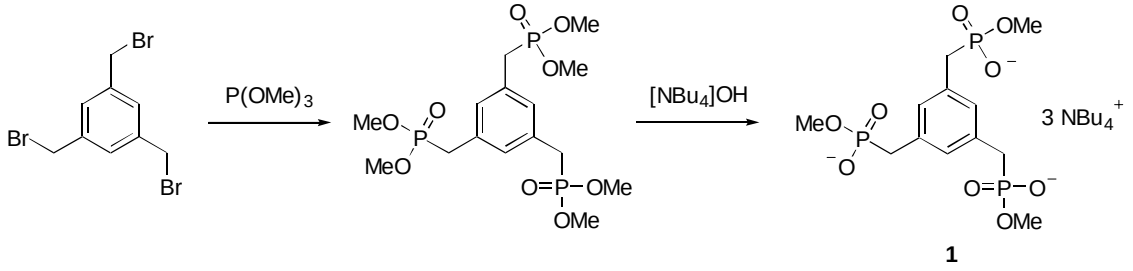
Supporting Information

General Methods. DMSO-d_6 (Aldrich), deuterium oxide (Merck) and methanol-d_4 (Merck) were purchased each in 99.8% purity. Thin layer chromatography (TLC) analyses were performed on silica gel 60 F_{254} (Merck) with a 0.2 mm layer thickness. Preparative chromatography columns were packed with silica gel 60 from Aldrich. All solvents were dried and freshly distilled before use.

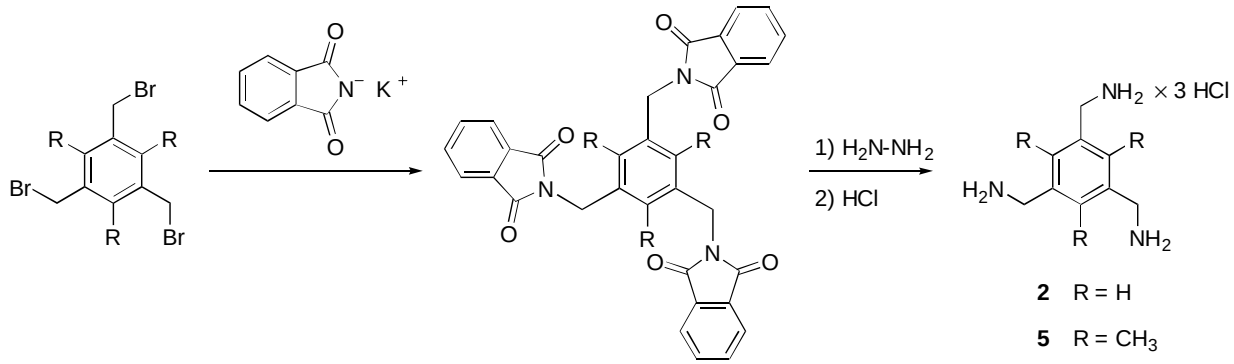


[**3,5-Bis(dimethoxyphosphorylmethyl)benzyl]phosphoric acid dimethyl ester.** 1,3,5-Tris(bromomethyl)benzene[1] (1.0 g, 2.80 mmol) was dissolved in trimethyl phosphite (5 mL) and refluxed for 3 hours. Evaporation of the solution gave a colorless oil, which was further purified by column chromatography ($CHCl_3$/MeOH, 9:1).

Yield: 1.05 g (84%). Mp 98 °C, colorless solid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.15 (d, 6 H, J = 22.1 Hz), 3.68 (d, 18 H, J = 10.7 Hz), 7.14 (br. q, 3 H, J = 2.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.7 (d, J_{CP} = 138 Hz), 52.9 (m), 129.9, 132.9. ^{31}P NMR (202 MHz, $CDCl_3$): δ 29.6. MS (CI, NH_3): *m/z* 462 (M + NH_4^+, 80%), 445 (M + H^+, 25). Anal. Calcd for $C_{15}H_{27}O_9P_3$: C, 40.55; H, 6.13. Found: C, 40.30; H, 6.29. R_f ($CHCl_3$/MeOH, 9:1) 0.37.

