Electronic Supplementary Material (ESI) for Organic & Biomolecular Chemistry.

SUPPORTING INFORMATION

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

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1 General Information

NMR spectra were recorded on a Bruker Advance III HD 500 MHz spectrometer with a cryo-enhanced probe and a Bruker Avance III 400 MHz spectrometer. All NMR spectra were referenced on the solvent peak. Melting points were measured on a Gallen Kamp melting point apparatus and are uncorrected. Infra-red spectra were recorded on an ATi Perkin Elmer Spectrum RX1 FT-IR spectrometer and on a Thermo Scientific Nicolet iS5 FTIR Spectrometer. High resolution mass spectra were recorded by the Mass Spectroscopy Services at the University of Manchester (http://www.chemistry.manchester.ac.uk/our-research/facilities/mass-spectrometry-service/) and at the University of Bristol (http://www.chm.bris.ac.uk/ms/mshome.xhtml). All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. All reactions were performed under an inert atmosphere. Starting 2-aminoisobutyric acid (Aib) compounds were synthesised as described previously.[1]

[1] (a) Angew. Chem. Int. Ed. **2009**, *48*, 5962–5965. (b) Angew. Chem. Int. Ed. **2010**, *49*, 6836–6839.

2 Titration studies of foldamer-ureas 1 by *in situ* formation of a chiral phosphate from phosphoric acids 2 (fixed amount) and proton sponge (variable amount)

2.1 Procedure for the titration of 1 (5 mM) with 3 equivalents 2

As foldamer-ureas **1** (0.003 mmol, 5 mM) showed limited solubility, they were directly weighed out in the NMR tube. The phosphoric acid **2** (0.009 mmol, 3 equiv, 15 mM) was added directly as a solid and THF-d_8 (600 µL) was added. This two component mixture was not soluble. A 1 mL solution of proton sponge was prepared (120 mM, 25.7 mg). Aliquots of this stock solution (12.5 µL, 0.5 equiv) were added to the NMR tube, the mixture was shaken and ^{13}C-DEPT135 and ^{1}H spectra were recorded at 296 K. The mixture dissolved during the addition of proton sponge. NMR spectra and plots of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in foldamer-ureas **1** *vs* the ratio **1**:proton sponge are shown in Figures 1-27**.**

Entry	Foldamer-urea	[mg]	chiral phosphoric acid	[mg]
1	**1a**	2.02	**2a**	5.41
2	**1a**	2.02	**2b**	7.89
3	**1a**	2.02	**2c**	6.78
4	**1a**	2.02	**2d**	3.13
5	**1b**	2.02	**2a**	5.41
6	**1c**	1.98	**2a**	5.41
7	**1d**	1.63	**2a**	5.41

2.2 Procedure for the titration of 1a (5 mM) with 1 equivalent 2a

Foldamer-urea **1a** (0.003 mmol, 2.1 mg, 5 mM) it was directly weighed out in the NMR tube. **2a** (0.003 mmol, 1.8 mg, 1 equiv, 5 mM) was added directly as a solid and THF-d_8 (600 µL) was added. This two component mixture was not soluble. A 1 mL solution of proton sponge was prepared 60 mM, 13 mg). Aliquots of this stock solution (10 µL, 0.2 equiv) were added to the NMR tube, the mixture was and shaken and ^{13}C-DEPT135 and ^{1}H spectra were recorded at 296 K. The mixture dissolved during the addition of proton sponge. NMR spectra and the plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio **1a**:proton sponge are shown in Figures 28-31**.**

2.3 Procedure for the titration of 1a (2 mM) with 3 equivalent 2a

1a (0.003 mmol, 2 mM) was directly weighed out in the NMR tube. The phosphoric acid **2a** (0.0036 mmol, 2.16 mg, 3 equiv, 6 mM) was added directly as a solid and THF-d_8 (600 µL) was added. This two component mixture was not soluble. A 1 mL solution of proton sponge was prepared (48 mM, 10.3 mg,). Aliquots of this stock solution (12.5 µL = 0.5 equiv) were added to the NMR tube, the

mixture was shaken and ^{13}C-DEPT135 and ^{1}H spectra of the solution were recorded at 296 K. The mixture dissolved during the addition of proton sponge. NMR spectra and the plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio **1a**:proton sponge are shown in Figures 32-35**.**

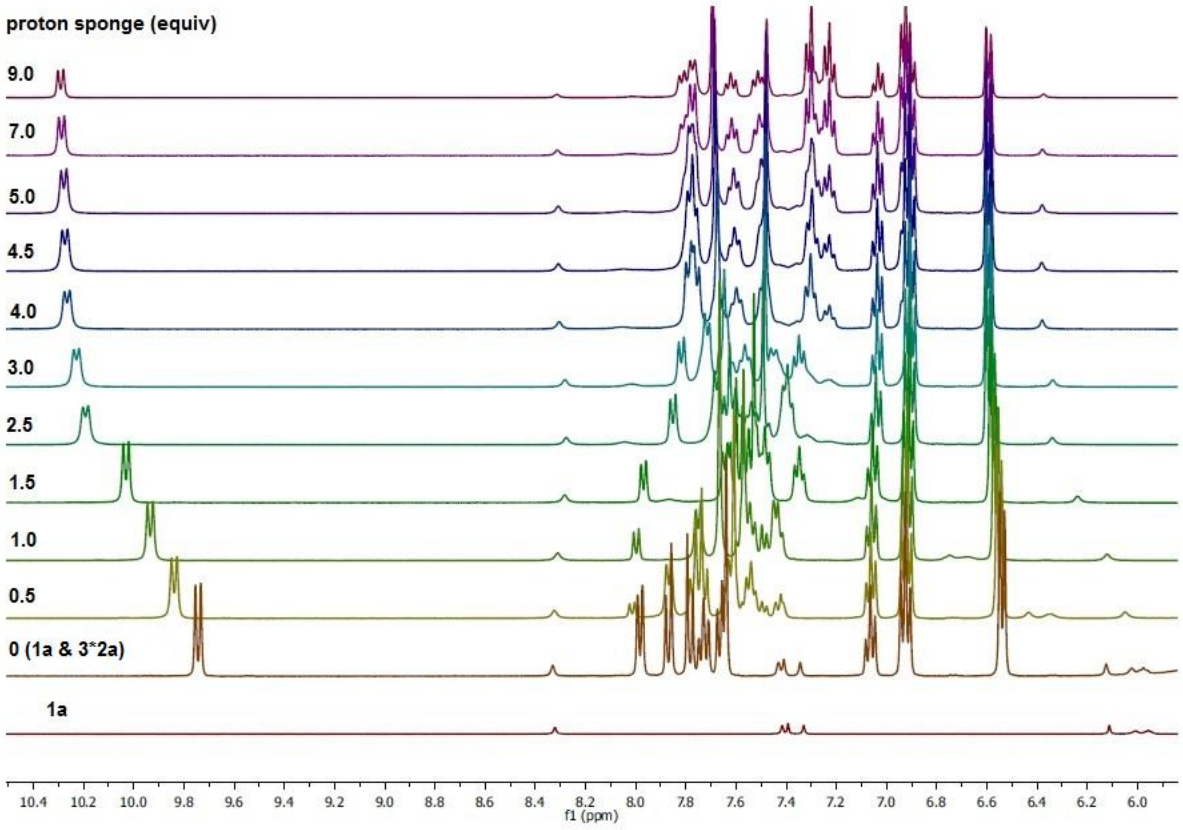


Figure 1 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

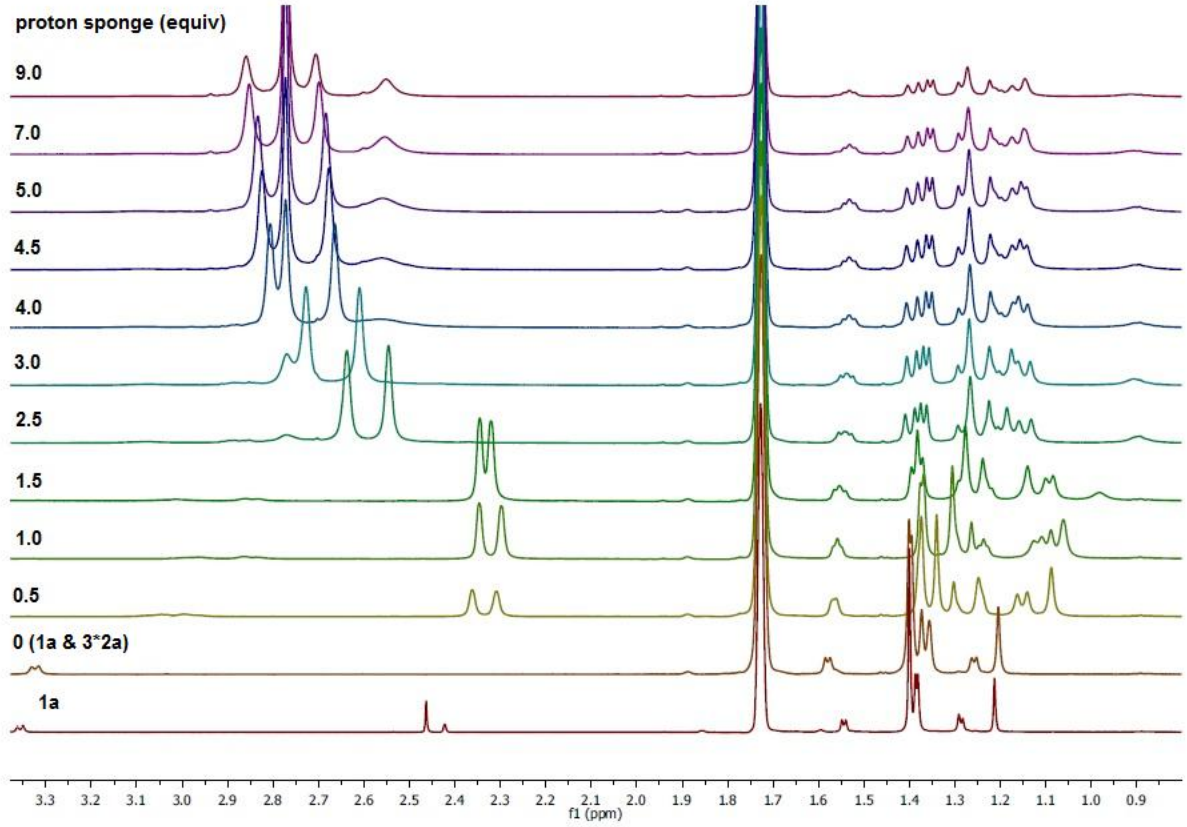


Figure 2 Part of the ^{1}H NMR (400 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

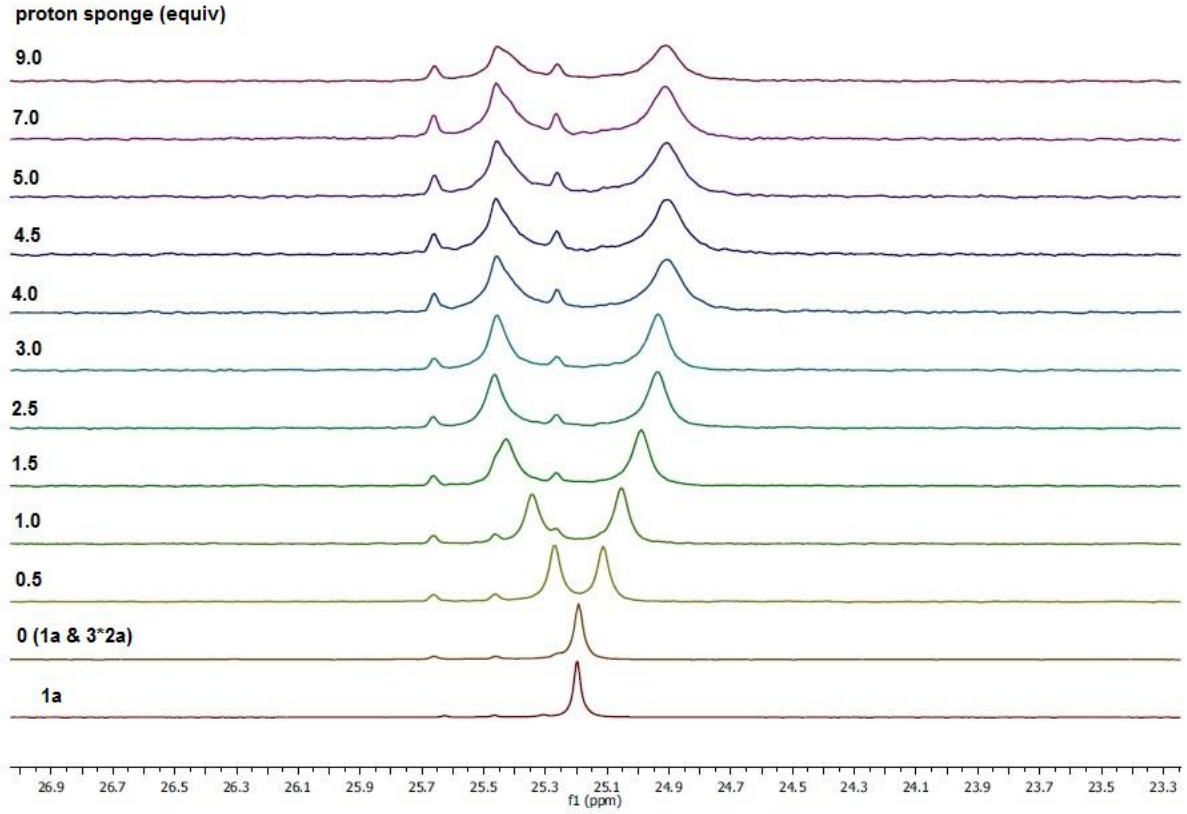


Figure 3 Part of the ^{13}C-DEPT NMR (101 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

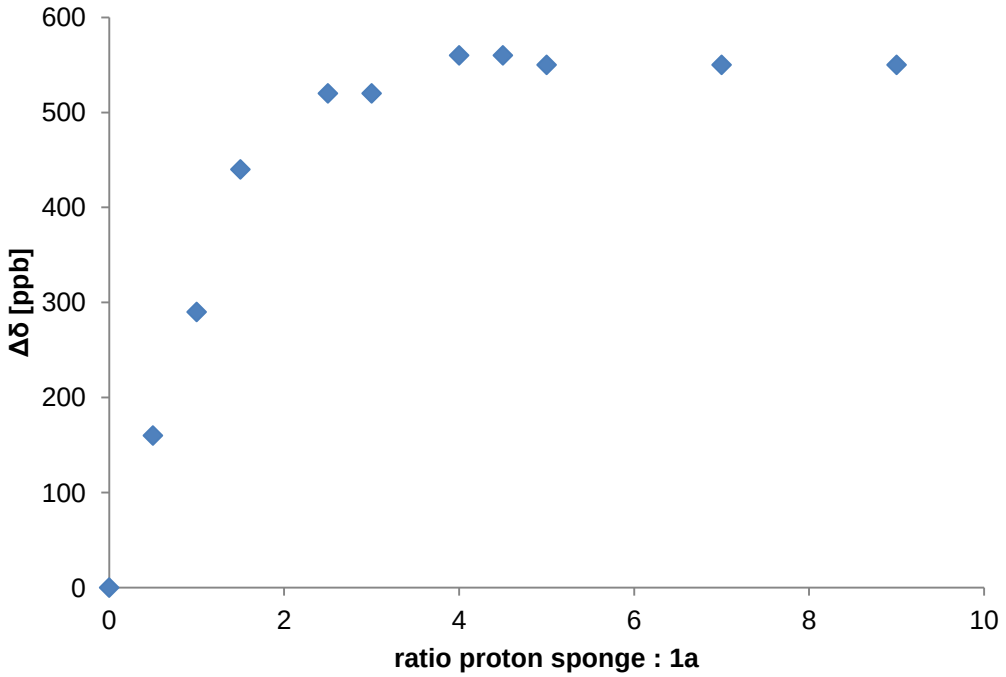


Figure 4 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 3.64 mM, $[\mathbf{2a}]_{initial} = 3*[\mathbf{1a}]_{initial}$

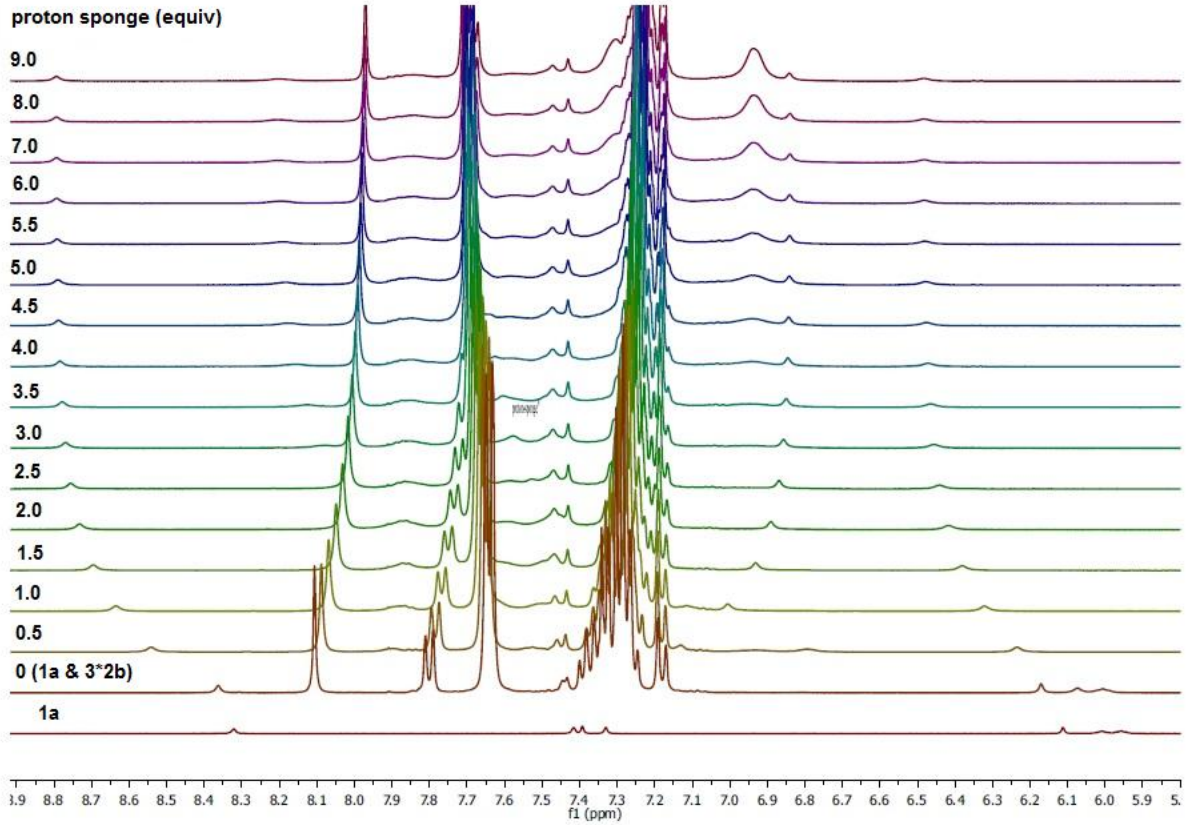


Figure 5 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2b** ($[\mathbf{2b}]_{initial} = 3*[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge.

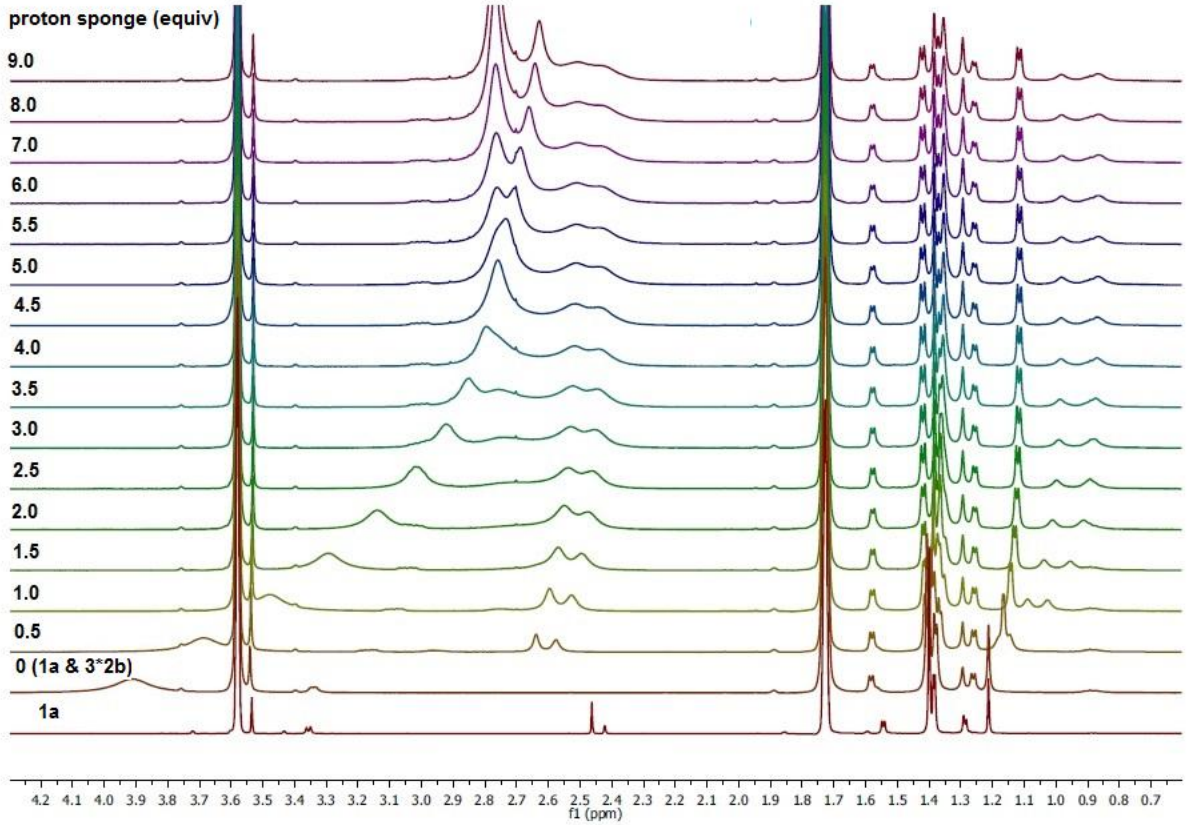


Figure 6 Part of the ^{1}H NMR (400 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2b** ([**2b**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

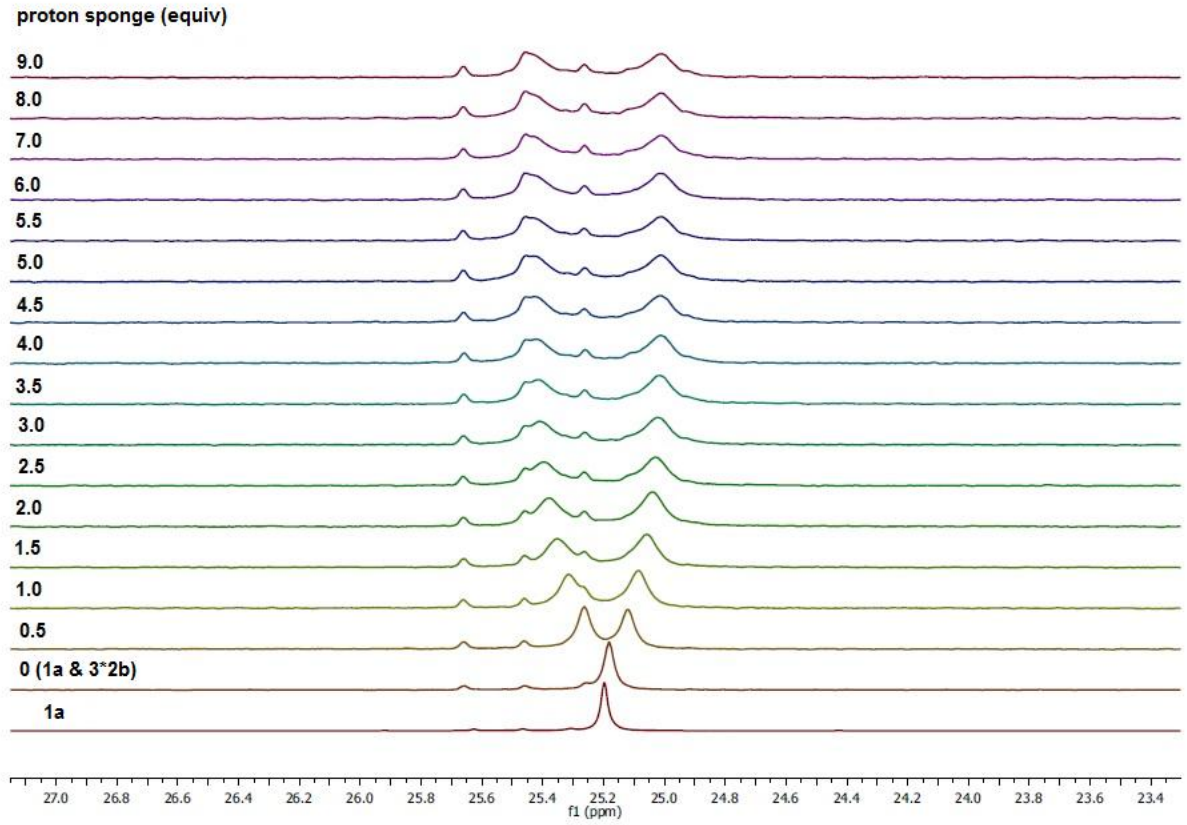


Figure 7 Part of the ^{13}C-DEPT NMR (101 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2b** ([**2b**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

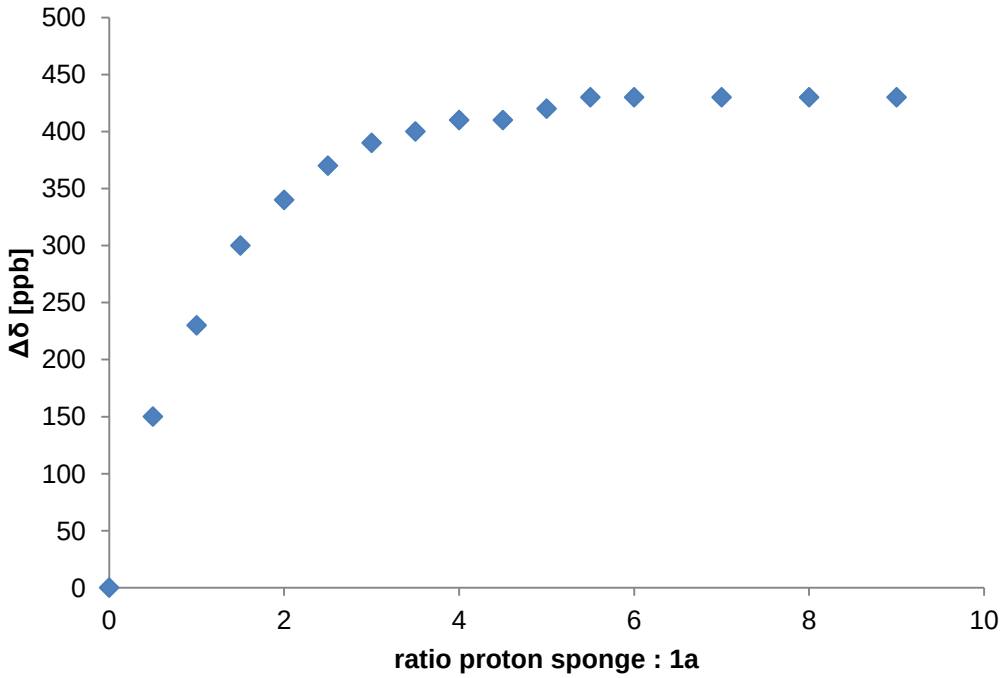


Figure 8 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 3.64 mM, $[\mathbf{2b}]_{initial} = 3*[\mathbf{1a}]_{initial}$

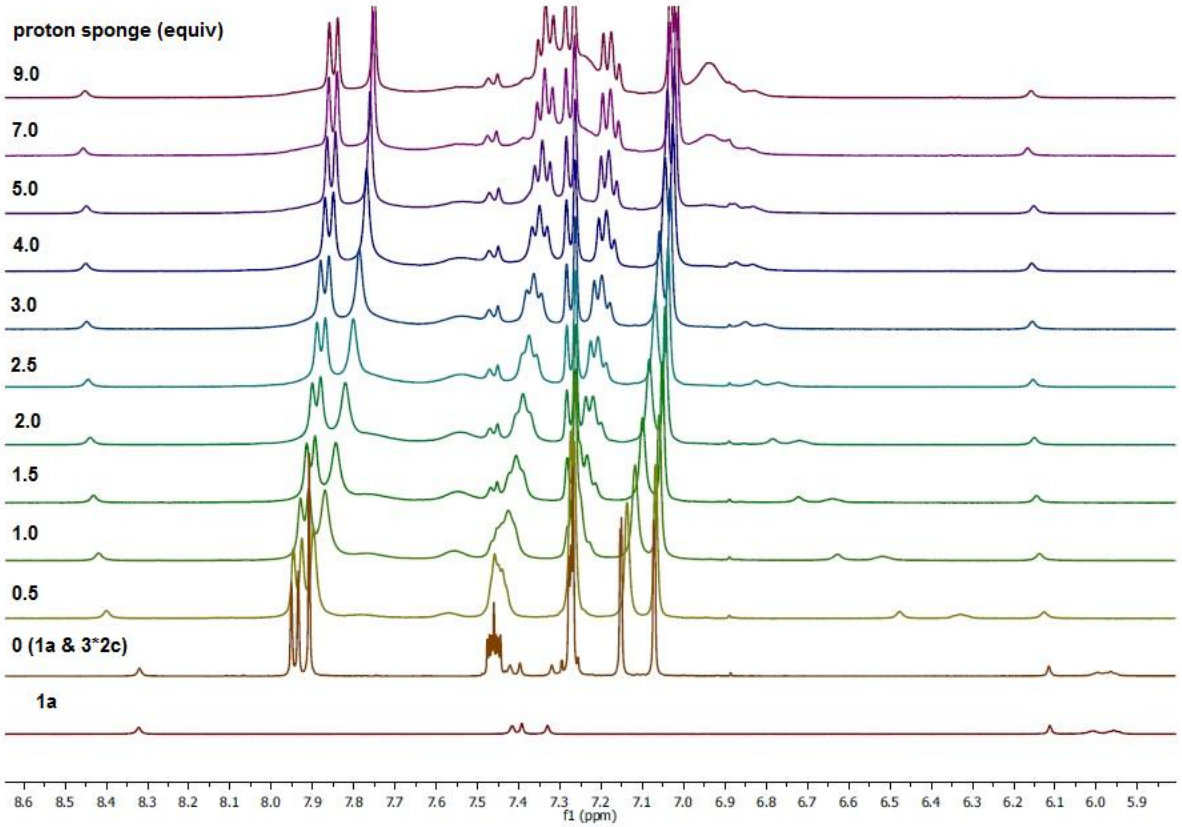


Figure 9 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2c** ($[\mathbf{2c}]_{initial} = 3*[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge.

