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Recognition Properties of Carboxylic Acid Bioisosteres: Anion Binding by Tetrazoles, Aryl Sulfonamides, and Acyl Sulfonamides on a Calix[4]arene Scaffold

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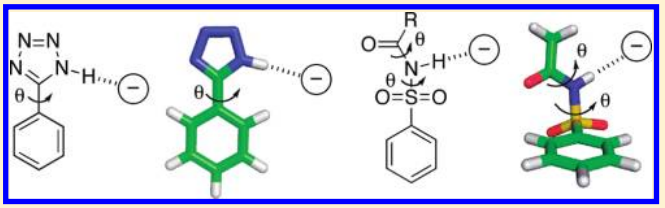
Supporting Information

ABSTRACT: Tetrazoles and acyl sulfonamides are functional groups that are common in medicinal chemistry but virtually unexplored as recognition elements in supramolecular chemistry. We report here on the anion binding properties of these highly acidic N−H functional groups. We have prepared two new calixarene-based tetrazole-containing hosts, as well as new acetyl sulfonamide and benzoyl sulfonamide hosts. We also report on analogous hosts bearing the better-known aryl sulfonamide functional group as a point of comparison. We find that these hosts are competent anion binders and that the recognition of anions by these groups is highly dependent on their conformational preferences. We also report in detail on the preferred molecular shape of each acid bioisostere as determined by calculations and structural database surveys, and discuss how these shapes impact binding in the context of the reported hosts.



INTRODUCTION

Tetrazoles, aryl sulfonamides, and acyl sulfonamides (Figure 1) are commonly used as carboxylic acid mimics in modern drug development, where they are valued for the acidity of their N−H functional groups. Relative to their carboxylic acid counterparts, compounds containing these groups often show improved oral availability, metabolic stability, and potency.[1−3] Not surprisingly, a vast number of small molecule therapeutic targets containing tetrazole,[4] aryl sulfonamide,[5,6] and acyl sulfonamide[7−9] functionality have been successfully developed. Losartan is one of the six approved tetrazole-containing angiotensin II type 1 receptor (AT_1) antagonists used for the treatment of hypertension.[10] Sulfanitran has been shown to stimulate transport properties of human multidrug resistance protein 2 (MRP2)[11] and is also an active ingredient in Novastat, a coccidiostat used in the poultry industry.[12] Navitoclax is a potent inhibitor of the antiapoptotic protein Bcl-x_L, overexpression of which is linked to several types of cancer.[13]

These classes of functional groups have two possible modes of encoding molecular recognition: when protonated, the acidic hydrogen atoms should be excellent hydrogen bond donors useful for binding anions and other hydrogen bond acceptors; when deprotonated, the resulting anionic conjugate bases of these functional groups are potential cation binders. Our group and others have investigated the recognition properties of deprotonated tetrazoles toward various cations.[14−20] Recently, we reported that a simple tris(tetrazole) host in its neutral, protonated form is among the most potent neutral binders of anions yet reported.[21] This spurred us to explore further the anion binding properties of tetrazoles and other acid bioisosteres. While aryl sulfonamides have been previously employed as anion recognition elements, the recognition properties of the more highly acidic acetyl and benzoyl sulfonamides have, to our knowledge, completely escaped the attention of supramolecular chemists.

RESULTS

To study these groups within the context of a well-understood scaffold, we carried out syntheses to affix each of them to calix[4]arene. We explored the binding of the resulting hosts with several biologically important halides and oxyanions and determined the roles of functional group conformational preferences on guest binding. We report that although the N−H proton acidities of the three classes of compounds are similar, tetrazoles proved to be superior anionic binders relative to their acyl and aryl sulfonamide analogues in this context.

The advanced bromocalixarene intermediates **4** and **5** were further converted to their cyano counterparts **6** and **7** (Scheme 1).[22] The copper-mediated cyanation of **4** to produce **6**[23] was hampered by solubility problems, low yields, and harsh conditions. Accordingly, we pursued a milder, palladium-catalyzed process for the synthesis of **7** that improved yields and reaction times. The tetrazole-containing hosts **8** and **9** were produced in good yield by treatment of each cyanated calixarene with $ZnBr_2$ and NaN_3 using a variation on the method of Demko and Sharpless.[24]

The known chlorosulfonyl calix[4]arene[25] **10** was the starting point for the synthesis of all reported aryl and acyl sulfonamide hosts. We found that stirring **10** with the appropriate *p*-substituted aniline in hot pyridine provided the best route to the aryl

