JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

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Characterization of a Saturated and Flexible Aliphatic Polyol Anion Receptor

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Supporting Information

ABSTRACT: Nature employs flexible molecules to bind anions in a variety of physiologically important processes whereas supramolecular chemists have been designing rigid substrates that minimize or eliminate intramolecular hydrogen bond interactions to carry out anion recognition. Herein, the association of a flexible polyhydroxy alkane with chloride ion is described and the bound receptor is characterized by infrared and photoelectron spectroscopy in the gas phase, computations, and its binding constant as a function of temperature in acetonitrile.

Anion transport plays a vital role in many cellular processes,[1] and enzymes that bind chloride, nitrate, phosphate, sulfate, and oxyanions have been identified.[2−6] Multiple hydrogen bonds using both NH and OH donors are exploited for this purpose as illustrated for the Charcot−Leyden crystal (ClC) chloride channel, where Cl^- is coordinated to the hydroxyl groups of serine 107 and tyrosine 445 along with the backbone amides of isoleucine 356 and phenylalanine 357 (Figure 1).[2] To mimic this behavior, the cooperative action of hydrogen bond donors such as amides, ureas, thioureas, and pyrroles have been incorporated into rigid acyclic and macrocyclic structural frameworks.[7] Only limited examples of hydroxyl-based receptors, however, have been reported.[8] Davis and co-workers showed that cholic acid esters, a steroid with three OH groups, can weakly bind tridentate anions in nonpolar media.[8b] Smith and co-workers explored the relative binding abilities of catechol and resorcinol (i.e., 1,2-$(HO)_2C_6H_4$ and 1,3-$(HO)_2C_6H_4$, respectively) with halide anions.[8d] Siloxanes that are capable of forming multiple hydrogen bonds also have been explored in acetonitrile.[8f] Based upon these results and others, it is widely held that rigid receptors are needed to reduce the entropic penalty for anion complex formation and that intramolecular hydrogen bonding has a deleterious effect on binding.[8e,f,9] In this report, however, a flexible aliphatic alcohol with seven hydroxyl groups that does not meet either of these two criteria is found to bind to a chloride anion. The resulting association complex was characterized in the gas phase by infrared photodissociation (IRPD) and photoelectron spectroscopy (PES), complementary computations were carried out, and binding constants were measured in a polar solvent as a function of temperature. This work represents to the best of our knowledge the first report of a flexible acyclic alcohol that binds a chloride anion.

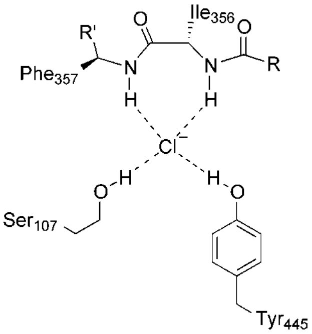

Figure 1. Schematic diagram of the Cl^- binding site of the ClC chloride ion channel.

Heptaol **1** $[(HOCH_2CH_2CH(OH)CH_2)_3COH]$[10] was found to readily form a 1:1 complex with a chloride anion upon its initial characterization by electrospray ionization (ESI) mass spectrometry. That is, an aqueous methanolic solution of **1** afforded an abundant $(M + Cl)^-$ anion ($\mathbf{1}\bullet Cl^-$) even though no chloride-containing salt was intentionally added. This suggests that **1** has a high chloride anion affinity, so we decided to characterize this complex in the gas phase via IRPD spectroscopy. This was done because this technique is well-suited for providing structural information about hydrogen bonded systems.

IRPD spectra were obtained with a Fourier transform mass spectrometer (FTMS) equipped with an optical parametric oscillator (OPO)/optical parametric amplifier (OPA) laser system that previously was described.[11] Our instrument currently has a useful operating range from 2700 to 4000 cm^{-1} over which the energy increases in a roughly linear fashion from 5 up to 26 mJ/pulse. Irradiation of $\mathbf{1}\bullet Cl^-$ from 2800 to 3800 cm^{-1} in 5 cm^{-1} steps led to its cleavage and the loss of HCl at select wavelengths. A plot of the amount of fragmentation vs wavelength revealed four broad bands at 2945, 3260, 3395, and 3540 cm^{-1} (Figure 2). The highest of these frequencies is smaller than the ~3660 cm^{-1} O−H stretch of a simple alcohol in the gas phase but is larger than the hydrogen-bond reduced value at ~3340 cm^{-1} in the liquid phase.[12] This enables us to assign this band to an OH stretch that is slightly weakened by a hydrogen bond, presumably due to an OH···OH

