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Intrinsic Reactivity of Sulfur Esters: Site Selectivity by Anions with Dimethyl Sulfate and Methyl Methanesulfonate

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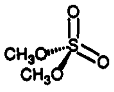
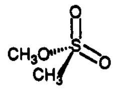
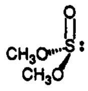
The thermally equilibrated (298 K) gas-phase ion–molecule reactions of a variety of anions with dimethyl sulfate and methyl methanesulfonate have been examined using the flowing afterglow technique. Two competitive pathways are observed for the reactions of dimethyl sulfate: reductive elimination across a C–O bond yielding $CH_3OSO_2^-$ as the ionic product and nucleophilic substitution at carbon yielding $CH_3OSO_3^-$ as the ionic product. Nucleophilic substitution is observed to some extent for every anion examined, while reductive elimination is observed for only the strongest bases (PA > 390 kcal mol^{-1}) examined. For methyl methanesulfonate, the reaction channels observed are nucleophilic substitution at carbon yielding $CH_3SO_3^-$ as the ionic product and proton transfer yielding $CH_3OSO_2CH_2^-$ as the ionic product. Proton transfer dominates the reaction of methyl methanesulfonate, while nucleophilic substitution is again observed to some extent for each of the anions studied. For neither dimethyl sulfate nor methyl methanesulfonate are products arising from reaction at sulfur found. The S_N2 reaction at carbon in both cases is believed to overwhelm the analogous S_N2-type process at sulfur because the substitution reaction at carbon displaces a much better leaving group.

Intramolecular competitive processes can be used to probe the mechanistic details of a gas-phase ion–molecule reaction.[1] Esters have at least two different reactive centers, thus making them ideal substrates to examine the competition between at least two distinct chemical processes or between similar processes at two different types of atomic centers. For example, the difference in elimination and substitution at a methyl center or the nucleophilic preference for substitution at carbon versus sulfur can be studied using dimethyl sulfate (**I**) and methyl methanesulfonate (**II**). In the liquid phase, both of these esters react exclusively and rapidly by nucleophilic substitution at carbon rather than at sulfur; this facile S_N2 proclivity makes dimethyl sulfate extremely useful in DNA sequencing where it is used to specifically methylate guanine residues.[2] Mesylates, such as **II**, are used as prototypical leaving groups for studying nucleophilic substitution reactions[3] and for synthetic applications of S_N2 processes.[4]


I


II


III

As part of our global investigations into the factors that control the intrinsic reactivity of esters, we found that dimethyl sulfite, **III**, displays different reactivity depending on the structure of nucleophile used even when thermodynamic differences are controlled.[5] For example, allyl anion, a delocalized base, prefers to react at the sulfur center rather than at carbon, while hydroxide, a localized anion with identical base strengh to allyl anion, prefers to react at carbon. In the gas-phase anion molecule reactions of trimethyl phosphite, the phosphoryl ester analogue of dimethyl sulfite, both carbon and phosphorus sites are reactive centers; however, most of the anionic nucleophilics examined react predominantly at phosphorus rather than carbon.[6] In direct contrast to trimethyl phosphite, all anionic nucleophilics so far examined react at carbon in trimethyl phosphate; trace amounts (<2%) of reaction at phosphorus are found only for methoxide and ethoxide.[7] Because anions react with trimethyl phosphite and dimethyl sulfite preferentially at phosphorus and sulfur, respectively (albeit with differing amounts of reaction at carbon), while trimethyl phosphate reacts exclusively at carbon, we anticipated that dimethyl sulfate (**II**), the sulfur analogue of trimethyl phosphate, would react with anionic nucleophiles exclusively at carbon and not by any sulfur-centered pathways.

In order to determine the intrinsic site selectivity of anions with alkyl sulfur(VI) esters, we chose to examine the reactions of dimethyl sulfate and methyl methanesulfonate using the room-temperature conditions readily obtained in a flowing afterglow.[8] A wide range of bases, varying in strength from amide ion to the conjugate base of hydrogen sulfide (a range spanning approximately 50% of the total anionic gas-phase basicity scale) and in structure from delocalized carbanions, such as the allyl anion, to localized heteroatomic bases, such as hydroxide,

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[†] Harvard University.

