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Synthesis and Reactivity of Polydisulfonimides

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Abstract: The first synthesis of alkyl disulfonimide oligomers is presented. In the process of synthesizing these oligomers, previously unreported reactivity of the N-substituted disulfonimide functional group was discovered. Under basic conditions, unexpected lengthening of the oligomers occurs through a "transdisulfonimidation" reaction, whereby new disulfonimides are synthesized from existing ones by reaction with sulfonamide anion. This process appears to proceed via formation of a sulfene intermediate. Support for the $E1cB_{Rev}$ mechanism includes isotope scrambling, substituent effects, and sulfene trapping.

Introduction

Polyanionic macromolecules are ubiquitous in biological systems. Both homogeneous polyanions, such as the phosphate backbone of nucleic acids, and heterogeneous polyanions, represented by the heavily sulfated and carboxylated glycosaminoglycans, participate in a variety of vital biochemical processes. Many of these polyanions interact with specific proteins, particularly enzymes. It is therefore surprising that there have been relatively few attempts to develop new types of polyanionic materials with useful biological properties. In this paper, we report on the synthesis and reactivity of oligomeric disufonimides, molecules that may be useful for mimicking biological polyanions. Disulfonimides possess many features that may make them a suitable functional group for mimicking various charged groups found in biological anions. They contain an acidic proton with a pK_a of approximately 1, and therefore exist in a largely anionic state at physiological pH[1] (Figure 1).Disulfonimides contain five atoms over which the charge may possibly be delocalized, which may give the functional group an ability to mimic various charged groups, such as phosphates, sulfates, and carboxylates. The disulfonimide may also engage in multidentate metal ligation, further expanding the ability of this functional group to mimic biological polyanions. Despite these potentially useful properties, little is known about the chemistry of this underutilized functional group. We therefore undertook a study of this functionalities' synthesis and chemical reactivity.

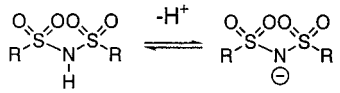

Figure 1. The disulfonimide functional group is fully deprotonated at physiological pH.

Crystal structures of both N-substituted and monoacidic disulfonimides exist. Cotton and Stokely report a structure of both the protonated and deprotonated forms of diphenyldisulfonimide.[2] In these two structures, the only statistically relevant bond length changes upon deprotonation are the S−N bonds. The sodium salt has a sulfur−nitrogen bond length significantly shorter than that of the protonated compound. Furthermore, Cotton and Stokely's structures show that the deprotonated disulfonimide places the aryl groups syn to one another so that the sodium cation may have the best possible interactions

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(1) King, J. In *The Chemistry of Sulphonic Acids, Esters and their Derivatives*; Patai, S., Rappaport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1991, Chapter 6.

(2) Cotton, F.; Stockely, P. *J. Am. Chem. Soc.* **1970**, *92*, 294−302.

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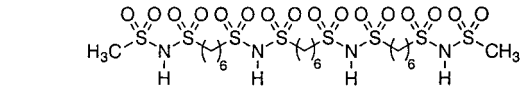

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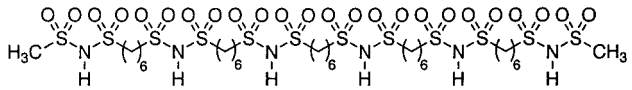


(11)

Figure 2. Oligodisulfonimide targets.

between the nitrogen and oxygen atoms of the entire disulfonimide functional group. Since this initial disulfonimide structure report, a plethora of structures have been obtained with a variety of neutral sulfonimides,[3] sulfonimide salts,[4] perfluoroalkyldisulfonimides,[5] and *N*-alkyl sulfonimides.[6]

Aside from the interest in their structure, the majority of earlier studies of disulfonimides deal with the use of disulfonimides as leaving groups in substitution and elimination reactions.[7] While disulfonimides are leaving groups of moderate reactivity, the elevated temperatures and long reactions times necessary to effect substitution decrease the general utility of this technique. The use of perfluorinated alkyl disulfonimides ameliorates these problems and improves the utility of this method. E2 eliminations have also been attempted with disulfonimide functional groups. They lead exclusively to Hofmann products in some cases, making them more selective than even ammonium leaving groups under similar conditions.[8]

Disulfonimide-containing compounds have found uses in material science as industrial polishes[9] and polymer curing substances.[10] Finally, one paper does report the use of a disulfonimide as a replacement for tetrazole in Angiotensin II receptor agonist, although this did not lead to a potent inhibitor.[11] We found no reports of aliphatic oligodisulfonimides, however, or their use in biochemical experiments. A few polymers containing disulfonimides exist, but these are all either aryl- or perflourinated polymers. Aryl polydisulfonimides were synthesized and tested as water-soluble adhesives, powder coating compounds, and photographic materials for printing plates.[12] Perfluorinated alkylpolydisulfonimides have limited use as fuel cell electrolytes.[13]

We sought to explore the synthesis, reactivity, and general properties of the disulfonimide functional group in the context of an oligomeric material. In designing these oligomers, we opted to insert a hexamethylene unit between adjacent functional groups, which would approximate the distance between charges in nucleic acids and/or glycosaminoglycans. We chose tetrameric (**7**) and hexameric (**11**) disulfonimide oligomers as our initial synthetic targets (Figure 2).

Results and Discussion

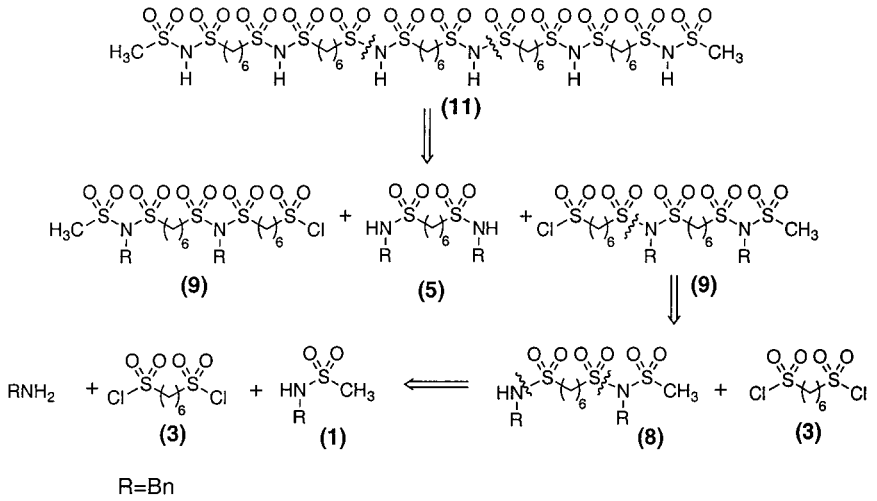
Synthetic Strategy. The strategy for the synthesis of the tetramer (**7**) and hexamer (**11**) required the preparation of a series of disulfonimide-containing molecules. A review of the literature indicated that the most frequent and highest yielding syntheses of disulfonimides utilize the reaction of a sulfonyl chloride with a deprotonated sulfonamide,[14] although other means for this bond construction have been employed.[15] We therefore chose sulfonyl chlorides and sulfonamides as building blocks for the polydisulfonimide. In considering the structure of our target molecules, we opted for a strategy of multiple bond disconnections (Scheme 1). The two major options involved either forming many bonds simultaneously in an oligomerization process or constructing bonds one at a time in a stepwise manner. We reasoned that a stepwise synthesis would permit better evaluation of the structure and purity of the compounds produced, as well as allowing us the opportunity of studying the chemistry of the disulfonimide functionality. Having chosen a stepwise approach to construct the molecule, a convergent synthesis rather than a linear one was then implemented.

Taking advantage of the molecule's symmetry led to the adoption of an "outside-in" approach. Scheme 1 outlines the retrosynthesis of hexamer (**11**). By making disconnections at two disulfonimide functionalities near the center of the molecule, the hexameric molecule was quickly reduced to two much simpler compounds. Disulfonamide **5** could be easily made from hexane-1,6-disulfonyl chloride (**3**). The terminal sulfonyl chloride **9**, which contained two internal disulfonimide functional groups, could be broken down into hexane-1,6-disulfonyl chloride (**3**) and a simpler sulfonamide (**8**). This terminal sulfonamide, containing only one internal disulfonimide, could be made from hexane-1,6-disulfonyl chloride (**3**) and *N*-benzyl methylsulfonamide (**1**). In this approach, hexane-1,6-disulfonyl chloride serves as the main carbon source for the target molecule. This material could be conveniently synthesized in two steps from 1,6-dibromohexane. Tetramer **7** was constructed using an analogous strategy.

