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Anions Stabilize Each Other inside Macrocyclic Hosts

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Abstract: *Contrary to the simple expectations from Coulomb's law, Weinhold proposed that anions can stabilize each other as metastable dimers, yet experimental evidence for these species and their mutual stabilization is missing. We show that two bisulfate anions can form such dimers, which stabilize each other with self-complementary hydrogen bonds, by encapsulation inside a pair of cyanostar macrocycles. The resulting 2:2 complex of the bisulfate homodimer persists across all states of matter, including in solution. The bisulfate dimer's OH···O hydrogen bonding is seen in a* ^{1}*H NMR peak at 13.75 ppm, which is consistent with borderline-strong hydrogen bonds.*

The fundamental role of Coulomb's law[1] is so ingrained in all areas of chemistry, biology, and physics that it is the starting point for formulating hypotheses on the behavior of matter. It governs the bonding in ionic solids, the salt-bridges that guide protein structure and function, and the movement of ions in electric fields. We rely daily upon the notion that like charges repel (Figure 1 a) and opposite charges attract (Figure 1 b). For this reason, it came as some surprise when Weinhold's recent theoretical work[2] and its commentary[3] suggested that anions can attract, instead of repel, each other to form dimers.[4]

Propositions that anions can stabilize each other are rare and the only unequivocal evidence for this phenomenon is in the solid state.[5] We found over 80 examples of HSO_4^- dimers (see the Supporting Information, Table S1),[6] as well as chains of HSO_4^-,[7] water-bridged sulfates,[8] and oligomers[9] and cyclic forms of hydrogen-bonded phosphates.[10] However, many forces other than anti-electrostatic hydrogen bonding,[2] for example, ionic bonding, can stabilize such anion dimers in crystals. In solution, where solvation overtakes ionic bonding, dimer salts do not appear to survive. Supramolecular encapsulation offers a way to stabilize unstable species in solution.[11] The only reports of complexes of anion dimers are with $H_2PO_4^-$ and are based on the observation of a 2:1 ratio of phosphate and receptor. Nevertheless, there are no direct observations of anion dimers in solution. With good reason, the authors of those works, Reinhoudt,[5a,12] Kubo,[13] Fabbrizzi,[5b,14] Sessler,[15] and Tomisič,[16] took care to circumscribe these claims with caveats such as "tentatively assigned". The idea that anions can be bound to each other in solution in a complex has yet to be substantiated.

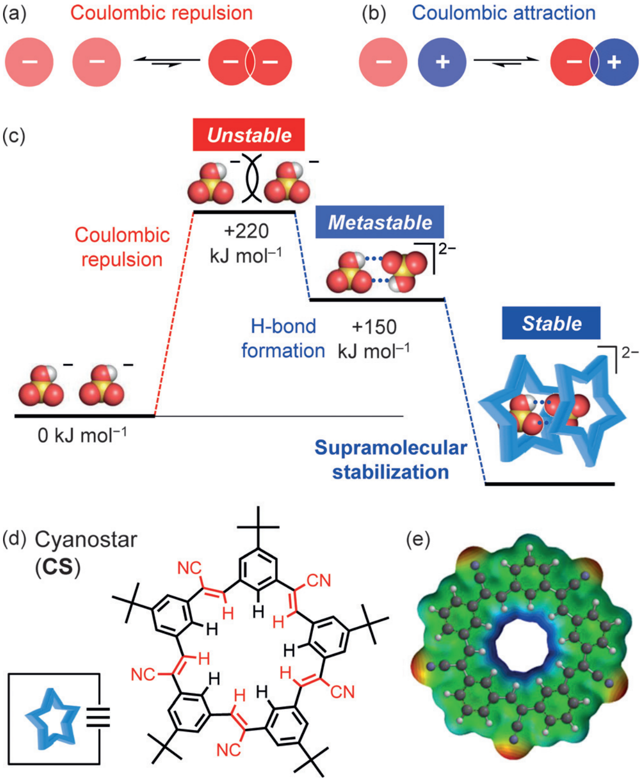

Figure 1. Coulomb's law of a) repulsion and b) attraction. c) Formation of bisulfate dimers made stable by self-complementary hydrogen bonds and complexation. d) Cyanostar (**CS**) macrocycles. e) Electrostatic potential map of cyanostar (red = −152 kJ mol^{-1}; blue = +190 kJ mol^{-1}).

