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Do sulfonamides interact with aromatic rings?

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Abstract: Aromatic rings form energetically favorable interactions with many polar groups in chemical and biological systems. Recent molecular studies have shown that sulfonamides can chelate metal ions and form hydrogen bonds, however, it is presently not established whether the polar sulfonamide functionality also interacts with aromatic rings. Here we report synthetic, spectroscopic, structural and quantum chemical analyses on 2,6-diarylbenzenesulfonamides, in which two flanking aromatic rings are positioned close to the central sulfonamide moiety. Fine-tuning the aromatic character by substituents on the flanking rings leads to linear trends in acidity and proton affinity of sulfonamides. Our physical-organic chemistry study demonstrates that aromatic rings have a capacity to stabilize sulfonamides *via* through-space NH–π interactions. These results have implications in rational drug design targeting electron-rich aromatic rings in proteins.

Introduction

Sulfonamides are an important class of molecules that play diverse roles in chemistry, most notably in medicinal chemistry, because they have been widely used as anti-bacterial, anti-inflammatory and anti-cancer agents.[1] Due to the prevalence of sulfonamides in drugs and inhibitors, their syntheses have aroused widespread interests. In addition to the most common way of sulfonamide preparation from amine with activated sulfonyl derivatives,[2] metal-catalyzed coupling reactions using sulfur dioxide surrogate have been developed recently.[3] Extensive medicinal and physical-organic chemistry studies have firmly established that sulfonamides chelate the zinc ion, using carbonic anhydrase as a well-characterized model protein.[4] In biomolecular systems, sulfonamides are also involved in hydrogen bonding, both as H-bond donors and H-bond acceptors.[5] However, it is currently unclear whether sulfonamides can form weak non-covalent interactions with electron-rich aromatic rings.

Studies of non-covalent interactions in chemical and biological recognition processes demonstrated that aromatic rings form energetically favorable interactions with many polar groups *via* so-called polar–π interactions, including π–π stacking, cation–π interactions, anion–π interactions, SH–π interactions, OH–π interactions, halogen–π interactions and CH–π interactions.[6] At present, however, it remains to be established whether aromatic rings can interact with polar sulfonamides. Inspired by recent physical-organic work on the examinations of polar–π interactions in 2,6-diaryl aromatic molecules,[7] we envisioned that 2,6-diarylbenzenesulfonamides are particularly well-suited model systems for probing the existence of through-space polar–π interactions between sulfonamides and aromatic rings

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(Figure 1). Based on the well-established role of the substituent effect on non-covalent interactions involving aromatic rings,[6e-g, 6o-q, 8] we hypothesized that the acidity and the proton affinity of the sulfonamide moiety in 2,6-diarylbenzenesulfonamides can be fine-tuned by substituents on the two flanking aromatic rings *via* through-space effect, indicating the presence of energetically favorable association between sulfonamide and aromatic rings.

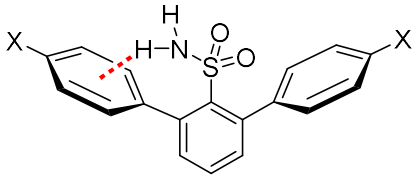
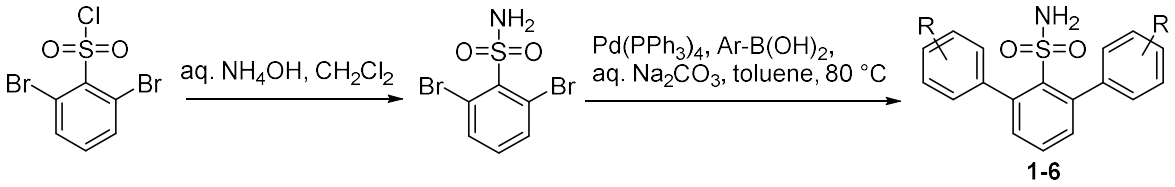


Figure 1. The 2,6-diarylbenzensulfonamide scaffold as a model system for examinations of polar–π interactions between the sulfonamide functionality and the aromatic ring.

Results and Discussion

Substituted 2,6-diarylbenzenesufonamides **1**–**6** were synthesized in two steps from 2,6-dibromobenzenesulfonyl chloride, which was initially converted to 2,6-dibromobenzenesulfonamide by treatment with aqueous ammonia in dichloromethane. Palladium-catalyzed Suzuki coupling of 2,6-dibromobenzesulfonamide with *para*/*meta*-substituted phenylboronic acids afforded 2,6-diarylbenzenesulfonamides **1**–**6** (Scheme 1).



Scheme 1. Synthesis of 2,6-diarylbenzenesulfonamides **1**–**6**.

We measured the pK_a values of 2,6-diarylbenzenesulfonamides **1**–**6** by UV-Vis spectroscopy in the pH range 9.0-13.5 (Table 1 and Figure S1).[7a] To ensure the solubility of all sulfonamides at these pH values, the solvent used contained buffered water and acetonitrile in the ratio 1:1. Plotting the pK_a values of *para*-substituted 2,6-diarylbenzenesulfonamides **1**–**5** against the Hammett sigma values (2σ, due to the presence of two flanking aromatic rings) revealed a strong linear correlation with the slope of -0.4 (i.e., ρ = +0.4) and R^2 = 0.99 (Figure 2). These results indicate that electron-donating groups make sulfonamides weaker acids, whereas the presence of electron-withdrawing groups leads to sulfonamides being stronger acids. We attribute these trends to the presence of energetically weak polar–π interactions

