

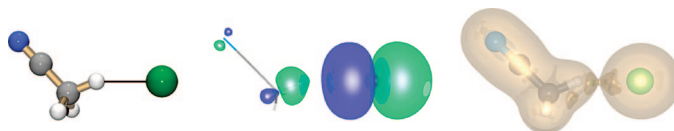
Aliphatic C–H···Anion Hydrogen Bonds: Weak Contacts or Strong Interactions?

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Electronic structure calculations, MP2/aug-cc-pVDZ, are used to determine C–H···Cl[−] hydrogen bond energies for a series of XCH₃ donor groups in which the electron-withdrawing ability of X is varied over a wide range of values. When attached to polarizing substituents, aliphatic CH groups are moderate-to-strong hydrogen bond donors, exhibiting interaction energies comparable to those obtained with O–H and N–H groups. The results explain why aliphatic C–H donors are observed to function as competitive binding sites in solution and suggest that such C–H···anion contacts should be considered as possible contributors when evaluating the denticity of an anion receptor.

Introduction

Over the past decade, anion complexation by synthetic host molecules has emerged as an important theme in supramolecular chemistry.¹ A key challenge is the a priori design of host structures that exhibit strong and selective anion binding. A variety of reversible binding interactions are being explored to address this challenge, such as hydrogen bonding, electrostatic interactions, and metal ion coordination. Understanding the structural and energetic aspects of individual binding interactions, one focus of our research,² provides a basis for the deliberate design of host architectures that are tailored for specific guests.

Among the various interactions under consideration, C–H···anion hydrogen bonds are drawing increasing attention. A recent

review of anion-arene adducts noted that aryl C–H···anion hydrogen bonding, rather than interaction with the π system, is by far the most prevalent motif observed in the solid state for the interaction of halides with arenes.³ Both theory and experiment have revealed that C–H hydrogen bonding between benzene and monovalent anions is significant in the gas phase, being roughly half the strength of conventional O–H and N–H hydrogen bonds.⁴ Subsequent theoretical analysis showed that aryl C–H···Cl[−] binding energies can be tuned from −8 to −16 kcal/mol on altering the ring substitution from NH₂ to NO₂.⁵ These observations suggest that the C–H donor groups in charge-neutral arenes are strong enough to be exploited effectively as anionophore binding sites.

Confirming the validity of this suggestion, two recent studies have demonstrated that halide receptors bearing only charge-neutral aryl C–H donor groups form anion complexes in solution. The structures of these receptors, **1** and **2**, are given in Figure 1. The preorganized and rigid macrocyclic architecture, **1**, binds Cl[−] with the remarkably high K_a value of 1.1×10^7 M^{−1} in CH₂Cl₂ solvent and exhibits a size-match selectivity for Cl[−] over the other halide anions ($K_a(\text{F}^-) = 2.8 \times 10^5$ M^{−1},

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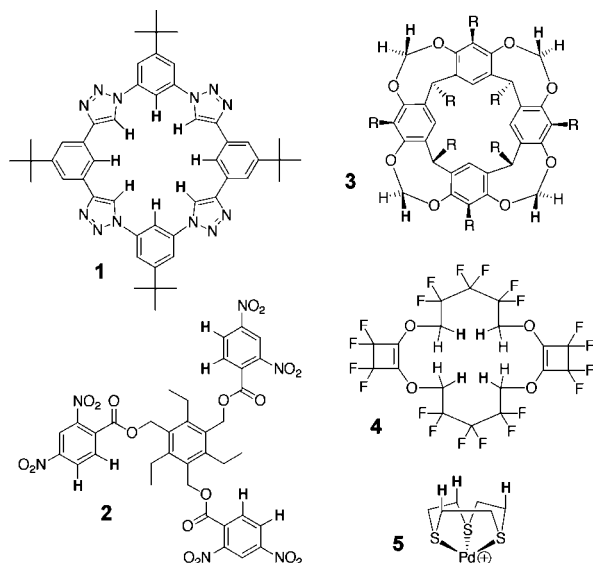


FIGURE 1. Anion receptors that interact solely via aryl C–H (**1** and **2**) or aliphatic C–H (**3**, **4**, and **5**) hydrogen bonding.

$K_a(\text{Br}^-) = 7.5 \times 10^6 \text{ M}^{-1}$, $K_a(\text{I}^-) = 1.7 \times 10^4 \text{ M}^{-1}$.⁶ The tripod architecture, **2**, forms relatively weak halide complexes in benzene solvent ($K_a(\text{Cl}^-) = 26 \text{ M}^{-1}$, $K_a(\text{Br}^-) = 18 \text{ M}^{-1}$, $K_a(\text{I}^-) = 11 \text{ M}^{-1}$).⁷ Consistent with these findings, it has been shown that the addition of an aryl C–H donor group in a strapped calixpyrrole serves to increase the binding affinity for Cl^- by 1 to 2 orders of magnitude over analogous structures lacking the additional donor group.⁸

If aryl C–H donors are effective anion binding groups, what about aliphatic C–H donors? The hydrogen atoms in nonpolar alkanes are considerably less acidic than those in arenes. This can be seen on comparison of gas-phase proton affinities for CH_3^- , -418 kcal/mol , versus C_6H_5^- , -401 kcal/mol .⁴ Thus, one might expect alkane hydrogen atoms to be much less effective as hydrogen bond donors. On the other hand, when electron-withdrawing groups are attached to the carbon atom, aliphatic C–H groups can become quite acidic, indicating that they should also form moderate to strong hydrogen bonds to anions. Numerous data exist to support this concept.