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are used to probe the reactivity of these esters. We are interested in what controls the intramolecular competition between reactive sites within a single ion–molecule complex containing an unsolvated ion and either dimethyl sulfate or methyl methanesulfonate and especially in how much, if any, reaction at sulfur occurs for different classes of bases.

Experimental Section

These experiments were carried out at ambient temperature (298 ± 3 K) and in 0.3 Torr of helium buffer gas (flow of helium $\sim$122 STP cm^3 s^{-1}) in a flowing afterglow[9,10] which has been previously described.[5,11] Amide, the atomic oxygen radical anion, methoxide, and fluoride were generated by dissociative electron attachment to ammonia (partial pressure 0.002 Torr), nitrous oxide (partial pressure 0.002 Torr), methanol (partial pressure $<10^{-4}$ Torr), and nitrogen trifluoride (partial pressure $<10^{-4}$ Torr), respectively. When methoxide or fluoride is used as a reagent ion, 3 mTorr of argon is added to the flow tube 15 cm downstream from the ion source (where CH_3OH or NF_3 is added) to quench any metastable helium atoms before dimethyl sulfate or methyl methanesulfonate is added. Hydroxide was generated by allowing the atomic oxygen anion to abstract a hydrogen atom from methane (eq 1).[12] Note that in eq 1b, "+5.9 kcal mol^{-1}" indicates

$$N_2O \xrightarrow{e^-} O^{\bullet -} + N_2 \tag{1a}$$

$$O^{\bullet -} + CH_4 \xrightarrow{1 \times 10^{-10}} HO^- + {}^{\bullet}CH_3 + 5.9\ \text{kcal mol}^{-1} \tag{1b}$$

that the reaction is 5.9 kcal mol^{-1} exothermic and the bimolecular rate coefficient shown above the arrow is in units of cm^3 molecule^{-1} s^{-1}; these conventions are used throughout this manuscript. HS^- was formed by allowing HO^- to react with carbon disulfide (eq 2).[13] All other reactant anions were produced by exothermic

$$HO^- + CS_2 \xrightarrow{1.5 \times 10^{-9}} HS^- + OCS + 48.7\ \text{kcal mol}^{-1} \tag{2}$$

proton transfers from an appropriate neutral to amide anion (e.g., $CH_3CH_2CH_2NH^-$ from $CH_3CH_2CH_2NH_2$, eq 3). When

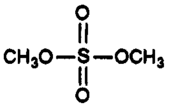
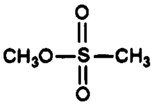
$$NH_3 \xrightarrow{e^-} H_2N^- + {}^{\bullet}H \tag{3a}$$

$$H_2N^- + CH_3CH_2CH_2NH_2 \rightarrow CH_3CH_2CH_2NH^- + NH_3 + 5.2\ \text{kcal mol}^{-1} \tag{3b}$$

synthesizing the reactant ion of interest in the flow tube by a series of reactions (e.g., HS^- via eqs 1a, 1b, and 2), care was taken to ensure that each reaction was taken to completion before the next reaction was initiated.

Dimethyl sulfate, $(CH_3O)_2SO_2$ (Aldrich, 99+%), and methyl methanesulfonate, $(CH_3O)(CH_3)SO_2$ (Aldrich, 99%), were used as received. Propylamine was distilled before use. All other reagents were obtained from standard commercial sources and were used as received. Before use, each liquid sample was subjected to several freeze–pump–thaw cycles to remove dissolved gases. Because dimethyl sulfate and methyl methanesulfonate are relatively nonvolatile liquids (bp$^{760\text{mm}}$ 188 °C and 202–203 °C, respectively),[14] for all of these experiments a low flow of sweep gas (helium) was gently bubbled through the liquid sample in order to carry them into the flow tube at higher flow rates than can be achieved by the normal direct distillation method.[5]