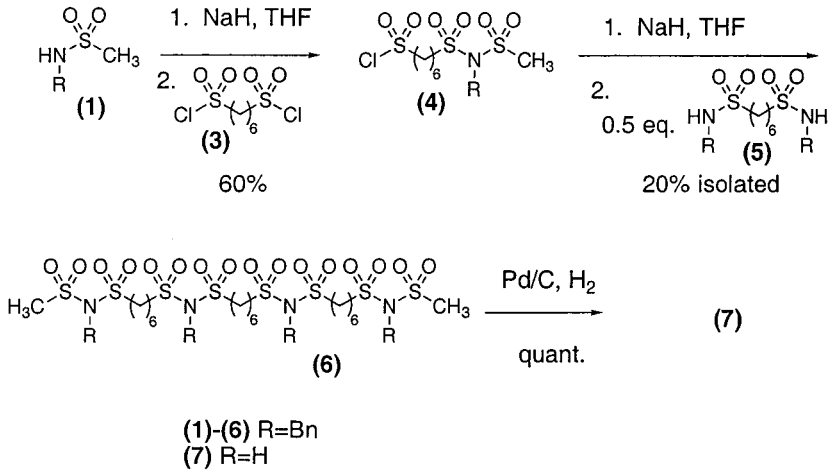
Scheme 2 depicts the synthesis of the tetrameric alkyldisulfonimide. One equivalent of *N*-benzyl methylsulfonamide (**1**) was deprotonated with sodium hydride and then treated with 1 equiv of the disulfonyl chloride **3**. This reaction yielded 30% of product **4** on the basis of the initial amount of sulfonamide, or 60% of the desired product on the basis of the statistical mixture obtained in a putative unselective reaction. One-third of an equivalent of disulfonyl chloride **3** was also recovered from this reaction. Attempts were made to increase this yield by adding excess disulfonyl chloride, but separation of the product from the excess disulfonyl chloride by silica gel chromatography then became difficult. Two equivalents of the terminal sulfonyl chloride **4** were next treated with 1 equiv of doubly deprotonated disulfonamide **5** to form two new disulfonimide linkages, thus completing the construction of the N-benzylated tetramer **6**. Finally, the protected tetramer **6** was hydrogenolyzed, in quantitative yield, to give the tetrameric sulfonimide **7**. The MALDI mass spectrum of the material contained five mass peaks corresponding to five distinct sodium adducts. The masses are consistent with the sodium adduct of the neutral molecule as well as the sodium adducts of the mono-, di-, tri-, and tetraanionic molecules.

(3) Attig, R.; Mootz, D. *Acta Crystallogr.* **1975**, *B31*, 1212−1214.
(4) (a) Haas, A.; Klare, Ch.; Betz, P. Bruckmann, J.; Kruger, C.; Tsay, Y.-H.; Aubke, F. *Inorg. Chem.* **1996**, *35*, 1918−1925. (b) Jones, P.; Moers, O.; Blaschette, A. *Acta Crystallogr.* **1997**, *C53*, 1811−1813.
(5) Xue, L.; DesMarteau, D.; Pennington, W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1331−1333.
(6) Jones, P.; Hamann, T.; Schaper, W.; Lange, I.; Blaschette, A. *Phosphorus, Sulfur Silicon Relat. Elem.* **1995**, *106*, 91−104.
(7) Baumgarten, R. *J. Chem. Educ.* **1966**, *43*, 398.
(8) Bartsch, R.; Allaway, J.; Ingram, D.; Lee, J.-G. *J. Am. Chem. Soc.* **1975**, *97*, 6873.
(9) *Chem. Abstr.* **1968**, *69*, 51835h.
(10) *Chem. Abstr.* **1992**, *116*, 85874z.
(11) Perez, D.; et al. *J. Med. Chem.* **1995**, *38*, 2357−2377.
(12) (a) *Chem. Abstr.* **1988**, *109*, 240726d. (b) *Chem. Abstr.* **1992**, *116*, 85874z. (c) *Chem. Abstr.* **1980**, *93*, 150945w.
(13) Appleby, A.; Velev, O.; LeHelloco, J. Parthasarthy, A.; Srinivasan, S.; DesMarteau, D.; Gillette, M.; Ghosh, J. *J. Electrochem. Soc.* **1993**, *140*, 109−110.
(14) DeChristopher, P.; Adamek, J. Lyon, G.; Klein, S.; Baumgarten, R. *J. Org. Chem.* **1974**, *39*, 3525−3532.
(15) (a) Juschke, R.; Kockerling, M.; Sartori, P. *Verlag Zeit. Natur.* **1998**, 135−144. (b) Kremlev, M.; Kharchencho, A.; Zyabrev, V.; Rudenko, E. *Z. Organich. Khimii* **1989**, *26*, 1368−1369.

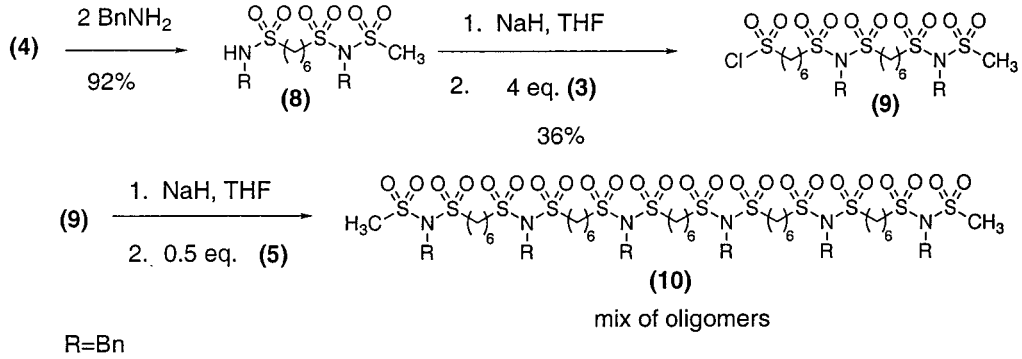
Scheme 1



Scheme 2



Scheme 3



The *N*-benzyl hexamer was constructed in an analogous manner, including one additional monomer elongation step (Scheme 3). After treating the sulfonyl chloride **4** with benzylamine to obtain the corresponding terminal sulfonamide **8** in high yield, sulfonamide **8** was deprotonated with sodium hydride and then treated with 4 equiv of hexane-1,6-disulfonyl chloride (**3**) to obtain the terminal sulfonyl chloride **9**. The use of excess hexane-1,6-disulfonyl chloride (**3**) minimized the undesired reaction of the product monosulfonyl chloride with residual sulfonamide anion. Isolated yields were significantly lower in this reaction (36%), compared to the synthesis of terminal sulfonyl chloride **4**, due to problems with purification. Terminal sulfonyl chloride **9** did not have good solubility in any applicable silica gel chromatography eluents. Although the yield of this reaction was relatively low, there was no difficulty in separating the excess disulfonyl chloride **3** from the product, and 2.5 equiv of the unreacted disulfonyl chloride was recovered.

Two equivalents of the terminal sulfonyl chloride **(9)**, which contains two internal disulfonimides, were next treated with 1 equiv of doubly deprotonated disulfonamide **5** to form two new disulfonimide linkages, thus forming the hexamer **10**. Workup of the reaction included partitioning the crude material between ethyl acetate and brine. A nonsoluble solid was filtered off, and the soluble organic material was analyzed. ^{1}H NMR of the crude, soluble material, which amounted to approximately half of the expected mass of the reaction, revealed what appeared to be a

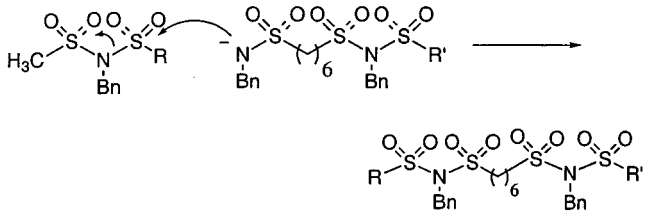
mixture of product and two sulfonamide-containing compounds. Purification by silica gel chromatography did not cleanly separate pure product from sulfonamide-containing impurities.

