Weak Interactions

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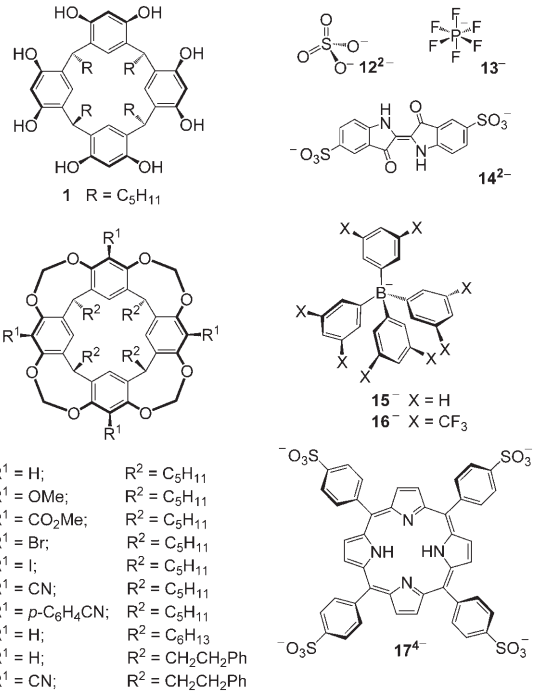
Anion Binding to Resorcinarene-Based Cavitands: The Importance of C–H···Anion Interactions**

*Sascha S. Zhu, Holger Staats, Kai Brandhorst, Jörg Grunenberg, Francesca Gruppi, Enrico Dalcanale, Arne Lützen, Kari Rissanen, and Christoph A. Schalley**

As one of the traditional work horses in supramolecular chemistry, resorcinarenes[1] represent a highly interesting multipurpose scaffold for numerous applications ranging from the assembly of capsules[2] such as the resorcinarene hexamers,[3] coordination cages,[4] and molecular loops,[5] to applications in supramolecular sensors[6] and phase-transfer catalysts.[7]

The simplest resorcinarenes such as **1** (Scheme 1) are held in a cone conformation through O–H···O hydrogen bonding along the upper rim and are well known to accommodate guest cations inside their cavities, for example, quaternary ammonium ions.[8] For anion binding,[9] more elaborate cavitand receptors have been developed,[10] in which the resorcinarene merely provides the scaffold, while the (thio)-urea, N-heterocyclic, or quaternary ammonium binding sites are located in the apical positions on the edge of the cavity. In quite a number of anion receptors, anion binding is supported by additional weaker interactions of the anion with aromatic C–H bonds.[11] However, reports on interactions between anions and nonaromatic CH groups as hydrogen-bond donors are rare,[12] and only two recent NMR spectroscopic and crystallographic studies[13] reported C–H···X hydrogen bonding involving the inwards oriented acetal hydrogen atoms of methylene-bridged cavitands comparable to **2** (Scheme 1).



Scheme 1. Resorcinarene-based hosts **1**–**11** and anions $\mathbf{12}^{2-}$–$\mathbf{17}^{4-}$ used in this study.

Gas-phase experiments are a powerful tool to examine the anion-binding capabilities of cavitands such as **2**–**11**. Unexpected effects of solvent or counterions can be ruled out, and it is possible to study the intrinsic properties of the anion–cavitand complexes.[14] Consequently, electrospray ionization Fourier-transform ion-cyclotron resonance mass spectrometric (ESI-FTICR-MS) experiments were used to assess the anion-binding behavior of hosts **1**–**11**.[15] When an acetone solution of $Me_4N^+\mathbf{13}^-$ with **1** was sprayed in the positive-ion mode, intense signals for cation–host complexes were observed, while with **2** no signals for complexes with the same guest cation were evident. In marked contrast, **1** did not give intense anion–host complexes $[\mathbf{13}@\mathbf{1}]^-$ in the negative-ion mode (Figure 1a), while a surprisingly clean mass spectrum (Figure 1b) was obtained with **2**. The host–guest complex $[\mathbf{13}@\mathbf{2}]^-$ is the predominant complex formed in the ion source. Thus, nonbridged resorcinarene **1** forms com-

[*] S. S. Zhu,[+] Prof. Dr. C. A. Schalley
Institut für Chemie und Biochemie
Freie Universität Berlin
Takustrasse 3, 14195 Berlin (Germany)
Fax: (+49) 30-838-55817
E-mail: schalley@chemie.fu-berlin.de

