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ORIGINAL ARTICLE

Multiple anion binding by a zinc-containing tetratopic cyclen-resorcinarene

Jing Wang · John D. Lamb · Lee D. Hansen · Roger G. Harrison

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Abstract The synthesis and binding properties of a new tetratopic anion receptor are reported. The resorcinarene ligand bearing four cyclen moieties is able to bind four Zn^{2+} ions and subsequently bind anions. NMR titrations show proton shifts during the binding of the first one or two anions. Isothermal titration calorimetry (ITC) titrations show that two or more anions bind to one tetramer. The tetratopic receptor in methanol has high affinity for dihydrogen phosphate, acetate, and halide ions and weak affinity for nitrate and perchlorate.

Keywords Resorcinarene · Anion binding · Zinc cyclen

Introduction

Due to the importance of anion sensing or removal in environmental and biological systems, a wide variety of anion receptors have been synthesized in an effort to bind anions strongly and/or selectively. Neutral anion receptors typically include urea [1], thiourea [2], or amide [3] functional groups and interact with the anion mainly through hydrogen bonding. Protonated ligands may also act as effective anion binders [4]. We found that a resorcinarene bearing four protonated 2,2′-dipicolylamine moieties on its upper rim binds strongly to anions of different geometries [5]. Also, the diprotonated octamethyl-octaundecylcyclo[8]pyrrole can extract sulfate anion in the presence of excess nitrate from aqueous media into a toluene organic phase [6].

Anion receptors that incorporate metal cations are also of interest [7–9]. Incorporating metal cations into anion binding receptors has several advantages. A bound cation can preorganize the receptor to improve anion selectivity, metal cations can be multiply charged and thus bind anions through strong electrostatic interactions, and anions may coordinate to transition metal cations via metal *d*-orbitals. Several metal containing receptors that bind anions but not by coordination to the metal ion have recently been reported [10–15]. For example, pyrrole-substituted bipyridine complexed with coordinatively saturated transition metals such as ruthenium and rhodium is a very selective anion receptor for dihydrogen phosphate [16]. Organometallic anion receptors containing ferrocene or cobaltocenium units with redox-active and photoactive properties are anion sensors [17, 18]. Few examples of metal containing receptors that bind anions to the metal ion have been reported. Two such anion receptors have metals bound in nitrogen containing heterocycles and bind phosphates and acetate strongly by coordination to the bound cation [19–21]. Another receptor contains two Zn^{2+} ions that cooperate to bind anions [22–24].

Zinc is an attractive candidate for incorporation into metal-ion-containing anion receptors because of its importance in biological systems, limited toxicity, and strong ligand binding [25, 26]. Zinc cations have a strong affinity for heterocycles such as 1,4,7,10-tetraazacyclododecane (cyclen) with a binding constant (log *K*) as high as 16.2 in saline solution [27]. Dicyclen-Zn^{2+} and triscyclen-Zn^{2+} complexes bind phosphate dianions in aqueous solution [28], but the affinity of common anions for alcohol-pendant cyclen-Zn^{2+} complexes is low [29].

Electronic supplementary material The online version of this article (doi:10.1007/s10847-009-9672-0) contains supplementary material, which is available to authorized users.

J. Wang · J. D. Lamb · L. D. Hansen · R. G. Harrison (✉)
Department of Chemistry and Biochemistry, Brigham Young University, Provo, UT 84602-5700, USA
e-mail: roger_harrison@byu.edu

To achieve better anion recognition, macrocyclic multitopic ligands that bind more than one ion have been developed [30, 31]. Several anion receptor units have been introduced into a rigid scaffold such as calixarene or resorcinarene [32, 33]. The incorporation of four amidourea units into the lower rim of a calix[4]arene forms a colorimetric anion sensor that binds two acetate anions [32]. Another set of anion receptors has one or two cyclens bound to a calix[4]arene, and after Zn^{2+} coordination, bind anions weakly [34].

This paper reports a new anion receptor with four metal sites on one face that are available for anion binding. The synthesis and coordination to Zn^{2+} of a resorcinarene bearing four cyclen moieties (**1**) is presented (Scheme 1). The zinc complex has a high affinity for anions.