We report the discovery of the first conclusive anion–anion dimerization of bisulfate, HSO_4^-, occurring inside supramolecular complexes in the solution phase (Figure 1 c). Bisulfate is a fairly chaotropic[17] hydroxyanion that is important in cloud formation.[18] We show that the bisulfate anions form hydrogen-bond-stabilized dimers, $[HSO_4 \cdots HSO_4]^{2-}$, from a 13.75 ppm resonance seen inside complexes with macrocyclic cyanostars[19] (**CS**, Figure 1 d). The cavity of cyanostar is size-matched to bisulfate (d_{ion} = 4.4 Å) and, from the behavior of perchlorate,[19–20] was expected to recruit two macrocycles to form a complex (Figure 1 e); the anion dimer was, however, unexpected. We propose that long-range repulsions between anions are offset by short-range attractions: two OH···O hydrogen bonds between bisulfates and the stabilization of the dianion dimer by 20 CH hydrogen bonds within the cyanostars.

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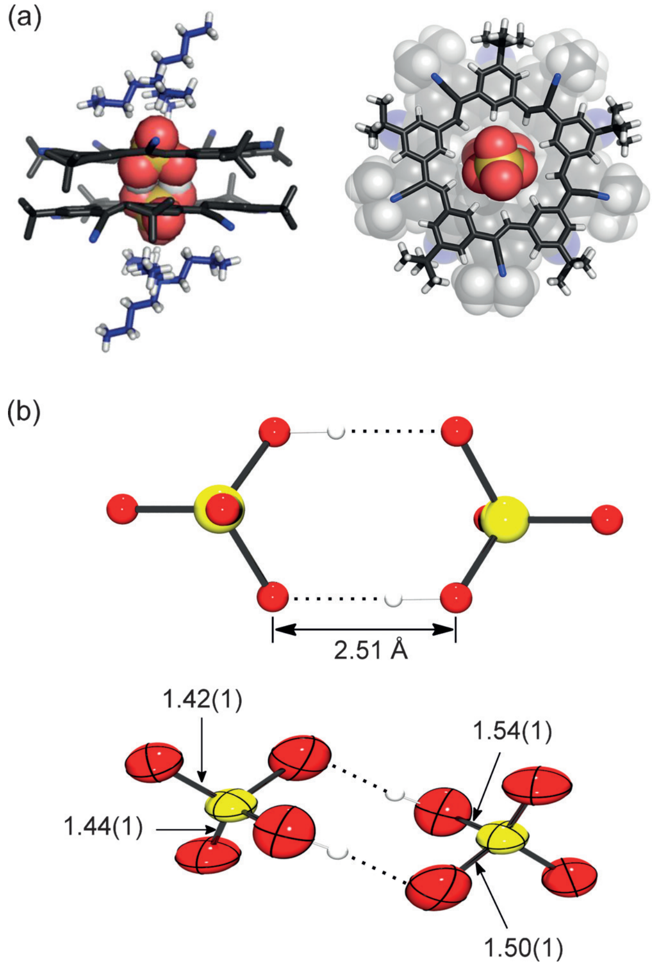

Figure 2. a) Crystal structure showing different views of the 2:2:2 complex $\mathbf{CS}_2(HSO_4)_2(NBu_4)_2$.[30] b) View of the encapsulated bisulfate dimer showing the self-complementary, anti-electrostatic hydrogen bonding (yellow = S, red = O). Thermal ellipsoids are drawn at 50% probability.

We were surprised to see a dimer of bisulfate anions in the crystal structure with cyanostar (Figure 2a). The dimer is inside a pair of cyanostars end-capped with two tetrabutylammonium (NBu_4^+) cations producing an overall 2:2:2 stoichiometry. The geometry of the bisulfate dimer $[HSO_4{\cdots}HSO_4]^{2-}$ (Figure 2b) shows a pair of short OH···O hydrogen bonds. The distance between donor and acceptor oxygens, $d_{OO} = 2.51$ Å, is shorter than in the parent salt (2.62 Å)[6a] and within the range observed for other bisulfate dimers ($d_{OO} = 2.47$–3.19 Å; Supporting Information, Table S1). Based on Jeffrey's classifications,[21] the bisulfate dimer in the cyanostar complex is on the 2.5-Å borderline between moderate and strong hydrogen bonds.