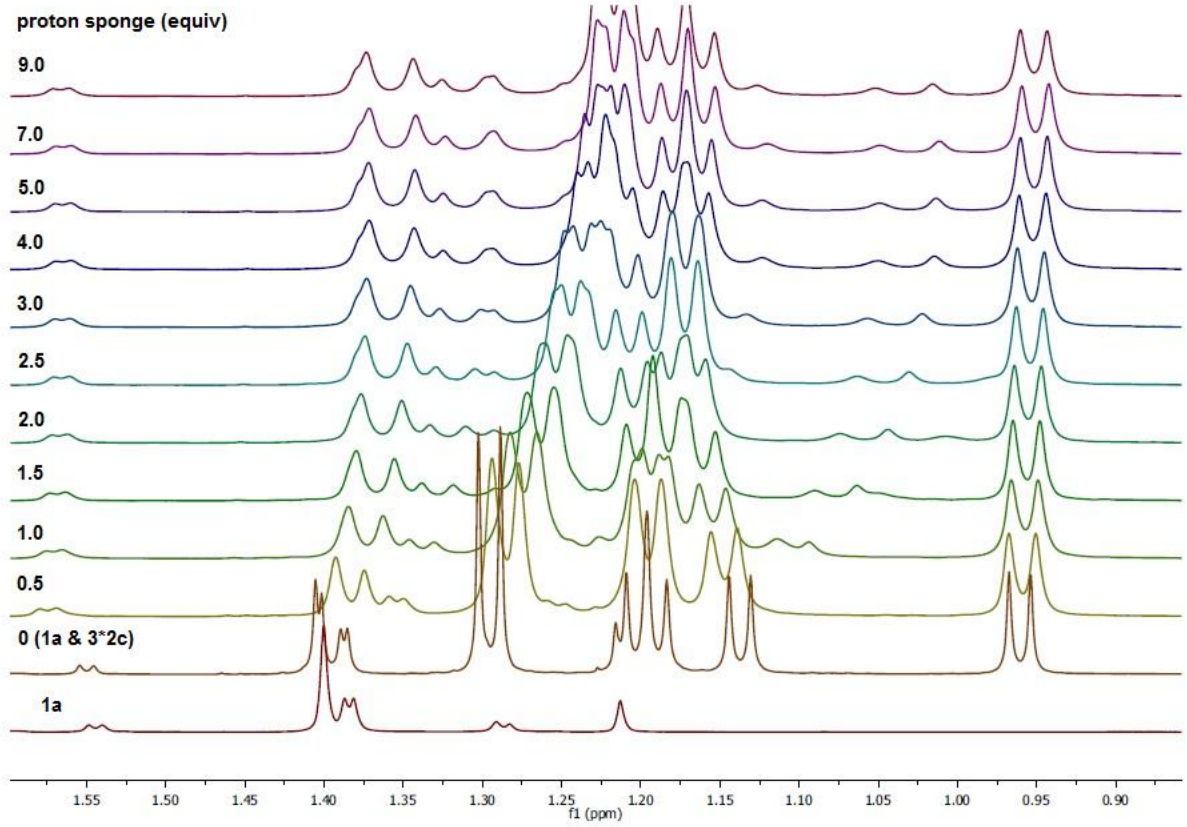


Figure 10 Part of the ^{1}H NMR (400 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2c** ([**2c**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

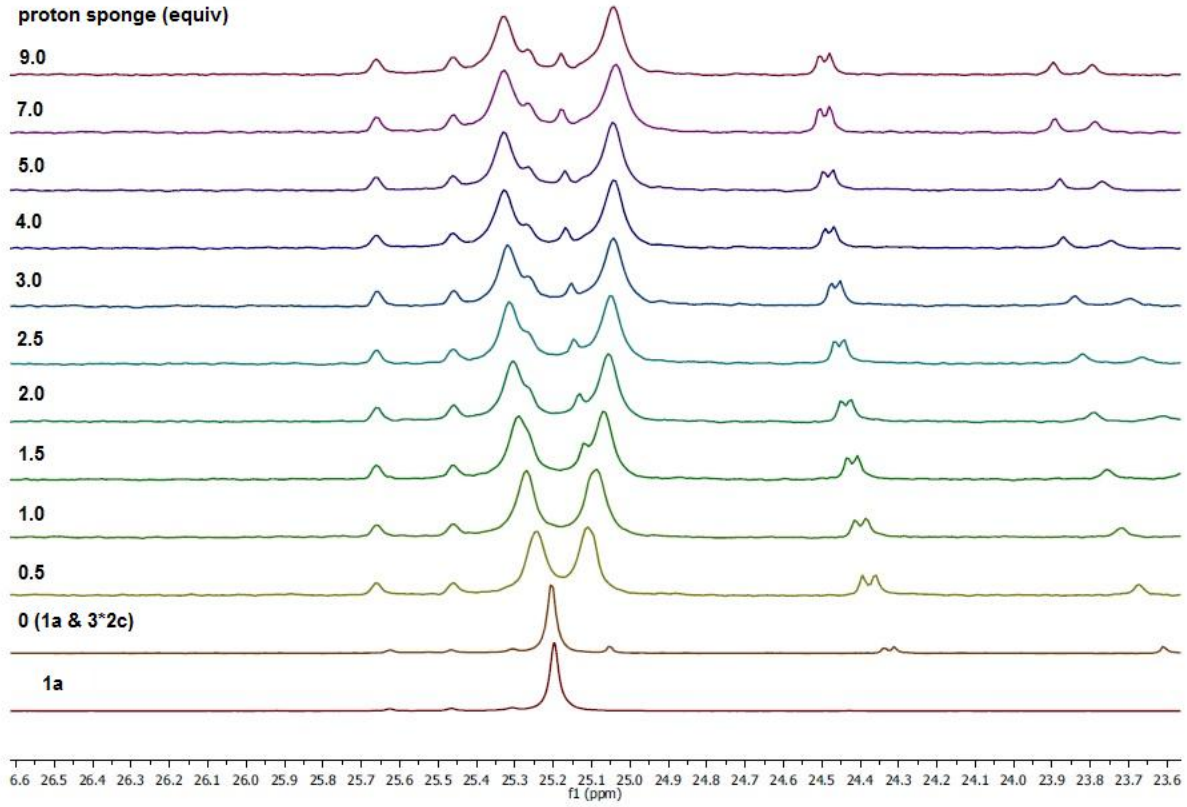


Figure 11 Part of the ^{13}C-DEPT NMR (101 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2c** ([**2c**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

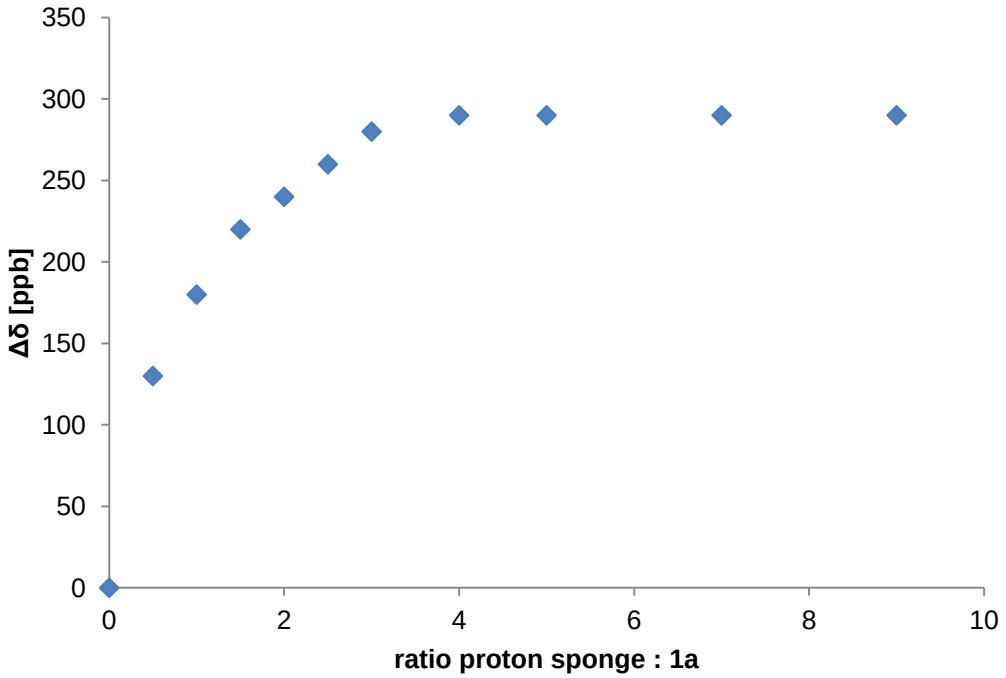


Figure 12 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 3.64 mM, $[\mathbf{2c}]_{initial} = 3*[\mathbf{1a}]_{initial}$

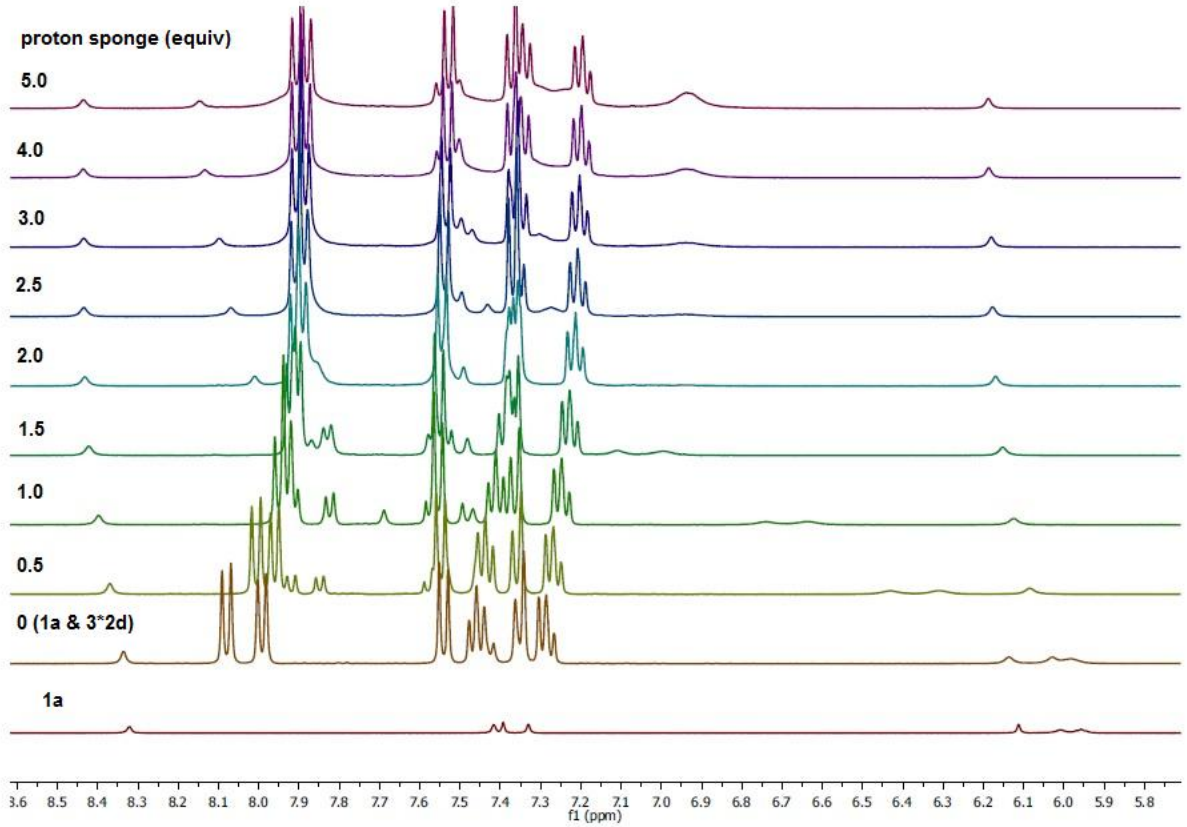


Figure 13 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2d** ($[\mathbf{2d}]_{initial} = 3*[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge.

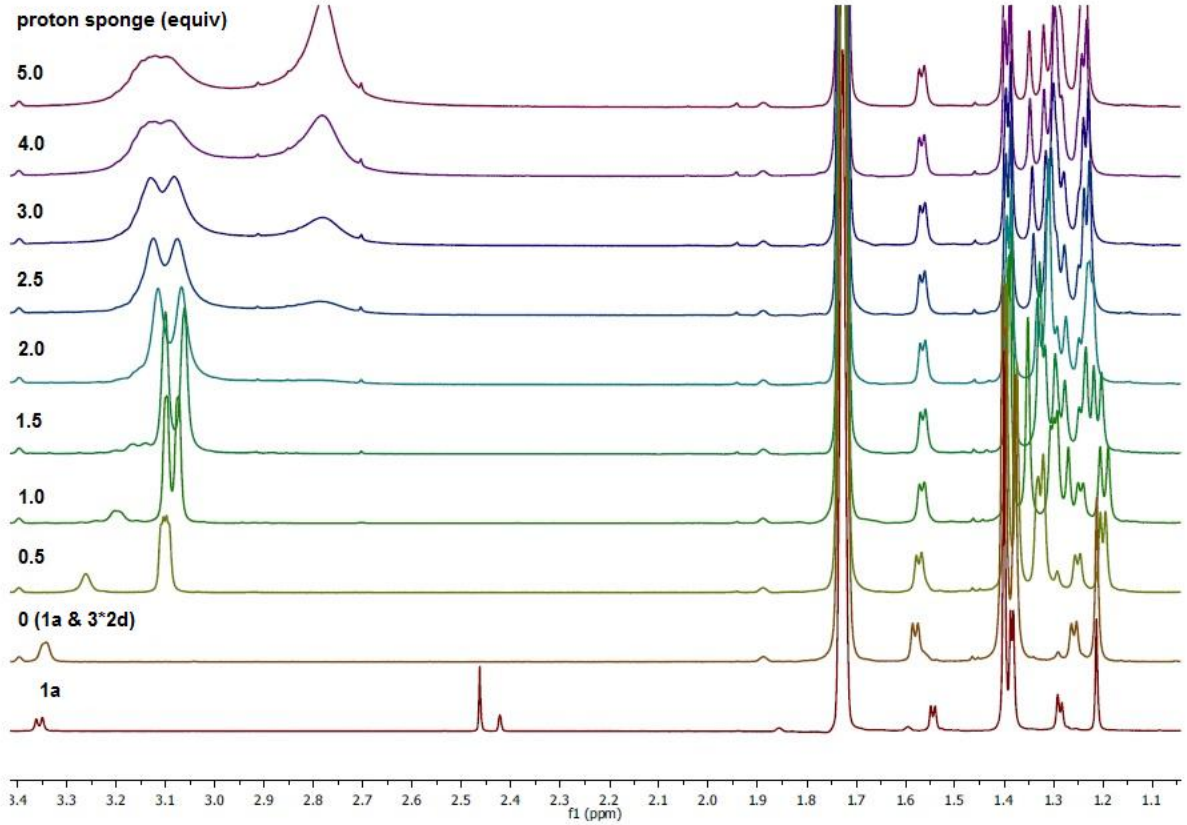


Figure 14 Part of the ^{1}H NMR (400 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2d** ([**2d**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

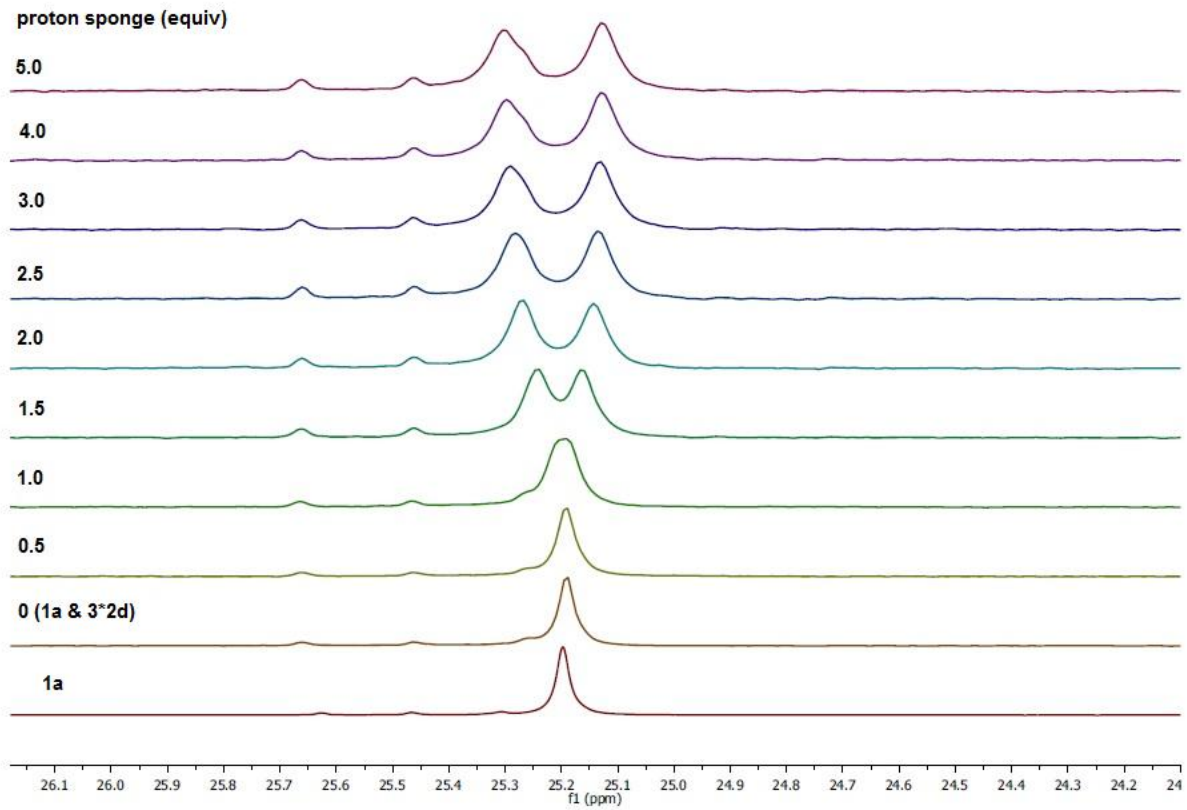


Figure 15 Part of the ^{13}C-DEPT NMR (101 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2d** ([**2d**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

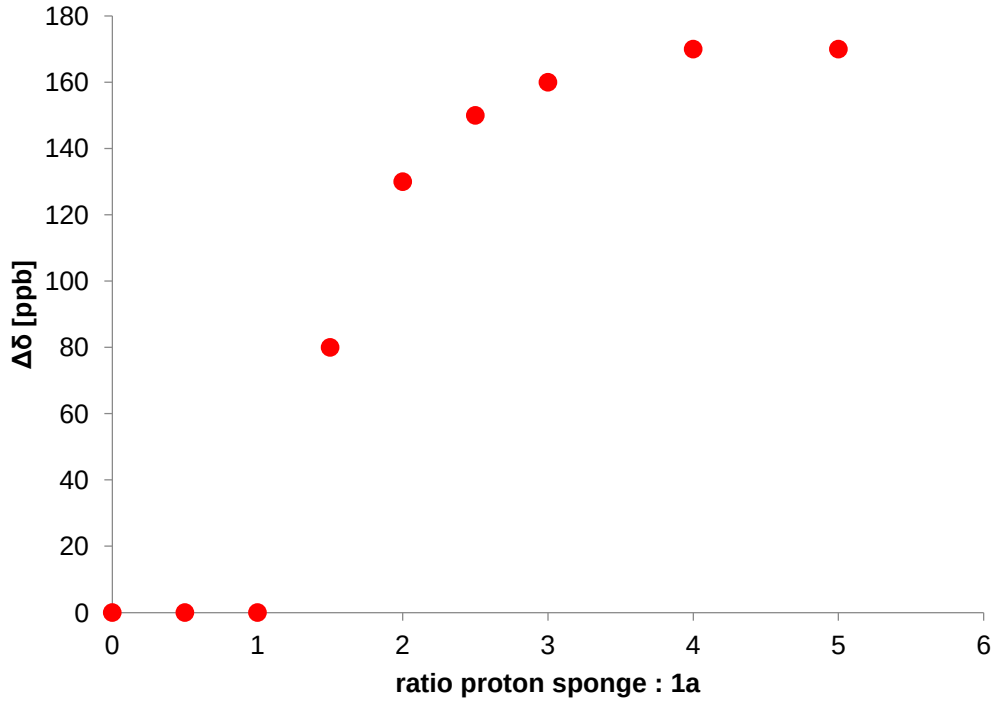


Figure 16 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 4.14 mM, $[\mathbf{2d}]_{initial} = 3*[\mathbf{1a}]_{initial}$

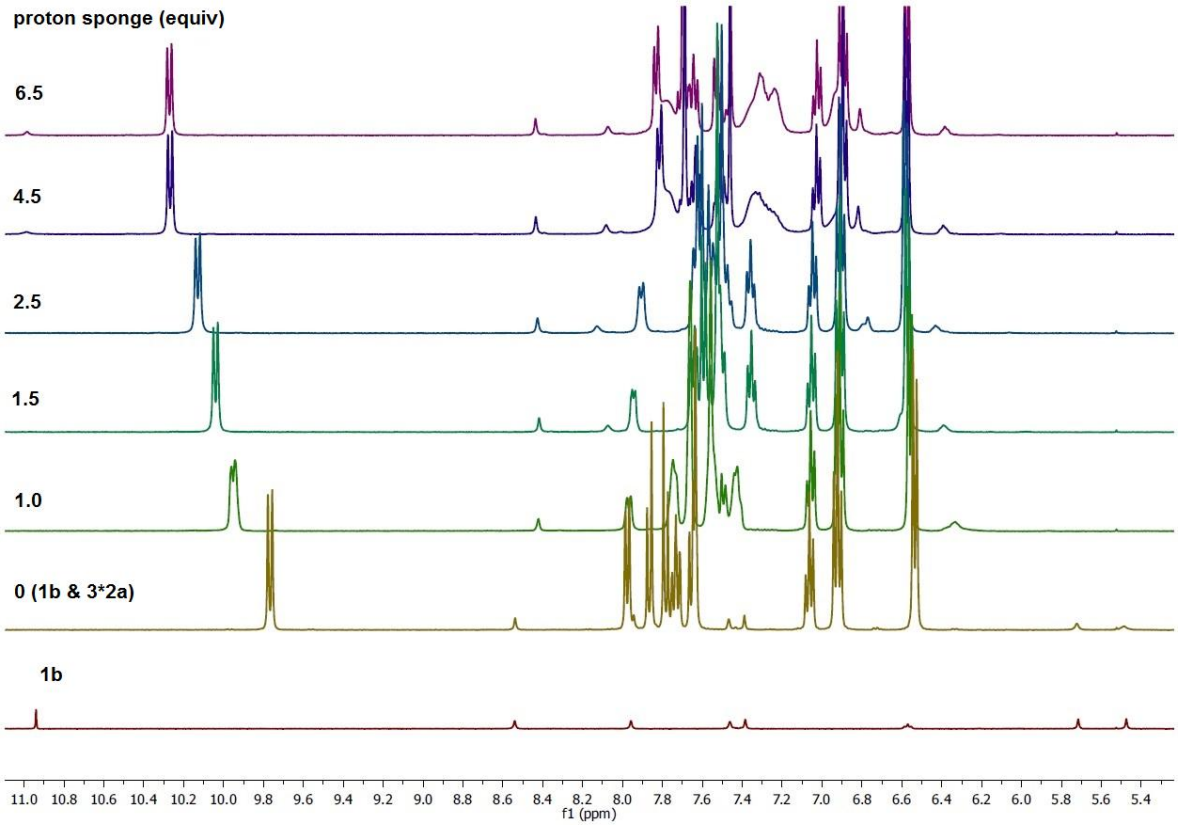


Figure 17 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1b** ($[\mathbf{1b}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ($[\mathbf{2a}]_{initial} = 3*[\mathbf{1b}]_{initial}$) with increasing equivalents of proton sponge.

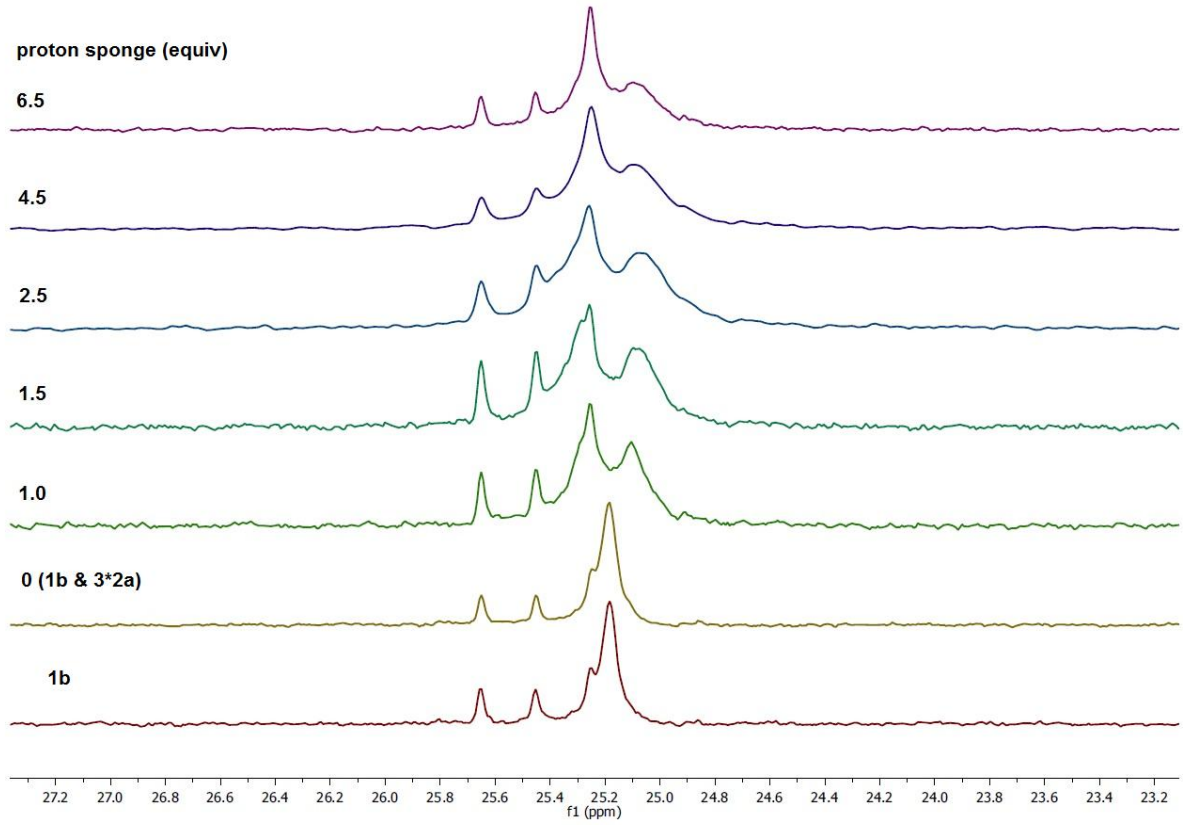


Figure 18 Part of the ^{13}C-DEPT NMR* (101 MHz, THF-d_8, 296 K) spectra from the titration of **1b** ([**1b**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1b**]$_{initial}$) with increasing equivalents of proton sponge. *Accurate measurement of Δδ was not possible as the solubility of this foldamer-urea was very low.

