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Signal transduction in oligoamide foldamers by selective non-covalent binding of chiral phosphates at a urea binding site

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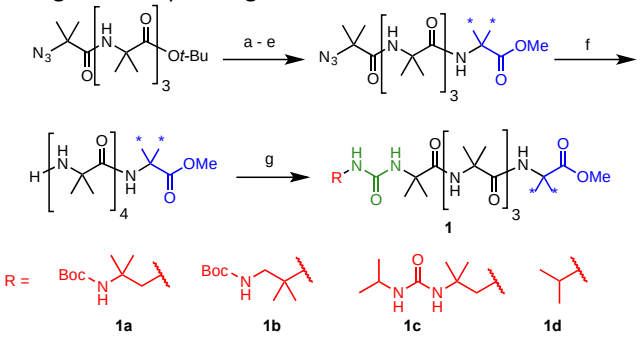
The transduction of biological signals depends on the spatial communication of conformational change. We report a synthetic mimic of this signal transduction process in which non-covalent binding induces a change in the position of equilibrium between two rapidly intercoverting screw-sense conformers of a synthetic helical polyamide. Selectivity was achieved by incorporating at the N terminus of the polyamide a urea-based anion recognition site capable of binding chiral phosphate anions. As a result of solvent-dependent binding, an induced conformational change propagates from the binding site through the amide chain, leading to a screw-sense preference detectable in the form of a chemical shift separation between two NMR active ^{13}C labels. The remote induction of screw sense preference indicates successful communication of a signal originating solely from non-covalent binding.

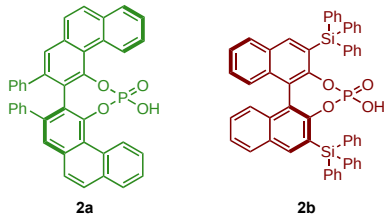
Introduction

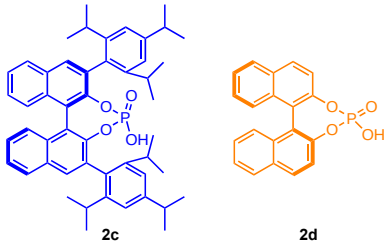
Foldamers were conceived as conformationally well defined synthetic equivalents of the biopolymers,[1] and foldamers have been reported having a wide range of catalytic and biological activity.[2-13] Nonetheless, biopolymers also display dynamic conformational properties[14-21] that are also in principle reproducible in foldamer structures. Dynamic conformational changes are especially important in biological signal transduction.[22] We have reported 'dynamic foldamers'[23] based on helical oligomers of 2-aminoisobutyric acid (Aib)[24-31] that undergo switching between alternative conformations in response to a variety of stimuli (pH,[32,33] irradiation with light,[33,34] or addition of ligands)[35] both in solution and in the membrane phase.[36,37] The utilisation of dynamic foldamers as signal transduction devices offers a potential synthetic approach to the construction of biomimetic signalling networks.

As part of this work, we showed that competitive binding of Brønsted acids at a basic, pyridine-derived binding site leads to dynamic induction of conformational preference in a foldamer chain.[32] Other examples similarly made use of specific functionality at a designed binding site (for example incorporating a boron,[35] zinc,[23] or copper[37] based 'cofactor') to enforce selective interactions with the foldamer chain.

The urea function[38] has emerged as a powerful and versatile host for the selective binding of anionic guests.[39-47] Recent work has furthermore shown that urea foldamers form selective complexes with phosphate and carboxylate anions.[48,49] We now report the intramolecular, non-covalent induction of a conformational preference in an amide foldamer purely through hydrogen-bonded interactions between a chiral anion and a suitable geometrically matched binding site incorporating a urea function.







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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

Fig 1. Achiral urea-capped foldamers **1** and chiral phosphoric acids **2**. Reagents: *a* CF_3CO_2H, CH_2Cl_2; *b* EDC.HCl, CH_2Cl_2, 0 °C-rt; *c* $HCl.H_2NC(^{13}CH_3)_2COOEt$; *d* LiOH, THF, H_2O, rt-70 °C; *e* $(CH_3)_3SiCHN_2$, Et_2O/MeOH; *f* Pd/C, H_2, MeOH; *g* **1a:** $BocAib^uOSu$ (1 equiv), DIPEA (2 equiv), acetonitrile, 0°C - rt, **1b:** $BocAib[R]^uOSu$ (1.2 equiv), DIPEA (2 equiv), acetonitrile, 0°C - rt, **1c: 1a** (1 equiv), CF_3CO_2H, CH_2Cl_2, then Et_3N (3 equiv), *i*-PrNCO (2 equiv), DMF, 0 °C - rt, **1d.** Et_3N (1 equiv), *i*-PrNCO (2 equiv), DMF, 0°C - rt. (* = $^{13}CH_3$).