Table I. Product Yields for the Reaction of Nucleophiles with Dimethyl Sulfate and Methyl Methanesulfonate at 298 K[a]

		 $CH_3O-S(=O)_2-OCH_3$		 $CH_3O-S(=O)_2-CH_3$	
nucleophile (HA^-)	ΔH°_{acid} $[H_2A]$[b] (kcal mol^{-1})	*m/z* 95 $E_{CO}2$	*m/z* 111 S_N2	*m/z* 95 S_N2	*m/z* 109 PT
H_2N^-	403.7	50	50	18	82
$C_6H_5^-$	400.7	12	88	20	80
$CH_3CH_2CH_2NH^-$	398.4	20	80	20	80
HO^-	390.8	11	89	17	83
$H_2C{=}CHCH_2^-$	390.8		100	30	70
CD_3O^-	382.0[c]		100	27	73
$PhCH_2^-$	380.7		100	27	73
H_2CCN^-	372.8		100	15	85
F^-	371.8		100	43	57
$H_2C{=}C(CH_3)O^-$	365.9		100	97	3
HS^-	351.1		100	100	

[a] A blank indicates that this product was not observed (≤1% yield). The mechanistic pathway assigned to each product ion is indicated under the ion's mass-to-charge ratio. [b] Unless otherwise noted, all acidities are taken from ref 16. [c] Reference 17.

Qualitative experiments entailed taking a complete mass scan of the ionic contents of the flow tube at each of several times during the course of a reaction. The relative product ion yields were obtained by measuring the heights of the appropriate peaks on the mass spectral plots. On the basis of comparisons made between more rigorously obtained product yields and those obtained herein, we estimate that the product yields reported are accurate to ± 5% (absolute yield). As described previously,[15] the operating characteristics of the quadrupole mass filter are chosen so as to minimize any mass-discrimination problem; therefore, for these experiments where we are interested in comparing *m/z* 95–111 (compound I) and *m/z* 95–109 (compound II), such errors are insignificant. As a final comment, we note that we have never noticed species-specific discrimination difficulties in our detection system (which is based on a conversion-dynode electron multiplier), a problem that has been encountered previously for ions derived from trimethyl phosphite detected by a conventional electron multiplier.[6]

Results

Dimethyl Sulfate (I). The product yields for the thermally equilibrated reactions of several anionic nucleophiles with dimethyl sulfate are summarized in Table I. Rapid reaction occurs for all anions studied, even acetone enolate and hydrosulfide. All nucleophiles yield a product ion at *m/z* 111, $CH_3OSO_3^-$, while the reactions of amide, phenide, propylamide, and hydroxide also produce an ion at *m/z* 95, $CH_3OSO_2^-$. As the reaction nears completion, we observe the onset of a secondary reaction in which the product ion *m/z* 95 reacts with a second molecule of dimethyl sulfate to yield additional *m/z* 111. This secondary reaction was examined inde-

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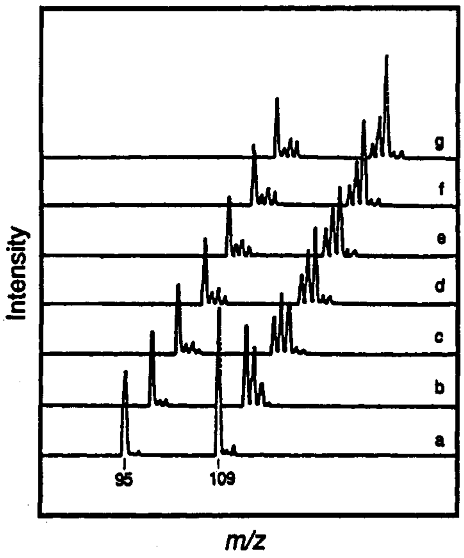

