Experimental and computational study of the inclusion complexes of β-cyclodextrin with the chemical warfare agent soman (GD) and commonly used simulants

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General Materials and Methods

NMR spectra were obtained on a JEOL Eclipse+ 500 instrument (operating at 500 MHz for ^{1}H and 202 MHz ^{31}P spectra) or at 9.4 Tesla using a Bruker AVHD4 spectrometer operating at 400 MHz (^{1}H) equipped with either a 5mm BBFO or TBO(^{19}F) room temperature probehead. Data was recorded at 293 K and acquired using Bruker Topspin 3.5.

Samples of GD (soman) were sourced internally and confirmed by in-house methods as >99% pure. Deuterated solvents were purchased from Goss Scientific Instruments Ltd. and used as provided. All other chemical were purchased from Sigma Aldrich Ltd (UK) and used without further purification.

Example Job plot method:

Solutions of tri-isopropyl phosphate (6 mL, 5.77×10^{-3} mol dm^{-3})* and β-cyclodextrin (6 mL, 5.77×10^{-3} mol dm^{-3}) were prepared in D$_2$O. These were then mixed in TiPP:β-CD solution volume ratios of 0:10, 1:9, 2:8 ….. 9:1 mL. A small aliquot (10 μL) of methanol D$_2$O solution was added to each sample before being transferred to NMR tubes (500 μL). ^{1}H NMR spectra were referenced against methanol internal standard and the β-CD mole fraction plotted against mol fraction x Δδ (ppm).

* Concentrations of guest species were selected on the ability to easily dispense whole μL volumes, and thus, along with β-CD concentrations, vary slightly between guests (4.4×10^{-3} to 7.9×10^{-3} mol dm^{-3}).

Example NMR titration method:

A D$_2$O (20 mL) solution of β-CD (13.75 mg, 6.1×10^{-4} mol dm^{-3})* was prepared and separated into 17 samples (1 mL). To the vials was added an aliquot of TiPP solution (0.03 mol dm^{-3}) of volume 0, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 50, 60, 80, 100, 140 and 200 μL to generate solutions with TiPP molar equivalents (compared to β-CD) of 0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.5, 3.0, 4.0, 5.0, 7.0 and 10.0.** A small aliquot (10 μL) of methanol D$_2$O solution was added to each sample before being transferred to NMR tubes (500 μL). ^{1}H NMR spectra were referenced against methanol internal standard and the chemical shift of the H-3 and H-5 β-CD internal cavity protons were monitored against changing TiPP concentration.

* Concentrations of guest species were selected on the ability to easily dispense whole µL volumes, and thus, along with β-CD concentrations, vary slightly between guests (6.1×10^{-4} to 4.4×10^{-3} mol dm^{-3}).

** For titrants with greater water solubility (e.g. DIMP, GD) these aliquot volumes were decreased to 0, 2, 4, 6, 8, 10, 22, 24, 26, 28, 30, 35, 40, 50, 70 and 100 µL. The scale of molar equivalents remains the same.

All NMR titration data was fit using the software programme EQNMR.[1]

Computational methods:

Calculations were undertaken using Spartan '16 Parallel Suite running on a Mac Pro with 3.5 GHz 6-Core Intel Xenon E5 processors and two threads per core.

β-CD proton numbering schematic[2]
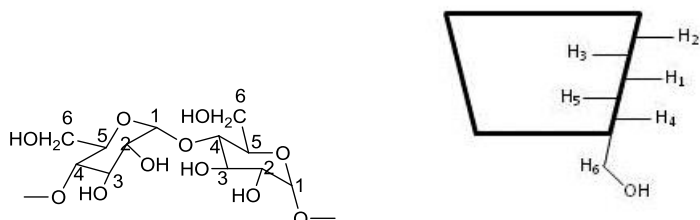
Figure S1. *Left: Proton numbering as shown for a disaccharide unit; right: schematic illustration of the internal and external cavity proton environments.*

