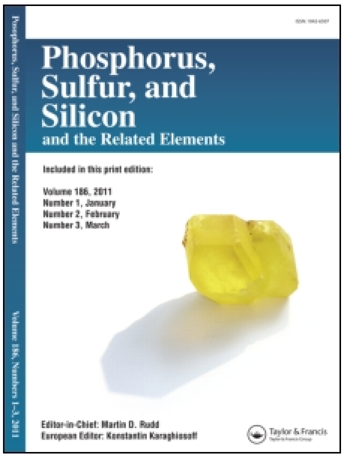

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THE EFFECT OF LOCATING THE SULFONYL GROUP IN A FIVE-MEMBERED RING ON THE BALANCE OF ELIMINATION VS. SUBSTITUTION REACTIONS OF SULFONIC ACID DERIVATIVES

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THE EFFECT OF LOCATING THE SULFONYL GROUP IN A FIVE-MEMBERED RING ON THE BALANCE OF ELIMINATION VS. SUBSTITUTION REACTIONS OF SULFONIC ACID DERIVATIVES[1]

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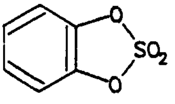
The simplest examples of both a five-membered cyclic sulfonic anhydride (ethane-1,2-disulfonic anhydride, **3**) and a sulfonylammonium salt (2,2-dimethylisothiazolidinium 1,1-dioxide fluorosulfate, **13**), are found to react with triethylamine and an alcohol via direct displacement at sulfur and not by way of the sulfene. When taken with previous observations these results lead to the conclusion that five-membered cyclic sulfonic acid derivatives can generally be expected to react entirely by direct displacement, even in those reactions in which the acylic or six-membered cyclic analogues react entirely via the sulfene.

Key words: Sulfenes, elimination, nucleophilic substitution, five-membered ring acceleration, Baldwin's rules, sulfonic anhydrides, sulfonylammonium salts.

INTRODUCTION

It has been known for quite a number of years that nucleophilic attack at a sulfonyl group is greatly accelerated when the sulfonyl function is part of a five-membered ring.[2] A particularly notable example is the 10^7-fold faster reaction of catechol sulfate (**1**) vs diphenyl sulfate (**2**) with aqueous hydroxide.[3] The "five-membered ring effect" is generally in evidence,[2] but it is not always nearly as large as that found in **1**; methanolysis and ethanolysis of ethane-1,2-disulfonic anhydride (**3**), for example, are reported[4] to proceed 503 and 225 times faster than the respective reactions of methanesulfonic anhydride. A substantial proportion of the "five-membered ring effect" on the direct nucleophilic displacement at a sulfonyl center is ascribed to relief of ring strain accompanying formation of the transition state.[2] As with the analogous effect on similar reactions at the phosphoryl group,[5] other factors are believed to contribute and the topic is not regarded as fully understood.[2c]



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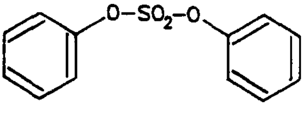

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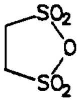
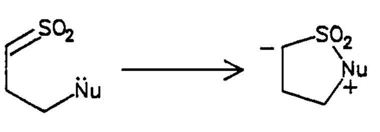


3

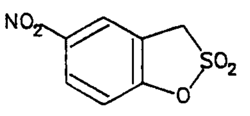
It is also well-established[6,7] that the reaction of a nucleophile with species of the general formula $RR'CHSO_2Lg$, where Lg is a "leaving group" or "nucleofuge," that there are two common processes, (i) direct displacement at sulfur, and (ii) elimination to form the sulfene (which is subsequently trapped by the nucleophile with recapture of a proton). With acyclic species of this structure, less-basic nucleophiles (e.g. water, alcohols, or azide anion) react by the displacement route, whereas relatively basic reagents (e.g. triethylamine or hydroxide) lead to sulfene formation.[6c] In contrast to the acceleration of nucleophilic displacement found when the sulfonyl group is in a five-membered ring, the formation of a sulfene from such a precursor may be expected to be greatly slowed. This point was first made by Williams and co-workers,[8] who described the reaction in terms of a transition state which "would be expected to resemble the perpendicular form of the sulphene and therefore provide a much less favourable pathway than the ElcB mechanism for the open chain form which presumably involves a planar incipient sulphene in the transition state."[8b] Another way of looking at such a reaction is to examine the reverse process **4** → **5**, in the light of Baldwin's rules for ring closure.[9]