The cyanostars stabilize the dianionic bisulfate dimer with 20 CH···O hydrogen bonds ranging from 2.35 to 2.88 Å. These distances are, respectively, shorter and longer than the sum of the van der Waals radii for hydrogen and oxygen (2.6 Å). A small portion of the dimer crests either end of the binding pocket. These ends are engaged in ion pairing with the NBu_4^+ cations, which form four short CH···O hydrogen bonds (2.19–2.70 Å) to the dimer's ends.

Electrospray ionization mass spectrometry (ESI-MS) (Figure 3a) was conducted to delineate which species may be present in solution. A proposed dimer is seen in the peak for a 2:2:1 assembly (*m*/*z* 2268.2), which is assigned to a $[\mathbf{CS}_2(HSO_4)_2(NBu_4)]^-$ species. An unexpected peak observed at *m*/*z* 1471.2 is assigned to a species composed of a triple-decker of macrocycles hosting a pair of bisulfates, $[\mathbf{CS}_3(HSO_4)_2]^{2-}$. The peaks for simpler complexes with 1:1 (*m*/*z* 1012.5) and 2:1 (*m*/*z* 1929.0) stoichiometries are also observed.

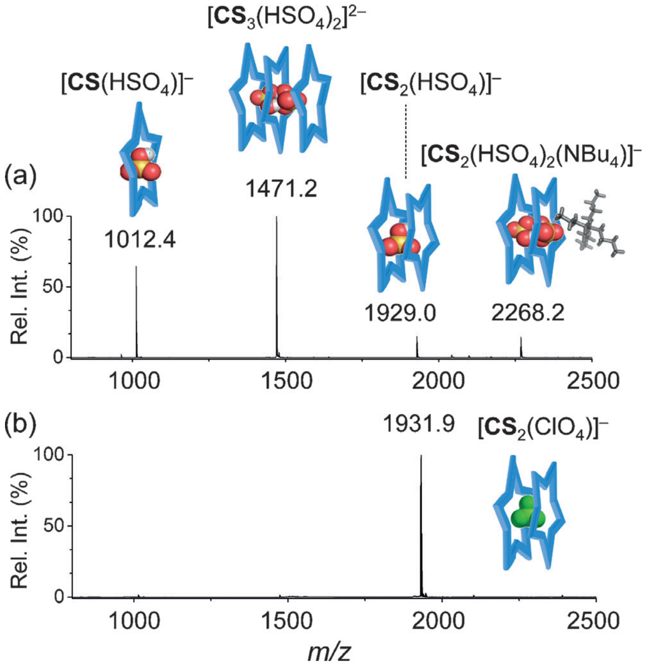

Figure 3. Negative-ion ESI-MS of solutions of cyanostar (2 mM) with either a) NBu_4HSO_4 (1 equiv) or b) NBu_4ClO_4 (1 equiv). Conditions: CH_2Cl_2, 50 °C source, 20 V cone voltage.

^{1}H NMR spectroscopy and titrations of cyanostar solutions with bisulfate show (Figure 4a) three out of the four complexes seen by mass spectrometry (2:1, 3:2, and 2:2). Correspondingly, plots of bisulfate-induced peak shifts and intensity changes (Figure 5a) show the three species in the early (0–0.5 equiv), mid (0.7 equiv), and late (>1 equiv) stages of the titration. The emergence of multiple bisulfate complexes during the course of the titration contrasts with perchlorate's formation of a single 2:1 complex (Figure 4b).

The only similarity between the titrations of bisulfate and perchlorate is the initial peak-shifting signature assigned to the formation of a 2:1 sandwich complex with bisulfate (0–0.5 equivalents); see the blue-colored peaks in Figure 4a,b. With further additions of bisulfate (0.5–1 equivalents), we see a multi-line signature attributed to the 3:2 species (red peaks) that reaches maximum intensity around 0.7 equiv. An eight-line signature (grey peaks, H^a and $H^{a'}$ are overlapping) for the 2:2 dimer also emerges in this region, from 1 equiv onwards.