Beginning in the 1970s, high-pressure mass spectrometry experiments and ion cyclotron resonance spectroscopy repeatedly established that aliphatic C–H groups form significant interactions with monovalent anions in the gas phase.⁹ A recent example of such gas-phase aliphatic C–H···anion hydrogen bonding was reported for adducts of anions and a resorcinarene cavitand, **3** (Figure 1), which adopts a bowl-shaped cavity that provides up to four convergent C–H groups.¹⁰ Theoretical calculations on halide adducts with methane^{11–13} and halomethanes^{12–14} fully support the existence of aliphatic C–H···anion hydrogen bonds.

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In 1990, a highly fluorinated macrocycle, **4** (Figure 1), was shown to bind the F^- anion via four aliphatic C–H hydrogen bonds, both by X-ray crystallography and by ^{19}F NMR in THF solution, representing the first receptor shown to bind an anion solely via C–H contacts in solution.¹⁵ Other examples of synthetic host–guest complexes in solution that are stabilized by aliphatic C–H hydrogen bonding alone are limited to a [9]ane S_3 macrocycle bound to a Pd^+ cation, **5** (Figure 1), which binds I^- with a $K_a = 2.2 \times 10^3 \text{ M}^{-1}$ in CDCl_3 solvent.¹⁶ There have been numerous recent observations of C–H···anion contacts in crystal structures of anion receptors, but these observations provide little information on bond strength and without exception the interactions were assumed to be weak in nature.^{17,18} There appears to be a general consensus among supramolecular chemists that such nonclassical aliphatic C–H hydrogen bonds are much weaker than traditional O–H and N–H donors, to the point where recent experimental observations to the contrary are thought to represent unexpected and novel findings.^{10,16,17a}

Gas-phase binding energies provide a quantitative scale to assess the relative strengths of hydrogen bonding interactions in the absence of complicating effects present in condensed phases. In this paper we use electronic structure calculations to further probe the structural and energetic aspects of aliphatic C–H···anion hydrogen bonding. With Cl^- as a representative anion, binding energies are determined for a series of XCH_3 donor groups in which the electron-withdrawing ability of the substituent X is varied over a wide range of values. The results establish that aliphatic C–H··· Cl^- binding energies range in strength from -3.6 to -21.9 kcal/mol . Substitution with even moderately electron-withdrawing groups yields C–H donors that are comparable in strength to their aryl counterparts, confirming that the aliphatic C–H hydrogen bond is a viable interaction motif for anion host design.

Results and Discussion

Structure and Bonding in Known Gas-Phase Complexes. Initial calculations focused on several organic molecules known to bind Cl^- in the gas phase via C–H··· Cl^- contacts. These include $\text{CH}_n\text{Cl}_{4-n}$ ($n = 1-4$), CH_3F , and CH_3CN . After an exhaustive search for all potential minima, geometry optimizations yielded the seven stable geometries shown in Figure 2. With the exception of CH_3CN , there is one and only one structural minimum for each complex at this level of theory. Complexes in which Cl^- contacts a single C–H group are observed for CH_4 , CH_2Cl_2 , CHCl_3 , and CH_3CN . Complexes

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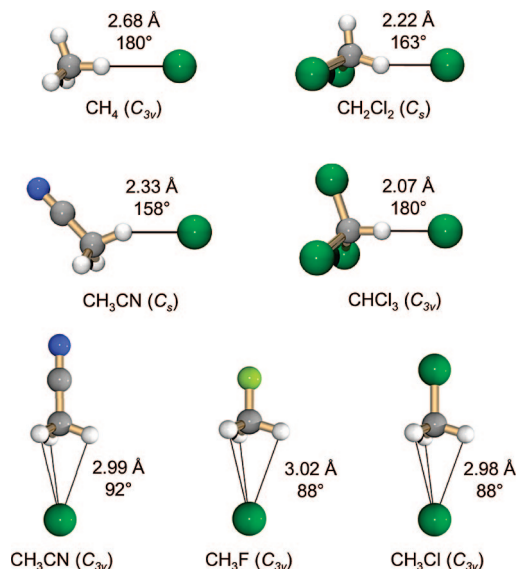


FIGURE 2. All stable geometries located at the MP2/aug-cc-pVDZ level of theory for Cl⁻ complexes with the C–H donor groups listed in Table 1. Calculated H···Cl⁻ distances, C–H···Cl⁻ angles, and point group are given for each geometry.

in which Cl⁻ contacts the face of a methyl group, where Cl⁻ is equidistant from all three C–H hydrogen atoms yielding a C_{3v} symmetric geometry, are observed for CH₃Cl, CH₃F, and CH₃CN (0.3 kcal/mol less stable than the single C–H contact geometry). These findings are fully consistent with prior electronic structure calculations concerning Cl⁻ complexes with CH₄ (MP2/6-31+G(d,p)),¹¹ and CH_nCl_{4-n} (B3LYP/6-31+G* and MP2/6-31+G(d,p)).^{12,13} However, an early theoretical study of the CH₃CN···Cl⁻ complex (HF/3-21G*) reported only the C_{3v} form as a minimum.¹⁹

