Conformational switching between diastereoisomeric atropisomers of arenedicarboxamides induced by complexation with Lewis acids†

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Tertiary diamides of xanthene-1,8-dicarboxylic acid and biphenyl-2,2′-dicarboxylic acid exhibit a thermodynamic preference for *anti* stereochemistry which is inverted in the presence of Ti- or Sn-based Lewis acids, allowing interconversion between kinetically stable *syn* and *anti* diastereoisomeric atropisomers.

The conversion of a macroscopic influence (temperature, photochemical, pH, redox or presence of a metal ion) to a change in shape or structure on the molecular scale is essential to the development of molecular devices or receptors.[1] A variety of structures have been reported to exhibit switching properties.[2] However, for switches to be functional, the structural change that occurs on switching has to be "readable"—there must be a measurable consequence of the switching process. Aromatic amides have been shown to be powerful controllers of a range of molecular conformational and reactivity properties,[3,4] and the ability to switch them from one orientation to another would provide a powerful basis for a family of molecular devices.[5] In this communication we report such a switching process for two classes of amides, in which reversible conversion from one orientation to another is determined by heating in the presence or absence of a chelating metal ion.

The amide groups of fully N-substituted xanthene-1,8-dicarboxamides **1** exhibit a thermodynamic preference for *anti* conformers, presumably due to dipole repulsion (Fig. 1).[3,6,7] Since the relatively electron rich oxygen atom of an amide is also a powerful coordinator of metal ions, we set out to use chelation of a metal by dicarboxamides[8] related to **1** as a means of switching *anti* stereochemistry to *syn*.

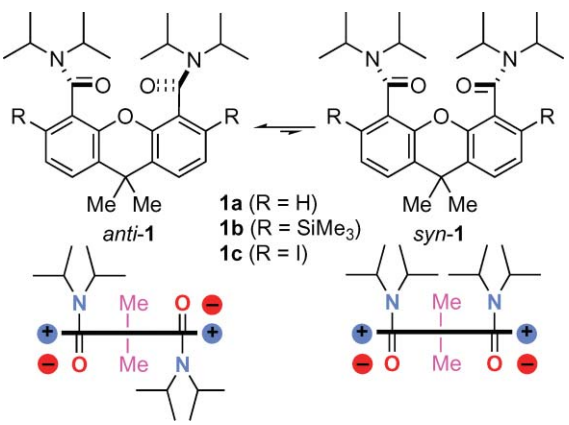


Fig. 1 *syn* And *anti* xanthenedicarboxamides.

Initial studies were carried out in an NMR tube. A solution of **1a** in $CDCl_3$ was titrated with titanium tetrachloride. As illustrated for **1a** in Fig. 2, on addition of 2 equiv. of $TiCl_4$, a single new symmetrical complex had formed (Scheme 1). This complex evidently had *syn* stereochemistry since the 6H singlet (labelled °) due to the *gem*-dimethyl group of the starting material had split into a pair of diastereotopic 3H singlets (labelled *). Addition of water to this *syn*-**1a**·[Ti] complex returned pure *anti*-**1a**—the *anti* → *syn* switch was reversed on aqueous work-up, presumably because the barrier to interconversion of the diastereoisomers of **1a** is too low to allow isolation of *syn*-**1a**.

Structures **1b** and **1c**, which incorporate 2,7-disubstitution, were expected[6,9] to possess diastereoisomeric conformers with a higher barrier to interconversion, and therefore may offer the possibility of isolation of the less stable *syn* atropisomer of **1**. *anti*-**1b** and *anti*-**1c** were made by double *ortho*-lithiation[6,10] of **1a**. In both, the

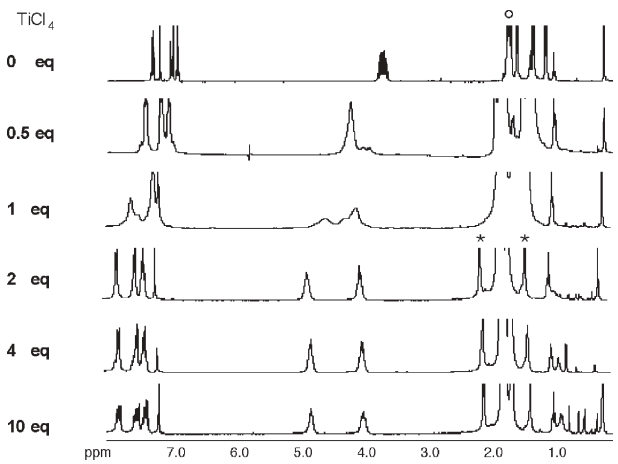
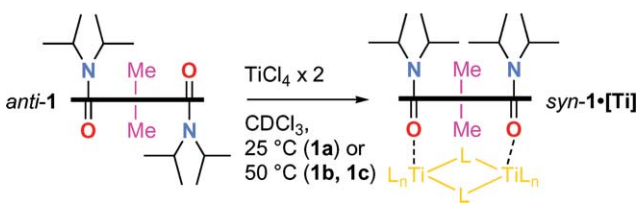


Fig. 2 Conversion of *anti* to *syn* xanthenedicarboxamide.