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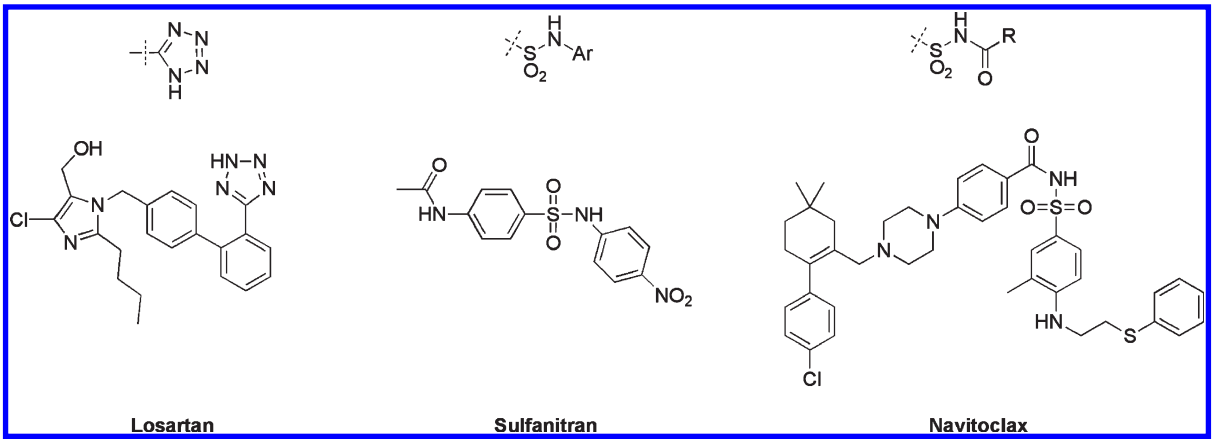
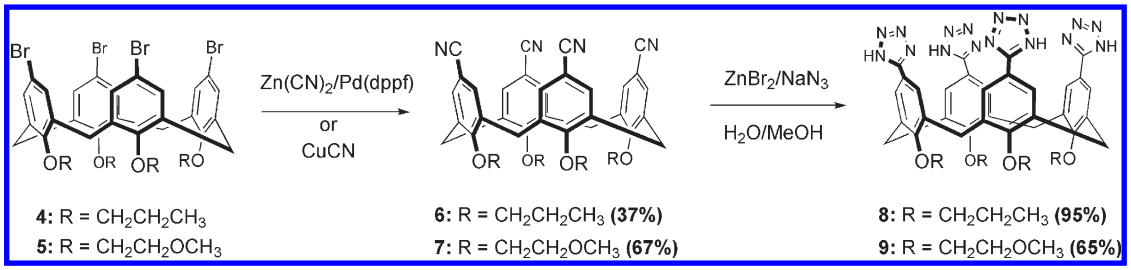
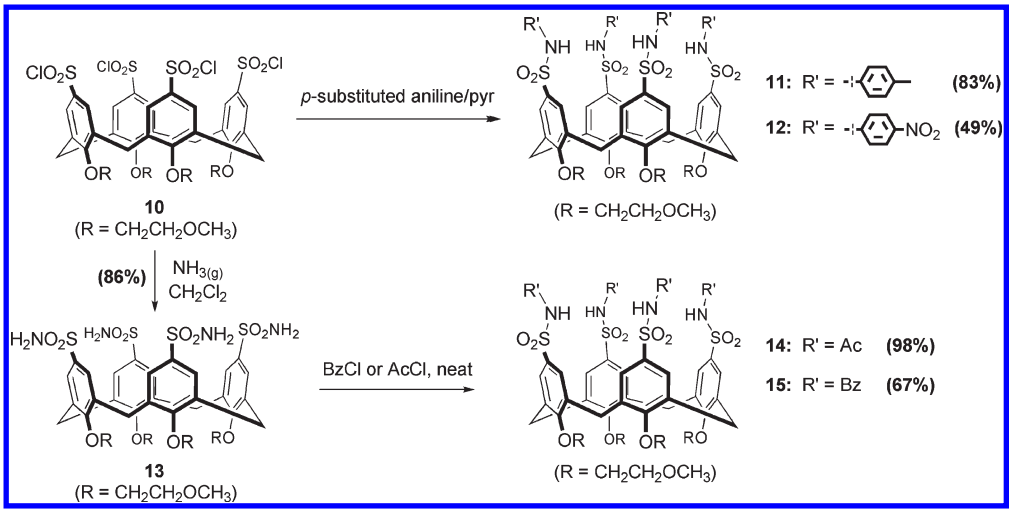


Figure 1. Representative drugs Losartan, Sulfanitran, and Navitoclax containing tetrazole, aryl sulfonamide, and acyl sulfonamide functionality, respectively.

Scheme 1. Synthesis of Tetrazole-Containing Hosts 8 and 9



Scheme 2. Synthesis of Aryl and Acyl Sulfonamide Hosts



sulfonamide hosts appended with a variety of anilines bearing electron-donating and -withdrawing substituents. While the more conventional conditions for sulfonamide synthesis (Et_2i-PrN ± DMAP) failed to provide fully tetra-substituted products, the method in neat pyridine consistently provided clean products and yields between 49% and 83%.

An extensive body of literature on the preparation of acyl sulfonamide exists,[26−31] but we found almost all literature methods incapable of providing the clean reactions and high conversions required in order to isolate significant quantities of the 4-fold-symmetric acyl sulfonamide products **14** and **15**. Synthesis of acyl sulfonamide hosts was first attempted using chlorosulfonyl **10** as starting material. Reaction of **10**, a primary amide (benzamide), and pyridine/DMAP even at reflux failed to produce the desired acyl sulfonamide product **15**. Use of Et_3N or Et_2i-PrN in various solvents at elevated temperatures led to complex mixtures and/or extremely slow reaction rates. We then turned our attention to *N*-acylation approaches that start instead with a primary sulfonamide. We created

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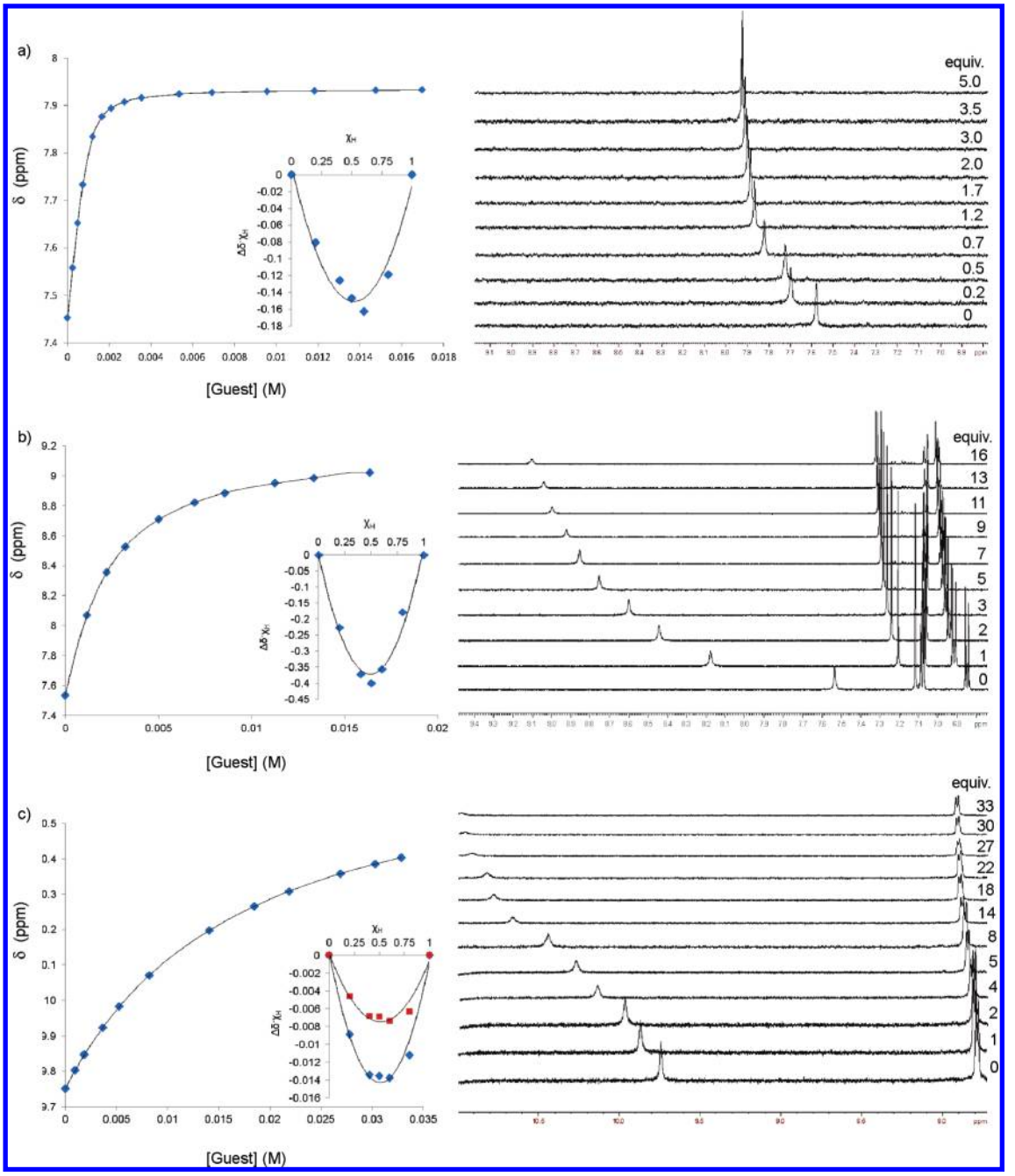