NMR spectra of GD, PMP and β-CD mixtures
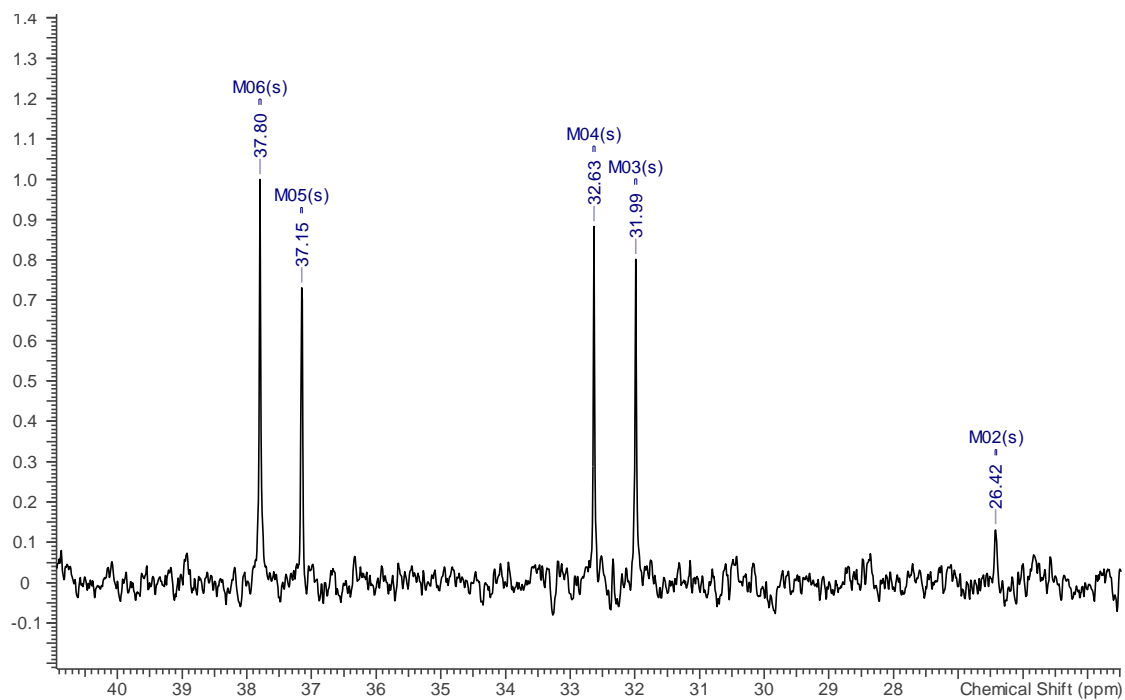
Figure S2. ^{31}P NMR spectrum of GD in D_2O (298 K).
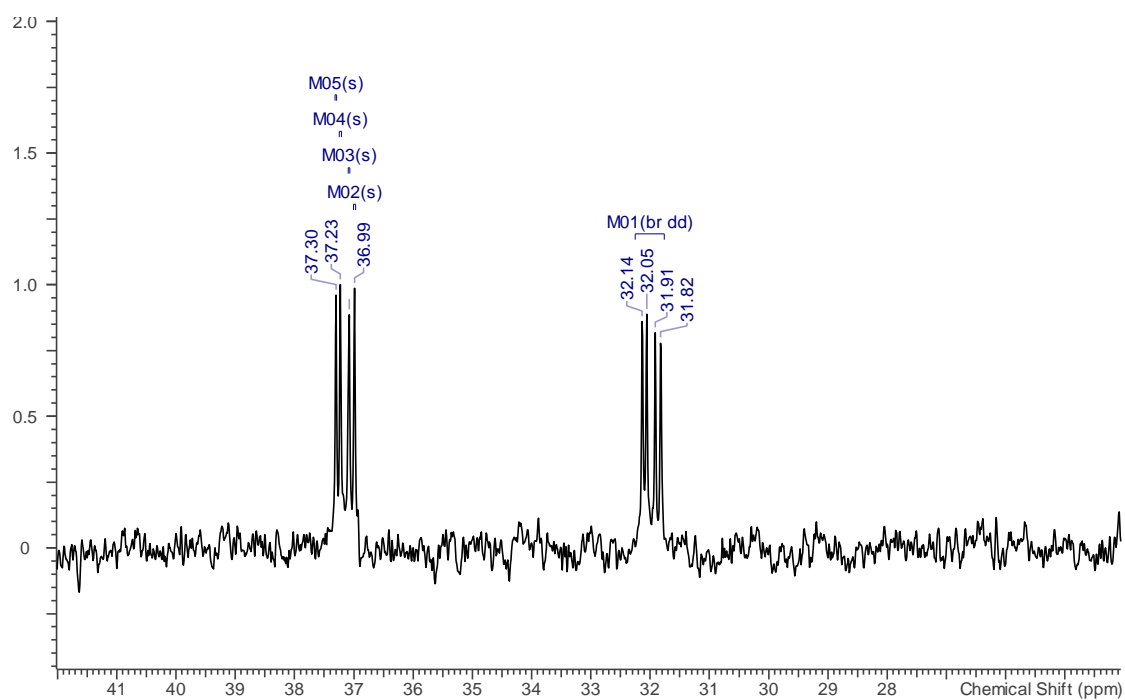
Figure S3. ^{31}P NMR spectrum of equimolar GD and β-cyclodextrin in D_2O (298 K).
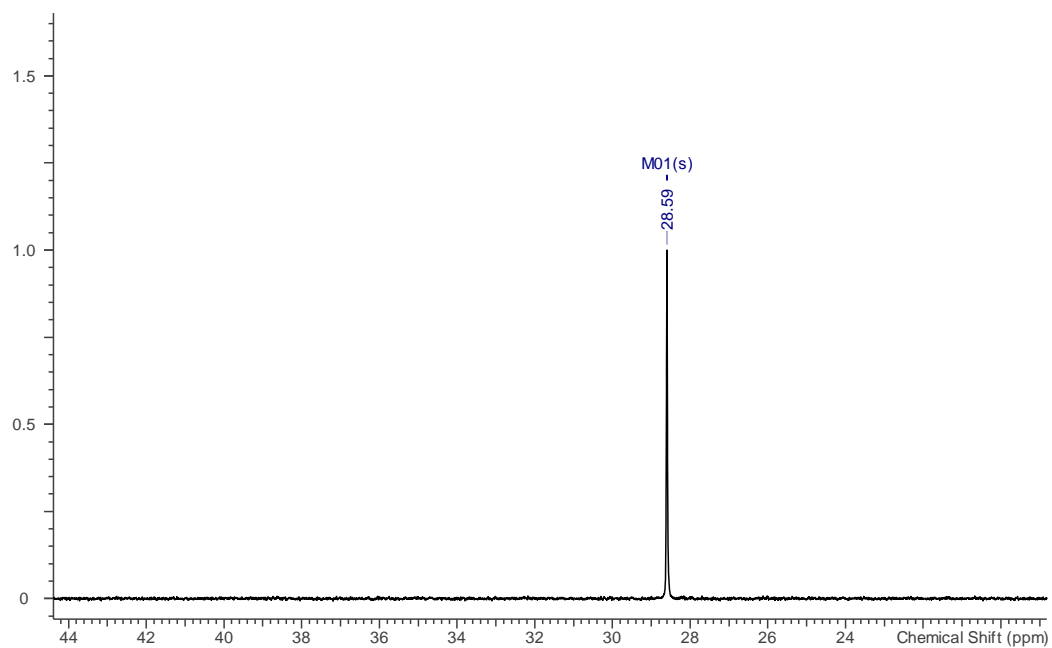
Figure S4. ^{31}P NMR of PMP in D_2O (298 K)
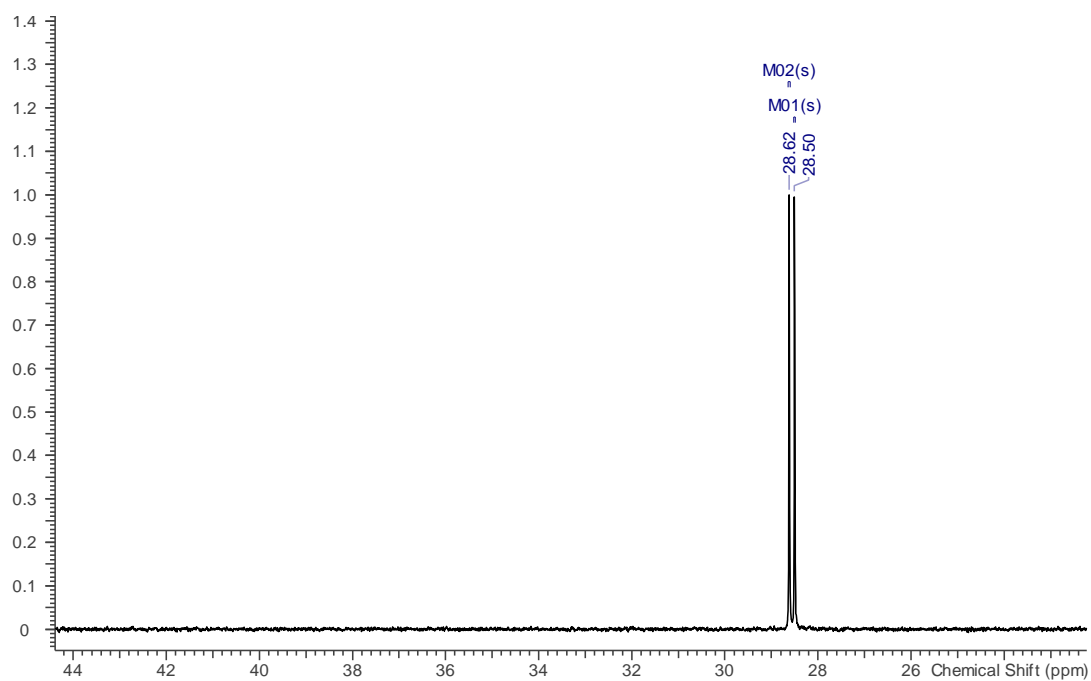
Figure S5. ^{31}P NMR spectrum of equimolar PMP and β-cyclodextrin in D_2O (298 K).
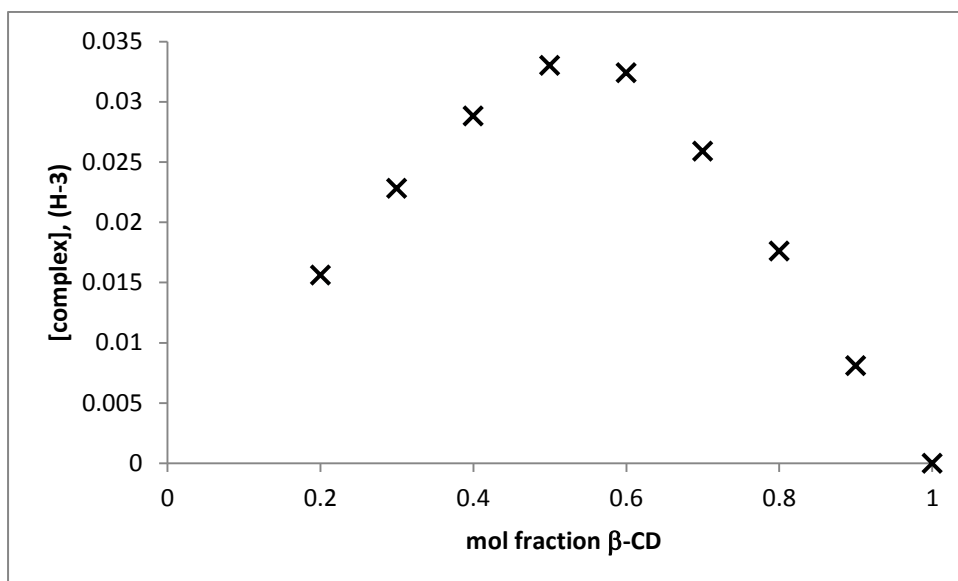
NMR Job plot and Titration Data