These six molecules were selected because measured gas-phase Cl⁻ binding enthalpies were available, thus providing a basis for benchmarking the level of theory used in this study. Calculated ΔE and ΔH values are summarized in Table 1. The difference between these values reveals that adjustments for zero point energy and thermal energy (see Methods) are small, on the order of a few tenths of a kcal/mol. The results for the C–H donors show that the MP2/aug-cc-pVDZ method in all cases reproduces measured ΔH values within experimental uncertainty. The values range from a low of -3.8 kcal/mol for CH₄ to a high of -19.5 kcal/mol for CHCl₃. Within this series the value for CH₄ is low as the remaining complexes exhibit ΔH values ≥ -10 kcal/mol. Thus, the bulk of these organic molecules, which contact Cl⁻ via C–H interactions alone, exhibit Cl⁻ binding strengths that are comparable to those attained by conventional O–H and N–H hydrogen bonding; see Table 1.

As noted in prior studies of halomethane-halide adducts,^{12,13} the structures shown in Figure 2 represent two distinct types of interaction. The forms that involve contact with a single

TABLE 1. Comparison of Gas-Phase Binding Energetics (ΔE and ΔH in kcal/mol) for Cl⁻ Adducts with Neutral Molecules

	ΔE_{calc}	ΔH_{calc}	ΔH_{obs}
C–H donors			
CH ₄	-3.6	-3.3	-3.8 ± 0.2^{12}
CH ₃ F	-10.3	-10.0	-11.5 ± 2.0^{9c}
CH ₃ Cl	-11.5	-11.7	$-11.7 \pm 0.2,^{12} -12.2 \pm 2.0^{9c}$
CH ₃ CN	-14.7	-14.6	$-14.4 \pm 0.1,^{20} -15.8 \pm 1.0^{21}$
CH ₂ Cl ₂	-15.3	-15.1	$-14.8 \pm 0.2,^{12} -15.5 \pm 0.3^{9a}$
CHCl ₃	-19.6	-19.6	$-19.5 \pm 0.2,^{12} -19.1 \pm 0.7^{9a}$
O–H and N–H donors			
NH ₃	-9.0	-8.6	$-10.5 \pm 4.0,^{9c} -8.2 \pm 0.1^{22}$
H ₂ O	-15.0	-14.5	$-14.9 \pm 0.2,^{23} -14.7 \pm 0.6^{23}$
CH ₃ OH	-16.6	-16.4	$-17.5 \pm 0.3,^{24} -17.1 \pm 0.1^{25}$
C ₄ H ₄ NH	-22.9	-23.0	-18.8 ± 2.0^{9c}

hydrogen atom are examples of C–H···Cl⁻ hydrogen bonding interactions, whereas the forms that involve contact with the face of a methyl group are examples of ion dipole interactions. The defining characteristics of these two interaction motifs are summarized below.

The C–H···Cl⁻ hydrogen bonds in the four complexes with single hydrogen contacts exhibit the same behavior as hydrogen bonds with conventional O–H and N–H donors. The C–H···Cl⁻ angles are near linear, ranging from 158° to 180° (Figure 2). The H···Cl⁻ distances, which range from 2.68 Å with CH₄ to 2.07 Å with CHCl₃, decrease in length as the interaction strength increases (Figure 2, Table 1). These trends track the increase in acidity of the C–H donor group. The interactions have a covalent contribution characterized by electron donation from a p orbital on Cl⁻ into the σ^* orbital of the C–H donor group, resulting in elongation of the C–H bond and a red shift of the C–H stretching frequency.^{13,14,26} At the MP2/aug-cc-pVDZ level of theory, these effects range from a $\Delta r = +0.005$ Å and $\Delta \nu = -46$ cm⁻¹ for CH₄ to a $\Delta r = +0.028$ Å and $\Delta \nu = -404$ cm⁻¹ for CHCl₃.

The three ion dipole complexes have three C–H contacts. These contacts, however, do not exhibit the characteristics of C–H hydrogen bonds. The C–H···Cl⁻ angles are severely bent, ranging from 88° to 92° (Figure 2). The H···Cl⁻ distances are long, ranging from 2.98 to 3.02 Å, and show only slight variation with interaction strength. There is no significant electron donation from Cl⁻ into the C–H σ^* orbitals. Rather than being elongated, the C–H bond distances are slightly shortened by Cl⁻ contact, resulting in a small blue-shifting of the C–H stretching frequencies.¹³ For example, in CH₃CN the ion dipole complex shows a $\Delta r = -0.002$ Å and $\Delta \nu = +25$ cm⁻¹.