Received: July 31, 2012
Published: October 2, 2012

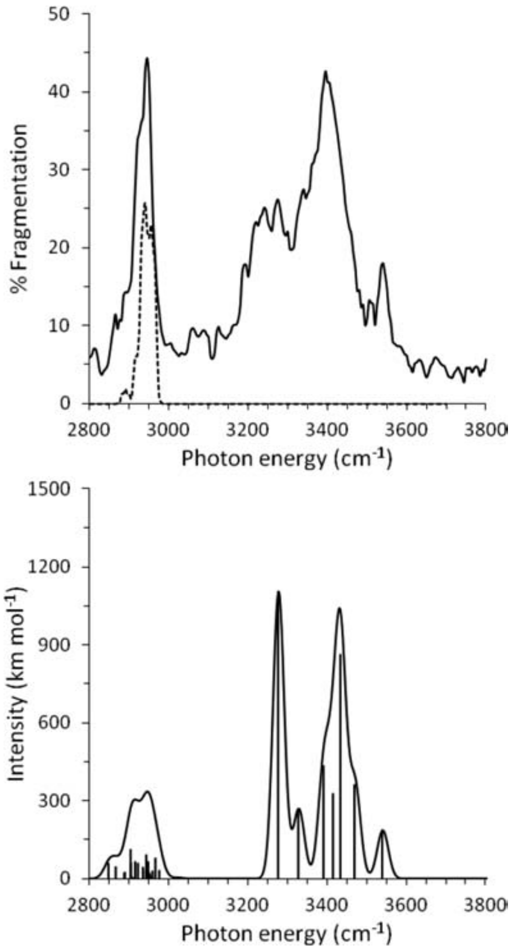

Figure 2. Experimenal IRPD spectrum of **1**•Cl$^-$ (solid line) and its d_7-ion (dotted line) [top], and the B3LYP/aug-cc-pVDZ calculated spectrum [bottom]. Computed frequencies were scaled by 0.964 at all wavelengths and are depicted by vertical lines. The simulated spectrum was obtained by using a Gaussian function with a peak width at half height of 35 cm^{-1}.

interaction. The middle two frequencies at 3260 and 3395 cm^{-1} also undoubtedly correspond to O−H stretches, but these values are reduced by stronger hydrogen bonds most likely as a result of OH···Cl$^-$ interactions. As for the lowest energy mode at 2945 cm^{-1}, it may be the result of an even weaker OH stretch or alternatively could arise from C−H vibrations. To resolve this issue, **1** was sprayed from CH_3OD and D_2O so that all seven hydroxyl hydrogens in **1**•Cl$^-$ were replaced by deuterium atoms. Given that isotopic substitution of a hydrogen by deuterium results in a reduction in the stretching frequency by a factor of ~1.41, all of the observed modes that are due to OH vibrations will move out of the experimentally accessible range and disappear from the spectrum. In accord with the above assignments, only the vibrational mode at 2945 cm^{-1} remained in the spectrum of **1-*d*$_7$**•Cl$^-$ (Figure 2), thereby indicating that this feature is the result of C−H stretching motions.

Two limiting structures can be envisioned for the proton bound cluster **1**•Cl$^-$ that differ in where a hydrogen atom is attached (i.e., ROH•Cl$^-$ vs RO$^-$•HCl). It was anticipated that the latter structure would be more stable since the tertiary hydroxyl group of **1** is predicted to be more acidic than HCl by ~14 kcal mol^{-1}.[13] The inherent preference for the tertiary alkoxide−HCl complex might be overcome by differential solvation, however, and it is difficult to account for the band at 3540 cm^{-1} in a C_3 symmetric RO$^-$•HCl structure. To probe this point further, B3LYP geometry optimizations were carried out with the aug-cc-pVDZ basis set (i.e., B3LYP/aug-cc-pVDZ) and M06-2X/maug-cc-pVT(+d)Z single point energies were computed.[14−17] The most stable structure that was located is a chloride anion−heptaol complex in which two primary and two secondary hydroxyl groups coordinate to the chloride anion via four hydrogen bonds in a distorted tetrahedral arrangement (Figure 3). Many other ROH•Cl$^-$ structures were located (see the Supporting Information), but the only tertiary alkoxide−HCl cluster that we found is 22.2 kcal mol^{-1} higher in energy and in it the HCl interacts with one of the primary OH groups rather than the charged alkoxide center.