H. Staats, Prof. Dr. A. Lützen
Kekulé-Institut für Organische Chemie und Biochemie
Universität Bonn
Gerhard-Domagk-Strasse 1, 53121 Bonn (Germany)

F. Gruppi, Prof. Dr. E. Dalcanale
Dipartimento di Chimica Organica ed Industriale
Università di Parma and INSTM UdR Parma
V.le G.P. Usberti 17/A, 43100 Parma (Italy)

Prof. Dr. K. Rissanen
Nanoscience Center
Department of Chemistry, University of Jyväskylä
P.O. Box 35, 40014 Jyväskylä (Finland)

K. Brandhorst, Dr. J. Grunenberg
Insitut für Organische Chemie, TU Braunschweig
Hagenring 30, 38106 Braunschweig (Germany)

[+] Present address:
Kekulé-Institut für Organische Chemie und Biochemie
Universität Bonn
Gerhard-Domagk-Strasse 1, 53121 Bonn (Germany)

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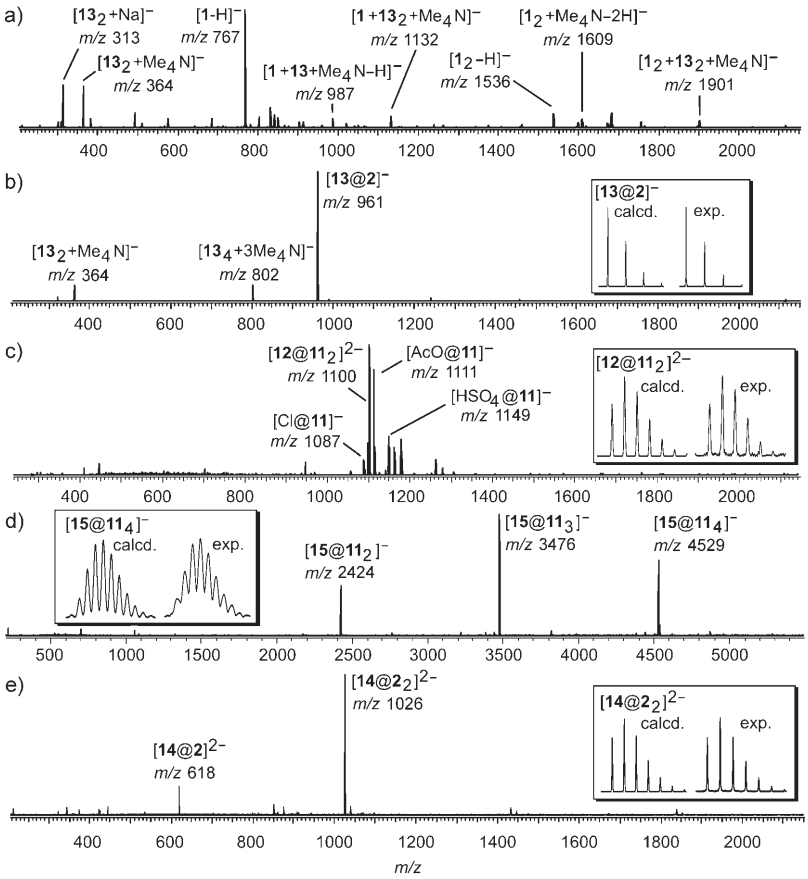

Figure 1. ESI-FTICR mass spectra of solutions of a) **1** + 1 equiv Me_4N^+**13**$^-$ (200 μM), b) **2** + 1 equiv Me_4N^+**13**$^-$ (200 μM), c) **11** + 10 equiv $(Me_4N^+)_2$**12**$^{2-}$ (680 μM), d) **11** + 0.25 equiv Na^+**15**$^-$ (250 μM), e) **2** + 0.5 equiv Na^+_2**14**$^{2-}$ (780 μM) in acetone (a–b,d) or acetone/MeOH (40:7 (c), and 40:1 (e)). AcO = acetate.

plexes with cations, even though it could bind anions through O–H···anion hydrogen bonds. In contrast, methylene-bridged cavitands have a significant preference for suitable anions, even when cations are present that could compete for binding. Experiments with other anions such as chloride, bromide, iodide, and nitrate also provided strong signals for the formation of anion–cavitand complexes.