The solid that had been filtered from the reaction mixture also corresponded to about half of the expected mass of the reaction. Characterization by NMR suggested that this solid was pure oligodisulfonimide. The NMR spectrum of this material appeared to support the proposed structure of **10** except that the relative integrations did not correspond to the expected values. Peaks for the methyl capping groups had a relatively low integration value compared to those of the internal methylene protons, indicating the presence of higher order oligomers with a relatively higher number of internal protons compared to the number of protons on the methyl capping group. At first, this result seemed surprising because we had assumed that the product disulfonimide would be unreactive and thus only one product would be obtained under the reaction conditions. To confirm the presence of higher order oligomers, the oligomer sample was fractionally separated on a silica gel column. NMR analysis revealed that the less polar fractions eluted from the column were indeed shorter oligomers than the more polar fractions, signifying that a continuum of molecular weight oligomer lengths were produced under these reaction conditions. Removal of the benzyl protecting groups in this material has not yet been effected.

Chemical Reactivity of the Disulfonimide Functional Group. The formation of higher order disulfonimide oligomers during a simple coupling reaction is unprecedented. Extant literature on disulfonimide reactivity does not directly address this unexpected result but does provide some salient facts. Sulfonimides, such as saccharin, were first explored as activating groups for the S_N2 displacement of amines. However, the nucleophile preferentially attacks the carbonyl group to cleave the sulfonimide.[16] Replacing the acyl group of the sulfonimide with a second sulfonyl group, to give a disulfonimide, eliminates some of these complications. *N*-(Alkyl)diaryl disulfonimides undergo S_N2 displacement in moderate yields when using nucleophiles such as bromide, iodide, and aniline at elevated temperatures and long reaction times.[17] Alternately, S−N bond cleavage occurs in these compounds with cyanide, hydroxide, or mercaptide nucleophiles. Perfluorinated disulfonimides react differently. Under mild conditions, di-triflated *N*-alkylamines are susceptible to S_N2 displacement by carbon nucleophiles such as cyanide and diethyl malonate, with no evidence of S−N bond cleavage.[18] These examples clearly show that disulfonimides may undergo sulfur−nitrogen bond cleavage. However, there were no reports of new disulfonimides forming as a result of these processes.

Mechanistic Investigations. The formation of oligomers longer than hexamers requires that some type of "trans-disulfonimidation" process takes place. To confirm the viability of this unprecedented reaction, it was reproduced in a model system (Scheme 4). Employing the same reaction conditions as those used in the coupling reaction, diethyldisulfonimide (**13**) was treated with the anion of propylsulfonamide (**14**). NMR analysis of the reaction revealed the "trans-disulfonimidation" reaction depicted in Scheme 5.[19] Assuming that the equilibrium ratio of the disulfonimides is equimolar, the half-life of this reaction is about 6 h.

Scheme 4



In contrast, deprotected dimethyldisulfonimide (**16**) did not react under similar conditions (Scheme 5B). An analogous observation has been made in the chemistry of sulfonimides, and this fact has been employed in "safety-catch" linkers for solid support synthesis.[20] N-Protonated sulfonimides are not cleaved under basic conditions, whereas alkylated sulfonimides are cleaved.

A number of plausible mechanisms may be proposed to account for the trans-disulfonimidation reaction. Two such mechanisms are shown in Scheme 6. The first mechanism (6A) involves nucleophilic attack of the sulfonamide anion on one of the sulfurs of the disulfonimide, yielding a new disulfonimide and sulfonamide. An alternative mechanism (6B) posits an elimination, in which the sulfonamide anion acts as a base to generate a sulfene, which would later be trapped to form a new disulfonimide.

A simple experiment to aid in distinguishing between these two mechanisms tests whether trans-disulfonimidation requires the presence of a hydrogen α to the disulfonimide. *N*-(Benzyl)-diphenyldisulfonimide (**18**) has no hydrogens in the α-position and therefore cannot form a sulfene. Scheme 7 details this experiment. When *N*-(benzyl)dimethyldisulfonimide (**15**) is treated with deprotonated *N*-(benzyl)ethylsulfonamide (**12**), the reaction yields trans-disulfonimidation products. On the other hand, exposure of *N*-(benzyl)diphenyldisulfonimide (**18**) to the same nucleophile yields only recovered starting materials. No reaction can be detected by TLC or NMR.

If direct attack of a sulfonamide upon a sulfur center of the disulfonimide were the mechanism of trans-disulfonimidation, diphenyl disulfonimides should undergo this reaction as well as alkyl disulfonimides. In fact, electronic effects would tend to favor it as a substrate for the reaction due to the increased nucleofugality of the sulfonamide leaving group. To obtain direct evidence that trans-disulfonimidation proceeds through a sulfene intermediate, sulfene trapping experiments were performed.

Numerous sulfene trapping reagents have been employed. Nucleophiles such as water, alcohols, and amines have been used to trap sulfenes, and cycloaddition reactions of sulfenes with vinyl ethers, dienes, and imines have been reported.[21] The most commonly used substrates for cycloaddition to sulfenes, however, are enamines.[22] Sulfene intermediates formed during

(16) DeChristopher, P.; Adamek, J.; Lyono, G.; Galante, J.; Haffner, H.; Boggio, R.; Baumgarten, R. *J. Am. Chem. Soc.* **1969**, *91*, 2384−2385.

(17) Hendrickson, J.; Okano, S.; Bloom, R. *J. Org. Chem.* **1968**, *34*, 3434−3438.

(18) (a) Glass, R. *Chem. Commun.* **1971**, 1546−1547. (b) Hendrickson, J.; Bergeron, R.; Giga, A.; Sternbach, D. *J. Am. Chem. Soc.* **1973**, *95*, 3412−3413.

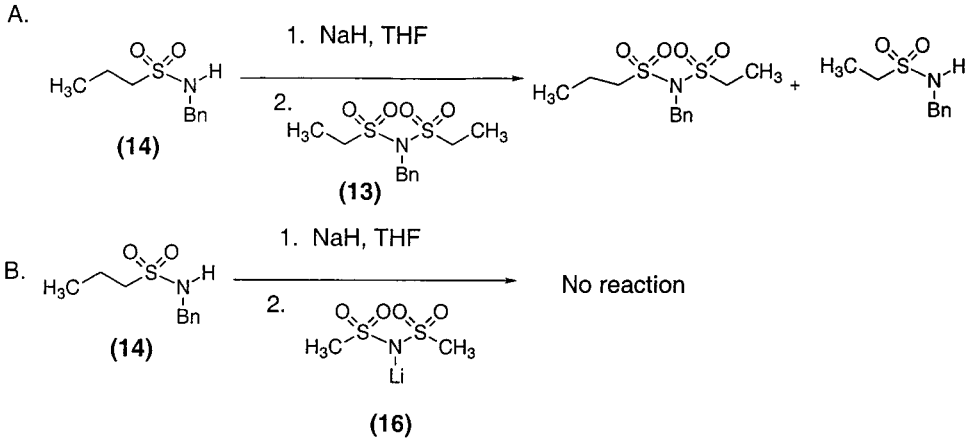
(19) The benzylic protons of the starting material, propylsulfonamide, and the product, ethylsulfonamide, are doublets near 4.3 ppm and may be easily distinguished from one another. The protons of the disulfonimides, in contrast, are difficult to distinguish due to overlap of their signals, although it was assumed that the ethylpropyldisulfonimide and the dipropyldisulfonimide were formed in the reaction. To validate this proposition, we treated dimethyldisulfonimide with the same reaction conditions. The benzylic protons of the starting materials, methylsulfonamide, methylpropyldisulfonimide, and dipropyldisulfonimide were all easily distinguishable by NMR in this case.

(20) (a) Backes, B.; Virgilio, A.; Ellman, J. *J. Am. Chem. Soc.* **1996**, *118*, 3055−3056. (b) Kenner, G. W.; McDermott, J. R.; Sheppard, R. C. *J. Chem. Soc., Chem. Commun.* **1971**, 636−637.