Figure 2. Exemplary binding data for each functional group studied. Left: Experimental data fit to a 1:1 binding isotherm arising from titrations of $Bu_4N^+ Cl^-$ into (a) tetrazole host **9** at 1 mM, (b) aryl sulfonamide host **11** at 1 mM, and (c) acyl sulfonamide host **15** at 1 mM. Insets: Job plots for each host plus (♦) $Bu_4N^+Cl^-$. Data for (■) $Bu_4N^+TsO^-$ also included for host **15**. Total concentrations for all Job plots = 5 mM. Right: Stacked plots of partial ^{1}H NMR spectra arising from the same titrations. Equivalents of $Bu_4N^+Cl^-$ added are indicated at far right.

the known primary sulfonamide **13**[25] in one step by treating **10** with NH_3 and reacted it with benzoyl chloride in pyridine/DMAP; again, conversions were extremely low, and **15** could not be isolated from the complex mixture. We attempted to couple **13** with benzoic acid[32] using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) in the presence of tertiary amine bases but observed instead rapid formation of benzoic anhydride from self-coupling of benzoic acid prior to slow reaction of the resulting anhydride to give some acyl sulfonamide-containing products. Finally, we found that solvent- and base-free conditions,[32] in which the primary sulfonamide **13** is treated with neat benzoyl chloride or acetyl chloride at high temperatures, proved to be a superb method that produced **14** and **15** in 98% and 67% yields, respectively.

Binding constants were determined by duplicate or triplicate ^{1}H NMR titrations. Host solutions (1 mM) in CD_3CN were first prepared, and portions of each were used to make up guest solutions (30−80 mM) in order to ensure that the host concentrations were kept constant throughout the titration. Representative binding curves and Job plots for each functional group, along with stacked plots following the downfield shifts of N−H signals for **11**, **12**, **14**, and **15** and aryl C−H signals for **8** and **9** from which these curves were generated, are shown in Figure 2.

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Table 1. Anion Affinities in CD_3CN of Tetrazole Functionalized Hosts 8 and 9, Aryl Sulfonamide Functionalized Hosts 11 and 12, and Acyl Sulfonamide Functionalized Hosts 14 and 15

	K_{assoc} $(M^{-1})^a$					
host	$Bu_4N^+Cl^-$	$Bu_4N^+Br^-$	$Bu_4N^+I^-$	$Bu_4N^+TsO^-$	$Bu_4N^+NO_3^-$	$Bu_4N^+HSO_4^-$
8	8450 ± 983	716 ± 72	62 ± 16	1407 ± 300	5796 ± 1481	656 ± 338
9	3560 ± 1395	804 ± 57	70 ± 9	515 ± 44	328 ± 13	336 ± 12
11	616 ± 78	116 ± 16	29 ± 12	59 ± 1	39 ± 15	49 ± 1
12	1026 ± 52	322 ± 4	41 ± 2	246 ± 11	98 ± 3	183 ± 12
14	389 ± 23	94 ± 5	24 ± 7	124 ± 2	55 ± 1	105 ± 4
15	112 ± 57	28 ± 4	<10[b]	116 ± 112	75 ± 4	72 ± 11

[a] Values reported are the averages resulting from tracking multiple host signals during 2−3 titrations for each host/guest pair. Errors reported are standard deviations. [b] Insignificant chemical shifts observed during titrations.

Association constants are reported in Table 1. The effect of remote substitution on the lower rim was tested by comparing propyl-substituted **8** and glycol-substituted **9**. The propyl-substituted host **8** showed increased binding potency (>2-fold for chloride and tosylate, >10-fold for nitrate) relative to the glycol lower-rim substitution (**9**), indicating binding affinity and selectivity depends somewhat on the conformational control provided by lower-rim functionality.[33] All other sulfonamide and acyl sulfonamide hosts were prepared with the glycol feet, however, which improved their solubility in CD_3CN and also provided a common basis for comparison.

Affinities ranged up to 8.5×10^3 M^{-1}, with each host showing the highest affinities for chloride among all anions tested (Table 1). In general, tetrazole-functionalized hosts **8** and **9** bound most anions almost an order of magnitude more tightly than their aryl and acyl sulfonamide analogues **11**−**12** and **14**−**15**. Among the aryl sulfonamides the binding of nitro-substituted host **12** to various guests was tighter than the corresponding methyl-substituted host **11**, as expected on the basis of the increased acidity and corresponding increase in hydrogen bond donation ability for **12**. This trend was not observed when the comparison was extended to include acyl sulfonamides **14** and **15**. Although acetyl and benzoyl sulfonamides like **14** and **15** are several orders of magnitude more acidic than aryl sulfonamides like **11** and **12**, the binding of anions by acyl sulfonamides was found to be significantly weaker than binding by aryl sulfonamides for all cases tested.

