Using iSUSTAIN™ to validate the chemical attributes of different approaches to the synthesis of tacn and bridged *bis*(tacn) ligands

C. J. Coghlan,[a,b] E. M. Campi,[a] W. R. Jackson[a] and M. T. W. Hearn[a]

Electronic Supplementary Material

Experimental

Materials and Methods

All chemicals were purchased from commercial suppliers and were used as received. Common laboratory reagents and compounds were purchased from Sigma Aldrich Corp. (Castle Hill, NSW, Australia) and Merck Millipore Limited (Kilsyth, Victoria, Australia). Flash chromatography was performed using Merck Silica Gel 60, 40-63 μm, code 9385.

The ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker DPX 300 or a Bruker DPX 400 spectrometer. The ^{1}H NMR spectra were recorded as solutions in deuterated, base-washed (Na_2CO_3) chloroform ($CDCl_3$) with TMS (tetramethylsilane) used as the internal standard reference (δ 0.00 ppm) with the $CDCl_3$ solvent peak (δ 77.26 ppm) used as the internal standard reference for ^{13}C NMR spectra. Spectra were also recorded as solutions in deuterated water (D_2O) where the residual internal solvent peak was used as the standard reference for ^{1}H NMR spectra.

Electrospray ionisation mass spectra (ESI) were recorded on a Micromass Platform II API QMS Electrospray mass spectrometer and all samples were run as methanol (MeOH) solutions unless otherwise indicated. The samples were run in positive (ESI^+) mode. Melting points were determined using a Buchi melting point B–545 melting point apparatus and are uncorrected. Microanalyses were performed by The Campbell Microanalytical Laboratory, in Dunedin, New Zealand

Synthetic Experimental Procedures

The details described below summarise the essential information that is required for input as data into iSUSTAIN in order to allow the analysis of the green chemical attributes.

1,4,7-Tris(*p*-toluenesulfonyl)-1,4,7-triazacyclononane (Tos_3tacn) (4)

A 3 L Erlenmeyer flask was charged with H_2O (500 mL), anhydrous K_2CO_3 (162 g, 1.18 mol) and diethylenetriamine (36.4 g, 0.35 mol) and the solution heated to 90°C while being vigorously stirred using an overhead mechanical stirrer. Tosyl chloride (209.2 g, 1.09 mol) was added in small portions (approximately 20 g, every 10 min). After complete addition, the suspension was stirred for an additional 3 h at 90°C. Solid NaOH (127.2 g, 3.2 mol) was slowly added followed by a solution of tetrabutylammonium bromide (10.4 g, 32.26 mmol) in H_2O (40 mL) and then toluene (1.6 L). The temperature was maintained at 90°C and a total of 120 mL of 1,2-dibromoethane was added in 20 mL aliquots by pipette over 8 h. After the final addition, the reaction mixture was stirred at 90°C for a further 8 h, and subsequently cooled to room temperature with stirring overnight. The resulting white precipitate was collected by filtration using a large Buchner funnel, washed with copious amounts of H_2O (1–3 L), and dried overnight at 50°C in a vacuum oven to give tos_3tacn (**4**) as a white precipitate. Yield 138.8 g (66%). mp. 222.3–223.8°C (Lit.[1] mp. 222–223°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.45 (9H, s, CH_3), 3.44 (12H, s, ring CH_2), 7.37 (6H, m, ArH), 7.74 (6H, m, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 22.1 (CH_3), 54.1 (tacn CH_2), 128.2 (ArCH), 131.3 (ArCH), 134.9 (ArCH), 144.9 (ArCH). The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[2,3]

1,4,7-Triazacyclononane trihydrochloride (tacn.3HCl) (5)