between the polar NH group of sulfonamide and the π system of the flanking aromatic ring. Electron-rich aromatic rings caused by electron-donating groups form stronger polar–π interactions, leading to weaker acids (because the acidic NH exists in protonated form, as it forms NH–π interactions). On the other hand, electron-poorer aromatic rings as a result of the presence of electron-withdrawing groups, form weaker polar–π interactions, leading to stronger acids. To further support the presence of through-space polar–π interactions, we also measured pK_a values of *meta*-F 2,6-diarylbenzenesulfonamide **6**. Comparisons of pK_a values between *meta*/*para*-substituted F showed that despite significant differences in Hammett sigma values (0.06 for *para*-F vs. 0.34 for *meta*-F), both sulfonamides have virtually the same pK_a value (12.04 for *para*-F vs. 12.02 for *meta*-F), further supporting the stabilization of sulfonamides by through-space effect over distinct through-bond effect (e.g. resonance and/or inductive) (Table 1).

Table 1. pK_a Values for Sulfonamides **1–6**.

compd	X	σ	pK_a[a]
1	H	0.00	12.14
2	*p*-OMe	–0.27	12.34
3	*p*-Me	–0.17	12.24
4	*p*-F	0.06	12.04
5	*p*-CF_3	0.54	11.74
6	*m*-F	0.34	12.02

[a] Determined in H_2O:acetonitrile = 1:1.

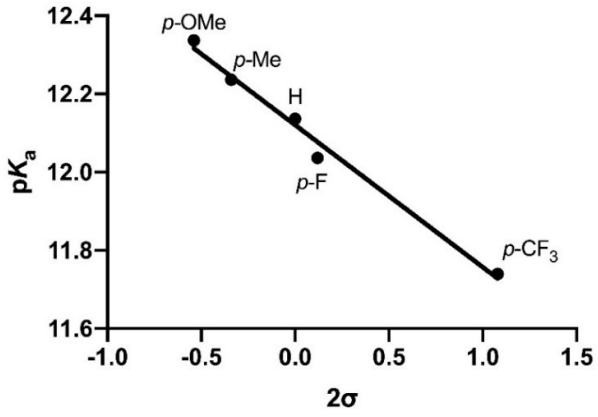


Figure 2. Correlation between pK_a values of sulfonamides **1**–**5** and the Hammett sigma values (2σ).

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Having shown that substituents at the distant *para*-position of flanking aromatic rings affect the acidity of 2,6-diarylbenzenesulfonamides, we carried out a solid-state structural analysis to provide an insight into the geometry and architecture of the scaffold. The single crystal X-ray structure of **4** reveals that the flanking aromatic rings are not in the same plane as the central benzene ring (Figure 3, Figure S2, and Tables S1–S5). They are close to an eclipsed conformation when viewing parallel to the plane of the central benzene ring (Figure S2). The interplanar angles between these flanking rings and the central benzene ring are 65.9° (φ_1) and 55.7° (φ_2) (Figure 3). The two hydrogen atoms of the sulfonamide moiety form different types of H-bonds. The H1B atom forms an intramolecular H-bond with the flanking aromatic ring (H···centroid distance is 2.681 Å), supporting the presence of through-space NH–π interactions. The H1A atom forms an intermolecular H-bond with the oxygen atom in an adjacent molecule of sulfonamide (H···O distance is 2.072 Å, Figure S2) such that the crystal lattice is constructed from H-bonded pairs (Figure S2). The structure of **4** indicates that a direct interaction between the central sulfonamide moiety and any *meta*/*para*-substituents on the flanking aromatic rings is not expected.

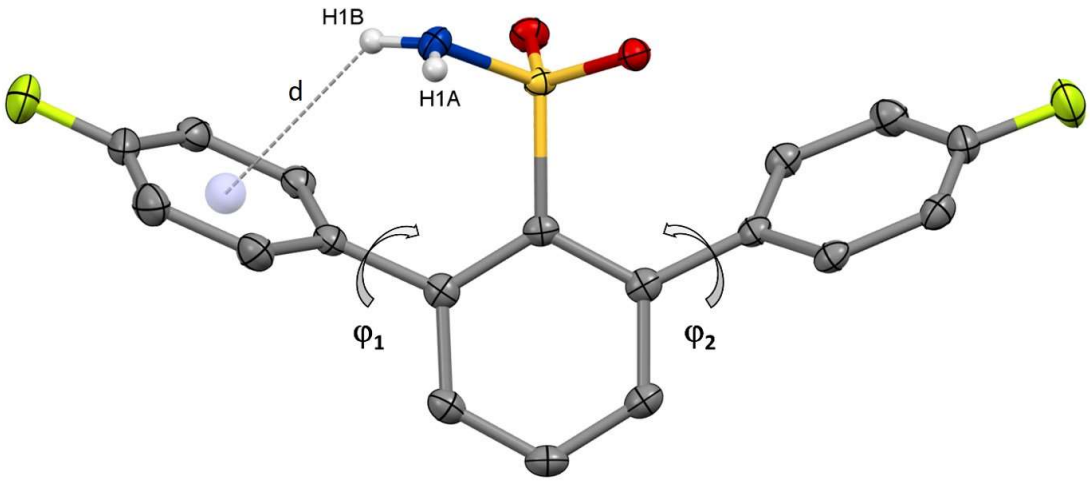

Figure 3. The crystal structure of **4**, with the H1B···centroid distance (d = 2.681 Å) shown. Non-hydrogen atoms are drawn with 50% probability ellipsoids.

