An Anomeric Answer to Sulfenamide Stability and α-Nucleophilicity

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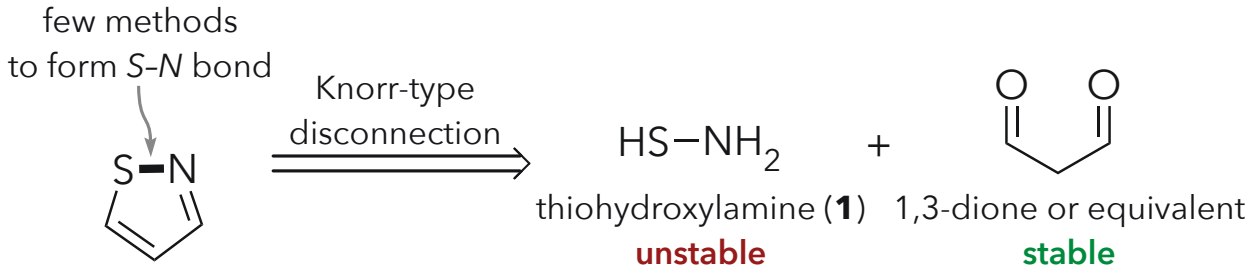
Abstract

The S–N bond remains a synthetically challenging motif for organic chemists to access. The problem arises from instability in many sulfenamide derivatives which have led to fewer S–N bond surrogate molecules compared to its hydroxylamine (NH_2OH) and hydrazine (NH_2NH_2) analogs. In turn, sulfenamides have been often omitted in studies regarding α-nucleophilicity. Herein we provide factors responsible for the stability of the sulfenamide motif, and provide new insight on the nucleophilic properties of sulfenamides as they relate to the α-effect.

Introduction

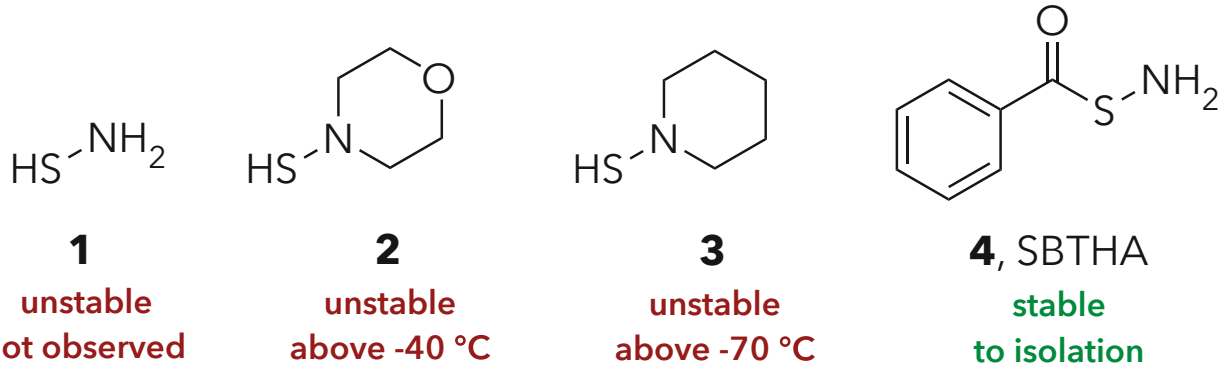
The sulfur-nitrogen bond is prevalent within pharmaceuticals,[1–3] polymers,[4,5] and natural products.[6] Recently, sulfenamides have been identified as the ideal functional group for accessing higher-oxidation state sulfur-nitrogen species[7–11] and for thioamination.[12] Despite this prominence, the S–N bond remains a synthetically challenging motif that often requires alternative strategies for formation.[13,14] Isothiazole, for example, contains a formal S–N single bond that requires creative solutions and synthetic designs to access. Strategies that form

isothiazole have included late-stage S–N bond formation,[15,16] rearrangements of complex precursors,[17,18] or transition metal catalyzed reactivity[19]—all strategies which address the formation of the troublesome S–N bond.



Scheme 1: Retrosynthetic analysis of isothiazole utilizing sulfenamide, thiohydroxylamine, as a synthon.