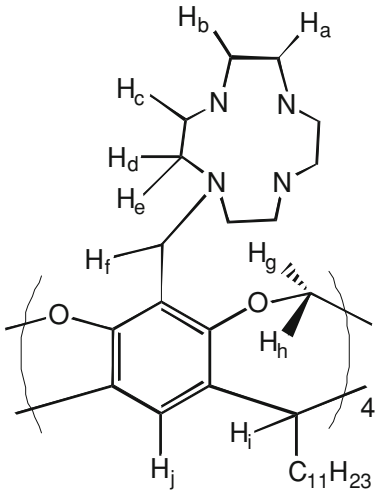


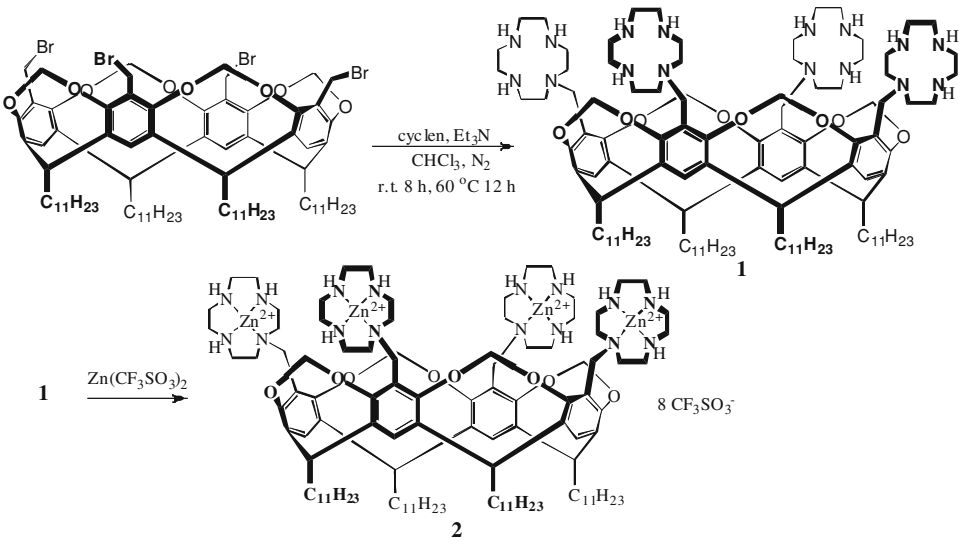
Fig. 1 Proton labels on **1**

Results and discussion

A resorcinarene molecule with four attachment points on one face was chosen as a template molecule. Four cyclen heterocycles were bound to the resorcinarene (Scheme 1). Zinc cations were coordinated to the cyclen units to form a tetratopic cationic receptor (**2**) with four zinc cations on one face. Due to their distance from each other, two cyclen units cannot bind the same zinc cation, but flexible bonds could allow the zinc complexes to come into proximity to one another and bind an anion.

Upon complexation with four Zn^{2+} ions to form **2** (see Experimental) the proton NMR signals on **1** shifted downfield, except for the methylene etheric hydrogen (H_g) that points into the cavitand (Fig. 1). The downfield shifts are attributed to the electron-withdrawing effect of Zn^{2+} on the ligand. The maximum downfield shift (0.44 ppm) was observed from the hydrogens H_f on the benzylic carbon that connects the resorcinarene and the cyclen units.

The binding affinity of **2** for anions was measured by ^1H NMR titration in methanol-d_4 and by isothermal titration calorimetry (ITC) in methanol. In the NMR titrations, the concentration of **2** was constant while the ratio of anion to receptor was increased from 0 to 10. The addition of tetrabutylammonium acetate to the solution of **2** resulted in upfield NMR chemical shifts for most protons, except for the methylene proton H_f (Fig. 2, SM1). During the titration, the methylene proton H_h pointing out of the cavity displayed a significant upfield shift, which indicates interaction between this proton and the anion, potentially through C–H hydrogen bonding [35, 36]. This result demonstrates that the resorcinarene moiety may not only provide a platform for the cyclen groups, but also provide



Scheme 1 Synthesis of cyclen resorcinarene **1** and cyclen resorcinarene-Zn^{2+} complex **2**