[3,5-Bis(hydroxymethoxyphosphorylmethyl)benzyl]phosphoric acid monomethyl ester, tris(tetrabutylammonium) salt (1). [3,5-Bis(dimethoxyphosphorylmethyl)benzyl]phosphoric acid dimethyl ester was treated with 3.0 equiv of aqueous [NBu_4]OH and refluxed for 2 weeks. After evaporation of the solvent, the crude product was extracted with chloroform. The solution was dried ($MgSO_4$), filtered, and evaporated to dryness. The colorless amorphous solid was then dried at 50°C/10^{-3} bar. Yield: 87%. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (t, 36 H, J = 7.6 Hz), 1.41 (sextet, 24 H, J = 7.6 Hz), 1.61 (m, 24 H), 2.90 (d, 6 H, J = 20.1 Hz), 3.25 (m, 24 H), 3.54 (d, 9 H, J = 10.1 Hz), 7.14 (br. q, 3 H, J = 1.9 Hz). ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.76, 19.72, 24.09, 34.87 (d, $^1J_{CP}$ = 124.2 Hz), 51.68 (d, $^2J_{CP}$ = 5.0 Hz), 58.30, 128.18, 136.49. ^{31}P NMR (505 MHz, $CDCl_3$): δ 19.88. MS (FAB, glycine matrix, Xe): *m/z* 1126 (M + H^+, 55%), 242 (NBu_4^+, 100). Anal. Calcd for $C_{60}H_{126}N_3O_9P_3$ (× 6 H_2O): C, 58.37; H, 11.27; N, 3.40. Found: C, 58.45; H, 11.51; N, 3.67.

[1] Plater, M. J.; Praveen, M.; Stein, B. K.; Ballantine, J. A *Tetrahedron Lett*. **1996**, *37*, 7855–7856.



General procedure for the preparation of 1,3,5-tris(phthalimidomethyl)benzene compounds. The 1,3,5-tris(bromomethyl)benzene compound, 3.6 equiv of potassium phthalimide and 0.3 equiv of 18-crown-6 were dissolved in toluene under a dry argon atmosphere. After heating to 100°C for 24 h, water was added to the reaction mixture. The aqueous layer was extracted four times with dichloromethane. The combined organic layers were dried over Na_2SO_4, evaporated, and the residue was purified by column chromatography (CH_2Cl_2/acetone, 20:1).

1,3,5-Tris(phthalimidomethyl)benzene. Yield: 71%. ^{1}H NMR (500 MHz, $CD_2Cl_2/CDCl_3$): δ 4.78 (s, 6 H), 7.35 (s, 3 H), 7.70–7.82 (AA'BB'). ^{13}C NMR (125 MHz, $CD_2Cl_2/CDCl_3$): δ 166.95, 136.50, 133.07, 13.16, 126.68, 122.40, 40.23. MS (CI, NH_3): *m/z* 573 (M + NH_4^+, 100%). Anal. Calcd for $C_{33}H_{29}N_3O_6$: C, 71.34; H, 3.81; N, 7.56. Found: C, 71.46; H, 3.70; N, 7.58. R_f (CH_2Cl_2/acetone, 20:1) 0.55.

1,3,5-Tris(phthalimidomethyl)-2,4,6-trimethylbenzene. Yield: 82%. ^{1}H NMR (500 MHz, $CD_2Cl_2/CDCl_3$): δ 2.42 (s, 9 H), 3.57 (s, 6 H), 7.60–7.69 (AA'BB'). ^{13}C NMR (125 MHz, $CD_2Cl_2/CDCl_3$): δ 171.03, 137.34, 132.92, 131.01, 128.39, 122.23, 37.54, 16.27. MS (CI, NH_3): *m/z* 615 (M + NH_4^+, 100%). Anal. Calcd for $C_{36}H_{27}N_3O_6$: C, 72.41; H, 4.56; N, 7.04. Found: C, 72.26; H, 4.45; N, 6.88. R_f (CH_2Cl_2/acetone, 20:1) 0.6.