Encouraged by these results, we extended the study to sulfate as an example of a small dianion. Isolated sulfate dianions are calculated to be roughly 1.3–1.6 eV ($\approx$130–160 kJ mol^{-1}) higher in energy than the corresponding anions and thus would spontaneously undergo electron autodetachment when generated under gas-phase conditions.[16] Therefore, sulfate can be observed in the gas phase only if solvated, for example, by at least three water molecules.[17] Despite the inherent instability of sulfate, the ESI-FTICR mass spectrum (Figure 1c) obtained from spraying an acetone/methanol solution of **11** and $(Me_4N^+)_2$**12**$^{2-}$ reveals the abundant formation of the 2:1 complexes [**12**@**11**$_2$]$^{2-}$. With cavitand **2**, formation of [**12**@**2**$_2$]$^{2-}$ was likewise observed.

To gain further insight, we conducted tandem MS experiments with mass-selected [**12**@**2**$_2$]$^{2-}$ and [**12**@**11**$_2$]$^{2-}$ ions (for experimental details, see the Supporting Information). In a collision-induced-decomposition (CID) experiment using argon as the collision gas, [**12**@**2**]$^{2-}$ cleanly fragments through the loss of one cavitand (Figure 2a, process A). The formation of the 1:1 complex [**12**@**2**]$^{2-}$ provides evidence for the sufficient stabilization of sulfate against electron autodetachment even through binding to only one cavitand. Even if theory[16] overestimates the energy gain from electron autodetachment (130–160 kJ mol^{-1}) to some extent, the cavitand–anion binding energy must be higher than that and is thus substantial.

When the same experiment is performed with cyano-substituted [**12**@**11**$_2$]$^{2-}$ (Figure 2b), three fragmentation pathways are populated (Scheme S1 in the Supporting Information): A) loss of one neutral cavitand, B) a charge-separating loss of [HSO_4@**11**]$^-$ involving the formation of a deprotonated cavitand, and C) loss of CH_2O and SO_3 through nucleophilic substitution and fragmentation. Two subsequent 1,2-elimination reactions of styrene and/or CO follow the primary reaction in pathway B; pathway C can lead to the subsequent loss of a neutral cavitand. The results are remarkable in that deprotonation of an acetal proton can compete not only with electron autodetachment but also with breaking covalent interactions for [**12**@**11**$_2$]$^{2-}$, while this is not true for [**12**@**2**$_2$]$^{2-}$. Consequently, the binding energy of **11** to sulfate must even be

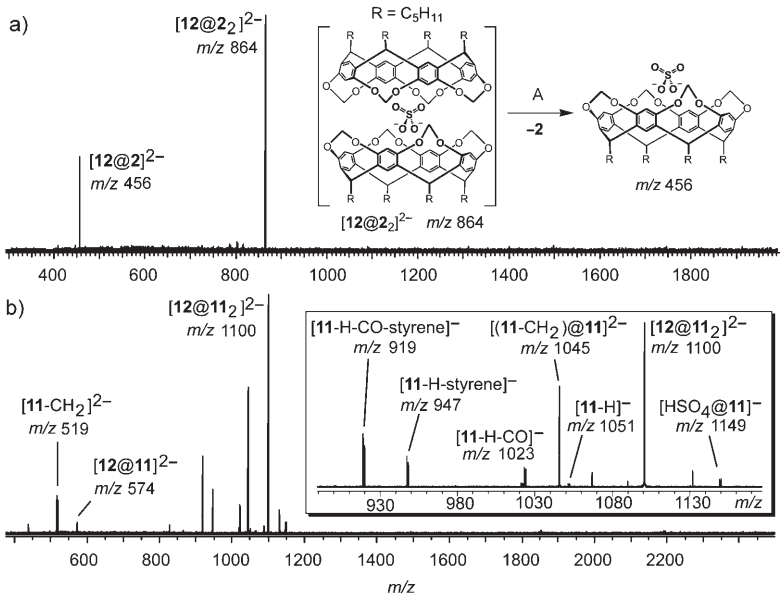

Figure 2. CID mass spectra with mass-selected a) [**12**@**2**$_2$]$^{2-}$ and b) [**12**@**11**$_2$]$^{2-}$ (for experimental details, see the Supporting Information).

significantly higher than that of **2**. A rationalization for this feature is the direct conjugation of the acetal oxygen with the nitrile group. An electron-withdrawing substituent such as the nitrile group thus increases the positive partial charge on the acetal hydrogens and increases the strength of their interactions with anions (also see below).

