ChemComm

This article is part of the

Chirality
web themed issue

Guest editors: David Amabilino and Eiji Yashima

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COMMUNICATION

Giving substance to the *Losanitsch* series†‡

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A series of oligoparaxylene model compounds with two to six paraxylene units was synthesised and the resulting mixtures of atropisomers with one to five axes of chirality were analysed by dynamic ^{1}H NMR spectroscopy. The number of atropisomers was found to constitute part of the *Losanitsch* series.

A molecule containing more than one chiral element leads to the existence of a number of possible isomers which is not always trivial to deduce. When the chiral elements are associated with a constitutionally unsymmetrical compound, the number of isomers A as a function of chiral elements n is

$$A = 2^n. \qquad (1)$$

When the chiral elements are located in a symmetrical linear manner in the molecule, however, the number of isomers is not so simple to deduce because of the possibility of *meso* compounds, that is, achiral isomers which are superimposable on their mirror images. This problem in the mathematical sciences is often referred to[1] as "beads on a string" and is described as the number of possibilities associated with arranging black or white beads on a string. There are, for example, three possibilities arranging two black or white beads on a string, black-black, white-white, and black-white, which is the same as white-black. This same problem is transferred to many areas of stereochemistry[2] such as in carbohydrates,[3] mechanically interlocked molecules,[4] and atropisomers,[5] to name but a few, where the presence of multiple chiral centres, axes, and planes leads to a complex mixture of isomers, complicating the characterisation of such compounds. Identifying a formula describing the number of isomers as a function of the chiral elements is central to overcoming the challenging characterisation and analysis. It is not trivial, however, because one has to differentiate whether there are odd or even numbers of chiral elements. In the case of compounds containing chiral axes, only an even number of axes of chirality leads to the existence of *meso* compounds.

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† This article is part of the *ChemComm* 'Chirality' web themed issue.
‡ Electronic supplementary information (ESI) available: experimental details, variable temperature ^{1}H NMR spectra of the mixtures and structural details of the 10 individual isomers of the **5-mers** and the 20 isomers of the **6-mers**. See DOI: 10.1039/c2cc17734j

Losanitsch investigated this problem as early as in the end of the 19th century while he was analysing isomers of paraffins[6] and establishing the *Losanitsch* series (2, 3, 6, 10, 20, 36, 72, 136, 272...). The series can be described using the following formula[1b] with A being the number of isomers, n being the number of chiral elements, and [·] being the *Gauss* bracket§ where $[(n + 1)/2]$ is the largest integer not greater than $(n + 1)/2$:

$$A = 2^{n-1} + 2^{[(n + 1)/2]-1} \qquad (2)$$

In order to give expression to the *Losanitsch* series, we have designed and synthesised a series of model compounds containing one to five chiral elements. Several design criteria were taken into account to provide a system which exists as an equilibrating mixture of isomers and which is synthetically accessible. For the chiral elements we decided to choose axes of chirality,[7] since the formation of one compound leads after equilibration to a mixture of all possible isomers. Oligoparaxylenes (OPXs)[8] are ideally suited for this task. The steric hindrance between the *ortho*-methyl groups on each biphenyl subunit renders the planar conformation of the molecule a high energy state and results in a twist between the planes of adjacent phenylene units. As a consequence, nonplanar isomers are generated with chiral axes whose helical sense is maintained as a result of hindered rotation about the single aryl–aryl bonds. The linear arrangement of modules with chiral axes leads to the formation of atropisomers with barriers to rotation[9] of about 18 kcal mol^{-1} which are ideal $\Delta G^{\neq}$ values for the targeted experiments because they are low enough to permit isomerisation and equilibration, yet high enough to be probed on the ^{1}H NMR time-scale. Furthermore the methyl groups in the OPXs are ideal ^{1}H NMR probes of the stereochemistry. Compounds **2-mer**–**6-mer** (Fig. 1) were synthesised employing transition metal catalysed *Suzuki–Miyaura*[10] cross-coupling reactions (see the ESI for details‡).
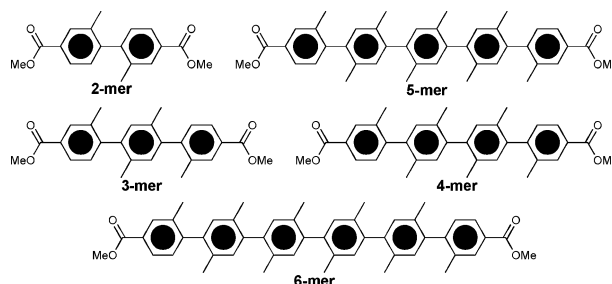