General procedure for the preparation of 1,3,5-tris(aminomethyl)benzene compounds. The phthalimide compound was dissolved in a hot mixture of dry ethanol/toluene (2:1) and refluxed with 6 equiv of hydrazine hydrate for 72 hours. The reaction mixture was evaporated, and the residue was first suspended in ether, then shaken with a cold 40% aqueous solution of potassium hydroxide. The extraction was repeated four times, and the combined organic extracts were dried over Na_2SO_4 and filtered. Dry hydrogen chloride was then bubbled through the filtrate. The yellow precipitate was collected by suction filtration and dried.

1,3,5-Tris(aminomethyl)benzene trihydrochloride (2). Yield: 53%. Mp 102°C. ^{1}H NMR (500 MHz, CD_3OD): δ 4.22 (s, 6 H), 7.67 (s, 3 H). ^{13}C NMR (125 MHz, CD_3OD): δ 43.81, 131.73, 136.37. Anal. Calcd for $C_9H_{18}Cl_3N_3$: C, 39.58; H, 6.64; N, 15.39. Found: C, 39.22; H, 6.45; N, 15.56. MS of the free base (CI, NH_3): *m/z* 183 (M + NH_4^+, 100%).

1,3,5-Tris(aminomethyl)-2,4,6-trimethylbenzene trihydrochloride (5). Yield: 62%. Mp 108°C. ^{1}H NMR (500 MHz, CD_3OD): δ 2.56 (s, 9 H), 4.36 (s, 6 H). ^{13}C NMR (125 MHz, CD_3OD): δ 17.14, 38.90, 131.34, 141.29. MS of the free base (CI, NH_3): *m/z* 225 (M + NH_4^+, 100%). Anal. Calcd for $C_{12}H_{24}Cl_3N_3$: C, 45.74; H, 7.68; N, 13.34. Found: C, 45.46; H, 7.73; N, 13.45.

A chemical ionization mass spectrum showed a molecular ion peak for the 1:1 complex between **1** and trisamidine **7**. MS (CI, NH_3): *m/z* 792 (complex + NH_4^+, 2%). No additional peaks for higher aggregates were found.

Entropy calculations.

Following Whitesides's conformational entropy model,[2] we estimated the change in conformational entropy ΔS by adding the changes in entropy due to restricted torsions around individual bonds. If the binding enthalpy ΔH for the cyclic phosphonate/ammonium array was regarded as constant, the difference in free binding energies for trisammonium ions should, because of a varying number of flexible bonds, reflect their total difference in torsional entropy.

It is reasonable to assume that the benzylic (12 J mol^{-1} K^{-1}) as well as the C—P bonds (11 J mol^{-1} K^{-1}) contain more torsional entropy ΔS than the C—N bonds (7 J mol^{-1} K^{-1}).[2] These values have been applied to the trication/trisphosphonate complexation, and the resulting absolute sums were compared to the differences in total binding enthalpy ΔG calculated from the NMR titrations:

Since $\Delta G = -RT \ln K_a$ we note that

ΔG = –6.3 kcal mol^{-1} for tris(aminoethyl)amine **4**,

ΔG = –6.9 kcal mol^{-1} for mesitylenetriamine **5**, and

ΔG = –8.0 kcal mol^{-1} for cyclohexanetriamine **6**.

The difference in entropy between these complexes was calculated by adding entropy values for all those bonds that have to be restricted in motion for complexation. Thus, the difference in ΔG between tren **4** and cyclohexanetriamine **6** is calculated as [3 × C—N (7.0 J mol^{-1} K^{-1})] + [3 × C—C (7.5 J mol^{-1} K^{-1})] = 3.1 kcal mol^{-1} at 293 K. Compare to the experimental $\Delta\Delta G$ of 1.7 kcal mol^{-1} at 293 K.

The difference in ΔG between mesitylenetriamine **5** and cyclohexanetriamine **6** is calculated is [3 × C—$C_{benzylic}$ (12.0 J mol^{-1} K^{-1})] = 2.6 kcal mol^{-1} at 293 K. Compare to the experimental $\Delta\Delta G$ of 1.1 kcal mol^{-1} at 293 K.

The difference in ΔG between tren **4** and mesitylenetriamine **5** is calculated as [3 × C—N (7.0 J mol^{-1} K^{-1})] + [3 × C—C (7.5 J mol^{-1} K^{-1}) – [3 × C—$C_{benzylic}$ (12.0 J mol^{-1} K^{-1})] = 0.6 kcal mol^{-1} at 293 K. Compare to the experimental $\Delta\Delta G$ of 0.5 kcal mol^{-1} at 293 K.