Figure S6. *Job plot analysis of β-CD H-3 environment with GD . [total] = 6.5 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
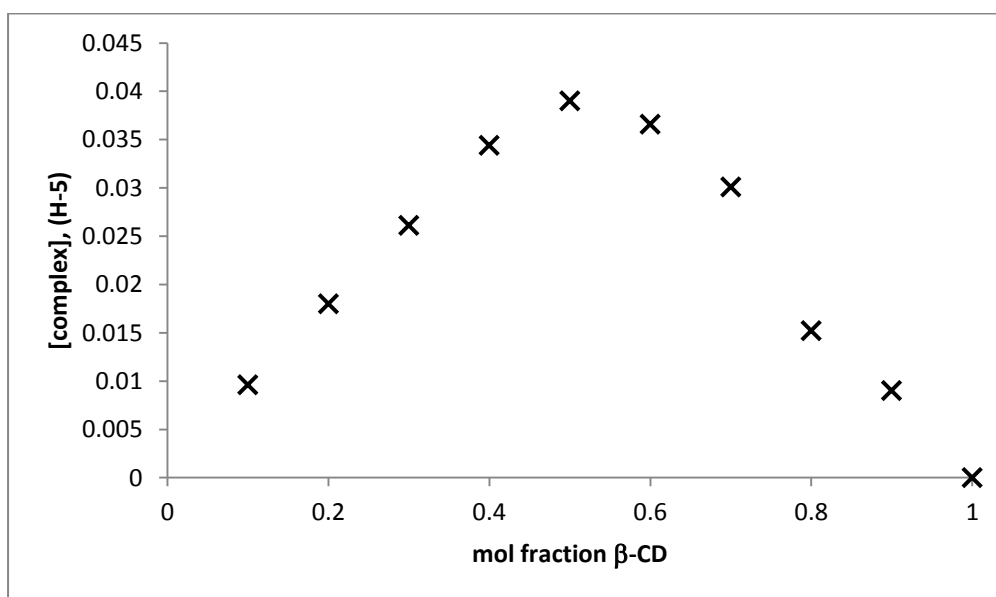
Figure S7. *Job plot analysis of β-CD H-5 environment with GD. [total] = 6.5 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
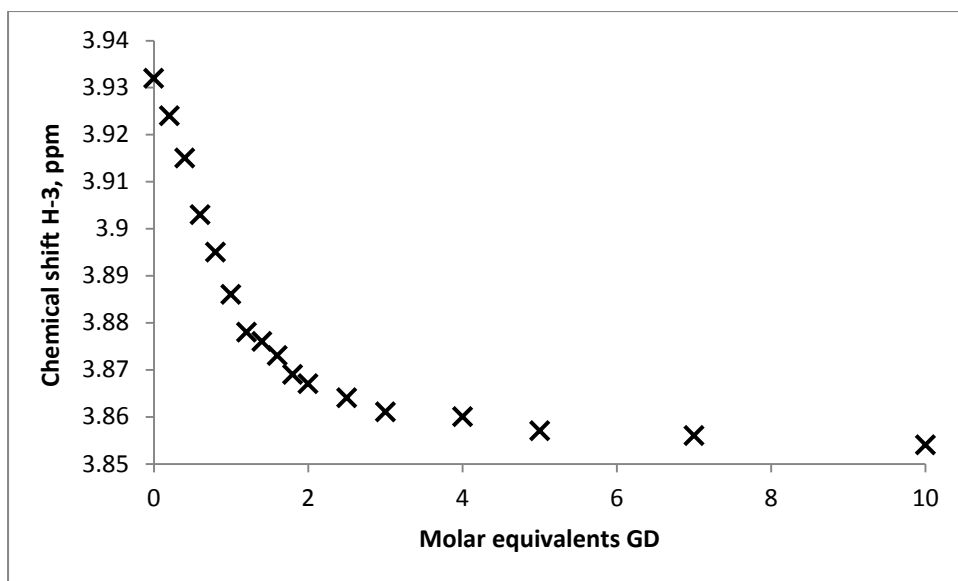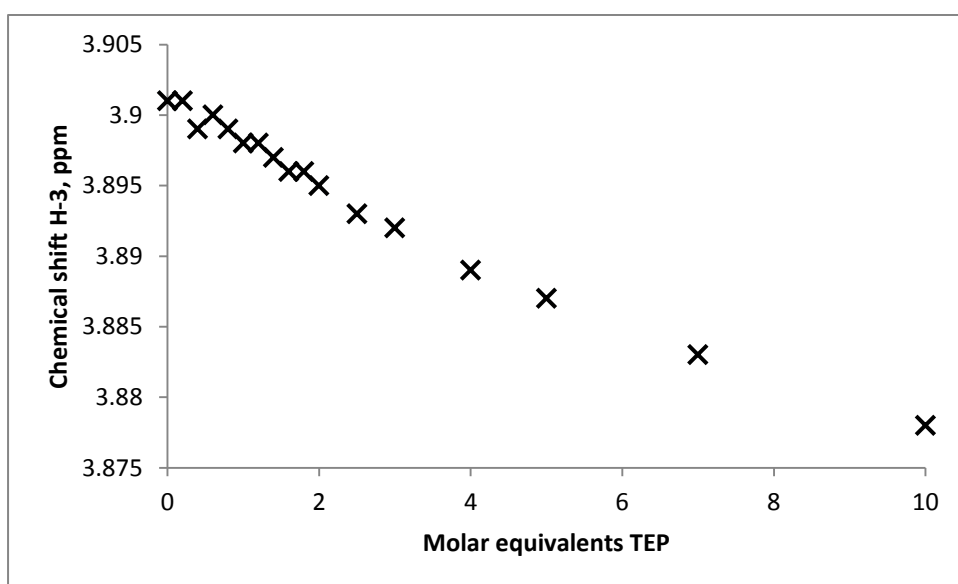
Figure S8. ^1H NMR titration of β-CD with GD monitoring the H-3 proton environment. [β-CD]$_{initial}$ = 1.1 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.
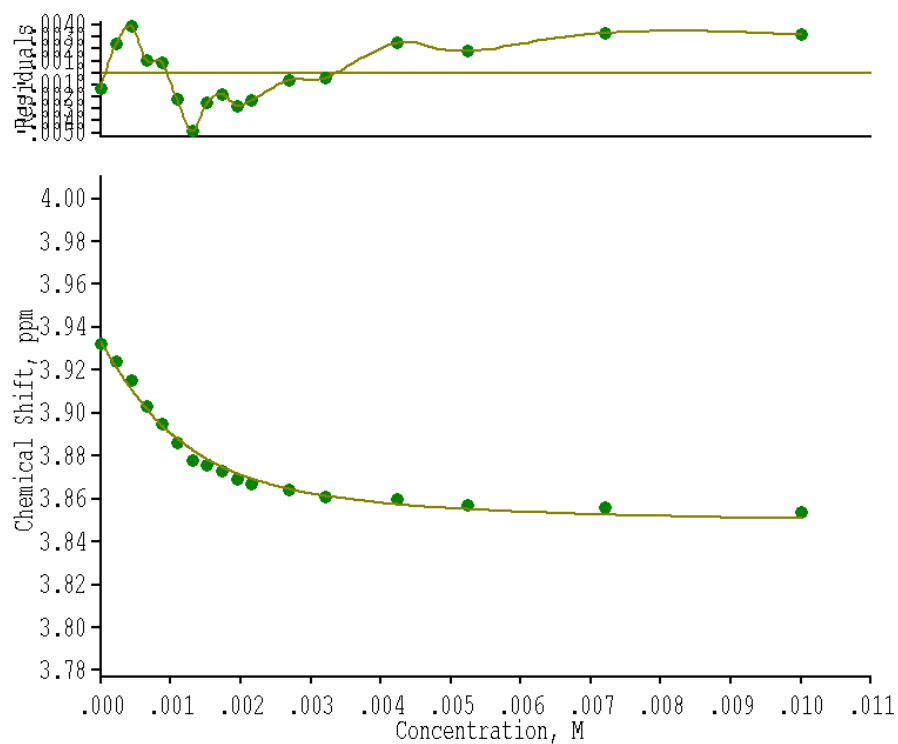
Figure S9. Data fitting of the ^1H NMR titration of β-CD with GD monitoring the H-3 proton environment. [β-CD]$_{initial}$ = 1.1 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.
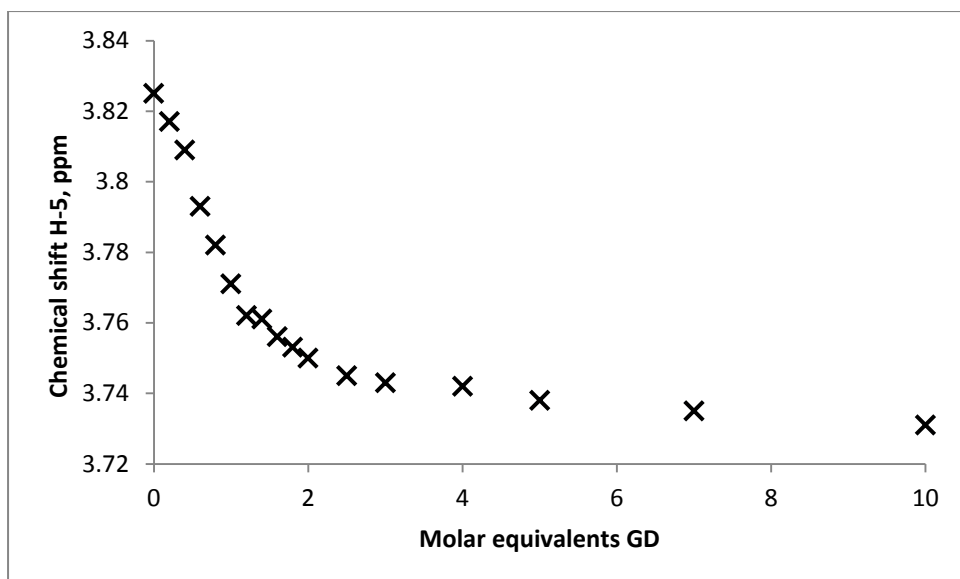
Figure S10. *^{1}H NMR titration of β-CD with GD monitoring the H-5 proton environment. [β-CD]$_{initial}$ = 1.1 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
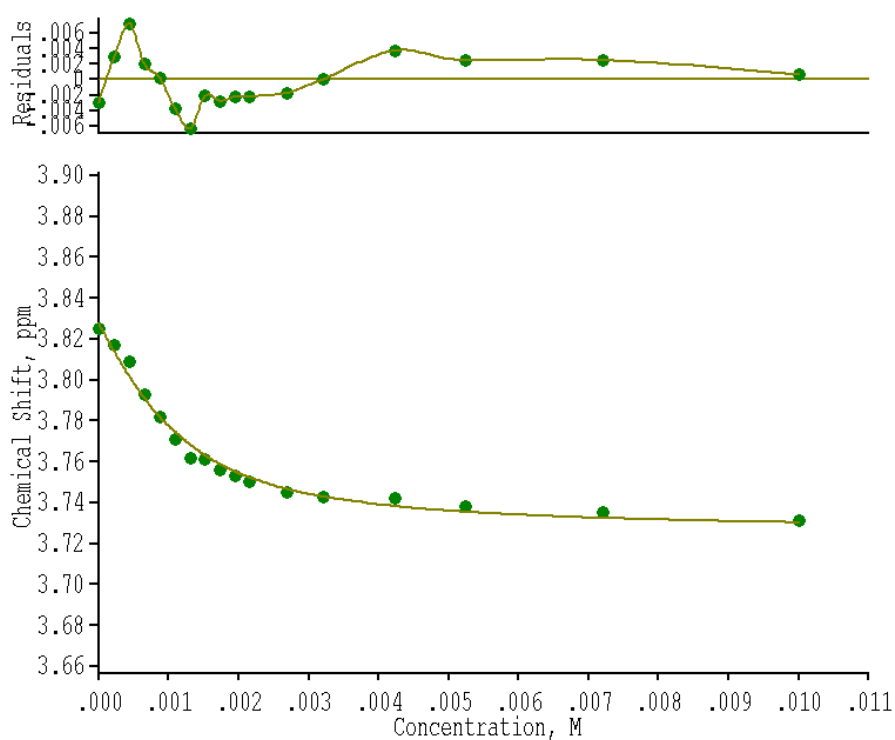
Figure S11. *Data fitting of the ^{1}H NMR titration of β-CD with GD monitoring the H-5 proton environment. [β-CD]$_{initial}$ = 1.1 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
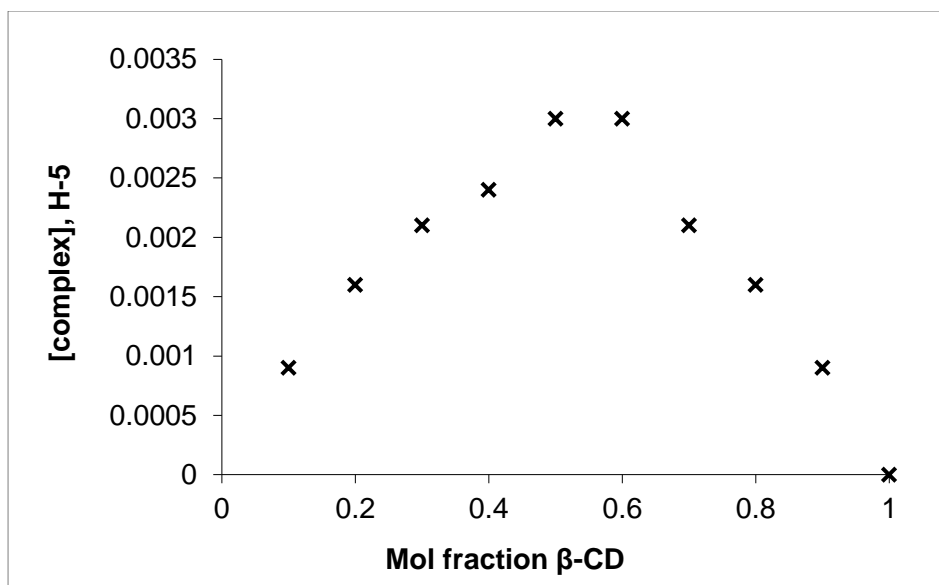
Figure S12. *Job plot analysis of β-CD H-5 environment with TEP . [total] = 7.9 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
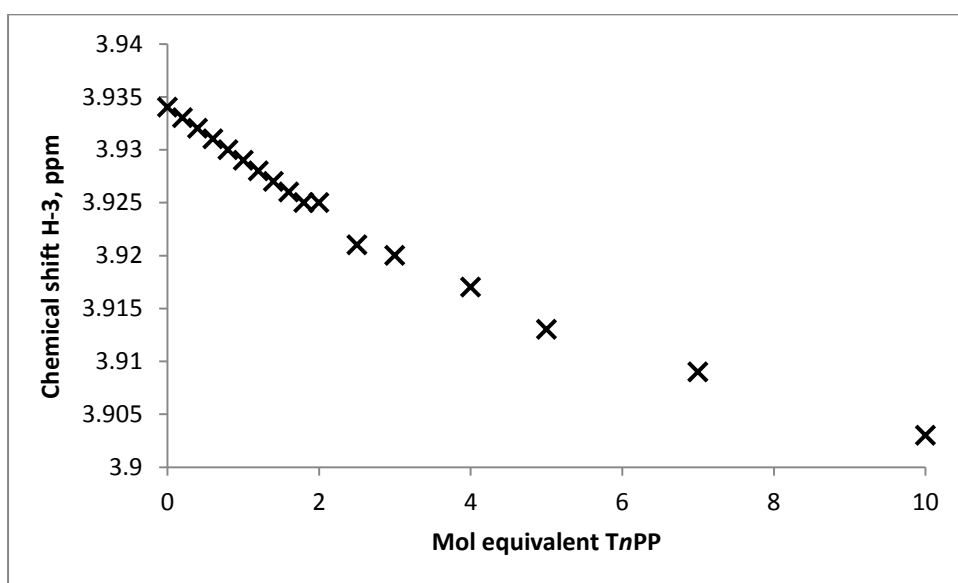