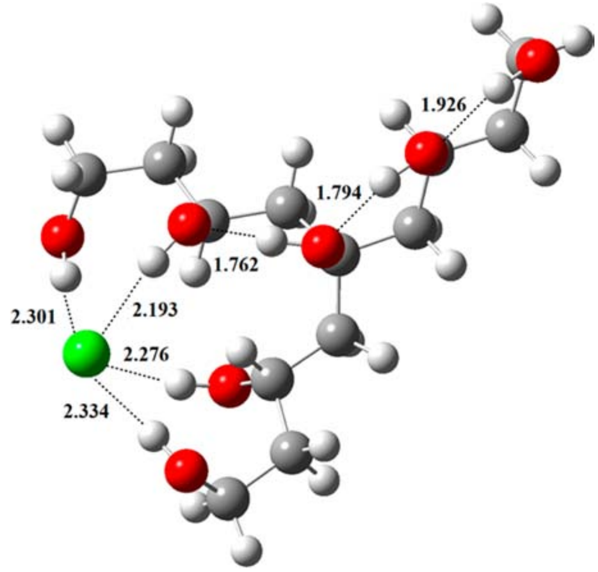

Figure 3. Lowest energy B3LYP/aug-cc-pVDZ structure for the addition complex of **1** and Cl$^-$.

The B3LYP IR spectrum was computed for **1**•Cl$^-$ (Figure 2). As can be seen, there is excellent accord between the predicted spectrum and the experimental results with the calculated bands (2949, 3265, 3434, and 3540 cm^{-1}) being within 4 to 39 cm^{-1} of the observed frequencies. The computed spectrum is also in accord with the band assignments that were deduced from the experimental data. That is, the calculated band at 2949 cm^{-1} corresponds to a combination of C−H stretching modes, the absorption at 3540 cm^{-1} is due to the O−H stretch of the primary (terminal) hydroxyl group that does not interact with the chloride anion, and the two frequencies at 3265 and 3434 cm^{-1} correspond to overlapping O−H combination bands interacting with Cl$^-$.

To assess the stability of **1**•Cl$^-$, its negative ion photoelectron spectra were recorded at 193 nm (6.424 eV, ArF laser) and 157 nm (7.867 eV, F_2 laser) at 20 K (Figure 4).[18] One high energy band is seen, and based upon a linear extrapolation of the rapidly rising onset region, an estimate for the adiabatic electron detachment energy (ADE) of 6.0 eV is obtained. An M06-2X/maug-cc-pVT(+d)Z//B3LYP/aug-cc-pVDZ computational prediction of 6.02 eV is in excellent accord with the experimental result and is in keeping with previous reports showing that the M06-2X functional in combination with a large (i.e., triple-ζ) basis set provides accurate ADEs;[10,16b,19] in

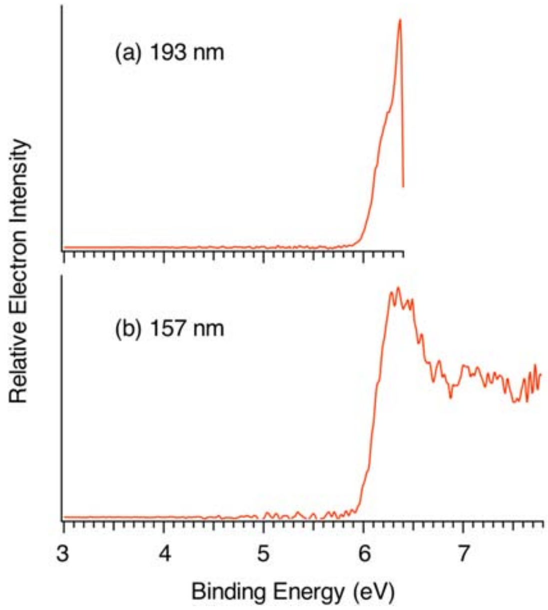

Figure 4. Low temperature (20 K) photoelectron spectra of **1**•Cl^- at 193 nm (6.424 eV) (a) and 157 nm (7.867 eV) (b).

contrast, B3LYP energies are sometimes too small by signficant amounts as is the case here (i.e., the B3LYP/aug-cc-pVDZ ADE is 5.33 eV which is too low by 0.67 eV).[20] Coordination of the chloride anion by **1** increases the electron binding energy relative to Cl^- (ADE = 3.6131 eV)[21] by 2.4 eV or 55 kcal mol^{-1}. This difference reflects the stabilization of the chloride anion by multiple hydrogen bonds. Given that the hydration of Cl^- leads to a similar stabilization (i.e., ADE($Cl^-(H_2O)_4$) − ADE(Cl^-) = 2.31 eV or 53.3 kcal mol^{-1}),[22] the experimental data suggest that **1** forms four hydrogen bonds to the chloride anion in their association complex.[23,24] Computations are in accord with this structural assignment (Figure 3) and indicate that the enthalpy for the fragmentation of **1**•Cl^- to its two separate constituents is endothermic by 48.8 kcal mol^{-1} at 298 K. Similarly, the complete dehydration of $Cl^-(H_2O)_4$ has been measured and requires 50.1 kcal mol^{-1}.[25]