Four foldamers, **1a-d** (Fig 1) were synthesised, in each of which an achiral but helical Aib pentamer[50,51] is capped, at its N-terminus, by a urea function. At the C-terminus, the terminal Aib carries a pair of ^{13}C-labelled methyl groups to act as a marker of conformational induction. In the conformationally racemic state of this achiral molecule, with both screw-sense conformers of the helix equally populated, the ^{13}C NMR signals of these labels will have identical chemical shifts, but when a screw-sense preference is induced, the signals will become anisochronous. Provided there is no direct interaction between the N terminus of the foldamer and the labelled Aib, their chemical shift difference (anisochronicity) will be proportional to the helical excess induced in the foldamer.[52-54]

These urea-capped foldamers were only sparingly soluble in acetonitrile and in tetrahydrofuran. Each foldamer was mixed with a three-fold excess of the phosphoric acid **2a** (Fig. 1) and THF-d_8 was added. This mixture did not form a homogeneous solution, so base was added in order to promote *in situ* formation of a phosphate anion. Proton sponge[55] (1,8-bis(dimethylamino)naphthalene) was chosen as the base, since its conjugate acid would not participate in hydrogen bonding or disrupt the expected interactions between the resulting phosphate anion and the urea.[32] By this method, solutions were formed from all four foldamers **1a-1d**. ^{13}C NMR spectra were recorded using samples to which increasing amounts of proton sponge were added, and Fig. 2 shows the resulting change in anisochronicity $\Delta\delta$ of the two ^{13}C signals arising from the labelled methyl groups of each foldamer.[56]

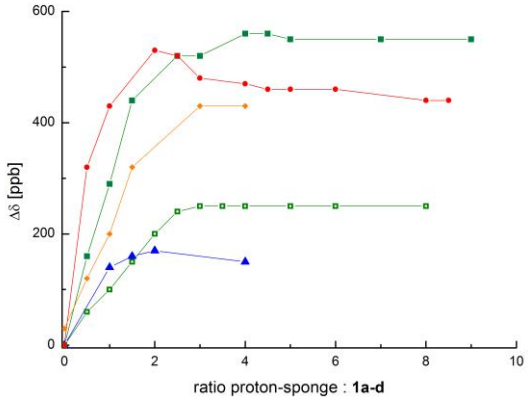

Fig 2. Variation of Δδ with number of equivalents of proton sponge: Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals in foldamer-ureas **1a-1d** vs the ratio proton sponge:**1** in the presence of 3.0 equiv. (*R*)-VAPOL phosphoric acid **2a** at 296 K in THF-d_8; $[\mathbf{1a\text{-}d}]_{initial}$ = 5 mM; ■ (1a), ▲(1b), ◆ (1c) and ● (1d); In CD_3CN: □ (1a).

Only for urea **1c** was any anisochronicity between the ^{13}C labels observed in the absence of base, and even then the value was small. Anisochronicity in all four foldamers in the presence of base increased to a maximum before reaching a plateau at around 3 equiv proton sponge. **1d** showed a maximum Δδ of 530 ppb at 2:1 ratio proton sponge:**1d**, followed by a decrease to a value of about 440 ppb that may indicate competitive formation of complexes other than 1:1 with this less hindered urea.[32] By contrast **1a** and **1b** show titration curves that plateau around 2:1 binding stoichiometry and appear to show intermolecular binding of the *in situ*-created phosphate anion to the foldamer. **1a** was chosen for further experiments as it showed the highest maximum value of Δδ, indicating the greatest ability to convert non-covalent binding into conformational preference. Although the structural difference between **1a** and **1b** is small, they show a significantly different conformational response to the phosphate anion, presumably because the location of the *gem*-dimethyl group affects both the binding of the anion and the conformation of the foldamer. Similar changes in conformational responses were seen in other urea foldamers containing these diamine subunits.[48b]

Changing the solvent from THF-d_8 to CD_3CN decreased the value of Δδ at all ratios of proton sponge:**1a**. Comparison with known values for Δδ in these solvents[51] suggested that while **2a** induced a screw sense preference in **1a** of 28% helical excess (h.e.) in solution in THF-d_8, the induction of screw sense preference in CD_3CN reaches only 16% h.e.

In order to establish whether the absolute concentration of the foldamer-phosphate mixture affects the degree of induction of screw-sense preference, a series of NMR spectra were acquired in which the concentration of a 1:3:4 mixture of **1a**:**2a**:proton sponge was varied (Fig. 3). The variation of Δδ with concentration indicated that at concentrations above 2 mM in THF-d_8 conformational preference does not change with concentration, but that below 2 mM, the induced conformational preference diminishes.