Size-selectivity experiments with large monoanions such as tetraphenylborates $\mathbf{15}^-$ and $\mathbf{16}^-$ may provide insight into the binding mode. Upon addition of 0.25 equiv $Na^+\mathbf{15}^-$ to a solution of **11**, dimeric, trimeric, and tetrameric complexes ($[\mathbf{15}@\mathbf{11}_2]^-$, $[\mathbf{15}@\mathbf{11}_3]^-$, $[\mathbf{15}@\mathbf{11}_4]^-$) were observed in the mass spectrum (Figure 1 d). Similar results were also obtained with cavitands **2**, **9**, and **10**. In marked contrast, cavitand **8** with its extended cavity, gave rise exclusively to the 1:1 complex $[\mathbf{15}@\mathbf{8}]^-$. Apparently, this is a result of the steric congestion caused by the longer and quite rigid side chains on the upper rim of **8** and points to anion binding in the cavitand's cavity. In control experiments with the sterically more demanding guest $Na^+\mathbf{16}^-$, no complex formation occurred with cavitands **9** and **11**, and free $\mathbf{16}^-$ was the only ion observed. Each phenyl group of tetraphenylborate ($\mathbf{15}^-$) can dive into one cavitand cavity to form complexes with compositions of up to 4:1. This binding mode is unavailable when the size of the phenyl groups is increased by the attachment of two CF_3 groups in the 3- and 5-positions. Anion $\mathbf{16}^-$ is thus incongruent with the cavity in size and shape.

Finally, larger dianions such as $\mathbf{14}^{2-}$ and $\mathbf{17}^{4-}$ were studied. The mass spectrum (Figure 1 e) obtained from a solution of **2** and $Na^+_2\mathbf{14}^{2-}$ clearly shows the predominant presence of the dimer–guest complex $[\mathbf{14}@\mathbf{2}_2]^{2-}$ accompanied by the corresponding monomer–guest complex $[\mathbf{14}@\mathbf{2}]^{2-}$. With the tetrasulfonated porphyrin $\mathbf{17}^{4-}$, 4:1 complexes $[\mathbf{17}@\mathbf{2}_4]^{4-}$ of cavitand and tetraanion were observed as the base peak in the ESI mass spectrum.

With guest $\mathbf{14}^{2-}$ and a 1:1 mixture of two different cavitands, it is possible to generate heterodimeric host–guest complexes. Upon addition of $\mathbf{14}^{2-}$ to a mixture of two cavitands such as **2** and **3**, which have the same overall structure but carry different substituents, heterodimeric cavitand–dianion complexes such as $[\mathbf{14}@\mathbf{2}_1\mathbf{3}_1]^{2-}$ were observed in the gas phase. After mass-selection of the heterodimeric complexes, CID experiments were performed. A qualitative ranking of the relative intrinsic strengths of the cavitand–sulfonate interactions can be easily determined by comparing the intensities of fragment ions such as $[\mathbf{14}@\mathbf{2}]^{2-}$ and $[\mathbf{14}@\mathbf{3}]^{2-}$ for three reasons:[18]

1) Fragmentation occurs exclusively through the loss of one neutral cavitand, which is not significantly influenced by the other because of the distance between the two anionic sites on the guest.
2) The ratio of two fragment ions in the CID spectra is independent of ionization processes and spectrometer settings, because a true gas-phase experiment is performed.
3) The number of vibrational degrees of freedom into which the internal energy can be distributed in either fragment is not significantly different.

