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Giving substance to the Losanitsch series†‡

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A series of oligoparaxylenes model compounds with two to six paraxylenyl units was synthesised and the resulting mixtures of atropisomers with one to five axes of chirality were analysed by dynamic 1H 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

\[ A = 2^n. \]

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 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 such as in carbohydrates, mechanically interlocked molecules, and atropisomers, 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.

Losanitsch investigated this problem as early as in the end of the 19th century while he was analysing isomers of paraffins and establishing the Losanitsch series (2, 3, 6, 10, 20, 36, 72, 136, 272...). The series can be described using the following formula with \( A \) being the number of isomers, \( n \) being the number of chiral elements, and \([\cdot]\) being the Gauss bracket

\[ A = 2^{n-1} + \frac{2(n+1)^{-1}}{2}. \]

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, since the formation of one compound leads after equilibration to a mixture of all possible isomers. Oligoparaxylenes (OPXs) 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 of about 18 kcal mol\(^{-1}\) which are ideal \( AG^\ddagger \) values for the targeted experiments because they are low enough to permit isomerisation and equilibration, yet high enough to be probed on the \( ^1H \) NMR time-scale. Furthermore the methyl groups in the OPXs are ideal \( ^1H \) NMR probes of the stereochemistry. Compounds 2-mer–6-mer (Fig. 1) were synthesised employing transition metal catalysed Suzuki–Miyaura cross-coupling reactions (see the ESI for details‡).

Fig. 1 Model compounds 2-mer–6-mer containing one to five chiral axes.

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‡ Electronic supplementary information (ESI) available: experimental details, variable temperature \( ^1H \) 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
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 (C7D8) as the solvent was found to afford the best resolution between signals for the probe methyl group protons in the different isomers. All 1H 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 C7D8 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 C2 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 1H 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 C2 symmetry and are chiral. The meso-isomer (RS)-3-mer has reflection symmetry (C1) and is achiral. While the enantiomers (RR)/(SS)-3-mer behave as one compound in the 1H 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 C7D8 during VT 1H 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 enantiotropic 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/(SRR)-4-mer, and (RRR)-4-mer/(SSR)-4-mer. VT NMR experiments of 3-mer (d) and 4-mer (e) in deuterated toluene (C7D8) revealing four anisochronous methyl peaks in the case of the 3-mer and 12 in the case of the 4-mer at low temperatures.

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, (RRS)-4-mer/(SRR)-4-mer, and (RRR)-4-mer/(SSR)-4-mer. VT NMR experiments of 3-mer (d) and 4-mer (e) in deuterated toluene (C7D8) revealing four anisochronous methyl peaks in the case of the 3-mer and 12 in the case of the 4-mer at low temperatures.
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.

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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., ⌊2.5⌋ = 2). For n = 1, the Losanitsch formula gives $A = 2^n + 2^n = 4$. For $n = 2$, $A = 2^2 + 2^2 = 8$. For $n = 3$, $A = 2^3 + 2^3 = 16$. For $n = 4$, $A = 2^4 + 2^4 = 32$.

† 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.