4 **5**

It is immediately apparent that the reaction is, in Baldwin's notation, 5-*Endo-Trig*, a "disfavored" pathway. "Disfavored" need not mean absolutely forbidden, but rather that there is a sizeable energy barrier and hence the reaction is much slowed relative to a "favored" process; reactions proceeding via 5-*Endo-Trig* transition states have been described.[9b,10]

In this context it is to be expected that the incorporation of the system $RR'CHSO_2Lg$ into a five-membered ring would completely upset the balance between elimination to form the sulfene and direct nucleophilic substitution at the sulfur atom, and, in fact, one example has been described. Kaiser and co-workers[11] were able to show that the S—O bond cleavage in the reaction of **6** with hydroxide, occurs by nucleophilic displacement at sulfur and not via the sulfene. The straight chain analogues **7a** and **7b**, on the other hand, have been shown to hydrolyze with aqueous bases more or less entirely by way of formation of the arylsulfene.[8a,12,13]



6

$ArCH_2{-}SO_2{-}OAr'$

7

a) $Ar = Ph$, $Ar' = 4{-}NO_2{-}C_6H_4$

b) $Ar = 3{-}NO_2{-}C_6H_4$, $Ar' = 4{-}NO_2{-}C_6H_4$

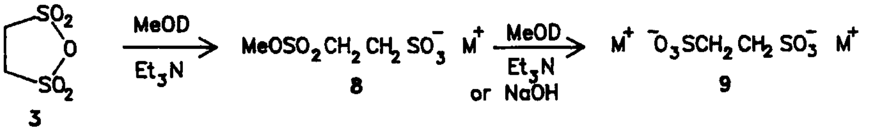
It is also known that changes in the structures of the reactants may alter the balance of elimination vs substitution. Of special relevance to the present work are the observations of Pregel and Buncel[14] on the reaction of a series of aryl methanesulfonates, CH_3SO_2OAr, with sodium ethoxide in ethanol. They concluded that

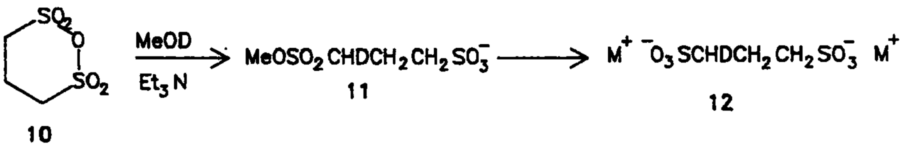
(a) when Ar was 4-nitrophenyl the reaction was primarily a sulfene process, (b) when Ar was 3-nitrophenyl it was mostly a displacement reaction with a small proportion of sulfene formation, and (c) with Ar = 4-trifluoromethylphenyl the reaction was entirely a displacement at sulfur. Apparently the greater the nucleofugality of the leaving group the greater the tendency for sulfene formation. The question then arises, is it possible for the presence of a powerfully nucleofugal group in the five-membered cyclic array to lead to sulfene formation (via a 5-*Endo-Trig* process)? This paper describes our examination of the reaction of two such five-membered sulfonyl-containing species with base.

RESULTS AND DISCUSSION

Sulfonic Anhydrides

Ethane-1,2-disulfonic anhydride (**3**) was allowed to react with triethylamine and methanol-*d*. The initial product of the reaction was the half-ester (**8**) which showed no sign of any deuterium incorporation; **8** reacts readily with solvent or any excess triethylamine to form the disulfonate (**9**) along with the protonated solvent (and, presumably, dimethyl ether) or the triethylmethylammonium cation (Et$_3$NMe$^+$).



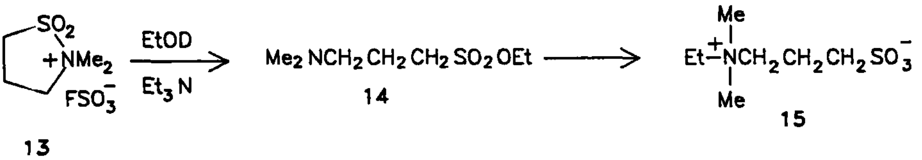


To simplify the spectrometric characterization, the initial crude product was run through a cation exchange resin and then hydrolyzed to **9** (M = Na) with 2 M aqueous NaOH. There was no indication of any deuterium incorporation in either the ^{1}H or ^{13}C NMR spectra of **9**.