Following the experimental examinations of 2,6-diarylbenezensulfonamides **1**–**6**, we carried out quantum chemical analyses aimed at understanding the precise role of through-space polar–π interactions in a series of substituted 2,6-diarylbenzenesulfonamides. Similar analyses on 2,6-diarylanilines, 2,6-diarylpyridines, 2,6-diarylphenols, and 2,6-diarylthiophenols provided a fundamental insight into the mechanism of stabilization of polar

groups by flanking aromatic rings.[7a, 7c-e] To this end, our main objectives were: (1) to determine the dependence of the energy (enthalpy) change for $ArSO_2NH_2 \rightarrow ArSO_2NH^- + H^+$ on the *para* vs. *meta* position of the substituent; (2) for X = H (i.e., sulfonamide **1**), to compute the barrier for internal rotation around the C–C bond linking the central benzenesulfonamide ring and the adjacent flanking aryl groups (i.e., the lowest energy of X = H is computed, followed by calculation of the rotational barrier around C–C for the left ring that associates with the NH group, while keeping the other ring at the lowest energy conformation); and (3) to reveal electronic mechanism behind the through-space polar–π interactions by means of an energy decomposition analysis (EDA). This computational analysis has been done using the ADF program at the BLYP-D3BJ/TZ2P level of dispersion-corrected DFT in aqueous solvation simulated using COSMO (Tables S6–S11).[9]

At difference with previous analyzed systems,[7a, 7c-e] the optimization of 2,6-diarylbenzenesulfonamides only drives to the eclipsed (or parallel) conformation (Figure 3), i.e., conformation with respect to the dihedral angle with the two aryl rings, both in the gas phase and in water, in agreement with X-ray structural analysis of sulfonamide **4** (Figure 3). The staggered conformation is not obtained, due to a more pronounced steric repulsion caused by the sulfonamide group. For all substituents X, it is observed how one of the N-H bonds points towards the center of one of the two aryl rings, with distances between the H and the center of the ring between 2.53 and 2.60 Å (Table 2), in line with the distance obtained from the X-ray structure of **4** (Figure 3). This observation supports the expected intramolecular interaction between sulfonamide NH group and the π-system, which will be quantified in the EDA calculations below. Geometries experience a small change with different X substituents, as reflected by the dihedral angles φ_1 and φ_2 enclosed in Table 2. For completeness, Table 2 also encloses the N–H stretching frequency shifts of this series of compounds. Electron-donating substituents go with lower N–H stretch frequencies than electron-withdrawing ones, consistent with a stronger N–H•••π interaction in the case of electron-donating substituents.

Figure 4 encloses the rotational barrier calculated for 2,6-diarylbenzenesulfonamide **1** in the range 0–180º and a more zoomed view in the range of 30–100º. Only the φ_1 dihedral angle was varied, whereas the other angle was kept at either 56.9º (water) or 55.6º (gas). In the range φ_1 = 130–180º, the close proximity between the H of the ring and the sulfonamide group causes steric repulsion, and such a sudden increase of the barrier. This is the reason why the staggered conformation was not found for this set of compounds. The conformers in the range φ_1 = 40–

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80º differ by less than 3 kcal mol^{-1}, with the minima at 58.6 and 57.3º in water and *in vacuo*, respectively.

Table 2. Dihedral angles φ_1 and φ_2 (in degrees, as shown in Figure 3), the closest distance between H of NH_2 and center of the ring (d, in Å), and N-H•••π stretching frequency shifts (NH st, in cm^{-1}) of the 2,6-diarylbenzenesulfonamides in water and in the gas phase.

	water				gas			
compd	**φ_1**	**φ_2**	**d**	**N-H st**	**φ_1**	**φ_2**	**d**	**N-H st**
1	58.6	56.9	2.544	3337.1	57.3	55.6	2.561	3366.5
2	57.3	55.2	2.528	3330.2	56.6	53.6	2.553	3353.7
3	57.9	55.9	2.536	3330.8	56.7	54.4	2.548	3359.9
4	58.2	56.3	2.561	3341.8	56.8	54.7	2.581	3369.4
5	58.8	57.4	2.579	3347.0	57.2	56.2	2.597	3374.1
6	59.3	57.6	2.558	3344.0	58.2	57.1	2.579	3372.0

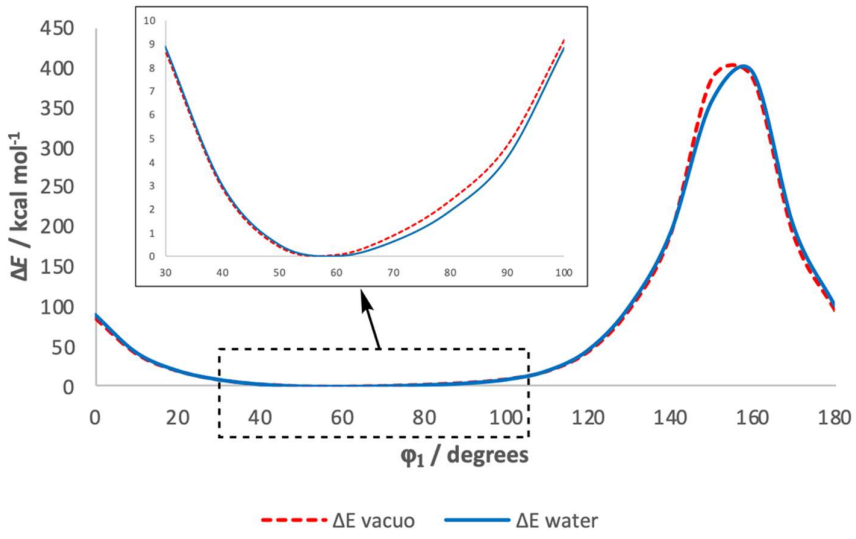

Figure 4. Relative energy ΔE (in kcal mol^{-1}) of 2,6-diarylbenzenesulfonamide **1** as a function of the rotation of the dihedral angle φ_1 (in degrees) in vacuo and in water.

