Supplementary Material (ESI) for Chemical Communications

ESI : Parker ; *Chem. Commun*., 2006

1. **Experimental**
2. **NMRD and VT 17-O (2.1T) NMR profiles for 4, 5 and 6**
3. **Sample low and high-resolution electrospraymass spectra for 4 and 5.**

1. Experimental

General. CH_2Cl_2 distilled from CaH_2. THF distilled from Na/benzophenone. NEt_3 distilled from CaH_2. Anhydrous nitromethane was purchased from Fluka. Gel filtration chromatography was performed with Biogel P-6 gel fine (column 2.5 cm x 98 cm) eluting with water at 0.7 mL min^{-1}. Detection was performed with a Knauer Differential Refractomer. Glucose and galactose pentabenzoate were prepared according to F. W. Lichtenthaler, E. Kaji and S. Weprek *J. Org. Chem.* 1985, *50*, 3505-3515.

***Tris(β-D-glucopyranosyloxymethyl)-methylamine,* 2**

Prepared according to the method described by P. R. Ashton, S. E. Boyd, C. L. Brown, N. Jayaraman, S. A. Nepogodiev and J. F. Stoddart *Chem. Eur. J.* **1996**, *2*, 1115-1128. Analytical data were in agreement with those reported in the literature.

Glu_{12}GdgDOTA, 4

To a suspension of GdgDOTA (16 mg, 18 μmol) and NEt_3 (13 μL, 115 μmol) is DMF (1 mL) was added *O*-benzotriazol-1-yl-*N*, *N*, *N'*, *N'*- tetramethyluronium tetrafluoroborate (37 mg, 115 μmol) and the mixture allowed to stir for few minutes. The amine tris(*β*-D-glucopyranosyloxymethyl)methylamine (88 mg, 132 μmol) was added to the reaction, and the mixture allowed to stir overnight at 40 ^{0}C under an atmosphere of dry argon. The pH of the reaction was then measured to be approximately 4 and further NEt_3 (30 μL) was added until the pH was around 8. Further *O*-benzotriazol-1-yl-*N*, *N*, *N'*, *N'*- tetramethyluronium tetrafluoroborate was added (40 mg) and the reaction left to stir at 40 ^{0}C for a futher 2.5 h. The reaction was then partioned between water (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 10 mL) and freeze-dried to afford a white solid.

Purification by gel-filtration chromatography (Biogel P-6) afforded a colourless solid (25 mg, 43%) as a fluffy white powder after lyophilization.
ES-MS: $[M]^{2-}$ = 1601.05, $[M]^{3-}$ = 1067.35 .
HRMS (ES^-) calcd. for $C_{116}H_{196}N_8O_{84}$ Gd $[M]^{2-}$: 1601.0242; found 1601.0243.

N^{α}-(Benzyloxycarbonyl)-N-[tris(hydroxymethyl)methyl]glycinamide

Hydroxybenzotriazole (1.35 g, 9.99 mmol) was added to a solution of carbobenzyloxyglycine (2.00 g, 9.56 mmol) and 1,3-dicyclohexylcarbodiimide (2.06 g, 9.98 mmol) in DMF (20 mL). When all reagents were dissolved, TRIS (2.32 g, 19.15 mmol) was added. The reaction mixture was stirred overnight at room temperature under an atmosphere of argon. After completion of the reaction (TLC), DMF was removed under vacuum and the white solid obtained was dissolved in EtOH (20 mL). The white slurry was filtered and the filtrate evaporated to dryness. The product was purified by column chromatography (SiO_2, CH_2Cl_2 / MeOH 1%→CH_2Cl_2 / MeOH 5%) to yield a white solid (0.86 g, 28%).

ES-MS: m/z 335 $[M + Na]^+$, 647 $[2\times M + Na]^+$
HRMS (ES^+) calcd. for $C_{14}H_{20}N_2O_6$ $[M + Na]^+$: 335.1214; found 335.1214
δ_H (DMSO, 300 MHz): 3.51 (6H, d, J = 6.0 Hz, CH_2OH), 3.62 (2H, d, J = 6.0 Hz, CH_2NH), 4.69 (3H, t, J = 6.0 Hz, O*H*), 5.02 (2H, s, CH_2Ph), 7.13 (5H, bs, Ph-H), 7.32 (1H, s, $C_{(quat)}$NH), 7.44 (1H, m, CH_2N*H*).
δ_C (DMSO, 75 MHz): 44.2 (*C*H_2NHCO), 61.0 (*C*H_2OH), 62.40 (CH_2*C*(quat)), 66.8 (*C*H_2Ph), 127.7, 128.0, 128.4 (Ph-C), 136.9 (Ph-C(quat)), 158.0 (*C*OCH_2NH), 171.6 (COOCH2Ph).

N^{α}-(Benzyloxycarbonyl)-N-[tris(2,3,4,6-tetra-O-benzoyl-β-D-glucopyranosyloxymethyl)methyl]glycinamide