In contrast, the six-membered ring anhydride, propane-1,3-disulfonic anhydride (**10**), gave, via the half-ester **11**, principally (~85%) the monodeuterated salt **12** (M = Na) with the remainder the undeuterated dianion (SO$_3^-$CH$_2$CH$_2$CH$_2$SO$_3^-$). The ^{1}H NMR spectrum of the sample of methanol-*d* used in these experiments showed it to contain up to 10% of CH$_3$OH, and since there is also protium added to the active hydrogen pool from the protons removed from the substrate to form the sulfene, it is likely that most and perhaps all of the reaction proceeds by way of the sulfene. Truce and Campbell[15] had previously reported that methanesulfonic anhydride reacts with triethylamine and methanol-*d* in benzene at least partly via sulfene.

Sulfonylammonium Salts

The cyclic sulfonylammonium fluorosulfate **13** on reaction with ethanol-*d* and triethylamine gave initially ethyl 3-(*N*,*N*-dimethylamino)propane sulfonate (**14**) which is easily removed from other components of the crude reaction product by trituration with carbon tetrachloride. The ester (**14**) is readily converted to the betaine (**15**) by intermolecular ethyl transfer, simply by allowing it to stand overnight at room temperature. The ^1H NMR spectrum of the betaine (**15**) so obtained from the reaction with ethanol-*d* was identical to that obtained from a betaine similarly prepared from ordinary (undeuterated) ethanol; deuterium analysis (falling drop method) confirmed the complete absence of deuterium.



This result is to be contrasted with earlier observations[16,17] on acyclic analogues of the general structure $CH_3SO_2\overset{+}{N}R_3\ FSO_3^-$. Their reactions and those of methanesulfonyl chloride with the corresponding amine (NR_3) in buffered D_2O containing acetonitrile and 1,2-dimethoxyethane (DME) have been quantitatively described[17] in terms of a complex multiexchange manifold involving the sulfonylammonium salt, its zwitterionic conjugate base ($\bar{C}H_2SO_2\overset{+}{N}R_3$) and sulfene. It was concluded that in the reaction of diethylmethyl(methylsulfonyl)ammonium fluorosulfate ($CH_3SO_2\overset{+}{N}Et_2Me\ FSO_3^-$) in this medium the ratio of deprotonation to $\bar{C}H_2SO_2\overset{+}{N}Et_2Me$ (and hence to the sulfene) to direct displacement to give $CH_3SO_3^-$, is about 50:1.

This rather indirect route to the ratio of deprotonation to displacement was necessitated by the fact that the reactions of sulfonylammonium salts in the presence of active deuterium sources (D_2O, $ArND_2$, etc.) can lead to extensive multiexchange,[16] forming, for example, $CD_3SO_3^-$ and $CHD_2SO_3^-$, in addition to $CH_2DSO_3^-$. A more direct piece of evidence for sulfene formation from $CH_3SO_2NEt_2Me^+FSO_3^-$ is its reaction with an enamine, 1-(2-methylpropenyl)-pyrrolidine, to give the characteristic four-membered cyclic sulfene-enamine adduct in roughly 50% yield (as estimated from the ^1H NMR spectrum of the crude product).[16b] By way of comparison, the same enamine on reaction with methanesulfonyl chloride and triethylamine has been reported to give the same adduct in 80% yield when the reaction is carried out in ether,[18] and in 68% yield in DME.[19]

Attempts to investigate the corresponding reaction of the six-membered cyclic analogue (2,2-dimethyltetrahydro-1,2-thiazinium 1,1-dioxide fluorosulfate) were thwarted by the formation of only tarry materials in its reaction with triethylamine in the presence of an alcohol[20]; the reaction in the *absence* of triethylamine does give an amino ester, however.[20,21]

As a final comment on the sulfonylammonium salts we point out that the lack of any deuterium-substituted materials in the product from **13** shows not only the absence of sulfene generation but also the lack of formation of the zwitterionic conjugate base. The extent to which this is due to (a) the five-membered ring enhancement of the direct attack at sulfur or to (b) a slowing of the rate of carbanion formation, has not been determined. The somewhat lower acidity of a five-membered cyclic sulfone (pK_a 13.9) vs an acyclic analogue (pK_a 12.5)[22] suggests that the second factor could at least contribute to some extent.