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Next, we computed proton affinities (ΔE^{PA}) of the set of 2,6-diarylbenzenesulfonamides that follow the same trend, both in water and in vacuo (Table 3 and Figure 5). The ΔE^{PA} values have been plotted against twice the Hammett constant (2σ), achieving a good correlation in vacuo (slope = –8.00, $R^2 = 0.94$), and in water (slope = –1.11, $R^2 = 0.87$) (Figure 5). The larger proton affinities in vacuo than in water are supported by the larger slope of the former. Consistent with earlier work on related systems,[7a, 7c-e] the smaller $\Delta\Delta E^{PA}$ in water is caused by the stronger solvation of the proton than of the neutral sulfonamide. Notably, the similar ΔE^{PA} for *m*-F and *p*-F in water supports the presence of through-space interaction in this series of substituted 2,6-diarylbenzenesulfonamides.

Table 3. Proton affinities (in kcal mol^{-1}) of the 2,6-diarylbenzenesulfonamides in the gas phase and in water

	water		**gas**	
compd	ΔE^{PA}	ΔG^{PA}	ΔE^{PA}	ΔG^{PA}
1	178.8	166.6	346.9	330.5
2	179.8	166.3	348.8	332.2
3	179.4	167.2	348.2	330.5
4	178.5	166.4	342.5	326.1
5	178.0	165.8	336.5	321.4
6	178.0	166.0	342.6	326.1

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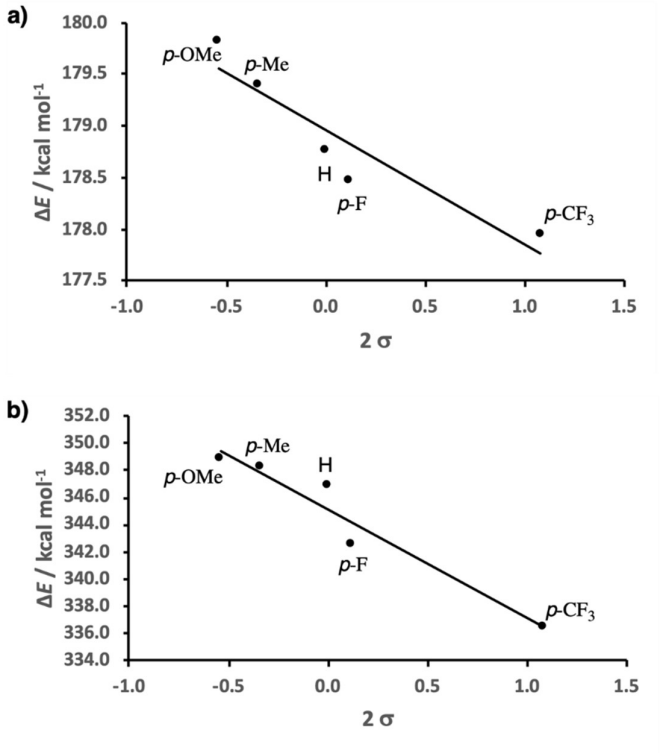

Figure 5. Dependence of calculated proton affinities Δ*E* on the Hammett sigma values (2σ) of *para*-substituted 2,6-diarylbenzenesulfonamides a) in water and b) in vacuo. Proton affinities were computed by removing the proton that interacts with the aromatic ring.

Aimed at obtaining a deeper understanding of through-space polar–π interactions between the sulfonamide functionality and the aromatic ring, we have analyzed the effect of distance and geometry on such interaction by means of an energy decomposition analysis (EDA) on a model system based on sulfonamide **1** (**H** in Figure 6). In particular, we will focus on the interaction between the N-H and the aryl ring (Figure 3). For such, the right aryl was substituted by a hydrogen atom, whereas we have broken the C-C bond between the central and left ring, terminated them by hydrogens, and placed the aromatic ring completely perpendicular to the N-H bond, keeping exactly the same distance between H of NH_2 and the center of the ring (d) as in equilibrium structure **1** (Figure 6). The EDA data for this model system (ΔE_{Pauli} = 25.2, ΔV_{elstat} = –9.7, ΔE_{oi} = –7.8, ΔE_{disp} = –8.1, and ΔE_{int} = –0.3 kcal mol^{-1}) indicate that the interaction between the sulfonamide group and the aryl ring is slightly attractive. Then, two different approaches were followed with the aim to probe how the through-space interaction is affected by: 1) the distance between the H atom and the center of the ring (model $\mathbf{H^d}$ in Figure 6); and 2) the angle between the N-H and the center of the ring (model $\mathbf{H^a}$ in Figure 6).