AgOTf (0.50 g, 1.94 mmol) was activated by dissolving in anhydrous $PhCH_3$ (10 mL) and the solvent was removed under vacuum. This procedure was repeated a further two times. A mixture of **7** (0.147 g, 0.47 mmol), AgOTf and 2,4,6-collidine (190 μL, 1.44 mmol) in CH_2Cl_2 (4.4 mL) and $MeNO_2$ (4.4 mL) was stirred at -30 ^{0}C. A solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-glucopyranosyl bromide (1.10 g, 1.67 mmol) in CH_2Cl_2 (4.4 mL) was added dropwise over 20 min to this suspension. Stirring was continued for 30 min at the same temperature and then the reaction mixture was for 2 h at 0 ^{0}C, then overnight at room temperature. After completion of the reaction (TLC), C_5H_5N (1.0 mL) was added to the

reaction mixture, which was left to stir for 30 min and then diluted with CH_2Cl_2 (20 mL) before being filtered through Celite. The filtrate was washed successively with aqueous $Na_2S_2O_3$ solution (1 M, 2 x 50 mL), aqueous HCl solution (0.1 M, 2 x 50 mL), saturated aqueous $NaHCO_3$ solution (2x50 mL) and H_2O (2x50 mL). The organic phase was dried over Na_2SO_4 and the solvent was removed in *vacuo* to afford crude product, the TLC of which showed a main product (R_f (EtOAc/Hex 3:7) = 0.2; H_2SO_4) and few other minor components. The main product was separated by column chromatography (SiO_2, EtOAc / Hex, 3:7) to afford the product as a white foamy solid (0.47 g, 49%).

ES-MS: *m/z* 2071 $[M + Na]^+$, 4119 $[2\times M + Na]^+$

HRMS (ES^+) calcd. for $C_{116}H_{98}N_2O_{33}$ $[M + 2Na]^{2+}$: 1046.2918; found 1046.2935

δ_H ($CDCl_3$, 300 MHz): 3.50 (3H, d, $^2J_{CHa,CHb}$ = 10.0 Hz, C(quat)CH_a), 3.60 – 3.70 (5H, m, H-5), 4.16 (3H, d, $^3J_{1,2}$ = 9.0 Hz, H-1), 4.24 (3H, d, $^2J_{CHa,CHb}$ = 10.0 Hz, $C_{(quat)}CH_b$), 4.38 (3H, dd, $^3J_{5,6a}$ = 4.5 Hz, $^2J_{6a,6b}$ = 12.0 Hz, H-6a), 4.54 (3H, app.d, $^2J_{6a,6b}$ = 12.0 Hz, H-6b), 5.18 (2H, s, CH_2Ph), 5.35 (4H, app.t, $^3J_{1,2} \sim {}^3J_{2,3}$ = 8.5 Hz, H-2 and CH_2NH), 5.55 (3H, app. t, $^3J_{3,4} \sim {}^3J_{4,5}$ = 9.5 Hz, H-4), 5.69 (3H, app. t, $^3J_{2,3} \sim {}^3J_{3,4}$ = 9.5 Hz, H-3), 6.01 (1H, s, N*H* carbamate), 7.28 – 8.06 (60H, m, Ph-*H*).

δ_C ($CDCl_3$, 75 MHz): 58.4 ($C_{(quat)}$), 59.3 (CH_2NHCO), 61.9 (C-6), 65.9 (CH_2Ph), 66.9 ($C_{(quat)}CH_2$), 68.5 (C-4), 70.9 (C-5), 71.0 (C-2), 71.5 (C-3), 100.3 (C-1), 127.3 – 128.9 (Ph ring carbons), 132.1 (Ph*C*(quat)), 164.0 ($COCH_2$NH), 165.0 ($COOCH_2$Ph).

N^{α}-(Benzyloxycarbonyl)-N-[tris(β-D-glucopyranosyloxymethyl)-methyl]glycinamide

A solution of *N*-α-(benzyloxycarbonyl)-*N*-[tris(2,3,4,6-tetra-*O*-benzoyl-*β*-D-glucopyranosyloxymethyl)methyl]glycinamide (0.47g, 0.23 mmol) in 0.10 M methanolic NaOMe (20 mL) was stirred at room temperature overnight. The solution was treated with Amberlite IR-120(PLUS) ion-exchange resin, filtered and the solvents were removed *in vacuo*. The resulting solids were partitioned between H_2O (20 mL) and Et_2O (15 mL). The aqueous layer was washed with further Et_2O (3 x 15 mL) and then freeze-dried to obtain the product as a fluffy white powder (0.16 g, 87%).

ES-MS: *m/z* 821 $[M + Na]^+$, 1619 $[2\times M + Na]^+$

HRMS (ES^+) calcd. for $C_{32}H_{50}N_2O_{21}$ $[M + Na]^+$: 821.2798; found 821.2791

δ_H (D_2O, 500 MHz): 3.11 (3H, app. t, *J* = 7.5 Hz, H-2), 3.19 – 3.32 (9H, m, H-3, H-4, H-5), 3.55 (3H, dd, $^3J_{5,6a}$ = 5.5 Hz, $^2J_{6a,6b}$ = 12.0 Hz, H-6a) 3.66 (2H, s, CH_2NHCO), 3.74 (3H, dd,

H-5, $^{3}J_{5,6b}$ = 2.0 Hz, $^{2}J_{6a,6b}$ = 12.0 Hz, H-6b), 3.78 (3H, d, $^{2}J_{CHa,CHb}$ = 10.5 Hz, C(quat)CH_a), 4.08 (3H, d, $^{2}J_{CHa,CHb}$ = 10.5 Hz, C(quat)CH_b), 4.28 (3H, d, $^{3}J_{1,2}$ = 8.0 hz, H-1), 5.00 (2H, s, CH_2Ph), 7.29 (5H, m, Ph-H).

δ_C (D_2O, 125.67 MHz): 44.1 (Gly-CH_2), 59.1 (C(quat)), 60.8 (C-6), 67.6 (CH_2Ph), 67.7 (C(quat)CH_2), 69.8 (C-4), 73.2 (C-2), 75.6 (C-3), 76.1 (C-5), 103.1 (C-1), 127.9-128.6 (Ph ring carbons), 157.8 (COCH$_2$NH), 172.2 (Gly-CO).