Note that all the calculated $\Delta\Delta G$ values are higher than the corresponding experimental $\Delta\Delta G$ values. This may have two reasons: a) The exact entropy values for our trisammonium compounds may be smaller than those taken from simple model compounds or b) cooperative effects probably make the entropic cost for freezing the torsion around the second bond smaller than for the first bond. However, a good qualitative correlation is found between theory and experiment concerning the relative amount of torsional entropy in different C—C and C—N bonds. Because of the large torsional entropy content of benzylic C—C bonds, the drop in experimental $\Delta\Delta G$ from the rigid cyclohexanetriamine **6** to mesitylenetriamine **5** is much more dramatic (1.1 kcal mol^{-1}) than that from mesitylenetriamine to the highly flexible tren **4 (**0.6 kcal mol^{-1}). This goes for both, calculated and experimental $\Delta\Delta G$ values!

[2] (a) Mammen, M.; Shakhnovich, E. I.; Whitesides, G. M. *J. Org. Chem*. **1998**, *63*, 3168–3175. (b) Mammen, M.; Shakhnovich, E. I.; Deutch, J. M.; Whitesides, G. M. *J. Org. Chem*. **1998**, *63*, 3821–3830.

Computational methods

The program INSIGHT II,[3b] version 98.0, was used for model building procedures and as graphical interface. Force field parameters were taken from the INSIGHT residue library. The "ion pair" has been surrounded by a layer of distinct solvent molecules (H_2O, 5 Å). Energy minimizations were carried out with the DISCOVER simulation package implemented in INSIGHT II, using the *cff91* force field without cross and Morse terms on a Silicon Graphics, Indigo 2 workstation. The energy minimizations were conducted with over 5000 iterations using the VA09A algorithm,[3a] a variant of an iterative Newton-Raphson method.

^{1}H NMR Titrations.

Ten NMR tubes were filled each with 0.8 mL of a solution of the guest compound (c_{guest} = 0.5–4 mM) in a deuterated solvent (methanol-d_4, or D_2O). The host compound (1.525 equiv corresponding to the guest) is dissolved in 0.61 mL of the same solvent, and the resulting solution is added with increasing volumes from 0 to 5 equiv to the guest solution in ten NMR tubes.

Owing to its strong hygroscopicity, the tetrabutylammonium phosphonate solution contained appox. 0.3–0.6 % of water. Volume and concentration changes were taken into account during analysis. The association constants were calculated by non-linear regression methods.[4]