Figure S13. *^{1}H NMR titration of β-CD with TEP monitoring the H-3 (r.h.s. triplet) proton environment. [β-CD]$_{initial}$ = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
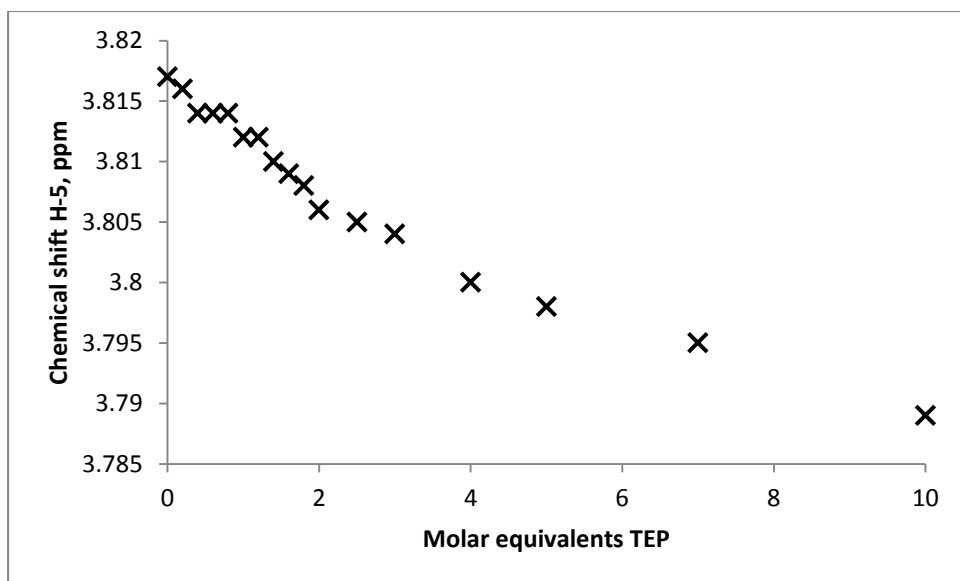
Figure S14. *¹H NMR titration of β-CD with TEP monitoring the H-5 proton environment. [β-CD]$_{initial}$ = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
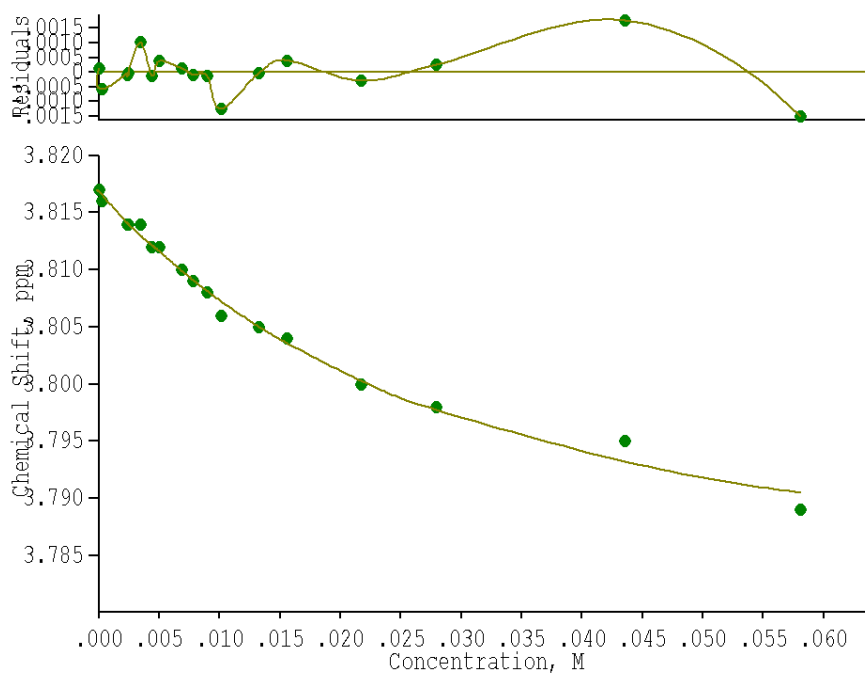
Figure S15. *Data fitting of the ¹H NMR titration of β-CD with TEP monitoring the H-5 proton environment. [β-CD]$_{initial}$ = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
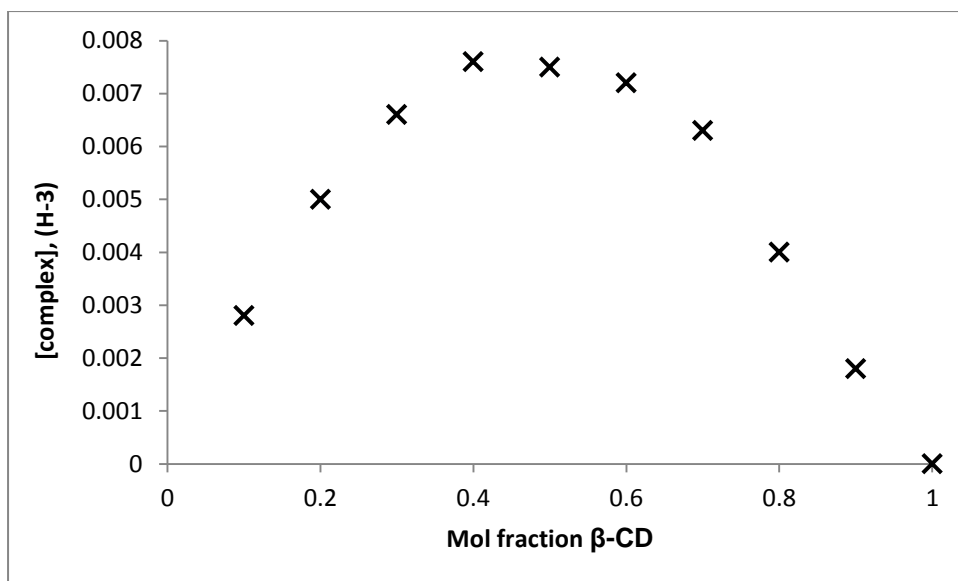
Figure S16. *Job plot analysis of β-CD H-3 environment with TnPP . [total] = 6.0 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*