A round bottom flask (1 L) was charged with 18M H_2SO_4 (450 mL) and 1,4,7-tris(*p*-toluenesulfonyl)-1,4,7-triazacyclononane (**4**) (138.8 g, 0.234 mol) added in small portions (approximately 10 g every 5 min). The mixture was heated with stirring in a heat block for 3 days at 120°C. The resulting black solution was cooled to room temperature and added dropwise using a dropping funnel to a vigorously stirred mixture of cold absolute EtOH/Et_2O (1.5 L/900 mL) cooled in an ice bath. An overhead stirrer was used to ensure efficient stirring. A sticky hygroscopic brown/grey precipitate formed, which was isolated quickly by vacuum filtration and immediately dissolved in de–ionised H_2O (1 L). The mixture was heated for 2 h at 60°C. The mixture was then cooled to room temperature, filtered through Celite and the resulting solution concentrated to 250 mL under reduced pressure at 65°C. Conc. HCl (200 mL) was added followed by absolute EtOH until the solution became cloudy. The mixture was stored at 4°C overnight to promote precipitation. The white precipitate was collected by filtration and washed with ice cold absolute EtOH (3 x 50 mL), followed by Et_2O (2 x 50 mL) to yield tacn.3HCl (**5**) as a white crystalline powder. Yield 44.9 g (80%). mp. 268.1–270.0°C (Lit.[4] mp. 280–281°C). ^{1}H NMR (300 MHz, D_2O) δ_H 3.48 (12H, s, CH_2). ^{13}C NMR (75 MHz, D_2O) δ_C 43.1 (CH_2). ESI–MS *m*/*z* $[M + H]^+$ 130.1. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[3,4]

1,4,7-Triazacyclononane trihydrochloride (**5**) was also prepared from tos_2tacn (**9**). A round bottom flask (50 mL) was charged with 18M H_2SO_4 (25 mL) and 1,4-di(tosyl)-1,4,7-triazacyclononane (**9**) (3.10 g, 6.9 mmol) was added slowly. The method described above for the detosylation of tos_3tacn (**4**) was then followed. The white precipitate was filtered, washed with ice cold absolute EtOH (3 x 20 mL), followed by Et_2O (2 x 20 mL) to give tacn.3HCl **(5)** as a white crystalline solid. Yield 2.13 g (84%). The ^{1}H and ^{13}C NMR spectral data and mp. value were consistent with the data given above.

1,4,7-Triazacyclononane, [9]aneN3 (tacn) (1).

1,4,7-Triazacyclononane trihydrochloride (**5**) (44.49 g, 186.9 mmol) was dissolved in H_2O (500 mL) and solid NaOH (35.5 g, 890 mmol) was added (with the solution maintained at pH 12). Following dissolution, the solvent was completely removed under reduced

pressure. Toluene (500 mL) was added and an azeotropic distillation was performed using a Dean-Stark apparatus to remove any residual H_2O. The toluene/tacn/NaCl mixture was filtered and the filter residue extracted again with fresh toluene (500 mL) and the procedure repeated. The combined toluene mixture was refluxed for approximately 3 h with vigorous stirring between additions of fresh toluene. The combined filtrates were concentrated using a rotary evaporator to remove the toluene, yielding the free base, tacn (**1**), as a white solid. Yield 17.49 g (72%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.16 (3H, s, NH), 2.76 (12H, s, CH_2). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 47.7 (CH_2). ESI–MS *m/z* $[M + H]^+$ 130.1. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[5-7]

1,4,7-Triazatricyclo[5.2.1.0]decane (tacn orthoamide) (10).
1,4,7-Triazatricyclo[5.2.1.0]decane (**10**) was prepared following modification of literature methods.[8,9] 1,4,7-Triazacyclononane (**1**) (17.49 g, 135.0 mmol) was dissolved in toluene (250 mL). Dimethylformamide dimethyl acetal (DMF-DMA) (16.08 g, 163.0 mmol) was added and the solution refluxed overnight under Dean-Stark conditions. Toluene was removed *in vacuo* to produce a clear yellow oil. The oil was distilled using Kugelrohr distillation (bp. (oven) 80°C/0.5 mm) (Lit.[10] bp. 160°C) to give the orthoamide **10** as a colourless oil. Yield 15.02 g (64%). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.89 (6H, m, CH_2), 3.13 (6H, m, CH_2), 5.36 (1H, s, CH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 52.8 (CH_2), 105.5 (CH). ESI–MS *m/z* $[M + H]^+$ 140.2. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[9]