Fig. 1 Model compounds **2-mer**–**6-mer** containing one to five chiral axes.
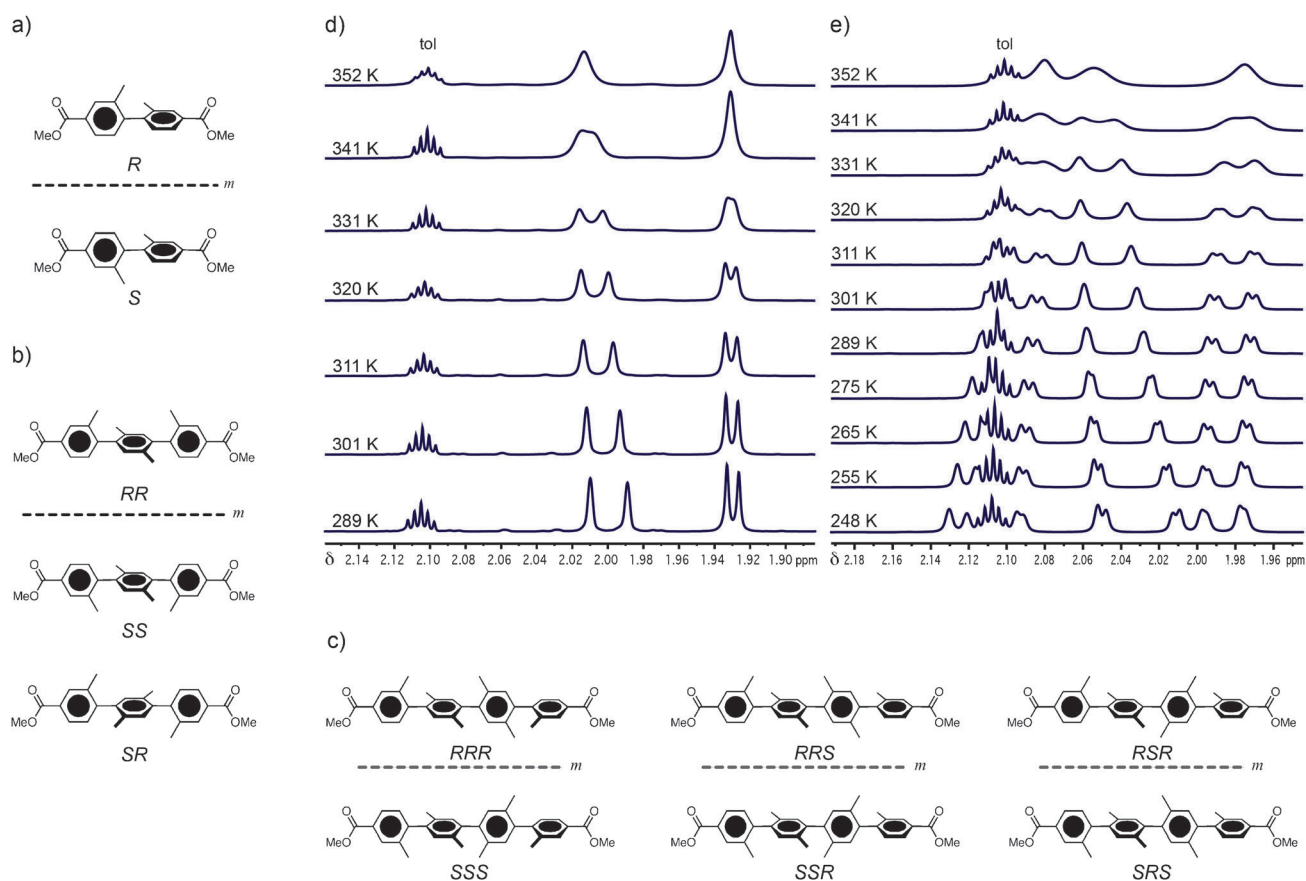
Fig. 2 (a) (*R*)-**2-Mer** and its mirror image (*S*)-**2-mer**. (b) (*RR*)-**3-Mer**, its enantiomer (*SS*)-**3-mer** and the *meso* compound (*RS*)-**3-mer**. (c) The **4-mer** with its three axes of chirality leads to three pairs of enantiomers, namely (*RRR*)-**4-mer**/(*SSS*)-**4-mer**, (*RSR*)-**4-mer**/(*SRS*)-**4-mer**, and (*RRS*)-**4-mer**/(*SSR*)-**4-mer**. VT NMR experiments of **3-mer** (d) and **4-mer** (e) in deuterated toluene (C_7D_8) revealing four anisochronous methyl peaks in the case of the **3-mer** and 12 in the case of the **4-mer** at low temperatures.