***N-[Tris(β-D-glucopyranosyloxymethyl)methyl]glycinamide,* 3**

A suspension of N^{α}-(benzyloxycarbonyl)-N-[tris(β-D-glucopyranosyloxymethyl)-methyl]glycinamide (0.47 g. 0.23 mmol) in 10 mL of H_2O/ EtOH (1:1) and $Pd(OH)_2$/C (0.17 g) was hydrogenolysed overnight using a hydrogenator (40 psi H_2). The reaction mixture was filtered over Celite, the solvent was evaporated under reduced pressure and the residue was dissolved in H_2O (15 mL) and freeze-dried to afford a white powder (0.146 g, 96%).

ES-MS: *m/z* 687 $[M + Na]^+$, 1351 $[2\times M + Na]^+$.
HRMS (ES^+) calcd. for $C_{24}H_{44}N_2O_{19}$ $[M + Na]^+$: 687.2430; found 687.2426
δ_H (D_2O, 500 MHz): 3.14 (3H, app. t, $^{3}J_{1,2}$ = 8.5 Hz, H-2), 3.22 (3H, app. t, $^{3}J_{3,4}$ = 9.5 Hz, H-4), 3.28–3.34 (8H, m, H-3, H-5, CH_2NH$_2$), 3.55 (3H, d, $^{2}J_{6a,6b}$ = 12.5 Hz, H-6a), 3.76 (3H, d, $^{2}J_{6a,6b}$ = 12.5 Hz, H-6b), 3.79 (3H, d, $^{2}J_{CHaCHb}$ = 10.0 Hz, C(quat)CH_a), 4.12 (3H, d, $^{2}J_{CHa,CHb}$ = 10.0 Hz, C(quat)CH_b), 4.31 (3H, d, $^{3}J_{1,2}$ = 7.5 Hz, H-1).
δ_C (D_2O, 125.67 MHz): 42.9 (Gly-CH_2), 57.5 (C(quat)), 60.8 (C-6), 67.8 (C(quat)CH_2), 69.9 (C-4), 73.2 (C-2), 75.7 (C-3), 76.1 (C-5), 100.1 (C-1), 172.3 (CONH).

Analytical data in good agreement with P. R. Ashton *et al. Chem. Eur. J.* **1996**, *2*, 1115-1128.

Glu_{12}glyGdgDOTA, 5

To a suspension of GdgDOTA (15 mg, 0.017mmol) in *N*-methylmorpholine (12 μL, 0.11 μmol) and DMF (0.82 mL) was added *O*-benzotriazol-1-yl-*N*, *N*, *N'*, *N'*- tetramethyluronium tetrafluoroborate (40 mg, 0.12 mmol) and the mixture allowed to stir for few minutes. A solution of the amine N-[tris(β-D-glucopyranosyloxymethyl)methyl]glycinamide (70 mg, 0.13 mmol) was added to the reaction, and the mixture allowed to stir overnight at 40 ^{0}C under an atmosphere of argon. The reaction was portioned between water (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was washed with CH_2Cl_2 (10 mL) and freeze-dried. The

crude of the reaction is a mixture of the fully substituted tetra-amide (major product) and the under-substituted triamide and diamide (minor products). Purification by gel-filtration chromatography afforded the pure tetra-substituted product (19 mg, 32%), as confirmed by electrospray analysis.

ES-MS: $[M]^{2-}$ = 1715.07.

HRMS (ES^-) calcd. for $C_{124}H_{204}N_{12}O_{88}$ Gd $[M]^{2-}$:1715.0712; found 1715.0716.

$(TRIS)_4$GdgDOTA, 6

To a suspension of GdgDOTA (109 mg, 126 μmol) in NEt_3 (105 μL, 0.75 mmol) and DMF (2.0 mL) was added *O*-benzotriazol-1-yl-*N*, *N*, *N'*, *N'*- tetramethyluronium tetrafluoroborate (247 mg, 0.77 mmol) and the mixture allowed to stir for few minutes. Tris(hydroxymethyl)methylamine (200 mg, 1.65 mmol) was added and the mixture allowed to stir overnight at 40 ^{0}C under an atmosphere of argon. The reaction was portioned between water (20 mL) and CH_2Cl_2 (20 mL). The aqueous layer was washed with CH_2Cl_2 (20 mL) and freeze-dried. Purification by gel-filtration chromatography afforded the pure tetra-substituted product (83 mg, 52%), as confirmed by electrospray analysis.

ES-MS: $[M]^-$ =1258.4

HRMS (ES^-) calcd. for $C_{44}H_{76}N_8O_{24}$ Gd$[M]^-$: 629.2112; found 629.2113.

N^{α}-(Benzyloxycarbonyl)-N-[tris(2,3,4,6-tetra-O-benzoyl-β-D-galactopyranosyloxymethyl)methyl]glycinamide

AgOTf (1.006 g, 3.92 mmol) was activated by dissolving in anhydrous $PhCH_3$ (10 mL) and the solvent then removed under vacuum. This procedure was repeated a further two times. A mixture of N^{α}-(benzyloxycarbonyl)-*N*-[tris(hydroxymethyl)methyl]glycinamide (300 mg, 961 μmol), AgOTf and 2,4,6-collidine (444 μl, 3.36 mmol) in CH_2Cl_2 (7 mL) and $MeNO_2$ (7 mL) was stirred at approximately -30 ^{0}C under an argon atmosphere. A solution of 2,3,4,6-tetra-*O*-benzoyl-α-D-galactopyranosyl bromide (2.22 g, 3.37 mmol) in CH_2Cl_2 (7 mL) was added dropwise over 20 min to the reaction mixture. Stirring was continued for 30 min at the same temperature and the reaction mixture then stirred for 2 h at 0 ^{0}C, then overnight at room temperature. The reaction mixture was then diluted with CH_2Cl_2 (100 mL) before being filtered through Celite. The filtrate was washed successively with aqueous $Na_2S_2O_3$ solution (1 M, 2 x100 mL), aqueous HCl solution (1 M, 100 mL), saturated aqueous $NaHCO_3$ solution (100 mL) and H_2O (100 mL). The organic phase was dried over $MgSO_4$ and the solvent was

removed in *vacuo* to afford crude product. The main product was separated by column chromatography (SiO_2, EtOAc / Hex, 3:7 to 4:7) to yield the title compound (1.26 g, 64%) as a foamy white solid.