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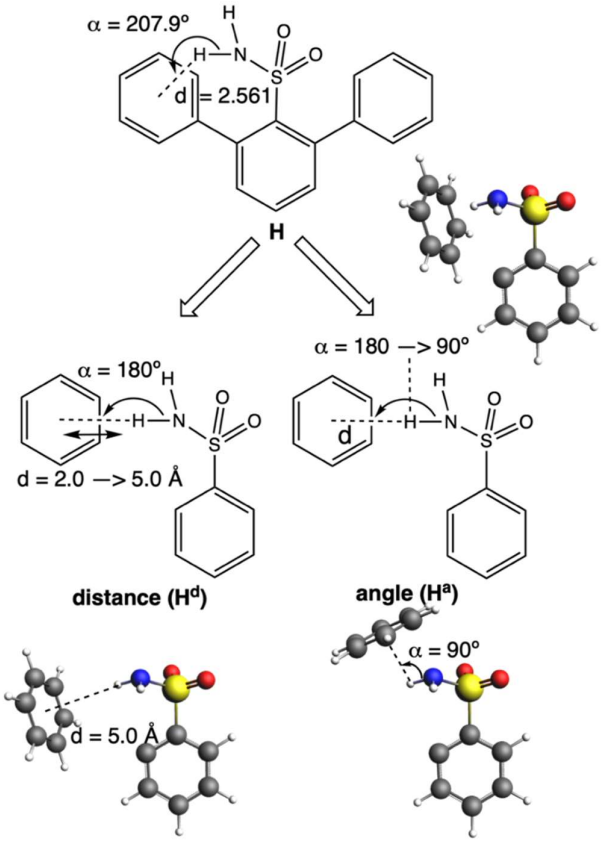

Figure 6. Model systems used for the analysis of the effect of distance (**H**^{d}) and angle (**H**^{a}) on through-space NH–π interactions.

Figure 7 shows how the interaction between the sulfonamide group and the aromatic ring is affected by the distance between the NH and the center of the aryl ring. Whereas d = 2.561 Å in system **H** (ΔE_{int} = –0.3 kcal mol^{-1}), the most attractive interaction is found at 3.1 Å with ΔE_{int} = –4.5 kcal mol^{-1}. Any distance smaller than 2.5 Å, i.e., smaller than d in **H**, causes a repulsive interaction due to the steric Pauli repulsion. From this distance the three attractive terms, i.e., ΔV_{elstat}, ΔE_{oi} and ΔE_{disp}, compensate ΔE_{Pauli} (Figure 7). Thus, it is proven how such polar–π interaction clearly depends on the distance between the NH and the π-ring.

The second analysis focused on analyzing how the N-H-center of the ring angle (α) influences the interaction energy between the sulfonamide and the aromatic ring (**H**^{a} in Figure 6). For such analysis, an EDA was performed from 180 to 90º, in opposite direction to the other aryl group. The analysis was performed at the most stable distance as observed in Figure 7, i.e., d = 3.1 Å instead of d = 2.561 Å as in equilibrium system **H** (Figure S3). The ΔE_{int} depicted in Figure 8 shows how the most attractive interaction is obtained at 175º (–4.7 kcal mol^{-1}), but ΔE_{int} for angles from 180 to 150º differ by less than 1 kcal mol^{-1}. Inside this range there is

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enclosed that for the equilibrium structure of **H** (152.1º). As for the above analysis, inside the EDA terms, ΔE_{Pauli} experiences the largest change.

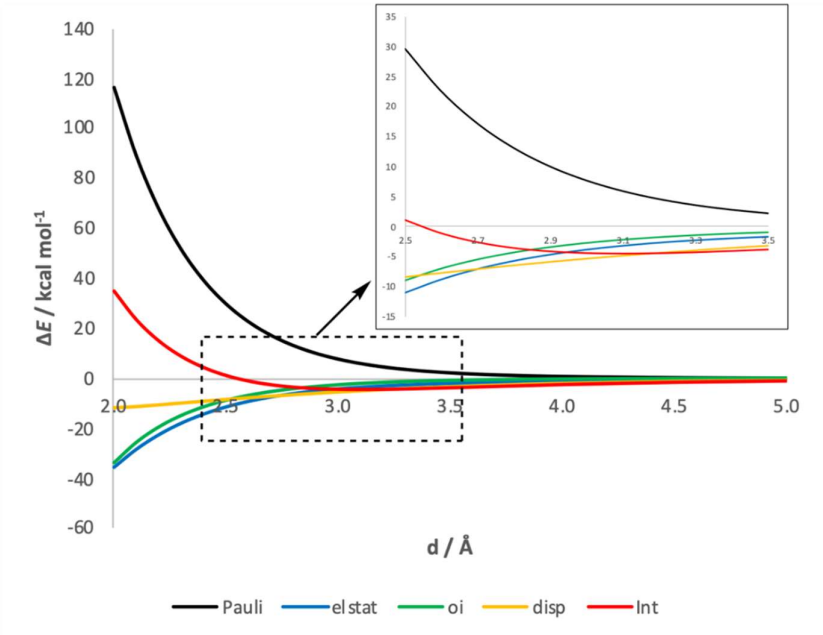

Figure 7. Energy decomposition analysis of system **H**[d] when varying the distance between the NH group and the center of the ring (d) from 2.0 to 5.0 Å at 180°.