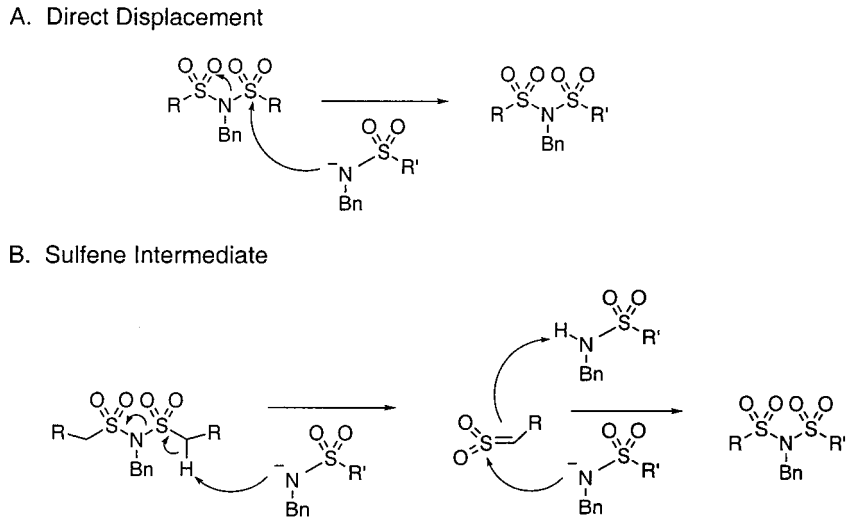
(21) King, J.; Rathore, R. In *The Chemistry of Sulphonic Acids, Esters and their Derivatives*; Patai, S., Rappaport, Z., Eds.; John Wiley & Sons: Chichester, UK, 1991, Chapter 17.

(22) Borowitz, I. *J. Am. Chem. Soc.* **1963**, *86*, 1146−1149.

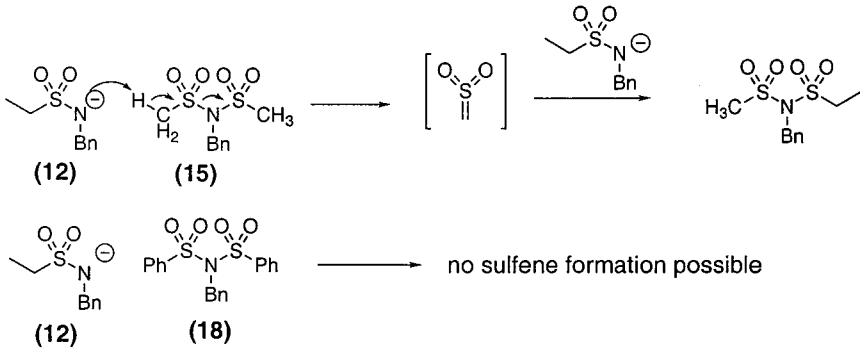
Scheme 5



Scheme 6



Scheme 7



the trans-disulfonimidation reaction could, in principle, be scavenged during the reaction by 1-morpholino-1-cyclohexene via a 2 + 2 cycloaddition.

In a seminal paper concerning the cycloaddition of sulfenes, Stork and Borowitz reported that treatment of methanesulfonyl chloride with TEA in the presence of an enamine gives a cyclic sulfone, presumably through a 2 + 2 cycloaddition. We performed the analogous experiment to determine whether a disulfonimide would undergo the same type of reaction (Scheme 8). Premixing 1-morpholino-1-cyclohexene and *N*-(benzyl)-dimethyldisulfonimide (**15**) at −78 °C, followed by treatment with butyllithium, resulted in the formation of a sulfone adduct (**22**). This sulfone matches the characteristics of an authentic sample synthesized as previously reported.[23] The yield of the trapping experiment was 20%,[24] a value consistent with similar sulfene trapping experiments.[25] This result confirms that elimination from the disulfonimide anion proceeds to give substantial quantities of an intermediate sulfene.

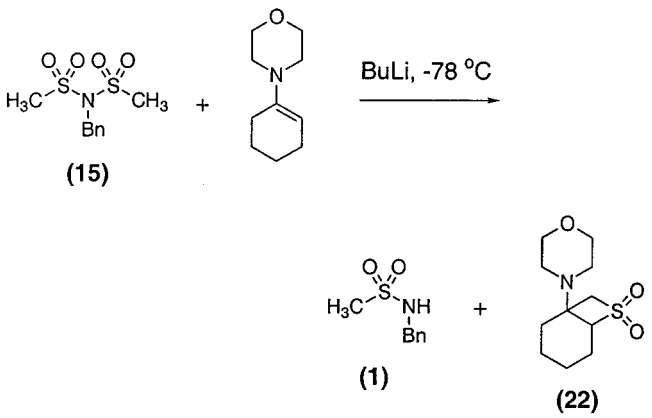
Sulfene Studies. Sulfene formation is expected to occur by one of three pathways. The reaction may involve a reversible deprotonation followed by elimination of the leaving group

(23) (a) Stork, G.; Borowitz, I. *J. Am. Chem. Soc.* **1962**, *84*, 3.

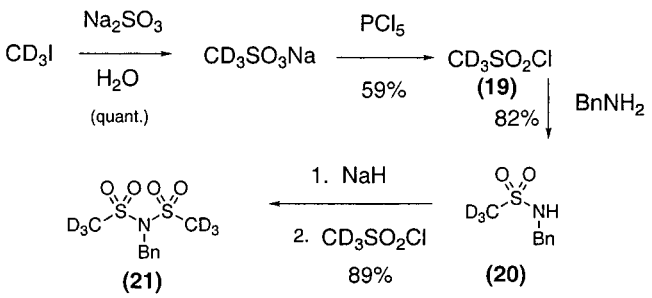
(24) After 1 h at −78 °C, the reaction was quenched with tosic acid. NMR analysis of the mixture indicated that approximately 55% of the disulfonimide **15** had broken down to sulfonamide **1**, suggesting that as much sulfene had been formed. Of this theoretical amount of sulfene formed, 20% was trapped as sulfone **22**.

(25) Pregel, M.; Buncel, E. *J. Chem. Soc., Perkin Trans. 2* **1991**, 307−311.

Scheme 8



Scheme 9



($E1cB_{Rev}$), an irreversible deprotonation followed by elimination ($E1cB_{Irrev}$), or a concerted deprotonation/elimination event (E2). To investigate these possibilities, isotope effect experiments were conducted.

Toward this end, (D_6)-*N*-(benzyl)dimethyldisulfonimide (**21**)-was synthesized as shown in Scheme 9. Treatment of D_3-methanesulfonyl chloride (**19**)[26] with benzylamine gave the sulfonamide **20**. Deprotonation of sulfonamide **20** and treatment with another equivalent of sulfonyl chloride **15** yielded the deuterated product **21** with less than 5% hydrogen incorporation detected by NMR.

The perdeuterated disulfonimide **21** was used to explore the detailed mechanistic pathway of sulfene formation. A 50/50 mixture of (D_6)-dimethyldisulfonimide (**21**) and (H_6)-dimethyldisulfonimide (**15**) was treated with a solution of deprotonated propyl sulfonamide. Initially, a singlet at 3.05 ppm was observed for the methyl groups of the disulfonimide, but as the reaction progressed, peaks for mono- and dideuterated methyldisulfonimide were seen. This isotope scrambling is consistent with a reversible deprotonation mechanism (Scheme 10). Similar results have been invoked to support reversible $E1cB_{Rev}$ elimination to form a sulfene from sulfonate esters.[27] Aryl sulfonate esters may form sulfenes by either reversible or irreversible deprotonation, depending on the leaving group ability of the phenol.[28] These results demonstrate that sulfonamides have a lower nucleofugality than stable phenoxides in this reaction and that the carbanion is a discrete intermediate.

The stability of the deprotonated disulfonimide was further investigated by irreversibly deprotonating the disulfonimide. Dimethyldisulfonimide **15** was treated with 1 equiv of *n*-butyllithium at −78 °C for 5 min, followed by quenching with D_4-methanol. Addition of tosic acid, followed by warming to room temperature, afforded a mixture of deuterated starting material and methyl sulfonamide. The recovered disulfonimide starting material was mono-deuterated, showing full deprotonation by the butyllithium. Approximately 10% of the anion had undergone elimination to give methyl sulfonamide.