HRMS (ES^+) calcd. for $C_{116}H_{98}O_{33}N_2Na_2$ $[M + 2Na]^{2+}$: 1046.2908; found 1046.2907.
^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.59 (2H, d, J = 10.5 Hz, glyCH_2), 3.58 - 3.67 (3H, m, $C_{quat}CH_a$), 3.78 (3H, t, J = 7.0 Hz, H-5), 4.15 (3H, d, $^3J_{1,2}$ = 7.0 Hz, H-1), 4.36 – 4.40 (6H, m, H-6a, $C_{quat}CH_b$), 4.55 (3H, dd, $^3J_{5,6a}$ = 6.5 Hz, $^2J_{6a,6b}$ = 11.0 Hz, H-6b), 5.11 (1H, d, $^2J_{CHa,CHb}$ = 12.5 Hz, PhCH_a), 5.16 (1H, d, $^2J_{CHa,CHb}$ = 12.5 Hz, PhCH_b), 5.24 (1H, bs, NH), 5.42 (3H, dd, $^3J_{3,4}$ = 3.5 Hz, $^3J_{2,3}$ = 10.5 Hz, H-3), 5.65 (3H, dd, $^3J_{1,2}$ = 7.0 Hz, $^3J_{2,3}$ = 10.5 Hz, H-2), 5.87 (3H, app. t, $^3J_{3,4} \approx {}^3J_{4,5}$ = 3.5 Hz, H-4), 6.00 (1H, bs, NH), 7.27 – 8.08 (65H, band, 13 x Ph).
^{13}C NMR (125 MHz, $CDCl_3$): δ = 44.6 (gly$C$H$_2$), 61.8 (C-6), 67.2 (PhCH$_2$), 68.1 (C-4, $C_{quat}CH_2$), 70.1 (C-2), 71.3 (C-3), 71.4 (C-5), 102.0 (C-1), 125.1 – 134.1 (Ph ring carbons), 156.5 (urethane C=O), 165.1, 165.7, 165.8, 166.1 (PhCO), 169.0 (NHCO).

Proton and carbon assignments confirmed by COSY and HSQC experiments.

N$^{\alpha}$-(Benzyloxycarbonyl)-N-[tris(β-D-galactopyranosyloxymethyl)-methyl]glycinamide

A solution of *N*-α-(benzyloxycarbonyl)-*N*-[tris(2,3,4,6-tetra-*O*-benzoyl-β-D-galactopyranosyloxymethyl)methyl]glycinamide (1.26 g, 0.616 mmol) in 0.1 M methanolic NaOMe (50 mL) was stirred at room temperature overnight. It was then neutralized with Amberlite IR-120(PLUS) ion-exchange resin, filtered and the solvents were removed *in vacuo*. The resulting solids were partitioned between H_2O (20 mL) and Et_2O (15 mL). The aqueous layer was washed with further Et_2O (3 x 15 mL) and then freeze-dried to obtain the product as a fluffy white powder (433 mg, 88%).

HRMS (ES^+) calcd. for $C_{32}H_{50}O_{21}N_2Na$ $[M + Na]^+$: 821.2789; found 821.2785.
^{1}H NMR (500 MHz, H_2O): δ = 3.37 (3H, app. t, $^3J_{1,2} \approx {}^3J_{2,3}$ = 8.0 Hz, H-2), 3.46 – 3.51 (6H, m, H-3, H-5), 3.56 – 3.64 (6H, m, H-6a, H-6b), 3.68 (2H, s, glyCH_2), 3.74 (3H, d, J = 3.0 Hz, H-4), 3.82 (3H, d, $^2J_{CHa,\,CHb}$ = 10.5 Hz, $C_{quat}CH_a$), 4.10 (3H, d, $C_{quat}CH_b$), 4.22 (3H, d, $^3J_{1,2}$ = 8.0 Hz, H-1), 5.01 (2H, s, PhCH_2), 7.26 – 7.33 (5H, m, Ph-H).

^{13}C NMR (125 MHz, H_2O): δ = 44.1 (gly*C*H_2), 60.1 (*C*$_{quat}$), 61.1 (C-6), 67.4 (C$_{quat}$*C*H_2), 68.7 (C-4), 70.9 (C-2), 72.7, 75.3 (C-3, C-5), 103.7 (C-1), 127.8, 128.5, 129.0, 136.5 (Ph ring carbons), 158.6 (*C*=O urethane), 172.0 (*C*=O glycine).

Proton and carbon assignments confirmed by COSY and HSQC experiments.

N-[Tris(β-D-galactopyranosyloxymethyl)-methyl]glycinamide

A suspension of N^{α}-(Benzyloxycarbonyl)-*N*-[tris(*β*-D-galactopyranosyloxymethyl)-methyl]glycinamide (433 mg. 0.54 mmol) in H_2O/ EtOH (10 mL, 1:1) and 20%Pd(OH)$_2$/C (85 mg) was hydrogenated at room temperature overnight using a Parr hydrogenator (40 psi H_2). The reaction mixture was filtered over Celite, the solvent was evaporated in *vacuo* and the residue was dissolved in H_2O (15 mL) and freeze-dried to afford a white powder (360 mg, 100%).