The difference between the two bonding motifs is clearly observed on examination of molecular orbital (MO) and electron density isosurfaces. Figure 3 shows the MO that exhibits the greatest degree of mixing between Cl⁻ orbitals and orbitals on the organic molecule for each of the complexes. The C–H hydrogen-bonded complexes show significantly more mixing than the ion dipole complexes, confirming that the former motif has more covalent character than the latter one. It has been suggested that this covalent character, resulting from the Cl⁻ p to C–H σ^* donation, plays an important role in stabilizing the hydrogen-bonded complexes, since an electrostatic interaction alone does not account for the strong bond formed between Cl⁻ and CHCl₃ (dipole moment of 1.02 D is smaller than the dipole

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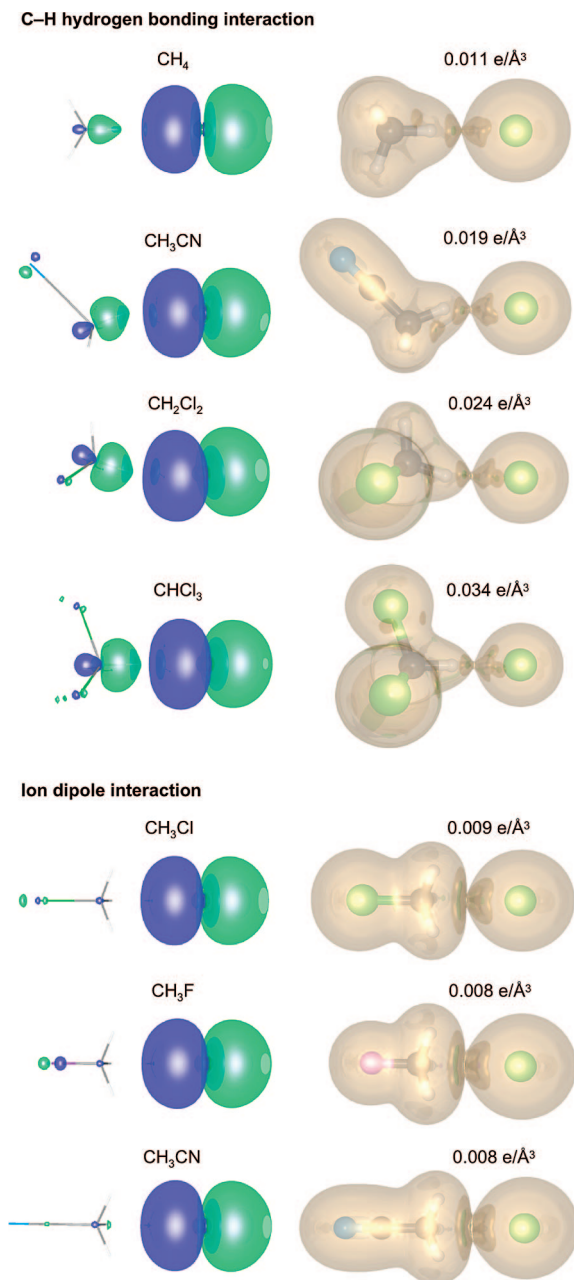


FIGURE 3. Graphical evaluation of the wave functions for Cl^- complexes with the C–H donor groups (Figure 2, Table 1). All MO surfaces are rendered at an isovalue of $0.032 (\text{e}/\text{\AA}^3)^{1/2}$. Electron density surfaces are rendered at the ρ_{max} value for each structure.

moment CH_3Cl , 1.87 D, but the ion dipole interaction with CH_3Cl is much weaker than the C–H hydrogen bond with CHCl_3 .¹²

The degree of covalent character in an interaction can be graphically quantified through the evaluation of electron density isosurfaces.³ The method involves locating the maximum shared electron density between the bonded species, ρ_{max} , by adjusting the isosurface value until the surface between the two species just becomes discontinuous. Figure 3 also shows electron density isosurfaces rendered at the ρ_{max} value for each of the complexes. With the C–H hydrogen bond interactions, which exhibit ρ_{max} values ranging from 0.011 to 0.034 $\text{e}/\text{\AA}^3$, the maximum shared electron density occurs along the $\text{H}\cdots\text{Cl}^-$ bond. The ρ_{max} values are comparable to those observed in weakly covalent σ

TABLE 2. Minima and ΔE (kcal/mol) Values for $\text{XCH}_3\cdots\text{Cl}^-$ Adducts

X	contacts	sym	ΔE
H	1 C–H	C_{3v}	–3.6
CH_3	1 C–H	C_s	–4.6
NH_2	N–H	C_1	–10.5
Ph	aryl H + $\text{CH}_2\text{–H}$	C_s	–11.6
F	CH_3 face	C_{3v}	–10.3
Cl	CH_3 face	C_{3v}	–11.5
Br	CH_3 face	C_{3v}	–11.9
OCH_3	2 $\text{CH}_2\text{–H}$	C_s	–9.0
OCH_3	CH_3 face	C_s	–6.7
OH	O–H	C_s	–15.9
C(=O)H	$\text{C(=O)–H} + 2 \text{C–H}$	C_s	–13.0
C(=O)CH_3	2 $\text{CH}_2\text{–H}$	C_s	–15.0
C(=O)OCH_3	1 C–H (gauche)	C_1	–9.3
CF_3	1 C–H	C_s	–11.8
CF_3	CH_3 face	C_{3v}	–11.5
CN	1 C–H	C_s	–14.7
CN	CH_3 face	C_{3v}	–14.4
NO_2	1 C–H	C_s	–15.9
NO_2	CH_3 face	C_s	–15.8
POCl_2	1 C–H	C_s	–17.9
POCl_2	1 C–H	C_1	–17.5
POCl_2	CH_3 face	C_s	–16.5
S(=O)CH_3	2 $\text{CH}_2\text{–H}$	C_s	–21.1
SO_2NH_2	N–H + C–H	C_1	–25.3
SO_2NH_2	CH_3 face	C_1	–13.9
SO_2CF_3	1 C–H	C_s	–19.1
SO_2CF_3	CH_3 face	C_s	–19.5
SO_2CN	1 C–H	C_s	–21.9
SO_2CN	1 C–H	C_1	–21.7
SO_2CN	CH_3 face	C_s	–21.8
SO_2Cl	1 C–H	C_s	–21.3
SO_2Cl	CH_3 face	C_s	–20.7

