereoisomeric pairs in the solution followed by the selection and co-crystallization of (*S*,*aS*,*S*)- and (*R*,*aR*,*R*)-enantiomers assembled into homochiral bands. In the latter process the (*S*,*S*)- and (*R*,*R*)-configurations of chiral centres are transcribed into (*aS*)- and (*aR*)-configurations of biphenyls, respectively, as in the case of gelation. Hence, a similar type of self-assembly and diastereomeric self-sorting are likely to occur in the gel and in the solid state.

The analysis of the (*S*,*aS*,*S*)-**4** hydrogen bonded dimer found in the crystal structure of *rac*-**4** explains the origin of chirality transfer in the assembled molecules. In accord with other crystal structures of bis(amino acid or amino alcohol) oxalamide gelators[16] in the Leu-oxalamide fragment the M (medium; methyl ester) and L (large; *i*Bu) groups are oriented above and below the oxalamide plane with the S (small; H) group being close to the *syn*-periplanar position to the oxalamide carbonyl group (Fig. 3, inset). In the dimer, the chiral centre of the first molecule comes in the close proximity of the biphenyl unit of the second one (Fig. 3). In the (*S*,*aS*,*S*)-**4** dimer the (*aS*)-biphenyl configuration allows accommodation of the M group (Fig. 3a) while the (*aR*)-biphenyl configuration of the (*S*,*aR*,*S*)-**4** dimer prevents it (Fig. 3b). The latter provides plausible rationale for the observed self-sorting processes in gelation and crystallization of the racemate.

The amino acid derived oxalamide gelators **4–7** incorporating 2,2′-substituted proatropoisomeric biphenyl are good gelators of aromatic solvents and various alcohols. Efficient central to axial chirality transfer was observed for such molecules when assembled in gel or solid state aggregates. In contrast to molecular systems where a short 3–4 bond intramolecular distance between chiral centres and biphenyl units is critical for chirality transfer to occur here we show that for the self-assembled enantiomers of **4** it occurs despite the large, 9 bond intramolecular distance between biphenyl and chiral centres. Crystal structure of *rac*-**4** reveals that chirality transfer may occur by intermolecular interactions between chiral centres and biphenyl located in the close spatial proximity in

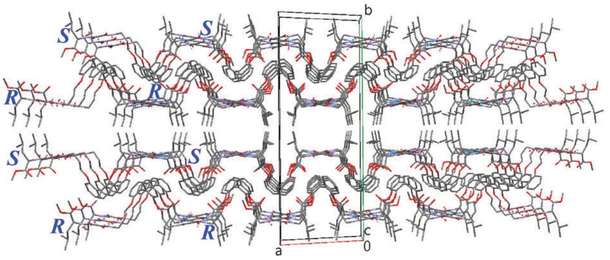

Fig. 2 Crystal structure of *rac*-**4** (hydrogens omitted for clarity) showing stacked corrugated bilayers of molecules of single chirality along the crystallographic *c* axis.

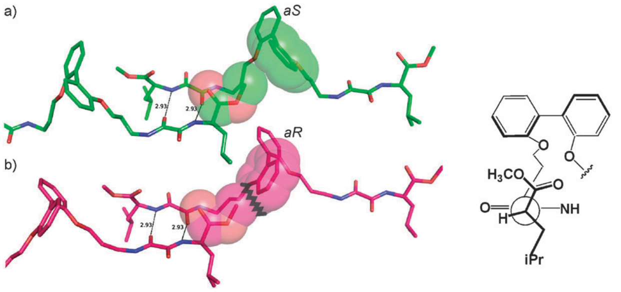

Fig. 3 Diastereoisomeric (a) (*S*,*aS*,*S*)-**4** (green) and (b) (*S*,*aR*,*S*)-**4** (red) dimers showing sterically favourable (a) and sterically unfavourable (b) biphenyl-methyl ester group interactions. Inset: conformation of the LeuOMe fragment.

the aggregates. The presented results could be of interest in design of novel chirality controlled self-assembled systems possessing axial chirality in the aggregated state and lacking it in the disaggregated one. Such systems may find application in the materials and biological sciences and technologies.

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