The 2:2 dimer was unambiguously confirmed by NMR techniques and from a control using a cyanostar that cannot form π-stacked dimers.[22] The eight-line pattern was assigned

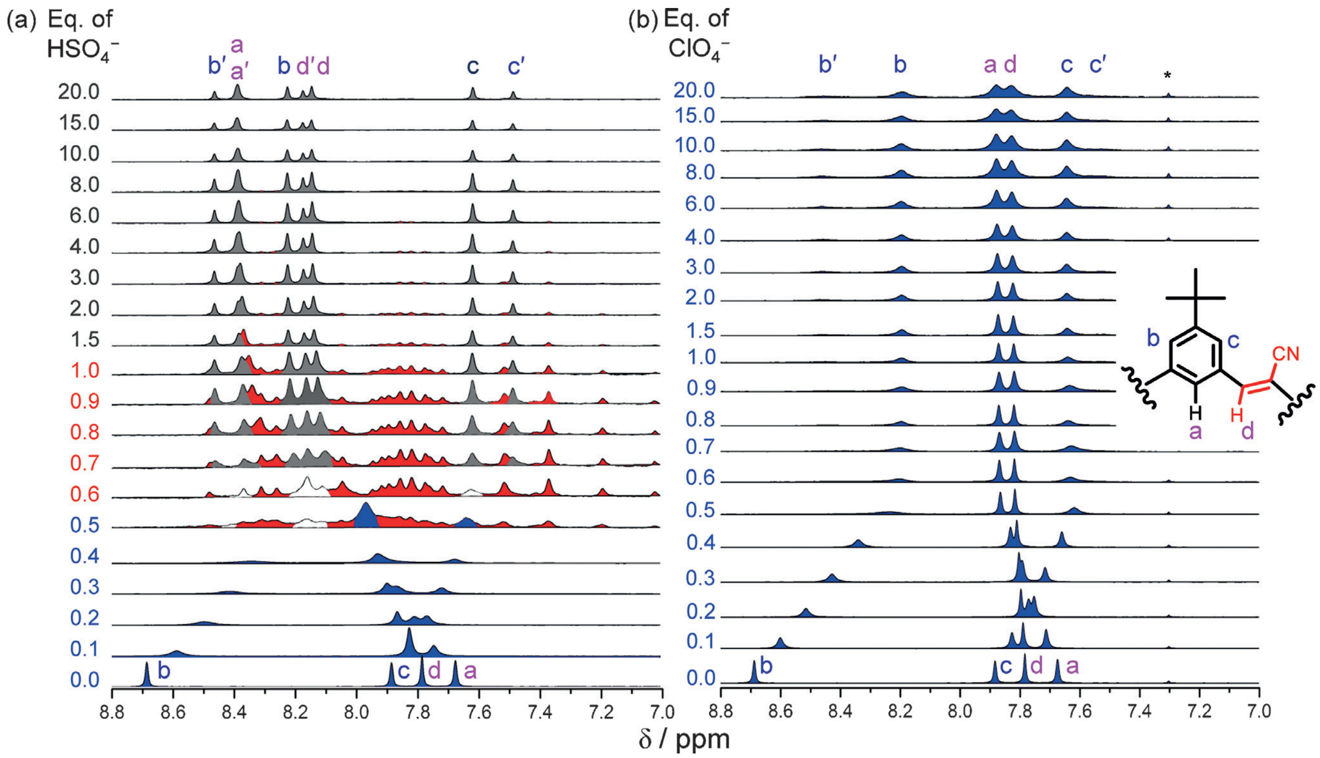

Figure 4. a) ^{1}H NMR spectra showing titration of cyanostar (1 mM) with NBu$_4$HSO$_4$. b) Control titration of cyanostar (1 mM) with NBu$_4$ClO$_4$. Conditions: CD$_2$Cl$_2$, 298 K, 500 MHz, dilution corrected titrations; * represents CHCl$_3$.

with the aid of two-dimensional NMR techniques (gCOSY, dqCOSY and TOCSY, see the Supporting Information). The pattern results from a pair of diastereomers for the 2:2 complexes, which contribute four lines each: meso (H^a, H^b, H^c, H^d) and chiral (H$^{a'}$, H$^{b'}$, H$^{c'}$, H$^{d'}$). When cyanostars form π-stacked dimers they produce shallow bowls with *M* or *P* chirality.[23] Thus, they can stack as an *MP* combination (meso) and as *MM* or *PP* pairs (chiral). The meso *MP* dimer is favored 60:40 over the chiral dimers, which matches the 66:33 ratio seen previously.[19–20]