Our results to this point suggest that **1** is a good receptor for the chloride ion in the gas phase and that it might be one in solution as well. This runs counter to the paradigm in the field of anionic molecular receptors since **1** is a flexible aliphatic alcohol and can form intramolecular hydrogen bonds. The association of **1** with Cl^- in acetonitrile, consequently, was examined by ^{1}H NMR spectroscopy.[26] Addition of increasing amounts of tetrabutylammonium chloride relative to **1** led to downfield shifts of all of the hydroxyl hydrogens due to complexation with the chloride anion, but only the resonance for the tertiary OH group was used to calculate the binding constant; the other hydroxyl signals are broader and overlap carbon−hydrogen resonances in some of the spectra. An *x*-reciprocal or Scatchard plot of the change in the chemical shift ($\Delta\delta$) divided by the chloride anion concentration versus $\Delta\delta$ affords a straight line (Figure 5, $\Delta\delta/[Cl^-] = -362.0 \times \Delta\delta + 246.4$, $r^2 = 0.998$) where the association constant is given by the negative of the slope (i.e., $-m$) and the maximum value for the change in the chemical shift ($\Delta\delta_{max}$) is given by the intercept divided by $-m$.[27] That is, $K = 362$ M^{-1} and $\Delta\delta_{max} = 0.68$ ppm at 22.0 °C. Alternatively, a nonlinear fit of the 1:1 binding isotherm gives the same result ($K = 359$ M^{-1} and $\Delta\delta_{max} = 0.68$ ppm, Supporting Information) but is sometimes considered to be more accurate.[28]

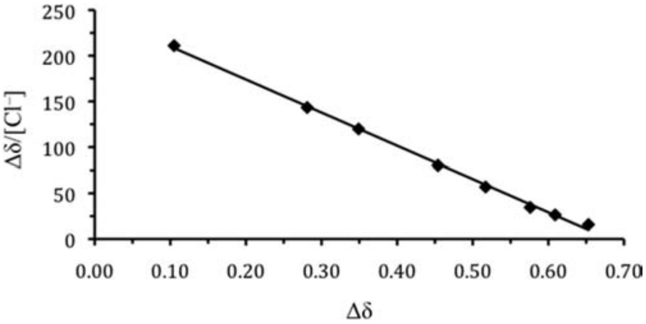

Figure 5. Scatchard *x*-reciprocal plot for the binding of **1** with chloride ion at 22.0 °C.

Similar data were obtained at −23.0 and 56.2 °C, and the nonlinear approach affords $K = 827$ and 199 M^{-1}, respectively. Since the largest equilibrium constant was found at the lowest temperature that we examined, and the smallest equilibrium constant was obtained at the highest temperature that we studied, either the entropy for association must be negative or the heat capacity ($\Delta C_p°$) has to have a negative value. A three point van't Hoff plot ($R \ln K = 2920/T + 1.71$, $r^2 = 0.997$) affords $\Delta H° = -2.9$ kcal mol^{-1} and $\Delta S° = 1.7$ cal mol^{-1} K^{-1} indicating that $\Delta S°$ is positive (favorable) and that $\Delta C_p°$ is negative. This is consistent with previous anion binding studies that found entropically favored associations, presumably because of the poorer solvation of the bound complex.[29] Moreover, Anslyn and others found that the heat capacity changes with temperature in some such processes and is large and negative (unfavorable) in polar solvents (i.e., −30 to −560 cal mol^{-1} K^{-1}).[29b] When the change in the heat capacity is accounted for in our data, then $\Delta H° = -3.1$ kcal mol^{-1}, $\Delta S° = 1.3$ cal mol^{-1} K^{-1}, and $\Delta C_p° = -10.3$ cal mol^{-1} K^{-1} are obtained. This suggests that the binding enthalpy is worth ∼1 kcal mol^{-1} per hydrogen bond to the chloride anion and that the flexibility of the substrate leads to a less negative heat capacity than previously reported.

Larger association constants presumably can be obtained in a less polar solvent by increasing the acidity of the primary and secondary hydroxyl groups or optimizing the cavity size of the substrate so that a less distorted tetrahedral arrangement of hydrogen bonds can form around the chloride anion. A flexible polyhydroxy alkane that is capable of forming intramolecular hydrogen bonds, nevertheless, was found to bind to Cl^-. Additional anion receptors based upon such species, consequently, are worth exploring.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental and computational details along with calculated structures and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Generous support from the National Science Foundation and the Minnesota Supercomputer Institute for Advanced Computational Research are gratefully acknowledged. The photoelectron spectra work was supported by the Division of Chemical Sciences, Geosciences, and Biosciences, Office of Basic Energy Sciences, U.S., Department of Energy (DOE), and was performed at EMSL, a national scientific user facility sponsored by DOE's Office of Biological and Environmental Research and located at Pacific Northwest National Laboratory, which is operated by Battelle for DOE.

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