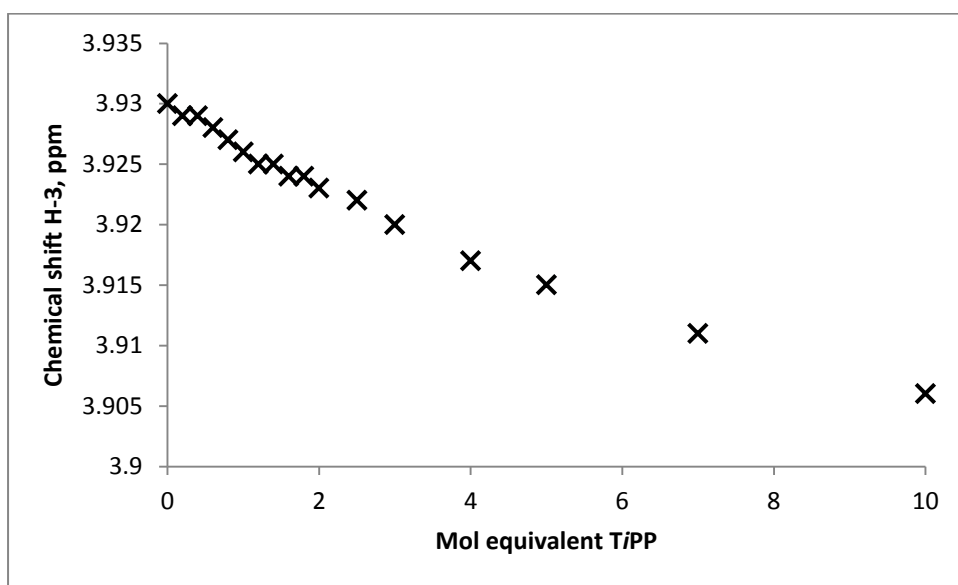**Figure S17.** *^{1}H NMR titration of β-CD with TnPP monitoring the H-3 proton environment. [β-CD]$_{initial}$ = 6.3 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
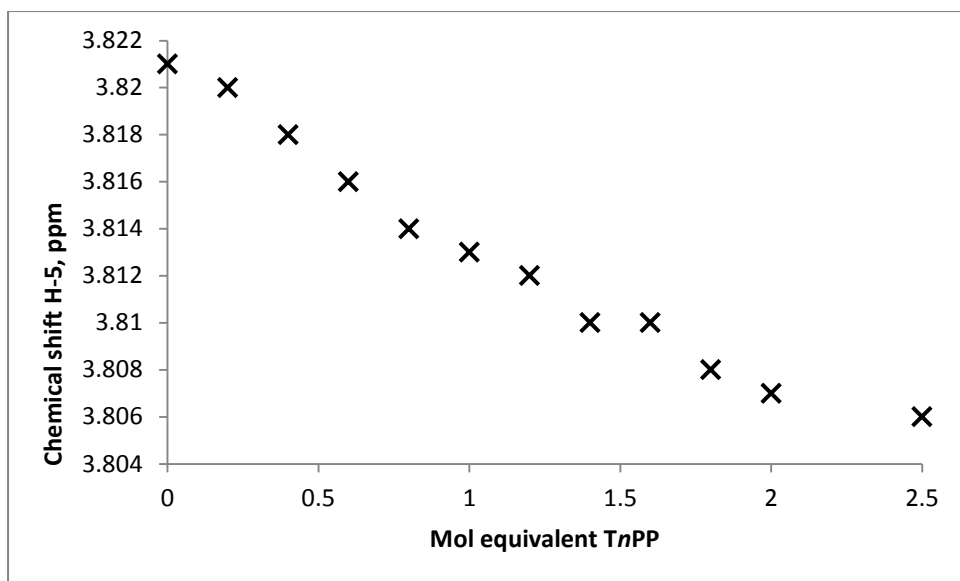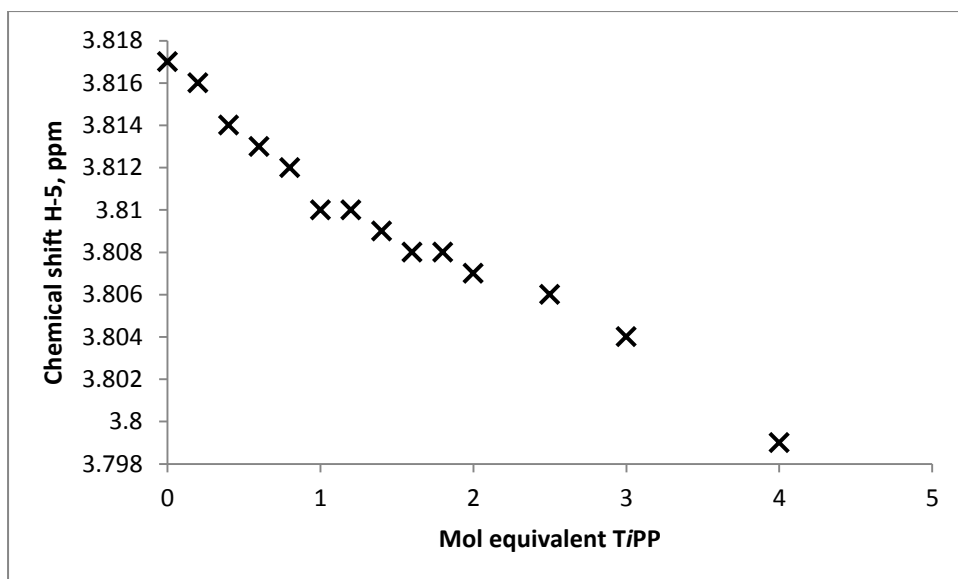
Figure S18. *Partial ^{1}H NMR titration of β-CD with TnPP monitoring the H-5 proton environment up to 2.5 molar equivalents of TnPP added (clarity/resolution of individual proton environment challenging beyond 2.5 equivalents). [β-CD]$_{initial}$ = 6.0 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
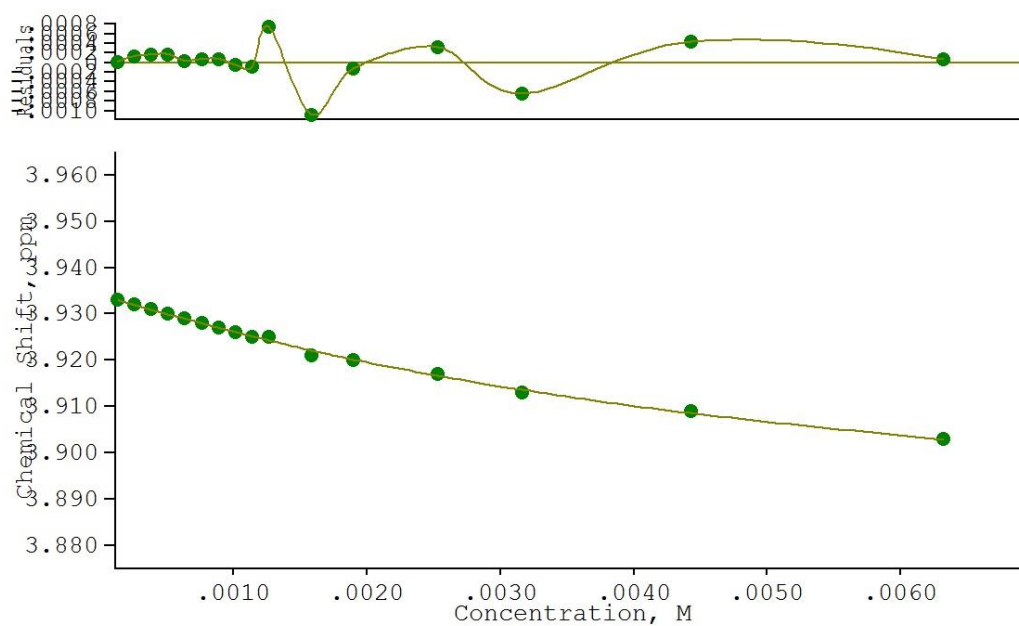
Figure S19. *^{1}H NMR titration of β-CD with TnPP monitoring the H-3 proton environment. [β-CD]$_{initial}$ = 6.0 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
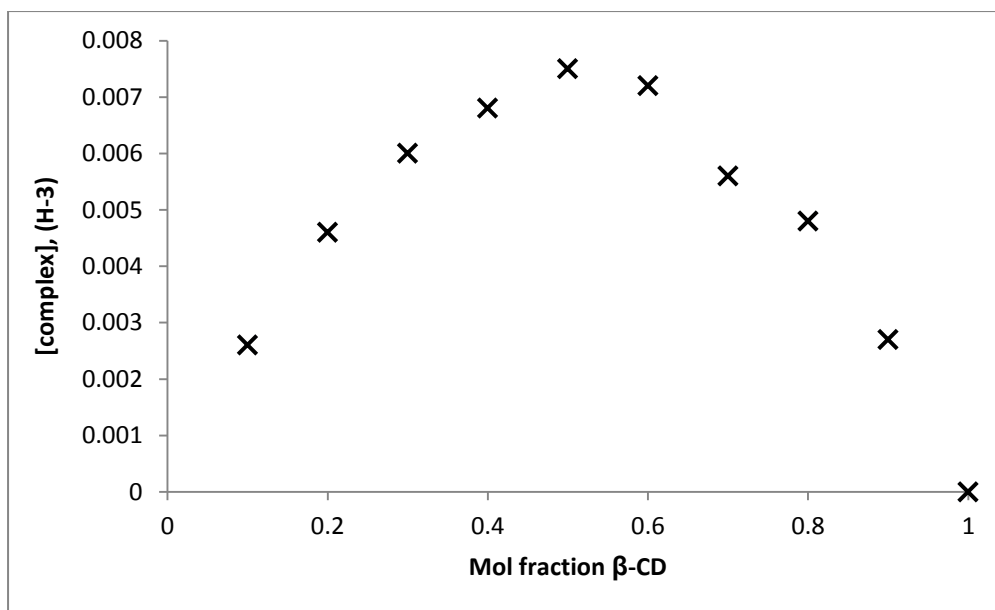
Figure S20. *Job plot analysis of β-CD H-3 environment with TiPP . [total] = 5.77 x 10⁻³ mol dm⁻³, 293 K, D₂O.*