Di-*tert*-butyl 1,4,7-triazonane-1,4-dicarboxylate (Boc_2tacn) (12).
Triethylamine (81.3 mL, 58.3 mmol) was added to a solution of tacn **(1)** (25.4 g, 196.6 mmol) in $CHCl_3$ (500 mL). A solution of Boc-ON (96.48 g, 392 mmol) in $CHCl_3$ (500 mL) was added with stirring over 1 h at room temperature. Stirring was maintained overnight and the mixture concentrated under reduced pressure. The resulting residue was dissolved in EtOAc (750 mL) and washed successively with 4% aq. $NaHCO_3$ (750 mL), and saturated aq. NaCl (750 mL), and then extracted with 10% aq. citric acid (3 x 750 mL). The citric acid extract was rendered alkaline (pH 10) by the addition of 10 M aq. NaOH and extracted with $CHCl_3$ (3 x 500 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield the title compound **12** as an amber gum. Yield 35.5 g (54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.43 (18H, s, $C(CH_3)_3$), 2.88 (4H, m, tacn CH_2), 3.20 (4H, m, tacn CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.5 (CH_3), 47.3, 47.7, 48.1, 48.2, 49.6, 49.8, 50.4, 51.6, 52.4, 52.5 and 53.0 (ring CH_2), 79.7 ($C(CH_3)_3$), 79.8 ($C(CH_3)_3$), 156.0 (C=O). ESI–MS *m/z* $[M + H]^+$ 330.2. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[2] The EtOAc layer was concentrated to give pure Boc_3tacn[11] (14.4 g, 18%) as a side product.

3,6-Di(tosyl)-3,6-diazaoctane-1,8-di(toluene-*p*-sulfonate) (7)
3,6-Di(tosyl)-3,6-diazaoctane-1,8-di(toluene-*p*-sulfonate) **(7)** was prepared following modification of a literature method.[12] A solution of tosyl chloride (100.01 g, 524 mmol) in anhydrous 98 % pyridine (140 mL) was added over 2 h with vigorous stirring to a solution of N,N'-bis(2-hydroxyethyl)ethylenediamine **(6)** (19.45 g, 131 mmol) in pyridine (140 mL) cooled to 0°C under N_2. The solution was stirred for 4 h and the temperature allowed to increase to 25°C. The solution was then added to a mixture of conc. HCl (200 mL) in ice (200 mL) with vigorous stirring. The suspension was filtered and the precipitate washed with H_2O and MeOH. The solid was dissolved in CH_2Cl_2 (100 mL) and the solution washed with H_2O (3 x 100 mL). The organic layer was dried using Na_2SO_4 and then concentrated to give a brown oil. MeOH (350 mL) was added and a yellow precipitate formed. The precipitate was collected by filtration and recrystallised from hot CH_3CN to yield the product **7** as a pale yellow solid. Yield 76.1 g, (75%). mp. 146.4–148.4°C (Lit.[13] mp. 147–149°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.44 (12H, s, CH_3), 3.30 (4H, s, CH_2), 3.36 (4H, t, J = 5.4, CH_2), 4.14 (4H, t, J = 5.4 Hz, CH_2), 7.35 (8H, d, J = 8.3 Hz, ArH), 7.72 (4H, d, J = 8.3 Hz, ArH), 7.78 (4H, dd, J = 8.3 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.7 (CH_3), 49.6 (CH_2), 50.0 (CH_2), 69.1 (CH_2), 127.6 (ArCH), 128.2 (ArCH), 130.2 (ArCH), 132.7 (ArC), 135.3 (ArC), 144.2 (ArC), 145.3 (ArC). ESI–MS *m/z* $[M + Na]^+$ 786.9. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[13]