complexes formed between halides and arenes,³ which range from 0.014 to 0.031 $\text{e}/\text{\AA}^3$. In contrast, the ion dipole complexes have a maximum shared electron density along the C_3 axis rather than between the Cl^- and H atoms. The ion dipole complexes exhibit small ρ_{max} values, $\leq 0.009 \text{e}/\text{\AA}^3$, which are comparable to those observed in noncovalent anion- π interactions,³ $< 0.012 \text{e}/\text{\AA}^3$.

Evaluation of $\text{XCH}_3\cdots\text{Cl}^-$ Complexes. To better understand the nature of these interactions, we determined the structures and binding energies for a series of $\text{XCH}_3\cdots\text{Cl}^-$ complexes in which the electron-withdrawing ability of substituent X was varied over a wide range. Exhaustive searches for all potential minima involving a contact between a methyl C–H donor group and the Cl^- anion were performed at the MP2/aug-cc-pVDZ level of theory, where a contact was defined as an $\text{H}\cdots\text{Cl}^-$ distance $\leq 3.10 \text{\AA}$. Table 2 gives the substituent X, the type of contact, the symmetry of the structure, and the binding energy, ΔE , for all minima that were located. Out of a total of 32 structures, 12 involved a single $\text{C–H}\cdots\text{Cl}^-$ hydrogen bonding interaction, 12 involved ion dipole interactions (binding the CH_3 face), and 6 involved chelating interactions with hydrogen bonding contacts to one or more methyl C–H groups. Only two of the ligands, CH_3NH_2 and CH_3OH , fail to exhibit stable complexes with at least one $\text{C–H}\cdots\text{Cl}^-$ contact.

The properties of these $\text{XCH}_3\cdots\text{Cl}^-$ complexes are consistent with those shown in Figure 2. Complexes with single C–H hydrogen bonds have $\text{H}\cdots\text{Cl}^-$ distances ranging from 2.12 to 2.66 \AA with an average value of $2.32 \pm 0.19 \text{\AA}$ and $\text{C–H}\cdots\text{Cl}^-$ angles ranging from 144° to 180° with an average value of $162 \pm 10^\circ$. Interaction energies range from a low of -3.6 kcal/mol for CH_4 to -21.9 kcal/mol for $\text{CH}_3\text{SO}_2\text{CN}$. The ion dipole complexes have $\text{H}\cdots\text{Cl}^-$ distances from 2.86 to 3.10

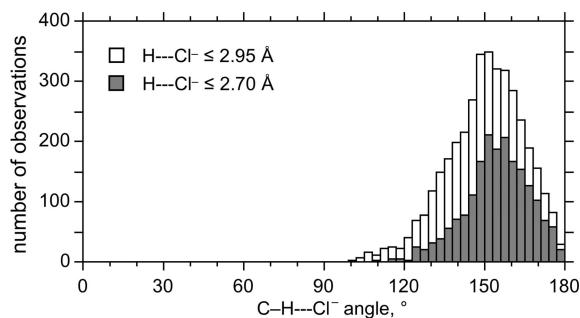


FIGURE 4. Distributions of C–H \cdots Cl $^-$ angles for 3846 contacts where the H \cdots Cl $^-$ distance is $\leq \Sigma vdw$ radii (2.95 Å) and 810 contacts where the H \cdots Cl $^-$ distance is ≤ 2.70 Å.

Å with an average value of 2.97 ± 0.08 Å and C–H \cdots Cl $^-$ angles ranging from 86 to 92° with an average value of $89 \pm 2^\circ$. Interaction energies span a range similar to the C–H hydrogen bonds, from -6.7 kcal/mol for CH_3OCH_3 to -21.8 kcal/mol for $\text{CH}_3\text{SO}_2\text{CN}$. Although a few of the donor molecules exhibit only C–H hydrogen-bonded forms and a few exhibit only ion dipole forms, both interaction motifs are observed as minima when the methyl substituent X becomes sufficiently electron-withdrawing. In these cases, the two motifs are similar in energy. With one exception, $\text{CH}_3\text{SO}_2\text{CF}_3$, the C–H hydrogen-bonded forms are more stable than the ion dipole forms, on average, by 0.5 kcal/mol.