Figure S21. *¹H NMR titration of β-CD with TiPP monitoring the H-3 proton environment. [β-CD]ᵢₙᵢₜᵢₐₗ = 6.1 x 10⁻³ mol dm⁻³, 293 K, D₂O.*

Figure S22. *Partial ^{1}H NMR titration of β-CD with TiPP monitoring the H-5 proton environment up to 4.0 molar equivalents of TiPP added (clarity/resolution of individual proton environment challenging beyond 4.0 equivalents). [β-CD]$_{initial}$ = 6.0 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
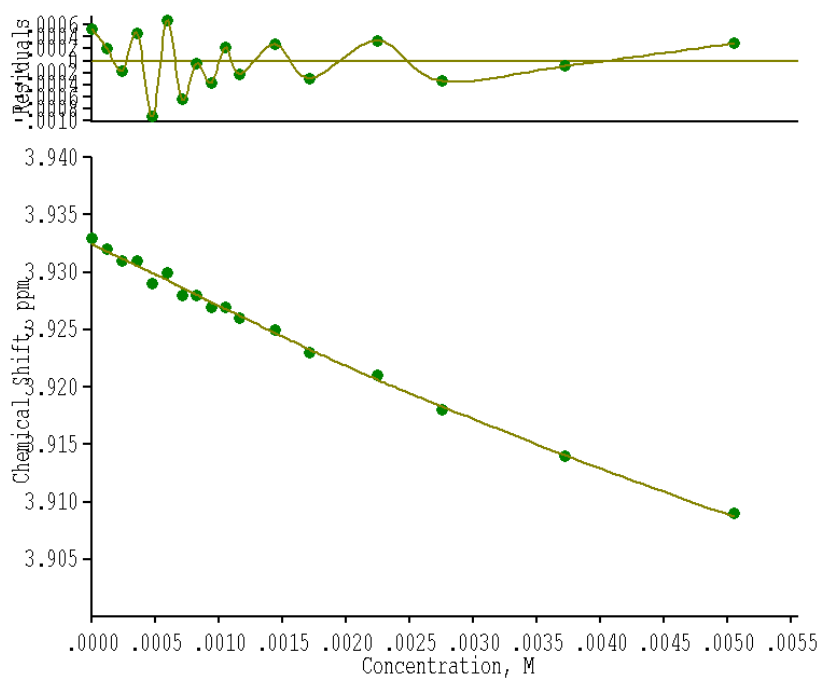
Figure S23. *^{1}H NMR titration of β-CD with TiPP monitoring the H-5 proton environment. [β-CD]$_{initial}$ = 6.0 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
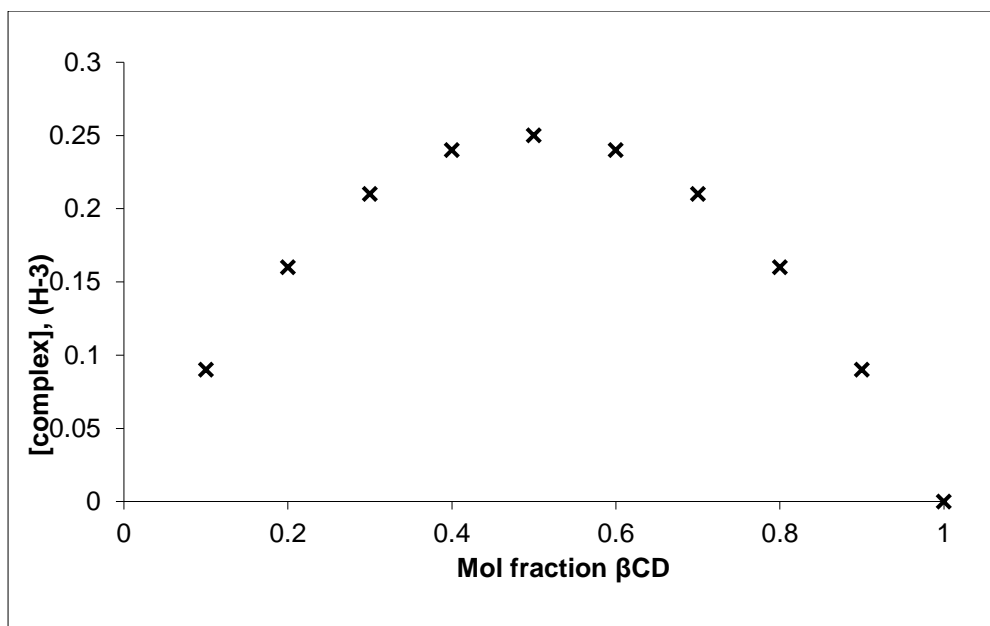
Figure S24. *Job plot analysis of β-CD H-3 environment with DEMP. [total] = 7.9 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
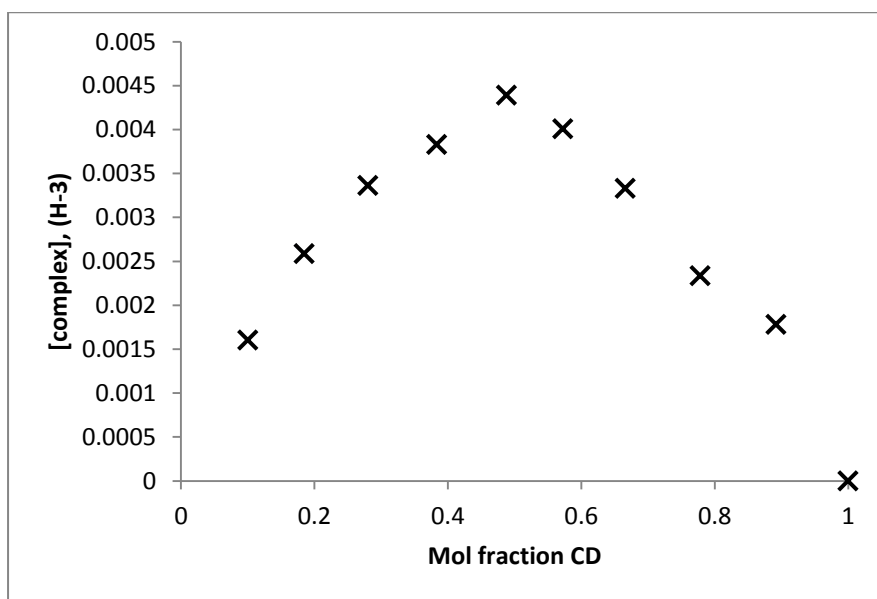