1-Benzyl-4,7-di(*p*-toluenesulfonyl)-1,4,7-triazacyclononane (8)
1-Benzyl-4,7-di(tosyl)-1,4,7-triazacyclononane (**8**) was prepared following modification of a literature method[13]. A mixture of 3,6-di(tosyl)-3,6-diazaoctane-1,8–di(toluene-*p*-sulfonate) (**7**) (50.03 g, 65 mmol), benzylamine (7.6 mL, 72 mmol) and K_2CO_3 (19.91 g, 0.143 mol) in CH_3CN (600 mL) was stirred for 2 h under N_2. The reaction mixture was then heated at reflux for 6 days. The mixture was allowed to cool to room temperature and the inorganic salts removed by filtration. The solvent was removed and the resulting oil was dissolved in hot EtOH and the solution allowed to cool to room temperature. The resulting white crystalline needles of **8** were collected by filtration. Yield 22.00 g (62%). mp. 149.1–151.3°C (Lit.[13] mp. 149–151°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.45 (6H, s, CH_3), 2.98 (4H, m, CH_2), 3.15 (4H, m, CH_2), 3.49 (4H, s, CH_2), 3.77 (2H, s, CH_2), 7.29 (2H, m, ArH), 7.30 (3H, m, ArH), 7.37 (4H, m, ArH), 7.65 (4H, d, J = 8.3 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.7 (CH_3), 51.7 (CH_2), 52.6 (CH_2), 54.9 (CH_2), 61.4 (NCH_2Ph), 127.4 (ArCH), 128.5 (ArCH), 129.3 (ArCH), 129.9 (ArCH), 135.7 (ArC), 139.6 (ArC), 143.6 (ArC). ESI–MS *m/z* $[M + H]^+$ 528.1. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[13]

1,4-Di(*p*-toluenesulfonyl)-1,4,7-triazacyclononane (9)
Pd/C (800 mg, 0.74 mmol) was added to a solution of 1-benzyl-4,7-di(*p*-toluenesulfonyl)-1,4,7–triazacyclononane (**8**) (2.0 g, 3.8 mmol) in glacial acetic acid (50 mL) in a 100 mL Fisher-Porter vessel and the mixture placed in a hydrogen atmosphere (20 psi). The mixture was stirred at room temperature overnight. The reaction mixture was filtered through a Celite pad which was then washed with MeOH (50 mL) and EtOAc (50 mL). The filtrate was concentrated under reduced pressure and the yellow solid so obtained was dissolved in $CHCl_3$ (50 mL) and stirred vigorously with a 10% solution of NaOH (50 mL). After 1 h the two layers were separated and the aqueous layer extracted with $CHCl_3$ (3 x 50 mL). The combined organic layers were dried over anhydr. $MgSO_4$ and concentrated under reduced pressure to give **9** as a white solid. Yield 1.5 g (92%). mp. 224.5–226.1°C (Lit.[14] mp. 217–218°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.43 (6H, s, CH_3), 3.20, (8H, s, CH_2), 3.45 (4H, s, CH_2), 7.32

(4H, d, J = 7.7 Hz, ArH), 7.68 (4H, d, J = 7.8 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.5 (CH_3), 48.9 (CH_2), 53.1 (CH_2), 53.9 (CH_2), 127.2 (ArCH), 129.8 (ArCH), 135.1 (ArC), 143.7 (ArC). ESI–MS m/z $[M + H]^+$ 438.1. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[14]

The bis(tacn) compounds were then prepared from the tacn orthoamide according to modifications to a literature method (Reactions 9 and 10).[15]

Method 1: Basic hydrolytic workup:

2,6-Bis(1,4,7-triazacyclonon-1-ylmethyl)benzene (L^{mx}) (2a)

A solution of α,α′-dibromo-*m*-xylene (2.84 g, 10 mmol) in CH_3CN (40 mL) was added dropwise to a solution of 1,4,7–triazacyclo[5.2.1.0]decane **(10)** (3.0 g, 22 mmol) in CH_3CN (70 mL) with stirring under N_2 at ambient temperature for 48 h. The white bis(tacn) amidinium salt precipitate was collected by filtration, washed with Et_2O (3 x 50 mL) and dried under reduced pressure. The white solid was dissolved in H_2O (100 mL) and the solution heated under reflux for 4 h. NaOH pellets (0.12 mol) were carefully added to the solution and the mixture heated under reflux for a further 3 h. The solution was cooled and extracted with $CHCl_3$ (3 x 50 mL) and the extract dried over anhydr. $MgSO_4$. The solvent was removed under reduced pressure to yield 2,6-bis(1,4,7-triazacyclonon-1-ylmethyl)benzene **(2a)** (as the free base) as a clear oil. Yield 3.13 g (80 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 2.07 (4H, s, NH), 2.53 (16H, m, tacn CH_2), 2.67 (8H, s, tacn CH_2), 3.61 (4H, s, CH_2Ar), 7.11 (3H, m, ArH), 7.24 (1H, s, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 46.6 (tacn CH_2), 46.9 (tacn CH_2), 52.9 (tacn CH_2), 61.6 (ArCH_2), 127.9 (ArCH), 128.4 (ArCH), 129.9 (ArCH) 140.0 (ArC). ESI–MS m/z $[M + H]^+$ 361.3. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[16,17]