DISCUSSION

These functional groups are known first and foremost for their acidity. Representative N−H pK_a values are 4.6, 8.5, and 5.2 for exemplary tetrazole,[34] aryl sulfonamide,[35] and acyl sulfonamide[8] moieties, respectively. The large discrepancies between the anion binding strength of the aforementioned hosts were unexpected and do not follow a simple pK_a trend between the different classes of acid bioisoteres. We hypothesized that their varying conformations, largely ignored in their simple classification as interchangeable replacements for carboxylic acids, might play a large role in determining their anion-binding affinities. Molecular modeling studies were carried out to investigate the structures of the host−guest complexes. We were able to find a local minimum for each host in which the calixarene is in a perfect "cone" conformation and all four H-bond donor groups engage a central anion symmetrically (Figure 3), as well as a collection of local minima for each host involving puckered "pinched cone" calixarene conformations that allow only 3 N−H donors to engage the anion (see Supporting Information). Despite the gross differences in scaffold conformations, we noted similarities in the functional groups' own dihedral angles between both families of complexes. Our NMR data did not reveal which of the two types of calixarene conformation were operative in solution (it is probably a mixture of both), so we probed instead the role of each functional groups' conformational preferences in host−guest complex formation.

We examined the inherent conformational preferences of each of these acid bioisosteres, isolated and detached from the calixarene, using HF dihedral driving calculations about each rotatable bond in each of the functional groups. These calculations were put on a solid footing of experimental data by mining the CSD for all existing crystal structures containing relevant fragments and determining the relative occurrences of different dihedral angles. The combined computational and data-mining analyses for the key dihedral angles that define the inherent shapes of these bioisosteres are presented in Figures 4 (tetrazoles) and 5 (aryl and acyl sulfonamides).

Computational analysis of phenyl-(5-tetrazole)'s relative energy as the dihedral angle about the biaryl bond is driven from 0 to 180° shows a barrier of 13 kJ/mol on the potential energy surface at an angle of 90°, when conjugation with the benzene ring is broken (Figure 4b). Unlike related systems such as biphenyl, the potential energy surface remains completely flat until the phenyl-tetrazole bond is twisted ≥30° out of co-planarity. Surveying the CSD for similar fragments (Figure 5a) revealed a generally similar trend, with the large majority of structures having a dihedral angle ±50° from co-planar and a paucity of structures with dihedral values near 90°. In this case the CSD data is biased away from co-planarity of tetrazole and arene by the preponderance of crowded *ortho*-substituted 2-(5-tetrazolyl)-biphenyls, as in Losartan (Figure 1), in the CSD. Superimposing this simple angular preference onto the more complex structures of hosts **8** and **9** reveals why they are less potent than our earlier tris(tetrazole) host despite the inherent strength of the tetrazole NH···X^- hydrogen bond; The complex of a simplified analogue of host **8** with Cl^- (Figure 3a) demands that this dihedral is at the disfavored 90° angle (costing ∼13 kJ/mol per tetrazole) in order for all four tetrazole moieties to engage the guest simultaneously.

The shapes of the aryl and acyl sulfonamides are defined by three important dihedral angles. The conformations of the rotatable carbon−sulfur bonds for aryl sulfone type functionalities (θ_1, Figure 5a) have been reported in detail elsewhere and are

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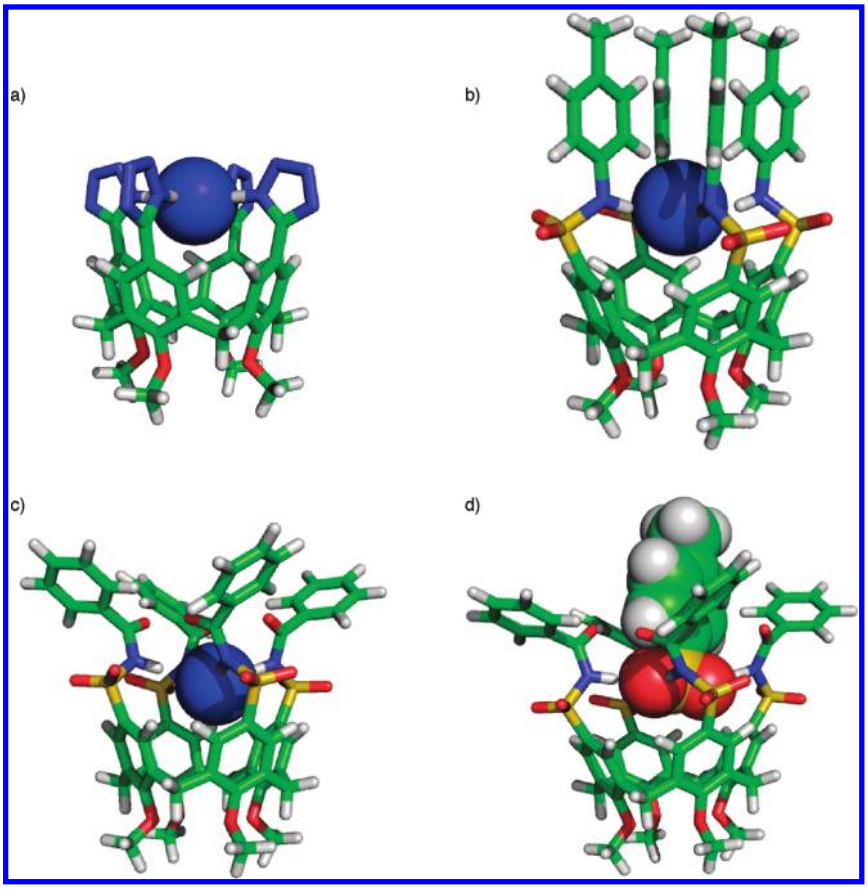

Figure 3. Local minima that involve the maximum four host−guest hydrogen bonds for representative host−guest complexes (HF/6-31+G*). Lower-rim substituents have been omitted. (a) Tetrazole functionalized host **8**/**9** complexed with Cl^-. Calculated average phenyl-tetrazole biaryl dihedral angle 86.6 ± 0.1°. (b) Aryl sulfonamide functionalized host **11** complexed with Cl^-. Calculated average θ_2 and θ_3 dihedral angles 167.9 ± 0.5° and 50.5 ± 1.0°, respectively. (c) Acyl sulfonamide functionalized host **15** complexed with Cl^-. Calculated average θ_2 and θ_3 dihedral angles 162.8 ± 3.8° and 28.1 ± 8.4°, respectively. (d) Acyl sulfonamide host **15** complexed with TsO^-. Calculated average θ_2 and θ_3 dihedral angles 160.5 ± 3.4° and 11.9 ± 3.0°, respectively.