Figure 1. Mass spectral plots for the reaction of $CH_3OSO_2CH_2^-$ and CD_3OD; only the region in which product ions are detected is shown. The reactant ion spectrum (a) shows *m/z* 95, $CH_3SO_3^-$, and *m/z* 109, $CH_3OSO_2CH_2^-$, generated from the reaction of amide and methyl methanesulfonate. In spectra b–g CD_3OD has been added to the flow tube at different reaction times; spectrum b corresponds to the shortest reaction time, while spectrum g corresponds to the longest reaction time. The small peaks in spectrum a at *m/z* 96 and 110 are M + 1 isotope peaks, while *m/z* 97 and 111 correspond to M + 2 isotope peaks. In spectra b–g, the small peak at *m/z* 112 is both the M + 1 isotope peak of the d_2-anion and the M + 2 isotope peak of the d_1-anion, while the small peak at *m/z* 113 corresponds to the M + 2 isotope peak of the d_2-anion.

pendently by preparing $CH_3OSO_2^-$ from the reaction of hydroxide with dimethyl sulfite[5] and then adding dimethyl sulfate to the flow tube under conditions optimized to study this reaction; the only product from the bimolecular reaction is *m/z* 111, identified through mechanistic considerations as $CH_3OSO_3^-$.

Methyl Methanesulfonate (II). Table I also contains the product yields for the thermally equilibrated reactions of methyl methanesulfonate with the same anionic nucleophiles examined with dimethyl sulfate. Methyl methanesulfonate reacts rapidly with all anions examined to yield two product ions: *m/z* 95, $CH_3SO_3^-$, and *m/z* 109, $CH_3OSO_2CH_2^-$. When the reaction is followed to near-completion, the onset of a secondary reaction is observed in which *m/z* 109 reacts with a second molecule of methyl methanesulfonate to yield *m/z* 95. The structure of the *m/z* 109 product ion was probed by generating it from the reaction of amide and methyl methanesulfonate and then allowing *m/z* 109 to react with methanol-d_4; two rapid hydrogen/deuterium (H/D) exchanges[18] are observed, as shown in Figure 1, indicating that the *m/z* 109 contains two readily exchangeable hydrogens. The spectra in Figure 1 also show that up to three deuteriums are slowly incorporated into "*m/z* 95"; the label exchanged into *m/z* 95 comes from a displacement reaction of label methyl methanesulfonate with methoxide in one of the ion–neutral complexes formed during the exchange process (vide infra). As is evident in Figure 1, H/D exchange only occurred for the acidic hydrogens in the conjugate base of $CH_3OSO_2CH_3$, no methyl group exchange occurred for this species (i.e., $CD_3OSO_2CD_2^-$ was not observed).

Discussion

We can account for the reactions of dimethyl sulfate with a variety of nucleophiles using a general mechanistic scheme that involves two reaction pathways that occur exclusively at carbon: (i) reductive elimination across a carbon–oxygen bond ($E_{CO}2$, Scheme I), producing $CH_3OSO_2^-$ and (ii) nucleophilic substitution at carbon (S_N2, Scheme I), yielding $CH_3OSO_3^-$. Reaction of a nucleophile, HA^-, *at sulfur* would lead to the formation of an ion–neutral complex containing CH_3O^- and CH_3OSO_2AH (not shown). From this latter complex, methoxide could in principle, either freely dissociate or abstract a proton or a methyl group yielding CH_3O^-, $CH_3OSO_2A^-$, or $HASO_3^-$ as the observed ions, respectively. Without exception, products from reaction at sulfur are not observed. Note that in Scheme I the species shown in square brackets are what we postulate as the key ion–molecule complexes on the reaction coordinate, but these species are not directly observed.