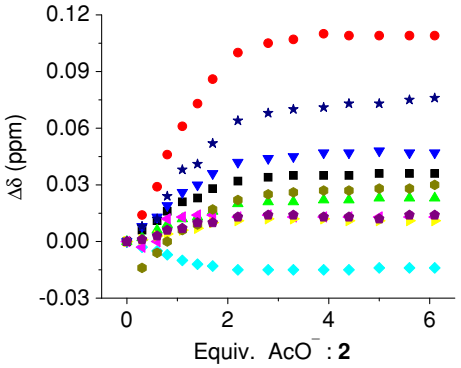


Fig. 2 NMR titration curves of **2** (4.4 mM) with tetrabutylammonium acetate in methanol-d_4 at 298 K. The symbols correspond to different hydrogens on **2**. Hydrogen key: H_h (●), H_a (★), H_g (▼), H_j (■), H_b (*), H_i (▲), H_d (◀), H_e (*), H_c (▶), H_f (◆)

extra interaction sites with the anion. Proton H_f on the carbon that connects the cyclen to resorcinarene moved downfield, which suggests that the chemical environment for this proton is different from the others.

Figure 3 shows the NMR titration curves for all anions using the $\Delta\delta$ values for proton H_h. The NMR titration curves in Fig. 3 indicate the effects of anion binding on proton shifts in **2** were reached at one, two, or three equivalents of anion depending on the anion. This implies that conformational changes to **2** have stopped at around two equivalents of anion. Most of the titration curves have little or no curvature up to the maximum $\Delta\delta$ and thus anion binding is strong. Due to the strong binding, binding constants for most of the anions were too large to be accurately calculated from the NMR titration data [37]. Also, the complex binding stoichiometries beyond 1:1 prohibit calculating reliable binding constants from these data.

Incremental isothermal titration calorimetric (ITC) measurements were performed to obtain more definitive information on the stoichiometry and strength of anion binding. Anion titrations of **2** with I^-, Br^-, Cl^-, F^-, $H_2PO_4^-$ and AcO^- give a near constant heat per injection up to near 1:1 stoichiometry, followed by a longer region of near constant heat per injection up to 1:3 stoichiometry, then slowly approach zero heat per injection (SM2). These results are seen in Fig. 4 where the total heat to any point in the titration is plotted versus the mole ratio.

In Fig. 4, linear regions are seen between moler ratios 0–0.5 and 1.2–3. This linearity shows that the reactions corresponding to these regions are quantitative. The first region corresponds to 1:1 stoichiometry and the second to 1:2 and 1:3. For a quantitative reaction, ΔH is equal to the slope (i.e. ΔmJ/$\Delta\mu$mol) and a lower limit on the value of K can be determined from well-established relations that assume 95% reaction completion [38]. Because the reactions are quantitative in these portions of the titration curve, only lower limits for binding constants can be established. Assessing the reactions at the equivalence points to be more than 95% complete, the first binding constants for I^-, Br^-, Cl^-, F^-, $H_2PO_4^-$, and AcO^- are all $>10^6$ [39].[1] The very short rounded end point region at 1:1 stoichiometric position on the curves indicates the binding constants for the 1:1 reaction and subsequent reactions, i.e. 1:2 and 1:3, are of similar magnitude.

The second linear region in Fig. 4 goes through the 2:1 and 3:1 stoichiometries. This has two possible causes: the ΔH values for binding the 2nd and 3rd chloride ions are nearly identical or K_3 is greater than K_2 and therefore K_3 dominates in producing the measured heats. If $K_3 > K_2$, no significant concentration of the 1:2 complex exists and thus the reaction $Cl^- + Cl^-$-**2** $= Cl_2^-$-**2** makes no significant contribution to the total heat. In this case ΔH can only be determined for the reaction $2Cl^- + Cl^-$-**2** $= Cl_3^-$-**2**. Indeed, the NMR data support the scenario in which $K_3 > K_2$. Specifically, the NMR data show that binding the second anion causes conformational changes, but no conformational change, occurs on binding the third anion to **2**. Thus with the conformational changes that occur, it is not likely that ΔH_2 is equal to ΔH_3. ITC data for the other strongly bound anions show the same trends as the data for Cl^- and therefore have also been analyzed with the assumption that $K_3 > K_2$ (Table 1). These data show that for halides and AcO^- two or three anions are tightly bound to the receptor and at least one more anion is more loosely associated, as seen by the curvatures in the heat plots beyond three equivalents of anion (Fig. 4). In the case of $H_2PO_4^-$, four anions are tightly bound and at least one more is loosely bound.