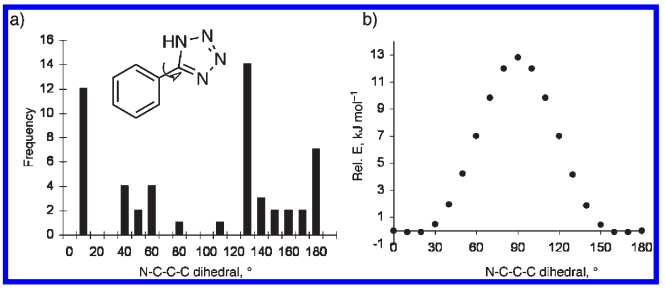

Figure 4. (a) Histogram generated by a survey of the Cambridge Structural Database (CSD) showing frequencies of biaryl dihedral angles reported in the literature for a simplified phenyl-(5-tetrazole) model. (b) Energy diagram calculated at the HF/6-31+G* level of theory when driving the biaryl dihedral angle from 0 to 180° in phenyl-(5-tetrazole).

similar (at θ_1 = ~90°) for both classes of compounds.[36,37] We analyzed the sulfonamide dihedral for rotation about the S−N bond (θ_2, Figure 5a) and the amide/aniline dihedrals that define rotation about the neighboring N−C bonds (θ_3, Figure 5a) in an attempt to help us understand the experimental anion binding data that we reported above. Calculated energy profiles show that both acyl sulfonamides and aryl sulfonamides share the same preference for conformation about their S−N bonds (θ_2 = ~60°, Figure 5e), although the depths of the energy wells are different. Data from the CSD (histograms in Figure 5c and d) show perfect agreement with the calculated angular preferences. In contrast, we find a strong divergence in the shape preferences of acyl and aryl sulfonamides about the N−C dihedral θ_3. In acyl sulfonamides, a strong preference for the planar *trans* (θ_3 = 180°) or *cis* (θ_3 = 0°) amide conformations is revealed by both the crystallographic data (Figure 5f) and the strong preference for these angles observed in the DFT-calculated potential energy surface (Figure 5h). In contrast, the calculations and CSD data show that the rotation of the equivalent bond in the aryl sulfonamides, in this case an aniline N−C type functional group, is essentially a flat potential energy surface with no preferences or barriers to rotation (Figure 5h). Again, the CSD data agree, in this case showing that aryl sulfonamides can adopt almost any value for θ_3 with no discrimination between conformations (Figure 5g). These data help us to evaluate the shapes of the host−guest complexes shown in Figure 3 and in the Supporting Information. Regardless of the calixarenes' conformations, the acyl and aryl sulfonamides must adopt a conformation wherein θ_2 = 160−170° (calculated values: aryl sulfonamides ~168°, acyl sulfonamides ~160°, see Figure 3) in order to direct their N−H bonds toward the guest. This is disfavored in both types of sulfonamide, and the larger penalty paid for the acyl sulfonamide (~40 kJ/mol per functional group) must be at least in part

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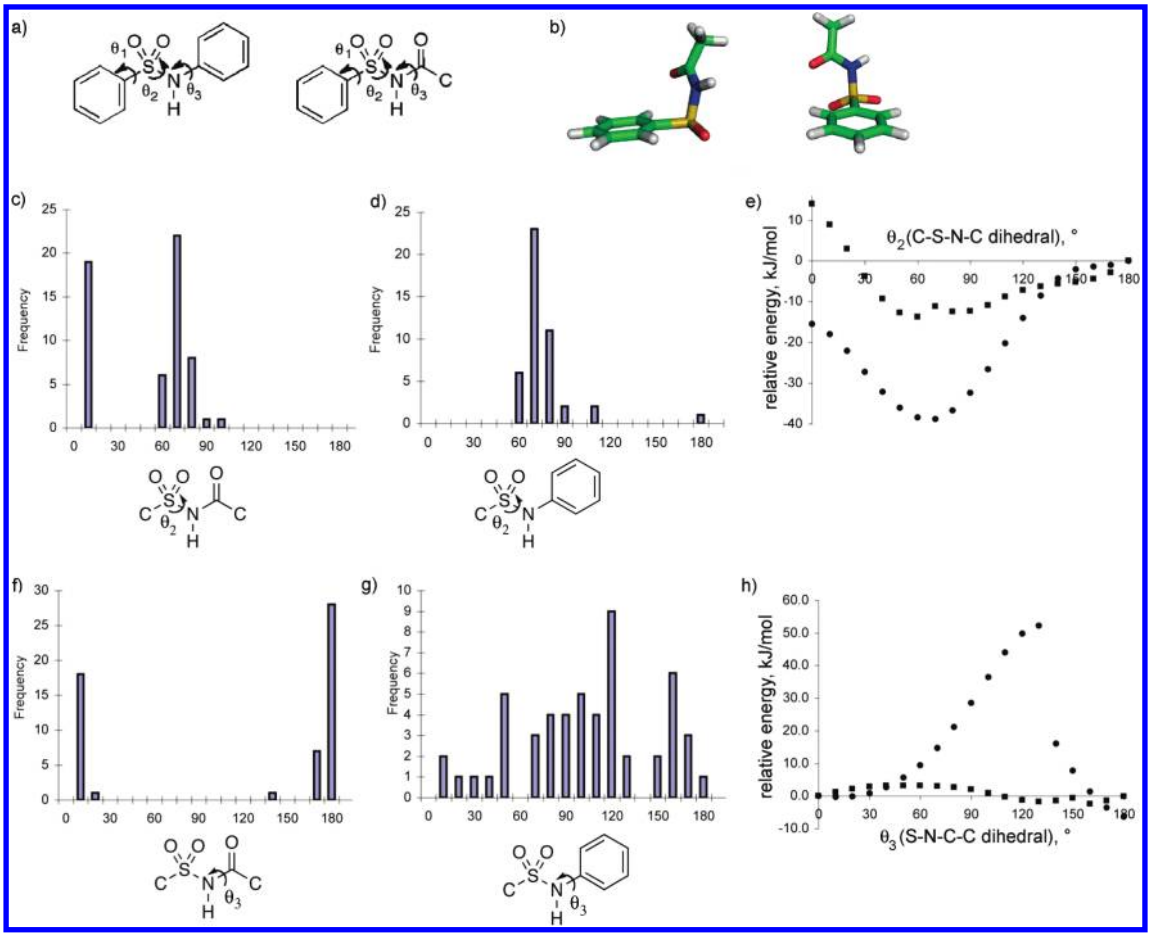