Preparation of bis(tacn).6HCl salts from bis(tacn) free base.

1,3-Bis(1,4,7-triazacyclonon-1-ylmethyl)benzene.6HCl (2a) (L^{mx}.6HCl)

The free base of 1,3-Bis(1,4,7-triazacyclonon-1-ylmethyl)benzene **(2a)** (4.98 g, 14 mmol) was dissolved in distilled H_2O (50 mL) with stirring. Conc. HCl (50 mL) was added and the solution stirred for an additional 1 h. The solvent was concentrated to allow the compound to crystallise to give 1,3-bis(1,4,7-triazacyclonon-1-ylmethyl)benzene.6HCl.4H_2O **(2a)** as a white powder. Yield 4.09 g (82 %). ^{1}H NMR (300 MHz, D_2O) δ_H 3.09 (8H, m, tacn CH_2), 3.30 (8H, m, tacn CH_2), 3.68 (8H, s, tacn CH_2), 3.99 (4H, s, CH_2Ar), 7.51 (4H, m, ArH). ^{13}C NMR (300 MHz, D_2O) δ_C 42.4 (tacn CH_2), 43.8 (tacn CH_2), 47.7 (tacn CH_2), 58.9 (ArCH_2), 129.5 (ArCH), 130.3 (ArCH), 132.2 (ArCH), 135.9 (ArC). Found: C, 36.6; H, 7.6; N, 12.5. Calc. for $C_{20}H_{50}Cl_6N_6O_4$: C, 36.9; H, 7.7; N, 12.9%. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data for the analogous 6 HBr salt.[18]

Method 2: Acidic hydrolytic workup:

3,5–Bis(1,4,7–triazacyclonon–1–ylmethyl)nitrobenzene.6HCl (2b) (L^{nix}.6HCl)

A solution of 3,5–bis(bromomethyl)nitrobenzene (2.93 g, 9.5 mmol) in CH_3CN (40 mL) was added dropwise to a solution of 1,4,7–triazacyclo[5.2.1.0]decane **(10)** (2.65 g, 18 mmol) in CH_3CN (70 mL) with stirring under N_2. The mixture was stirred at ambient temperature for 48 h. The white bis(tacn) amidinium salt precipitate was collected by filtration, washed with Et_2O (3 x 50 mL) and dried under reduced pressure. The white precipitate was dissolved in 5 M HCl (50 mL) and the mixture heated under reflux for 18 h. The solution was concentrated under reduced pressure and the precipitate collected by filtration and washed with cold absolute EtOH (50 mL) to give the 6HCl salt of 3,5-bis(1,4,7-triazacyclonon-1-ylmethyl)-nitrobenzene **(2b)** as a white solid. Yield 3.08 g (52%). ^{1}H NMR (400 MHz, D_2O) δ_H 2.92 (8H, m, tacn CH_2) 3.20 (8H, m, tacn CH_2), 3.56 (8H, s, tacn CH_2), 3.92 (4H, s, CH_2Ar), 7.68 (1H, t, J = 1.3 Hz, ArH), 8.12 (2H, d, J = 1.3 Hz, ArH). ^{13}C NMR (100 MHz, D_2O): 42.1 (tacn CH_2), 43.6 (tacn CH_2), 47.3 (tacn CH_2), 57.5 (ArCH_2), 124.4 (ArCH), 137.7 (ArC), 137.9 (ArCH), 148.3 (ArC). ESI–MS m/z $[M + H]^+$ 406.3. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[19]