^{1}H NMR (500 MHz, H_2O): δ = 3.36 – 3.41 (5H, H-2, glyC*H*$_2$), 3.48 – 3.54 (6H, m, H-3, H-5), 3.57 – 3.67 (6H, H-6a, H-6b), 3.77 (3H, d, J = 3.0 Hz, H-4), 3.81 (3H, d, $^2J_{CHa,CHb}$ = 10.5 Hz, C$_{quat}$C*H*$_a$), 4.14 (3H, d, $^2J_{CHa,Chb}$ = 10.5 Hz, C$_{quat}$C*H*$_b$), 4.25 (3H, d, $^3J_{1,2}$ = 7.5 Hz, H-1).

^{13}C NMR (125 MHz, H_2O): δ = 42.6 (gly*C*H_2), 60.1 (*C*$_{quat}$), 61.1 (C-6), 67.8 (C$_{quat}$*C*H_2), 68.7 (C-4), 70.8 (C-2), 72.7, 75.3 (C3, C5), 103.7 (C-1), 171.1 (*C*=O glycine).

Proton and carbon assignments confirmed by COSY and HSQC experiments.

HRMS (ES$^+$) calcd. for $C_{24}H_{44}O_{19}N_2Na$ $[M + Na]^+$: 687.2430; found 687.2428

Gal$_{12}$glyGdgDOTA

To a suspension of GdgDOTA (19 mg, 22 μmol) and NEt_3 (18 μL, 129 μmol) is DMF (1 mL) was added *O*-benzotriazol-1-yl-*N*, *N*, *N'*, *N'*- tetramethyluronium tetrafluoroborate (40 mg, 134 μmol) and the mixture allowed to stir for few minutes. The amine *N*-[tris(*β*-D-galactopyranosyloxymethyl)-methyl]glycinamide (88 mg, 132 μmol) was added to the reaction, and the mixture allowed to stir overnight at 40 ^{0}C under an atmosphere of dry argon. The pH of the reaction was then measured to be approximately 4 and further NEt_3 (30 μL) was added until the pH was around 8. Further *O*-benzotriazol-1-yl-*N*, *N*, *N'*, *N'*-tetramethyluronium tetrafluoroborate was added (35 mg) and the reaction left to stir at 40 ^{0}C for a further 2.5 h. The reaction was then partioned between water (10 mL) and CH_2Cl_2 (10 mL). The aqueous layer was washed with CH_2Cl_2 (2 x 10 mL) and freeze-dried to afford

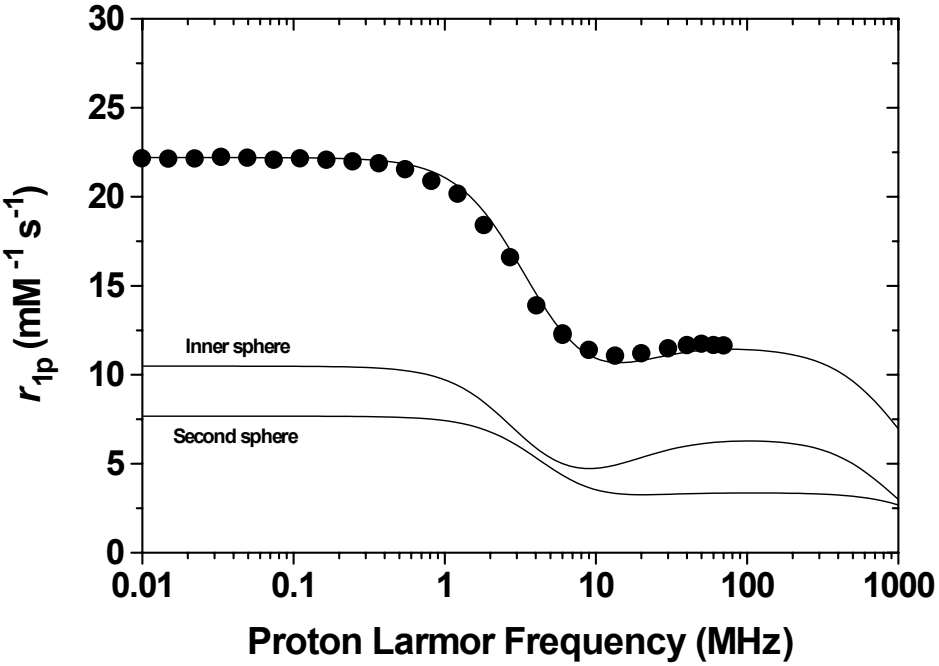
white solids. Purification by gel-filtration chromatography (Biogel P-6) afforded the pure product (32 mg, 42%) as a fluffy white powder after lypholization, as confirmed by electrospray analysis.