Figure 5. (a) Labeling of key dihedral angles θ_2 and θ_3 in acyl and aryl sulfonamides. (b) Two views of the global minimum energy conformation of a representative acyl sulfonamide fragment, *N*-acetyl benzenesulfonamide. (c, d) Histograms showing the frequencies of reported θ_2 dihedral angles for (c) acyl sulfonamide fragments and (d) aryl sulfonamide fragments from among all structures in the Cambridge Structural Database (CSD). (e) Energy profiles calculated for the same fragments while driving θ_2 from 0 to 180° in the acyl sulfonamide (●) and aryl sulfonamide (■) fragments. (f, g) Histograms showing the frequencies of reported θ_3 dihedral angles for (f) acyl sulfonamide fragments and (g) aryl sulfonamide fragments from among all structures in the CSD. h) Energy profiles calculated for the same fragments while driving θ_3 from 0 to 180° in the acyl sulfonamide (●) and aryl sulfonamide (■) fragments. All energies calculated at the HF/6-31+G* level of theory.

responsible for the binding constants we observe for hosts **14** and **15** being so much lower than would be predicted by their high acidity.

■ CONCLUSION

Our experimental binding data show that all three of these carboxylic acid bioisosteres are capable of forming well-ordered complexes with anions using their acidic N−H hydrogen bond donors. Tetrazoles have demonstrated their high inherent affinity for anions, and their ability to outperform carboxylic acids in a prior study[21] and sulfonamides in this study suggests that they should find expanded use as potent binders of anions that operate in a variety of structural contexts. Whereas aryl sulfonamides have been repeatedly explored as anion binders,[38] acetyl and benzoyl sulfonamides have not. Although the calixarene scaffold employed here does not effectively present the NH groups in a convergent manner, we feel that acyl sulfonamides have unique properties that hold promise for their further development. They are much more acidic than their normal sulfonamide counterparts. More importantly, we've shown that their shapes are rigidly defined by strong conformational preferences at all three rotatable dihedral bonds (see Figure 5b for the globally "perfect" shape that meets all of the dihedral preferences). We are continuing in our efforts to expand the supramolecular toolbox using new and readily accessible functional groups.

■ EXPERIMENTAL SECTION

Proton (^{1}H) NMR spectra were recorded on 500, 360, or 300 MHz spectrometers, as indicated in each case. Carbon (^{13}C) NMR spectra were recorded 125, 90, or 75 MHz as indicated in each case. Masses were acquired using high-resolution electrospray ionization mass spectra (HR-ESI-MS). Infrared spectra were recorded on KBr pellets as neat films, using thin films on KBr plates. All reactions were carried out under nitrogen unless otherwise indicated. Procedures for the preparation of **4**,[23] **6**,[23] **10**,[25] and **13**[25] have been previously reported.

25,26,27,28-Tetrakis(propoxy)-5,11,17,23-tetrakis-(tetrazole)calix[4]arene (8). 25,26,27,28-Tetrakis(propoxy)-5,11,17,23-tetrakis(cyano)calix[4]arene **6** (275 mg, 0.36 mmol), zinc bromide (656 mg, 2.9 mmol), and sodium azide (190 mg, 2.9 mmol) were added to a pressure tube containing MeOH (5 mL) and H_2O (5 mL). The tube was sealed, and the mixture was heated to 140 °C for 24 h with vigorous stirring. The reaction was allowed to cool to ambient temperature, and 1 M HCl (10 mL) and ethyl acetate (10 mL) were added. The mixture was stirred until all solid had dissolved, and the aqueous layer

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was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were evaporated, 0.5 M NaOH (30 mL) was added, and the mixture was stirred at ambient temperature for 2 h. The resulting zinc hydroxide precipitate was filtered, and with vigorous stirring the filtrate was acidified with 1 M HCl to pH 1. The crude brown solid was filtered, allowed to air-dry, and purified by flash chromatography (SiO_2, 10−20% MeOH in CH_2Cl_2 gradient) to afford 180 mg (95%) of a brown solid. Mp: 175 °C (dec). IR (KBr, thin film): 2962w, 2922w, 2872w, 1617w, 1559 m, 1458 m, 1358s, 1213 m, 1043w, 1005w, 962 m, 896 m, 752w, 563w. ^{1}H NMR (CD_3OD, 500 MHz): δ 1.09 (t, J = 7.4 Hz, 12 H), 2.02 (6, J = 7.5 Hz, 8 H), 3.45 (d, J = 1.7 Hz, 4 H), 4.03 (t, J = 7.3 Hz, 8 H), 4.64 (d, J = 13.7 Hz, 4 H), 7.42 (s, 4 H). ^{13}C NMR (CD_3OD, 125 MHz): δ 10.9, 24.7, 32.04, 78.7, 119.4, 128.8, 137.6, 156.7, 160.9. LR-MALDI-MS: 887.5 (MNa^+, $C_{44}H_{48}N_{16}O_4Na^+$; calcd 887.4). HR-ESI-MS: 865.4175 (MH^+, $C_{44}H_{48}N_{16}O_4H^+$; calcd 865.4123).