Synthesis of Boc4(bis(tacn)) compounds (Reactions 12 and 13**).**

1,4-Di-*tert*-butyl 7,7'-(anisole-2,6-dyl)bis(1,4,7-triazonane-1,4-dicarboxylate) (13c)

Triethylamine (1 mL, 20 mmol) and 2,6–bis(bromomethyl)anisole (2.50 g, 8 mmol) were added to a solution of Boc_2tacn (**12**) (5.66 g, 16 mmol) in CH_3CN (100 mL) and the mixture was stirred for 3 days at reflux. The mixture was concentrated to a dark amber gum which was dissolved in CH_2Cl_2 (50 mL) and washed consecutively with 10% aq. NaOH (2 x 50 mL), H_2O (50 mL), and brine (50 mL). The aqueous phases were combined and back extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were concentrated to an amber gum which was redissolved in CH_2Cl_2 (4 mL) and chromatographed on silica (EtOAc/hexanes, 1:1→2:1) to give the Boc protected bis(tacn) compound **13c** as a yellow oil. Yield 5.55 g (81 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ_H 1.40 (36H, m, CH_3), 2.70 (8H, m, tacn CH_2), 3.28 (8H, m, tacn CH_2), 3.51 (8H, m, tacn CH_2), 3.70 (3H, s, OCH_3), 3.74 (4H, s, CH_2Ar), 7.40 (1H, m, ArH). 7.48 (2H, m, ArH). ^{13}C NMR (100 MHz, $CDCl_3$) δ_C 28.5 (CH_3), 49.3 (tacn CH_2), 49.7 (tacn CH_2), 50.3 (tacn CH_2), 53.2 (ArCH_2), 53.9 (OCH_3), 79.5 (ArC), 131.0 (ArCH), 132.3 (ArC), 155.5 (ArCH), 155.7 (C=O), 157.0 (ArC–O). ESI–MS m/z $[M + H]^+$ 791.4. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[20]

Preparation of Bis(tacn).6HCl salts from Boc4(bis(tacn)) compounds

2,6-Bis(1,4,7-triazacyclonon-1-ylmethyl)anisole.6HCl.3.5H_2O (2c) (L^{anx}.6HCl)

1,4-Di-*tert*-butyl 7,7'-(anisole-2,6–dyl)bis(1,4,7-triazonane-1,4-dicarboxylate) (**13c**) (5.55 g, 7 mmol) was dissolved in conc. HCl (50 mL) and the mixture stirred for 12 h at ambient temperature. The solution was concentrated under reduced pressure and the precipitate collected by filtration and **w**ashed with cold absolute MeOH (50 mL) to give the 6HCl salt **(2c)** as a white solid. Yield 3.90 g (90 %). ^{1}H NMR (400 MHz, D_2O) δ_H 2.94 (8H, m, tacn CH_2), 3.18 (8H, m, tacn CH_2), 3.46 (8H, s, tacn CH_2), 3.86 (3H, s, CH_3), 3.86 (4H, s, CH_2Ar), 7.08 (1H, m, ArH), 7.30 (2H, m, ArH). ^{13}C NMR (100 MHz, D2O) δ_C 41.5 (tacn CH_2), 42.7 (tacn CH_2), 46.8 (tacn CH_2), 52.5 (ArCH_2), 62.7 (OCH_3), 125.2 (ArCH), 128.0 (ArC), 132.9 (ArCH), 157.7 (ArC). ESI–MS m/z $[M + H]^+$ 390.3. The ^{1}H and ^{13}C

NMR spectral data were consistent with literature data.[20]

Synthesis of Tos_4bis(tacn) compounds using normal heating (Reactions 14 and 15).[21]

1,3-Bis[4,7-bis(*p*-toluenesulfonyl)]-1,4,7-triazacyclononan-1-yl)propane (14d)