A cursory retrosynthetic analysis of isothiazole leads to a simple Knorr-type disconnection[20] of a 1,3-dicarbonyl (or equivalent) and the ideal S–N bond donor, thiohydroxylamine (**1**, Scheme 1), the simplest sulfenamide. Unfortunately, this retrosynthetic disconnection is not productive, as **1**, and other sulfenamides exhibit a range of thermal instabilities, the reason for which remains poorly understood (Scheme 2). For instance, sulfenamide **1** has only been studied theoretically, and **2** and **3** are thermally unstable above -40°C.[21] In contrast, an *S*-substituted sulfenamide (**4**) and their derivatives are stable to isolation, with **4** being shelf-stable for more than 6 months.[22]



Scheme 2: Literature examples of sulfenamides and their relative stability.[21,22]

While the properties of sulfenamide **1** have been explored through computational studies, it remains largely irrelevant to synthetic chemists due to its instability. However, **4**

has been shown to react to form thio-oxime materials which are H_2S-releasing and have been incorporated into polymers.[4,23,24] Matson and co-workers even propose that **4** acts as a click-reaction partner with aldehydes, similar to the click-reactions already known for hydroxylamine and hydrazine.[24] But as we demonstrate, the behavior of **4** is different from those classical α-effect nucleophiles comprised of only second-row elements.

Indeed, a deeper understanding of the factors that stabilize sulfenamides could provide new avenues for both their synthesis and utility in making higher-value products. Motivated by disagreement in the justification for the stability of sulfenamide derivatives, we sought to characterize the reactivity and nucleophilicity of the stable sulfenamides with respect to secondary bonding and molecular orbital considerations.

Herein, we characterize the orbital interactions active in the synthetically useful sulfenamide derivative **4**. Additionally we characterize the nucleophilicity of sulfenamide **4** by analyzing its nucleophilicity in comparison to hydroxylamine and hydrazine. Sulfenamide nucleophiles are often omitted from study, and to our knowledge, the nucleophilicity of non-ionic sulfenamides have never before been characterized.

Results and Discussion

Stability and Conformational Preference of Sulfenamides

It may be unsurprising that the S–N bond of sulfenamides is unstable due to the union of a hard nitrogen and soft sulfur atom (a non-classical example of the concept of hard and soft acids and bases).[25] The relative stability of **4**, compared to sulfenamides **1**–**3**, has been rationalized in a number of ways. The free-SH form of sulfenamides (**1**-**3**) are prone to rapid liberation of gaseous H_2S upon protonation of the adjacent *N*-atom. Therefore, acylation (**4**) suppresses destructive side-reactions.[21] Alternatively, *S*-delocalization into adjacent π-acceptor orbitals can lower the reactivity of the moiety overall.[22]

Sulfenamides are also known to produce diastereomeric compounds according to NMR,

where the S–N bond is the chiral axis because of a rotational barrier about S–N. This barrier has been attributed to steric interactions[26,27] between *N*- and *S*-substitutents, and in some cases a negative hyperconjugative effect between the $n_N \rightarrow \sigma^*_{S\text{–}C}$ has been suggested but was not quantified.[28] Such interactions between lone-pair electrons and $\sigma^*_{S\text{–}C}$ orbitals have been exploited to bias specific conformers in drug molecules.[29] We hypothesized that the $n_N \rightarrow \sigma^*_{S\text{–}C}$ interaction could explain the stabilities observed for sulfenamides **1-4**, where **1-3** have enhanced instability because they have no $\sigma^*_{S\text{–}C}$ bond available to interact with.

We first synthesized **4** using existing procedures in the literature, however we had difficulty isolating this molecule at any scale due to the air-sensitivity of the starting material thioacid and unproductive side-reactivity. Anoxic conditions at lower temperatures enabled us to reliably synthesize **4** in high yields at gram-scale quantity. We also provide the first complete NMR characterization of this starting sulfenamide since its discovery[22] (See Supplementary Information).