Regardless of the interaction motif, inspection of Table 2 reveals that the majority of the XCH_3 molecules are capable of forming quite stable gas-phase adducts with Cl^- , suggesting that it should be possible to observe these interactions in condensed phases. This observation prompted several searches of the Cambridge Structural Database (CSD).²⁷ A search for Cl^- anions within van der Waals contact with at least one methyl hydrogen atom of an XCH_3 group (X = any atom), in other words, with an H \cdots Cl $^-$ distance of ≤ 2.95 Å,²⁸ yielded 3846 hits with a mean H \cdots Cl $^-$ distance of 2.78 ± 0.13 Å. Although these contacts are on average several tenths of an angstrom longer than those in the calculated structures (a feature also seen with aryl C–H hydrogen bonds),³ the majority of the contacts are several tenths of an angstrom shorter than expected for a simple van der Waals contact, indicative of attractive interactions. The distribution of C–H \cdots Cl $^-$ angles for these contacts, shown in Figure 4, reveals the presence of a distinct directionality, mean value of $150 \pm 15^\circ$, consistent with a hydrogen bonding interaction. The directionality becomes more pronounced at shorter contact distances, providing further evidence that these contacts represent hydrogen bonding rather than van der Waals interactions.²⁹ For example, constraining the H \cdots Cl $^-$ contact distance to ≤ 2.70 Å reduces the number of hits to 810 (Figure 4), yielding a mean H \cdots Cl $^-$ distance of 2.63 ± 0.06 Å and mean C–H \cdots Cl $^-$ angle of $157 \pm 11^\circ$. The observed directionality is similar to the spread of values observed in the calculated structures, $162 \pm 10^\circ$.

Although the calculated ion dipole binding motifs are similar in energy to the C–H hydrogen bonding motifs, they are not

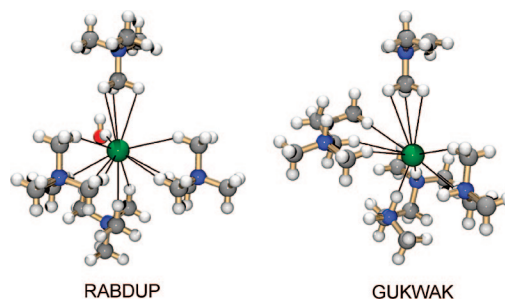


FIGURE 5. The only two structures located in the CSD that contain examples of $\text{XCH}_3\cdots\text{Cl}^-$ ion dipole interactions. In RABDUP,^{30a} the Cl^- is engaged in one ion dipole interaction, nine C–H hydrogen bonds, and one O–H hydrogen bond. In GUKWAK,^{30b} the Cl^- is engaged in one ion dipole interaction, five C–H hydrogen bonds, and two N–H hydrogen bonds.

prevalent in the CSD. A search²⁷ for examples of $\text{XCH}_3\cdots\text{Cl}^-$ interactions in which Cl^- was in contact with all three methyl H atoms within the sum of van der Waals radii, 2.95 Å, and the X–C \cdots Cl $^-$ angle was 160 – 180° yielded no hits. Loosening the contact distance criteria by 0.3 Å, from 2.95 to 3.25 Å, yielded only 2 examples, both involving methyl groups on tetralkylammonium cations.³⁰ In these examples, shown in Figure 5, each Cl^- is engaged in only one ion dipole interaction but multiple C–H \cdots Cl $^-$ hydrogen bonding interactions.

The paucity of structures representative of ion dipole interactions may be attributed to (a) the fact that the ion dipole motif is a shallow minimum separated from the three deeper minima of the C–H hydrogen bonding motifs by a very low barrier (with CH_3CN , the barrier between the ion dipole form and the hydrogen-bonded form is only 0.08 kcal/mol) and (b) relatively few examples in which the substituent X is a sufficiently strong electron-withdrawing group. Whatever the explanation, it is clear that C–H hydrogen bonding is the dominant interaction motif in the solid state.

Strength of Individual C–H \cdots Cl $^-$ Hydrogen Bond Interactions. To tackle the question posed in this paper's title, we now return attention to the strength of C–H \cdots Cl $^-$ hydrogen bonds. Only 10 of the 21 XCH_3 molecules listed in Table 2 form minima that directly address this question, in other words, that contain a single C–H hydrogen bond with the anion (see Table 2). The other molecules were problematic. Three molecules, the monohalogenated methanes, showed only the ion dipole motif, two molecules formed complexes via N–H or O–H hydrogen bonds alone, and the rest had multiple binding interactions.

In an effort to evaluate the strength of C–H \cdots Cl $^-$ hydrogen bonding interactions across the entire range of substituents, further calculations were performed using geometric constraints to isolate individual C–H \cdots Cl $^-$ interactions in the problematic cases. In these cases, the C–H \cdots Cl $^-$ angle was constrained to 160° and the dihedral angle X–C–H \cdots Cl $^-$ was constrained to 180° . After optimizing the remaining degrees of freedom, it was possible to locate at least one geometry for each of the molecules that involved a single C–H hydrogen bonding interaction with the Cl^- anion. In cases where different hydrogen positions could lead to two possible geometries, for example, *trans* versus *gauche*, both possibilities were investigated.