1,3-Diaminopropane (0.242 g, 3.0 mmol) was added to a stirred mixture of 3,6-di(tosyl)-3,6-diazaoctane-1,8-di(toluene-*p*-sulfonate) (**7**) (5.00 g, 7.0 mmol) and K_2CO_3 (1.87 g, 180 mmol) in CH_3CN (60 mL). The reaction was heated at reflux for 10 days under N_2. The mixture was allowed to cool and the inorganic salts filtered off. The solvent was removed under reduced pressure to leave the crude product **14d** as a yellow oil which was purified by silica column chromatography using EtOAc/hexane (40:60). Yield 2.45 (81 %). ^{1}H NMR (300 MHz, $CDCl_3$) δ_H 1.63 (2H, m, $CH_2CH_2CH_2$), 2.39 (12H, s, $ArCH_3$), 2.59 (4H, t, J = 7.2 Hz, $NCH_2CH_2CH_2N$), 2.85 (8H, m, tacn CH_2), 3.21 (8H, br s, tacn CH_2), 3.44 (8H, s, tacn CH_2), 7.26 (8H, d, J = 8.2 Hz, ArH), 7.65 (8H, d, J = 8.0 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 21.7 ($ArCH_3$), 25.9 ($NCH_2CH_2CH_2N$), 51.6 (tacn CH_2), 52.8 (tacn CH_2), 56.0 ($NCH_2CH_2CH_2N$), 57.5 (tacn CH_2), 127.4 (ArCH), 129.3 (ArCH), 135.7 (ArC), 143.5 (ArC). ESI–MS m/z $[M + H]^+$ 915.2. The ^{1}H and ^{13}C NMR spectral data were consistent with literature data.[21]

Synthesis of Tos_4bis(tacn) compounds using microwave heating

1,3-Bis[4,7-bis(*p*-toluenesulfonyl)]-1,4,7-triazacyclononan-1-yl)propane (14d)

1,3-Diaminopropane (0.26 mmol) was added to a stirred solution of 3,6-di(tosyl)-3,6-diazaoctane-1,8-di(toluene-*p*-sulfonate) (**7**) (0.52 mmol) and K_2CO_3 (5.2 mmol) in CH_3CN (4 mL) in a 5 mL microwave vial. The mixture was allowed to stir for 5 minutes. The vial was placed in a Biotage Initiator 8 microwave reactor and irradiated at 140, 160 or 180°C for 20 or 40 minutes, with 10 seconds of pre-stirring. The mixture was quickly cooled, the inorganic salts removed by filtration and the solvent removed to give the crude product which was analysed by ^{1}H NMR spectroscopy to estimate the extent of conversion. The reaction condition at 180°C for 40 min. gave a 91% conversion. The product from a reaction at 180°C for 20 min. was purified by column chromatography (silica, CH_2Cl_2/EtOH (80:20)) to yield pure **14d** as a white solid. Yield 0.14 g (56%). The ^{1}H and ^{13}C NMR spectroscopic data were consistent with the data mentioned above for the preparation of **14d** using normal heating.

Preparation of Bis(tacn).6HCl salts from Tos_4(bis(tacn)) compounds

1,3-Bis(1,4,7-triazacyclonon-1-ylmethyl)propane.6HCl (2d) (L^{pro}.6HCl)

1,3-Bis[4,7-bis(*p*-toluenesulfonyl)]-1,4,7-triazacyclononan-1-yl)-propane (**14d**) (2.0 g, 22 mmol) was added slowly to 18 M H_2SO_4 (10 mL). The mixture was heated with stirring in a heat block for 3 days at 120°C. The resulting black solution was cooled to room temperature and added dropwise using a dropping funnel to a vigorously stirred mixture of cold absolute EtOH/Et_2O (150 mL/100 mL) cooled in an ice bath. The brown precipitate was isolated quickly by vacuum filtration and immediately dissolved in de-ionised H_2O (20 mL). The mixture was heated for 2 h at 60°C, cooled to room temperature, filtered through Celite and the resulting solution concentrated to 4 mL under reduced pressure at 65°C. Conc. HCl (4 mL) was added followed by absolute EtOH until the solution became cloudy. The mixture was stored at 4°C overnight to promote precipitation. The white precipitate was collected by filtration and washed with ice cold absolute EtOH (3 x 5 mL), followed by Et_2O (3 x 5 mL) to give bis(tacn)propyl.6HCl **2d** as a white powder. Yield 0.49 g (76 %). ^{1}H NMR (400 MHz, D_2O) δ_H 1.82 (2H, m, $NCH_2CH_2CH_2N$), 2.72 (4H, t, $NCH_2CH_2CH_2N$), 3.02 (8H, m, tacn CH_2), 3.29 (8H, m, tacn CH_2), 3.54 (8H, m, tacn CH_2). ^{13}C NMR (100 MHz, D_2O) δ_C 18.7 ($NCH_2CH_2CH_2N$), 42.0 (tacn CH_2), 43.4 (tacn CH_2), 47.2 (tacn CH_2), 52.2 ($NCH_2CH_2CH_2N$).

