Conformational Analysis

Using Dipoles to Control the Directionality of Functional Groups: *Syn*- and *Anti*-Oriented Benzene-1,3-dicarboxamides**

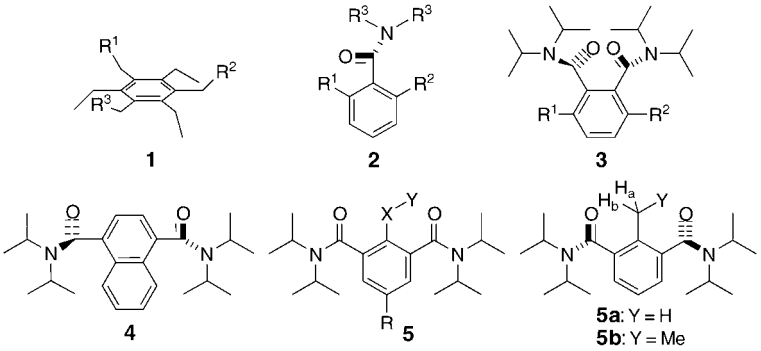
Mark S. Betson, Jonathan Clayden, Ho Kam Lam, and Madeleine Helliwell*

The control of conformation, which until quite recently was feasible only in cyclic compounds, now appears to be a realistic target for stereoselective synthesis[1–3] alongside its traditional goal of controlling configuration. The relative spatial orientation of pairs or triads of functional groups attached to an aromatic ring can be used to modulate the binding properties of ligands, receptors, and sensors[4–8] and the bulk properties of liquid crystals.[9] From the crystallographic work of MacNicol et al.[10,11] and the theoretical and dynamic NMR spectroscopic studies of Mislow and coworkers[12] on polyalkylbenzenes, it has been generally assumed that the *syn* orientation of functions carried by an aromatic ring may be favored by interposing cylindrically unsymmetrical groups, such as ethyl or alkoxy, between them. A growing number of ligands of general structure **1** (Scheme 1) have been designed on this basis.[4,13] It is clear that the 1,3-*syn* conformation of polysubstituted arenes is favored (usually[14]) in the crystalline state,[10,11,15] in metal–arene complexes (by NMR spectroscopic studies),[12,16,17] and in calculated ground states.[12,16] However, there is to date neither direct empirical evidence for the magnitude of the effect in solution nor data on the role of the intervening substituent.[18]

Herein we present the first direct evidence from NMR spectroscopic studies that 1) a group interposed between two *meta*-related functions may indeed force them to adopt a *syn* orientation with high selectivity and 2) the magnitude of the effect is critically dependent on the nature of the group. We show that a pair of *meta*-related amide groups on an aromatic ring have a natural tendency to lie facing in opposite directions with a conformational selectivity of $>95{:}5$ *anti*. Their relative orientation may be completely inverted to $>95{:}5$ *syn*, but only if a polar group with an associated dipole is placed in between them—a polar group such as acetyl exerts a far more powerful effect than the widely used ethyl group. Steric effects alone are insufficiently powerful to overturn the preference of the amides to adopt an *anti* conformation.

The hydrogen-bonding and metal-binding capacity of secondary aromatic amides has earned them the pivotal role in molecules designed to adopt specific conformations[19] or to exhibit molecular recognition.[20] However, rapid bond rotations in secondary amides frequently renders detailed studies of their conformational properties in solution difficult over the temperature ranges attainable in common solvents. Tertiary aromatic amides **2** (Scheme 1), which usually adopt conformations in which the plane of the amide is more or less perpendicular to the plane of the aromatic ring,[21] undergo much slower bond rotations and are readily studied by dynamic NMR spectroscopic or saturation transfer techniques.[22–24]

In the benzene-1,2-dicarboxamide **3**, the amide groups align themselves such that their carbonyl groups are oriented in opposite directions, whether for steric or electronic reasons (Scheme 1).[25,26] We prepared simple benzene-1,4-dicarboxamide and benzene-1,3-dicarboxamide derivatives **4** and **5a** by standard methods[27] and found that a strong orientational preference also persists in these compounds. Conformers about the Ar–CO bond of *ortho*-substituted tertiary amides such as **4** and **5a** are expected to interconvert only slowly on the NMR timescale even at 25 °C,[21,23] but their NMR spectra essentially show a single set of peaks at both 20 °C and −50 °C in $CDCl_3$. An X-ray crystal structure of **5a** (Figure 1a) shows an *anti* alignment of the amides in the solid state.



Scheme 1. Conformational preference in arene-1,2-, -1,3-, and -1,4-dicarboxamides.

The ^{1}H NMR spectrum ($CDCl_3$, 20 °C) of the closely related 2-ethyl-substituted isophthalamide **5b** shows a mixture of conformers in a ratio of approximately 5:1. The ethyl group of the major conformer is an ABX_3 system, while the equivalent signal in the minor conformer is a simple A_2X_3 quartet + triplet. As the *anti* conformer is chiral and the *syn* conformer is achiral, with a plane of symmetry lying through the ethyl group, these observations allow us to assign with certainty *anti* stereochemistry to the major conformer of **5b**. When the solvent is changed to CD_3OD, **4** and **5a** also show two conformers at 20 °C in a ratio of 6:1 for **4** and 2:1 for **5a**. We assume that the major conformer is still *anti*, although the lack of a stereochemical marker makes it impossible to assign the stereochemistry with certainty.