This observation allows for a qualitative comparison of the relative nucleofugality of sulfonamide anions vs alkoxides as leaving groups. It has been suggested that sulfene formation proceeds through a late transition state compared to alkene-forming eliminations, and therefore the rate of reaction is relatively dependent on the leaving group nucleofugality.[29] The disulfonimide anion formed was relatively unstable at even −78 °C, yielding a sulfonamide product consistent with a putative sulfene intermediate. On the basis of the observation that sulfonate ester carbanions are stable to −40 °C,[30] the sulfonamide anion appears to be a better leaving group than an alkoxide ion.

Conclusions

A novel, unnatural anionic oligomer joined by hexamethylene linkers has been synthesized in a stepwise, convergent approach. The reactivity of disulfonimides has been investigated, and N-substituted disulfonimides should not be assumed to be base-stable. The swapping of sulfonamide units in a disulfonimide oligomer via a "trans-disulfonimidation" reaction occurs under basic conditions. Isotope scrambling, substituent effects, and sulfene trapping data are most consistent with a reaction mechanism that includes an $E1cB_{Rev}$ elimination to form a sulfene intermediate. In sulfene-forming eliminations, the sulfonamide anion is a better leaving group than an alkoxide anion but worse than activated phenoxide leaving groups. These studies form the groundwork for an understanding of the synthesis and reactivity of the disulfonimide functional group, a moiety with potential utility as a mimic of biological anions.

Experimental Methods

General Information. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled under nitrogen from sodium−benzophenone ketyl. Methylene chloride (CH_2Cl_2) was distilled from calcium hydride. Pyridine (Pyr) was distilled from barium oxide. Commercial reagents were used as received unless otherwise stated. All reactions were conducted under an inert argon or nitrogen atmosphere. Previously reported compounds are indicated by a footnote after the compound number.

Chromatography. Analytical thin-layer chromatography (TLC) was performed on precoated (0.25 mm thickness) glass plates (E. Merck, silica gel 60 F-254). Components were visualized by UV light (254 nm) if possible and by staining plates with either an acidic solution of $(NH_4)_6Mo_7O_{24}{\cdot}H_2O$ and ceric sulfate or an acidic ethanolic solution of *p*-anisaldehyde, followed by heating. Column chromatography was performed using Kieselgel-60 230−400 mesh silica gel (E. Merck). Bulk solvent removal was carried out on a rotary evaporator at water aspirator pressure. All nonvolatile compounds were routinely dried under high vacuum.

Physical Data. Proton nuclear magnetic resonance spectra (^1H NMR) were recorded on a Varian 300 (300 MHz) and Varian-400 (400 MHz) spectrometers. The chemical shifts are reported in parts per million (δ, ppm) relative to an internal tetramethylsilane standard. Coupling constants are reported in hertz (Hz), and the data are presented in the

(26) In the process of making disulfonimide **21**, we sought a new synthesis of (D_3)-methanesulfonyl chloride (**19**). Many preparations of (D_3)-methanesulfonyl chloride (**19**) have been reported, but they are all either low yielding, time-consuming, or very inconvenient. We found a more facile procedure involves submitting (D_3)-methyl iodide to the Strecker reaction and treating the resultant sodium sulfonate salt with phosphorus pentachloride. This simple two-step procedure gives an overall yield of (D_3)-methanesulfonyl chloride (**19**) of 59%, which is comparable to other procedures but does not require the use of chlorine gas or extended reaction times.

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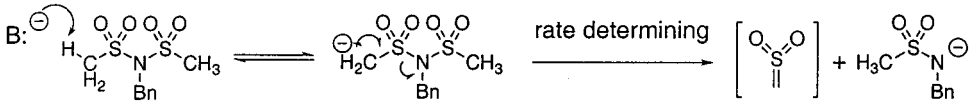
Scheme 10



following form: chemical shift (multiplicity, number of protons, coupling constants). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad; dd, doublet of doublets; *J*, coupling constant (Hz). Phosphorus-31 nuclear magnetic resonance (^{31}P NMR) spectra were recorded on a Varian 300 spectrometer at 121.5 MHz. The chemical shifts are reported in parts per million (δ, ppm) relative to an external neat H_3PO_4 standard ($\delta = 0$ ppm). Carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra were recorded on Varian-300 (75 MHz) and Varian-400 (101 MHz) spectrometers. All spectra are reported with the corresponding solvent. Infrared (IR) spectra (neat film or KBr pellet) were recorded on a Mattson Galaxy 4020 FT-IR instrument. High-resolution mass spectra (HRMS) and high-resolution FAB mass spectra (HRFABMS) were recorded on a Kratos MS-80. Melting points were determined in a Thomas capillary melting point apparatus and are uncorrected.

***N*-(Benzyl)methylsulfonamide (1).**[31] Benzylamine (10.7 g/100 mmol) was dissolved in 100 mL of dry THF, and the resulting solution was cooled to 0 °C. Mesyl chloride (5.7 g/50 mmol) was added to the reaction flask dropwise, and the mixture was permitted to stir for 3 h. The solvent was removed, and the crude material was dissolved in ethyl acetate and then washed three times with 30 mL of 2 N HCl. The organic layer was dried with $MgSO_4$, and the solvent was removed, yielding 6.74 g of **1** (73%): ^{1}H NMR ($CDCl_3$) δ 2,83 (s, 3H); 4.30 (d, 2H, $J = 7.6$ Hz); 4.98 (br. s, 1H); 7.35 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 41.2, 47.3, 128.1, 128.3, 129.1, 136.9 ppm; IR (KBr pellet) 3232, 3018, 2847, 1458, 1300, 1134 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_8H_{11}NO_2S\cdot H^+$ 186.0588, found 186.0585.

Disodium Hexane-1,6-disulfonate (2).[32] Sodium sulfite (63.02 g/0.500 mol) and 1,6-dibromohexane (48.79 g/0.200 mol) were boiled under reflux in 100 mL of water for 72 h. The solvent was evaporated under reduced pressure. The crude solid was recrystallized from a minimum amount of water/methanol. Collection after two crops yielded 51.9 g (89%): ^{1}H NMR (D_2O) δ 1.32 (m, 4H); 1.61 (m, 4H); 2.78 (m, 4H) ppm; ^{13}C NMR (D_2O) δ 19.2, 22.7, 46.3 ppm; IR (KBr pellet) 3547, 2922, 2874, 2235, 2092, 1626, 1155 cm^{-1}.

Hexane-1,6-disulfonyl Chloride (3).[33] The bis sulfonate sodium salt **2** was dried at 80 °C under reduced pressure to a constant weight of 13.8 g (47 mmol). Solid PCl_5 (23.8 g/114 mmol) was mixed thoroughly with **2**. The reaction flask was fitted with a condenser and was heated to 90 °C for 4 h. The reaction was quenched with ice water (30 mL), which was then decanted. The crude solid was washed with water (2 × 30 mL) and then dissolved in ethyl acetate. The ethyl acetate was dried ($MgSO_4$) and evaporated under vacuum. The product was recrystallized from a minimum amount of ethyl acetate/hexanes. Two recrystallizations yielded 10.5 g (78%): ^{1}H NMR ($CDCl_3$) δ 1.58 (m, 4 H); 2.06 (m, 4 H); 3.67 (m, 4 H) ppm ^{13}C NMR ($CDCl_3$) δ 24.1, 27.0, 65.0 ppm; IR (KBr pellet) 2993, 2933, 2868, 1471, 1355, 1157, 758 cm^{-1}.