Gratifyingly, confirmation for the proposed $n_N \rightarrow \sigma^*_{S\text{–}C}$ anomeric interaction was found in the X-ray crystal structure obtained for **4** (Figure 1). Here the –NH_2 moiety is poised so that it is aligned with the $\sigma^*_{S\text{–}C}$ in both the crystal structure and its optimized gas-phase geometry.[30]

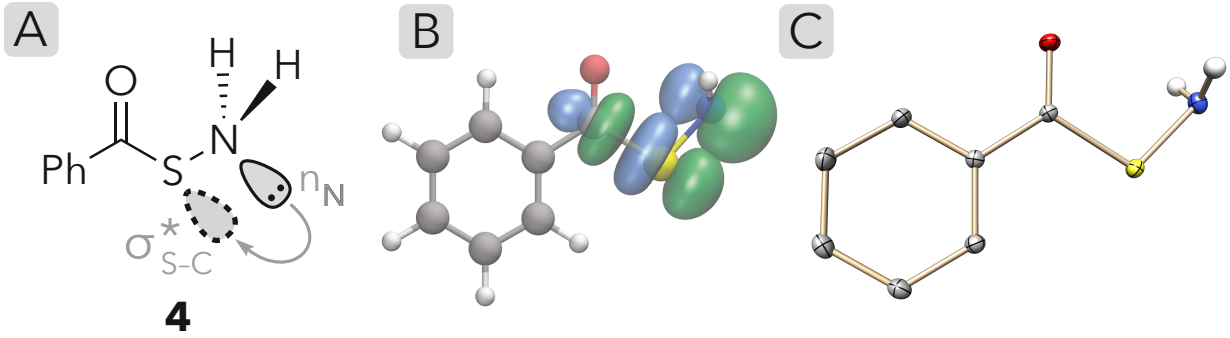


Figure 1: **A.** Notional image of proposed $n_N \rightarrow \sigma^*_{S\text{–}C}$ interaction in **4**. **B.** Optimized gas-phase geometry of **4** with relevant natural bond orbitals (NBOs) shown at 0.06 isovalue and calculated at M06-2X/6-311++G(d,p). **C.** X-ray crystal structure of **4**, H atoms found objectively using a Fourier difference map and refined riding model.

Further evidence for the $n_N \rightarrow \sigma^*_{S\text{–}C}$ interaction is demonstrated in the torsional energy

scan around the X–NH_2 bond of **4** and **5** (Figure 2). The ΔE for **4** reaches a minimum when the nitrogen lone-pair aligns with the σ^*_{S-C}. Likewise, the S–C bond undergoes a corresponding lengthening, indicative of donation into the anti-bonding orbital. Intruigingly, the longest S–C bond is observed at dihedral angles of 0°/360°, for which minimal donation into the σ^*_{S-C} should be possible. We propose that this lengthening may be due to filled-filled interactions between the nitrogen and carbonyl lone-pairs. The oxygen analogue (**5**) to sulfenamide **4** was also analyzed in a similar manner. In general, the ΔE profile for any possible O–N bond rotation is much shallower. While the O–C bond for **6** also lengthens when the nitrogen lone-pair is aligned with the σ^*_{O-C}, conformations between 120° to 240° dihedrals are within 0.1 kcal/mol from one another, suggesting that such an anomeric interaction is less significant for **5**.

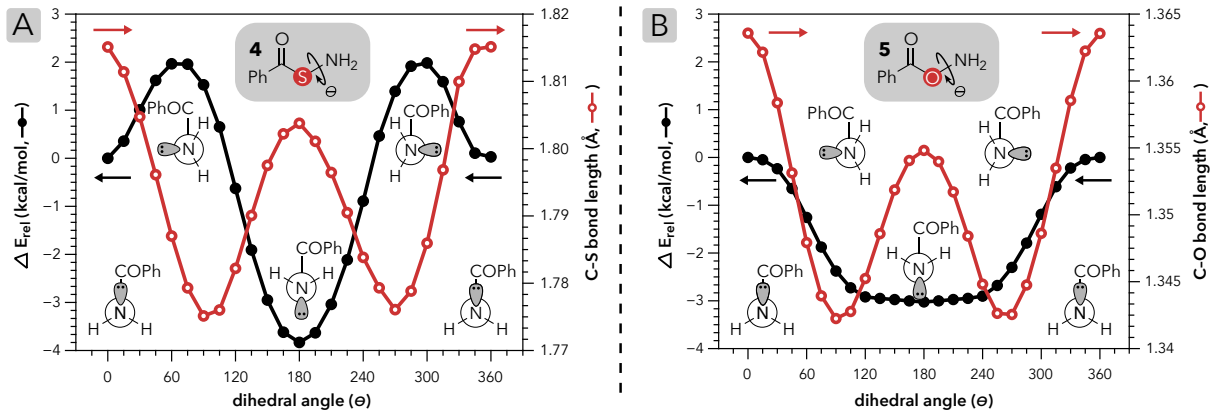


Figure 2: Analysis of electronic energy (black) and C–X bond length (red) as a consequence of rotation around the X–N bond where X = S or O (dihedral angle defined by C–X–N–:) calculated at M06-2X/6-311++G(d,p).