Scheme 1 Conversion of *anti* to *syn* xanthenedicarboxamide.

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gem-dimethyl group was apparent as a 6H singlet, and **1c** was separable by HPLC on a chiral stationary phase into two enantiomers. Silane **1b** was not resolvable, probably because the $SiMe_3$ groups provide an insufficiently high barrier to interconversion of the enantiomers of the *anti* isomer.[9] Addition of two equivalents of $TiCl_4$ to **1b** in $CDCl_3$ showed no immediate change in structure, but heating this mixture to +50 °C led to formation of the Ti complex of *syn*-**1d** (as indicated by the appearance of two 3H singlets). The conversion of *anti*-**1c** to *syn*-**1c** in the presence of 2 equiv. $TiCl_4$ was slower, but was complete in 3 h at +50 °C. Both solutions were cooled to −50 °C and CD_3OD was added to release the *syn*-**1** from the Ti complexing agent. An NMR spectrum acquired immediately after decomplexation showed however that conversion to *anti*-**1b** or *anti*-**1c** is almost instantaneous: uncomplexed *syn*-**1** evidently has a very low barrier to relaxation to *anti*-**1** even at low temperature.

Biphenyl-2,2′-dicarboxamides **2** exhibit a rather weaker preference for *anti* stereochemistry (Fig. 3),[3] and both *syn* and *anti* biphenyldicarboxamides exhibit kinetic stability and have previously been isolated.[11] We therefore also explored this class of molecule as substrates for selective switching using metal ions.

Biphenyl-2,2′-dicarboxamide **2a** was *ortho*-lithiated[10,11] and iodinated (either directly or, for higher yields, *via* **2b**, treating **2b** with iodine monochloride) to yield **2c** as a mixture of diastereoisomers with *syn*-**2c** predominating. Identification of the stereochemistry of the diastereoisomers of **2c** was made easy by the fact that *syn*-**2c**, which is achiral, gives a single peak on analysis by HPLC on a chiral stationary phase, while *anti*-**2c**, which is chiral, gives a pair of peaks. Both diastereoisomers were furthermore crystalline, and Fig. 4 shows their X-ray crystal structures.§

Heating *syn*-**2c** in a variety of solvents caused it to convert to *anti*-**2c** with solvent-dependent stereoselectivity (Table 1). In toluene, up to 10 : 1 selectivity for *anti*-**2c** was obtained, reducing to 2 : 1 in polar solvents. Presumably the preference for *anti* stereochemistry is driven by dipole repulsion,[12] which is greatest in non-polar solvents. Monitoring epimerisation from *syn* to *anti*-**2c** in toluene at 77 °C allowed evaluation of a half-life for this process of 32.2 h, corresponding to a barrier to interconversion *syn*-**2c** → *anti*-**2c** of 109.5 kJ mol^{-1} and from *anti*-**2c** → *syn*-**2c** of 103.1 kJ mol^{-1}.

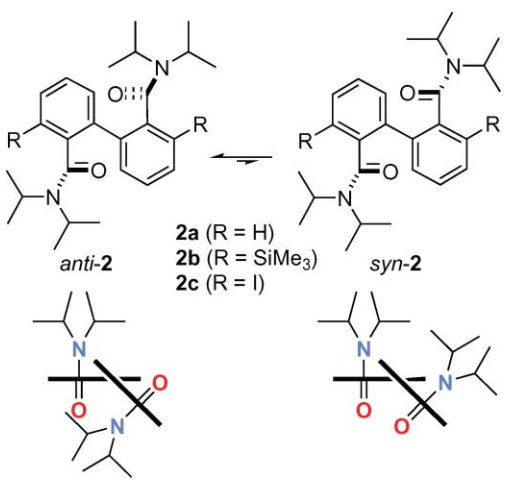


Fig. 3 *syn* And *anti* biphenyl-2,2′-dicarboxamides.