In contrast to the nucleophilic substitution at carbon channel, which is observed for every nucleophile examined, the reductive elimination channel is only found for the strongest, localized bases examined (i.e., those bases stronger than or equal to hydroxide). The largest amount of elimination channel was found for the strongest base utilized (H_2N^-); as the base strength of the anion decreases, so does the yield of this elimination channel. For example, amide gives 50% elimination, while propylamide, 5.3 kcal mol^{-1} weaker than amide, yields 20% elimination, and hydroxide, 12.9 kcal mol^{-1} less basic than amide, produces only 11% elimination. The strongly basic carbanion, phenide, 3.0 kcal mol^{-1} less basic than amide, gives just 12% elimination; this relatively low yield for phenide is not surprising since localized carbon bases tend to be kinetically poorer bases than localized heteroatomic bases with the same base strength.[5] The failure to observe elimination products for the reaction of allyl anion, while hydroxide, an anion with the same base strength, yields $E_{CO}2$ products, is in agreement with the similar generalization that delocalized carbon anions are also kinetically poor bases compared to localized heteroatomic bases.[5,19] The dependency of the yields for the $E_{CO}2$ channel on the basicity of the nucleophile has also been noted for dimethyl sulfite,[5] trimethyl phosphate,[7] and ethyl dimethyl phosphate.[20]

Methyl methanesulfonate has the same reaction channels ($E_{CO}2$ and S_N2) available as dimethyl sulfate; the presence of an acidic proton opens up an additional pathway, proton transfer. A general scheme involving two reactions at carbon ((i) nucleophilic substitution (S_N2, Scheme II) and (ii) proton transfer (PT, Scheme II)) describes the observed reactions of anions with methyl methanesulfonate. If a nucleophile HA^- reacts at sulfur, a product ion–neutral complex containing CH_3O^- and CH_3SO_2AH would be formed; methoxide could, in prin-

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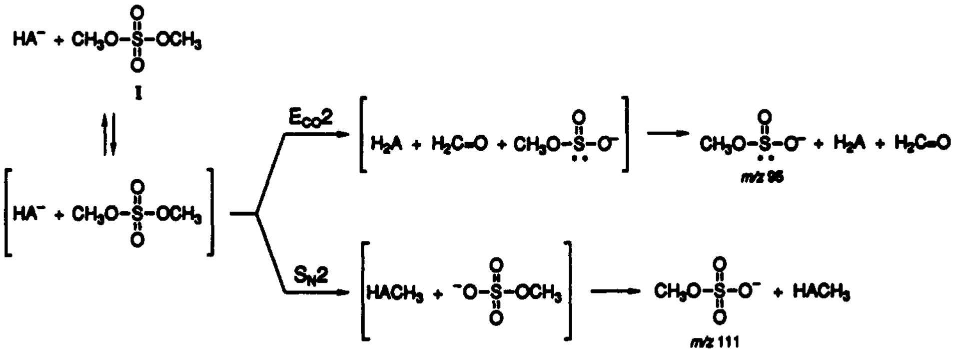
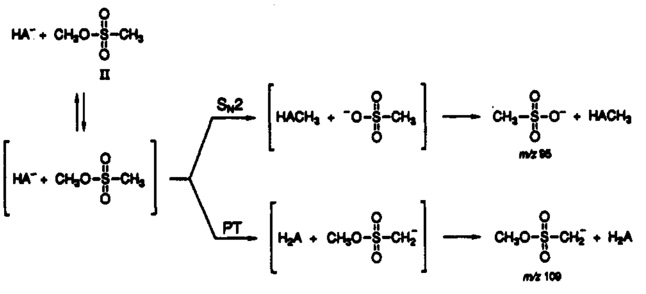
Scheme I. Generalized Scheme for the Reaction of Nucleophiles with Dimethyl Sulfate



Scheme II. Generalized Scheme for the Reaction of Nucleophiles with Methyl Methanesulfonate



ciple, freely dissociate or abstract a proton yielding either CH_3O^-, $CH_3SO_2A^-$, or $HASO_2CH_2^-$; products from reaction at sulfur are not observed. Likewise, the product from the reductive elimination channel, $CH_3SO_2^-$, was not observed.