Utilizing the coordinates of the local minima and maxima for the torsional energy scan, we identified transition state structures for **4** and **5**. By doing so we could derive the individual torsional barriers for **4** and **5** which are 4.9 kcal/mol and 2.4 kcal/mol respectively. To validate the favorability of the $n_N \rightarrow \sigma^*_{X-C}$ we employed natural bond orbital (NBO) analysis. NBO second-order perturbation theory (Figure 3) revealed that the donor-acceptor energies for the anomeric interaction between NBOs for $n_N \rightarrow \sigma^*_{S-C}$ was 9.2 kcal/mol in the case of

4, which is 0.9 kcal/mol greater than the $n_N \rightarrow \sigma^*_{O\text{-}C}$ in **5**.

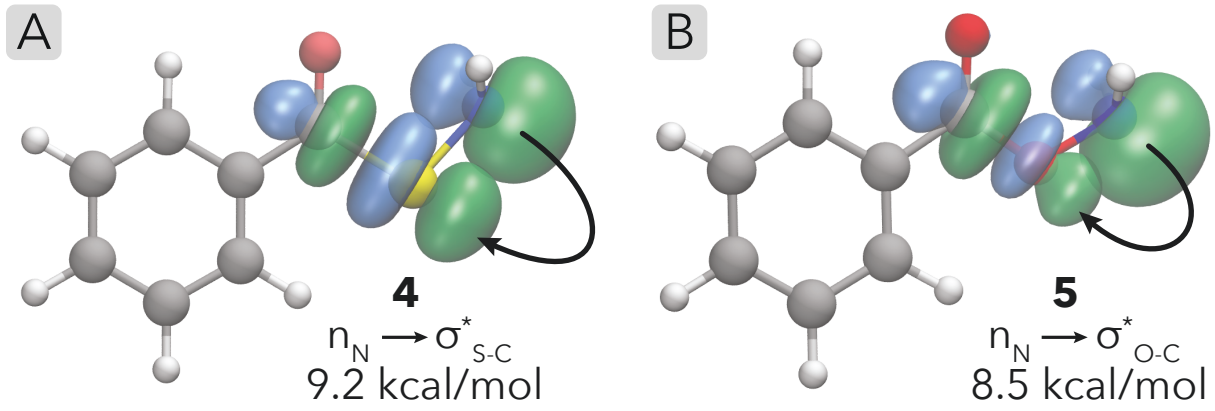


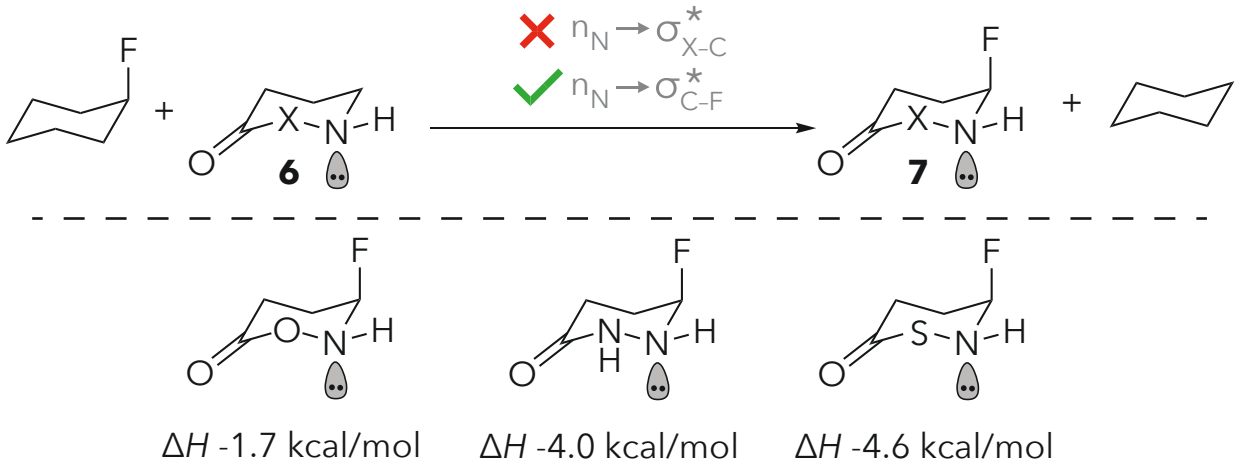
Figure 3: Natural Bond Orbitals (NBOs) of **4** and **5** (shown at 0.06 isovalue). Donor-acceptor energies for $n_N \rightarrow \sigma^*_{X\text{-}C}$ interactions were computed for the NBO method using the second-order perturbation approximation at M06-2X/6-311++G(d,p).