Figure S25. *Job plot analysis of β-CD H-3 environment with DIMP . [total] = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
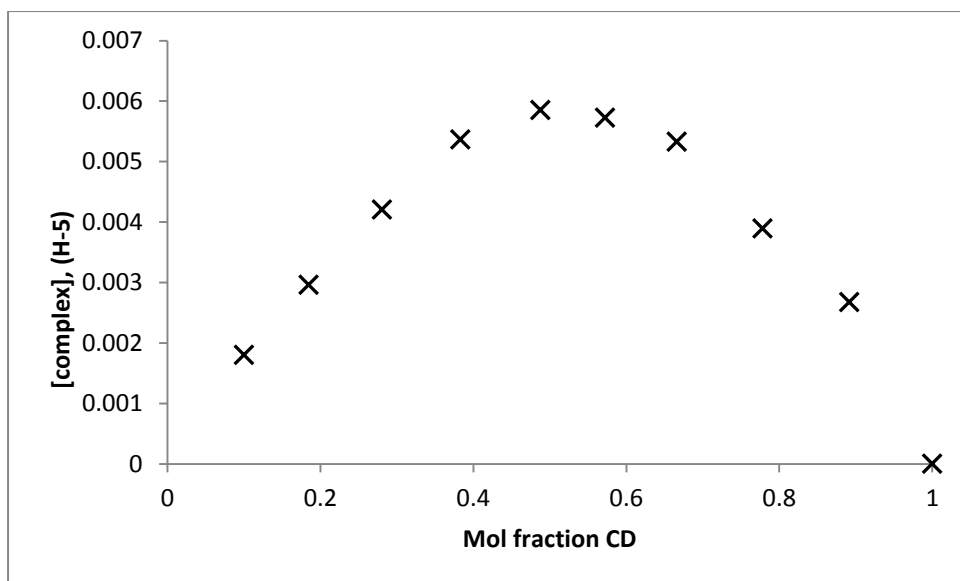
Figure S26. *Job plot analysis of β-CD H-5 environment with DIMP . [total] = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
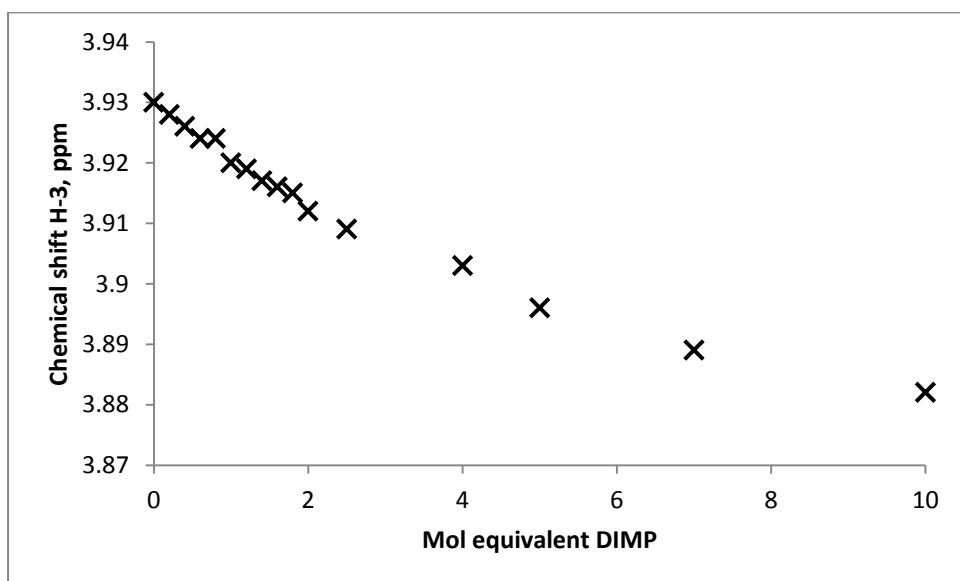

Figure S27. *^{1}H NMR titration of β-CD with DIMP monitoring the H-3 proton environment. [β-CD]$_{initial}$ = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
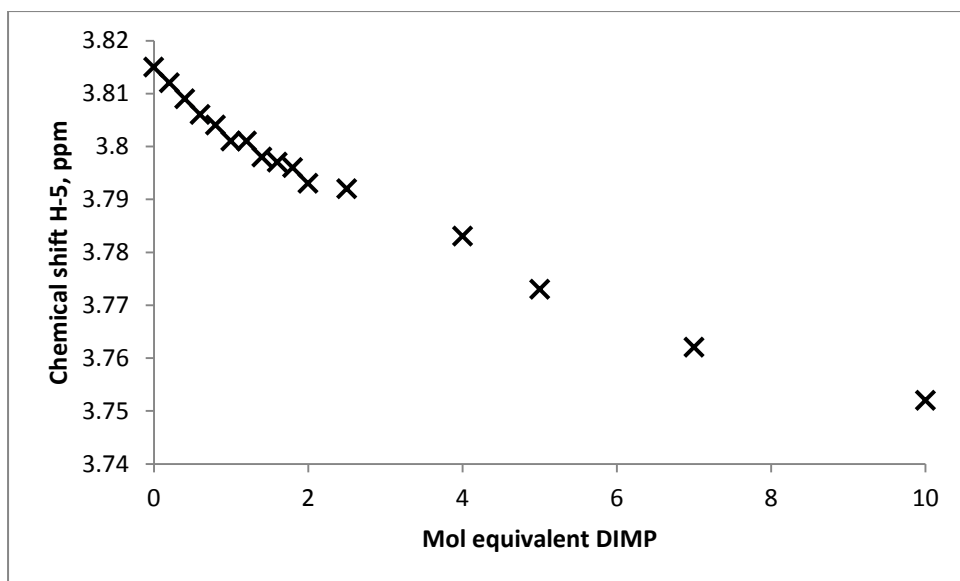
Figure S28. *^{1}H NMR titration of β-CD with DIMP monitoring the H-5 proton environment. [β-CD]$_{initial}$ = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
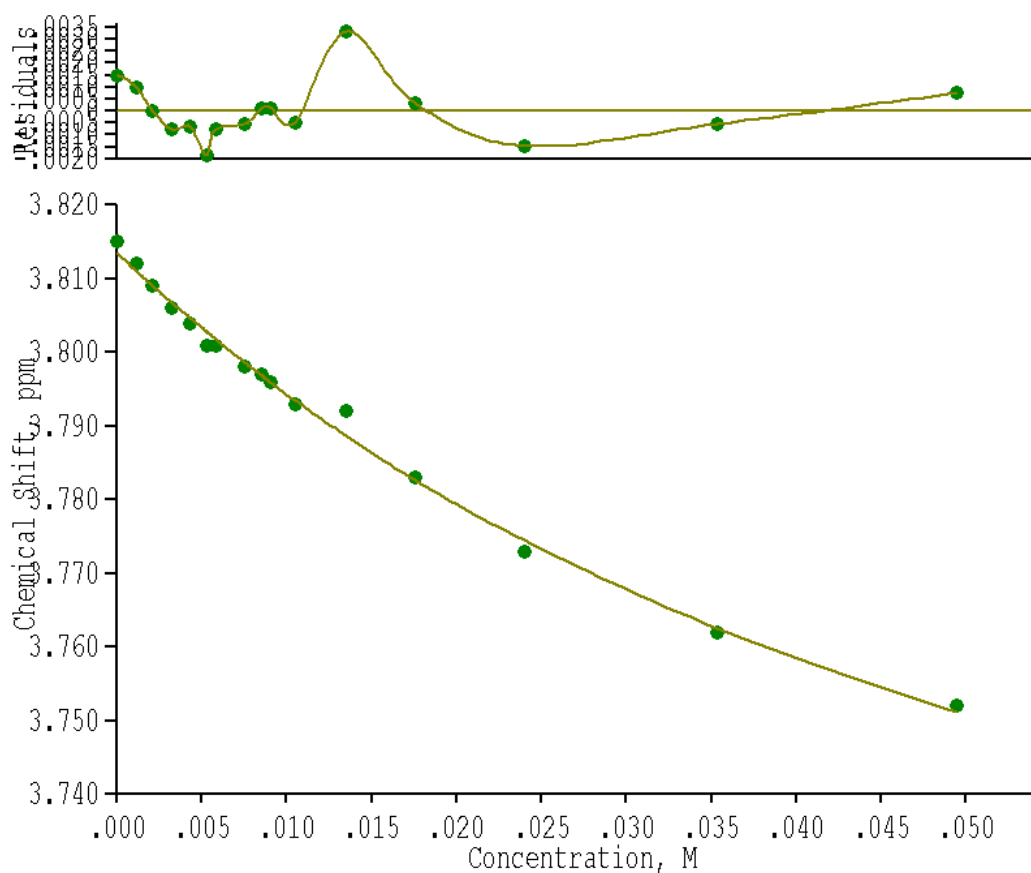
Figure 29. *Data fitting of the ^{1}H NMR titration of β-CD with DIMP monitoring the H-5 proton environment. [β-CD]$_{initial}$ = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
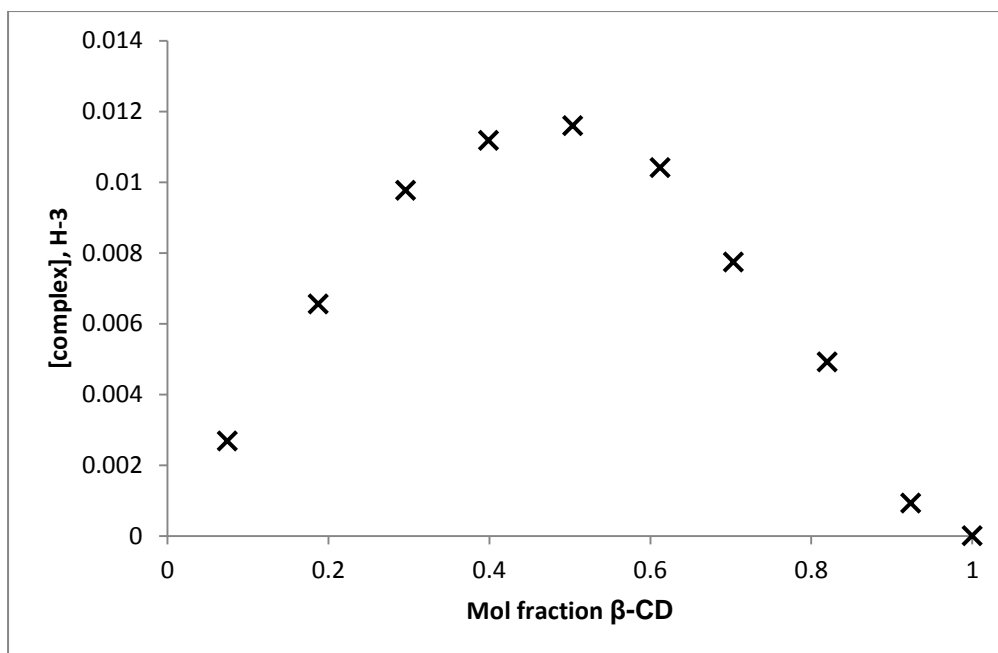
Figure S30. *Job plot analysis of β-CD H-3 environment with PMP . [total] = 7.9 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*
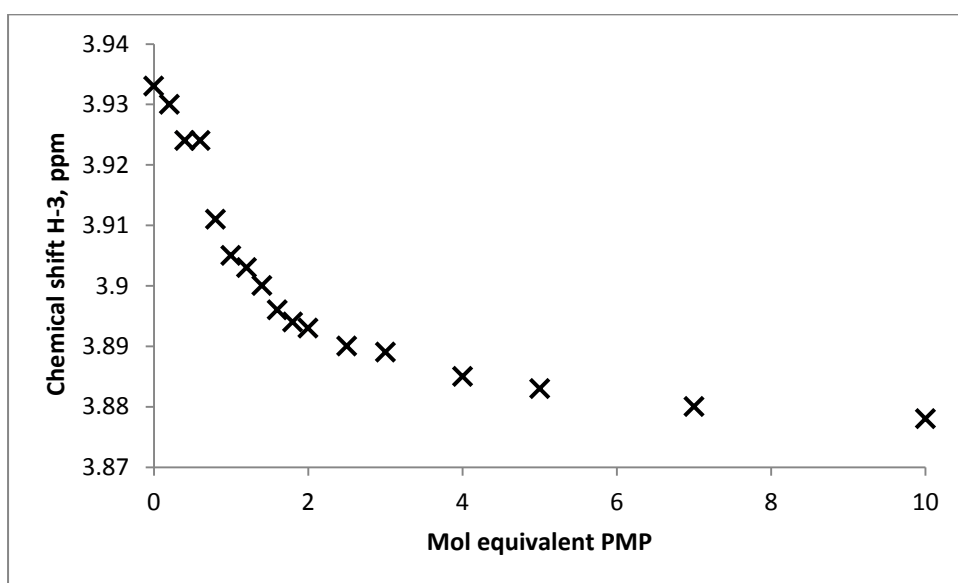