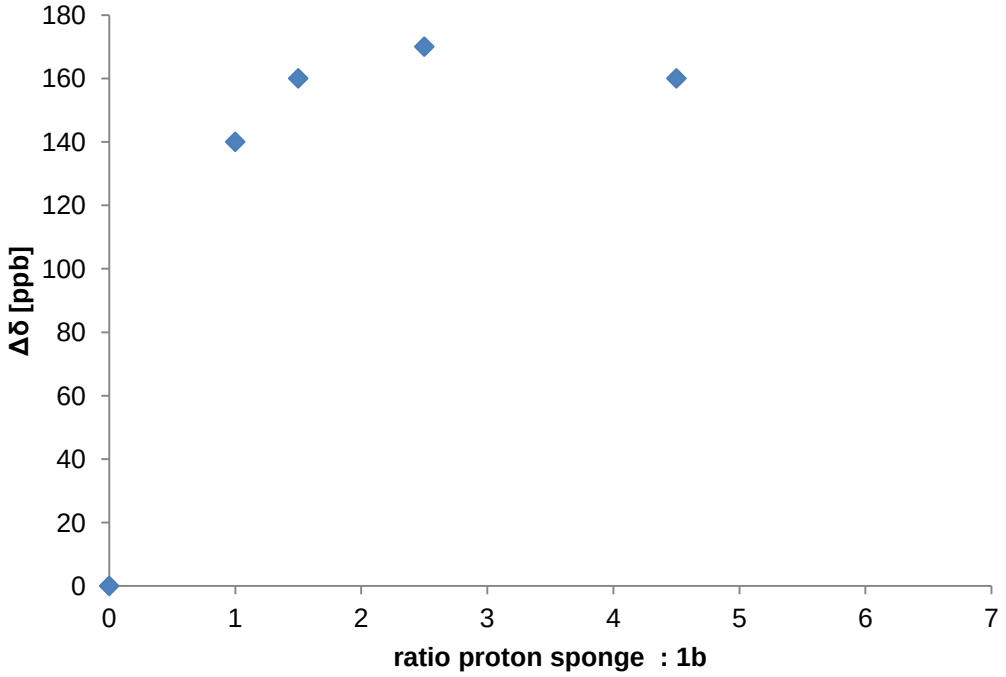


Figure 19 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1b** *vs* the ratio proton sponge:**1b** recorded in THF-d_8 at 296 K; [**1b**]$_{initial}$ = 5 mM, [**1b**]$_{end}$ = 4.29 mM, [**2a**]$_{initial}$ = 3*[**1b**]$_{initial}$

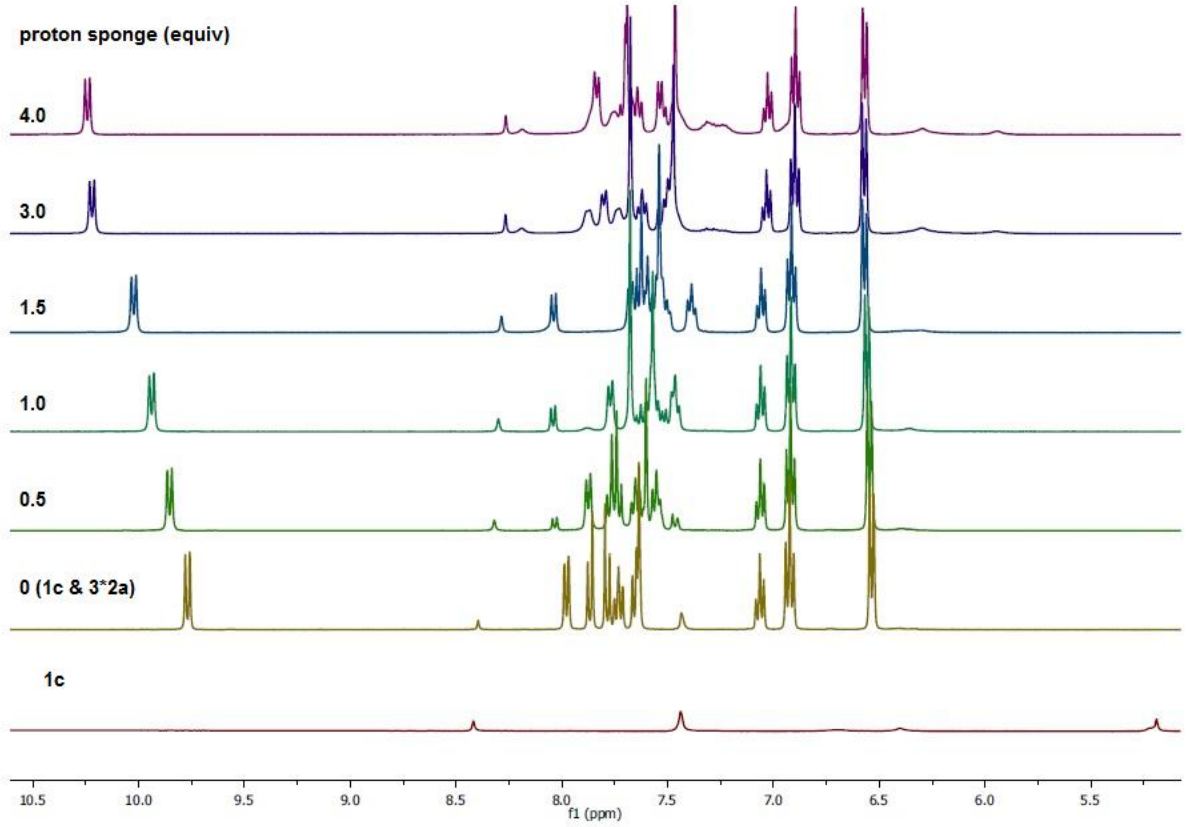


Figure 20 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1c** ([**1c**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1c**]$_{initial}$) with increasing equivalents of proton sponge.

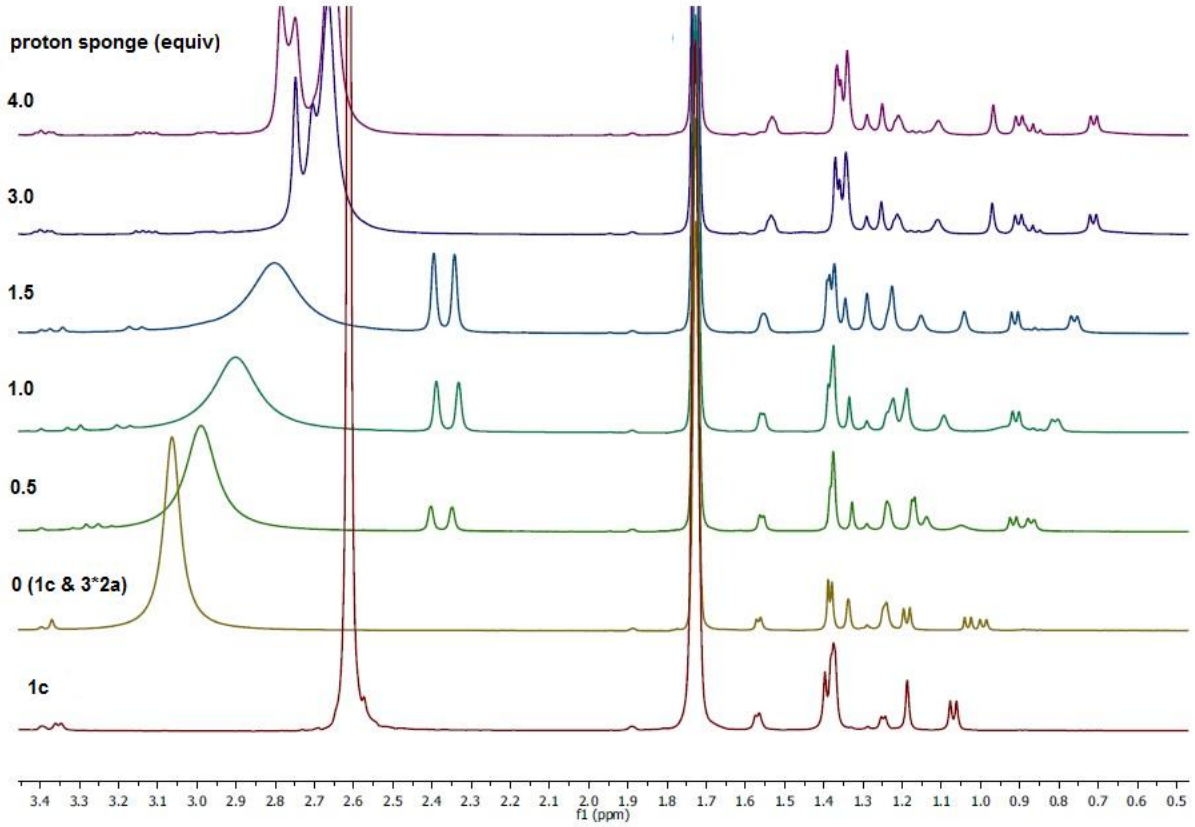


Figure 21 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1c** ([**1c**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1c**]$_{initial}$) with increasing equivalents of proton sponge.

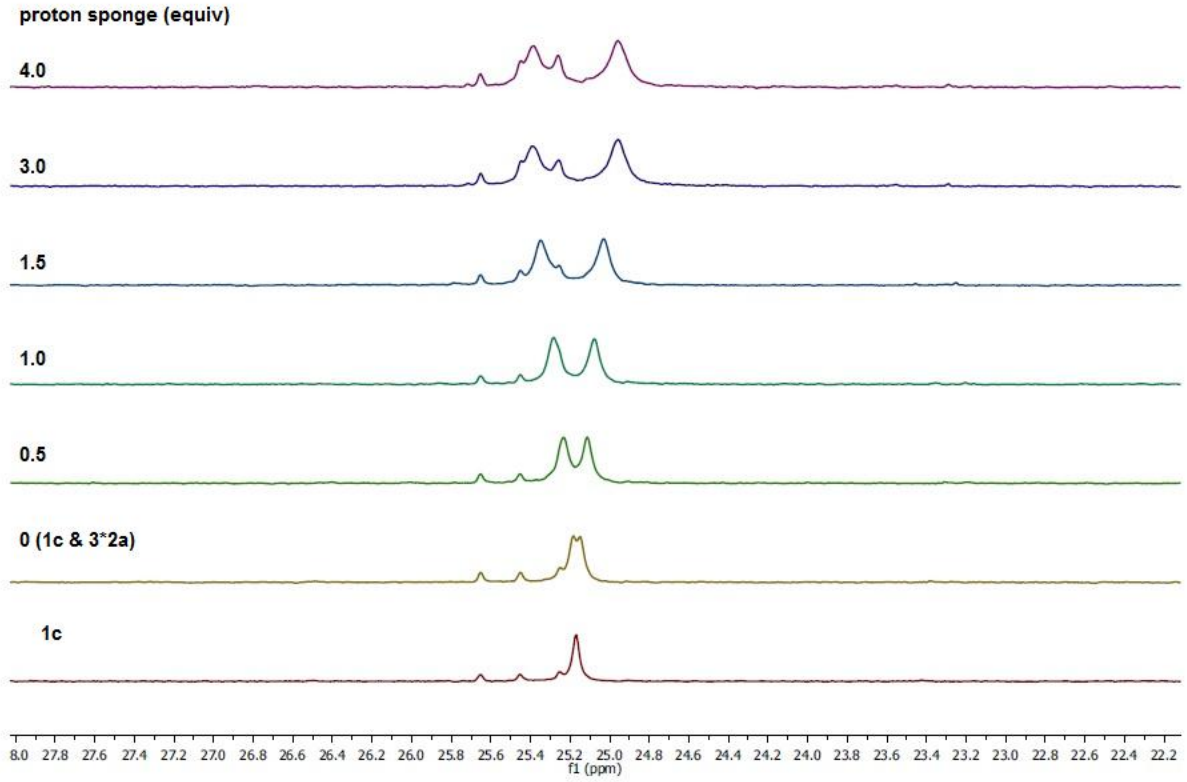


Figure 22 Part of the ^{13}C-DEPT NMR (101 MHz, THF-d_8, 296 K) spectra from the titration of **1c** ([**1c**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1c**]$_{initial}$) with increasing equivalents of proton sponge.

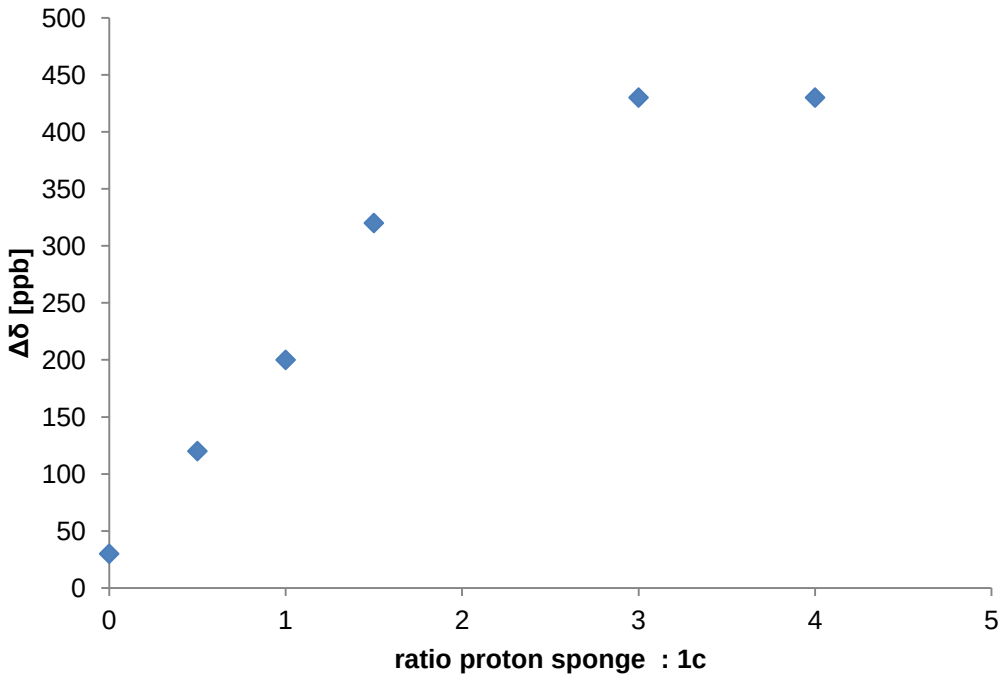


Figure 23 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1c** *vs* the ratio proton sponge:**1c** recorded in THF-d_8 at 296 K; [**1c**]$_{initial}$ = 5 mM, [**1c**]$_{end}$ = 4.53 mM, [**2a**]$_{initial}$ = 3*[**1c**]$_{initial}$

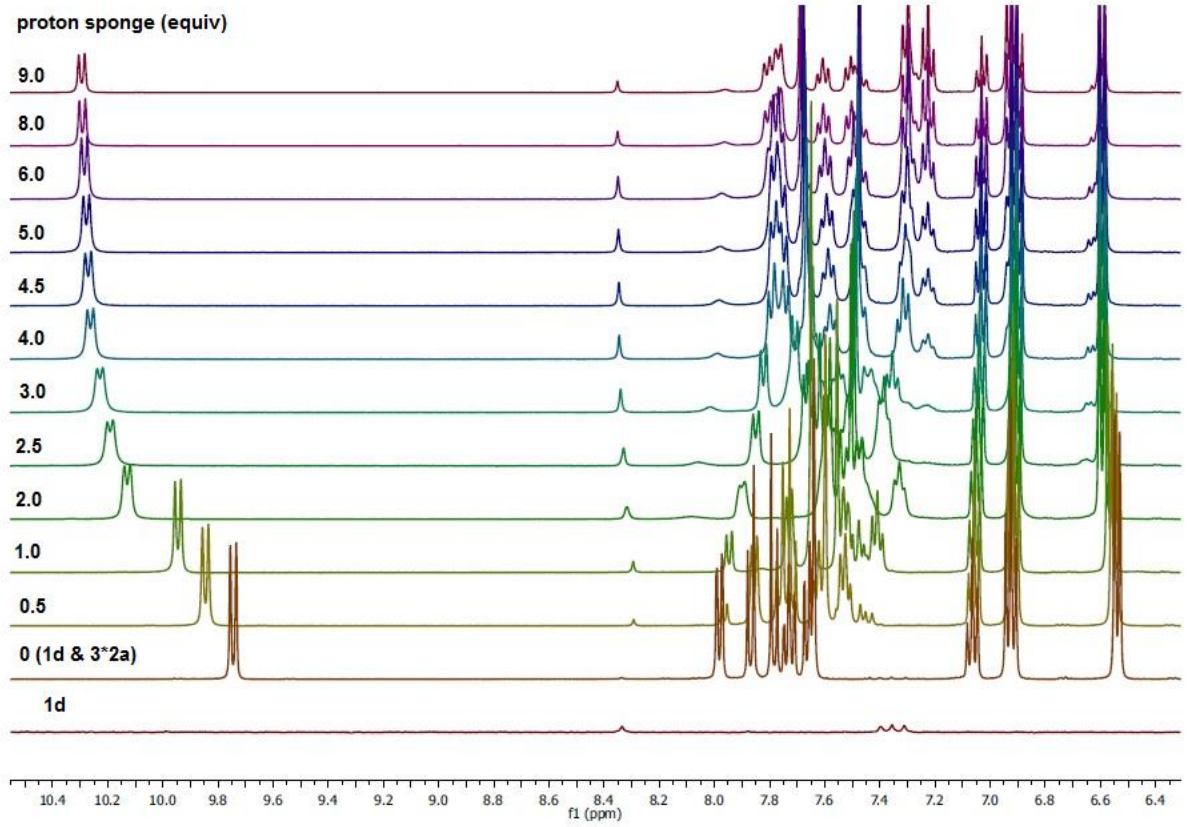


Figure 24 Part of the ^{1}H NMR (400 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1d** ([**1d**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1d**]$_{initial}$) with increasing equivalents of proton sponge.

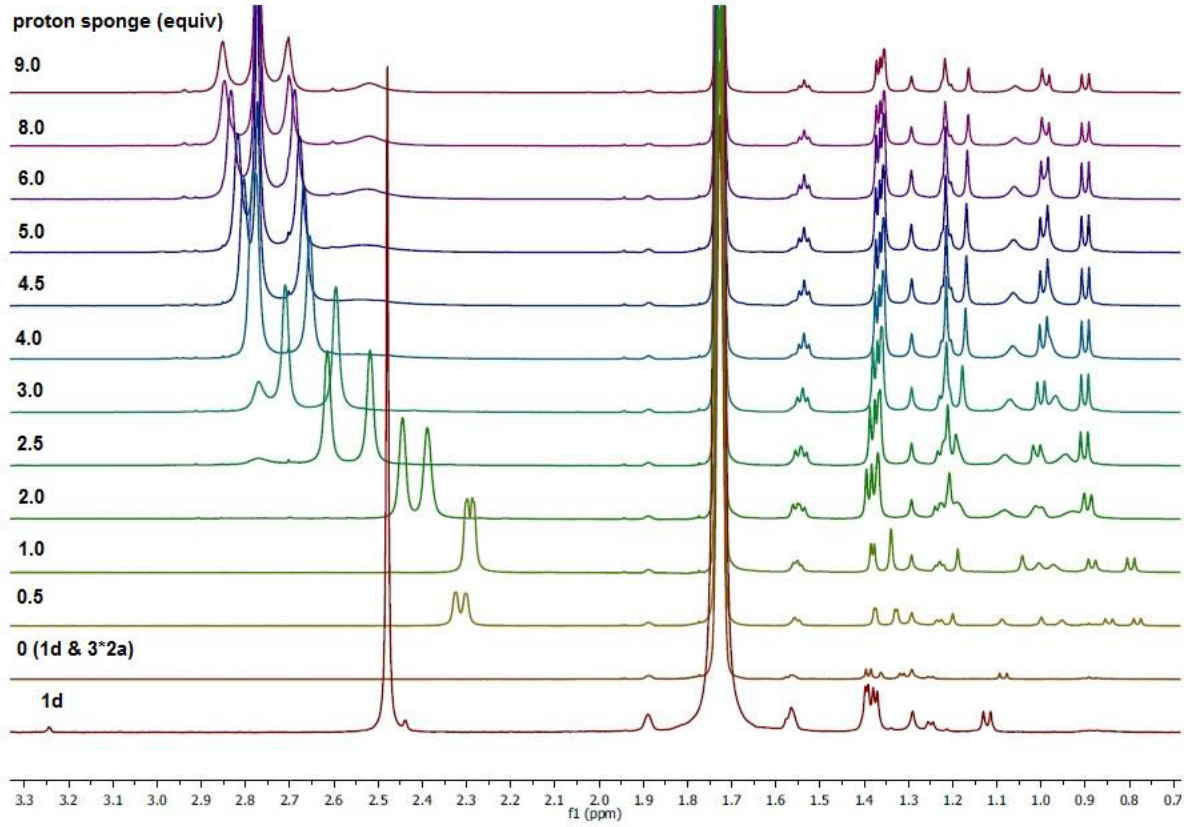


Figure 25 Part of the ^{1}H NMR (400 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1d** ([**1d**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1d**]$_{initial}$) with increasing equivalents of proton sponge.

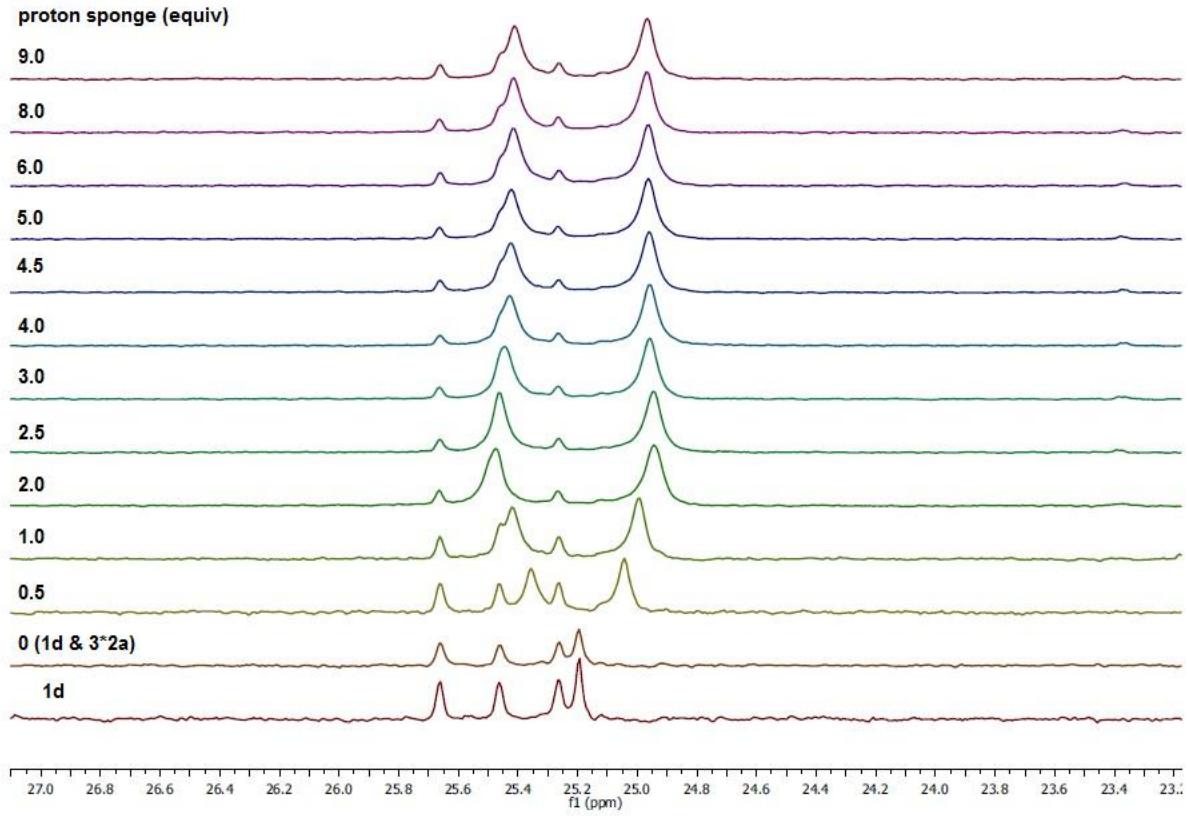


Figure 26 Part of the ^{13}C-DEPT NMR (101 MHz, THF-d_8, 296 K) spectra from the titration of **1d** ([**1d**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1d**]$_{initial}$) with increasing equivalents of proton sponge.

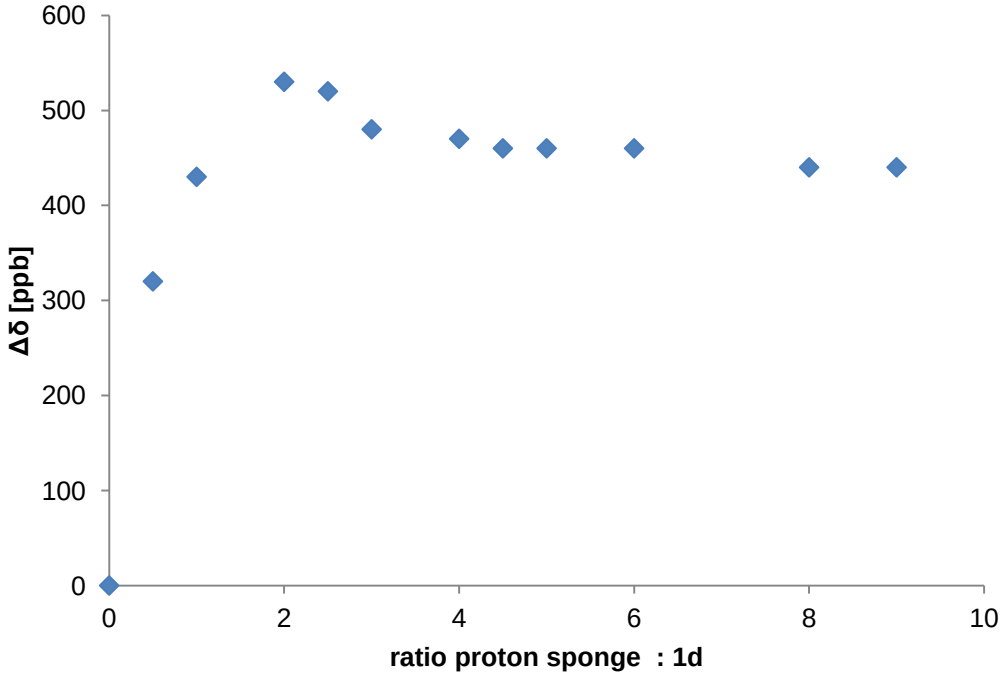


Figure 27 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1d** *vs* the ratio proton sponge:**1d** recorded in THF-d_8 at 296 K; [**1d**]$_{initial}$ = 5 mM, [**1d**]$_{end}$ = 3.64 mM, [**2a**]$_{initial}$ = 3*[**1d**]$_{initial}$

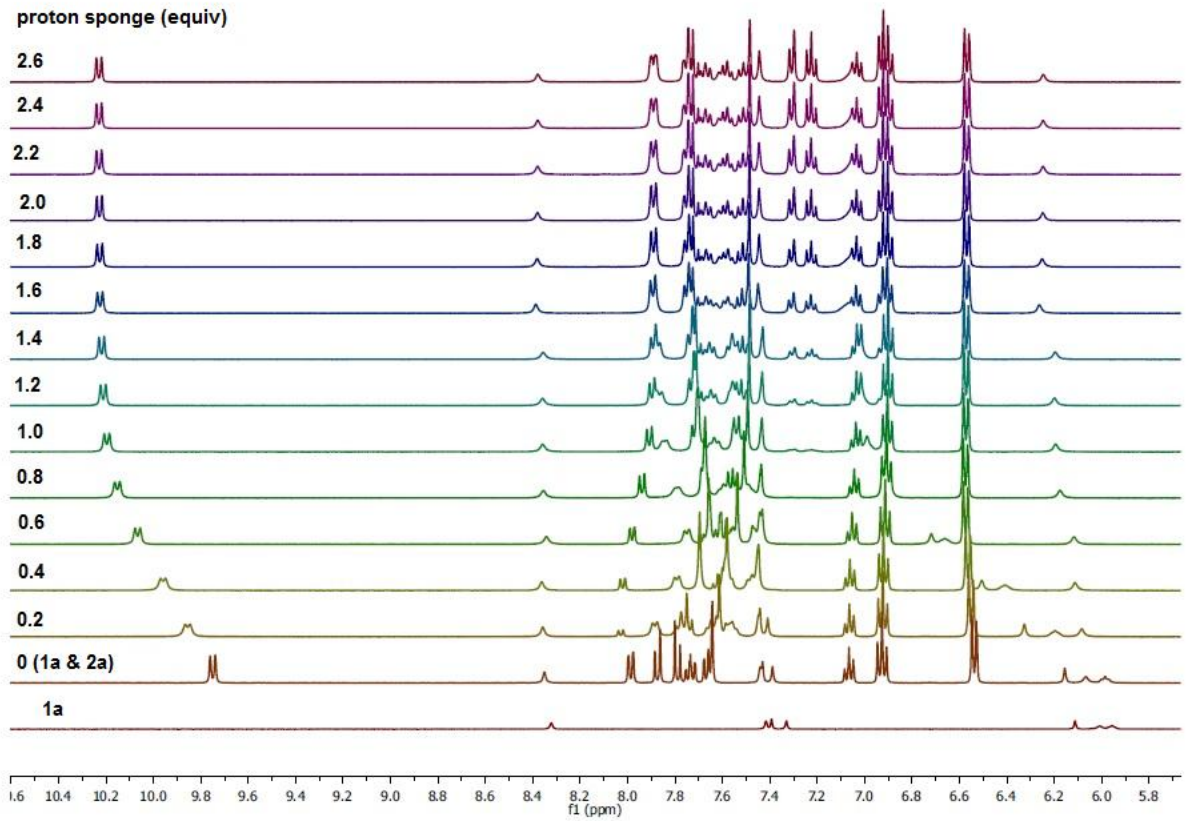


Figure 28 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = [**1a**]$_{initial}$) with increasing equivalents of proton sponge.