α-Nucleophilicity of Sulfenamides

Secondary bonding interactions have major implications for the nucleophilicity of sulfenamides. As such we also characterized the competition between the proposed secondary orbital interactions and the relative nucleophilicity at nitrogen. Despite the community's interest in understanding the underpinnings of the α-effect,[31] studies have often omitted sulfenamides from analysis. Unfortunately, analysis of the α-effect in sulfenamides has been isolated to *in-silico* studies of only *S*- or *N*-anionic derivatives.[32] Alabugin and co-workers have underscored the sensitive interplay between anomeric and α-effects for non-ionic α-nucleophiles.[31] To our knowledge only one study has explored the nucleophilicity of acyl-substituted α-nucleophiles, but did not explore any α-effects of sulfur.[31] Thus sulfenamide **4** represents an under-explored and unique variation in the structure of the nucleophile, where the *N*-adjacent atom is a sulfur. Additionally, We characterized the extent of the α-effect of **4** using computational tools already validated for hydroxylamine and hydrazine nucleophiles.[31]

We first sought to interrogate the nucleophilicity of the nitrogen in the absence of any effects that might attenuate the electron density on nitrogen due to $n_N \rightarrow \sigma^*_{X\text{-}C}$ donation

(where X = O, N, or S). In order to extract the contribution of the α-effect towards nucleophilicity, we utilized the isodesmic reaction[33] in Scheme 3, in which the ΔH of the reaction allows for the quantitative comparison of the electron density of the $-NH_2$ group across all three molecules. The conformation of the nitrogen lone-pair in **7** is positioned such that the interaction under consideration is purely a classical anomeric interaction with the σ^*_{C-F} bond, avoiding any potential interaction with the σ^*_{X-C}. The magnitude of ΔH of the reaction increases because of the stronger the $n_N \rightarrow \sigma^*_{C-F}$ anomeric interaction, as a proxy for electron density and nucleophilicity of the nitrogen atom.[31] We evaluated the -ΔH of the reaction below for three different heteroatoms, where X = O, N, or S. The magnitude of -ΔH allowed us to rank the electron density on the $-NH_2$ group and estimate their relative strengths as nucleophiles with respect to the α-effect. We found that the ΔH for S–N and N–N nucleophiles was similar (difference of 0.6 kcal/mol), which indicates that in the absence of any competing effects, the nucleophilicity of sulfenamides should be similar in nucleophilicity to hydrazines. However, the stabilization gained from the anomeric interaction for the O–N nucleophiles was significantly less in comparison (2-3 kcal/mol lower) and can be attributed to non-stereoelectronic factors such as inductive withdraw from the adjacent O-heteroatom.[31]



Scheme 3: Isodesmic reaction isolating the classical $n_N \rightarrow \sigma^*_{C-F}$ anomeric interaction