25,26,27,28-Tetrakis(ethoxymethoxy)-5,11,17,23-tetrakis (bromo)calix[4]arene (5). Adapted from a previously reported procedure.[23] 25,26,27,28-Tetrakis(ethoxymethoxy)calix[4]arene (410 mg, 0.7 mmol) and NBS (623 mg, 3.5 mmol) were stirred in anhydrous DMF (10 mL) for 24 h at room temperature. The reaction was quenched by the dropwise addition of 1 M HCl (6 mL). The precipitate was filtered and recrystallized in MeOH, yielding 420 mg (66%) of a white solid. The crude product was purified by flash chromatography (SiO_2, 3% EtOAc in hexanes) yielding 420 mg (66%) of a white solid. Mp: 180−182 °C. IR (KBr, thin film): 2924s, 1572w, 1456s, 1197s, 1127s. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 3.06 (d, J = 13.6 Hz, 4 H), 3.35 (s, 12 H), 3.72 (t, J = 5.0 Hz, 8 H), 4.05 (t, J = 5.3 Hz, 4 H), 4.41 (d, J = 13.5 Hz, 4 H), 6.79 (s, 8 H). ^{13}C NMR ($CDCl_3$, 90 MHz): δ 30.5, 58.6, 71.7, 73.3, 115.5, 131.1, 136.4, 155.3. HR-ESI-MS: 994.9643 (MNa^+, $C_{40}H_{44}O_8Na^+Br_4$; calcd 994.9633).

25,26,27,28-Tetrakis(ethoxymethoxy)-5,11,17,23-tetrakis (cyano)calix[4]arene (7). Compound **5** (450 mg, 0.46 mmol), $Zn(CN)_2$ (950 mg, 8.2 mmol), $Pd_2(dba)_3$ [tris(dibenzylideneacetone)dipalladium(0)] (92 mg, 0.1 mmol), and dppf (128 mg, 0.23 mmol) were added to an oven-dried Schlenk flask that was then purged with nitrogen and evacuated three times. Anhydrous DMF (5.0 mL) was added, and the flask was sealed and heated at 140 °C for 96 h. The reaction was then allowed to cool to ambient temperature and transferred to a round-bottom flask, and the DMF removed *in vacuo*. The crude black product was purified by flash chromatography (SiO_2, 20% CH_2Cl_2 in EtOAc) yielding 228 mg (67%) of a brown solid. Mp: 212 °C. IR (KBr, thin film): 2927w, 2881w, 2819w, 2225s, 1471s, 1125s, 1036s, 895 m, 735 m. ^{1}H NMR ($CDCl_3$, 360 MHz): δ 3.21 (d, J = 13.9 Hz, 4 H), 3.34 (s, 12 H), 3.71 (t, J = 4.43 Hz, 8 H), 4.15 (t, J = 4.8 Hz, 8 H), 4.54 (d, J = 13.8 Hz, 4 H), 6.99 (s, 8 H). ^{13}C NMR ($CDCl_3$, 90 MHz): δ 30.5, 58.9, 71.8, 74.2, 107.3, 118.4, 132.7, 136.0, 160.0. HR-ESI-MS: 779.3054 (MNa^+, $C_{44}H_{44}N_4O_8Na^+$; calcd 779.3057).

25,26,27,28-Tetrakis(ethoxymethoxy)-5,11,17,23-tetrakis (tetrazole)calix[4]arene (9). Compound 7 (275 mg, 0.36 mmol), zinc bromide (656 mg, 2.9 mmol), and sodium azide (190 mg, 2.9 mmol) were added to a pressure tube containing MeOH (5 mL) and H_2O (5 mL). The tube was sealed, and the mixture was heated to 140 °C for 24 h with vigorous stirring. The reaction was allowed to cool to ambient temperature, and 1 M HCl (10 mL) and ethyl acetate (10 mL) were added. The mixture was stirred until all solid had dissolved, and the aqueous layer was extract with ethyl acetate (3 × 15 mL). The combined organic layers were evaporated, 0.5 M NaOH (30 mL) was added, and the mixture was stirred at ambient temperature for 2 h. The resulting zinc hydroxide precipitate was filtered, and with vigorous stirring the filtrate was acidified with 1 M HCl to pH 1. The crude brown solid was filtered, allowed to air-dry, and purified by flash chromatography (SiO_2, 10−20% MeOH in CH_2Cl_2 gradient) yielding 220 mg (65%) of a yellow solid. Mp: 230−232 °C (dec). IR (KBr, thin film): 2923 m, 1616w, 1559 m, 1460s, 1456s, 1220w, 1123 m, 1040 m. ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.43 (s, 12 H), 3.46 (d, J = 13.6 Hz, 4 H), 3.92 (t, J = 4.7 Hz, 8 H), 4.32 (t, J = 4.7 Hz, 8 H), 4.78 (d, J = 13.6 Hz, 4 H), 7.53 (s, 8 H). ^{13}C NMR (CD_3OD, 75 MHz): δ 31.8, 59.0, 73.2, 75.1, 119.3, 128.6, 137.5,156.5, 160.7. HR-ESI-MS: 951.3735 (MNa^+, $C_{44}H_{48}N_{16}O_8Na^+$; calcd 951.3739).

General Procedure for the Preparation of Aryl Sulfonamide Substituted Calix[4]arenes 11 and 12. A flask containing chlorosulfonyl calix[4]arene **10** (50 mg, 0.048 mmol), the appropriate *p*-substituted aniline (0.77 mmol), and pyridine (4 mL) was heated to 70 °C with stirring. The reaction was left to stir for an additional 8 h at which point it was quenched with 1 M HCl (10 mL) and diluted with CH_2Cl_2 (15 mL). The organic layer was washed with 1 M HCl (3 × 10 mL), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The crude products were purified by flash chromatography (SiO_2, 10% MeOH in CH_2Cl_2).

25,26,27,28-Tetrakis(ethoxymethoxy)-5,11,17,23-tetrakis (*p*-toluenesulfamoyl)calix[4]arene (11). Brown solid. Yield = 53 mg, 83%. Mp: 140−144 °C. IR (KBr, thin film): 3251 m, 2923 m, 1511s, 1463 m, 1451 M, 1332 m, 1301 M, 1264 m, 1149s, 1105m. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.28 (s, 12 H), 3.08 (d, 4 H, J = 13.7 Hz), 3.25 (s, 12 H), 3.64 (t, 8 H, J = 4.4 Hz), 4.08 (s, 8 H), 4.46 (d, 8 H, J = 13.7 Hz), 6.90−7.23 (m, 24 H). ^{13}C NMR (CD_3CN, 75 MHz): δ 20.9, 31.5, 58.6, 72.5, 74.8, 123.9, 128.2, 130.7, 135.2, 135.5, 136.3, 136.4, 161.0. HR-ESI-MS: 1355.3998 (MNa^+, $C_{68}H_{76}N_4O_{16}S_4Na$, calcd 1355.4037).