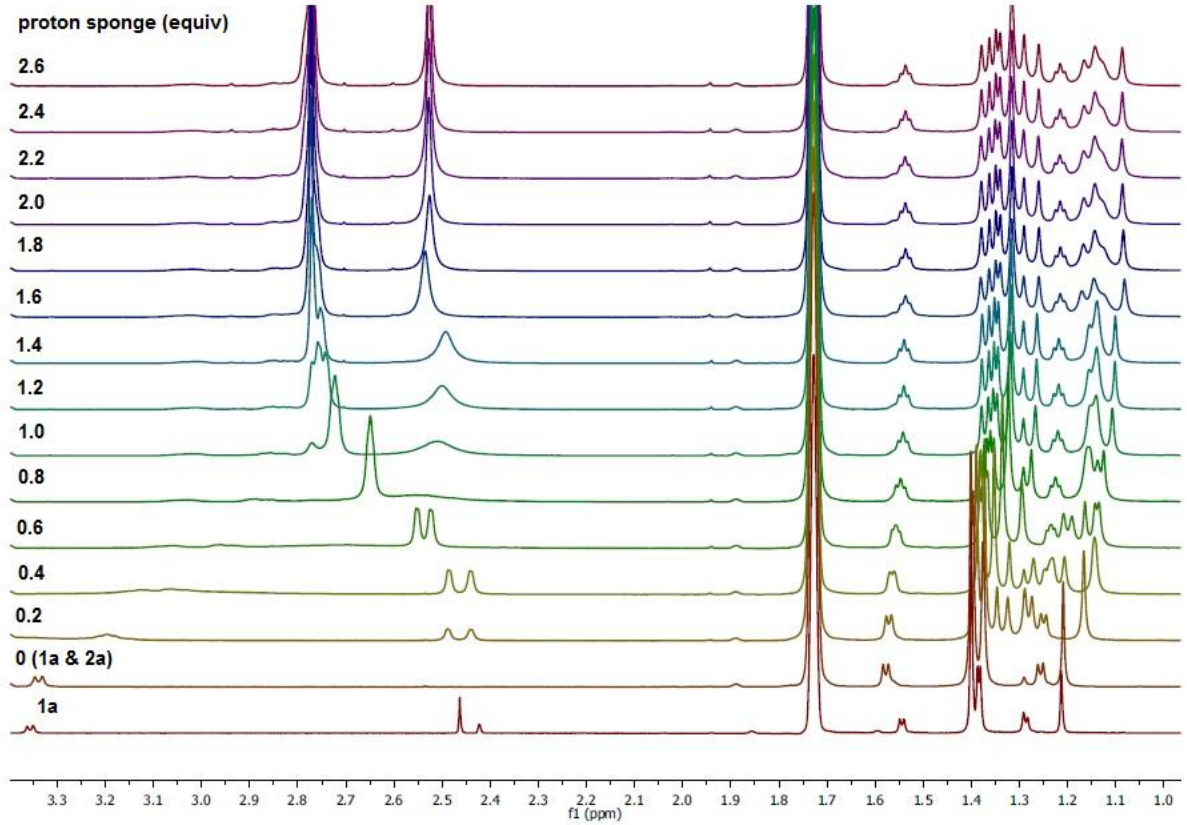


Figure 29 Part of the ^{1}H NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = [**1a**]$_{initial}$) with increasing equivalents of proton sponge.

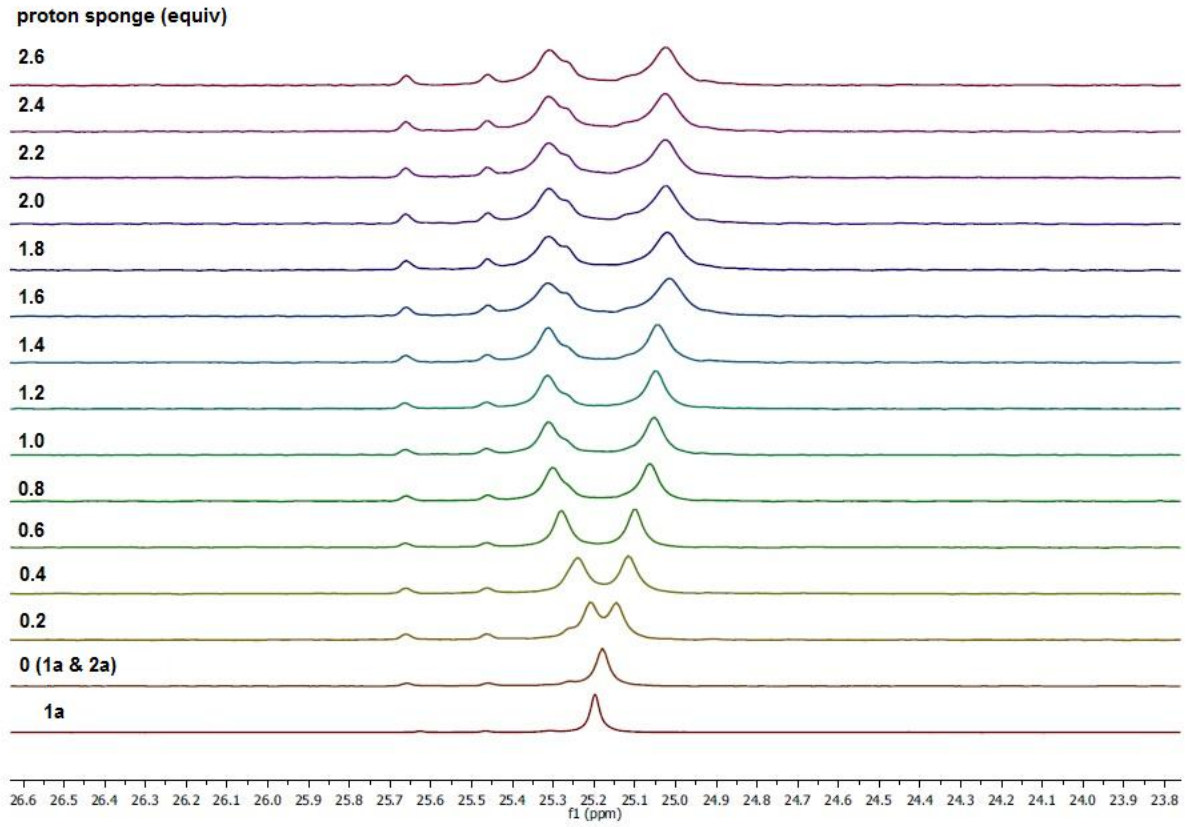


Figure 30 Part of the ^{13}C-DEPT NMR (101 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = [**1a**]$_{initial}$) with increasing equivalents of proton sponge.

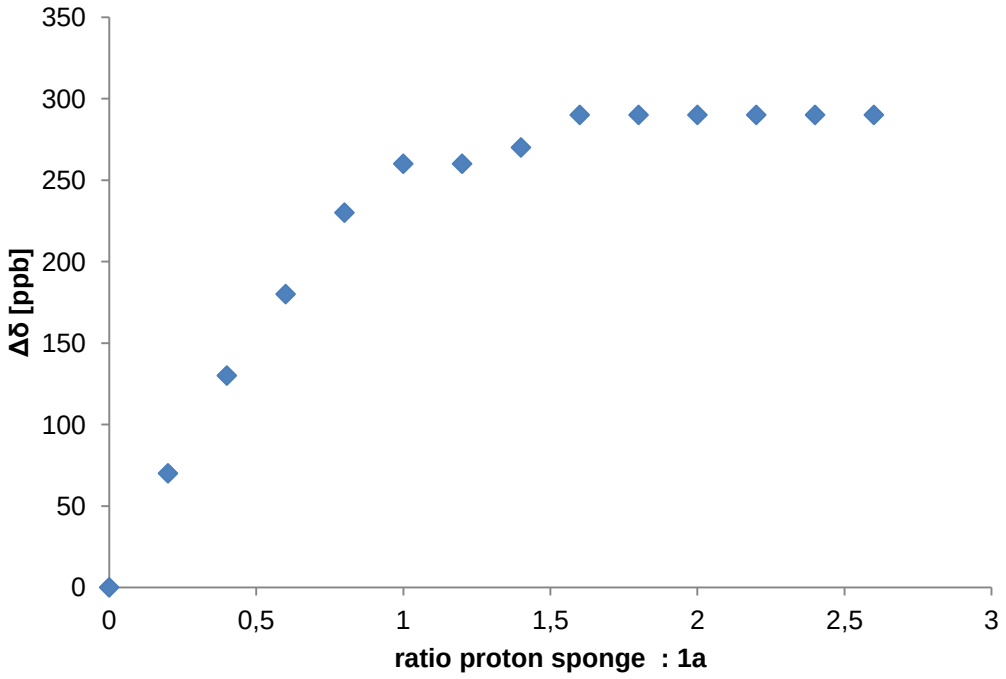


Figure 31 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; [**1a**]$_{initial}$ = 5 mM, [**1a**]$_{end}$ = 4.11 mM, [**2a**]$_{initial}$ = [**1a**]$_{initial}$

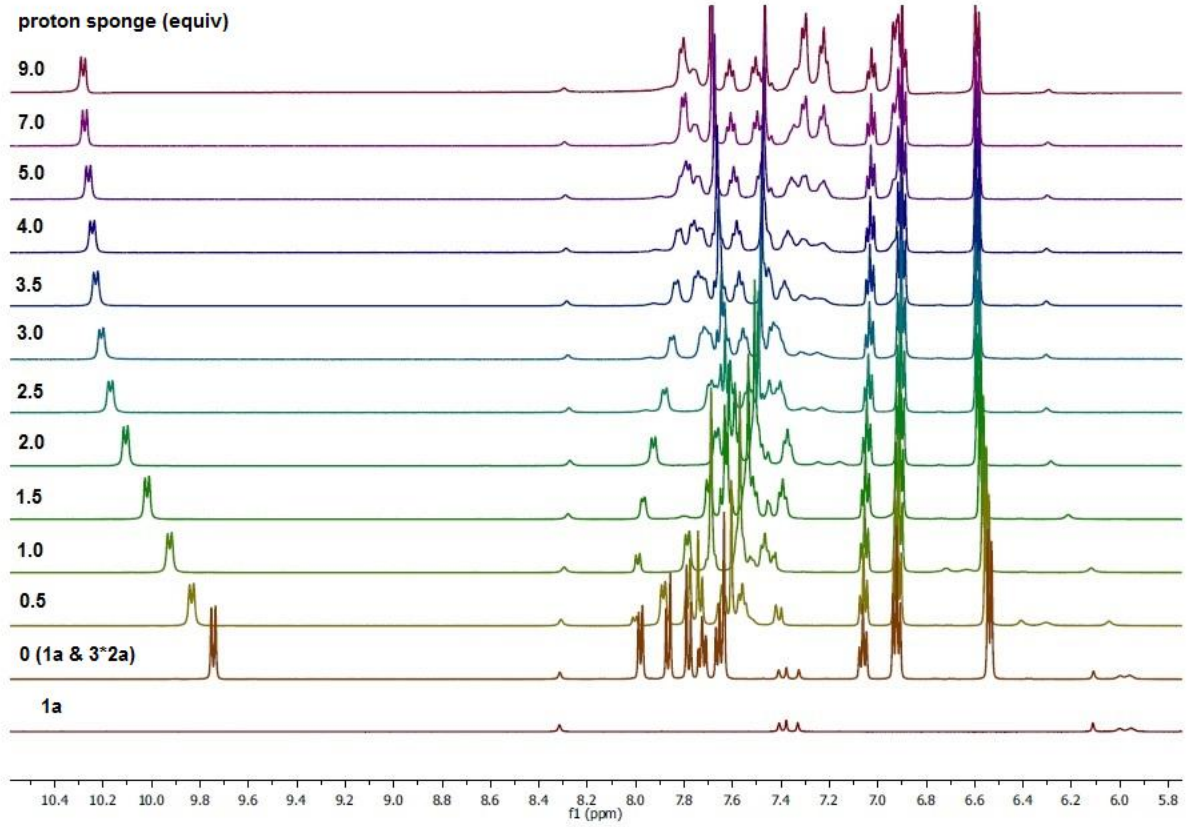


Figure 32 Part of the ^{1}H NMR (500 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 2 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

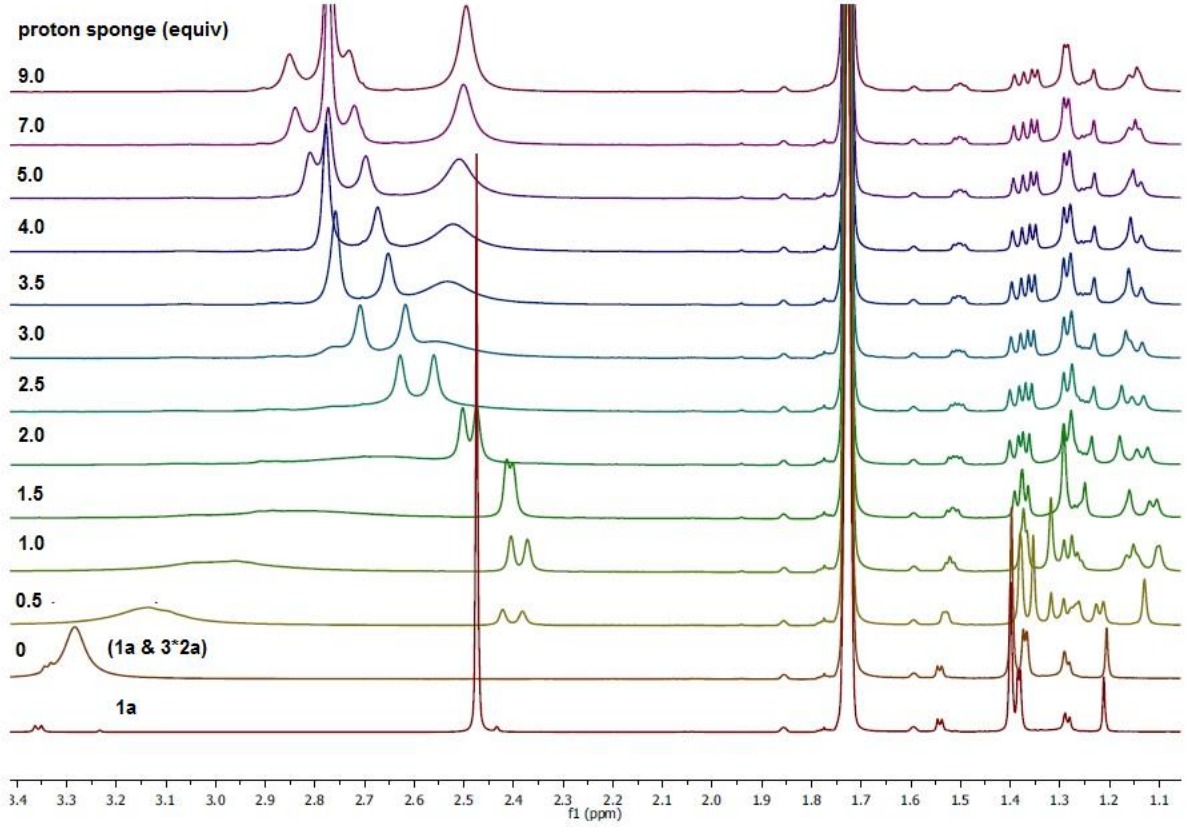


Figure 33 Part of the ^{1}H NMR (500 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 2 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

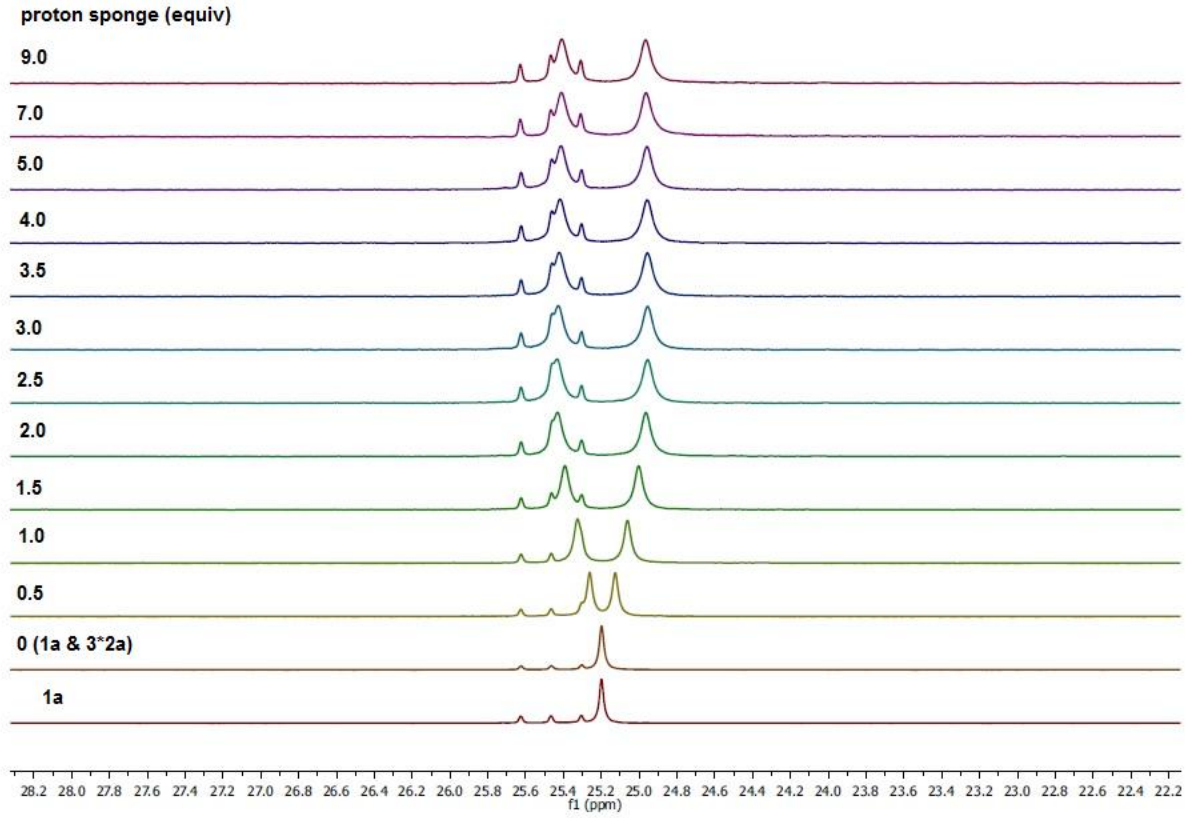


Figure 34 Part of the ^{13}C-DEPT NMR (126 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 2 mM) by *in situ* formation of a chiral phosphate from **2a** ([**2a**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

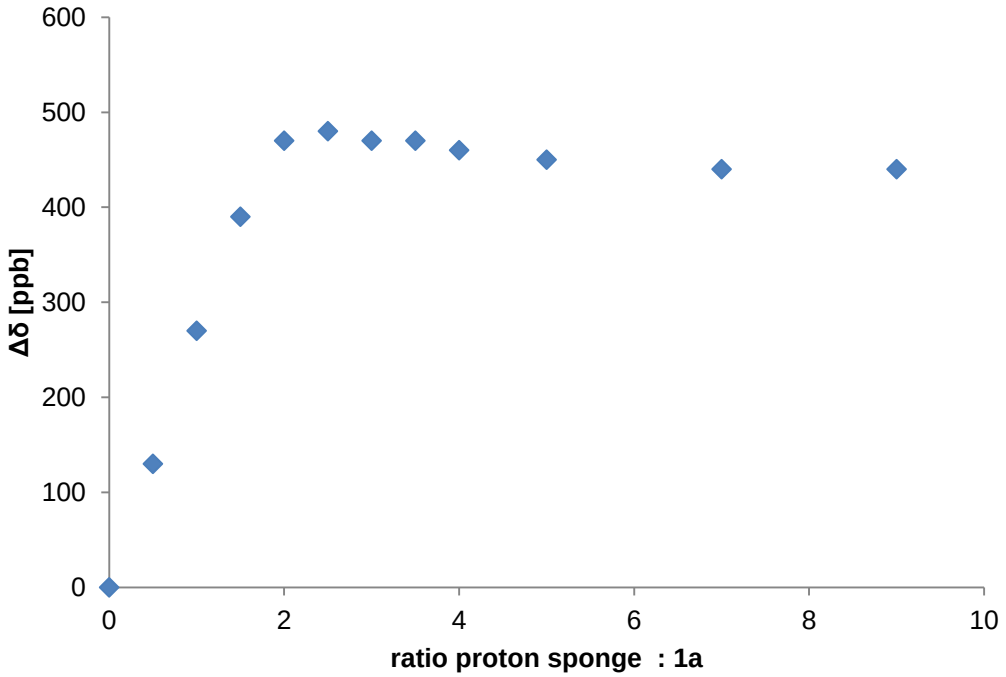


Figure 35 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; [**1a**]$_{initial}$ = 2 mM, [**1a**]$_{end}$ = 1.45 mM, [**2a**]$_{initial}$ = 3*[**1a**]$_{initial}$

3 Investigation of solvent effects

To estimate the influence of solvent effects on the binding between peptide and chiral anion, titration experiments of foldamer-urea **1a** by *in situ* formation of a chiral phosphate from phosphoric acid **2a** (fixed amount) and proton sponge (variable amount) in acetonitrile as a polar solvent were performed.

3.1 Procedure for the titration of 1a (5 mM) with 3 equivalent 2a in acetonitrile

Foldamer-urea **1a** (0.003 mmol, 2.0 mg, 5 mM) was directly weighed out in the NMR tube. The phosphoric acid **2** (0.009 mmol, 5.4 mg, 3 equiv, 15 mM) was added directly as a solid and CD_3CN (600 µL) was added. This two component mixture was not soluble. A 1 mL solution of proton sponge was prepared (120 mM, 25.7 mg). Aliquots of this stock solution (12.5 µL, 0.5 equiv) were added to the NMR tube, the mixture was shaken and ^{1}H and ^{13}C-DEPT135 spectra were recorded at 296 K. Contrary to the same experiment in THF-d_8, the mixture did not dissolve during the addition of proton sponge. NMR spectra and the plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio **1a**:proton sponge are shown in Figures 36-39**.**

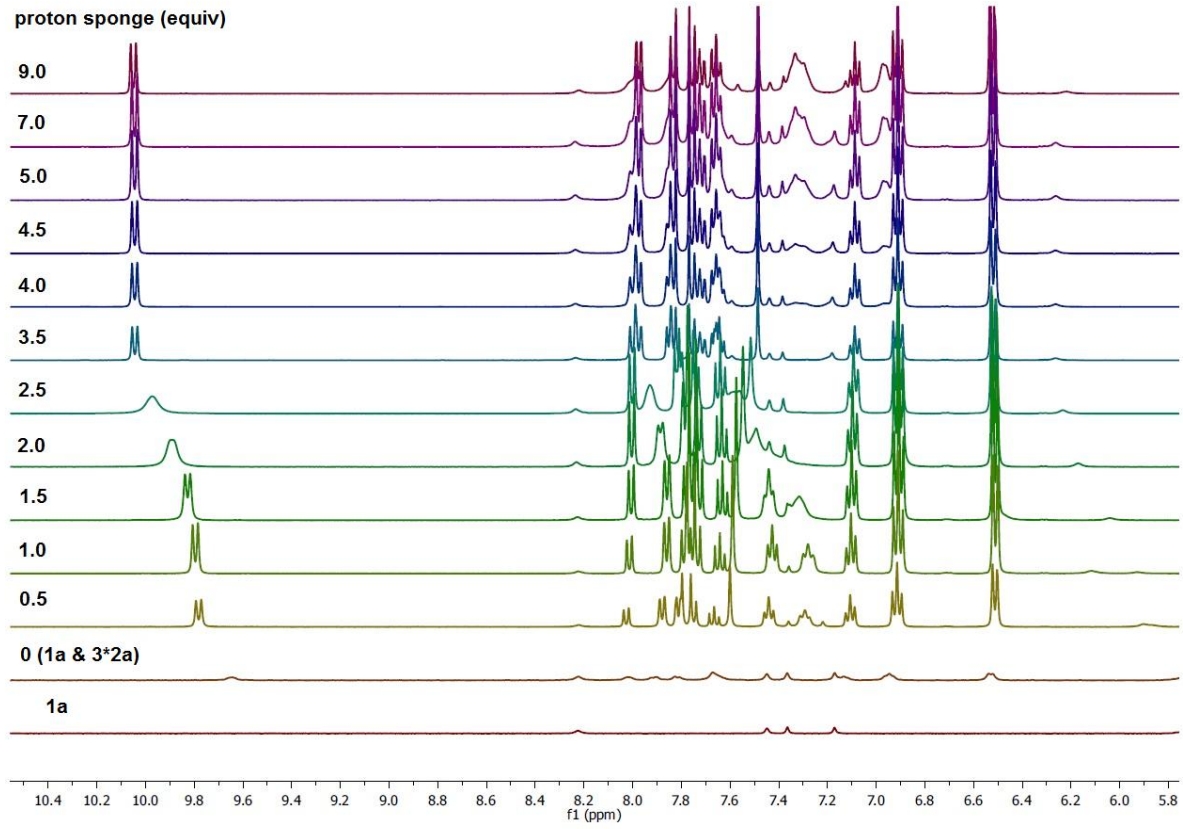


Figure 36 Part of the ^{1}H NMR (400 MHz, CD_3CN, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ($[\mathbf{2a}]_{initial}$ = 3*$[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge.

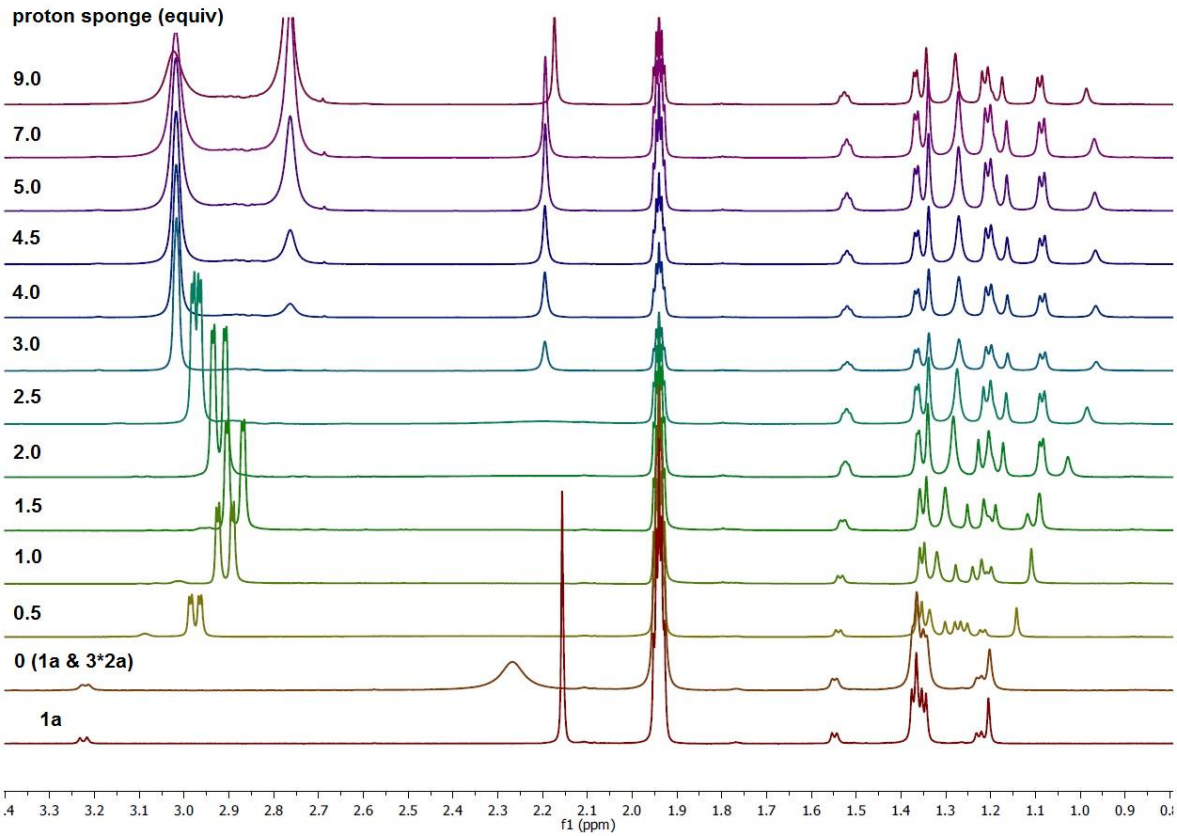


Figure 37 Part of the ^{1}H NMR (400 MHz, CD_3CN, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ($[\mathbf{2a}]_{initial}$ = 3*$[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge.