To probe further the influence of the substituent that lies between the two amides on their relative conformation, we prepared a series of isophthalamides **5a–s**.[27] Where feasible, an isopropyl substituent was incorporated at the 5 position to act as a symmetry reporter—in the achiral *syn* conformers the

[*] Dr. M. S. Betson, Prof. J. Clayden, H. K. Lam, Dr. M. Helliwell
Department of Chemistry
University of Manchester
Oxford Road
Manchester M13 9PL (UK)
Fax: (44) 161-275-4612
E-mail: j.p.clayden@man.ac.uk

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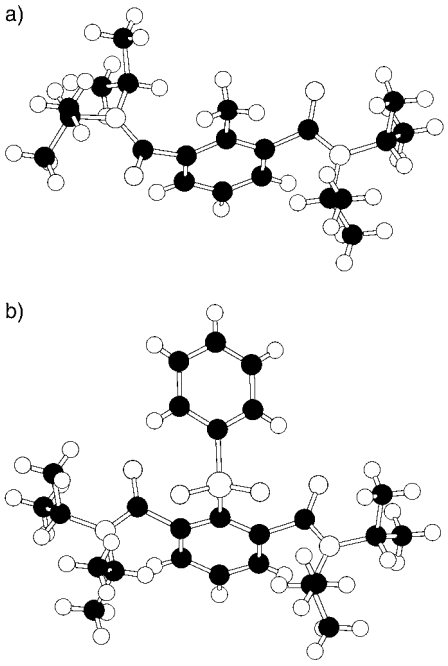

Figure 1. a) X-ray crystal structure of *anti*-**5** (**5a**). b) X-ray crystal structure of *syn*-**5** (**5s**).

Table 1: Conformations of benzene-1,3-dicarboxamides

Entry	Compound	-X–Y	R	Ratio *anti*:*syn*	Notes
1	**5a**	Me	H	>93:7	[a,b]
2	**5a**	Me	H	67:33	[a,c]
3	**5b**	Et	H	83:17	[d]
4	**5c**	Cl	H	>95:5	[a]
5	**5d**	OMe	*i*Pr	57:43	[d]
6	**5e**	OBn[e]	*i*Pr	54:46	[d]
7	**5f**	OSEM[e]	*i*Pr	54:46	[d]
8	**5g**	O*i*Pr	*i*Pr	35:65	[d]
9	**5g**	O*i*Pr	*i*Pr	18:82	[d,f]
10	**5h**	OPh	H	35:65	[a]
11	**5i**	SMe	H	40:60	[a]
12	**5j**	SPh	H	35:65	[a]
13	**5k**	OAc	*i*Pr	<7:93	[d]
14	**5k**	OAc	*i*Pr	<7:93	[d,f]
15	**5l**	OBz[e]	*i*Pr	<4:96	[d]
16	**5m**	$OCOC_5H_4OMe$	*i*Pr	<4:96	[b,d]
17	**5n**	OTs[e]	*i*Pr	<7:93	[d]
18	**5o**	OMs[e]	*i*Pr	14:86	[d]
19	**5p**	$OCONiPr_2$	*i*Pr	<4:96	[d]
20	**5q**	$OCONEt_2$	*i*Pr	<5:95	[d]
21	**5r**	SO_2Me	H	<5:95	[a]
22	**5s**	SO_2Ph	H	<5:95	[a,g]

[a] Stereochemical assignment unconfirmed, but proposed by analogy with related compounds. [b] X-ray crystal structure indicates *anti* stereochemistry in the solid state. [c] Ratio determined in CD_3OD. [d] Stereochemical assignment on the basis of topicity of signals. [e] Bn = benzyl, SEM = 2-trimethylsilylethoxymethoxy, Bz = benzoyl, Ts = *p*-toluenesulfonyl, Ms = methanesulfonyl. [f] Ratio determined in $(CD_3)_2SO$. [g] X-ray crystal structure indicates *syn* stereochemistry in the solid state.

isopropyl group will exhibit a homotopic pair of methyl groups, whereas in the chiral *anti* conformers its methyl groups may be a diastereotopic pair of 3H doublets. The conformational ratios, obtained by ^1H NMR spectroscopy in $CDCl_3$ at ambient temperature unless otherwise stated, are shown in Table 1.