To confirm that the dimer seen in the solid state is retained in solution we were fortunate to see evidence for self-complementary OH···O hydrogen bonding in unique ^{1}H NMR peaks: The bisulfate dimer in the 3:2 species has a ^{1}H NMR peak at 12.9 ppm (Figure 6a), which upon cooling to 218 K (Figure 6b) appears as two peaks at 13.10 and 13.12 ppm. Under these same conditions we see a peak at 13.75 ppm that we assign to the bisulfate dimer inside the 2:2 complex. As a control, no peaks were observed in the same region in studies conducted with perchlorate (Figure 6c) or when bisulfate (Figure 6d) was examined in the absence of cyanostar at near saturated concentrations (1 M). Furthermore, careful scrutiny of all prior works claiming the observation of $H_2PO_4^-$ dimers[5a,b, 12–16] did not find any corresponding signature of a hydrogen bonded −OH group.

The appearance and disappearance of the bisulfate's OH peak at 12.9 ppm (Figures 5c and the Supporting Information, Figure S3) coincides with the spectroscopic signature for the 3:2 complex seen in the aromatic peaks. The intensities of the 14-ppm peak for the 2:2 species also agree with the species distribution (Supporting Information, Figure S4).

This is the first NMR spectroscopic signature obtained for hydrogen bonding between two anions. The 13.75-ppm peak position supports borderline-strong[21] hydrogen bonds for the bisulfate dimer inside the 2:2 species as predicted from the crystal structure. The 13-ppm peak positions support moderate hydrogen bonds[21] in the 3:2 complex.

To confirm that the bisulfate dianion dimer is located inside the pair of cyanostars, we see close proton–proton contacts (Figure 7) from NOE cross-peaks originating from bisulfate and from cyanostar. Specifically, the 13.75-ppm peak is correlated with proton H^d at 8.05 ppm and both peaks originate from the 2:2 species. The 13.2-ppm peak is correlated with a resonance at 8.01 ppm for the 3:2 species.

The NBu$_4^+$ cations undergo moderate ion pairing with the dianionic 2:2 species. Consistently, the diffusion coefficients and chemical shifts determined from protons on the NBu$_4^+$ cation and from the cyanostar both respond to an increase in concentration and equivalents of salt added. The ion-paired species cannot be the 2:2:2 species and is best formulated as 2:2:*x*, with $x = 0$, 1, or 2 cations. The diffusion coefficients for the cation are lower than those observed in solutions of the parent salt alone. However, they are higher than the cyanostar in the resulting 2:2:*x* complex (Supporting Information, Figure S6). If the 2:2:2 assembly were present, all species would diffuse at the same speed.

We determined the stabilities of the various complexes to shed light on any anion–anion stabilization. The bisulfate complexes have remarkably large overall stabilities in solution (Table 1). The stability constants were quantified in dichloromethane using a combination of methods following procedures developed and used in the past whenever there

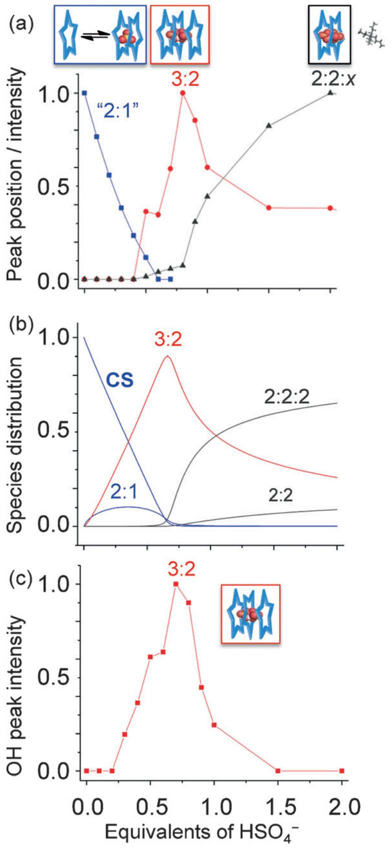

Figure 5. a) Plots of normalized peak positions (H^b, ca. 8.69 ppm; "2:1" = average of empty **CS**, 2:1 and 3:2) or intensities (3:2, 7.82 ppm; 2:2, H^c, 7.48 ppm) for addition of bisulfate to **CS** (10 mm, CD_2Cl_2). b) Distribution of species calculated from stability constants (Table 1, 10 mm). c) Bisulfate peak intensities (12.9 ppm) versus equivalents of HSO_4^- added (10 mm, CD_2Cl_2, 298 K).