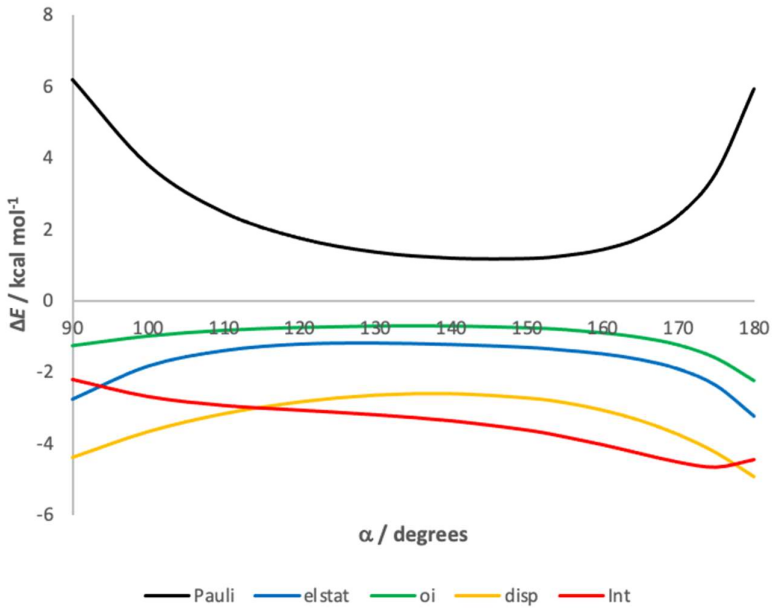

Figure 8. Energy decomposition analysis of system **H**[a] when varying the angle between the N-H group and the center of the ring (α) from 180 to 90º with d = 3.1 Å.

With the aim to go beyond the 2,6-diarylbenzenesulfonamide model system and show a universal presence of polar–π interaction in stabilization of sulfonamides by aromatic rings, substituted benzene in the above model system has been analyzed. Thus, we have built the equivalent to **H^{d}** system (Figure 6) for all *para*-X and *meta*-X compounds under analysis by following the same procedure, and analyzed the interaction between the sulfonamide N-H and the π-ring by means of an EDA analysis with a distance d = 3.1 Å and angle α = 180º (Figure S4). The results enclosed in Table 4 confirmed the presence of energetically favorable NH–π interaction across the whole series. EDA analysis further revealed that the most attractive interaction is found for anisol (i.e., with electron-donating *p*-OMe, ΔE_{int} = –4.8 kcal mol^{-1}), whereas the least energetically favorable interaction was found in trifluoromethylbenzene (i.e., with electron-withdrawing *p*-CF_3, ΔE_{int} = –3.6 kcal mol^{-1}). The more attractive electrostatic interaction ΔV_{elstat} is determinant at the stronger interaction in case of anisole, despite its larger Pauli repulsion compared to the latter. The reason why ΔE_{Pauli} is not the same in all cases is due to the fact that the occupied π system (amplitudes along the six C atoms) differs along the different X-Ph. This is even more clearly observed when we compare *p*-F-Ph to *m*-F-Ph (Table 4), with a small difference in ΔE_{Pauli} caused by the change in the relative orientation between F-Ph and NH.

Table 4. Energy decomposition analysis (in kcal mol^{-1}) of the interaction between the sulfonamide and the π-ring in benzene and substituted benzene.

compd	ΔE_{Pauli}	ΔV_{elstat}	ΔE_{oi}	ΔE_{disp}	ΔE_{int}
H-Ph	5.9	–3.2	–2.3	–4.9	–4.5
MeO-Ph	8.5	–4.7	–3.0	–5.5	–4.8
Me-Ph	6.9	–3.8	–2.5	–5.2	–4.7
F-Ph	6.2	–2.8	–2.3	–5.0	–3.9
CF_3-Ph	4.7	–1.7	–1.9	–4.8	–3.6
m-F-Ph	5.6	–2.2	–2.2	–4.9	–3.6

For completeness, the role of the SO_2 moiety in the sulfonamide-group interaction has been further analyzed by considering other model systems in which this group has been replaced by other ones. In particular, the SO_2 moiety in the above analyzed 2,6-diarylbenzenesulfonamide system has been substituted by SO (sulfinamide), S (thiohydroxylamine), O (hydroxylamine) and CH_2 (methanamine). The results of these

computations further highlight the particular role and behavior of SO_2 compared to the other groups (Tables S12-S14 and Figure S5-S6): 1) sulfonamide yields the shortest distance between H of NH_2 and center of the ring; 2) SO_2 also gives the smallest proton affinity; and 3) it also presents the most attractive interaction energy between the benzene ring and the sulfonamide.

Conclusion

Our physical-organic chemistry study on 2,6-diarylbenzenesulfonamides has demonstrated that the polar sulfonamide functionality has an ability to form energetically favorable polar–π interactions with aromatic rings. Experimental measurements of pK_a values and computational calculations of proton affinities of 2,6-diarylbenzenesulfonamides have revealed that there is a linear correlation with Hammett sigma values of substituents located at the distant *para* position of flanking aromatic rings. Supported by structural analyses, these results indicate that 2,6-diarylbenzenesulfonamides are stabilized by intramolecular through-space polar–π interactions. More detailed quantum chemical analyses further showed that very similar geometries across the series of 2,6-diarylbenzenesulfonamides are obtained both in vacuo and in water, with the N-H group pointing towards one of the aryl rings. More generally, energy decomposition analyses on the effect of the distance and the geometry on the through-space interaction between the sulfonamide and the aromatic ring have further demonstrated that the strength of NH–π interactions depends both on the NH–π distance and NH–π angle, in agreement with overall trends of weak non-covalent interactions in chemical and biological systems.[6a, b] These findings have implications in rational drug design and development, because sulfonamides have found wide applications in medicinal chemistry as drugs targeting various diseases.