Consequently, it is possible to examine how the electronic nature of electron-withdrawing or electron-donating substituents on the cavitands' upper rims influences complex stabilities. Following this protocol, CID experiments were conducted with mass-selected $[\mathbf{14}@\mathbf{5}_1\mathbf{7}_1]^{2-}$, $[\mathbf{14}@\mathbf{5}_1\mathbf{6}_1]^{2-}$, $[\mathbf{14}@\mathbf{4}_1\mathbf{6}_1]^{2-}$, $[\mathbf{14}@\mathbf{2}_1\mathbf{4}_1]^{2-}$, and $[\mathbf{14}@\mathbf{2}_1\mathbf{3}_1]^{2-}$ ions (Figure 3 a–e). These CID spectra clearly show that the strengths of cavitand–sulfonate interactions increase as follows: $\mathbf{3} \leq \mathbf{2} \ll \mathbf{4} \ll \mathbf{5} \approx \mathbf{6} \ll \mathbf{7}$. In terms of the substituents' electronic nature, the order is: $OMe \leq H \ll CO_2Me \ll Br \approx I \ll CN$. The experimentally obtained tendency is in good agreement with the electron-withdrawing or -donating ability of the aromatic substituents. The only exception is the CO_2Me group, which apparently affects the complexation through its conformationally flexible methoxy arms which extend to the vicinity of the binding sites. Nevertheless, this effect is not too prominent since **4** still binds sulfonate far better than **2** and **3** do.

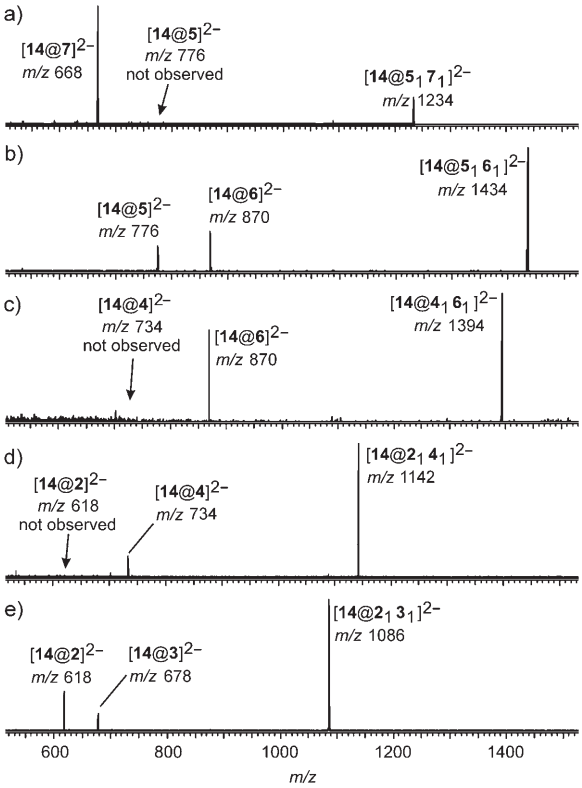

Figure 3. CID experiments with mass-selected, doubly charged heterodimer indigo carmine complexes: a) $[\mathbf{14}@\mathbf{5}_1\mathbf{7}_1]^{2-}$, b) $[\mathbf{14}@\mathbf{5}_1\mathbf{6}_1]^{2-}$, c) $[\mathbf{14}@\mathbf{4}_1\mathbf{6}_1]^{2-}$, d) $[\mathbf{14}@\mathbf{2}_1\mathbf{4}_1]^{2-}$, e) $[\mathbf{14}@\mathbf{2}_1\mathbf{3}_1]^{2-}$.

These experiments provide evidence for a cavitand–anion interaction mediated by C–H···anion hydrogen bonds that involve the acetal protons pointing into the cavitand bowl. The following points support this conclusion:

1) Anion–π interactions[19] do not play a significant role, since otherwise, **1** would be expected to be an equally good host for anions.
2) The substantial stability of the cavitand—anion complexes, particularly that of $[\mathbf{12}@\mathbf{11}_2]^{2-}$, indicates that complexation is mediated by multiple interactions and thus likely occurs inside the cavitand bowl.

3) Cavitand **8** has the same alkyl feet as **2**–**7** but displays a significantly different complexation behavior with $\mathbf{14}^{2-}$ and $\mathbf{15}^{-}$. This excludes binding of the anions at the bottom rim, since then no such effects would be expected to occur. Steric effects attributed to the longer cyanophenyl substituents can easily be understood, however, if anion binding inside the cavity is assumed.
4) The fragmentation of $[\mathbf{12@11_2}]^{2-}$ includes the deprotonation of one of the acetal positions, suggesting sulfate binding to occur close to the methylene inner protons.
5) Substituent effects revealed by the CID spectra of heterodimeric host–guest complexes with $\mathbf{14}^{2-}$ provide evidence for the binding sites to be located in the "influence region" of substituents at the upper rim. This applies in particular to the acetal protons which carry a higher positive partial charge when electron-withdrawing substituents are present.