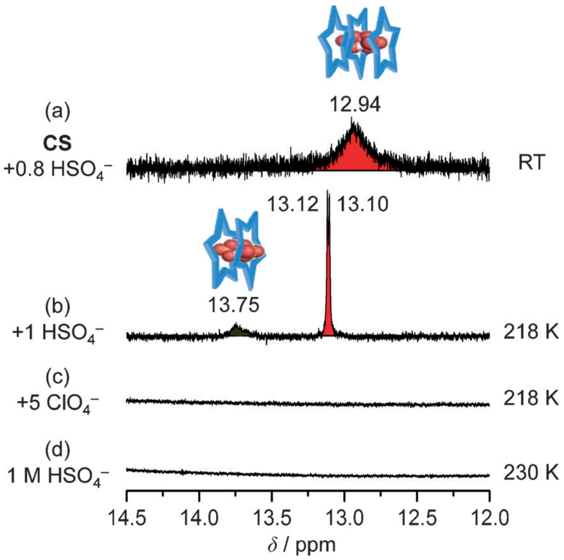

Figure 6. ^1H NMR signatures of a), b) the bisulfate dimers and c, d) controls in CD_2Cl_2: (a) 10 mm **CS** with 0.8 equiv of NBu_4HSO_4, (b) 10 mm **CS** with 1.0 equiv NBu_4HSO_4, (c) 10 mm **CS** with 5 equiv NBu_4ClO_4, and (d) 1 m NBu_4HSO_4 at 230 K.

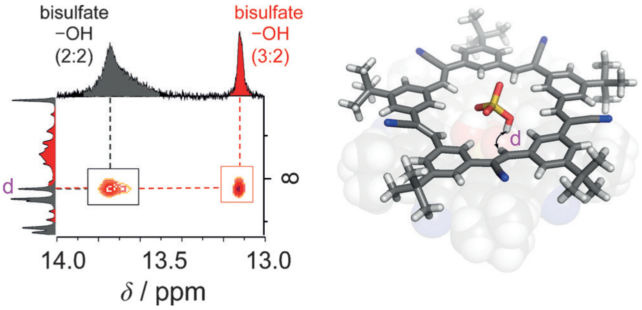

Figure 7. Through-space correlations confirming solution-phase structures; structures with NOE correlations labeled for HSO_4^- protons proximal to inner **CS** protons in CD_2Cl_2 and ^1H–^1H NOESY spectra with mixing time of 800 ms of **CS** (10 mm) with 4 equiv NBu_4HSO_4 (218 K, CD_2Cl_2).

Table 1: Experimental free energies in solution[a]

Equilibrium	Exp. ΔG [kJ mol^{-1}]	Eq.
$2\,HSO_4^- \rightleftharpoons [HSO_4\cdots HSO_4]^{2-}$	[b]	1
$\mathbf{CS} + HSO_4^- \rightleftharpoons [\mathbf{CS}(HSO_4)]^-$	[b]	2
$2\,\mathbf{CS} + HSO_4^- \rightleftharpoons [\mathbf{CS}_2(HSO_4)]^-$	-64 ± 4	3
$2\,\mathbf{CS} + 2\,HSO_4^- \rightleftharpoons [\mathbf{CS}_2(HSO_4)_2]^{2-}$	-96 ± 6	4
$3\,\mathbf{CS} + 2\,HSO_4^- \rightleftharpoons [\mathbf{CS}_3(HSO_4)_2]^{2-}$	-130 ± 6	5
$2\,\mathbf{CS} + 2\,HSO_4^- + 2\,NBu_4^+ \rightleftharpoons \mathbf{CS}_2(HSO_4)_2(NBu_4)_2$	-139 ± 10	6
$\mathbf{CS} + ClO_4^- \rightleftharpoons [\mathbf{CS}(ClO_4)]^-$	< -20	7
$2\,\mathbf{CS} + ClO_4^- \rightleftharpoons [\mathbf{CS}_2(ClO_4)]^-$	-68 ± 4	8

[a] Mean values and errors for the equilibria were established by fitting 12 independent titrations conducted over a concentration range of 2 μm to 10 mm recorded using UV/Vis and ^1H NMR spectroscopy. [b] Not observed.

are multiple equilibria.[24] To ensure that self-consistent values are obtained and that they are actually constants, 12 titrations were conducted across a wide concentration range of 2 μm–10 mm. Nevertheless, such multi-equilibrium data fitting can suffer from over-parameterization.[25] Therefore, the magnitudes of the stability constants were independently verified by competition experiments undertaken against perchlorate.