Conclusions

Both of the five-membered species incorporating the RR'CHSO$_2$Lg unit examined in this study undergo nucleophilic attack by basic reagents via a direct displacement process, and not by way of the sulfene route found with six-membered cyclic or acyclic analogues. This switch in mechanism is ascribed to a combination of the acceleration of direct displacement and the suppression of sulfene formation, in the five-membered ring compounds. The results described in this work, when taken with earlier observations on the reactions of **6**, lead to the conclusion that five-membered cyclic sulfonyl systems can generally be expected to behave differently from other simple analogues, and to react by the direct displacement pathway.

EXPERIMENTAL

Melting points were determined using either a Kofler Hot Stage or a Gallenkamp melting point apparatus and are uncorrected. ^1H NMR spectra were obtained used XL-200, Gemini 200 or Gemini 300 spectrometers, or where specifically indicated, an XL-100 spectrometer; ^{13}C NMR spectra were determined (at 75.43 MHz) on the XL-300 or Gemini 300 instruments. Sodium trimethylsilylpropanesulfonate (DSS) was used as the reference for NMR spectra of D_2O solutions.

Reagent grade chemicals and solvents were used as received unless otherwise noted. Triethylamine was distilled from CaH. Acetonitrile, absolute ethanol, and benzene were dried over CaH and distilled. Evaporation of solvents was carried out with a Büchi rotary evaporator connected to a water aspirator.

The cyclic anhydrides were prepared the procedure of McIlvain, *et al.*[23] Ethane-1,2-disulfonic anhydride (**3**), mp 145–147°C (sealed tube) (lit.[23] mp 145–146°C); IR (Nujol): ν_{max} 1383, 1275, 1225, 1196, 1169, 673 cm^{-1}; ^1H NMR (CD_3NO_2) δ 4.45(s); ^{13}C NMR δ 53.0. Propane-1,3-disulfonic anhydride (**10**), mp 196–197°C (lit.[23] mp 194–196°C); IR (KBr): 1379, 1309, 1294, 1179, 1038, 1021, 870, 840, 723 cm^{-1}; ^1H NMR (CD_3NO_2) δ: 2.73 (m, 2H), 3.72 (t, 4H). The cyclic sulfonylammonium fluorosulfate (**13**) was prepared as previously described.[21]

Reaction of Ethane-1,2-disulfonic Anhydride (**3**) *with Methanol-d and Triethylamine.* Ethane-1,2-disulfonic anhydride (**3**, 100 mg, 0.58 mmol) in dry acetonitrile (3 mL) was added dropwise to a mixture of CH_3OD (384 mg, 11.6 mmol) and triethylamine (76 mg, 0.75 mmol) in dry benzene (3 mL) at room temperature; the mixture was stirred for 10 min. Water (5 mL) and CH_2Cl_2 (20 mL) were added and the mixture shaken in a separatory funnel. Evaporation of the water layer gave a white solid (166 mg), which, from its ^1H NMR spectrum (D_2O) was evidently a mixture consisting of the $CH_3OSO_2CH_2CH_2SO_3^-$ anion (**8**) (δ_H 4.00 (s) plus a pair of multiplets at 3.28–3.38 and 3.68–3.78 symmetrically arranged about 3.53 ppm) and the $SO_3^-CH_2CH_2SO_3^-$ dianion (**9**) (δ_H 3.23 (s)), in a 3:2 ratio, along with the Et_3NH^+ (δ_H 1.27 (t), 3.20 (q) and $Et_3NCH_3^+$ (δ_H 1.29 (t of 1:1:1 t's), 2.91 (s), 3.30 (q)) cations in the ratio 4:1. The solid was dissolved in water and the solution was passed through excess Rexyn 101 (H^+ form) resin; the water was evaporated and the residue taken up in aqueous 2 M NaOH, the solution was heated at reflux for 2 h, and the water was then evaporated; the NMR spectra showed signals due to **9** (M = Na) (δ_H 3.26 (s), δ_C 49.2) plus about 10% of the $Et_3NCH_3^+$ cation (δ_H 1.30 (tt), 2.9 (s), and 3.30 (q)). Authentic sodium ethane-1,2-disulfonate, (**9**, M = Na) prepared from 1,2-dibromoethane, showed NMR signals at δ_H 3.27 (s) and δ_C 49.1.