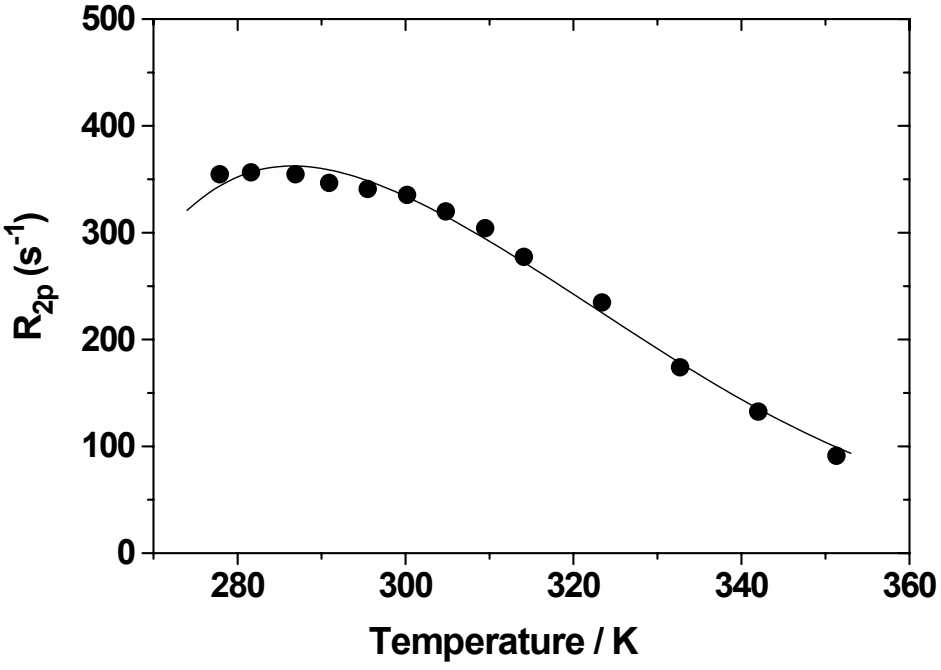
ES-MS: $[M]^{2-}$ = 1715, $[M]^{3-}$ = 1143 (tetraamide product).

HRMS (ES^-) calcd. for $C_{124}H_{204}N_{12}O_{88}$ $[M]^{2-}$:1715.0712; found 1715.0714.