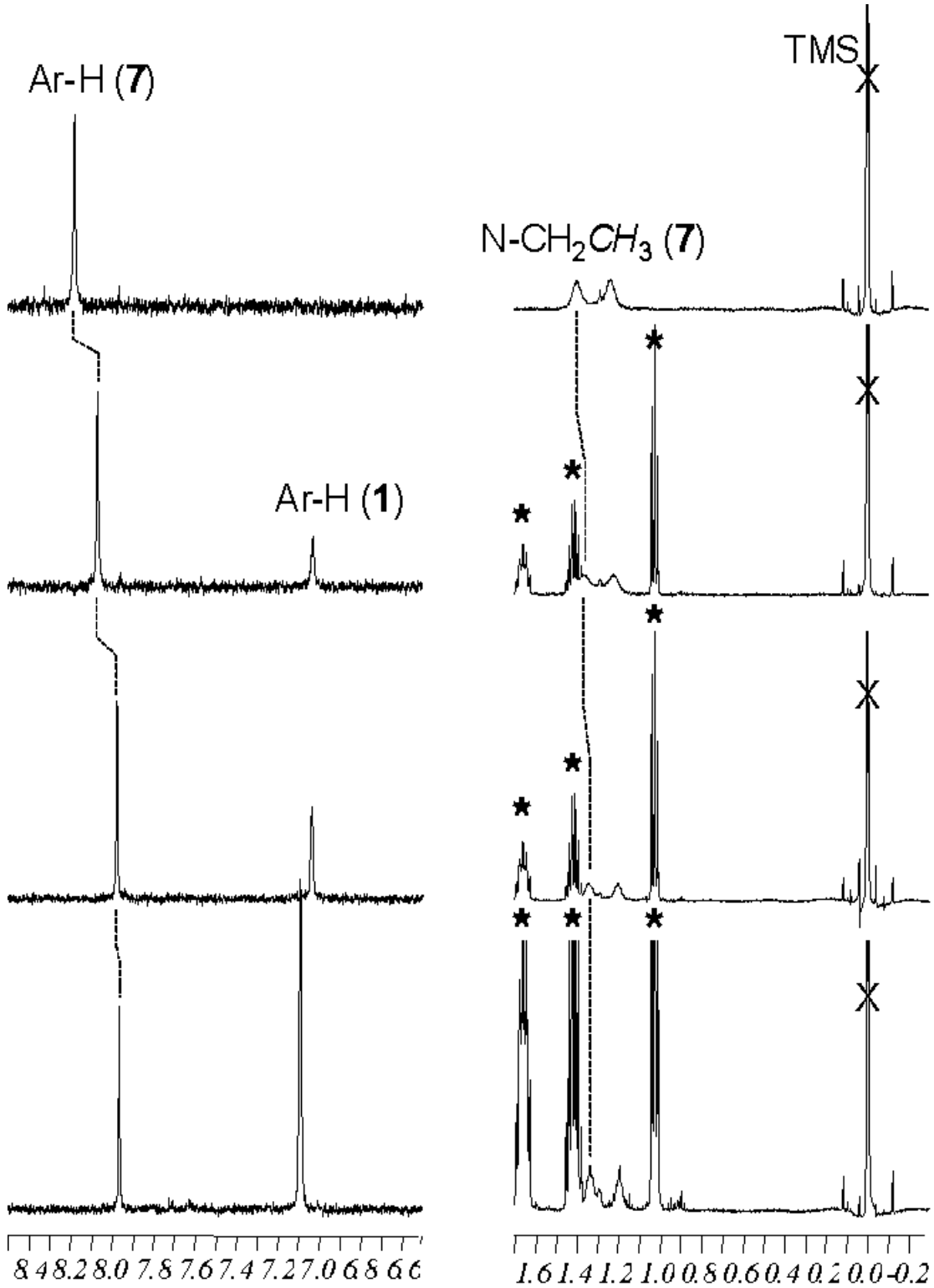
Job plots. Equimolar solutions (10 mmol/10 mL, approx. 10 μM) of trication and trisphosphonate were prepared and mixed in various amounts. ^{1}H NMR spectra of the mixtures were recorded, and the chemical shifts were analysed by Job's method[5a] modified for NMR results.[5b]

[3] (a) Mackay, D. H.; Cross, A. J.; Hagler, A. T. in *Prediction of Protein Structure and the Principles of Protein Conformation*; Fasman, G. D., Ed.; Plenum Press: New York, **1989**; pp. 317–358. (b) INSIGHT II, Version 98.0, 1999, MSI, San Diego.

[4] (a) Schneider, H. J.; Kramer, R.; Simova, S.; Schneider, U. *J. Am. Chem. Soc.* **1988**, *110*, 6442. (b) Wilcox, C. S. in *Frontiers in Supramolecular Chemistry and Photochemistry*; Schneider, H.-J., Dürr, H., Eds.; VCH: Weinheim, **1991**; pp. 123–143. c) Macomber, R. S. *J. Chem. Educ.* **1992**, *69*, 375–378.