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TABLE 3. Strengths of Isolated X–CH₂–H···Cl[–] Contacts

X	σ_m^a	min ^b	hydrogen ^c	ΔE (kcal/mol)
NH ₂	–0.16		H–N–C–H, 56°	–5.9
CH ₃	–0.07	yes		–4.6
H	0.00	yes		–3.6
Ph	0.06		C–C–C–H, 0°	–8.3
			C–C–C–H, 90°	–7.1
OH	0.12		H–O–C–H, 0°	–7.7
			H–O–C–H, 180°	–4.8
OCH ₃	0.12		C–O–C–H, 49°	–7.3
			C–O–C–H, 180°	–5.4
F	0.34			–8.6
C(=O)H	0.35		O=C–C–H, 124°	–11.3
			O=C–C–H, 0°	–6.8
C(=O)CH ₃	0.36		O=C–C–H, 135°	–11.6
			O=C–C–H, 0°	–5.6
Cl	0.37			–10.4
C(=O)OCH ₃	0.38	yes	O=C–C–H, 101°	–9.3
			O=C–C–H, 0°	–6.4
Br	0.39			–10.9
CF ₃	0.43	yes		–11.8
S(=O)CH ₃	0.52		O=S–C–H, 160°	–17.2
			O=S–C–H, 88°	–10.7
SO ₂ NH ₂	0.53		N–S–C–H, 180°	–12.5
CN	0.56	yes		–14.7
NO ₂	0.71	yes		–15.9
P(=O)Cl ₂	0.78	yes	O–P–C–H, 180°	–17.9
		yes	O–P–C–H, 68°	–17.5
SO ₂ CF ₃	0.83	yes	C–S–C–H, 180°	–19.1
SO ₂ CN	1.10	yes	C–S–C–H, 180°	–21.9
		yes	C–S–C–H, 50°	–21.7
SO ₂ Cl	1.20	yes	Cl–S–C–H, 180°	–21.3

^a The σ_m values were taken from ref. ^b Yes indicates the structure is a minimum (Table 2). ^c Dihedral angle identifying the C–H group involved in the hydrogen bonding interaction.

The C–H hydrogen bond strengths obtained from true minima (Table 2) and from constrained geometry optimizations are summarized in Table 3. The relative strength of these aliphatic C–H hydrogen bonds can be assigned on the basis of a gas-phase scale proposed by Jeffrey: weak, ≤ 4 kcal/mol; moderate, 4–15 kcal/mol; strong, ≥ 15 kcal/mol.³¹ In accordance with this scale only one of these interactions, CH₄···Cl[–], would be identified as a “weak” hydrogen bond. The remaining ones would be classified as either moderate (21 examples) or strong (8 examples) hydrogen bonds. For a given XCH₃ donor, the strength of the interaction depends on the orientation of the donating C–H group with respect to the substituent, X. This effect ranges from a minimum $\Delta\Delta E$ of 0.4 kcal/mol in CH₃P(=O)Cl₂ to a maximum $\Delta\Delta E$ of 6.5 kcal/mol in CH₃S(=O)CH₃.

The ΔE values in Table 3 would be expected to show some correlation with the electron-withdrawing ability of the substituent, X. In other words, as the substituent becomes more electron-withdrawing, the methyl H atoms should become more acidic and the interaction should become stronger. Plots of ΔE versus various substituent parameters, including σ^* , σ_I , σ_p , and σ_m ,³² were attempted. Figure 6 shows the most linear correlation, which was obtained using σ_m values (see Table 3). This correlation, $\Delta E = -4.961 - 14.85 \times \sigma_m$, predicts ΔE values for most of the calculated XCH₃···Cl[–] hydrogen bonds to within ≤ 3 kcal/mol, providing a method for estimating the hydrogen bonding strength for substituents not present in Table 3. For example, this relationship predicts that when C–H groups are

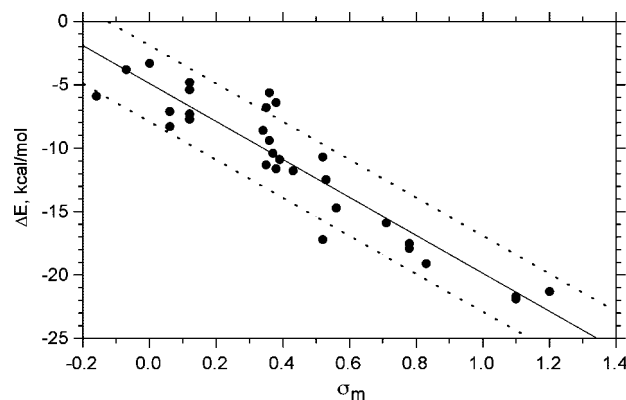


FIGURE 6. Plot of the ΔE versus σ_m data in Table 3. Dotted lines are placed 3 kcal/mol above and below the best-fit solid line (slope = -14.85 , intercept = -4.961 , $r = 0.930$).

attached to an R₃N⁺ substituent ($\sigma_m = 0.80$), they should form strong C–H···Cl[–] hydrogen bonds, on the order of -17 ± 3 kcal/mol. This result suggests that the aliphatic C–H contacts reported in protonated aza macrocycles and cryptands, which involve H atoms from R₃N⁺-CH₂-R,¹⁸ are making significant and strong contributions to the overall anion binding energy. It also helps to understand why a Cl[–] encapsulated in a hexa-protonated octaamino cryptand can interact with the ligand solely via C–H, rather than N–H, hydrogen bonds.^{18b}

The ΔE values in Table 3 reveal that the presence of a single electron-withdrawing substituent can significantly strengthen the C–H hydrogen bonding interaction compared to the relatively weak interaction obtained with simple alkanes. Thus, one might anticipate that the presence of two electron-withdrawing substituents would have a greater impact. This situation exists in two of the receptors mentioned in the introduction, **3** and **4** (Figure 1). In **3**, each methylene donor is attached to two ether oxygen groups. In **4**, each methylene donor is attached to an ether oxygen group and a fluorinated alkyl group. Further calculations were performed to quantify the influence of placing two electron-withdrawing substituents on the C–H donor carbon atom.