1-[6-Hexylsulfonyl chloride]-*N*-(benzyl)methyldisulfonimide (4). A 60% oil dispersion of sodium hydride (0.44 g/11 mmol) was washed with pentane (2 × 8 mL) and dried under nitrogen. **1** (1.85 g/10 mmol) was dissolved in 10 mL of dry THF and added dropwise to the sodium hydride. An additional 20 mL of dry THF was added to the thick suspension. The mixture was stirred for 1 h. 2.830 g (10 mmol) of dichloride **3** was dissolved in 10 mL of dry THF, and the deprotonated sulfonamide solution was added quickly to the dichloride. After 1 h, the reaction was quenched with saturated ammonium chloride, the solvent was removed, and the crude mixture was partitioned between 75 mL of ethyl acetate and distilled water. The organic layer was washed with water, separated, dried over magnesium sulfate, and evaporated. The crude material was purifed by column chromatography (3:1 methylene chloride:hexane) and 1.29 g of the product (60% of theoretical yield based on **1** was obtained): mp 70 °C; ^{1}H NMR ($CDCl_3$) δ 1.45 (m, 4H); 1.76 (m, 2H); 2.01 (m, 2H); 2.97 (s, 3H); 3.30 (m, 2H); 3.65 (m, 2H); 4.90 (s,2H); 7.53,7.38 (m, 5H) ppm ^{13}C NMR δ 22.47, 23.89, 26.79, 27.16, 43.76, 52.15, 56.20, 64.96, 128.64, 128.81, 129.35, 134.84 ppm; IR (KBr pellet) 3028, 2949, 1466, 1359, 1163, 1055 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{14}H_{22}ClNO_6S\cdot H^+$ 432.0376, found 432.0368. Anal. Calcd for $C_{14}H_{22}ClNO_6S_3$: C, 38.93; H, 5.13; N, 3.24. Found: C, 38.84; H, 5.15; N, 3.20.

Hexane-1,6-di-[*N*-(benzyl)sulfonamide] (5). Benzylamine (4.7 g/44 mmol) was dissolved in 20 mL dry THF and allowed to stir at 0 °C for 15 min. The disulfonyl chloride **3** (3.1 g/11 mmol) was dissolved in 10 mL of dry THF and was added dropwise to the reaction, which was allowed to warm to room temperature and stir for 3 h. To the reaction mixture was added 50 mL of ethyl acetate and 30 mL of 2 N HCl. The organic layer was separated and washed with 30 mL of 2 N HCl. The organic layer was separated, dried ($MgSO_4$), and evaporated. The crude product was recrystallized from THF/water. Recrystallization yielded 4.26 g (91%): mp 171 °C; ^{1}H NMR (DMSO) δ 1.20 (m, 4 H); 1.55 (m, 4 H); 2.84 (m, 4 H); 4.12 (d, 4 H, $J = 6.4$ Hz); 7.35 (m, 10 H); 7.62 (t, 2H, $J = 6.4$ Hz) ppm ^{13}C NMR (DMSO) δ 22.8, 26.9, 45.8, 51.5, 127.1, 127.6, 128.3, 138.4 ppm; IR (KBr pellet) 3279, 3032, 2920, 2362, 1429, 1323, 1136 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{20}H_{28}N_2O_4S_2\cdot H+$ 425.1569, found 425.1567; Anal. Calcd for $C_{20}H_{28}N_2O_4S_2$: C, 56.58; H, 6.65; N, 6.60. Found: C, 56.44; H, 6.58; N, 6.57.

6-[6-[6-[*N*-(Benzyl)methyldisulfonimidoylhexyl]-*N*-(benzyl)methyldisulfonimidoylhexyl]-*N*-(benzyl)methyldisulfonimidoylhexyl]-*N*-(benzyl)methyldisulfonimide (6). Sodium hydride (0.11 g, 2.8 mmol) was washed with pentane and dried under nitrogen. Disulfonamide **5** (0.46 g, 1.1 mmol) was dissolved in 15 mL of dry THF and 1 mL of DMSO. The solution was added into the base and stirred for 10 h. The chloride **4** (0.93 g, 2.2 mmol) was dissolved in 5 mL of dry THF and added to the reaction mixture to stir for 3 h. The solvent was evaporated under vacuum, and the crude was taken up in 50 mL of methylene chloride, filtering insoluble material. The organic layer was washed three times with brine, dried over magnesium sulfate, and evaporated. Silica gel column chromatography (1% MeOH/CH_2Cl_2) gave some separation to yield 0.26 g (20%) of pure product and 0.45 g of partially purified product. ^{1}H NMR ($CDCl_3$): δ 1.27 (m, 12H); 1.66 (m, 12H); 2.96 (s, 6H); 3.14 (m, 8H); 3.26 (m, 4H); 4.88 (s, 4H); 4.89 (s, 4H) 7.53, 7.37 (m, 20H) ppm. ^{13}C ($CDCl_3$): δ 22.39, 22.55, 27.22, 43.87, 52.26, 52.42, 56.42, 128.72, 128.84, 128.88, 129.47, 129.60, 134.99, 135.32 ppm.

6-(6-(6-(Methyldisulfonimidoylhexyl)methyldisulfonimidoylhexyl)-methyldisulfonimidoylhexyl)methyldisulfonimide (7). The *N*-benzyl-protected tetrakisdisulfonimide **6** (0.24 g) was dissolved in 30 mL of THF, and about 50 mg of Pd−C was added. The flask was purged with argon, and then hydrogen gas was added. The reaction was stirred for 1 h, the vessel was purged with argon, and the solution was filtered and evaporated under vacuum to give 0.168 g (100%) of product: ^{1}H NMR (D_2O) δ 1.26 (m, 12H); 1.59 (m, 12H); 2.87 (s, 6H); 3.00 (m, 12H) ppm; ^{13}C NMR (D_2O) δ 23.02, 26.03, 42.43, 54.16, 54.44 ppm. (unreferenced); IR (KBr pellet) 3281, 2939, 1450, 1354, 1147, 877 cm^{-1}. MALDI MS (dihydroxybenzoic acid matrix) (*m*/*z*) calcd for $C_{20}H_{46}N_4O_{16}S_8\cdot Na$ 877.057, found 877.271; $C_{20}H_{45}N_4O_{16}S_8\cdot Na_2$ 899.039, found 899.282; $C_{20}H_{44}N_4O_{16}S_8\cdot Na_3$ 921.021, found 921.274; $C_{20}H_{43}N_4O_{16}S_8\cdot Na_4$ 943.003, found 943.281; $C_{20}H_{42}N_4O_{16}S_8\cdot Na_5$ 964.985, found 965.297.

1-[6-Hexyl-*N*-(benzyl)sulfonamide]-*N*-(benzyl)]methyldisulfonimide (8). 4 (1.29 g, 3.0 mmol) was dissolved in 25 mL of THF and cooled to 0 °C. Benzylamine (0.85 mL, 7.5 mmol) was added dropwise to the reaction, which was stirred for 1.5 h. The THF was removed

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under vacuum, and the crude material was partitioned between 50 mL of ether and 50 mL of of 2 M HCl. The organic layer was separated, washed with brine, dried over magnesium sulfate, and evaporated under vacuum, leaving 1.387 g of product with no need for further purification (92.4%): mp 118 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 4H); 1.70 (m, 4H); 2.86 (m, 2H); 2.93 (s, 3H); 3.28 (m, 2H); 4.29 (d, 2H, J = 6.4 Hz); 4.77 (t, 1H, J = 6.4 Hz); 4.89 (s, 2H)7.55, 7.35 (m, 10H) ppm; ^{13}C NMR δ 22.52, 23.18, 27.28, 27.35, 43.85, 47.12, 52.26, 52.97, 56.35, 127.93, 128.06, 128.68, 128.85, 129.39, 134.89, 136.93 ppm; IR (KBr pellet) 3250, 3032, 2941, 1462, 1358, 1151 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{21}H_{30}N_2O_6S_3 \cdot H^+$ 503.1344, found 503.1337. Anal. Calcd for $C_{21}H_{30}N_2O_6S_3$: C, 50.18; H, 6.02; N, 5.57. Found: C, 49.91; H, 5.82, N, 5.45.

