Transmitting information along oligo-*para*-phenylenes: 1,12-stereochemical control in a terphenyl tetracarboxamide†

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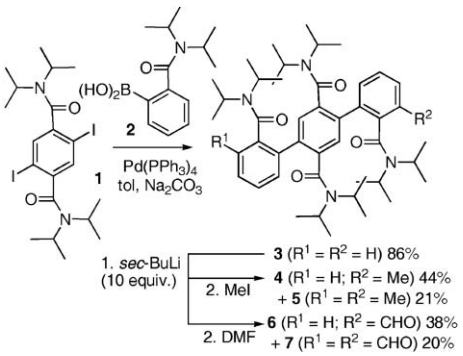
Amide-substituted terphenyls adopt a well-defined conformation that allows the transmission of stereochemical information from a controlling centre to a reaction site 11 bond lengths away, providing a model of how extended polymeric systems might be used to communicate binary information.

While biological systems make extensive use of conformational changes to relay information through molecules (in membrane-bound receptors and allosterically modulated enzymes, for example[1]), the same principle has rarely been used as a means of communicating information through non-biological systems.[2] Despite the huge number of molecules that have been identified as molecular switches,[3] in only a few instances has the effect of the switch been transmitted over any significant distance on a molecular scale.[2,4] We show in this paper that a terphenyl oligo-*para*-phenylene has the ability to mediate the communication of conformational information across a total of eleven bond lengths, a linear distance of over 1 nm, despite the lack of proximity between the sites of cause and effect, separated as they are by three aromatic rings.

Amide groups bonded to aromatic rings tend to align themselves antiparallel with their neighbours to reduce overall dipole moments,[5] and this tendency has been used as the basis of conformational relay systems.[2,6–8] Investigating relay effects over longer distances using a single extended aromatic system poses many synthetic problems, so instead we aimed to employ a known polymeric scaffold, supporting a series of amide groups, as a "conductor" for stereochemical information. Some degree of rigidity is necessary to ensure that the amides maintain a defined spatial relationship, and given previous successes with biphenyldicarboxamides[8] and trisxanthenehexacarboxamide oligomers,[2] a scaffold based on poly-*para*-phenylene seemed an ideal choice.[9]

Terphenyl **3**, carrying four amide groups, was assembled in 86% yield using a double Suzuki coupling of the diiododiamide **1**[10] with boronic acid **2** (Scheme 1).[11] Broadened signals in the ^{1}H NMR spectrum at both +23 and −80 °C suggested that **3** exists as an interconverting mixture of conformers. To decelerate conformational exchanges and restrict the number of conformations accessible, further steric encumbrance was introduced to **3** by double *ortho*-lithiation[12] and methylation. As is common with molecules containing numerous alkyllithium-coordinating sites,[7,8]



Scheme 1 Construction of a terphenyltetracarboxamide.

a large excess of *sec*-BuLi was required for this lithation, and even then the dimethylated product, **5**, was obtained in only 21% yield, with monomethylated **4** being the more significant product.

The terminal amide groups of **5** are each flanked by two substituents and are therefore likely to exhibit atropisomerism;[13] two diastereoisomers of **5** are possible, with these groups aligned *anti* or *syn*, respectively, as shown in Fig. 1. Nonetheless, its sharp and simple NMR spectrum indicated (a) that **5** was stereochemically pure, (b) that it was conformationally uniform at the (non-atropisomeric) bonds linking the central ring to its two amide substituents,[14] and (c) that it had an axis, plane or centre of symmetry. No change in composition by NMR was observed on heating a sample of **5** for several hours in toluene, confirming that the conformation observed is, moreover, the most stable one possible. Biphenyl-2,2′-dicarboxamides prefer conformations in which the amide groups lie *anti* across the biaryl C–C bond,[8] and combining this preference with a presumed *anti* preference across the central aryl ring[5] led us to expect **5** to prefer a conformation approximating to **5a**. However, a HLPC study of **5** on a chiral stationary phase (Whelk-O1) indicated that it was racemic; the centrosymmetry of **5a** rules out the existence of enantiomers, so we

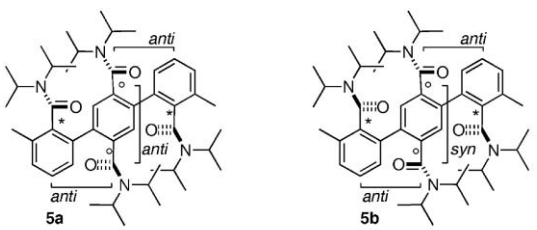


Fig. 1 Conformers of **5**.

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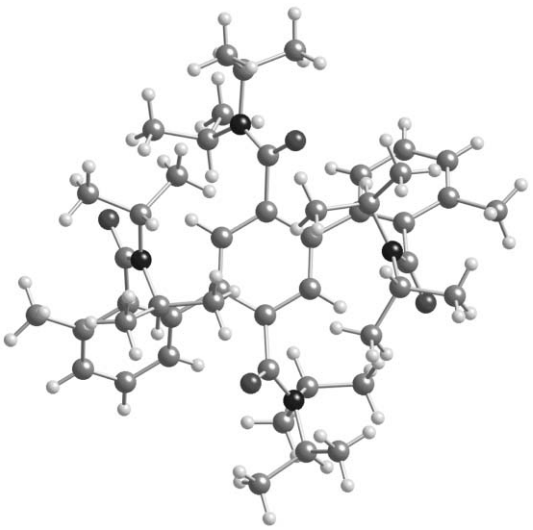