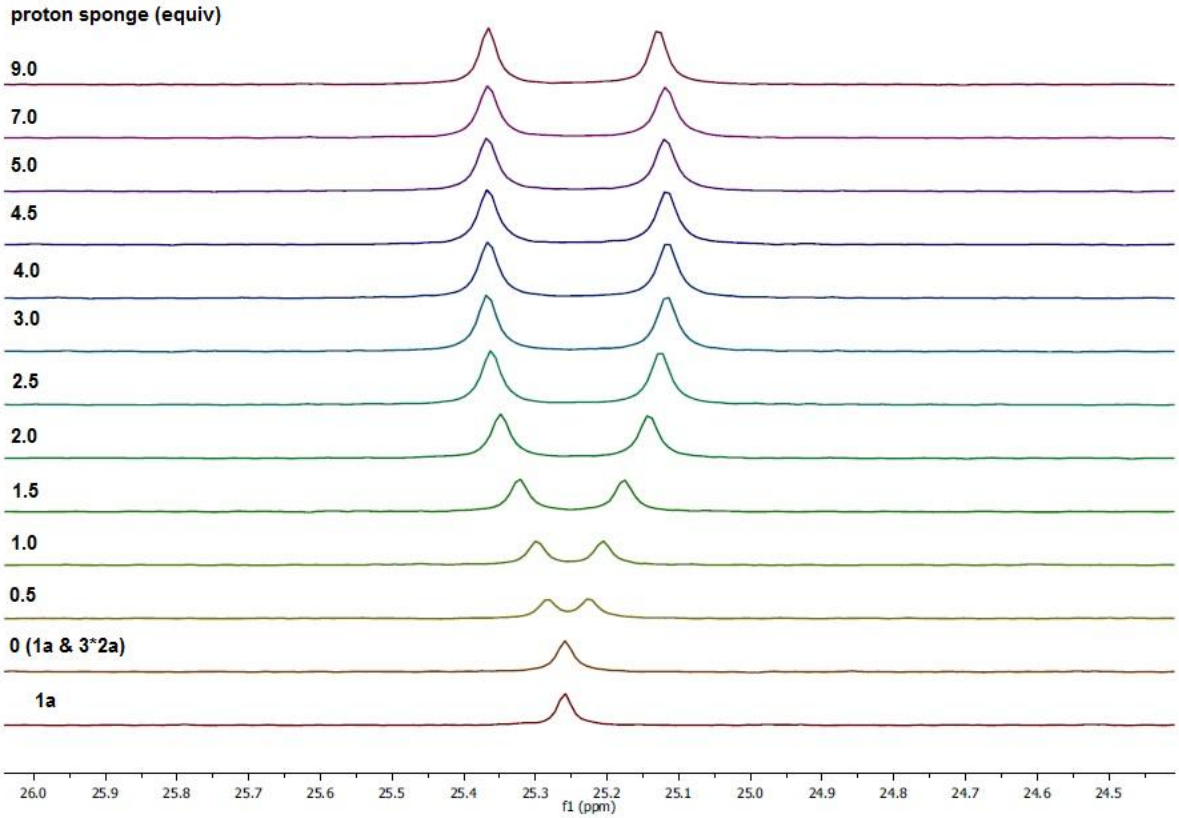


Figure 38 Part of the ^{13}C-DEPT NMR (101 MHz, CD_3CN, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ($[\mathbf{2a}]_{initial}$ = 3*$[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge.

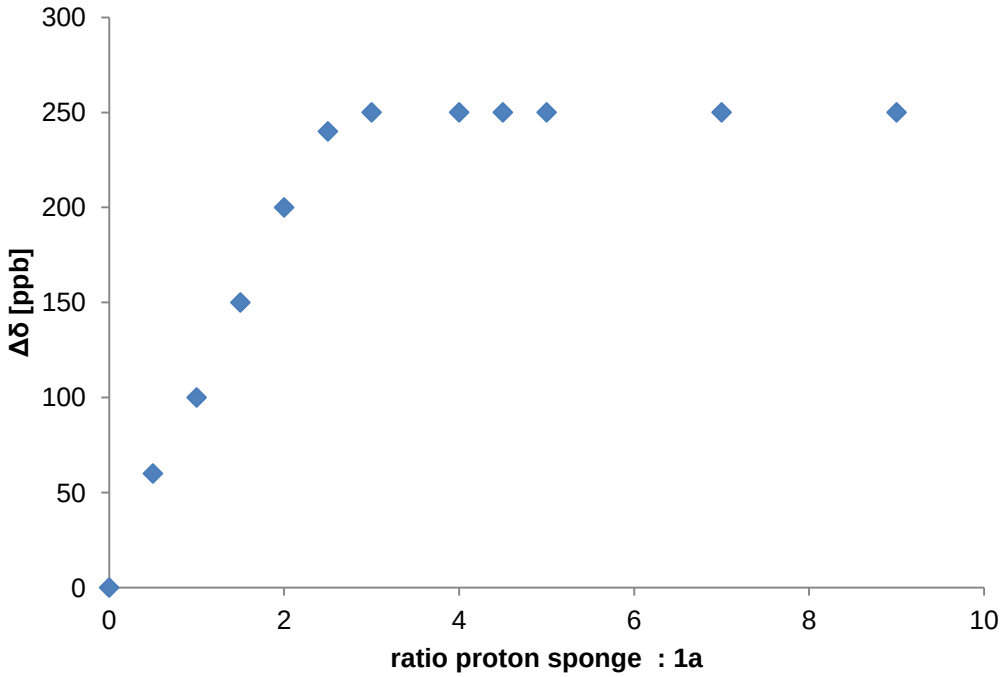


Figure 39 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in CD_3CN at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 3.64 mM, $[\mathbf{2a}]_{initial} = 3*[\mathbf{1a}]_{initial}$

4 Titration studies of foldamer-ureas 1a with a chiral phosphate from phosphoric acids 2 and proton sponge

4.1 Procedure for the titration of 1a with premade chiral phosphate from 2d and proton sponge

Formation of chiral phosphate: (*S*)-(+)-1,1'-Binaphthyl-2,2'-diyl hydrogenphosphate (**2d**) (185.72 mg, 0.533 mmol, 1 equiv) and proton sponge (114.28 mg, 0.533 mmol, 1 equiv) were dissolved in dry CH_2Cl_2 and stirred for 30 min. The solution was concentrated and dried *in vacuo* for several hours. The formed phosphate didn't dissolve in THF-d_8 and could therefore not be used for titration experiments.

4.2 Procedure for the titration of 1a with premade chiral phosphate from 2a and proton sponge

Formation of chiral phosphate: (*R*)-VAPOL phosphoric acid (**2a**) (14.07 mg, 0.023 mmol, 1 equiv) and proton sponge (5.02 mg, 0.023 mmol, 1 equiv) were dissolved in dry CH_2Cl_2 and stirred for 30 min. The solution was concentrated and dried *in vacuo* for several hours giving 19.10 mg of product.

Titration experiment: Foldamer-urea **1a** (0.003 mmol, 2.0 mg, 5 mM) was directly weighed out in the NMR tube, followed by the addition of THF-d_8 (600 µL). A 1 mL solution of the chiral phosphate was prepared (23.44 mM, 19.1 mg). Aliquots of this stock solution (32 µL, 0.25 equiv) were added to the NMR tube, the tube was shaken and ^1H and ^{13}C-DEPT135 spectra of the solution were recorded at 296 K. NMR spectra and the plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio **1a:** proton sponge are shown in Figures 40-43**.**

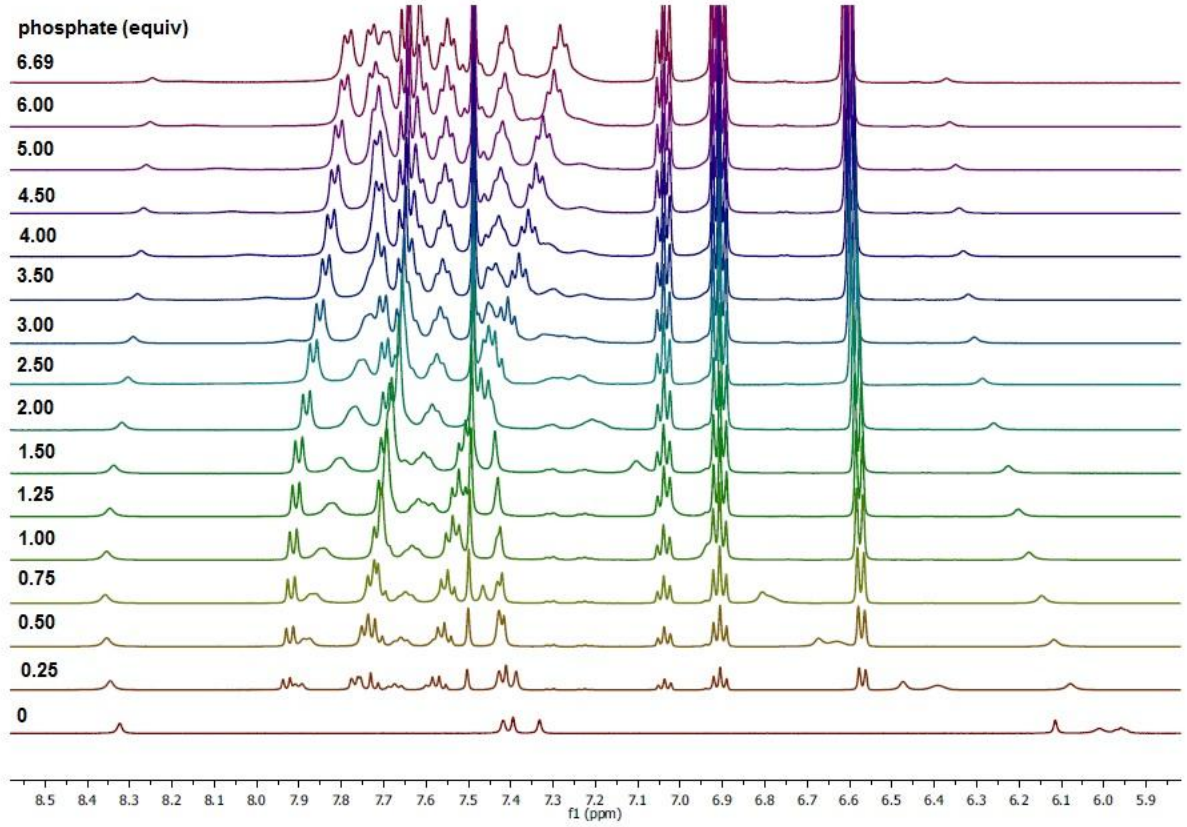


Figure 40 Part of the ^{1}H NMR (500 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) with increasing amounts of a chiral phosphate from phosphoric acid **2a** and proton sponge.

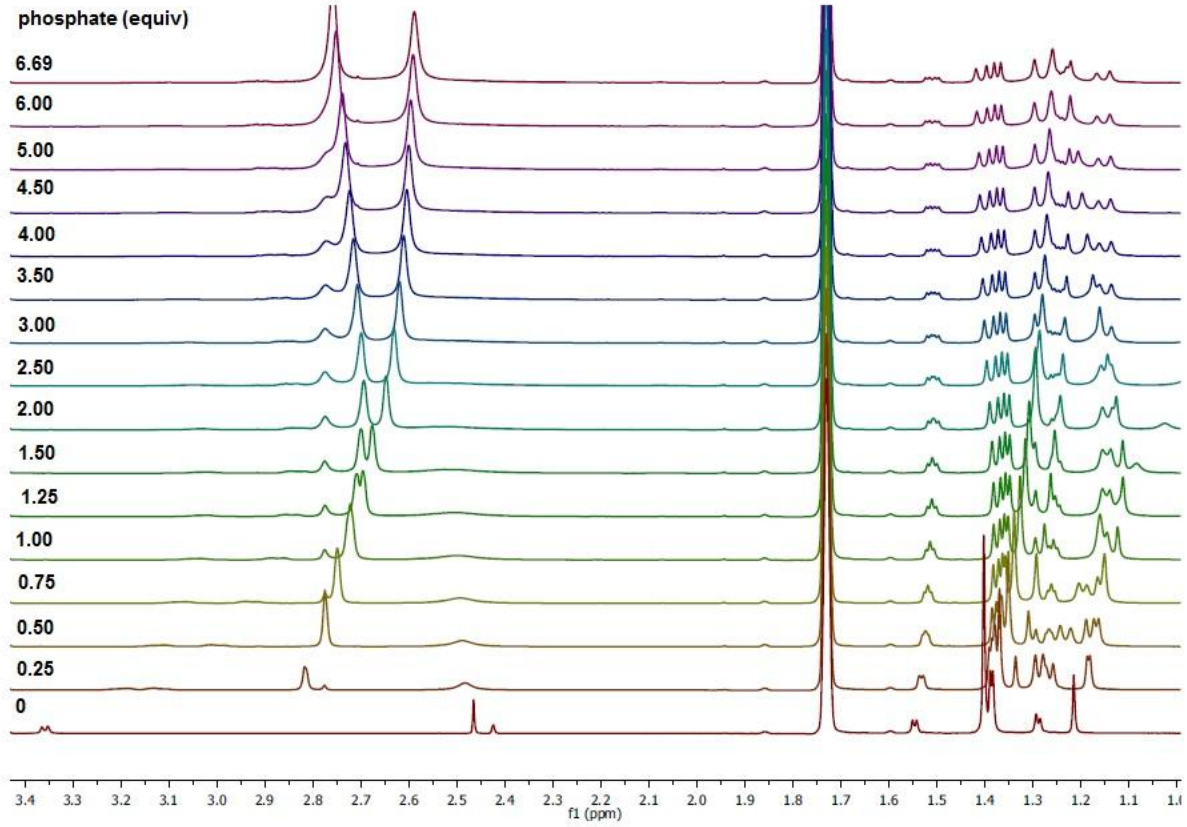


Figure 41 Part of the ^{1}H NMR (500 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) with increasing amounts of a chiral phosphate from phosphoric acid **2a** and proton sponge.

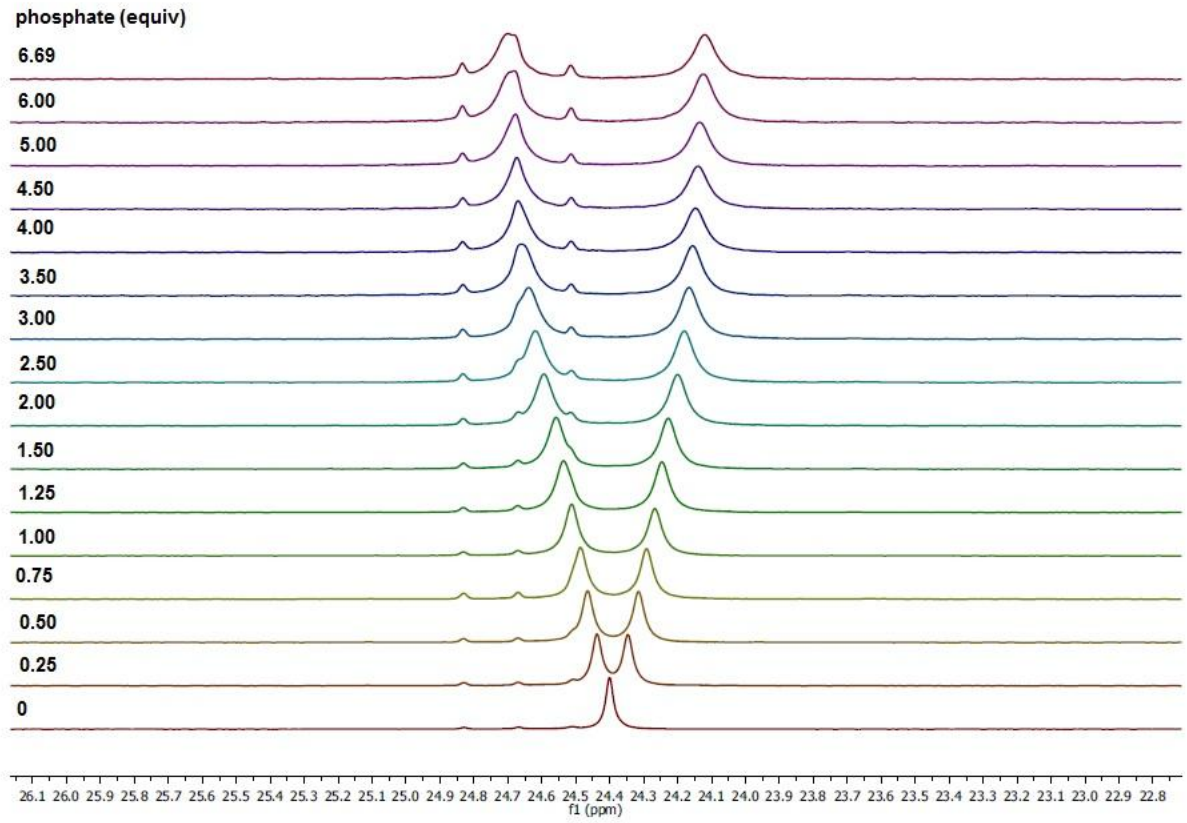


Figure 42 Part of the ^{13}C-DEPT NMR (126 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) with increasing amounts of a chiral phosphate from phosphoric acids **2a** and proton sponge.

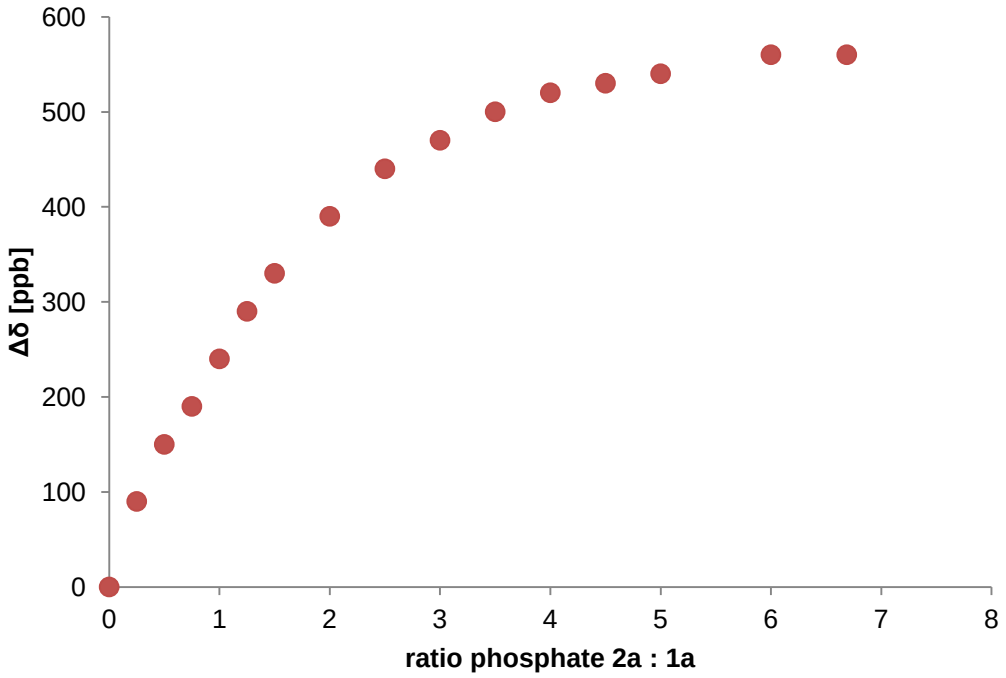


Figure 43 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the phosphate from **2a**:**1a** recorded in THF-d_8 at 296 K; [**1a**]$_{initial}$ = 5 mM, [**1a**]$_{end}$ = 2.06 mM, [**2d**]$_{initial}$ = 3*[**1a**]$_{initial}$

5 Titration studies of foldamer-ureas 1a by *in situ* formation of a chiral phosphate from phosphoric acids 2 (variable amount) and proton sponge (variable amount)

5.1 Procedure for the titration of 1a with 2d

Foldamer-urea **1a** (0.003 mmol, 2.0 mg, 5 mM) was directly weighed out in the NMR tube. The phosphoric acid **2d** (0.018 mmol, 6.30 mg, 6 equiv, 30 mM) was added directly and THF-d_8 (600 µL) was added. A 1 mL solution of proton sponge was prepared (300 mM, 64.30 mg, 5 µL = 0.5 equiv). Aliquots of this stock solution were added to the NMR tube until a 9:1 ratio proton sponge**:1a** was reached (excess proton sponge com2red to acid). Then another portion of **2d** (0.009 mmol, 3.13 mg, 3 equiv, 15 mM) was added to the NMR tube. Again aliquots of the proton sponge stock solution were added to the NMR tube until a 12:1 ratio proton sponge**:1a** was reached (excess proton sponge com2red to acid). Then a third portion of **2d** (0.009 mmol, 3.13 mg, 3 equiv, 15 mM) was added to the NMR tube, followed by addition of 5 µL aliquots of the proton sponge stock solution to the NMR tube until a 15:1 ratio proton sponge:**1a** was reached (excess proton sponge com2red to acid). After every addition of either proton sponge or **2d**, ^{13}C-DEPT135 spectra of the solution were recorded at 296 K. NMR spectra and the plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge: **1a** are shown in Figures 44 and 45**.**

5.2 Procedure for the titration of 1a with 2a

Foldamer-urea **1a** (0.003 mmol, 2.0 mg, 5 mM) was directly weighed out in the NMR tube. The phosphoric acid **2a** (0.018 mmol, 10.81 mg, 6 equiv, 30 mM) was added directly and THF-d_8 (600 µL) was added. A 1 mL solution of proton sponge was prepared (300 mM, 64.30 mg, 5 µL = 0.5 equiv). Aliquots of this stock solution were added to the NMR tube until a 9:1 ratio proton sponge:**1a** was reached (excess proton sponge com2red to acid). Then another portion of **2d** (0.009 mmol, 5.41 mg, 3 equiv, 15 mM) was added to the NMR tube. Again aliquots of the proton sponge stock solution were added to the NMR tube until a 12:1 ratio proton sponge**:1a** was reached (excess proton sponge com2red to acid). Then a third portion of **2d** (0.009 mmol, 5.41 mg, 3 equiv, 15 mM) was added to the NMR tube, followed by addition of 5 µL aliquots of the proton sponge stock solution to the NMR tube until a 15:1 ratio proton sponge**:1a** was reached (excess proton sponge com2red to acid). After every addition of either proton sponge or **2d**, ^{13}C-DEPT135 spectra of the solution were recorded at 296 K. NMR spectra and the plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge: **1a** are shown in Figures 46 and 47**.**

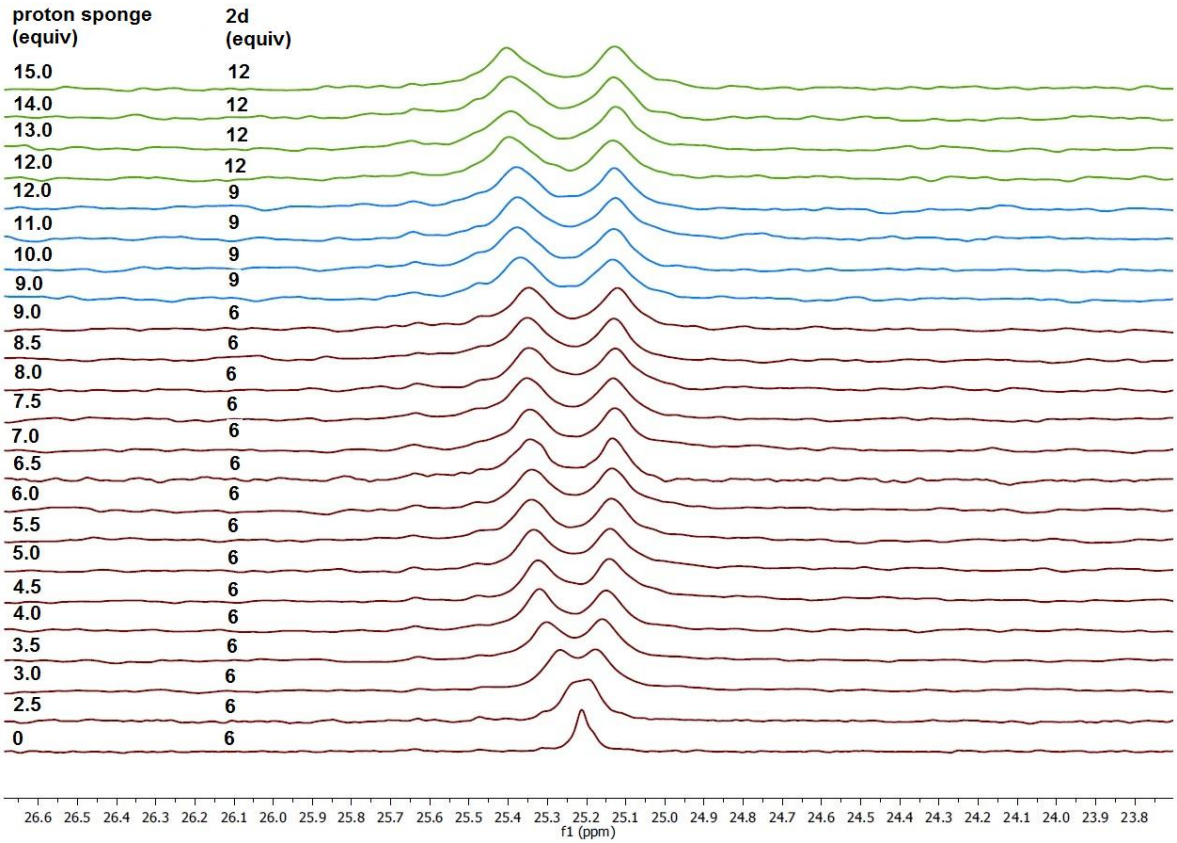


Figure 44 Part of the ^{13}C-DEPT NMR (126 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2d** ($[\mathbf{2d}]_{initial}$ = 6*$[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge and **2d**.

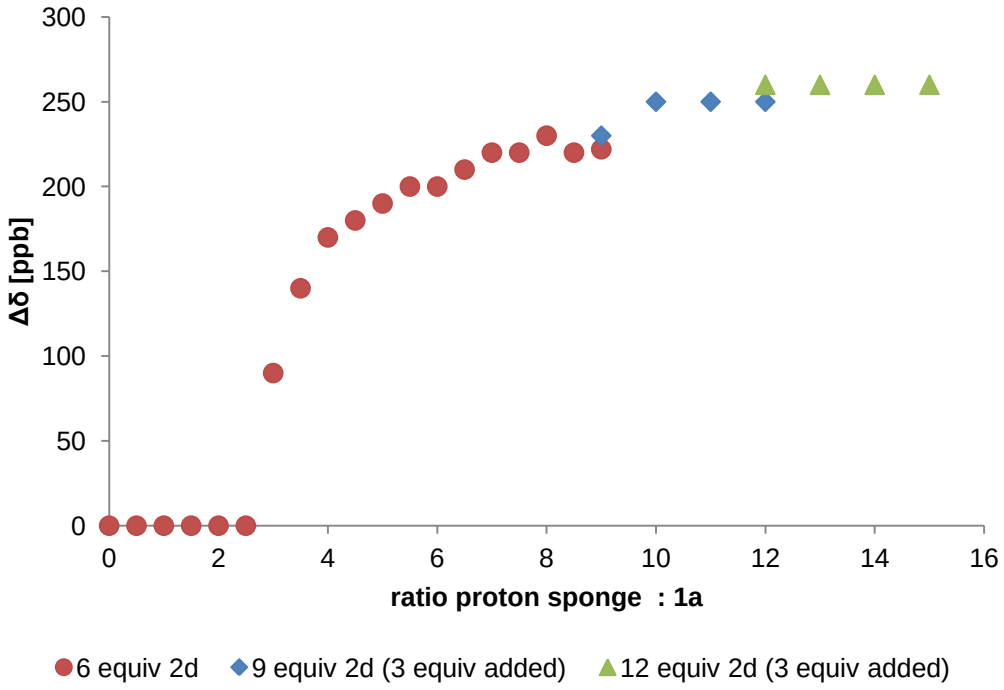


Figure 45 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 4 mM, $[\mathbf{2d}]_{initial}$ = 6*$[\mathbf{1a}]_{initial}$

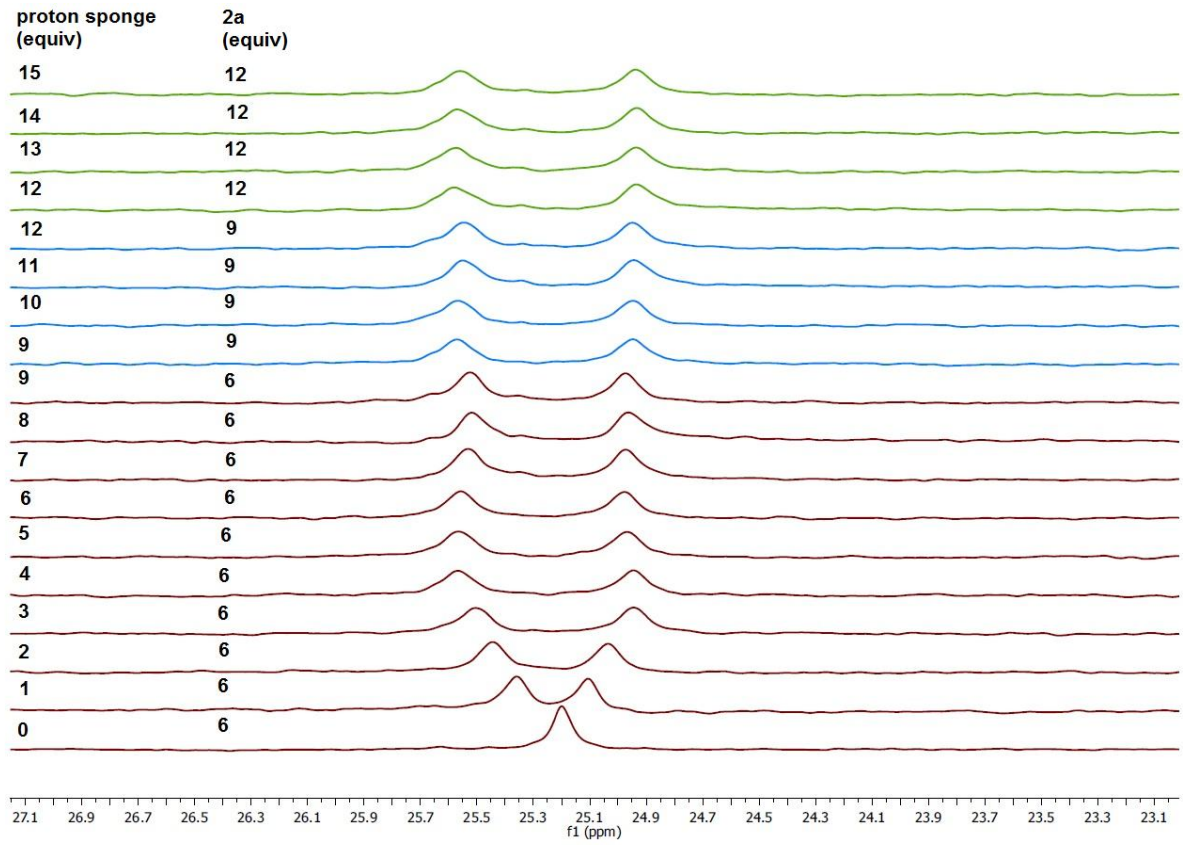


Figure 46 Part of the ^{13}C-DEPT NMR (126 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from **2a** ($[\mathbf{2a}]_{initial}$ = 6*$[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge and **2a**.