The differences between ITC and NMR results could be a consequence of the different effects the two techniques measure, as others have noted [40]. The NMR chemical shifts stop changing at around two equivalents of anion, while heat changes occur beyond the addition of four anions as seen by ITC data. The protons apparently do not experience further differences in the chemical environments after two equivalents of anion are bound even though heat changes continue to occur. This result illustrates the value of complementary NMR titration data with ITC.

While only lower limits on most K's could be calculated, it was possible to accurately assign ΔH's for the same reactions. For the halides and AcO^- enthalpies of binding for the first three anions (first four for $H_2PO_4^-$), were calculated in two ways: from the slopes of the linear

[1] Note that the 1:1 end point indicated by the intersection of the lines from extrapolating the linear portions is slightly less than 1 for all the strongly bound anions. This indicates the concentration of **2** was $\approx$9% less than that calculated from the mass, but does not appreciably affect the following calculations.

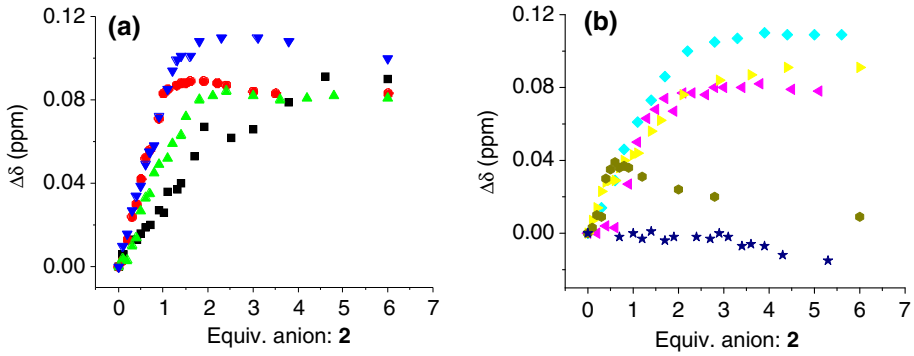


Fig. 3 NMR titration curves of **2** (4.4 mM, proton H_h) and tetrabutylammonium salts in methanol-d_4 at 298 K for proton H_h. Titrations were performed with (a) halides and (b) oxoanions. The symbols represent different anions: F^- (■), Cl^- (●), Br^- (▲), I^- (▼), AcO^- (◆), $H_2PO_4^-$ (◀), NO_3^- (▶), HSO_4^- (*) and ClO_4^- (★)

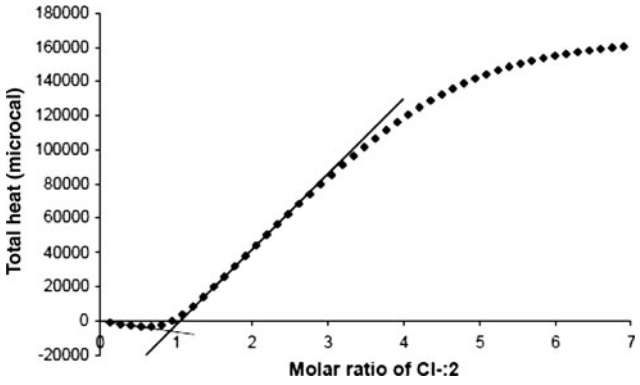


Fig. 4 Plot of total heat as a function of the Cl^-:**2** molar ratio. The lines show the linearity of the data from 0 to 0.5 and 1.2 to 3

portions of plots of total heat as a function of the mole ratio of anion to host and from the average of the heat per injection from the same region of the curve. The ΔH values were identical from both calculations. Heats of binding are given in Table 1. Enthalpy changes and binding constants for binding the 4th anion (5th in the case of $H_2PO_4^-$) could be obtained from Scatchard plots, i.e. plots of Q_{total}^{-1} versus $[\text{anion}]^{-1}$ due to sufficient curvature in the data (SM3) [38]. The K values calculated using the Scatchard plots can be compared to each other, but are not specific for K_4 (K_5 for $H_2PO_4^-$) because the slow curvature in the data beyond three equivalents does not indicate which equivalent of anion is binding. According to the double reciprocal form of the Scatchard equation: $Q_{\text{total}}^{-1} = \Delta H^{-1} + (K/\Delta H)[\text{anion}]^{-1}$, ΔH is equal to the reciprocal of the intercept and the slope is equal to $K/\Delta H$. In these plots, the free anion concentration, [anion], was approximated using the total anion concentration. The linearity of the plots demonstrated this was a valid approximation. The NO_3^- and ClO_4^- anions show weaker binding and binding constants and enthalpy changes were obtained by fitting the data to a two sites model [41].