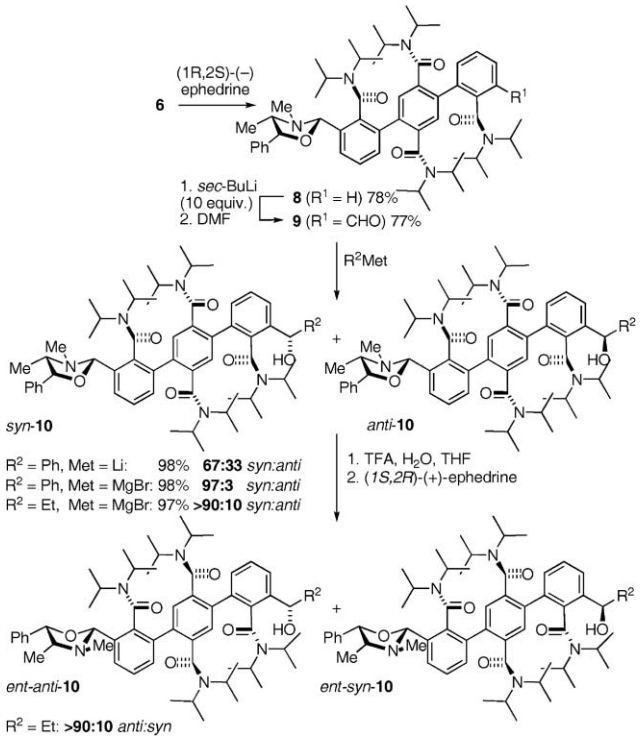
Fig. 2 X-Ray crystal structure of **5b**.

conclude that **5** has the chiral structure **5b**, its symmetry arising from the C_2 axis perpendicular to the central ring. The X-ray crystal structure of **5** (Fig. 2)[15] confirmed this stereochemical assignment in the solid state. Presumably any *anti* preference of the amides on the central ring is more than overridden by dipole repulsion[5] between the two "upper" and two "lower" amides.

The conformational uniformity of **5** indicates that the amide groups are in communication with one another and, in principle, could form a relay system for carrying stereochemical information across the terphenyl system if a means of controlling absolute stereochemistry were introduced at one end of the oligophenylene chain. Mono-lithiation of **3**, under the conditions of Scheme 1, yielded 38% of the aldehyde **6**, along with dialdehyde **7**. Condensation of **6** with (−)-ephedrine provided a single diastereoisomer of **8** as a single conformer (by NMR). Ephedrine-derived oxazolidines[16] are known to exert powerful absolute conformational control over the orientation of an adjacent amide axis.[17] Further lithiation and formylation of this compound returned aldehyde **9**, whose sharp, clean NMR spectra indicated that the conformational uniformity had been maintained.

The global conformation of **9** is under the control of the ephedrine-derived oxazolidine, but only the closest amide is likely to influence diastereoselective reactions at the formyl group[18]—in other words, there is the potential for remote stereocontrol in the addition reactions of **9**. Phenylmagnesium bromide, phenyllithium and ethylmagnesium bromide were added to **9** and gave, in near quantitative yield, the alcohols **10** in the diastereoisomeric ratios (determined by HPLC) shown in Scheme 2. High selectivities in favour of *syn*-**10**[18] were obtained upon addition of the Grignard reagents to the reactions, which therefore display 1,12 remote stereocontrol by the benzylic centre of oxazolidine over that bearing the new hydroxyl group.[19] Phenyllithium reacted less selectively, but the presence of the minor diastereoisomer allowed us to quantify the degree of stereocontrol in the addition of PhMgBr.

Intramolecular relay of stereochemical information through the conformationally interlocked amide substituents is the most likely, but by no means only possible, explanation for the stereoselectivity observed.§ To confirm that switching the stereochemistry of one of



Scheme 2 Stereochemical relay through a terphenyl.

the two benzylic centres has an effect that is communicated to the other, the oxazolidine ring of **10** was hydrolysed by warming in aqueous acid. The aldehyde product of this reaction is a mixture of atropisomers by NMR, but on re-formation of the oxazolidine with (1*S*,2*R*)-(+)-ephedrine, which switches absolute stereochemistry at the left hand end of the molecule as depicted in Scheme 2, a clear change in local stereochemistry at the right hand end was also observed in the ^{1}H NMR spectrum of **10** in the form of an upfield shift and a change in the coupling pattern of the C*H*OH proton; an effect unlikely to be due to any direct (un-relayed) interaction between the oxazolidine ring and hydroxyl group.

Terphenyls **3–10** provide a model of how more extended, but nonetheless structurally simple, oligomers might be used to relay—or even process and amplify—binary stereochemical information.

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Notes and references

§ For example, it is conceivable, if unlikely, that one molecule of **9** may act as a chiral metal ligand during the organometallic addition reaction to a second molecule of **9**. In previous related work (ref. 2), we ruled out this possibility by carrying out the reaction with a racemic material.

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14 In common with most bonds linking two aryl rings, each bearing only one *ortho* substituent, the biaryl bonds in **3–10** are not stereogenic. See, for examples and counter-examples: C. Wolf, *Chem. Soc. Rev.*, 2005, **34**, 595. As a means of clarifying which bonds are stereogenic (rotate slowly on the lab timescale) and which are not (but may still give rise to conformers distinguishable on the NMR timescale) we employ here Bringmann's symbols of * for a configurationally stable (*atropos*) stereogenic axis and ° for a configurationally unstable (*tropos*) non-stereogenic axis. See, for example: G. Bringmann, J. Hinrichs, T. Pabst, P. Henschel, K. Peters and E.-M. Peters, *Synthesis*, 2001, 155.
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