In order to investigate the different isomers generated by multiple axes of chirality (Table 1), variable temperature (VT) NMR spectroscopy¶ was performed over a range of temperatures from 360 K down to 240 K. Deuterated toluene (C_7D_8) as the solvent was found to afford the best resolution between signals for the probe methyl group protons in the different isomers. All ^{1}H NMR spectra were recorded – after the samples had been allowed to stand in the NMR probe to equilibrate at selected temperatures for 15 min – in C_7D_8 at 10 degree intervals.

As the simplest member in the series of model compounds, the **2-mer** consists (Fig. 2a) of two paraxylene units and one chiral axis, leading to two enantiomers, namely (*R*)-**2-mer** and (*S*)-**2-mer**. As a consequence of the C_2 symmetry present in both the (*R*)- and (*S*)-isomers, both methyl groups are homotopic by internal comparison and equivalent by external comparison, resulting in only one (isochronous) methyl resonance being observed in the ^{1}H NMR spectrum of the racemic modification.

Adding a second axis of chirality as in the **3-mer** leads to the existence of three isomers (Fig. 2b), namely (*RR*)-, (*SS*)- and (*RS*)-**3-mer**. The two enantiomers (*RR*)- and (*SS*)-**3-mer** have C_2 symmetry and are chiral. The *meso*-isomer (*RS*)-**3-mer** has reflection symmetry (C_i) and is achiral. While the enantiomers (*RR*)/(*SS*)-**3-mer** behave as one compound in the ^{1}H NMR spectrum, they are diastereoisomeric with the *meso*-isomer (*RS*)-**3-mer**. Overall, in the case of the **3-mer**, two compounds

can be identified in a mixture (and equilibrating) in C_7D_8 during VT ^{1}H NMR spectroscopy (Fig. 2d) at lower temperatures. Following coalescence at higher (~340 K) temperatures, two broad resonances for the constitutionally heterotopic methyl group protons are observed at 352 K, both of which subsequently separate out, giving a total of four equal intensity anisochronous signals for the two homotopic pairs in the enantiomers and the two enantiotopic pairs in the *meso*-isomer.

Composed of four torsionally hindered paraxylene units, the **4-mer** has three axes of chirality, leading to the existence of six isomers – namely, three pairs of enantiomers, (*RRR*)-**4-mer**/(*SSS*)-**4-mer**, (*RRS*)-**4-mer**/(*SSR*)-**4-mer**, and (*RSR*)-**4-mer** and (*SRS*)-**4-mer**. The four conformational symmetrical (C_2) isomers, namely the (*RRR*)-, (*SSS*)-, (*RSR*)- and (*SRS*)-isomers all contain three enantiotopic pairs of constitutionally heterotopic methyl groups giving rise to three anisochronous signals in the low temperature ^{1}H NMR spectrum for each enantiomeric pair, *i.e.*, six resonances overall for the (*RRR*)-, (*SSS*)-, (*RSR*)- and (*SRS*)-isomers. In the case of the conformationally unsymmetrical (C_1) enantiomers, (*RRS*)-**4-mer**/(*SSR*)-**4-mer**, all six methyl groups are heterotopic when atropisomerism is slow on the ^{1}H NMR time-scale and so they give rise to six anisochronous resonances in total in the low temperature ^{1}H NMR spectrum. At high temperatures, three broad resonances are observed in keeping with the constitution of the **4-mer**. On cooling down