25,26,27,28-Tetrakis(ethoxymethoxy)-5,11,17,23-tetrakis (4-Nitrobenzenesulfamoyl)calix[4]arene (12). Yellow solid. Yield: 49%. Mp: 140−144 °C. IR (KBr, thin film): 2926w, 1595s, 1520s, 1495 m, 1464 m, 1343s, 1264w, 1150s, 1106m. ^{1}H NMR (CD_3CN, 300 MHz): δ 3.15 (s, 12 H), 3.31 (d, 4 H, J = 13.7 Hz), 3.65 (t, 8 H, J = 4.6 Hz), 4.13 (t, 8 H, J = 4.6 Hz), 4.50 (d, 4 H, J = 13.5 Hz), 7.22 (m, 16 H), 8.14 (m AA′XX′, 8 H), 8.38 (s, 4 H). ^{13}C NMR (CD_3CN, 75 MHz): δ 31.4, 58.6, 72.5, 75.0, 119.7, 126.3, 128.1, 134.4, 136.8, 144.8, 144.8, 161.6. HR-ESI-MS: 1479.2854 (MNa^+, $C_{64}H_{64}N_8O_{24}S_4Na$, calcd 1479.2814)

25,26,27,28-Tetrakis(ethoxymethoxy)-5,11,17,23-tetrakis (acetylsulfonamido)calix[4]arene (14). A flask containing compound **13** (80 mg, 0.082 mmol) and acetyl chloride (3 mL) was brought to reflux with stirring. The mixture was stirred for an additional 24 h, and the acetyl chloride was removed *in vacuo* yielding 92 mg (98%) of a white solid that was used without further purification. Mp: 150−154 °C (dec). IR (KBr, thin film): 3220w, 2921w, 1686s, 1449s, 1419 m, 1343 m, 1266 m, 1151s, 1108s, 1044 m. ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.39 (s, 12 H), 3.52 (d, 4 H, J = 13.5 Hz), 3.88 (t, 8 H, J = 4.8 Hz), 4.33 (t, 8 H, J = 4.8 Hz), 4.72 (d, 4 H, J = 13.5 Hz), 7.50 (s, 8 H), 10.28 (s, 4 H). ^{13}C NMR (CD_3CN, 75 MHz): δ 24.0, 31.2, 58.9, 72.6, 75.3, 128.7, 134.8, 136.6, 161.6, 170.3. HR-ESI-MS: 1163.2567 (MNa^+, $C_{48}H_{60}N_4O_{20}S_4$-Na, calcd 1163.2581).

25,26,27,28-Tetrakis(ethoxymethoxy)-5,11,17,23-tetrakis (benzoylsulfonamido)calix[4]arene (15). A flask containing compound **13** (45 mg, 0.046 mmol) and benzoyl chloride (5 mL) was heated to 140 °C with stirring. The mixture was stirred for an additional 72 h and was then concentrated to near dryness *in vacuo*. Et_2O (5 mL) was added, and the resulting precipitate was filtered and air-dried. The white solid (43 mg, 67%) was collected and used without further purification. Mp: 260−265 °C (dec). IR (KBr, thin film): 2922w, 1699s, 1454s, 1435s, 1347 m, 1262 m, 1155s, 1108w. ^{1}H NMR (CD_3CN, 500 MHz): δ 3.28 (s, 12 H), 3.48 (d, 4 H, J = 13.7 Hz), 3.77 (t, 8 H, J = 4.6 Hz), 4.24 (t, 8 H, J = 4.3 Hz), 4.63 (d, 4 H, J = 13.5 Hz), 7.48 (t, 8 H, J = 7.7 Hz), 7.53 (s, 8 H), 7.62 (m AA′XX′, 8 H), 7.80 (m AA′XX′, 8 H), 9.77 (s, 4 H). ^{13}C NMR (CD_3CN, 125 MHz): δ 31.5, 58.8, 72.6, 75.2, 129.3, 129.3, 129.7, 133.7, 134.2, 134.5, 136.4, 161.9, 166.3. HR-ESI-MS: 1411.3231 (MNa^+, $C_{68}H_{68}N_4O_{20}S_4Na$, calcd 1411.3207).

Binding Studies. NMR binding studies were performed 500 and 360 MHz spectrometers for the sulfonamide- and tetrazole-containing

compounds, respectively. Deuterated acetonitrile was used as purchased from Cambridge Isotope Laboratories. Spectra were referenced to residual solvent. Binding constants were determined by duplicate or triplicate ^{1}H NMR titrations. Host solutions (1 mM) in CD_3CN were first prepared, and portions of each were used to make up guest solutions (30−80 mM) in order to ensure that the host concentrations were kept constant throughout the titration. Guest solutions were injected into host solutions incrementally, beginning with 10 μL injections and gradually raising the injection volume to 200 μL until the NMR tube was filled to capacity, resulting in final guest concentrations ranging from 5 to 52 equiv for strong- and weak-binding guests, respectively. Binding constants were determined by monitoring the downfield shifts of N−H protons for sulfonamide-functionalized hosts and C−H protons for tetrazole-functionalized host. Chemical shift data was fit to the 1:1 binding isotherm using a program developed by Dr. J.M. Sanderson, Centre for Bioactive Chemistry, Department of Chemistry, Durham University, Durham, U.K. that is available at http://dur.ac.uk/j.m.sanderson/science/downloads.

Molecular modeling. All molecular modeling was performed using Spartan '04 or Spartan '06 (Wave function, Inc.) at the HF/6-31+G* level of theory. For the dihedral driving calculations, structures were energy-minimized while selected dihedral angles were driven (one at a time) in 10° increments from 0 to 180°.

■ ASSOCIATED CONTENT

Supporting Information. Printouts of ^{1}H and ^{13}C NMR spectra for all new compounds and supplementary molecular modeling figure. This material is available free of charge via the Internet at http://pubs.acs.org.

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