1-[1-(6-Hexylsulfonyl chloride)-6-hexyl-*N*-(benzyl)hexyldisulfonimide]-*N*-benzyl)hexylmethyldisulfonimide (9). Sulfonamide **8** (1.36 g, 2.7 mmol) was dissolved in 30 mL of dry THF. The solution was added into sodium hydride (0.12 g, 3.0 mmol) that had been washed with 5 mL of pentane. The reaction was stirred for 2 h and grew mostly clear. Dichloride **3** (3.06 g, 11 mmol) was dissolved in 10 mL of dry THF. The deprotonated sulfonamide solution was added into the dichloride slowly and stirred overnight. The reaction was quenched with ammonium chloride, and the solvent was removed under vacuum. The crude was partitioned between 100 mL of ethyl acetate and 50 mL of water. The organic layer was separated, washed with an additional 50 mL of water and separated, dried with magnesium sulfate, and evaporated under vacuum. The crude product was dissolved in 25 mL of methylene chloride, and 5 g of silica gel was added. The solvent was removed to bind the crude product to the silica gel, and the mixture was placed on top of a silica gel column (CH_2Cl_2) and chromatographed, yielding 0.71 g of product (36% of theoretical yield based on **8**): ^{1}H NMR ($CDCl_3$) δ 1.28 (m, 4H); 1.42 (m, 4H), 1.68 (m, 6H); 2.00 (m, 2H); 2.96 (s, 3H); 3.17 (m, 4H), 3.26 (m, 2H); 3.63 (m, 2H); 4.88 (s, 2H), 4.89 (s, 2H); 7.55, 7.40 (m, 10H) ppm; ^{13}C NMR 22.17, 22.27, 23.72, 26.55, 26.93, 26.99, 43.61, 51.96, 52.13, 56.06, 56.13, 64.81, 128.47, 128.65, 129.17, 129.32, 134.85, 135.14 ppm; IR (KBr pellet) 3040, 2949, 1466, 1369, 1151, 796 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{27}H_{41}ClN_2O_{10}S_5 \cdot H^+$ 771.09514, found 771.0939.

6-[6-[6-[6-[6-[*N*-(Benzyl)methyldisulfonimidoylhexyl]-*N*-(benzyl)-methyldisulfonimidoylhexyl]-*N*-(benzyl)methyldisulfonimidoylhexyl]-*N*-(benzyl)methyldisulfonimidoylhexyl]-*N*-(benzyl)methyldisulfonimidoylhexyl]-*N*-(benzyl)methyldisulfonimide (10). Sodium hydride (0.036 g, 0.9 mmol) was washed with 5 mL of pentane. The bis sulfonamide **5** (0.15 g, 0.36 mmol) was dissolved in 5 mL of dry THF and 0.3 mL of DMSO, and it was then added to the sodium hydride. The thick slurry was stirred for 3 h. Sulfonyl chloride **9** (0.54 g, 0.72 mmol) was dissolved in 5 mL of dry THF and was added to the reaction mixture quickly. THF (10 mL) was added to the reaction, which was stirred for 20 h. The THF was removed, and the crude solid was dissolved/suspended in 100 mL of ethyl acetate and 100 mL of 0.1 M HCl. The remaining solid (0.350 g) was filtered, and the organic layer was separated, dried with magnesium sulfate, and evaporated. Column chromatography (1% MeOH/CH_2Cl_2) of the crude from the organic layer gave 67 mg of product (**10**) plus an additional 170 mg of slightly impure fractions of product. ^{1}H NMR ($CDCl_3$): δ 1.23 (m); 1.65 (m); 2.95 (s); 3.17 (m); 3.24 (m); 4.85 (s); 4.87 (s), 7.55−7.40 (m) ppm. ^{13}C NMR ($CDCl_3$): δ 22.34, 22.45, 27.18, 43.83, 52.21, 52.37, 56.38, 128.68, 128.80, 128.83, 129.42, 129.56, 134.97, 135.30 ppm.

***N*-(Benzyl)ethylsulfonamide (12).**[34] Benzylamine (4.4 mL, 40 mmol) was dissolved in THF at 0 °C. Ethyl sulfonyl chloride (1.9 mL, 20 mmol) was added to the reaction, which was allowed to warm to room temperature. The THF was evaporated under vacuum, and the crude material was partitioned between 50 mL of ether and 50 mL of 1 M HCl. The ether phase was separated and washed with 50 mL of 1 M HCl. The ether layer was separated, dried with magnesium sulfate, and evaporated under reduced pressure to yield a white solid (3.40 g, 85%): ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 3H, J = 7.2 Hz), 2.93 (q, 2H, J = 7.2 Hz), 4.28 (s, 2H), 4.82 (br s, 1H); 7.35 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) 8.17, 47.11, 47.53, 127.84, 127.97, 128.78, 136.98 ppm; IR (KBr pellet) 3288, 3035, 2976, 1453, 1313, 1138 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_9H_{13}NO_2S \cdot H^+$ 200.0745, found 200.0740.

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***N*-(Benzyl)diethyldisulfonimide (13).** Sodium hydride (0.22 g, 5.5 mmol) was washed with 5 mL of pentane. Sulfonamide **12** (0.99 g, 5 mmol) was dissolved in 10 mL of dry THF and added to the base. After 0.5 h, the solution grew clear. Ethyl sulfonyl chloride (0.52 mL, 5 mmol) was added to the reaction which grew cloudy quickly. After 1 h, the solvent was evaporated and the crude was partitioned between 50 mL of ether and 50 mL of 2 M HCl. The ether phase was washed with 50 mL of brine. The ether was separated, dried with magnesium sulfate, and evaporated under reduced pressure. The crude was chromatographed by silica gel chromatography (2:1 hexanes:ethyl acetate) to give 1.27 g (87%) of solid product: mp 72−73 °C; ^{1}H NMR ($CDCl_3$) δ 1.29 (t, 6H, J = 7.2 Hz), 3.23 (q, 4H, J = 7.2 Hz), 4.91 (s, 2H), 7−36−7.54 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 7.44, 51.38, 52.62, 128.60, 128.78, 129.48 ppm; IR (KBr pellet) 3508, 3063, 2987, 1460, 1365, 1145 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{11}H_{17}NO_4S_2 \cdot H^+$ 292.0677, found 292.0671. Anal. Calcd for $C_{11}H_{17}NO_4S_2$: C, 45.34; H, 5.88; N, 4.81. Found: C, 45.52; H, 5.93; N, 4.82.

***N*-(Benzyl)propylsulfonamide (14).**[35] Propylsulfonyl chloride (5.6 mL, 50 mmol) was dissolved in 50 mL of ether at 0 °C. Benzylamine (10.9 mL, 100 mmol) was added slowly to the reaction, which was then allowed to warm to room temperature. Then 50 mL of 1 M HCl was added to dissolve the benzylamine salt, and the ether layer was washed with 0.2 M HCl (50 mL) and brine (50 mL). The ether was dried with magnesium sulfate and evaporated under vacuum, yielding a white solid (9.427 g, 89%): ^{1}H NMR ($CDCl_3$) δ 0.953 (t, 3H, J = 7.6 Hz), 1.75 (m, 2H), 2.86 (m, 2H), 4.27 (d, 2H, J = 6.0 Hz), 4.94 (t, 1H, J = 6.0 Hz), 7.35 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.80, 17.23, 47.06, 54.93, 127.85, 127.91, 128.75, 137.03 ppm; IR (KBr pellet) 3285, 3036, 2926, 1431, 1325, 1132 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{10}H_{15}NO_2S \cdot H^+$ 214.0902, found 214.0905.

***N*-(Benzyl)dimethyldisulfonimide (15).**[36] Sodium hydride (0.24 g, 6.0 mmol) was washed with 5 mL of pentane. Sulfonamide **1** (0.926 g, 5 mmol) was dissolved in 10 mL of dry THF and added to the base. After 0.5 h, methanesulfonyl chloride (0.43 mL, 5.5 mmol) was added to the reaction. After 1 h, the solvent was evaporated and the crude was partitioned between 100 mL of ether and 50 mL of 2 M HCl. The ether was washed with 50 mL of brine. The ether was separated, dried with magnesium sulfate, and evaporated under reduced pressure. The crude was chromatographed by silica gel chromatography (2:1 hexanes: ethyl acetate) to give a white solid (0.94 g, 71%): ^{1}H NMR ($CDCl_3$) δ 3.07 (s, 6H), 4.92 (s, 2H), 7.37−7.54 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ44.02, 51.96, 128.66, 128.89, 129.26, 134.70 ppm. IR (KBr pellet) 3050, 2359, 1628, 1365, 1273, 1103 cm^{-1}.