2. NMRD and VT 17-O (2.1 T) Profiles

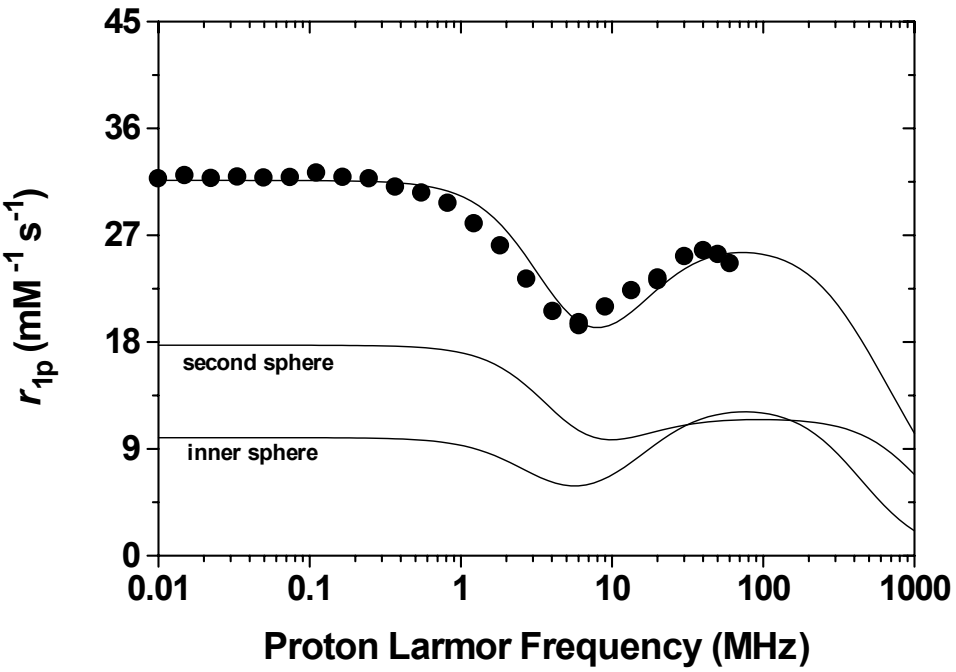
$(TRIS)_4$GdgDOTA, 6

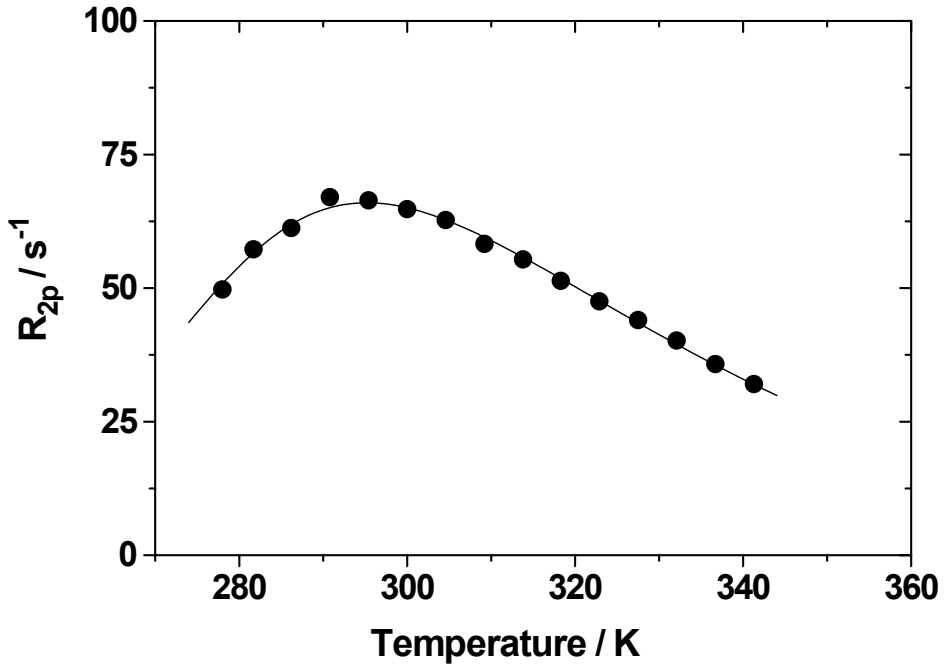




concentration of 6: 32mM

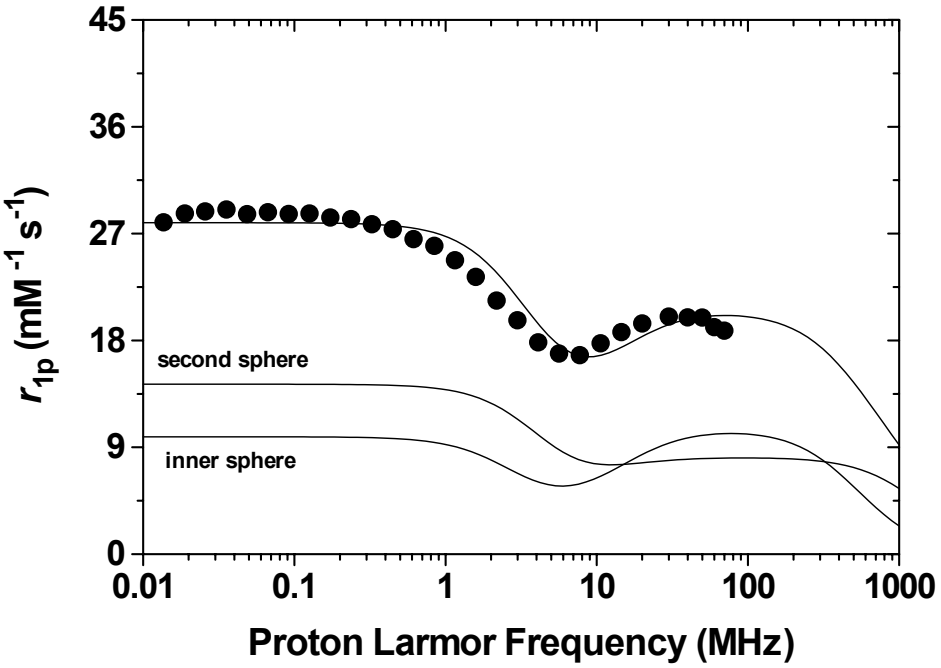
$(Glu)_{12}$GdgDOTA, 4

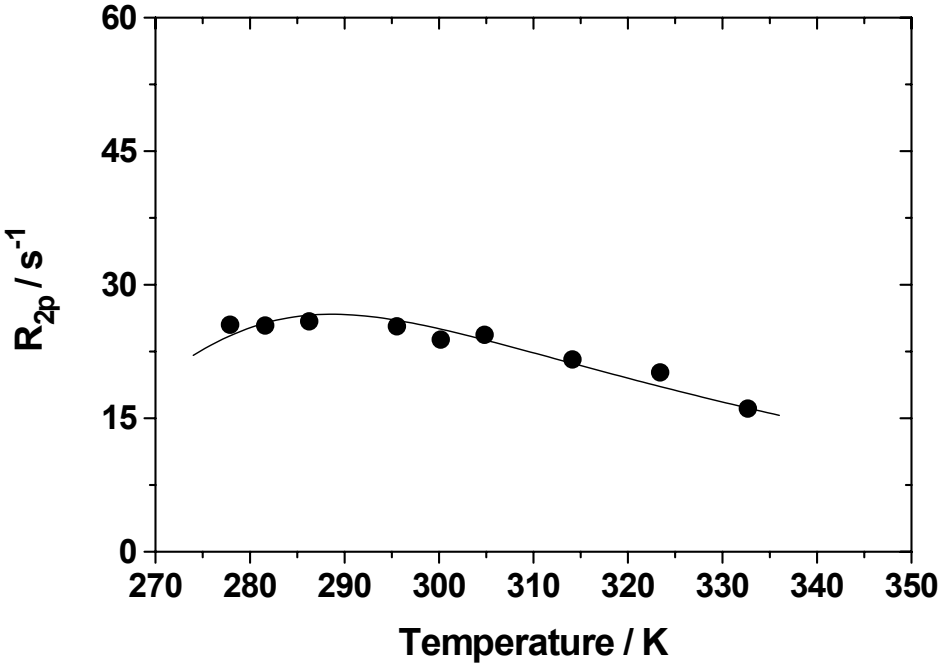




concentration of 4: 4 mM

$(Glu)_{12}$glyGdgDOTA, 5





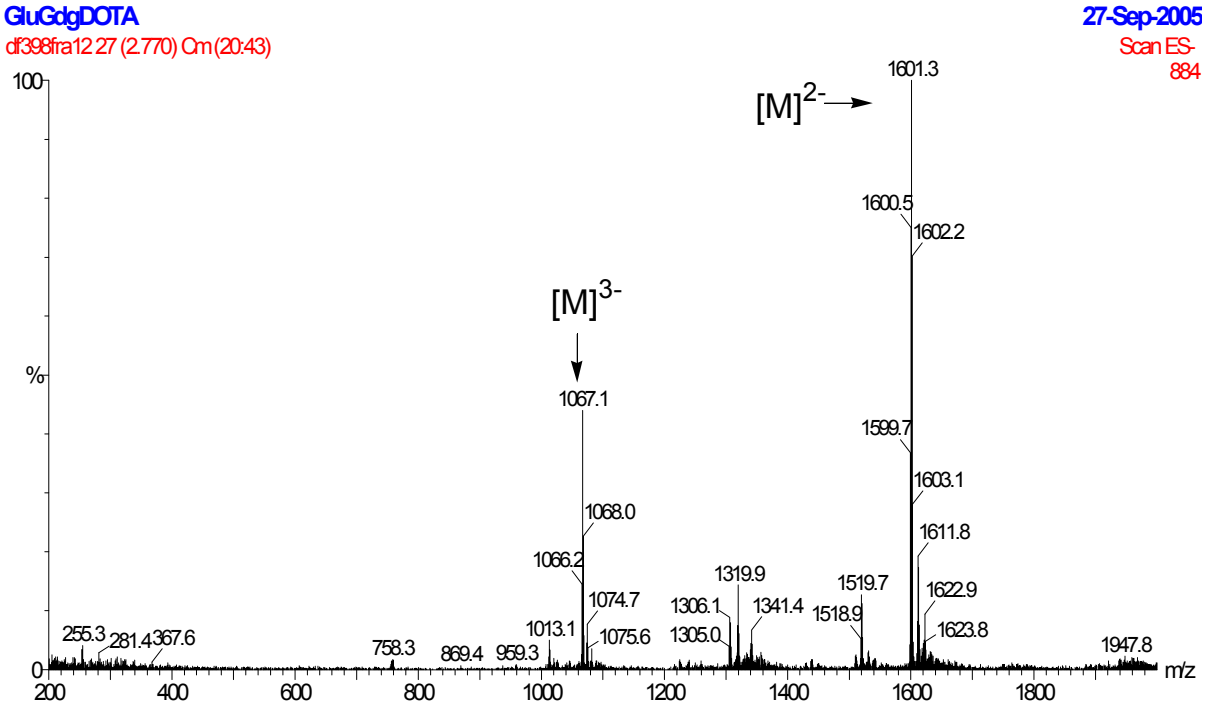
concentration of 5: 3mM

Best fit parameters (25°C) of NMRD and ^{17}O data

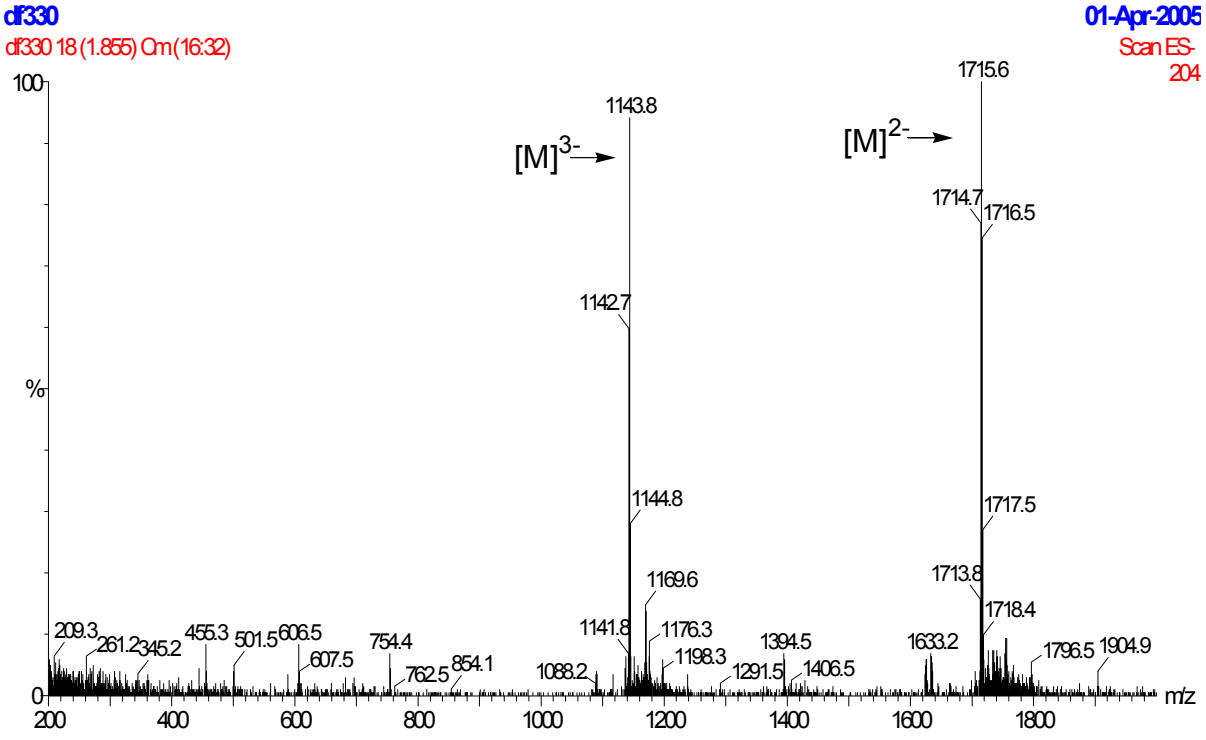
	4	5	6
Δ^2 (s^{-1};× 10^{-19})	3.7	3.4	3.7
τ_v (ps)	20.0	20.1	13.0
τ_R (ps)	390	318	173
τ_M (ns)	198	221	93
ΔH_M ($kJmol^{-1}$)	45.3	46.0	51.0
q	1	1	1
r (Å)	3.0	3.0	3.0
a (Å)	4	4	4
D ($cm^2 s^{-1}$; $\times 10^{-5}$)	2.24	2.24	2.24
q’	8	8	4
r’ (A)	3.70	3.8	3.73
τ_R’ (ps)	133	110	81

3. Sample low- and high-resolution electrospray mass spectra for 4 and 5.

$Glu_{12}GdgDOTA$ 4 (Low resolution electrospray mass spectrum) .



$Glu_{12}glyGdgDOTA$ 5 (Low resolution electrospray mass spectrum).



$Glu_{12}GdgDOTA$ 4 (High resolution electrospray mass spectrum) .