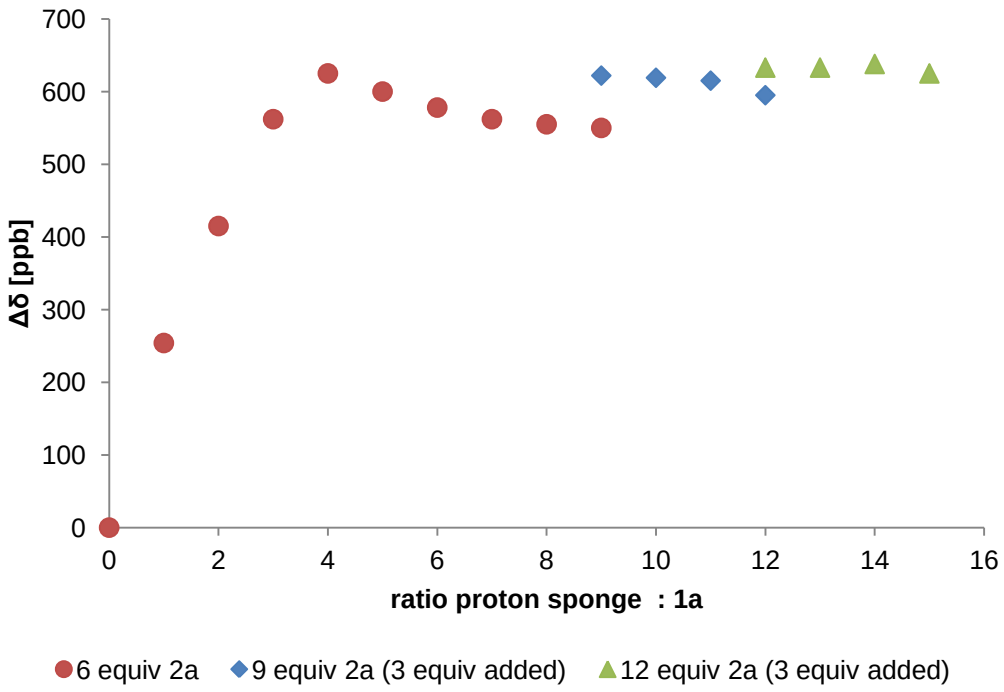


Figure 47 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 4 mM, $[\mathbf{2a}]_{initial}$ = 6*$[\mathbf{1a}]_{initial}$

6 Titration studies of foldamer-urea 1a by *in situ* formation of a chiral phosphate from washed phosphoric acid 2d (fixed amount) and proton sponge (variable amount)

*Procedure was washing of phosphoric acid **2d**:* Phosphoric acid **2d** (purchased from Aldrich) was dissolved in CH_2Cl_2, washed with an aqueous 2 N solution of HCl and water, dried over $NaSO_4$ and evaporated to dryness.

*Procedure for the titration of 1a with washed **2d**:* Foldamer-urea **1a** (0.003 mmol, 2.0 mg, 5 mM) was directly weighed out in the NMR tube. The washed phosphoric acid **2d** (0.009 mmol, 3.13 mg, 3 equiv, 15 mM) was added directly as a solid and THF-d_8 (600 µL) was added. This two component mixture was not soluble. A 1 mL solution of proton sponge was prepared (120 mM, 25.7 mg, 12.5 µL = 0.5 equiv). 12.5 µL portions of this stock solution were added to the NMR tube, the mixture was shaken and ^{1}H and ^{13}C-DEPT135 spectra of the solution were recorded at 296 K. NMR spectra and the plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio **1a**:proton sponge are shown in Figures 48-51**.**

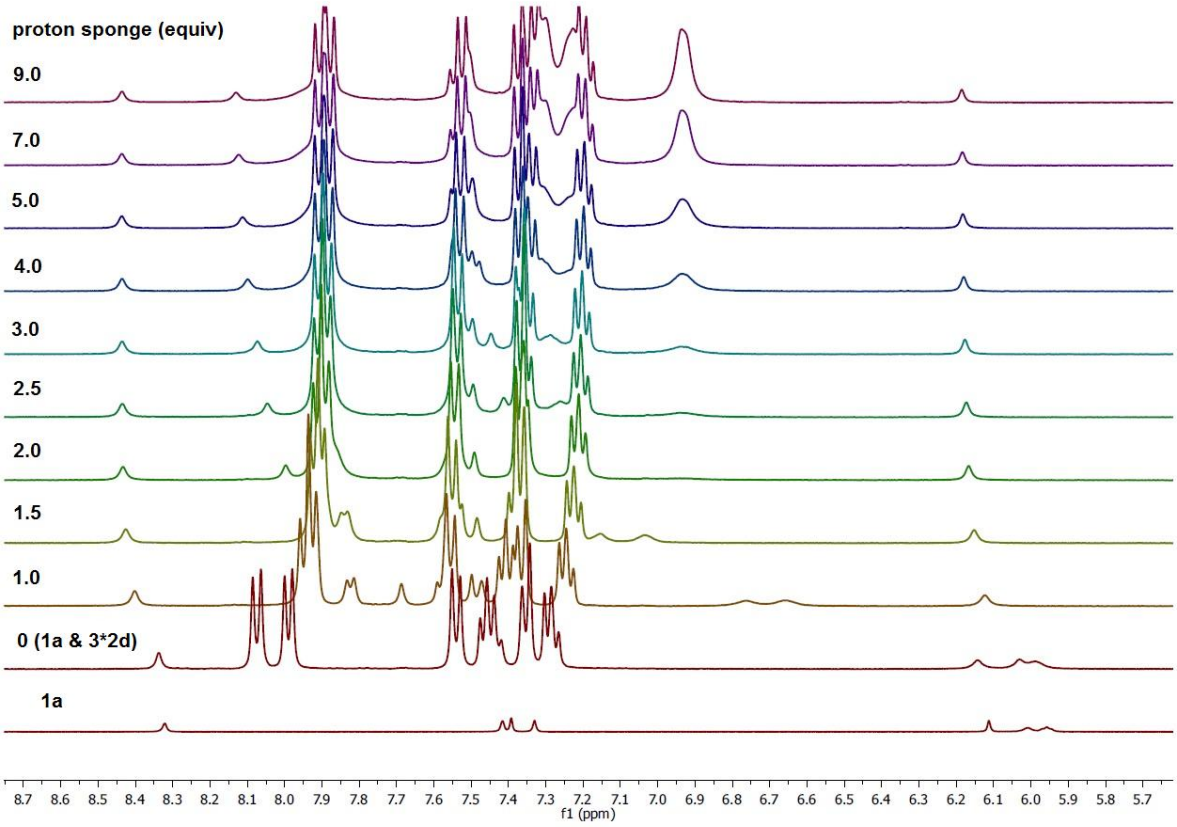


Figure 48 Part of the ^{1}H-NMR (400 MHz, THF-d_8, 296 K) spectra from the titration of **1a** ($[\mathbf{1a}]_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from washed **2d** ($[\mathbf{2d}]_{initial}$ = 3*$[\mathbf{1a}]_{initial}$) with increasing equivalents of proton sponge.

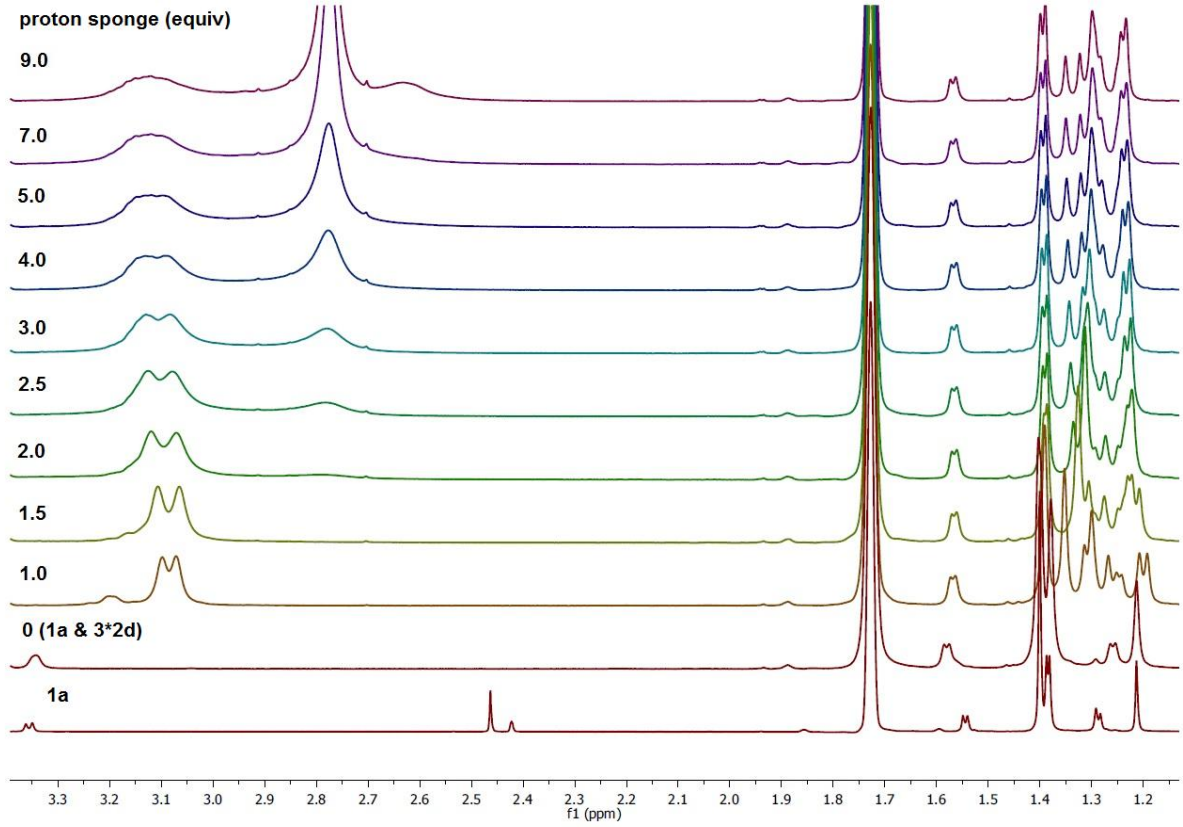


Figure 49 Part of the ^{1}H-NMR (400 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from washed **2d** ([**2d**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

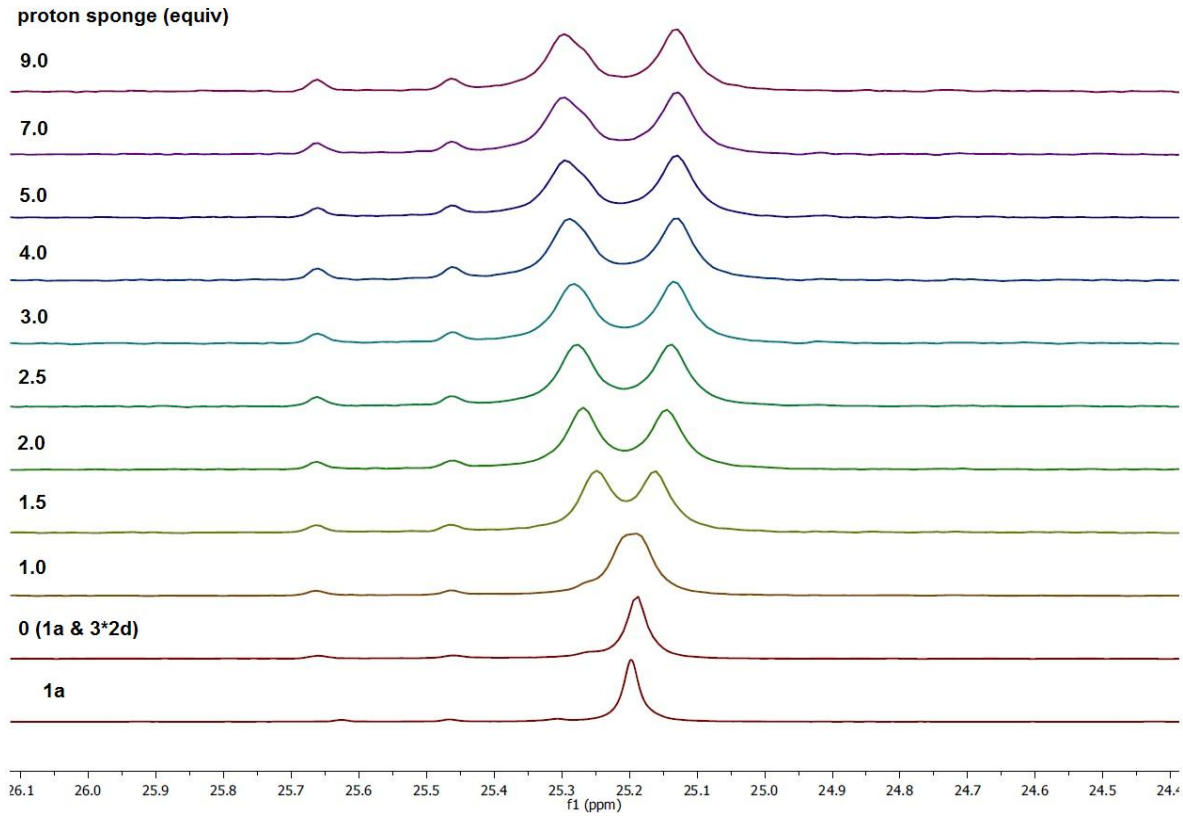


Figure 50 Part of the ^{13}C-DEPT NMR (101 MHz, THF-$d_{8,}$ 296 K) spectra from the titration of **1a** ([**1a**]$_{initial}$ = 5 mM) by *in situ* formation of a chiral phosphate from washed **2d** ([**2d**]$_{initial}$ = 3*[**1a**]$_{initial}$) with increasing equivalents of proton sponge.

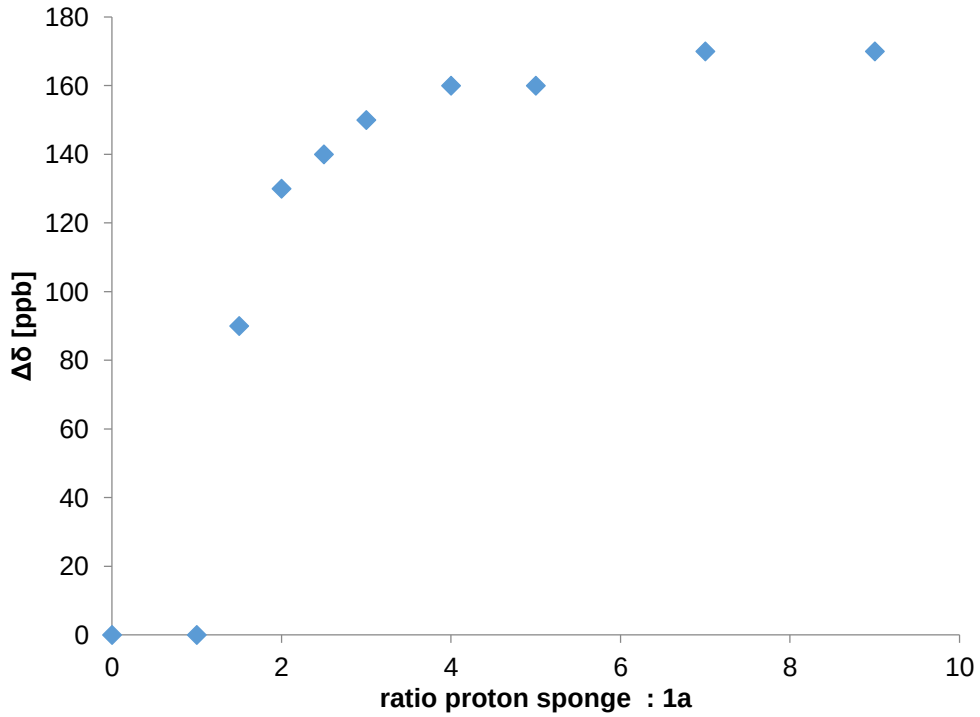


Figure 51 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* the ratio proton sponge:**1a** recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 3.64 mM, washed $[\mathbf{2d}]_{initial} = 3*[\mathbf{1a}]_{initial}$

7 Dilution study of titration with *in situ* formation of a chiral phosphate in a system 1a↔ 2a↔ proton sponge (fixed amounts)

Foldamer-urea **1a** (2.0 mg, 5 mM), phosphoric acid **2a** (3 equiv, 5.41 mg, 15 mM) and proton sponge (4 equiv, 2.6 mg, 20 mM) were directly weighed out in the NMR tube and dissolved in THF-d_8 (600 µL). This solution was diluted with THF-d_8 until [**1a**] = 0.5 mM, [**2a**] = 1.5 mM, [proton sponge] = 2.0 mM. After each dilution, the NMR tube was vigorous shaken and ^{1}H and ^{13}C-DEPT135 spectra were recorded at 296 K. The plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* [**1a**] (mM) is shown in Figure 52**.**

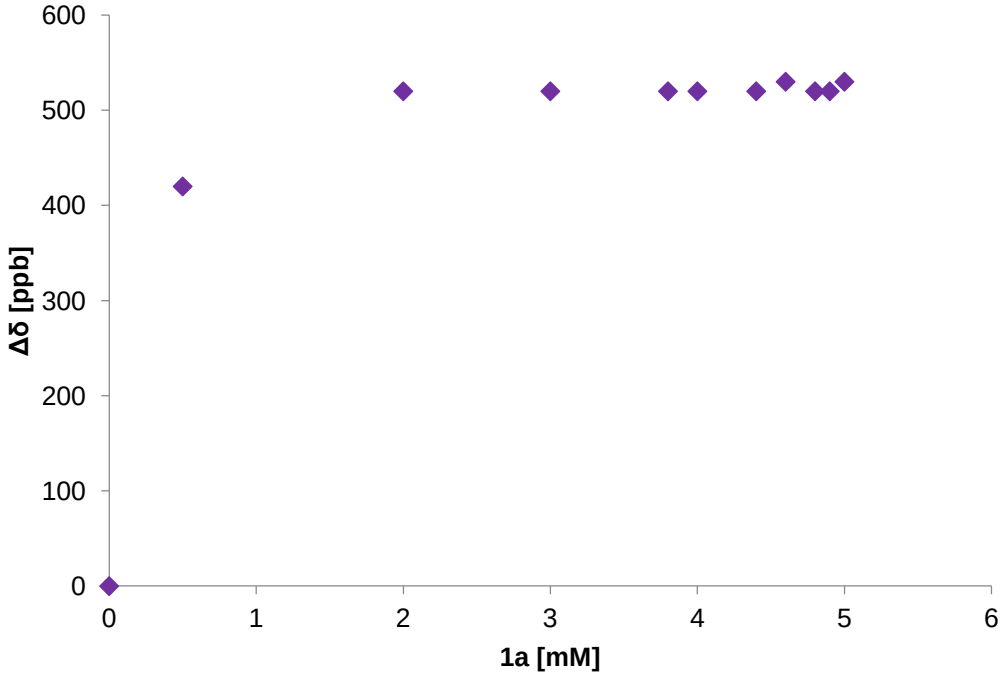
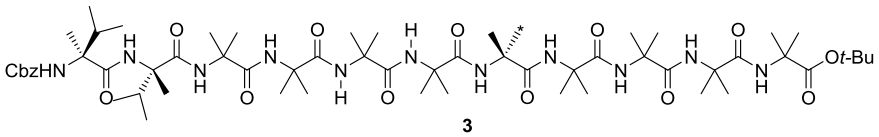


Figure 52 Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* decreasing **[1a]** recorded in THF-d_8 at 296 K; proton sponge:**1a**:**2a** = 4:1:3.

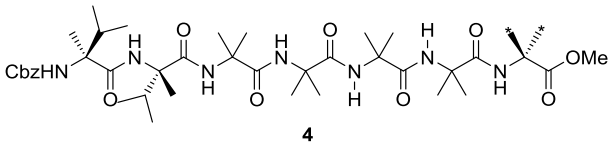
8 Estimation of $\Delta\delta_{slow}$ for foldamers with a $^{13}CH_3$,$^{13}CH_3$ NMR reporter in THF-d_8 and CD_3CN

Cbz*α*MeVal$_2$ covalently attached to the N-terminus positions of these Aib$_n$ foldamers was found to be the most potential chiral controller for intramolecular induction of screw-sense preference for foldamers from the N-terminus to a ^{13}C labelled Aib methyl ester probe located at their C-terminal position. Values of 92% for *h.e.* were determined for foldamer **3** in THF and $CDCl_3$[2].

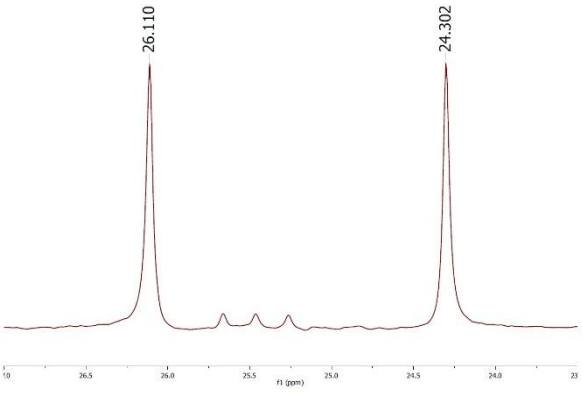


3 h.e. = 92% (THF-d_8/$CDCl_3$)[1]

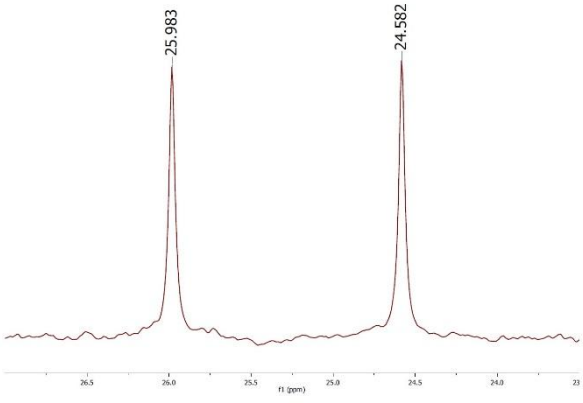
Since foldamer-ureas **1a-1d** also have a similar $^{13}CH_3$,$^{13}CH_3$ NMR reporter group located four Aib residues after the urea binding site (corresponding to the position of the intramolecular chiral controller in foldamers F1 and F2), their spectroscopic reporters should experience approximately equal local helical excess upon intermolecular chiral anion recognition of the urea with a chiral phosphate. With this assumption, values of $\Delta\delta_{slow}$ in THF-d_8 and CD_3CN for foldamers having a ^{13}C-labelled Aib methyl ester probe located at their C-terminal position were calculated from the measured $\Delta\delta_{fast}$ values obtained for $\Delta\delta_{fast}$ of foldamer **4.** These obtained $\Delta\delta_{slow}$ values were used to calculate the helical excess values for the above described titrations of foldamers **1a-1d**.



4



$\Delta\delta_{fast}$ (ppb) = 1810 (THF-d_8)



$\Delta\delta_{fast}$ (ppb) = 1410 (CD_3CN)

Calculation of $\Delta\delta_{slow}$: *h.e.* = $\Delta\delta_{fast}$ / $\Delta\delta_{slow}$ → $\Delta\delta_{slow}$ = $\Delta\delta_{fast}$ / *h.e.*

$\Delta\delta_{slow}$ (ppb) = 1967 (THF-d_8)

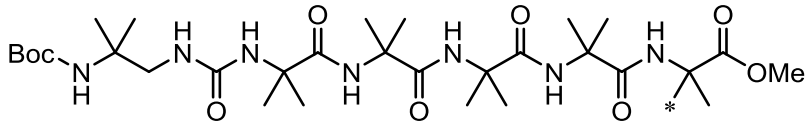
$\Delta\delta_{slow}$ (ppb) = 1522 (CD_3CN)

[2] (a) Angew. Chem. Int. Ed. **2014**, *53*, 151–155; (b) J. Am. Chem. Soc. **2015**, *137*, 6680−6691

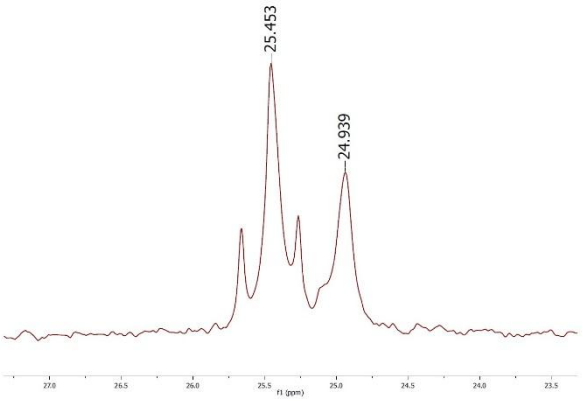
9 Determination of induction of screw sense preference in 1a* induced by (*R*)-2a and (*S*)-2e

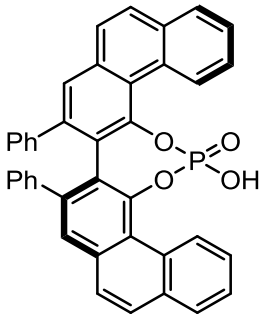
Procedure for the titration of 1a* with (*R*)-2a: Foldamer-urea **1a*** (0.003 mmol, 2.0 mg, 5 mM), chiral phosphoric acid **2a** (3 equiv, 5.41 mg, 15 mM) and proton sponge (4 equiv, 2.6 mg, 20 mM) were directly weighed out in the NMR tube, followed by the addition of THF-d_8 (600 μL). A ^{13}C-DEPT135 spectrum of the solution was recorded at 296 K.

Procedure for the titration of 1a* with (*S*)-2e: Foldamer-urea **1a*** (0.002 mmol, 1.50 mg, 5 mM), chiral phosphoric acid **2e** (3 equiv, 4.00 mg, 11 mM) and proton sponge (4 equiv, 2.0 mg, 15 mM) were directly weighed out in the NMR tube, followed by the addition of THF-d_8 (444 μL). A ^{13}C-DEPT135 spectrum of the solution was recorded at 296 K.



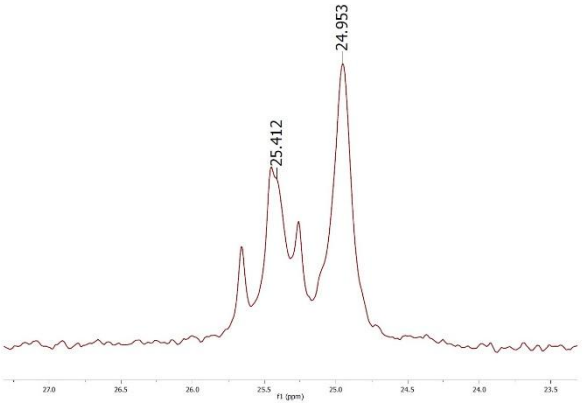
1a*

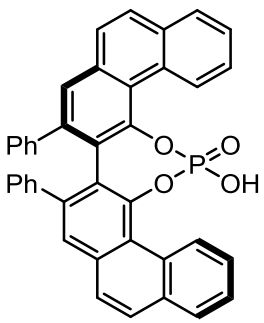




2a

(*R*)-VAPOL phosphoric acid **2a** preferentially induces right-handed (*P*)-helicity





2e

(*S*)-VAPOL phosphoric acid **2e** preferentially induces left-handed (*M*)-helicity

10 Estimation of binding constants for the system 1↔2↔proton sponge

The estimation of the order of magnitude of the binding constants K for the system **1↔2↔**proton sponge has been performed using the program DYNAFIT[3]. A 1:1 binding model has been used to fit the experimental data for the anisochronicities (Δδ) of the two diastereotopic signals $^{13}CH_3$ of the NMR probe plotted against the concentration of added base [M] in solution from the corresponding titration experiments described above. In all cases, input values for r(H.G) were calculated from Δδmax and the initial host (peptide) concentration (r(H.G) = Δδmax [ppb] / H [M]). For the estimation of binding constants K, for each input of data, the host concentration H [M] and the response 2rameters r(H.G) were left as variables to allow for errors in weighing, dilution and taking aliquots of the proton sponge stock solution.

Binding data has been estimated for titrations of **1a** with proton sponge and **2a** (3 equiv), **2b** (3 equiv), **2c** (3 equiv), **2a** (1 equiv) and with premade phosphate from **2a** and proton sponge (Figures 53-57). Despite the fact that most values for K have a rather big standard error and that in most cases the calculated host concentration is higher than it was for the actual experiments, the obtained calculations give a rough estimation of binding constants for chiral anion recognition between an achiral helix and a chiral anion. The determined K values lie in a range from 500 to 5000 M^{-1}.