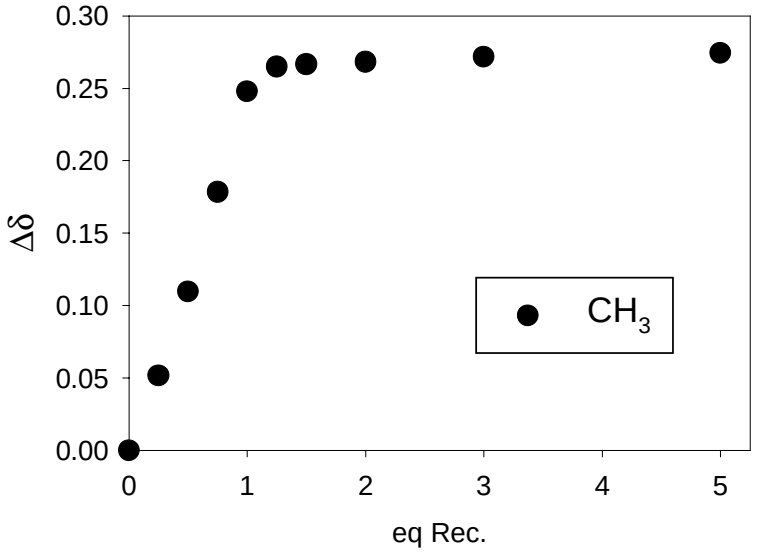
[5] (a) Job, P. *Ann. Chim.* **1928**, *9*, 113–203. (b) Blanda, M. T.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1989**, *54*, 4626–4636.

NMR-Titration curve of **1** with **7** (from top to bottom: 0, 0.5, 1.0 and 2.0 equivalents of **1** added). Various tetrabutylammonium signals are marked by an asterisk.

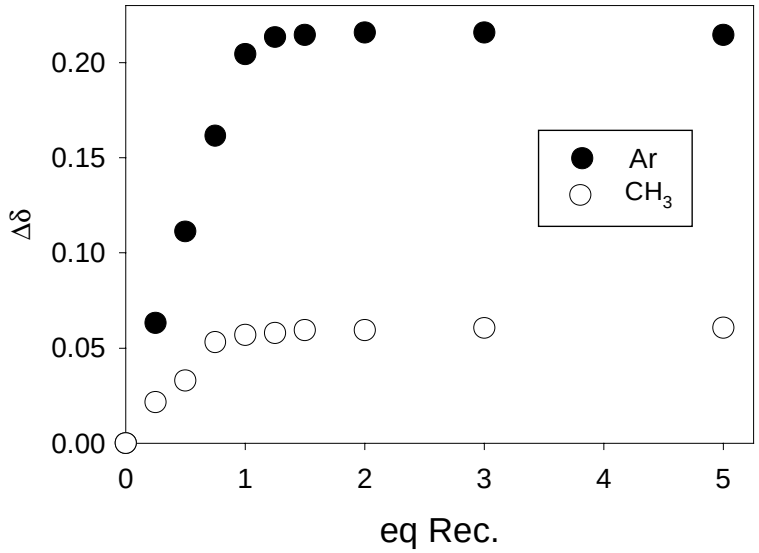


NMR titration curves and results from nonlinear regressions for the formation of various complexes between trisphosphonate receptor 1 and tricationic compounds in methanol-d_4 ($\Delta\delta = \delta_0 - \delta_{observed}$; the signals of the tricationic compound were followed):

1,3,5-Tris(aminomethyl)benzene trihydrochloride (K_a 75000 M^{-1})

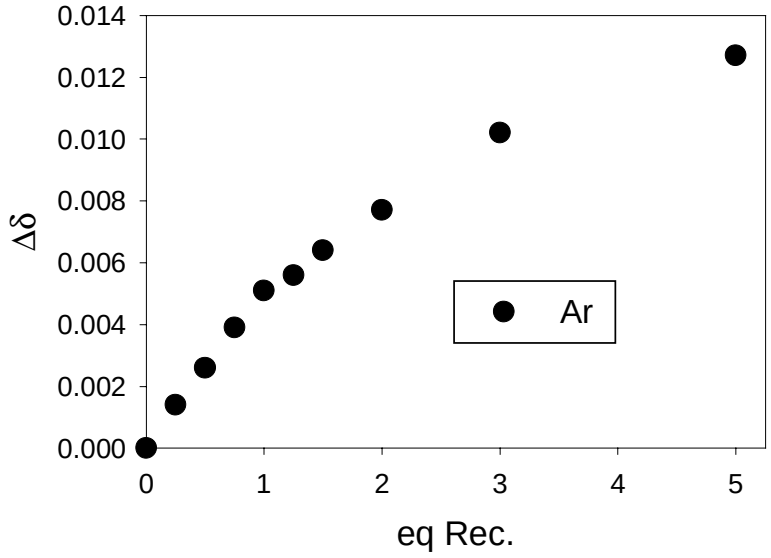


1,3,5-Tris(*N*,*N*'-diethylamidoyl)benzene trihydrochloride (K_a 1100000 M^{-1})