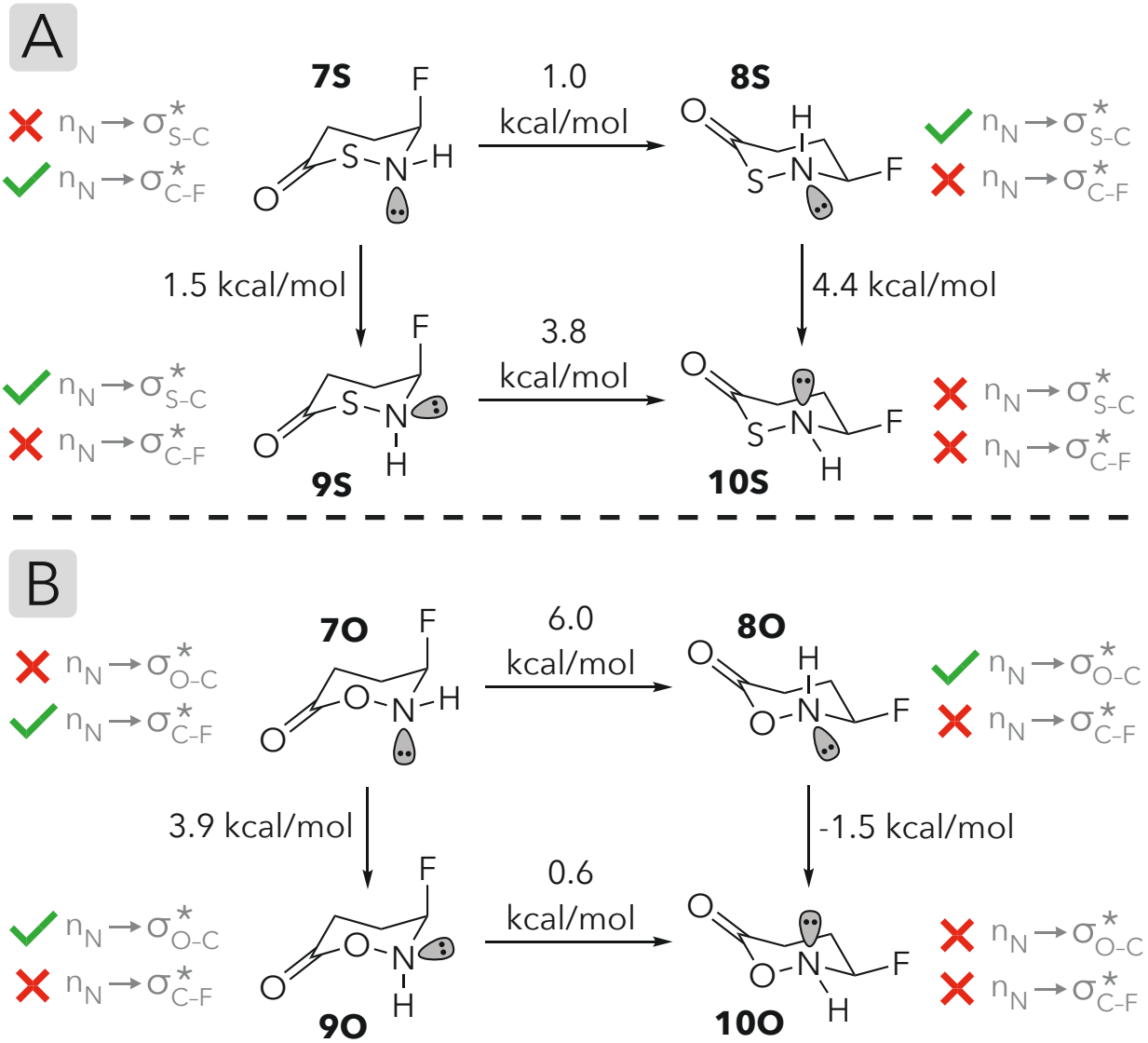
We next sought to interrogate the effect of adding in the competing $n_N \rightarrow \sigma^*_{X-C}$ interac-

tion. This additional effect would compete for the electron density of the nitrogen. To estimate the electron density of the –NH_2 group of **7**, we examined the conformational equilibria shown in Figure 4. Fluorine is expected to prefer the axial position if an anomeric interaction from an adjacent heteroatom is present. The extent to which the axial fluorine conformer is preferred is a measure of the electron density at the nitrogen heteroatom. Conformers **8** and **9** are two isomers that capture the energetic penalty associated with losing anomeric stabilization of the nitrogen lone pair with the $\sigma^*_{\text{C–F}}$ bond and gaining the $n_N \rightarrow \sigma^*_{C–X}$ interaction. Conformer **10** serves as a control in which both anomeric $n_N \rightarrow \sigma^*_{C–F}$ interactions are inactive. Finally, as an aside, the acyl-hydrazine analogue was not investigated because of complicating effects from the N-H group that compromise the analysis.[31]