Input example

```
Equilibrium constant fit for binding of urea + chiral acid and base
[task]
task = fit
data = equilibria
[mechanism]
H + G <==> H.G :          K          association
[constants]
K = 1000 ?
[concentrations]
H = 0.005 ?
[responses]
H =  0
H.G = 86000 ?
[data]
variable G
file ./KG-174.txt
[output]
directory ./KG-174/KG-174_1000x_0.005x_86000x
[end]
```

[3] P. Kuzmic, *Anal. Biochem.*, **1996**, *237*, 260–273.

No binding data could be obtained that correlated with the experimental data for the titration experiment in deuterated acetonitrile. The obtained output for the data fitting was that the model appeares to be severely over-2rametrised given the available data. This can be explained as the mixture **1a**:**2a**:proton sponge was not entirely soluble in acetonitile and so the actual concentration in solution is unknown.

The Dynafit calculations are shown on the following pages (Figures 53-57):

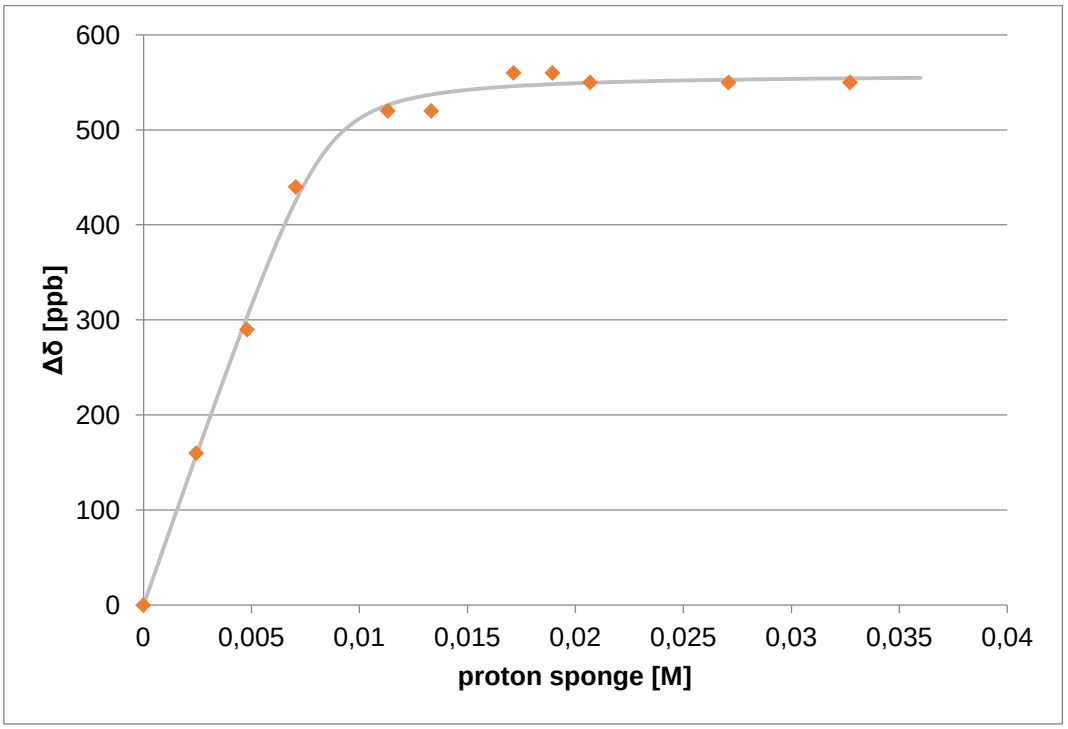


Figure 53. Fitted curve with DynaFit: K = 4631 (±2652) (grey); Experimental data: Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* proton sponge [M] recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 3.64 mM, $[\mathbf{2a}]_{initial}$ = 3*$[\mathbf{1a}]_{initial}$ (orange)

PARAMETERS AND CONFIDENCE INTERVALS

NO.	SET	2RAMETER	INITIAL	LIMIT-LO	LIMIT-HI	FIT	STDERR	CV%
1	*	K	1000	0.001	1.00E+09	4631.43	2652.14	57.264
2	*	association	1					
3	*	[H]	0.005	5.00E-06	5	0.00836015	0.00036855	4.40842
4	1	[G]	0					
5	1	[H.G]	0					
6	1	r(H)	0					
7	1	r(G)	0					
8	*	r(H.G)	112000	0.112	1.12E+11	66881.2	3497.66	5.22966
9	1	offset	0					
10	1	intensive	0					

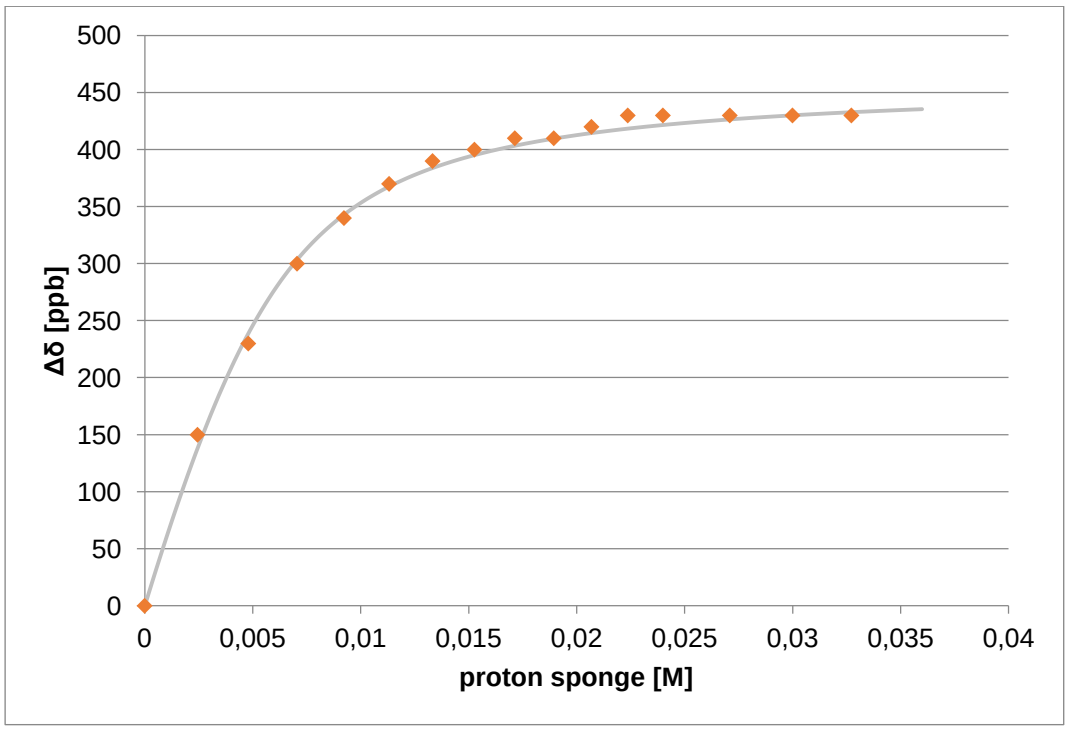


Figure 54 Fitted curve with DynaFit: K = 594 (±97) (grey); Experimental data: Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* proton sponge [M] recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 3.64 mM, $[\mathbf{2b}]_{initial}$ = 3*$[\mathbf{1a}]_{initial}$ (orange)

PARAMETERS AND CONFIDENCE INTERVALS

NO.	SET	2RAMETER	INITIAL	LIMIT-LO	LIMIT-HI	FIT	STDERR	CV%
1	*	K	1000	0.001	1.00E+09	594.156	97.1338	16.3482
2	*	association	1					
3	*	[H]	0.005	5.00E-06	5	0.0057193	0.000520432	9.09958
4	1	[G]	0					
5	1	[H.G]	0					
6	1	r(H)	0					
7	1	r(G)	0					
8	*	r(H.G)	86000	0.086	8.60E+10	80308.4	8190.45	10.1988
9	1	offset	0					
10	1	intensive	0					

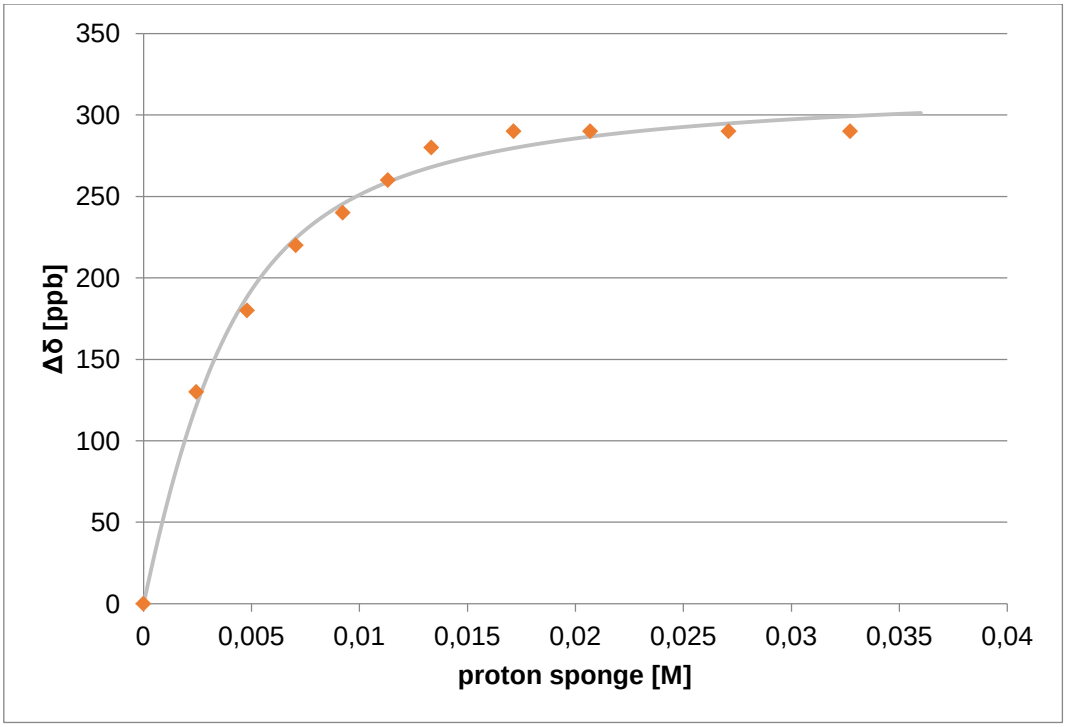


Figure 55 Fitted curve with DynaFit: K = 475 (±161) (grey); Experimental data: Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* proton sponge [M] recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 3.64 mM, $[\mathbf{2c}]_{initial}$ = 3*$[\mathbf{1a}]_{initial}$ (orange)

PARAMETERS AND CONFIDENCE INTERVALS

NO.	SET	2RAMETER	INITIAL	LIMIT-LO	LIMIT-HI	FIT	STDERR	CV%
1	*	K	1000	0.001	1.00E+09	474.855	161.207	33.9487
2	*	association	1					
3	*	[H]	0.005	5.00E-06	5	0.00303879	0.00127271	41.8823
4	1	[G]	0					
5	1	[H.G]	0					
6	1	r(H)	0					
7	1	r(G)	0					
8	*	r(H.G)	58000	0.058	5.80E+10	105448	47082.1	44.6494
9	1	offset	0					
10	1	intensive	0					

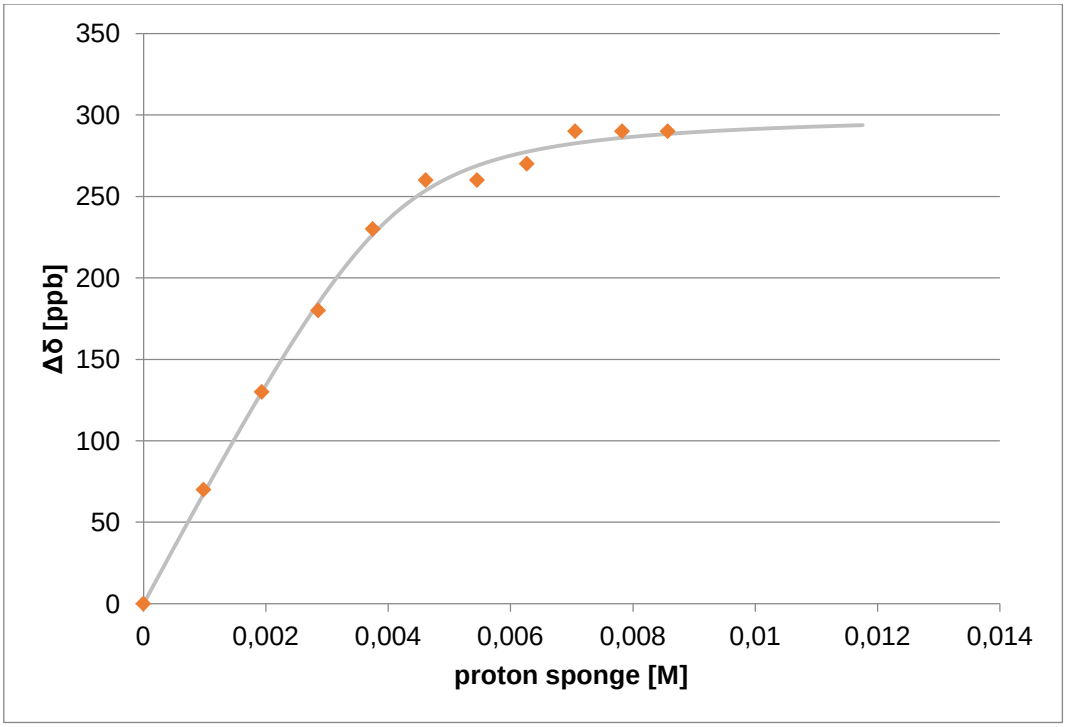


Figure 56. Fitted curve with DynaFit: K = 4475 (±161) (grey); Experimental data: Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* proton sponge [M] recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 4.11 mM, $[\mathbf{2a}]_{initial}$ = $[\mathbf{1a}]_{initial}$ (orange)

PARAMETERS AND CONFIDENCE INTERVALS

NO.	SET	2RAMETER	INITIAL	LIMIT-LO	LIMIT-HI	FIT	STDERR	CV%
1	*	K	1000	0.001	1.00E+09	4475.26	1398.39	31.2471
2	*	association	1					
3	*	[H]	0.005	5.00E-06	5	0.00410362	0.000165439	4.03154
4	1	[G]	0					
5	1	[H.G]	0					
6	1	r(H)	0					
7	1	r(G)	0					
8	*	r(H.G)	58000	0.058	5.80E+10	73618	3742.2	5.08327
9	1	offset	0					
10	1	intensive	0					

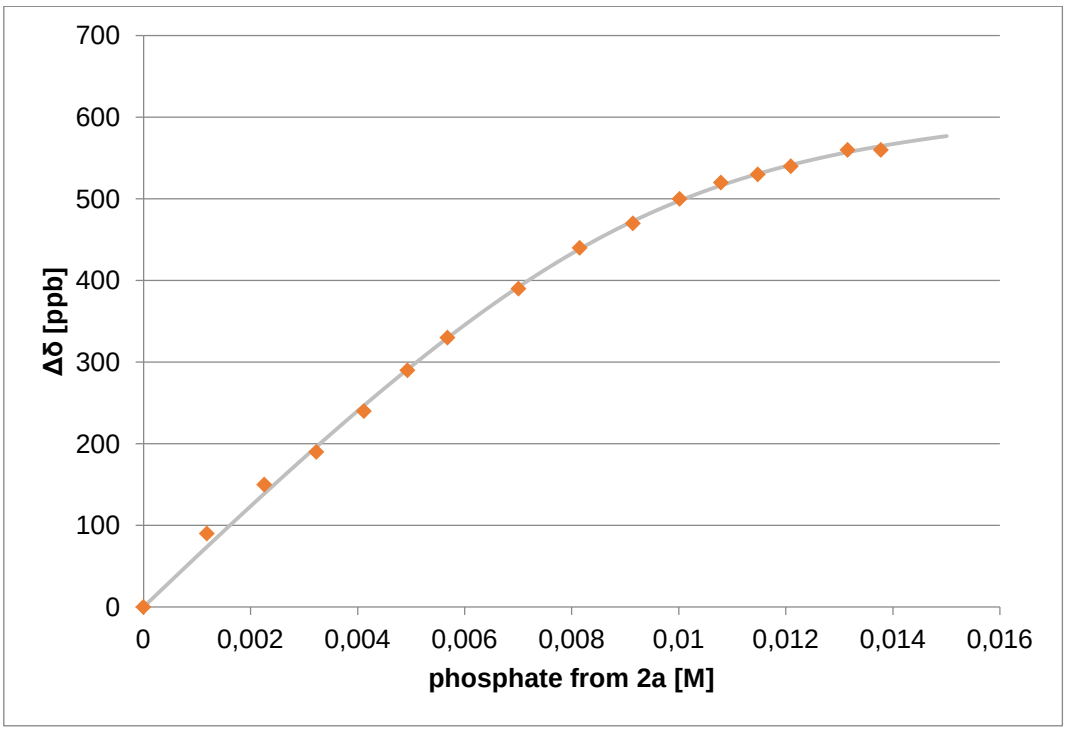
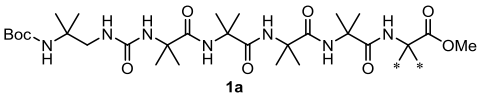


Figure 57. Fitted curve with DynaFit: K = 1175 (±358) (grey); Experimental data: Plot of the anisochronicity (Δδ, ppb) of the two diastereotopic $^{13}CH_3$ signals of the NMR probe in **1a** *vs* phosphate from **2a** [M] recorded in THF-d_8 at 296 K; $[\mathbf{1a}]_{initial}$ = 5 mM, $[\mathbf{1a}]_{end}$ = 2.06 mM, (orange)

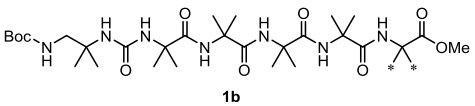
PARAMETERS AND CONFIDENCE INTERVALS

NO.	SET	2RAMETER	INITIAL	LIMIT-LO	LIMIT-HI	FIT	STDERR	CV%
1	*	K	1000	0.001	1.00E+09	1174.61	358.275	30.5015
2	*	association	1					
3	*	[H]	0.005	5.00E-06	5	0.00949726	0.000197563	2.08021
4	1	[G]	0					
5	1	[H.G]	0					
6	1	r(H)	0					
7	1	r(G)	0					
8	*	r(H.G)	112000	0.112	1.12E+11	68543.1	3149.35	4.59471
9	1	offset	0					
10	1	intensive	0					

11 Synthesis of foldamer-ureas

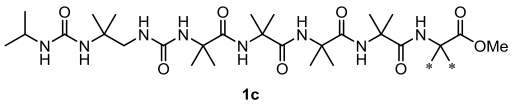

1a

Compound 1a. To a solution of H_2N-Aib_4(Aib**)OMe (0.22 mmol, 100 mg, 1 equiv) in acetonitrile (2.5 mL) was added DIPEA (0.44 mmol, 76 µL, 2 equiv) and the mixture cooled to 0 °C. A solution of BocAib^{u}OSu (0.22 mmol, 72 mg, 1 equiv) in acetonitrile (2.5 mL) was added dropwise and the reaction mixture was stirred at RT for 46 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in a 3:1 mixture of $CHCl_3$ and *i*PrOH (20 mL) and the organic layer was washed with saturated $NaHCO_3$ (2 x 10 mL) and 5% $KHSO_4$ (2 x 10 mL) and was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (CH_2Cl_2:MeOH – 99:1 to 95:5) provided the titled oligourea as a white solid (112 mg, 75%). M.p.: 244-245 °C; ^{1}H NMR (400 MHz, δ, $CDCl_3$/CD_3OH 95:5) 8.21 (1H, s, N*H*), 7.48 (1H, s, N*H*), 7.41 (1H, s, N*H*), 6.86 (1H, s, N*H*), 6.06 (1H, br s, N*H*), 5.95 (1H, s, N*H*), 5.30 (1H, br s, N*H*), 3.63 (3H, s, OCH_3), 3.21 (2H, d, *J* = 6.2 Hz, CH_2NH), 1.47 (6H, dd, *J* = 129 and 4.1 Hz, 2* ^{13}CH_3), 1.43 (6H, 2*CH_3), 1.39 (6H, s, 2*CH_3), 1.34-1.38 (21H, m, 7*CH_3), 1.20 (6H, s, 2*CH_3) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3$/CD_3OH 95:5) 175.7 (*C*=O), 175.5 (*C*=O), 175.2 (*C*=O), 175.0 (*C*=O), 174.6 (*C*=O), 158.7 (*C*=O), 56.7 (*C*), 56.5 (*C*), 56.4 (*C*), 56.3 (*C*), 53.7 (*C*), 51.9 (O*C*H_3), 49.3 ((*C*H_2)NH), 28.9 (C(*C*H_3)$_3$), 24.1-25.2 (2*^{13}*C*H_3 + 10**C*H_3) ppm (Not all carbon signals can be seen due to the low solubility of the compound); IR (solid): $\bar{\nu}$ = 3376, 3270, 2979, 2935, 1722, 1661, 1638, 1534, 1455, 1382, 1363, 1275, 1226, 1169, 1151cm^{-1}; MS (TOF MS ES$^+$, MeOH) *m/z* = 674.6 ([M+H]$^+$, 10%), 696.6 ([M+Na]$^+$, 70%); HRMS (micrOTOF ES+, MeOH): *m/z* calcd for $C_{29}{}^{13}C_2H_{58}N_7O_9$ = 674.4358; found 674.4349.


1b

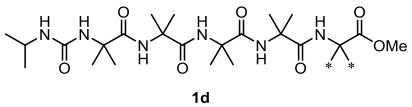
Compound 1b. To a solution of H_2N-Aib_4(Aib**)OMe (0.722 mmol, 332 mg, 1 equiv) in acetonitrile (10 mL) was added DIPEA (1.44 mmol, 250 µL, 2 equiv) and the mixture cooled to 0 °C. A solution of BocAib[R]^{u}OSu (0.865 mmol, 285 mg, 1.2 equiv) in acetonitrile (4 mL) was added dropwise and the reaction mixture was stirred at RT for 64 h. The reaction mixture was diluted with CH_2Cl_2 (200 mL) and the organic layer was washed with 5% $KHSO_4$ (2 x 50 mL) and saturated $NaHCO_3$ (2 x 50 mL) and was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (CH_2Cl_2:MeOH – 97:3 to 90:10) provided the titled oligourea as a white solid (39 mg, 8%). M.p.: 232-233 °C; ^{1}H NMR (400 MHz, δ, CD_3OH) 8.67 (1H, s, N*H*), 8.11 (1H, s, N*H*), 7.76 (2H, s, N*H*), 6.62 (1H, s, N*H*), 6.03 (1H, s, N*H*), 5.73 (1H, s, N*H*), 3.65 (3H, s, OCH_3), 3.25 (2H, d, *J* = 4.7 Hz, CH_2NH), 1.48 (6H, dd, *J* = 129 and 4.3 Hz, 2* ^{13}CH_3), 1.46 (6H, 2*CH_3), 1.45 (9H, s, C(CH_3)$_3$), 1.44 (6H, s, 2*CH_3), 1.43 (6H, s, 2*CH_3), 1.35 (6H, s, 2*CH_3), 1.25 (6H, s, 2*CH_3) ppm; IR (solid): $\bar{\nu}$ = 3295, 2981, 2933, 2869, 1746, 1705, 1662, 1638, 1543, 1464, 1455, 1439, 1383, 1361, 1270, 1228, 1197, 1167, 1148 cm^{-1}; MS (TOF MS ES$^+$, CH_2Cl_2) *m/z* = 674.6 ([M+H]$^+$, 100%), 696.6 ([M+Na]$^+$, 60%); HRMS (micrOTOF ES+, CH_2Cl_2): *m/z* calcd for

$C_{29}{}^{13}C_2H_{58}N_7O_9$ = 674.4363; found 674.4348.



1c

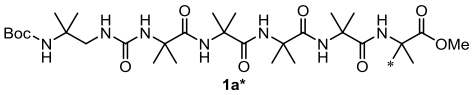
Compound 1c. To a solution of **1a** (0.092 mmol, 62 mg, 1 equiv) in CH_2Cl_2 (1.5 mL) was added TFA (0.5 mL) and the reaction mixture was stirred at RT for 4 h. TFA and CH_2Cl_2 were evaporated under reduced pressure and last traces of TFA were removed by co-evaporation with CH_2Cl_2 (3 x 5 mL). To the residue dissolved in DMF was added Et_3N (0.276 mmol, 39 µL, 3 equiv) and the solution was cooled to 0 °C. Isopropyl isocyanate (0.184 mmol, 18 µL, 2 equiv) was added dropwise and the reaction mixture was stirred at RT for 32 h. The reaction mixture was then diluted with a 3:1 mixture of $CHCl_3$ and *i*PrOH (75 mL) and the organic layer was washed with 1 M HCl (2 x 25 mL) and was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (CH_2Cl_2:MeOH – 96:4 to 90:10) provided the titled oligourea as a white solid (56 mg, 92%). M.p.: 219-220 °C; ^{1}H NMR (400 MHz, δ, $CDCl_3/CD_3OH$ 95:5) 8.22 (1H, s, N*H*), 7.44-7.56 (2H, m, N*H*), 7.00 (1H, s, N*H*), 6.47 (1H, br s, N*H*), 6.18 (1H, s, N*H*), 5.34 (1H, s, N*H*), 5.14 (1H, d, *J* = 6.1 Hz, N*H*), 3.67-3.80 (1H, m, NHC*H*$(CH_3)_2$), 3.63 (3H, s, OCH_3), 3.23 (2H, d, *J* = 5.0 Hz, CH_2NH), 1.46 (6H, dd, *J* = 129 and 3.8 Hz, 2* ^{13}CH_3), 1.43 (6H, 2*CH_3), 1.38 (6H, s, 2*CH_3), 1.36 (12H, s, 4*CH_3), 1.20 (6H, s, 2*CH_3), 1.07 (6H, d, *J* = 6.5 Hz, NHCH(CH_3)$_2$) ppm; ^{13}C NMR (100 MHz, δ, $CDCl_3/CD_3OH$ 95:5) 176.0 (*C*=O), 175.7 (*C*=O), 175.5 (*C*=O), 175.3 (*C*=O), 174.9 (*C*=O), 158.4 (*C*=O), 158.3 (*C*=O), 56.6 (*C*), 56.4 (*C*), 56.2 (*C*), 56.1 (*C*), 55.7 (t, J = 37 Hz, *C*(^{13}CH$_3$)$_2$), 53.4 (*C*), 52.0 (OCH_3), 50.1 ((*C*H_2)NH), 41.6 (*C*H), 25.7 (2**C*H_3), 23.8-25.4 (2*^{13}*C*H_3 + 8**C*H_3), 23.1 (CH(*C*H_3)$_2$) ppm; IR (solid): $\bar{\nu}$ = 3305, 2979, 2936, 2873, 1732, 1645, 1537, 1455, 1383, 1362, 1301, 1266, 1225, 1170, 1149 cm^{-1}; MS (TOF MS ES$^+$, MeOH) *m/z* = 659.6 ([M+H]$^+$, 100%), 681.6 ([M+Na]$^+$, 50%) ; HRMS (micrOTOF ES+, CH_2Cl_2): *m/z* calcd for $C_{28}{}^{13}C_2H_{57}N_8O_8$ = 659.4366; found 659.4360.