Figure S31. *^{1}H NMR titration of β-CD with PMP monitoring the H-3 proton environment. [β-CD]$_{initial}$ = 4.4 x 10^{-3} mol dm^{-3}, 293 K, D$_2$O.*

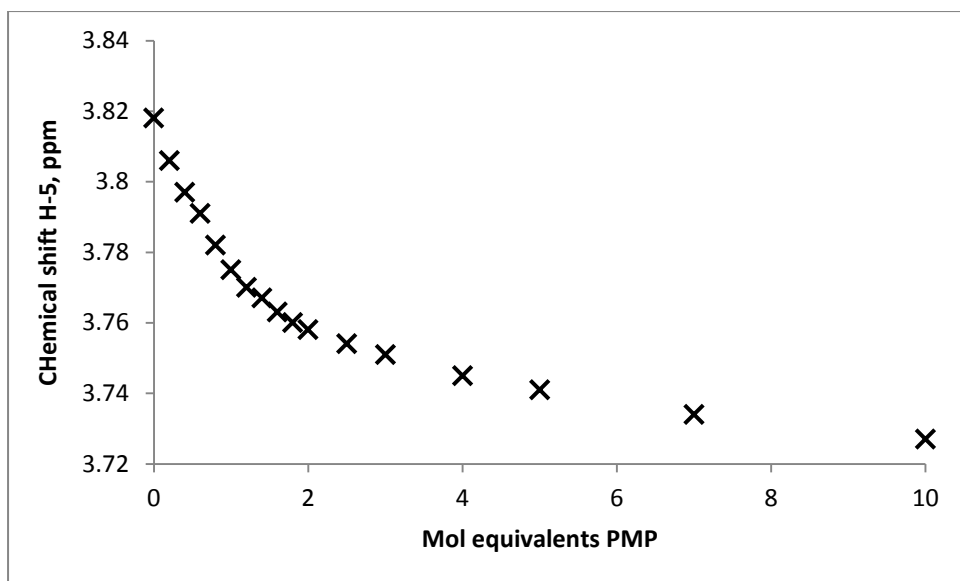**Figure S32.** ^1H NMR titration of β-CD with PMP monitoring the H-5 proton environment. $[β-CD]_{initial} = 4.4 \times 10^{-3}$ mol dm^{-3}, 293 K, D$_2$O.
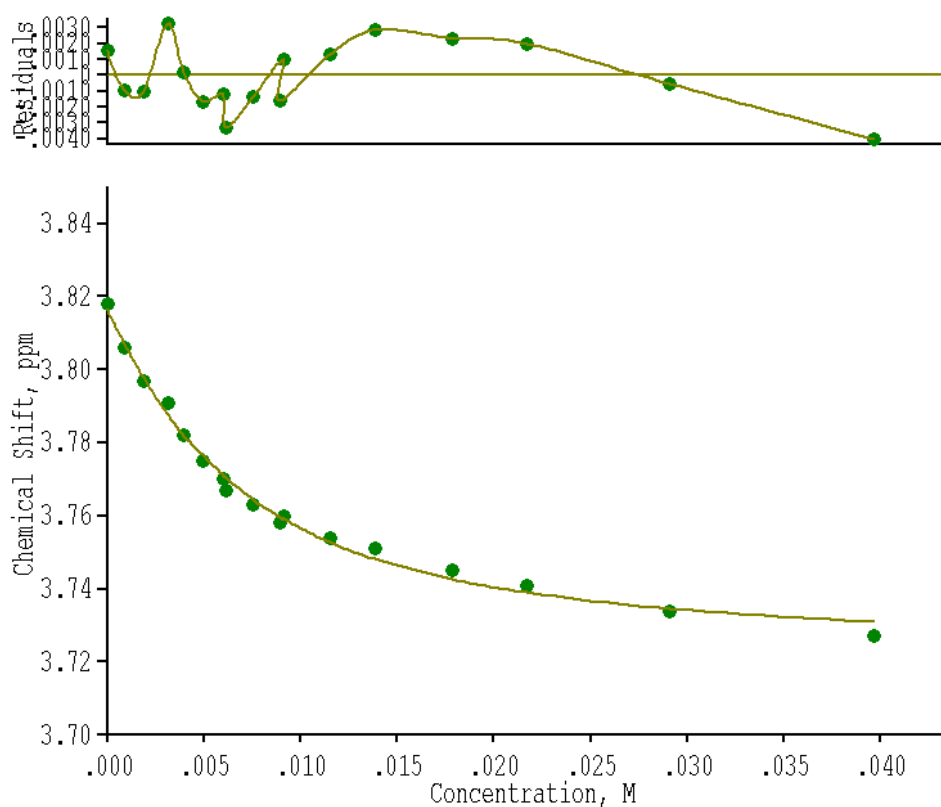

Figure S33. Data fitting of the ^1H NMR titration of β-CD with PMP monitoring the H-5 proton environment. $[β-CD]_{initial} = 4.4 \times 10^{-3}$ mol dm^{-3}, 293 K, D$_2$O.

References

1. M.J. Hynes, *J. Chem. Soc. Dalton Trans.,* 1993, 311.
2. H.J. Schneider, F. Hacket, V. Rüdiger, *Chem. Rev.* 1998, **98**, 1755-1785