In the case of the sulfur heteroatom ($\Delta H_{7\text{S}\rightarrow 8\text{S}}$), the energetic penalty for losing the anomeric $n_N \rightarrow \sigma^*_{C–F}$ interaction in favor of the anomeric $n_N \rightarrow \sigma^*_{S–C}$ interaction is not significant (1.0 kcal/mol), indicating that stabilization of the nitrogen lone pair through delocalization into the $\sigma^*_{S–C}$ orbital largely compensates for the loss of delocalization into the $\sigma^*_{C–F}$ orbital. Indeed, the magnitude of $\Delta H_{7\text{S}\rightarrow 10\text{S}}$ indicates that the strength of the $n_N \rightarrow \sigma^*_{S–C}$ (from Figure 4A) interaction contributes a similar stabilization effect as the more classical $n_N \rightarrow \sigma^*_{C–F}$ anomeric interaction (from Scheme 3).

The conclusions derived from the oxygen variant are similar to those derived from the rotational energy scan of **6** in Figure 2B. Alignment of the –NH_2 lone pairs with the acceptor $\sigma^*_{\text{O–C}}$ orbital provides negligible stabilizing compensation for loss of the $n_N \rightarrow \sigma^*_{C–F}$ anomeric interaction and results in an energetic penalty of 4–6 kcal/mol. Furthermore, the difference in $\Delta H_{8\rightarrow 10}$ in both cases quantifies the energy associated with the loss of the anomeric $n_N \rightarrow \sigma^*_{X–C}$ interaction. Surprisingly, the transition from $\Delta H_{8\text{O}\rightarrow 10\text{O}}$ is exothermic, indicating that losing the $n_N \rightarrow \sigma^*_{O–C}$ interaction leads to a net gain in stability (likely due to filled-filled interactions with the adjacent O-heteroatom), and confirming that the $\sigma^*_{O–C}$ orbital imposes no attenuation of nitrogen nucleophilicity due to an anomeric interaction. As before, for the $\Delta H_{8\text{S}\rightarrow 10\text{S}}$ equilibrium there is a 4.4 kcal/mol penalty for losing

Figure 4: Axial and equitorial equilibria of cyclic *S*–acyl thiohydroxylamines (**7S-10S**) and *O*–acyl hydroxylamines (**7O-10O**) demonstrating scenarios of different electronic interactions



structure	C–F bond (Å)	C–X bond (Å)	$n_N \rightarrow \sigma^*_{C-F}$	$n_N \rightarrow \sigma^*_{C-X}$
7O	1.398	1.360	✓	×
7S	1.410	1.796	✓	×
8O	1.371	1.373	×	✓
8S	1.378	1.804	×	✓
9O	1.383	1.365	×	✓
9S	1.379	1.798	×	✓
10O	1.371	1.363	×	×
10S	1.378	1.792	×	×

the $n_N \rightarrow \sigma^*_{S\text{–}C}$ anomeric interaction. This is in agreement with the calculated rotational barrier of 4.9 kcal/mol and similar to the 4.6 kcal/mol energy of the $n_N \rightarrow \sigma^*_{C\text{–}F}$ interaction (Scheme 3).

Conclusion

Sulfenamides, an often neglected functional group, are currently experiencing their renaissance as synthetic precursors to higher oxidation state sulfur-nitrogen species and in thioaminations.[7–12] Unfortunately, thermal stability issues have plagued the widespread utility of some sulfenamides.[21] We demonstrate the existence of an electronic interaction between the –NH_2 lone-pair electrons and the $\sigma^*_{S\text{–}C}$ bond via crystallographic and *in silico* methods. Previously, this proposed interaction was referred to as negative hyperconjugation,[28] however given the electronic interaction is ∼4-5 kcal/mol and similar in energy to classical anomeric interactions, this interaction is better described as a true anomeric interaction. We further propose that the poor stability associated with *S*-unsubstituted sulfenamides (as in **1**–**3**) can, in part, be attributed to a lack of a suitable, low-lying $\sigma^*_{S\text{–}C}$ acceptor orbital to stabilize the adjacent S–N bond.

Our systematic investigation of the conformational preferences of sulfenamides also represents the first attempt to quantify the nucleophilicity of sulfenamides and their relation to the α-effect. Sulfenamide nucleophiles are often omitted from study, and to our knowledge, the nucleophilicity of non-ionic sulfenamides has never before been characterized. By way of isodesmic reactions, we have shown that sulfenamides are similar in nucleophilic character to hydrazine-type α-nucleophiles. It is our hope that this study will assist synthetic chemists when rationalizing the stability of sulfur-nitrogen species. We also anticipate this work will provide additional insights into the sensitive interplay between anomeric interactions and the α-effect for *S*-containing α-nucleophiles.