For fluoride (ΔH°_{acid}[HF] = 371.4 kcal mol^{-1}) and any stronger base that is allowed to react with methyl methanesulfonate, we observe a major (>57%) product ion at m/z 109, $CH_3OSO_2CH_2^-$, which we attribute to a proton transfer reaction (PT, Scheme II). Little or no m/z 109 is observed for the reaction of acetone enolate (ΔH°_{acid}[CH_3COCH_3] = 369.0 kcal mol^{-1}) or any weaker base. Therefore, we suggest that the acidity of $CH_3SO_3CH_3$ is similar to that of acetone, a conclusion that is also supported by the exchange results between $CH_3OSO_2CH_2^-$ and CD_3OD. The yield of the proton transfer pathway remains essentially constant as the character of the base (PA > 373 kcal mol^{-1}) is varied from a heteroatomic nucleophile to a delocalized nucleophile; the specific nature of the base does not play an important role in the proton transfer pathway of methyl methanesulfonate. Thus, this proton transfer seems to depend only on a thermodynamic threshold of the reaction, even though delocalized carbanions are known to be kinetically poor bases compared to heteroatomic bases with the same base strength.[5,19]

The H/D exchange process between $CH_3OSO_2CH_2^-$ and CD_3OD is described in Scheme III in which the specific reactions for incorporation of the *second* deuterium is explicitly detailed; analogous reactions describe the first and third deuterium incorporations. As evident from the spectra in Figure 1, the simple exchange process ($CH_3OSO_2CH_2^- \rightarrow CH_3OSO_2CHD^- \rightarrow CH_3OSO_2CD_2^-$) is the most facile reaction. Also evident in Figure 1 is the slow incorporation of up to three deuteriums in m/z 95, the mechanism for this process in also included in Scheme III for the specific generation of m/z 97; analogous reactions describe the generation of m/z 96 and 98.

The second channel followed for the reaction of anions with methyl methanesulfonate yields a product ion at m/z 95, $CH_3SO_3^-$, which we assign as arising from nucleophilic substitution at carbon (S_N2, Scheme II). Even when the proton transfer pathway predominants, nucleophilic substitution is observed in minor but significant amounts (15–43%). As the proton transfer pathway becomes endothermic and is therefore reduced in yield, nucleophilic substitution remains thermochemically possible and thus becomes the major or exclusive pathway. Because $CH_3SO_3^-$ is an excellent leaving group, it is not surprising that nucleophilic substitution is found for all anions examined, in agreement with the observation that nucleophilic substitution occurs at methyl centers bearing good leaving groups.

When strong bases react with dimethyl sulfate, elimination across the carbon–oxygen bond occurs. Similar reductive eliminations have been observed for the reaction of strong bases with organic esters such as dimethyl sulfite,[5] trimethyl phosphate,[7] and dimethyl methylphosphonate.[21] An analogous reaction involving elimination across the C–S bond of dimethyl disulfide involves readdition of the leaving group to the thioformaldehyde produced (eq 4).

$$H_2N^- + CH_3SSCH_3 \xrightarrow{67\%} [NH_3 + H_2C{=}S + {}^-SCH_3] \rightarrow CH_3SCH_2S^- + NH_3 \quad (4)$$

Re-addition of the leaving group anion to the formaldehyde produced in the amide plus methyl pyruvate[22] reaction (eq 5) and in the amide plus dimethyl carbonate[23] reaction

$$H_2N^- + CH_3C(O)C(O)OCH_3 \xrightarrow{9\%} [NH_3 + CH_3C(O)^- + H_2C{=}O + CO] \rightarrow CH_3C(O)CH_2O^- + NH_3 + CO \quad (5)$$

$$H_2N^- + CH_3OC(O)OCH_3 \xrightarrow{36\%} [NH_3 + CH_3O^- + H_2C{=}O + CO] \rightarrow CH_3OCH_2O^- + NH_3 + CO \quad (6)$$