Using geometric constraints similar to those described above, single C–H hydrogen bond strengths were computed for Cl[–] complexes with the methylene H atoms of CH₃O-CH₂-OCH₃ and CH₃O-CH₂-CF₃. As anticipated, the strength of these hydrogen bonding interactions is stronger than obtained in complexes formed by monosubstituted methyl C–H donors (Table 3). The example with two OCH₃ substituents has a ΔE of -11.6 kcal/mol compared to the ΔE of -7.4 kcal/mol obtained for a single OCH₃ substituent. The example with one OCH₃ and one CF₃ substituent has a ΔE of -15.2 kcal/mol, which is stronger than either the -7.4 kcal/mol for one OCH₃ substituent or the -11.8 kcal/mol for one CF₃ substituent. A final example is found in the chlorinated methane derivatives where the dichlorinated methylene donor has a ΔE of -15.3 kcal/mol (Table 1) compared to the ΔE of -10.4 kcal/mol (Table 3) obtained with a single Cl substituent. In these three examples, the ΔE value for the disubstituted C–H donor group is on average 77% of the sum of ΔE values for the two monosubstituted C–H donor groups.

Conclusions

A wide variety of existing data, including direct observation in crystal structures,^{17,18} measured gas-phase binding

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energies,^{9,12,19–25} gas-phase vibrational spectroscopy,²⁶ solution binding studies,^{15,16} and electronic structure calculations,^{11–14} have conclusively established the aliphatic C–H group as an effective hydrogen bond donor for negatively charged acceptors. Herein, we have used electronic structure calculations to quantify the strength of such interactions, showing that the aliphatic C–H···Cl[–] hydrogen bond strength ranges from –3.6 to –21.9 kcal/mol. This range brackets that previously reported for aryl C–H hydrogen bonds.^{3–5}

Nonpolar alkanes are at the weak end of the scale and exhibit ΔE values that are roughly half or that observed for C₆H₆: –8.6 kcal/mol⁴ versus –4.6 kcal/mol for CH₃CH₃. Note, however, that substitution of the donor carbon with moderate electron-withdrawing groups, like Cl or C(=O)H, yields aliphatic C–H donors that are stronger than C₆H₆. With more potent electron-withdrawing groups, the C–H donors in XCH₃ (Table 3) are comparable in strength to those in XC₆H₅ (prior study):⁵ CF₃CH₃, –11.8 kcal/mol, versus CF₃C₆H₅, –13.5 kcal/mol; CNCH₃, –14.7 kcal/mol, versus CNC₆H₅, –15.6 kcal/mol; NO₂CH₃, –15.9 kcal/mol, versus NO₂C₆H₅, –16.0 kcal/mol.

Thus, when attached to polarizing substituents, aliphatic CH groups become moderate-to-strong hydrogen bond donors, exhibiting interaction energies comparable to those obtained with O–H and N–H groups. The results explain why aliphatic C–H donors have been observed to function as competitive binding sites in solution^{15,16} and indicate that such C–H···anion contacts should be considered as possible contributors when evaluating the denticity of an anion receptor. The aliphatic C–H hydrogen bond, which up till now has largely been dismissed as a “weak” interaction, should be added to the arsenal of interaction motifs under consideration in anion host design.

Methods

Electronic structure calculations were carried out with the NWChem program³³ using second order Möller-Plesset perturbation

theory (MP2).³⁴ Geometries were optimized using the augmented correlation consistent double- ζ basis set (aug-cc-pVDZ)³⁵ including all electrons in the correlation treatment. Frequency calculations were performed at the same level of theory to verify that geometries were minima and to obtain the zero point (ΔE_{ZPE}) and thermal energy ($\Delta E_{\text{thermal}}$) corrections needed for the calculation of enthalpies. Binding energies were calculated as follows: $\Delta E = E(\text{complex}) - E(\text{ligand}) - E(\text{Cl}^-)$. Binding enthalpies were calculated as follows: $\Delta H = \Delta E + \Delta E_{\text{ZPE}} + \Delta E_{\text{thermal}} + \Delta(\text{PV})$, where $\Delta(\text{PV}) = nRT = -0.593$ kcal/mol at 298.15 K. Electron density and molecular orbital isosurfaces were rendered with ECCE.³⁶

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Supporting Information Available: The full citations for refs 33 and 36, Cartesian coordinates and energies (Hartrees) for the MP2/aug-cc-pVDZ optimized geometries for all complexes listed in Tables 1, 2, and 3 and those described elsewhere in the manuscript. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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