To provide insight on the formation of the bisulfate dimer in the 2:2 species, we can rearrange equations 3 and 4 in Table 1 as follows:

$$[\mathbf{CS}_2(HSO_4)]^- + HSO_4^- \rightleftharpoons [\mathbf{CS}(HSO_4\cdots HSO_4)\mathbf{CS}]^{2-} \tag{9}$$

This association is favorable, $\Delta G = -32$ kJ mol^{-1}, when it takes place inside the pair of macrocycles in dichloromethane ($\varepsilon = 8.9$). In contrast, when it occurs in the gas phase ($\varepsilon = 1$) as modeled theoretically,[4a] it is not thermodynamically stable ($\Delta G \approx +150$ kJ mol^{-1}). Thus, any long-range repulsion between the two anions is offset by their mutual short-range attractions and by stabilization of the dianion inside the cyanostar's electropositive cavity. The fact that an anion dimer is not seen with perchlorate indicates that the hydrogen bonding between bisulfate anions is also critical to stabilizing the 2:2 complex.

DFT calculations on the key complexes were conducted to provide corroborating evidence for the mutual stabilization of the bisulfate dimer in the complexes and to investigate the charge distribution in the bisulfate dimers. A model of the cyanostar was used in the calculations in which hydrogen atoms replace *tert*-butyl substituents. As a starting point, the bisulfate dimer, $[HSO_4\cdots HSO_4]^{2-}$, is calculated in dichloromethane to be unstable ($+10\,kJ\,mol^{-1}$) relative to the two separated and individually solvated bisulfate anions, $2\,HSO_4^-$.

The calculated values (see the Supporting Information, Table S7) agree with the rank order of stabilities for the complexes (2:1 < 2:2 < 2:2:2). The optimized geometry of the 2:2:2 agrees with the experiments. The S–O bond lengths reflect sp^2/sp^3 hybridization at the oxygen atoms, which is consistent with the bulk of the negative charge of the two anions residing closer together rather than farther apart. This distribution of S–O bond lengths is retained with and without a cation (modeled as the tetramethylammonium cation). This last observation reinforces the idea that the bisulfate dimer and the stability of the 2:2 complex do not rely on anion–cation ion pairing for stability.

We propose that the unique encapsulation environment inside the stacked pair of cyanostar macrocycles contributes to the observation and stability of the bisulfate dimer. All prior works[5a,b,12–16] that proposed dimers of $H_2PO_4^-$ have solvent-exposed receptors. That exposure may inhibit the observation of a proton resonance for the $H_2PO_4^-$ dimer on account of exchange processes. The less polar CH donors might also enhance the formation of these dimers. Most anion receptors have polar NH donors,[26] which may better stabilize the negative charge, obviating the need for the formation of the self-complementary hydrogen bonds. Among the few receptors solely bearing CH donors that have been used to examine bisulfate, including a cationic benzobisimidazolium macrocycle,[27] Sindelar's bambusurils,[28] and Reany's semithiobambusurils,[29] no dimers were reported.

In conclusion, the first substantiated observation of a hydrogen-bonded pair of anions has been described. The bisulfate dimer, $[HSO_4\cdots HSO_4]^{2-}$, is stable in the solution phase when encapsulated as a supramolecular complex inside cyanostar macrocycles. The structural and spectroscopic signatures for the dimer correspond to Jeffrey's classifications of a hydrogen bond that sits on the border between strong and moderate. Beyond this present study, novel selectivities may emerge and be exploited for the recognition of anions and cations that have hydrogen bond donors and acceptors.

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Keywords: anion recognition · bisulfates · hydrogen bonding · macrocycles · supramolecular chemistry

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[30] CCDC 1486436 contains the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

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