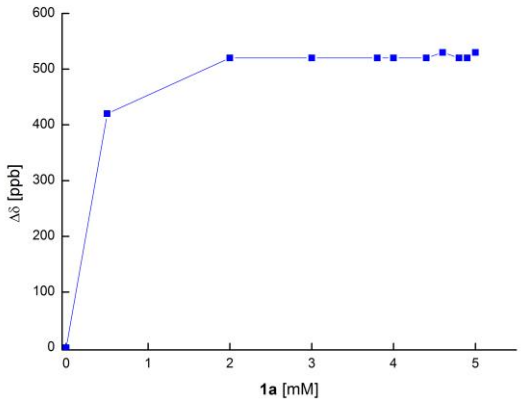

Fig 3. Concentration-dependence of induced conformational preference. Plot of the anisochronicity (Δδ, ppb) of the labelled $^{13}CH_3$ signals of **1a** *vs* concentration of **1a** [mM] recorded in THF-d_8 at 296 K. Ratio proton sponge:**1a**:**2a** = 4:1:3.

We next explored the ability of phosphate anions of alternative structure to induce a conformational preference.

Four phosphoric acids **2a-2d** (Figure 1) were compared. 3 equiv. of the acids were added to **1a**, and their ability to induce conformational changes monitored by measuring the resulting change in $\Delta\delta$. The results are shown in Figure 4.

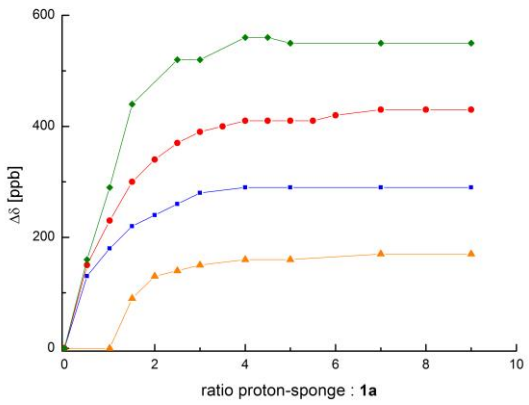

Fig 4. Induction of conformational preference as a function of phosphate anion structure. Plot of the anisochronicity (Δδ, ppb) of the labelled $^{13}CH_3$ signals of **1a** vs amount of added proton sponge for several phosphoric acids, recorded in THF-d8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{2}]_{initial}$ = 15mM; ◆ (**2a**), ● (**2b**), ■ (**2c**) and ▲(**2d**).

Among the four phosphoric acids tested, **2a** showed the highest induction of conformational preference in foldamer **1a**. In the case of phosphoric acids with bulky substituents, it is likely that steric interactions between the biaryl unit and the helix magnify the stereochemical inductive effect of the chiral phosphate within the urea binding site of the foldamer. In all four cases, Δδ increased with increasing concentration of base, reaching a plateau at a maximum value of 3 equivalents. The order of magnitude of the binding constants *K* for the paired foldamer-phosphate system was estimated[56] for *in situ* formation of phosphate using titrations of **1a** with proton sponge and **2a** (3 equiv), **2b** (3 equiv), **2c** (3 equiv), and **2a** (1 equiv). Binding constants were also estimated for the phosphate base preformed from **2a** with proton sponge (see supporting information for details).

The experimental titration plots plateau around 2:1 binding stoichiometry. In order to determine binding constants for the phosphate-foldamer interaction, the chemical shift difference Δδ was monitored as a response to the binding of the guest to the host. Fitting the change in Δδ to both a 2:1 and a 1:1 binding model indicated that close modelling of the data was possible only with a 1:1 binding model. Estimates of binding constants for **1a** and **2a** of K = 4600 ± 2700 M^{-1} (for 3 equiv **2a**) and K = 4500 ± 1400 M^{-1} (for 1 equiv **2a**) were obtained. For acids **2b** and **2c**, binding constants were obtained of 600 ± 100 M^{-1} and 480 ± 160 M^{-1} respectively. These are both smaller by a factor of 10 than the binding constant for **2a**, which also showed weaker induction of screw sense preference. Fitting of experimental data for **1a** binding the phosphate anion preformed from **2a** gave an estimated binding constant of 1200 ± 360 M^{-1}.