(eq 6) have also been observed. (Note that in eqs 4–6, the reactions shown are only one of several observed pathways; the yields of these channels are indicated by the percentage over the arrows.) On the basis of the examples shown above, when strong anionic bases react with methyl methanesulfonate, some reductive elimination across the carbon–oxygen bond, yielding $CH_3SO_2^- + H_2A + H_2C{=}O$, is expected. The failure to observe m/z 79, $CH_3SO_2^-$, might be explained by assuming that $CH_3SO_2^-$ may have re-added to formaldehyde within the product ion–neutral

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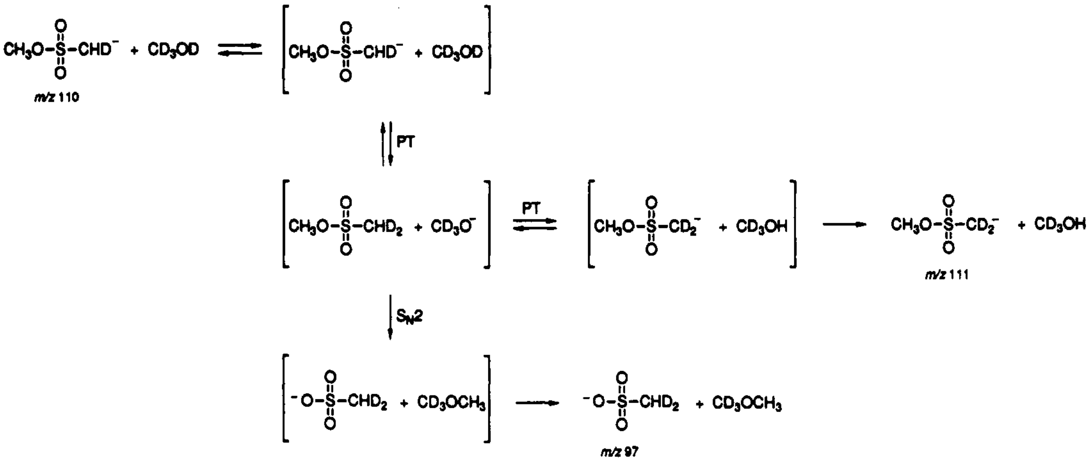
(21) Lum, R. C.; Grabowski, J. J. Unpublished results.
(22) Grabowski, J. J.; Goroff, N. S. Unpublished results.
(23) Grabowski, J. J. Unpublished results.

Scheme III. Mechanistic Scheme Describing the Facile H/D Exchange Process between the Conjugate Base of Methyl Methanesulfonate and Deuterated Methanol as Well as the Less Efficient S_N2 Process



complex, producing a m/z 109 of rearranged structure, namely, $CH_3SO_2CH_2O^-$. The reaction of m/z 109, however, formed from the reaction of amide with methyl methanesulfonate with methanol-d_4; yields two fast H/D exchanges; these results indicate that the m/z 109 is *not* the rearranged alkoxide. Thus, it is clear methyl methanesulfonate does not undergo reductive elimination.

Reaction at sulfur is not observed for either dimethyl sulfate or methyl methanesulfonate. When hydroxide reacts with either neutral substrate, however, we cannot unequivocally distinguish between reaction at sulfur and carbon sites since reactions at both centers yield the same products, $CH_3OSO_3^-$ from dimethyl sulfate and $CH_3SO_3^-$ from methyl methanesulfonate. Neither amide nor methoxide-d_3 react at sulfur; therefore, we expect that for both dimethyl sulfate and methyl methanesulfonate reaction at sulfur probably does not occur with hydroxide; experiments using ^{18}O-labeled hydroxide, using a SIFT apparatus currently under construction, are planned to confirm this expectation.