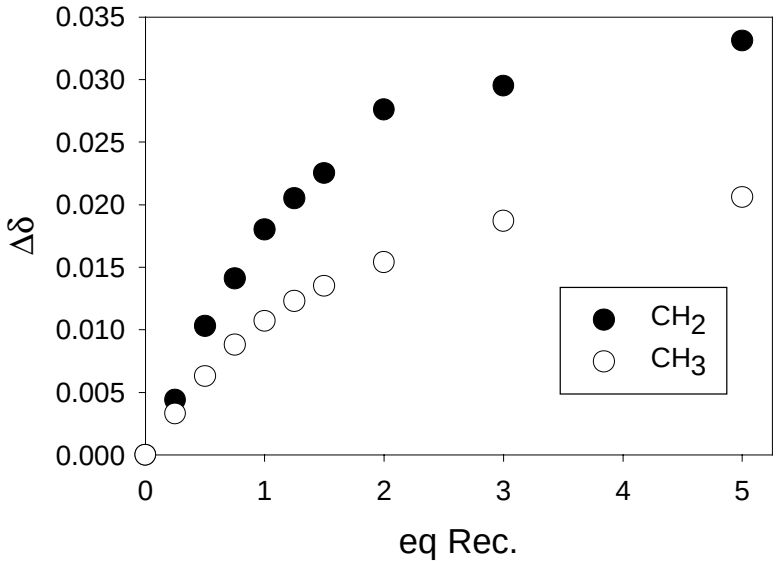


NMR titration curves and results from nonlinear regressions for formation of various complexes between trisphosphonate receptor 1 and tricationic compounds in deuterium oxide ($\Delta\delta = \delta_0 - \delta_{observed}$; the signals of the tricationic compound were followed):

1,3,5-Tris(*N*,*N*'-diethylamidoyl)benzene trihydrochloride (K_a 1100 M^{-1})

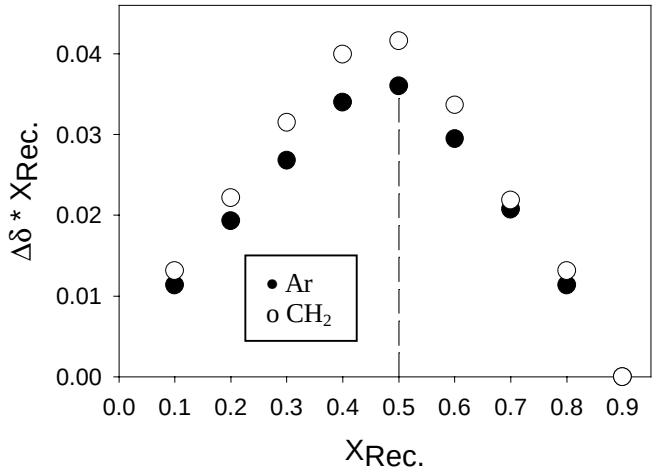


1,3,5-Tris(aminomethyl)benzene trihydrochloride (K_a 2600 M^{-1})

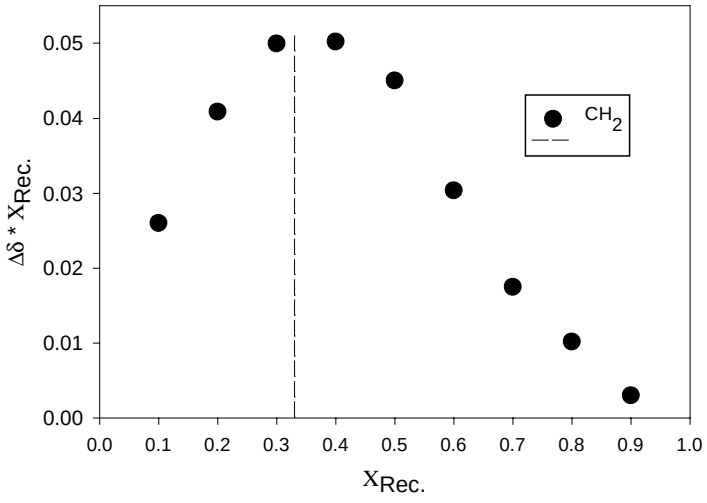


Job plots for formation of various complexes between trisphosphonate 1 and tricationic compounds in methanol-d_4:

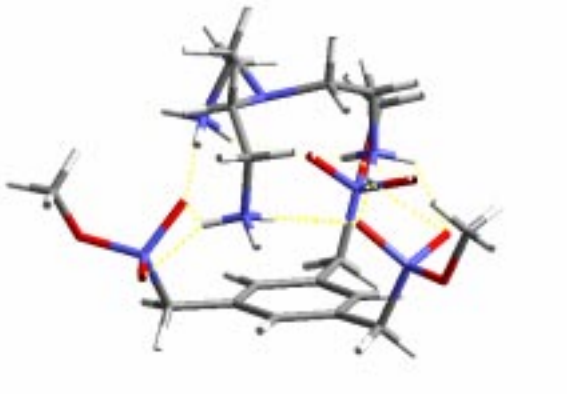
1,3,5-Tris(*N*,*N*'-diethylamidoyl)benzene trihydrochloride



1,4,7,10,13,16-Hexaaza-18-crown-6 hexahydrochloride

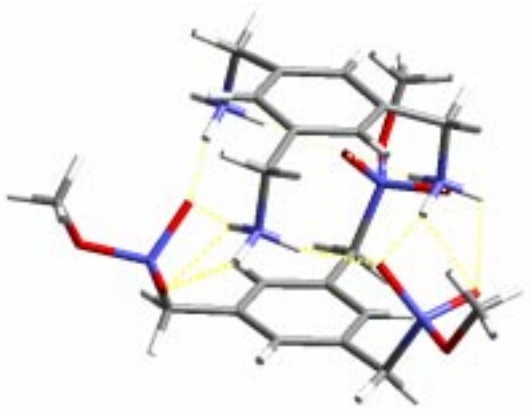


Complex geometries for selected complexes according to force-field calculations (Cerius2™, Dreiding 2.21 force field, Molecular Simulations):

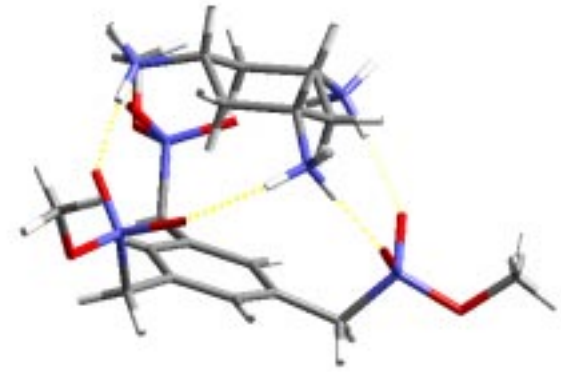


Tris(aminoethyl)amine trihydrochloride **4** with **1**

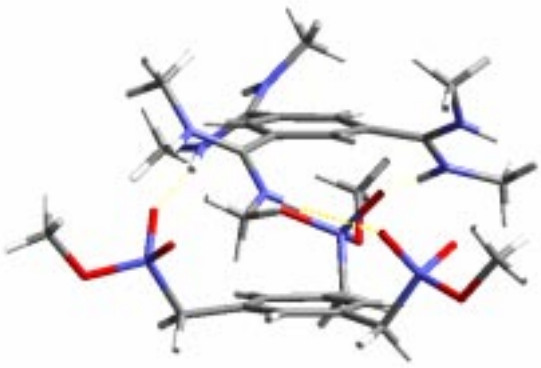
1,3,5-Tris(aminomethyl)-2,4,6-trimethyl-benzene trihydrochloride **2** with **1**



1,3,5-Tris(aminomethyl)benzene trihydrochloride **5** with **1**



cis,*cis*-1,3,5-Triaminocyclohexane trihydrobromide **6** with **1**



E,*Z*-1,3,5-Tris(*N*,*N*'-diethylamidoyl)benzene trihydrochloride **7** with **1**