All estimated binding constants *K* are within a range from 500 to 5000 M^{-1}, which confirms our observations that the affinity of foldamer-ureas and chiral phosphates is determined by chiral anion recognition via hydrogen bonding interactions.[39,49] These binding constants compare with other urea-anion systems. For example, Wilcox showed that mono-(*m*-nitroaryl)urea derivatives form stable 1:1 complexes with a benzoate (K = 2.7 x 10^4 M^{-1}) and with a phosphate (K = 9.0 x 10^3 M^{-1}) in chloroform,[57,58] and Guichard's aliphatic helical oligoureas give binding constants of K = 3500 M^{-1} for acetate anions in DMSO/CD_3CN (5:95).[49]

Assuming 1:2 binding with these values of binding constants, a maximum level of conformational control, and hence a maximum value of Δδ, will be reached even wih greater ratios of phosphoric acid **2a** to foldamer **1a**. Raising the initial amount of **2a** in solution from 3 equivalents to 6 and adding up to 9 equiv proton sponge gave a slightly increased Δδ(max) of 625 ppb (h.e. = 32%) at 6 equiv (▲ curve), compared to 560 ppb (h.e. = 28%) at 3 equiv (■ curve, Figure 5). However, with 6 equivalents **2a**, Δδ peaked at about 4 equiv proton sponge, then dropped back to the same 560 ppb plateau. In the same NMR tube, the amount of phosphoric acid was again increased by adding 3 equivalents solid **2a** twice more, leading to an increase of Δδ to the same value of ca 625 ppb (● and ◆ curves).

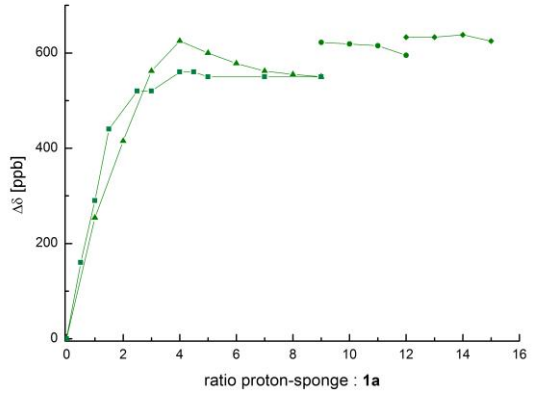

Fig 5. Plot of the anisochronicity (Δδ, ppb) of the labelled $^{13}CH_3$ signals of **1a** vs amount of added proton sponge for different starting ratios of **2a:1a**; ■ 3 equiv, ▲ 6 equiv, ● 9 equiv and ◆ 12 equiv phosphoric acid.

We thus conclude that a screw sense preference (helical excess) of around 30% may be induced by interaction of an appropriately chose chiral phosphate with a urea-capped foldamer, and that this value is reached more or less consistently at this concentration of **1a** when 3 equiv of phosphate are present. Adding even more phosphate may increase the level of control slightly, but the change is not significant.

In order to determine whether the induced screw sense is left- or right-handed, we modified **1a** by incorporation of an enantioselectively labelled *R*-Aib*OMe residue with 75% ^{13}C in the pro-*R* Me group and 25% ^{13}C in the pro-*S*,[59] giving labelled foldamer **1a***. Observation of the relative positions of the major and minor peaks in the ^{13}C NMR spectrum of **1a*** indicates that (*R*)-VAPOL-derived phosphoric acid **2a** (which

has *M* helicity) induces a right-handed *P* helix and that (*S*)-VAPOL-derived phosphoric acid **2e** (which has *P* helicity) induces a left-handed *M* helix (see Supporting Information). The binding model illustrated in Fig. 6, in which the phenanthrenes direct the twist of the peptide, accounts for this selectivity.

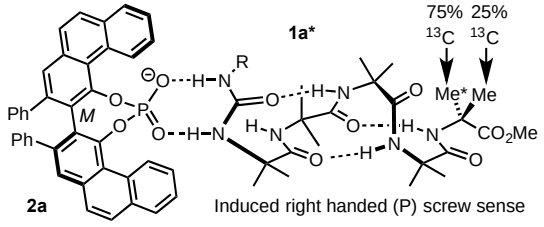

Fig 6. Screw-sense induction by binding of chiral phosphate **2a** to enantioselectively ^{13}C-labelled foldamer **1a***.

Conclusions

Selective interactions between designed binding sites and ligands are well established in supramolecular chemistry, and we have demonstrated the additional biomimetic feature of conformational responsiveness, designing molecules that undergo conformation changes, and ultimately induce chemical changes, by sensing their chemical environment. Incorporation of a urea-based anion recognition site into an amide foldamer allows the foldamer to respond to an environmental signal – a hydrogen-bonded interaction with a chiral anion – by changing its global conformational preference. This simple hydrogen-bonded mechanism of interaction complements the design of related binding sites based on boron,[35] copper,[37] or basic nitrogen[32] centres. Non-covalent interaction mediated by hydrogen bonding leads to solvent-dependent asymmetric induction of screw sense preference to differing extents, according to the pairing of various binding sites with various chiral phosphates. This intermolecular induction of conformational preference transforms a helical foldamer into a dynamic signal transduction device potentially capable of intermolecular information processing.[23] Future developments could see the use of this method in potential applications such as remote catalysis and transmembrane information processing, or in more complex foldamer-to-foldamer communication networks.

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Graphical abstract