These results show that the conformation of the isophthalamides is entirely dependent on the nature of the -X–Y substituent interposed between the two amides groups, and to explain this it is necessary to consider the preferred orientation of this substituent. For substituents other than -X–Y= Me (**5a**) or Cl (**5c**), steric hindrance between Y and the flanking amide groups requires that the Y group lie out of the plane of the ring. In *anti*-**5**, rotation about the Ar–X bond leads to a pair of rapidly interconverting but identical conformers with Y always lying *syn* to one amide C=O group and *anti* to the other, while in *syn*-**5**, rotation about Ar–X leads to two rapidly interconverting diastereoisomeric conformers with either two *syn* or two *anti* interactions between Y and the amide C=O groups (Figure 2). Thus whatever the nature of the interaction between Y and the amide groups, the interaction can be maximized in *syn*-**5** (as Y can choose whether to be *syn* or *anti* to either C=O or NR_2 of both amides simultaneously) whereas in *anti*-**5** the Y···amide interaction is lessened because Y can have a favorable interaction only with one amide group at a time. Super-

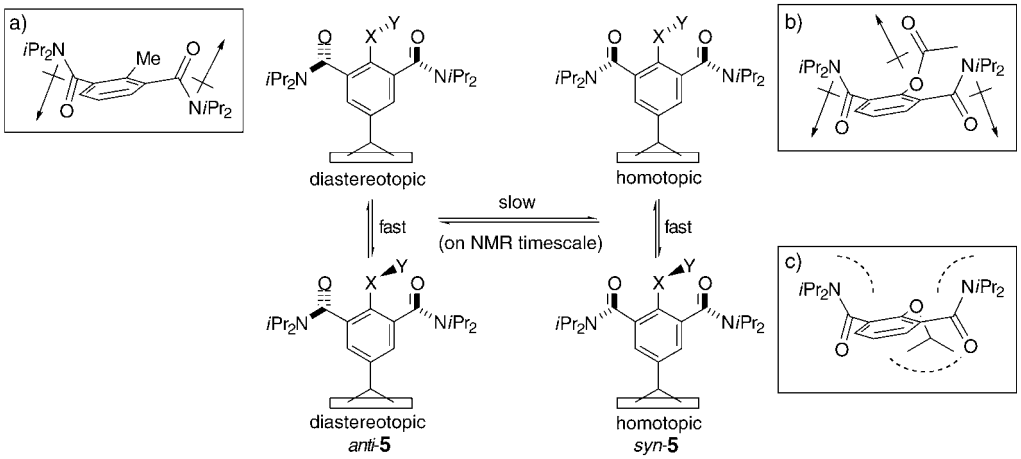

Figure 2. Factors governing the conformations in benzene-1,3-dicarboxamides.

imposed on this, direct interaction (i.e. one not mediated by -X–Y) between the amide groups, whether steric or electronic, must favor the *anti* conformer.

We already noted that in **5a** a single, presumably *anti*, conformer is indeed favored. The same is true for **5c**: both of the compounds have -X–Y groups which are essentially cylindrically symmetrical and therefore exert no conformational preference on the amide substituents. We therefore propose that in the absence of other conformational influences, a pair of *meta*-disposed amide groups will adopt a relative *anti* conformation presumably because of dipole repulsion between the two C=O groups (Figure 2a).[28]

In **5b**, with -X–Y = -CH_2–Me, the *anti* preference is lessened because Y (= Me) can interact only weakly and probably by steric repulsion with the NR_2 groups of the amides; direct repulsion between the amide groups is still however dominant. However, in the series of ethers **5d**–**5h** the preference switches from *anti* to *syn*, with a weak correlation between the size of Y and the *syn* preference. In these ethers and in the sulfides **5i** and **5j**, repulsion between Y and the amide NR_2 groups is great enough to overcome their tendency to lie *anti* (Figure 2c), particularly in a polar solvent (Table 1, entry 9).

The greatest ability to overturn the *anti* preference is shown by the -X–Y groups in compounds **5k**–**5s**, which have in common the presence of an electronegative oxygen atom within the group Y. The role of the oxygen atom in controlling the relative conformation of the amides must be to provide a third directed dipole that can simultaneously oppose the dipoles of both amide groups, as illustrated in Figure 2b. The importance of the oxygen atom is underlined by the difference in conformational preference between the isopropyl ether **5g** and the acetate ester **5k**, both of whose -X–Y groups are sterically similar, and between the sulfides **5i**,**j** and the sulfones **5r**,**s** where the sulfones have even less ability to impose steric differentation on the faces of the isophthalamide ring.

The X-ray crystal structure of sulfone **5s** (Figure 1b) confirms *syn* stereochemistry in the solid state. In the X-ray crystal structure of **5m**, however, the amides are aligned *anti*: a clear warning against the use of solid-state conformations to deduce the preferred structures in solution.[14,29] Calculations[30] of the conformations of **5a** (*anti* preferred by 2.9 kJ mol^{-1}), **5j** (*anti* and *syn* within 0.2 kJ mol^{-1}), and **5s** (*syn* preferred by 2.8 kJ mol^{-1}), though not **5k** (for which calculations predicted *anti* stereochemistry), agreed qualitatively with the reasoning in Figure 2.

To summarize, we have shown that by choosing carefully the nature of the substituent interposed between two functional groups, it is possible to control their relative orientation. We believe that the incorporation of polar substituents in polysubstituted arenes may play a greater role in the induction of *syn* orientations in future studies of sensors and ligands that contain these units.

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