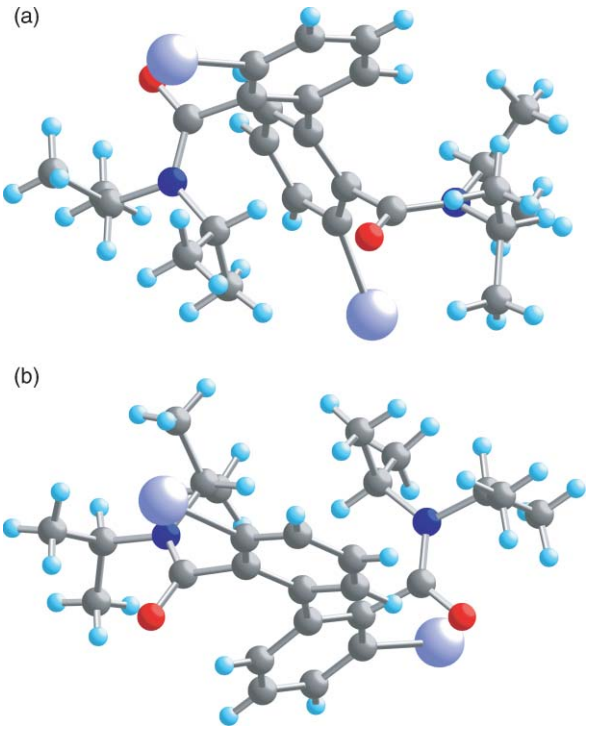


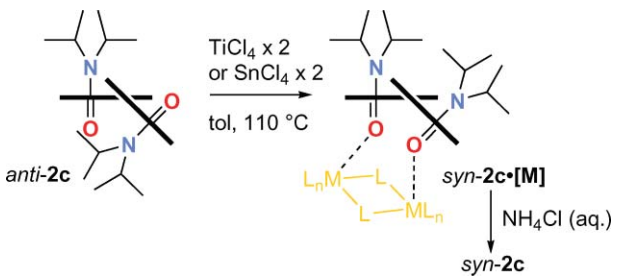
Fig. 4 a: X-Ray crystal structure of *anti*-**2c**; b: X-ray crystal structure of *syn*-**2c**.

Table 1 Solvent dependent stereoselectivity in the isomerisation of *syn* → *anti*-**2c**

Entry	Solvent	Ratio *anti*-**2c** : *syn*-**2c**[a]
1	Toluene	91 : 9
2	EtOAc	84 : 16
3	DME[b]	82 : 18
4	THF	83 : 17
5	MeOH	77 : 23
6	MeCN	74 : 26
7	AcOH	67 : 33

[a] Determined by NMR spectroscopy. [b] DME = dimethoxyethane.

anti-**2c** was dissolved in toluene and treated with two equiv. $TiCl_4$ (Scheme 2). No change was evident by TLC, but on heating in toluene, followed by aqueous work-up, an almost complete switch to *syn*-**2c**, evident by TLC and NMR spectroscopy and quantified by HPLC analysis, was observed (Table 2, entry 1). Similar results were obtained on treating *anti*-**2c** with 2 equiv. $SnCl_4$. With just one equiv. $SnCl_4$, or with other Lewis acids



Scheme 2 Conversion of *anti* to *syn* biphenyl-2,2′-dicarboxamide **2c**.

Table 2 Lewis acid dependent stereoselectivity in the isomerisation of *anti* → *syn*-**2c**

Entry	Lewis acid	Equiv.	Isolated ratio *syn*-**2c** : *anti*-**2c**[a]
1	$TiCl_4$	2	98 : 2
2	$SnCl_4$	2	98 : 2
3	$SnCl_4$	1	83 : 17
4	$Sn(OTf)_2$	2	93 : 7
5	$Sn(OTf)_2$	1	67 : 33
6	$Zn(OTf)_2$	2	46 : 54
7	$EtAlCl_2$	2	43 : 57
8	$Ti(O\textit{i}\text{-}Pr)_2Cl_2$	2	52 : 48
9	$Ti(O\textit{i}\text{-}Pr)_4$	2	9 : 91

[a] Determined by HPLC analysis.

($EtAlCl_2$, $Ti(O\textit{i}\text{-}Pr)_4$, $Ti(O\textit{i}\text{-}Pr)_2Cl_2$) lower selectivities were observed, as indicated in Table 2.

In summary, it is possible to switch both xanthenedicarboxamides **1** and biphenyl-2,2′-dicarboxamides **2** from their ground state *anti* conformation to a *syn* conformation by coordination with Ti or Sn derived Lewis acids. In the case of **1** the *syn* diastereoisomer is too unstable to exist in the absence of a Lewis acid, but **2** may be decomplexed and remains stable until heating returns it to the *anti* isomer.

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Notes and references

§ CCDC 658995 (*anti*-**2c**) and 658996 (*syn*-**2c**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b716105k

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