Why is reaction at sulfur unimportant in the gas phase for I and II? In solution, the mechanism for reaction at sulfur for diaryl sulfonates, aryl methanesulfonates, and diaryl sulfates involves either a pentavalent transition state or, less likely, an intermediate.[24–26] The pentavalent transition state resembles that for an S_N2 reaction at saturated carbon; the incoming nucleophile attacks at a side opposite the leaving group with simultaneous bond cleavage and formation.[24–26] Oxygen-18-labeled hydroxide tracer[27] experiments and stereochemical results[28] indicate that these reactions in solution proceed mainly by a pentavalent transition state. In contrast to the diaryl sulfates, diaryl sulfonates, and aryl methanesulfonates, when dimethyl sulfate or methyl methanesulfonate reacts with ^{18}O-labeled hydroxide in solution, exclusive cleavage of the C–O bond occurs; no products from reaction at sulfur are observed.[24,29] The failure to observe reaction at sulfur for the reactions of dimethyl sulfate and methyl methanesulfonate in both the liquid and the gas phase only indicates that the barrier for sulfur substitution is substantially larger than the barrier for carbon substitution but not that reaction at sulfur is inherently impossible. One important reason that the reaction at carbon is kinetically more facile than the reaction at sulfur is that the nucleophilic substitution at carbon displaces a better leaving group. If an anion attacks sulfur, the leaving group is methoxide; on the other hand, if an anion attacks carbon the leaving group is either $CH_3OSO_3^-$ (from dimethyl sulfate) or $CH_3SO_3^-$ (from methyl methanesulfonate). Methoxide ($\Delta H^\circ_{acid}[CH_3OH] = 381.7$ kcal mol^{-1}) is a much stronger base than either $CH_3OSO_3^-$ or $CH_3SO_3^-$ ($\Delta H^\circ_{acid}[RSO_3H \approx 309$ kcal mol^{-1}),[30] so in as much as weak bases indicate good leaving groups, the reaction at carbon outcompetes the reaction at sulfur simply because $CH_3OSO_3^-$ or $CH_3SO_3^-$ is a better leaving group than CH_3O^-.

In the gas phase, dimethyl sulfate and methyl methanesulfonate react exclusively at carbon, while dimethyl sulfite[5] reacts at both sulfur and carbon with reaction at sulfur preferred for delocalized anions. As noted above, similar results are found when the gas-phase reactions of phosphorus(V) and phosphorus(III) esters are compared; trimethyl phosphate[7] shows almost exclusive reaction at carbon, while trimethyl phosphite[6] reacts principally at phosphorus with a small amount of reaction at carbon. Phosphites and sulfites prefer to react via an addition–elimination type of mechanism, while phosphates, phosphonates, sulfates, and sulfonates prefer to react via an S_N2 type process. The loss of a methoxide leaving group from an addition–elimination pathway at sulfur can compete with the reaction at saturated carbon. Successful competition between $B_{AC}2$ at a carbonyl carbon with methoxide as a leaving group and other pathways has been observed for the reactions of anions with methyl acetate,[31] methyl pyruvate,[22] and methyl formate.[32] The loss of methoxide leaving group from a substitution reaction at

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sulfur, however, cannot compete with reaction at saturated carbon. Presumably, converting methoxide into a better leaving group would increase the probability that S_N2 at sulfur could compete with reaction at carbon in sulfates. Other factors that may contribute to controlling the competition between substitution at carbon versus sulfur include charge distribution (i.e., the strong S–O bonds leading to a strong electrostatic force directing the incoming anionic nucleophilic preferentially towards carbon) and steric crowding preventing attack at sulfur in **I** and **II** as compared to **III**. Obviously, considerable additional data will be required to pinpoint the importance of each of these factors.

Conclusions

Dimethyl sulfate and methyl methanesulfonate react with a variety of anions in the gas phase in a similar fashion. For both substrates no products from reaction at sulfur are observed. Dimethyl sulfate reacts primarily by nucleophilic substitution at carbon with reductive elimination across the carbon–oxygen bond occurring for localized anions stronger or equal to hydroxide in base strength. Methyl methanesulfonate reacts mostly by proton transfer while nucleophilic substitution at carbon is observed for all anions examined. For both dimethyl sulfate and methyl methanesulfonate, reaction at sulfur (which presumably occurs by an S_N2 type process) cannot compete with the S_N2 process at carbon.

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