Table 1 Conformational analysis of the isomers

Compound	Isomer	Point group	Heterotopic Me	
			Individual[a]	Total[b]
2-mer	*R/S*	**C₂**	1	1
3-mer	*RR/SS*	**C₂**	2	4
3-mer	*RS*	**Cᵢ**	2	
4-mer	*RRR/SSS*	**C₂**	3	12
4-mer	*RSR/SRS*	**C₂**	3	
4-mer	*RRS/SSR*	**C₁**	6	
5-mer	*RRRR/SSSS*	**C₂**	4	32
5-mer	*RSSR/SRRS*	**C₂**	4	
5-mer	*RRRS/SSSR*	**C₁**	8	
5-mer	*RRSR/SSRS*	**C₁**	8	
5-mer	*RRSS*	**Cᵢ**	4	
5-mer	*RSRS*	**Cᵢ**	4	
6-mer	*RRRRR/SSSSS*	**C₂**	5	80
6-mer	*RRSRR/SSRSS*	**C₂**	5	
6-mer	*RSSSR/SRRRS*	**C₂**	5	
6-mer	*RSRSR/SRSRS*	**C₂**	5	
6-mer	*RRRRS/SSSSR*	**C₁**	10	
6-mer	*RRRSR/SSSRS*	**C₁**	10	
6-mer	*RRRSS/SSSRR*	**C₁**	10	
6-mer	*RRSSR/SSRRS*	**C₁**	10	
6-mer	*RRSRS/SSRSR*	**C₁**	10	
6-mer	*RSRRS/SRSSR*	**C₁**	10	

a Number of heterotopic Me groups in ¹H NMR spectroscopy for every individual isomer. *b* Number of total heterotopic Me groups in ¹H NMR spectroscopy for a mixture of all isomers of a certain length.

the solution (Fig. 2e), these three resonances first of all separate into six and then finally into 12 peaks of similar intensities. These 12 peaks constitute the sum of three peaks for the (*RRR*) and (*SSS*) enantiomers, three peaks for the (*RSR*) and (*SRS*) enantiomers and six peaks for the (*RRS*) and (*SSR*) enantiomers.

Applying the *Losanitsch* formula to $n = 4$, 10 isomers are expected for the **5-mer**: two pairs of **C₂** enantiomers *RRRR*/ *SSSS* and *RSSR/SRRS*, two pairs of **C₁** enantiomers *RRRS*/ *SSSR* and *RRSR/SSRS* and two **Cᵢ** *meso*-isomers *RRSS* and *RSRS*, leading to a total number of 32 heterotopic methyl groups. For the **6-mer** ($n = 5$), 20 isomers are expected existing as: four pairs of **C₂** enantiomers *RRRRR/SSSSS*, *RRSRR*/ *SSRSS*, *RSSSR/SRRRS*, *RSRSR/SRSRS*, and six pairs of **C₁** enantiomers *RRRRS/SSSSR*, *RRRSR/SSSRS*, *RRRSS*/ *SSSRR*, *RRSSR/SSRRS*, *RRSRS/SSRSR*, *RSRRS/SRSSR* leading to a total number of 80 heterotopic methyl groups. It was not possible, however, to resolve all these peaks in the VT NMR spectra (see Fig. S1 and S2 in the ESI) recorded at 600 MHz.

In conclusion, we have prepared a series of model compounds consisting of one up to five axes of chirality arranged symmetrically in a linear oligoparaxylene system. These multiple chiral elements produce a number of atropisomers which were probed by VT NMR spectroscopy. The number of isomers

identified in the ¹H NMR spectra at low temperatures agrees with the number of isomers calculated using the *Losanitsch* formula, and hence we have shown experimentally that such multiple chiral element systems obey the *Losanitsch* series. These findings may be helpful in the characterisation of molecules with complex arrangements of chiral elements.

Notes and references

§ The *Gauss* bracket is defined by the floor function. Floor(*x*) = [*x*] is the largest integer not greater than *x*. The floor function maps a real number to the largest previous integer (The number in the *Gauss* bracket is rounded down, *i.e.*, [2] = 2, [2.5] = 2). For $n = 1$, the *Losanitsch* formula gives $A = 2^0 + 2^0 = 2$. For $n = 2$, $A = 2^1 + 2^0 = 3$. For $n = 3$, $A = 2^2 + 2^1 = 6$. For $n = 4$, $A = 2^3 + 2^1 = 10$. For $n = 5$, $A = 2^4 + 2^2 = 20$. For $n = 6$, $A = 2^5 + 2^2 = 36$, and so on.

¶ VT NMR spectra were recorded on a Bruker Avance 600 MHz spectrometer, which was temperature-calibrated using neat ethylene glycol or MeOH. The chemical shifts (δ) for ¹H spectra, given in ppm, are referenced to the residual proton signal of the deuterated solvent. All ¹H NMR spectra were recorded after the samples had been left in the NMR probe to equilibrate at every temperature for 15 min.

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