For more detailed insight into the thermodynamic forces driving anion binding to the cavitands through C–H···anion interactions, we performed a series of quantum chemical calculations on a C_{4v}-symmetric model system for $[\mathbf{13@2}]^-$ in which the C_5H_{11} moieties where replaced simply by H, and which is designated $[\mathbf{13@2'}]^-$ (Figure 4). Geometry optimizations and energy second-derivative calculations were conducted with the hybrid density functional B3LYP[20] with a split-valence double-zeta basis set augmented with one set of polarization functions and diffuse functions on all atoms (6-31++G(d,p)) as implemented in Gaussian03.[21] Adopting the rigid-rotor harmonic-oscillator approximation, the free energy of association at room temperature (ΔG°_{298}) for $[\mathbf{13@2'}]^-$ is calculated to be $-24.2\,\mathrm{kJ\,mol^{-1}}$, which is quite substantial in view of the assumed weak individual enthalpic contributions and the entropic cost of any associative mechanism. In a second step, generalized compliance constants[22] were calculated in order to quantify the individual contributions and, if possible, to discriminate between C–H···anion and possible anion–π interactions. To the best of our knowledge this is the first direct quantification of this type of weak, noncovalent C–H···ion interaction. The anion–π contacts measured as displacements of the internal coordinates between the fluorine atoms of the PF_6^- anion and aromatic carbons in the resorcinarenes are very soft, with compliance constants between 30 and 40 $\mathrm{Å\,mdyne^{-1}}$. Note that a higher compliance constant is connected with a softer interaction. Anion–π contacts can thus indeed be excluded as the enthalpic driving force during the association. On the other hand, the compliance constant for the **2′**C–H···F–PF_5^- interactions point to a hydrogen bond in the range between a strong N–H···O ($\approx 5\,\mathrm{Å\,mdyne^{-1}}$) and a C–H···O hydrogen bond ($\approx 20\,\mathrm{Å\,mdyne^{-1}}$). The strength of the **2′**C–H···F–PF_5^- interaction measured by generalized compliance constants is computed to be $15.2\,\mathrm{Å\,mdyne^{-1}}$. The four individual C–H···F contacts in $[\mathbf{13@2'}]^-$, which are intensified through the negative charge on the guest molecule, are therefore mainly responsible for the stability of the adduct.

In conclusion, mass spectrometric experiments together with theory indicate that suitably positioned C–H bonds can complex anions, if they are polarized by neighboring electronegative heteroatoms. The easy-to-access methylene-bridged resorcinarene cavitands provide exactly the right geometric arrangement of such groups to support anion binding through multiple interactions with up to four converging C–H groups. Particularly remarkable is the fact that even one cavitand is able to solvate a sulfate dianion well enough to prevent electron autodetachment. This experiment shows that the interaction strength between host and guest anion can amount to substantial values. From a fundamental point of view, this study provides new insight into the nature and importance of C–H···anion interactions. This mode of hydrogen bonding, that is, hydrogen bonds between an anion and a nonaromatic C–H bond, is very rare and not well studied so far. To the best of our knowledge, the phenomenon that neutral cavitands complex different anions exclusively through this type of weak interaction has not been described previously.

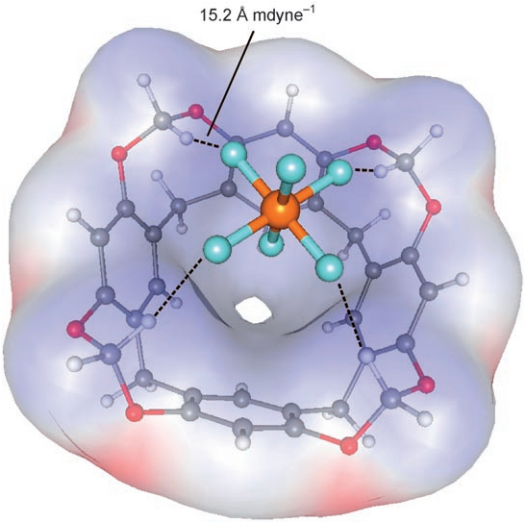

Figure 4. The B3LYP/6-31++G(d,p)-optimized structure of the model complex $[\mathbf{13@2'}]^-$ mapped with the electrostatic potential on the host surface. C–H···F hydrogen bonds are depicted.

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