Experimental Section

^{1}H and ^{13}C NMR spectra for all compounds were acquired in deuterated solvents (as indicated) on a Varian MR-400 at the field strength reported in the text. The chemical shift data are reported in units of δ (ppm) relative to residual solvent. Unless otherwise specified, all commercial products and reagents were used as purchased, without further purification. Solvents were reagent grade. Analytical thin-layer chromatography (TLC) of all reactions was performed on aluminum-backed silica gel plates (200 μm) purchased from SiliCycle. Flash chromatography of all reactions was performed on silica gel (40-63 μm, 230-400 mesh) purchased from SiliCycle Inc.

Synthesis of *S*-Benzoylthiohydroxylamine (SBTHA, 4) To a 250 mL round-bottom flask equipped with a stir bar (flask A), hydroxylamine-*O*-sulfonic acid (HOSA, 25.0 g, 221 mmol, 2.5 eq.) was added and sealed. Flask A was degassed in triplicate, back-filling with nitrogen gas, before being placed on ice to cool at 0°C. To a 500 mL round-bottom flask equipped with a stirbar (flask B), 100 mL of 1.1 *M* KOH (aq) solution was prepared. Flask B was sealed and degassed under vacuum with sonication in triplicate, back-filling with nitrogen gas, before being placed on ice to cool at 0°C. To a 250 mL round-bottom flask (flask C), 100 mL of 2.2 *M* KOH (aq) solution was prepared. Flask C was degassed under vacuum with sonication in triplicate, back-filling with nitrogen gas before being placed on ice to cool at 0°C. On ice, the 2.2 *M* KOH (aq) solution in flask C was transferred via cannula under inert atmosphere into flask A containing solid HOSA with stirring. Thiobenzoic acid (10.4 mL, 88.4 mmol, 1 eq.) was added slowly to flask B with stirring on ice to neutralize. The HOSA solution in flask A was then transferred via cannula under inert atmosphere into flask B containing thiobenzoic acid with *vigorous* stirring. Immediately a white precipitate formed and the solid suspension was allowed to stir for 15 minutes on ice. The suspension was then filtered, the fitrate resuspended in DCM, and added to a separatory funnel where any remaining water was drawn off. The organic layer was washed with brine (100 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The crude material was suspended in a min-

imal amount of DCM, adsorbed onto silica gel, and purified in via silica gel chromatography (100% DCM with 0.1% triethylamine) to yield **4** as a white solid (9.3 g, 69% yield). Characterization matched literature reported values.[22]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.3, 1.0 Hz, 2H), 7.59 (tt, J = 7.9, 1.2 Hz, 1H), 7.47 (t, J = 7.8 Hz, 2H), 2.76 (s, 2H).

^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 198.7, 135.0, 133.9, 129.0, 126.7.

Computational Methods

All density functional theory (DFT) computations were carried out using the Gaussian 09 and Gaussian 16 software package.[34–36] All computations including geometry optimization, frequency calculations, torsional scans, and natural bond orbital analysis of structures were carried out at M06-2X/6-311++G(d,p) level of theory.[37] All minimum geometries were verified to be local minima by the absence of imaginary frequencies in the Hessian calculation. All transition states were calculated using the QST3 method and were found to be local maxima by having exactly 1 imaginary frequency in the Hessian calculation. Relaxed potential energy scans were accomplished by varying the dihedral angle at 15° increments while freezing the H–C–X–N dihedral angle such that the lone pair of the –NH_2 were eclipsed with the –COPh moiety. Natural Bond Orbitals were calculated using NBO 3.1 as implemented in Gaussian 16.[38] VMD 1.9.4 was used to visualize the NBOs for publication.[39]

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Supporting Information Available

ASSOCIATED CONTENT:

- Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

- Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website. Coordinates of all computed structures, torsional scans, and files for reproduction of NBOs are available free of charge on Figshare at https://doi.org/10.6084/m9.figshare.23971923. CCDC 2279038 contains the supplementary crystallographic data for this paper.

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