References

1 J. E. Richman and T. J. Atkins, *J. Am. Chem. Soc.,* 1974, 2268–2270.

2 O. Iranzo, T. Elmer, J. P. Richard and J. R. Morrow, *Inorg. Chem.,* 2003, **42**, 7737–7746.

3 G. H. Searle and R. J. Geue, *Aust. J. Chem.*, 1984, **37**, 959–970.

4 R. Yang and L. J. Zompa, *Inorg. Chem.,* 1976, **15**, 1499–1502.

5 K. Wieghardt, W. Schmidt, B. Nuber and J. Weiss, *Chem. Ber*., 1979, **112**, 2220–2230.

6 D. W. White, B. A. Karcher, R. A. Jacobson and J. G. Verkade, *J. Am. Chem. Soc.*, 1979, **101**, 4921–4925.

7 A. J. Dickie, D. C. R. Hockless, A. C. Willis, J. A. McKeon and W. G. Jackson, Inorg. Chem., 2003, 42, 3822–3834.

8 T. J. Atkins, *J. Am. Chem. Soc,*. 1980, **102**, 6364–6365.

9 G. R. Weisman, V. Johnson and R. E Fiala, *Tetrahedron Lett.,* 1980, **21**, 3635–3638.

10 Q. Wu, M. L. Lee and R. G. Harrison, *J. Chromatogr., A,* 2002, **954**, 247–258.

11 S. Kimura, E. Bill, E. Bothe, T. Weyhermueller and K.Wieghardt, *J. Am. Chem. Soc.,* 2001, **123**, 6025–6039.

12 C. Nicolas, M. Borel, J. C. Maurizis, N. Gallais, M. Rapp, M. Ollier, M. Verny and J. C. Madelmont, *J. Labelled Cpd. Radiopharm.,* 2000, **43**, 585–594.

13 S. Pulacchini and M. Watkinson, *Eur. J. Org. Chem.,* 2001, **22**, 4233–4238.

14 J. L. Sessler, J. W. Sibert and V. Lynch, *Inorg. Chem.,* 1990, **29**, 4143–4146.

15 C. Bazzicalupi, A. Bencini, E. Faggi, A. Garau, C. Glorgi, V. Lippolis, A. Perra and B. Valtancoli, *J. Chem. Soc. Dalton Trans.,* 2006, 1409–1418.

16 L. J. Farrugia, P. A. Lovatt and R. D. Peacock, *J. Chem. Soc. Dalton Trans.* 1997, 911–912.

17 B. DasGupta, C. Katz, T. Isreal, M. Watson and L. J. Zompa, *Inorg. Chim. Acta,* 1999, **292**, 172–181.

18 B. Graham, G. D. Fallon, M. T. W. Hearn, D. C. R. Hockless, G. Lazarev and L. Spiccia, *Inorg. Chem*., 1997, *36*, 6366–6373.

19 C. J. Coghlan, E. M. Campi, C. M. Forsyth, W. R. Jackson and M. T. W. Hearn, *Polyhedron*, 2014, **69**, 219–224.

20 C. J. Coghlan, E. M. Campi, S. R. Batten, W. R. Jackson and M. T. W. Hearn, *Polyhedron*, 2016,**105**, 246–252.

21 S. Pulacchini, K. Shastri, N. C. Dixon and M. Watkinson, *Synthesis,* 2001, **16**, 2381–2383.