Experimental Section

Synthesis of 2,6-dibromobenzenesulfonamide. To a solution of 2,6-dibromobenzenesulfonyl chloride (500 mg, 1.50 mmol) in dichloromethane (5 mL) at 0 °C, saturated NH_4OH (0.8 mL, 15 mmol, 10 equiv) was added dropwise and then allowed to warm to room temperature. After stirring for another 2 hours, the solvent was evaporated to dryness and the residue was washed with minimum water to give the 2,6-dibromobenzenesulfonamide as a white solid without further purification.

2,6-dibromobenzenesulfonamide. White solid (442 mg, 94%); ^{1}H NMR (400 MHz, Methanol-d_4) δ 7.83 (d, J = 8.0 Hz, 2H), 7.22 (t, J = 8.0 Hz, 1H); ^{13}C{^{1}H} NMR (101 MHz, Methanol-d_4) δ 142.3, 137.0, 133.8, 122.6; HRMS (ESI): *m/z* calcd for $C_6H_5Br_2NNaO_2S$ [M + Na]$^+$: 335.8300, found 335.8289.

Synthesis of 2,6-diarybenzenesulfonamides. To a mixture of 2,6-dibromobenzenesulfonamide (60 mg, 0.190 mmol) and $Pd(PPh_3)_4$ (22 mg, 0.02 mmol, 0.1 equiv) in toluene (2 mL) were added a solution of arylboronic acid (2.5 equiv) in ethanol (2 mL) and an aqueous solution of Na_2CO_3 (2 M, 0.57 mL, 3 equiv). After it was heated at 100 °C under microwave for 24 hours, the reaction mixture was poured into 20 mL of water and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by flash column chromatography on silica gel (PE/EA) to give the 2,6-diarybenzenesulfonamide.

2,6-Diphenylbenzenesulfonamide ***(1)*** White solid (23 mg, 40%); mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.52 (m, 5H), 7.50–7.41 (m, 6H), 7.39–7.34 (m, 2H), 3.95 (s, 2H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.9, 141.3, 140.6, 131.9, 130.6, 129.3, 128.6, 128.3; HRMS (ESI): *m/z* calcd for $C_{18}H_{15}NNaO_2S$ [M + Na]$^+$: 332.0716, found 332.0725.

2,6-Di(4-methoxyphenyl)benzenesulfonamide ***(2)*** White solid (25 mg, 36%); mp 163−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.50 (m, 1H), 7.44–7.40 (m, 4H), 7.34 (d, J = 7.6 Hz, 2H), 7.30–7.25 (d, J = 7.6 Hz, 4H), 3.99 (s, 2H), 2.43 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 141.9, 140.6, 138.4, 138.1, 131.7, 130.5, 129.3, 129.1, 21.4; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}NNaO_4S$ [M + Na]$^+$: 392.0927, found 392.0908.

2,6-Di(4-methylphenyl)benzenesulfonamide ***(3)*** White solid (20 mg, 31%); mp 222−223 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55–7.47 (m, 1H), 7.47–7.43 (m, 4H), 7.32 (d, J = 7.6 Hz, 2H), 7.03–6.97 (m, 4H), 4.02 (s, 2H), 3.86 (s, 6H); ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$) δ 159.7, 141.7, 140.6, 133.5, 131.7, 130.5, 130.5, 114.0, 55.4; HRMS (ESI): *m/z* calcd for $C_{20}H_{19}NNaO_2S$ [M + Na]$^+$: 360.1029, found 360.1031.

2,6-Di(4-fluorophenyl)benzenesulfonamide ***(4)*** White solid (23 mg, 35%); mp 198−200 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57–7.53 (m, 1H), 7.52–7.47 (m, 4H), 7.34 (d, J = 7.6 Hz, 2H),

7.20–7.12 (m, 4H), 4.01 (s, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.7 (d, J = 248.5 Hz), 140.9, 140.4, 137.0 (d, J = 3.5 Hz), 132.0, 130.9 (d, J = 8.1 Hz), 130.6, 115.5(d, J = 21.6 Hz); ^{19}F NMR (376 MHz, Chloroform-*d*) -113.4; HRMS (ESI): *m/z* calcd for $C_{18}H_{13}F_2NNaO_2S$ $[M + Na]^+$: 368.0527, found 368.0520. The crystal used for single crystal X-ray diffraction was grown in methanol at room temperature by slow evaporation.

2*,6-Di(4-trifloromethylphenyl)benzenesulfonamide** ***(5) White solid (18 mg, 21%); mp 177−180 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76–7.72 (m, 4H), 7.70–7.59 (m, 5H), 7.38 (d, J = 7.7 Hz, 2H), 4.04 (s, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 140.9, 140.3, 132.4, 131.1, 130.5 (q, J = 32.6 Hz), 129.7, 125.5 (q, J = 3.7 Hz), 122.8. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.6; HRMS (ESI): *m/z* calcd for $C_{20}H_{13}F_6NNaO_2S$ $[M + Na]^+$: 468.0463, found 468.0452.