Dimethyldisulfonimide (16). The *N*-benzyl-protected disulfonimide **15** (0.58 g) was dissolved in 10 mL of THF, and 30 mg of Pd−C was added. The flask was purged with argon, and then hydrogen gas was added. The reaction was stirred for 1 h, the vessel was purged with argon, and the solution was filtered and evaporated under vacuum to give 0.384 g (100%) of product: ^{1}H NMR (d_6-acetone) δ 3.25 (s) ppm; ^{13}C NMR (d_6-acetone) δ 43.36 ppm.

***N*-(Benzyl)phenylsulfonamide (17).**[37] Phenylsulfonyl chloride (2.6 mL, 20 mmol) was dissolved in 100 mL of ether at 0 °C. Benzylamine (4.4 mL, 40 mmol) was added dropwise, and the reaction was allowed to warm to room temperature. Then 100 mL of 0.5 M HCl was added to dissolve the benzylamine salt. The ether phase was washed with an additional 100 mL of 0.5 M HCl. The ether was separated, dried with magnesium sulfate, and evaporated under vacuum to reveal 4.57 g (93%) of solid product: ^{1}H NMR ($CDCl_3$) δ 4.08 (d, 2H, J = 6.0 Hz), 5.39 (t, 1H, J = 6.0 Hz), 7.09−7.83 (m, 10H) ppm; ^{13}C NMR ($CDCl_3$) δ 47.01, 126.91, 127.62, 127.70, 128.45, 128.95, 132.48, 136.20, 139.78 ppm; IR (KBr pellet) 3331, 3063, 2930, 1445, 1325, 1151 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{13}H_{13}NO_2S$ 248.0745, found 248.0743.

***N*-(Benzyl)diphenyldisulfonimide (18).**[38] Sodium hydride (0.22 g, 5.5 mmol) was washed with 5 mL of pentane. Sulfonamide **17** (1.24 g, 5.0 mmol) was dissolved in 15 mL of dry THF and added to the base. After stirring for 0.5 h, phenylsulfonyl chloride (0.64 mL, 5 mmol)

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was added to the reaction which grew thinner. After 2 h, the reaction was quenched with ammonium chloride and the solvent was evaporated. The crude material was partitioned between 50 mL of ether and 50 mL of 2 M HCl. The ether was washed with 50 mL of brine. The ether layer was separated, dried with magnesium sulfate, and evaporated under reduced pressure. The crude reaction mixture was chromatographed by silica gel chromatography (1:1 hexanes:methylene chloride) to give 1.496 g (77.3%) of solid product: ^{1}H NMR ($CDCl_3$) δ 4.94 (s, 2H), 7.1−7.8 (m, 15H) ppm; ^{13}C NMR ($CDCl_3$) δ 52.48, 128.07, 128.38, 128.76, 129.17, 133.54, 134.47, 140.08 ppm; IR (KBr pellet) 3063, 2962, 1446, 1373, 1167 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_{19}H_{17}NO_4S_2 \cdot H^+$ 388.0677, found 388.0693.

Methanesulfonyl Chloride-d_3 (19).[39] Sodium sulfite (4.16 g, 33 mmol) was dissolved in 15 mL of water in a round-bottom flask sealed with a septum. Iodomethane-d_3 (5.0 g, 35 mmol) was added to the flask and stirred for 3 h, until no longer biphasic. The solvent was removed, and the crude white solid was dissolved in 12 mL of hot water and added into 200 mL of hot acetone. The solution was cooled overnight and the solid was then filtered. The solid was dried at 100 °C under vacuum for 2 h. PCl_5 (3.44 g, 16.5 mmol) was mixed thoroughly with 2.00 g (16.5 mmol) of the sodium salt and heated to 90 °C for 1 h under reflux. Dry ether (20 mL) was added to the flask, and the contents were stirred for 10 min. The flask was cooled to 0 °C, and 30 mL of ether was added. To the reaction was added 40 mL of 20% sodium bisulfite solution, and the reaction was stirred until no solid remained. The organic layer was collected and washed twice with 40 mL of 20% sodium bisulfite solution. The aqueous fractions were collected and back-extracted with 30 mL of ether. The ether fractions were collected and washed with 40 mL of 20% sodium bisulfite. The ether layer was dried over magnesium sulfate and evaporated to yield 1.15 g (59%) of a yellow tinted oil.

***N*-(Benzyl)methylsulfonamide-d_3 (20).** Deuterated benzylamine was prepared by stirring with deuterium oxide and extraction with ether. Methanesulfonyl chloride-d_3 **(19)** (0.94 g, 8.0 mmol) was dissolved in 25 mL of dried ether at 0 °C. Benzylamine-d_2 (2.2 mL, 20 mmol) was added to the reaction vessel slowly and then stirred at room temperature for 1.5 h. The creation was quenched with 25 mL of 2 M HCl. The ether layer was separated and washed with 20 mL of 2 M HCl. The ether layer was dried over magnesium sulfate and evaporated under reduced pressure to yield 1.24 g (82%) of an off-white solid: mp 64 °C; ^{1}H NMR ($CDCl_3$) δ 4.30 (s, 2H), 5.05 (br s, 1H), 7.30−7.37 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 47.06, 127.84, 127.98, 128.80, 136.74 ppm; IR (KBr pellet) 3234, 3034, 1456, 1435, 1304, 1141 cm^{-1}. HRFABMS (*m*/*z*) calcd for $C_8H_8D_3NO_2S \cdot H^+$ 189.0773, found 189.0773. Anal. Calcd for $C_8H_8D_3NO_2S$: C, 51.04; H+D as H, 5.89; N, 7.44. Found: C, 51.13; H+D as H, 5.92; N, 7.40.

***N*-(Benzyl)dimethyldisulfonimide-d_6 (21).** Sulfonamide **28** was dissolved in 50 mL of ether and washed with deuterium oxide (2 × 4 mL). The ether was dried with magnesium sulfate and evaporated. Sodium hydride (0.26 g, 6.4 mmol) was washed with 5 mL of pentane. The deuterated sulfonamide **20** was dissolved in 20 mL of dry THF and added slowly to the base. An additional 20 mL of dry THF was added to aid stirring for 2 h. Methanesulfonyl chloride-d_3 was dissolved in 10 mL of dry THF and added to the reaction, which grew thin and milky quickly. After 15 min, TLC showed complete reaction. Deuterated benzylamine was added to the reaction to scavenge any unreacted sulfonyl chloride. Deuterium oxide (0.5 mL) was added to quench the reaction. The THF was evaporated under reduced pressure, and the crude was partitioned between 100 mL of ether and 40 mL of 1 M HCl. The ether phase was separated and washed with 40 mL of 1 M HCl. The ether was dried over magnesium sulfate, and the ether was evaporated under reduced pressure. The crude solid was purified by column chromatography (2:1 Hex:Ethyl acetate) to yield 1.39 g (89%): mp 115 °C; ^{1}H NMR ($CDCl_3$) δ 3.03 (s, 0.12H), 4.91 (s, 2H), 7.3−7.4 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 51.87, 128.59, 128.84, 129.21, 134.83 ppm; IR (KBr pellet) 3234, 3011, 2262, 1338, 1159 cm^{-1}; HRFABMS (*m*/*z*) calcd for $C_9H_7D_6NO_2S \cdot H^+$, 270.0734, found 270.0747. Anal. Calcd for $C_9H_8D_6NO_2S$: C, 40.13; H+D as H, 4.86; N, 5.20. Found: C, 40.29; H+D as H, 4.88; N, 5.19.

4-(7,7-Dioxido-7-thiabicyclo[4.2.0]oct-1-yl)morpholine (22).[40] TEA (0.70 mL/5.0 mmol) and 4-(1-cyclohexen-1-yl)morpholine (0.84 mL/5.0 mmol) were dissolved in 5 mL of dry THF at room temperature under nitrogen. Mesyl chloride (0.39 mL/5.0 mmol) was added to the reaction flask dropwise. A white precipitate formed quickly. After stirring for 16 h, 30 mL of distilled water was added to the crude reaction, and the solution was shaken in a separatory funnel until a white solid formed. Then 30 mL of ether was added, and the suspension was shaken. The solid was filtered and dried under vacuum overnight to yield 0.46 g (38%) of **21**.

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