Reaction of Propane-1,3-disulfonic anhydride (**10**) *with Methanol-d and Triethylamine.* Propane-1,3-disulfonic anhydride (**10**, 100 mg, 0.54 mmol) in dry acetonitrile (2 mL) was added dropwise to a mixture of CH_3OD (355 mg, 10.7 mmol) and Et_3N (71 mg, 0.7 mmol) in dry benzene (3 mL) at room temperature; the mixture was stirred for 10 min. Water (10 mL) and CH_2Cl_2 (25 mL) were added, the mixture was shaken, and the layers were separated. Evaporation of the water gave a liquid (166 mg). The NMR spectra (D_2O) showed chiefly superimposed signals of triethylammonium cation (δ_H 1.27 (t) and 3.20

(q); δ_C 10.9 and 49.4) and mostly monodeuterated propane-1,3-disulfonate dianion (**12**) (δ_H 3.04 (m) and 2.02–2.24 (m)); the ratio of the integrals of the signals for the dianion corresponding to roughly 80% of $SO_3^- CH_2CH_2CHDSO_3^-$ (**12**) and 20% of $SO_3^- CH_2CH_2CH_2SO_3^-$; the ^{13}C NMR spectrum showed partially resolved signals at δ 22.57 (major) and 22.66 (minor) assignable to the monodeuterated and undeuterated dianions along with well-resolved signals at 3937, 3915 and 3894 Hz (intensity ratio 46:8:8) corresponding to the superposition of a singlet at δ_C 52.2 onto a 1:1:1 triplet at 51.9 ($J_{C\text{-}D}$ 21 Hz), with the intensities indicating a roughly 7:2 ratio of the monodeuterated to undeuterated dianions. The Et_3N was removed by dissolving the product in 1 M NaOH and extracting with CH_2Cl_2. The ^1H NMR spectrum obtained after evaporating the water and dissolving the residue in D_2O showed signals due to the propane-1,3-disulfonate (**12**, M = Na), none due to Et_3NH^+ and weak peaks at δ_H 1.3, 2.9, and 3.3 due to a small amount (<5%) of Et_3N^+Me cation; the integrals of the 3.0 and 2.15 peaks indicated 85% of the monodeuterated and 15% the undeuterated anions; the ^{13}C NMR spectrum showed the signals around 22 and 52 ppm as observed prior to removal of the Et_3N.

In a repeat experiment using the same reagents (respectively, 1.51, 14.0 and 1.96 mmol) and 3.5 mL of acetonitrile and 2.5 mL of benzene, the ^1H NMR spectrum of the product obtained after removal of the Et_3N showed 84% monodeuterated and 16% undeuterated anion along with about 14% of the Et_3NMe^+ cation.

Reaction of 2,2-Dimethylisothiazolidinium 1,1-Dioxide Fluorosulfate (**13**) *with Ethanol-d and Triethylamine.* Triethylamine (0.64 g, 6.3 mmol) was added quickly with stirring to a solution of EtOD (3.0 g, 65.2 mmol) and the sulfonylammonium salt (**13**), (1.6 g, 6.43 mmol) in CH_2Cl_2 (30 mL) at 0°C; the reaction was allowed to proceed for 1 h. Workup was carried out by first washing with aqueous Na_2CO_3 and H_2O, then evaporation of the organic layer, followed by trituration of the residue with CCl_4 and evaporation of the CCl_4 solution. The residue (crude **14**) was allowed to stand at room temperature overnight after which time it was fully converted to the betaine (**15**) (72%); recrystallization from MeOH-absolute EtOH gave white cubes melting at 309–311°C (with decomp); deuterium analysis: 0.00% atom % excess D. The ^1H NMR spectrum (D_2O, XL-100) showed δ_H 1.35 (m, 3H), 2.22 (m, 2H), 2.99 (t, 2H), 2.99 (t, 2H), 3.08 (s, 6H), 3.92 (m, 4H), identical to that of a specimen of undeuterated betaine obtained identically except for the use of EtOH instead of EtOD; mp. 307–309°C (decomp.). Anal. Calcd for $C_7H_{17}NO_3S$: C, 43.06; H, 8.77; N, 7.17. Found: C, 42.70, H, 8.81; N, 7.03.

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