Most of the 1:1 heats of reaction are exothermic, whereas the heats for subsequent reactions are endothermic. An endothermic heat of desolvation explains the endothermic heats. The entropies of binding must be favorable and dominant for the second, third, and forth binding steps. The more basic dihydrogenphosphate, acetate, and halides bind more tightly than the weakly basic nitrate and perchlorate.

Table 1 Binding constants and enthalpies for the interaction of anions with **2** in dry methanol at 25 °C by ITC

Anion	log K_1	ΔH_1 (kJ/mol)	log K_2K_3	Average of ΔH_2 and ΔH_3 (kJ/mol)	log K_4	ΔH_4 (kJ/mol)
I^-	>6	−120	>9	+150	4.0	+94
Br^-	>6	−14	>9	+120	3.5	+25
Cl^-	>6	−41	>9	+280	3.4	+63
F^-	>6	+200	>9	+240	4.1	+156
$H_2PO_4^-$	>6	−38	>9[a]	+330[b]	3.3(K_5)	+38(ΔH_5)
AcO^-	>6	+39	>9	+305	3.7	+79
ClO_4^-	3.74	−1.1	3.45(K_2)	−0.47(ΔH_2)		
NO_3^-	2.74	+6.7	2.1(K_2)	+37(ΔH_2)		

Tetra(*n*-butyl)ammonium salt solutions (50 mM for NO_3^- and ClO_4^-, and 23 mM for the other anions.) were incrementally titrated (50 additions of 4 μL) into a methanol solution of **2** (1.0 mM for NO_3^- and ClO_4^-, and 0.50 mM for the other anions). K_1 = [**2**-anion]/([**2**][anion]); K_2K_3 = [**2**-anion$_3$]/([**2**-anion][anion]^2); K_4 = [**2**-anion$_4$]/([**2**-anion$_3$][anion])

[a] log $K_2K_3K_4$

[b] Average of ΔH_2, ΔH_3 and ΔH_4

Conclusions

A new molecule with four cyclen moieties bonded to a resorcinarene scaffold has been synthesized. When Zn^{2+} ions are bound to the cyclens, the resulting complex (**2**) in methanol strongly binds dihydrogen phosphate, acetate, and halides and weakly binds NO_3^- and ClO_4^-. Exothermic and endothermic heats are associated with anion binding. Bonding four Zn^{2+}-cyclen molecules to a rigid resorcinarene platform, preorganizes the cationic sites and yields a design for a strong anion receptor.

Experimental

General

The bromoresorcinarene starting material (Scheme 1) was synthesized as previously published [42]. Other chemicals were purchased from commercial providers and used as received. A 500 MHz Varian NMR was used for ^{1}H and ^{13}C NMR characterization. An Agilent ESI-TOF mass spectrometer was used for mass spectra determination.

Cyclenresorcinarene (**1**)

Triethylamine (161 mg, 1.59 mmol) in 5 mL of dry chloroform was added dropwise under nitrogen to a solution of cyclen (219 mg, 1.27 mmol) and bromoundecylbowl (242 mg, 0.159 mmol) in 5 mL of dry chloroform. The reaction mixture was stirred at room temperature for 8 h, and then at 60 °C for 12 h. After cooling down to room temperature, the reaction mixture was extracted twice with 10 mL of 1.0 M NaOH solution to remove the cyclen residue. The organic layer was then washed twice with 10 mL of deionized water. After evaporating the chloroform in vacuo, a brown solid was obtained (260 mg, yield 86.7%). ^{1}H-NMR (CD_3OD, 500 MHz) δ (ppm): 7.29 (s, 1H, ArH), 5.95 (d, $J = 7.0$ Hz, 1H, OCH_2), 4.74 (t, $J = 7.5$ Hz, 1H, CH), 4.25 (d, $J = 7.0$ Hz, 1H, OCH_2), 3.34 (s, 2H, CH_2), 2.88 (brs, 1H, NCH_2), 2.77 (brs, 4H, NCH_2), 2.68 (brs, 4H, NCH_2), 2.55 (brs, 5H, NCH_2), 2.28 (brs, 2H, NCH_2), 1.46 (s, 2H, CH_2), 1.32 (brs, 18H, C_9H_{18}), 0.92 (t, $J = 6.0$ Hz, 3H, CH_3). ^{13}C-NMR (CD_3Cl_3, 500 MHz): 154.5, 137.8, 123.5, 119.8, 99.4, 50.8, 47.8, 47.1, 46.3, 44.9, 37.0, 32.0, 29.8, 29.4, 27.9, 22.7, 14.1. ESI-MS (*m/z*): Calcd for $[C_{112}H_{192}N_{16}O_8{\cdot}2H]^{2+}$: 946.4; Found 946.7.