1d

Compound 1d. To a solution of H_2N-Aib$_4$(Aib**)OMe (0.070 mmol, 32 mg, 1 equiv) in acetonitrile (0.7 mL) was added Et_3N (0.070 mmol, 10 µL, 1 equiv) and the mixture cooled to 0 °C. Isopropyl isocyanate (0.14 mmol, 14 µL, 2 equiv) was added dropwise and the reaction mixture was stirred at RT for 24 h. After evaporation of the solvent under reduced pressure, the residue was dissolved in a 3:1 mixture of $CHCl_3$ and *i*PrOH (20 mL) and the organic layer was washed with saturated $NaHCO_3$ (2 x 10 mL) and 5% $KHSO_4$ (2 x 10 mL) and was dried over $MgSO_4$. After evaporation of the solvent under reduced pressure, purification of the crude by column chromatography (CH_2Cl_2:MeOH – 97:3 to 91:9) provided the titled oligourea as a white solid (25 mg, 65%). ^{1}H NMR (400 MHz, δ, $CDCl_3/CD_3OH$ 95:5) 8.22 (1H, s, N*H*), 7.44-7.47 (1H, s, N*H*), 7.34 (1H, s, N*H*), 6.75 (1H, s, N*H*), 5.57 (1H, s, N*H*), 5.26 (1H, d, *J* = 8.8 Hz, N*H*), 3.70-3.84 (1H, m, NHC*H*$(CH_3)_2$), 3.64 (3H, s, OCH_3), 1.57 (6H, dd, *J* = 129 and 3.9 Hz, 2* ^{13}CH_3), 1.44 (6H, 2*CH_3), 1.40 (6H, s, 2*CH_3), 1.38 (6H, s, 2*CH_3), 1.35 (6H, s, 2*CH_3), 1.08 (6H, d, *J* = 6.4 Hz, NHCH(CH_3)$_2$) ppm; HRMS (micrOTOF ES+, MeOH): *m/z* calcd for

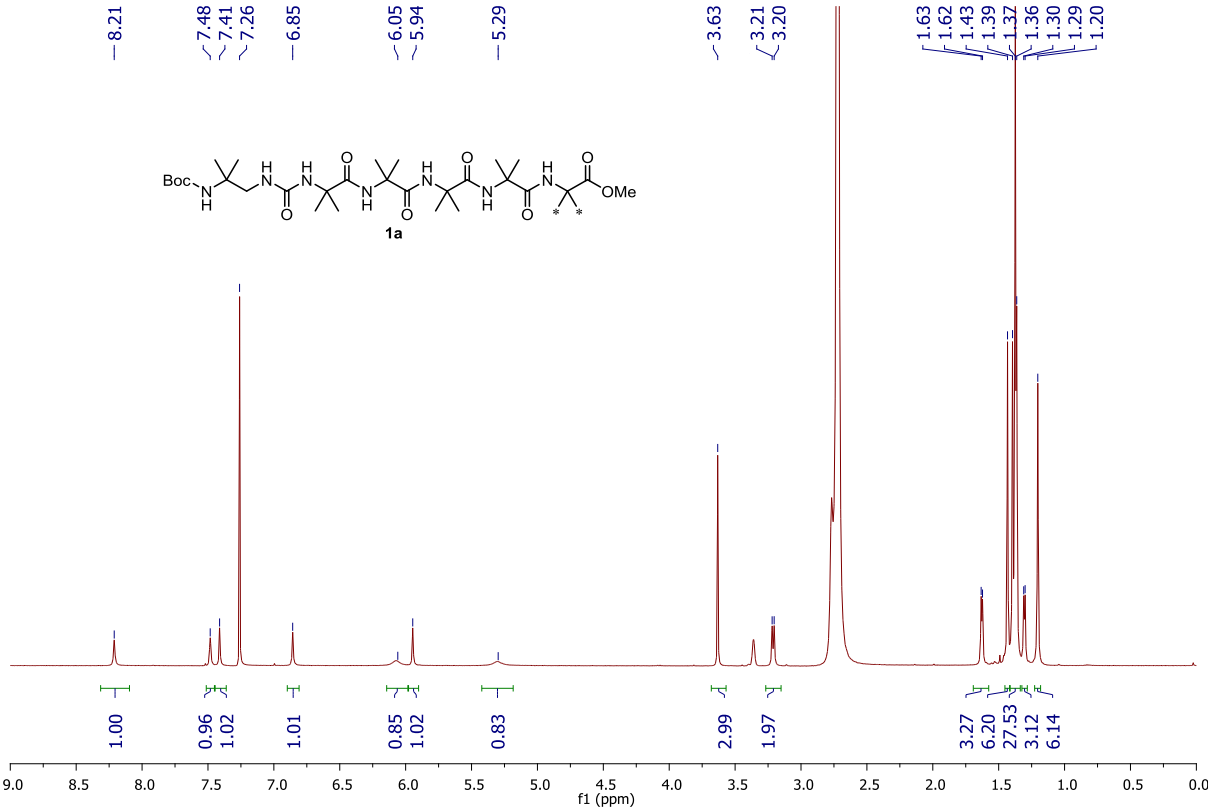
$C_{23}{}^{13}C_2H_{47}N_6O_7$: 545.3568 $[M+H]^+$; found: 545.3565; *m/z* calcd for $C_{23}{}^{13}C_2H_{46}N_6NaO_7$: 567.3387 $[M+Na]^+$; found: 567.3386.



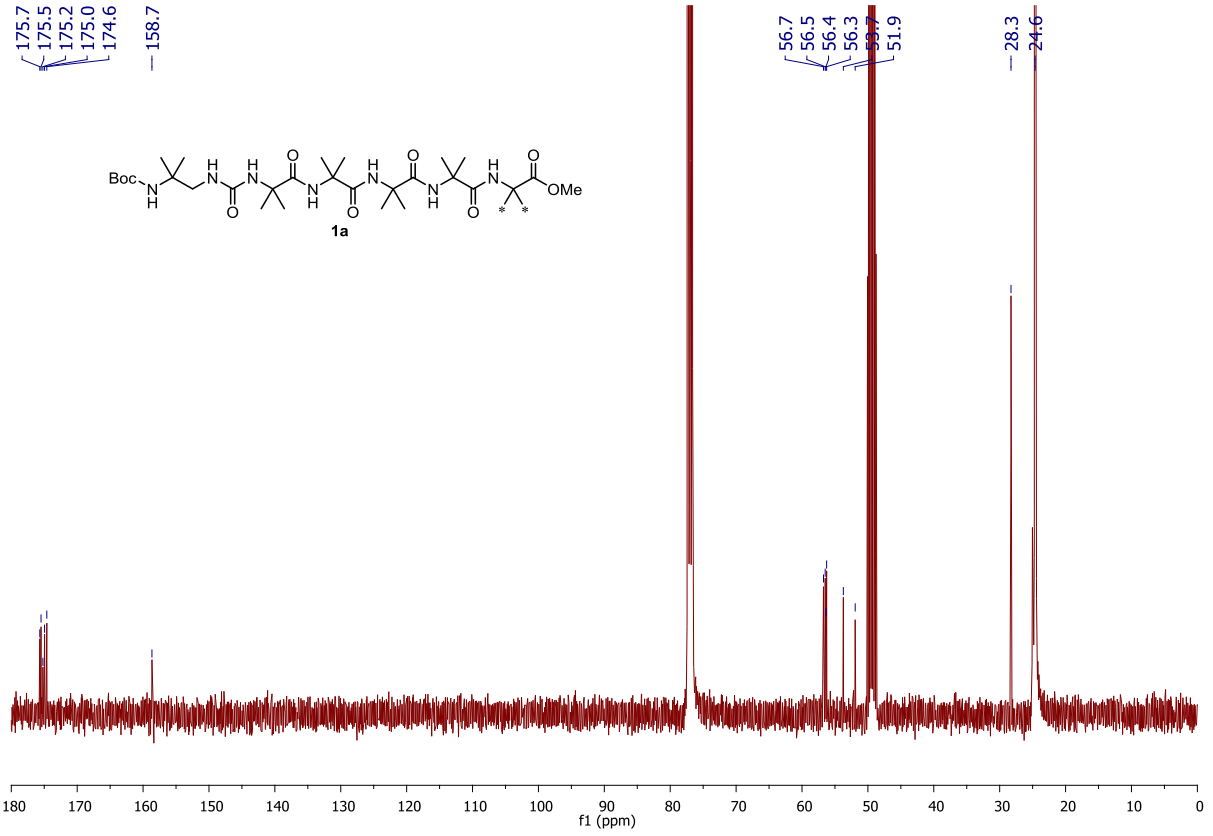
1a*

Compound 1a*. The amine H_2N-Aib$_4$(Aib*)OMe (0.11 mmol, 50 mg, 1 equiv) was dissolved in acetonitrile (5 mL / mmol, 600 μL), DIPEA (0.12 mmol, 21 μL, 1.1 equiv) was added and the mixture cooled to 0 °C. The carbamate (43.4 mg, 1 equiv) was dissolved in acetonitrile (800 μL) and added during 5 min and the reaction mixture was stirred for 40 h. The solution was concentrated, 20 mL of a 3:1-$CHCl_3$:*i*PrOH mixture was then added, followed by washing with $NaHCO_3$ (sat., 2 x 5 mL) 5% $KHSO_4$, (2 x 5 mL) and brine (5 mL), drying ($MgSO_4$), filtration and concentration *in vacuo*. The monolabelled foldamer-urea was then isolated by column chromatography (CH_2Cl_2:MeOH – 99:1 to 95:5) as a white solid in 76% yield (56 mg, 0.083 mmol). R_f (SiO_2/ CH_2Cl_2:MeOH-95:5) = 0.14; M.p.: 248-250 °C; ^{1}H NMR (400 MHz, δ, THF-d_8) 8.35 (1H, s, N*H*), 7.43-7.44 (2H, s, N*H*), 7.39 (1H, s, N*H*), 6.16 (1H, s, N*H*), 6.07 (1H, s, N*H*), 6.00-5.97 (1H, m, N*H*), 3.54 (3H, s, OC*H*$_3$), 3.35 (2H, d, *J* = 8 Hz, C*H*$_2$NH), 1.42 (3H, d, *J* = 128 Hz, ^{13}C*H*$_3$), 1.42 (3H, d, *J* = 4 Hz, ^{13}CH$_3$(C)C*H*$_3$), 1.40 (12H, s, 4*C*H*$_3$), 1.40 (9H, s, 3*C*H*$_3$), 1.39 (6H, s, 2*C*H*$_3$), 1.38 (6H, s, 2*C*H*$_3$), 1.21 (6H, s, 2* C*H*$_3$) ppm; ^{13}C NMR (126 MHz, δ, MeOD-d_4) 177.7 (*C*=O), 177.4 (*C*=O), 177.0 (*C*=O), 176.9 (*C*=O), 176.9 (*C*=O), 160.5 (*C*=O), 156.9 (*C*=O), 73.5 (*C*), 57.9 (*C*), 57.8 (*C*), 57.4 (*C*), 57.2 (*C*), 54.8 (*C*), 52.6 (O*C*H$_3$), 49.3 (*C*H$_2$)NH, 28.9 (C(*C*H$_3$)$_3$), 25.6 (*C*H$_3$), 25.2 (^{13}*C*H$_3$+), 25.0 (*C*H$_3$) ppm (Not all *C*H$_3$ signals can be seen); IR (film): $\bar{\nu}$ = 3307, 2982, 2934, 2472, 1715, 1653, 1534, 1472, 1384, 1364, 1230, 1175, 1096, 778 cm^{-1}; MS (TOF MS ES$^+$, MeOH) m/e= 674 ($[M+H]^+$, 100%), 550 ($[M+Na]^+$, 75%); HRMS (micrOTOF ES+): *m/z* calcd for $C_{30}{}^{13}CH_{58}N_7O_9$: 673.4324 $[M+H]^+$; found: 673.4316; *m/z* calcd for $C_{30}{}^{13}CH_{57}N_7NaO_9$: 695.4144 $[M+Na]^+$; found: 695.4141.

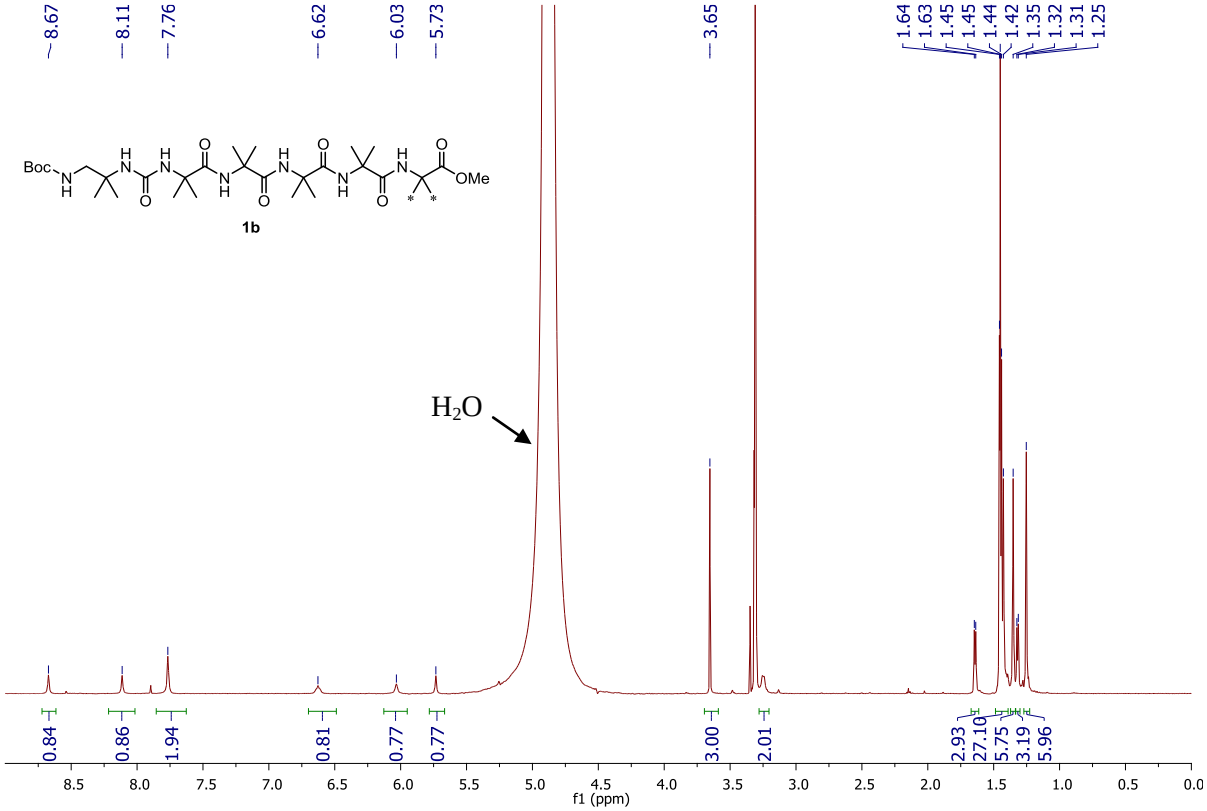
12 NMR spectra



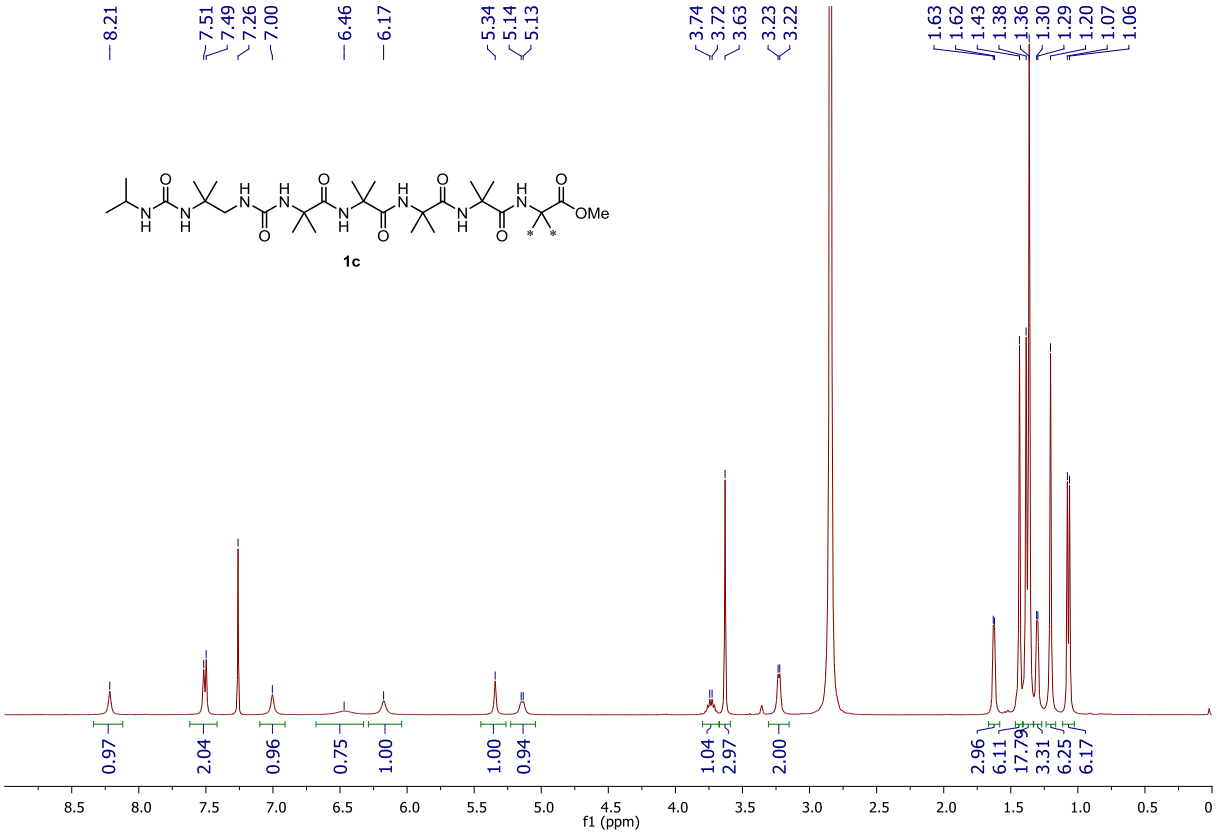
^{1}H-NMR (400 MHz, $CDCl_3$/CD_3OH 95:5) of **1a**



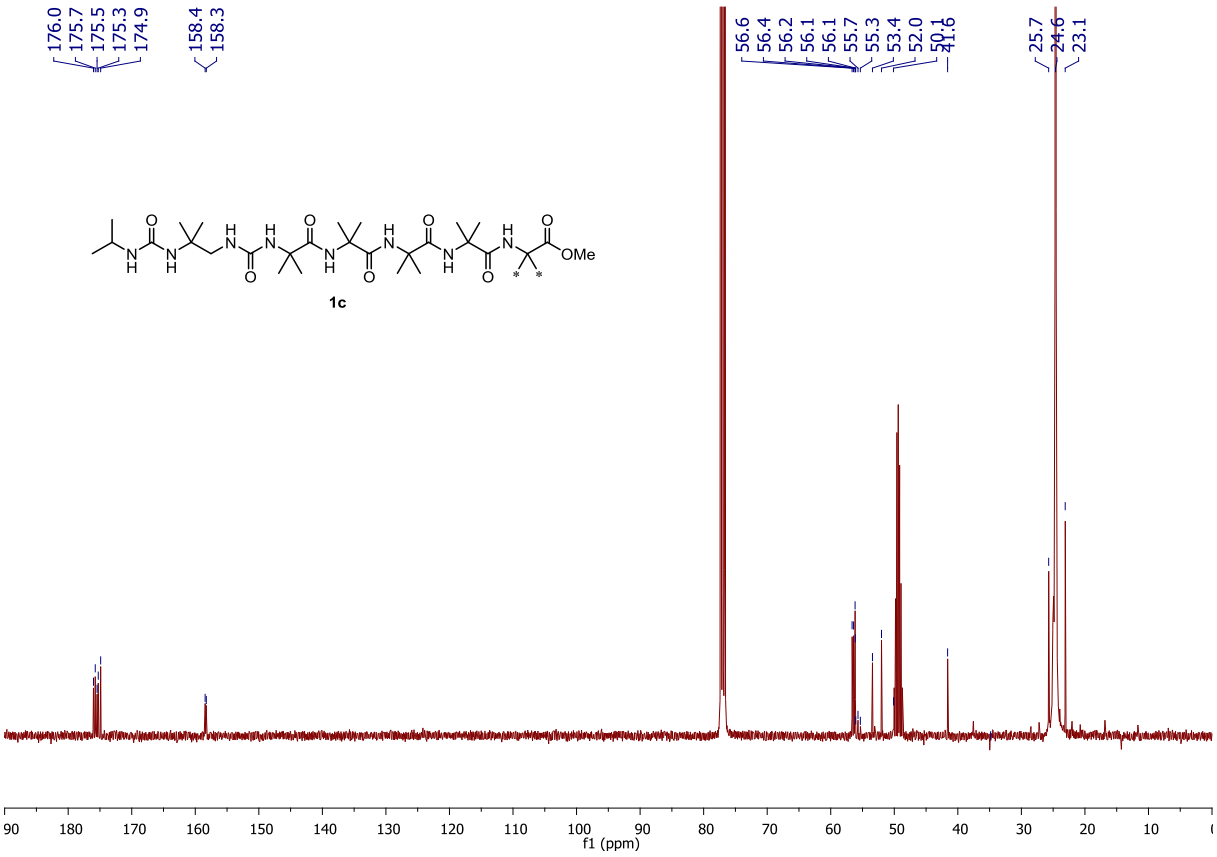
^{13}C-NMR (100 MHz, $CDCl_3$/CD_3OH 95:5) of **1a**



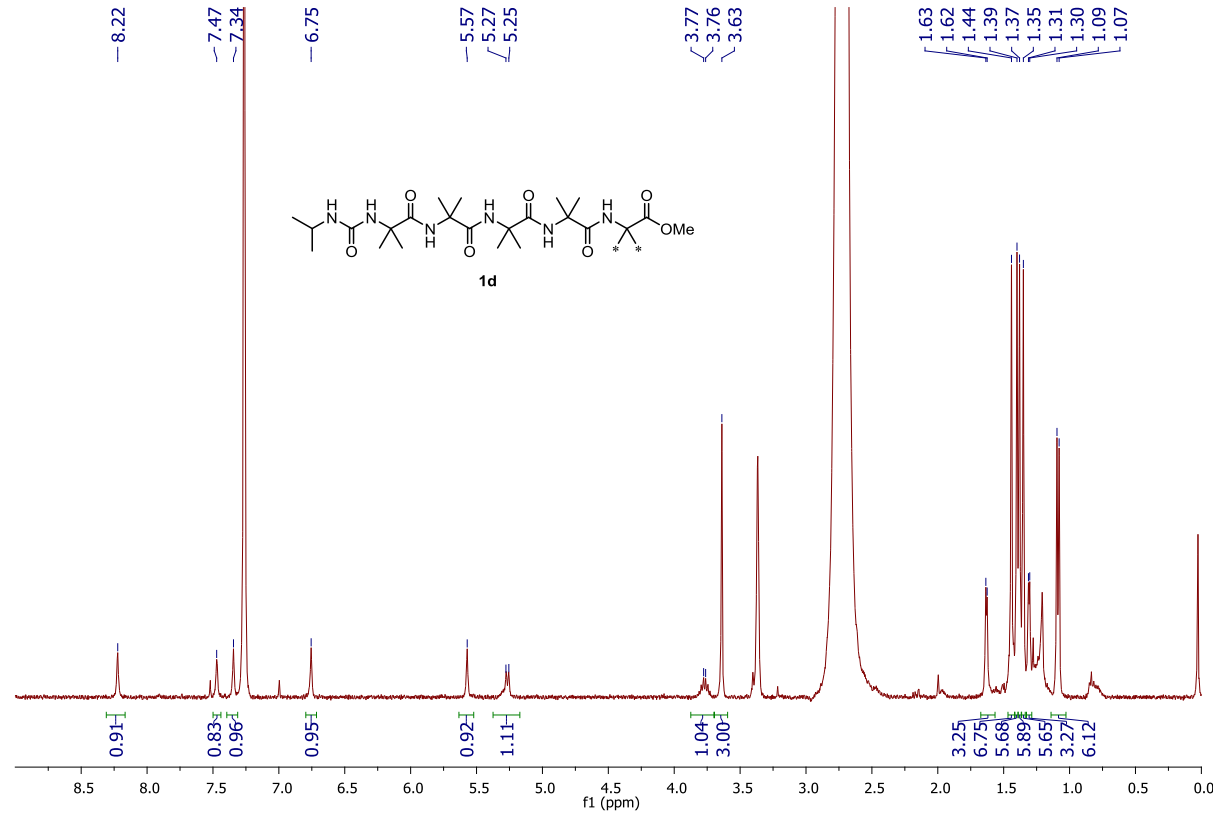
^{1}H-NMR (400 MHz, CD_3OH) of **1b**



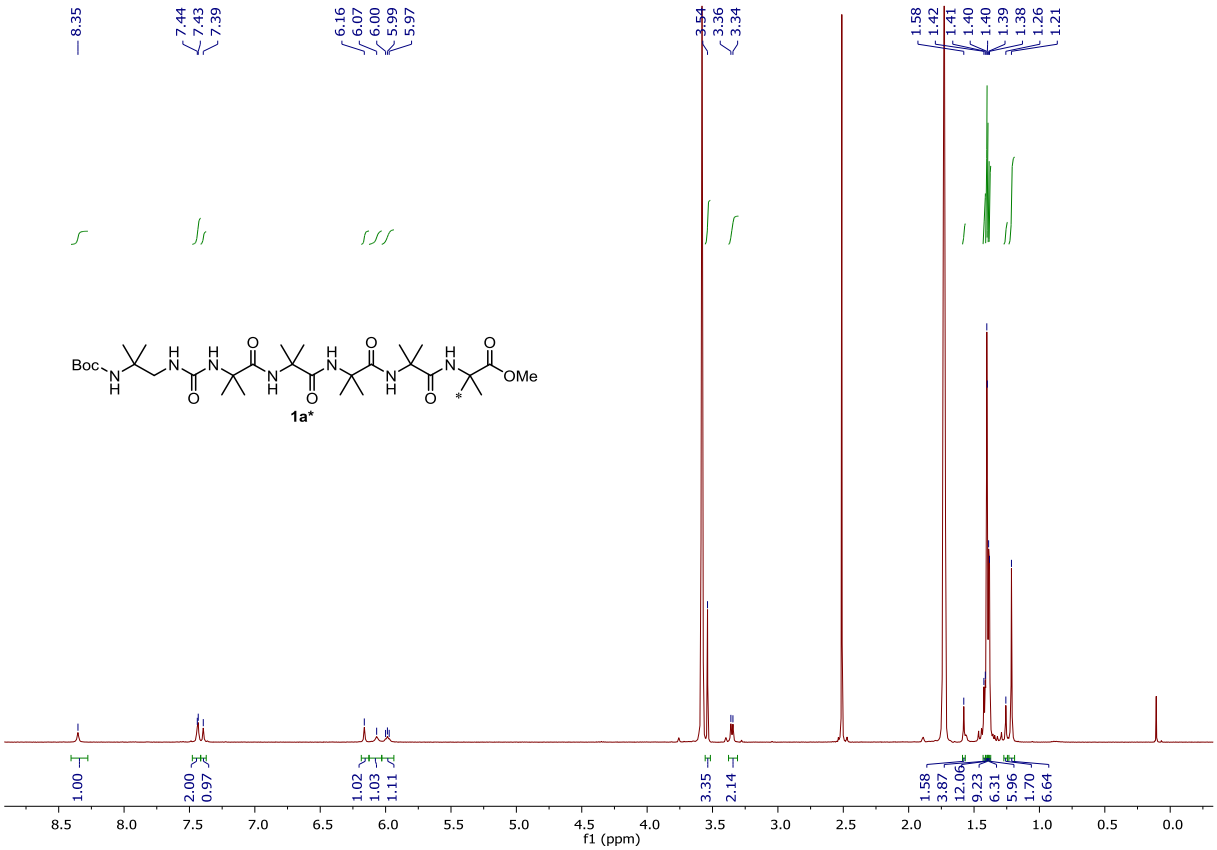
^{1}H-NMR (400 MHz, $CDCl_3/CD_3OH$ 95:5) of **1c**



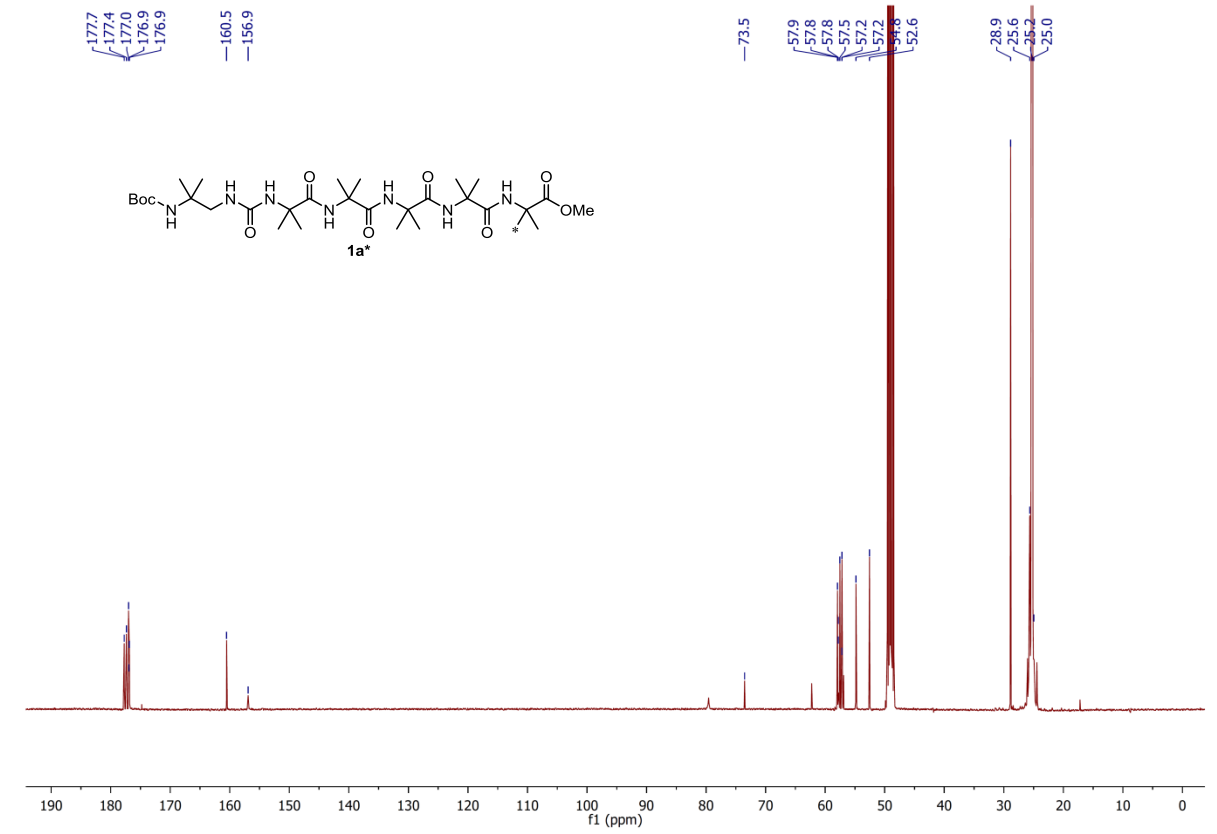
^{13}C-NMR (100 MHz, $CDCl_3/CD_3OH$ 95:5) of **1c**



^{1}H-NMR (400 MHz, $CDCl_3/CD_3OH$ 95:5) of **1d**



^{1}H-NMR (400 MHz, THF-d_8) of **1a***



^{13}C-NMR (126 MHz, CD_3OD) of **1a***