2,6-Di(3-fluorophenyl)benzenesulfonamide ***(6)*** Yellowish solid (19 mg, 29%); mp 198−199 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 – 7.53 (m, 1H), 7.44 (td, J = 8.0, 5.8 Hz, 2H), 7.37 (d, J = 7.6 Hz, 2H), 7.32 (dt, J = 7.7, 1.3 Hz, 2H), 7.22 (dt, J = 9.4, 2.1 Hz, 2H), 7.14 (tdd, J = 8.5, 2.6, 1.0 Hz, 2H), 4.07 (s, 2H); $^{13}C\{^{1}H\}$ NMR (101 MHz, $CDCl_3$) δ 162.6 (d, J = 247.6 Hz), 143.2 (d, J = 8.0 Hz), 140.7 (d, J = 2.0 Hz), 140.3, 132.2, 130.9, 130.1 (d, J = 8.4 Hz), 125.2 (d, J = 3.1 Hz), 116.4 (d, J = 22.4 Hz), 115.3 (d, J = 21.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ -112.2; HRMS (ESI): *m/z* calcd for $C_{18}H_{13}F_2NNaO_2S$ $[M + Na]^+$: 368.0527, found 368.0526.

pK_a measurements

pK_a values of benzenesulfonamides **1**–**6** were measured by UV-Vis spectroscopy, following a reported protocol.[7a] Briefly, a set of buffers covering a pH range of 9.0–13.5 was prepared. The pH range of 9.0–11.0 was covered by a borax/boronic acid buffer. The pH range of 11.0–13.0 was covered by a disodium hydrogen phosphate/sodium phosphate buffer. The pH range of 13.0–13.5 was covered by a KCl/KOH buffer. 25 ml of all buffers were adjusted to pH with 5M NaOH or 9M HCl and ionic strength (0.1 M) using KCl, and the volume was adjusted to 50 ml. To obtain final pH values, the solutions were measured again with 50% acetonitrile added, since pK_a measurements were performed under these conditions. Next, sulfonamides **1**-**6** were dissolved in acetonitrile to a concentration of 2.5 mM. A 96-well Microtiter Plate (UV star, greiner bio) was filled with buffers with increasing pH and in each well 80 µl acetonitrile, 100 µl buffer and 20 µl compound solution was pipetted. Measurements were performed using

a Tecan Spark M10 plate reader recorded in the range between 230–400 nm with a 2 nm resolution. Data were normalized and the spectral differences between the maximal and minimal spectra were plotted against the log(pH) (Figure S1). Finally, the pK_a values were determined using a 4-parameter fit in Prism GraphPad 6.

Single crystal X-ray crystallography

The data were collected at 100(1)K on a Synergy, Dualflex, AtlasS2 diffractometer using Cu$K\alpha$ radiation (λ = 1.54184 Å) and the *CrysAlis PRO* 1.171.40.29a suite.[10] Using SHELXLE[11] and Olex2[12] the structure was solved by dual space methods (SHELXT[13]) and refined on F^2 using all the reflections (SHELXL-2018/3).[14] All the non-hydrogen atoms were refined using anisotropic atomic displacement parameters and hydrogen atoms bonded to carbon inserted at calculated positions using a riding model. The sulfonamide hydrogen atoms (H1A, H1B) were located in the electron density difference maps and the coordinates refined. Data, data collection and structure refinement details are summarised in Table S1 and selected parameters in Tables S2–S5. Brief summary for $C_{18}H_{13}NO_2F_2S$ (M =345.35 g/mol): triclinic, space group $P\bar{1}$ (no. 2), a = 7.56370(10) Å, b = 10.6028(2) Å, c = 11.3685(2) Å, α = 114.260(2)°, β = 99.852(2)°, γ = 101.726(2)°, V = 780.05(3) Å^3, Z = 2, T = 100.00(14) K, μ(CuKα) = 2.147 mm^{-1}, *Dcalc* = 1.470 g/cm^3, 17436 reflections measured (8.902° ≤ 2Θ ≤ 148.274°), 3095 unique (R_{int} = 0.0211, R_{sigma} = 0.0132), which were used in all calculations. The final R_1 was 0.0282 (I > 2σ(I)) and wR_2 was 0.0719 (all data). The CCDC deposition number is 2030936. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Quantum Chemical Analyses

All calculations were carried out with the Amsterdam Density Functional (ADF) program using dispersion-corrected density functional theory at the BLYP-D3BJ/TZ2P level of theory. The effect of solvation in water was simulated by means of the Conductor like Screening Model (COSMO) of solvation as implemented in ADF. The role of distance and geometry on through-space interaction was analyzed within the framework of quantitative Kohn-Sham molecular orbital theory in combination with a quantitative energy decomposition analysis (EDA) in the gas phase. The interaction energy ΔE_{int} between the benzenesulfonamide and aryl fragments was decomposed into the classical electrostatic attraction ΔV_{elstat}, Pauli repulsion ΔE_{Pauli} between occupied orbitals, stabilizing orbital interactions ΔE_{oi}, and dispersion $\Delta E_{disp.}$[9, 15]

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: aromatic compounds • molecular recognition • non-covalent interactions • polar-π interactions • sulfonamides

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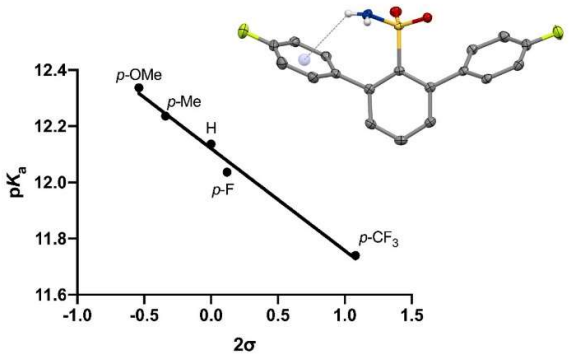
Graphical Abstract



Through space! We demonstrate, using experimental and quantum chemical techniques, that aromatic rings can stabilize sulfonamides *via* through-space NH–π interactions. Our findings have implications in rational drug design targeting electron-rich aromatic rings in proteins.