Cyclenresorcinarene-Zn^{2+}complex (**2**)

Compound **1** (20.0 mg, 0.0106 mmol) was dissolved in 0.5 mL of isopropanol and $Zn(CF_3SO_3)_2$ (15.4 mg, 0.0424 mmol) was added to the solution while stirring. After stirring for 0.5 hours and the precipitation of product, the supernatant was decanted and the solid was washed three times with isopropanol. After drying in vacuo, the yellow solid weighed 23.3 mg (yield 65.8%). ^{1}H-NMR (CD_3OD, 500 MHz) δ (ppm): 7.56 (s, 1H, ArH), 6.15 (s, 1H, OCH_2), 4.78 (d, $J = 7.5$ Hz, 1H, CH), 4.24 (d, $J = 5.5$ Hz, 1H, OCH_2), 3.78 (s, 2H, CH_2), 3.19 (brs, 2H, NCH_2), 2.93 (brs, 5H, NCH_2), 2.80 (brs, 5H, NCH_2), 2.58 (brs, 2H, NCH_2), 2.38 (brs, 2H, NCH_2), 1.46 (s, 2H, CH_2), 1.30 (brs, 18H, C_9H_{18}), 0.91 (t, $J = 6.5$ Hz, 3H, CH_3). ESI-MS (*m/z*): Calcd for $[C_{112}H_{192}O_8N_{16}Zn_4Cl_5]^{3+}$: 776.2; found 776.2. Anal. Calcd for $C_{120}H_{192}F_{24}N_{16}O_{32}S_8Zn_4$: C, 43.09; H, 5.79; N, 6.70. Found C, 44.83; H, 5.77; N, 6.85.

Isothermal titration calorimetry (ITC)

ITC experiments were performed with a Microcal MCS calorimeter (MicroCal Inc., Northhampton, MA, USA). The cell temperature was set at 25 °C, and the water jacket bath temperature was 20 °C. Both the salts and the ligand were dissolved in distilled dry methanol. Each tetrabutylammonium salt solution (50.0 mM for ClO_4^- and NO_3^-, 23.0 mM for all the other anions) in a 250-µl syringe was titrated into the solution **2** (1.0 mM for ClO_4^- and NO_3^-, 0.50 mM for all the other anions) loaded in the sample cell. A total of 50 × 4.0-µL injections were made, with 100 s of elapsed time between the injections. Blank experiments were carried out under the same conditions by injection of the salt solution into dry methanol. Blank heats were subtracted from the heats of binding. Titration runs were monitored by Microcal Observer 3.0. Data for the halides, $H_2PO_4^-$ and AcO^- were analyzed with Excel and data for NO_3^- and ClO_4^- were analyzed by Origin 4.1 (MicroCal Software Inc., Northampton, MA, USA). Equations for a multiple binding site model were used to fit the data for NO_3^- and ClO_4^- and are given in the Origin manual. Binding constant lower limits for the strongly bound anions were calculated using 95% reaction completion and the receptor concentration.

NMR titrations

$Zn(CF_3SO_3)_2$ (3.85 mg, 0.0106 mmol) was mixed with **1** (5.01 mg, 0.00265 mmol) and dissolved in 0.6 mL of CD_3OD to obtain a 4.42 mM solution of **2**. This solution was titrated with CD_3OD solutions of tetrabutylammonium salts (133 mM). The anion solution was added in small aliquots to the solution of **2** and the NMR spectrum was recorded after each addition.

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