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Thermolysis of Alkyl Sulfoxides and Derivatives: A Comparison of Experiment and Theory

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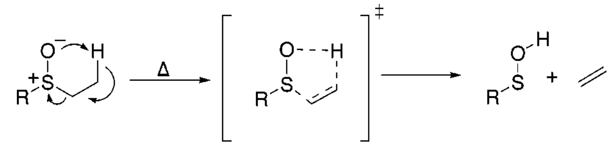
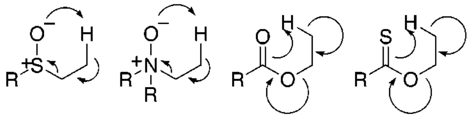
Gas-phase activation data were obtained for model sulfoxide elimination reactions. The activation enthalpy for methyl 3-phenylpropyl sulfoxide is 32.9 ± 0.9 kcal/mol. Elimination by methyl vinyl sulfoxide to form acetylene has an enthalpic barrier of 41.6 ± 0.8 kcal/mol and that of 3-phenylpropyl methanesulfinate to form hydrocinnamaldehyde is 34.6 ± 0.6 kcal/mol. Calculations at the MP2/6-311+G(3df,2p)//MP2/6-31G(d,p) level for simplified models of these reactions provide barriers of 32.3, 40.3, and 32.7 kcal/mol, respectively. A series of other compounds are examined computationally, and it is shown that the substituent effects on the sulfoxide elimination reaction are much more straightforward to interpret if ΔH data are available in addition to the usually determined $\Delta H^{\ddagger}$. The activation enthalpy of the reverse addition reaction is also subject to structural variation and can usually be rationalized on the basis of nucleophilicity of the sulfur or polarity matching between the sulfenic acid and olefin derivative.

Introduction

The internal elimination of sulfoxides to form olefins and sulfenic acids is well-established chemistry that has seen considerable use in organic synthesis.[1−3] Related reactions include eliminations of thiosulfinates,[4,5] *N*-tosylsulfilimines[6] (sulfoxide analogues in which the O atom is replaced by an *N*-Ts group), selenoxides,[7−9] and at least in limited cases sulfones.[10−13] In this paper, we report an experimental and computational study on the sulfinyl syn-elimination reaction that addresses structural effects on activation parameters and includes an extensive set of molecules whose activation barriers are predicted. It is argued that in many cases the enthalpic barrier is controlled largely by the overall enthalpy change of the reaction, but that between sets of closely related reactions, the part of the barrier above the endothermicity (i.e., the barrier to the reverse addition reaction), can be related to conjugation in the transition state, polarity matching between reacting partners, and the acid/base properties of the molecules.

Throughout the paper, we use the ylide notation for the sulfinyl group rather than the more traditional S═O notation.[14−18] This is done to emphasize the electronic aspects of the reaction. For instance, the ylide notation makes it clear that no S−O π-bond is broken. We argue that the Ei reaction of sulfinyl derivatives is a direct relative of the Cope elimination of amine oxides[19−24] and a more distant cousin of any pericyclic[25] or pseudopericyclic[26] reaction, such as the elimination reactions of xanthates or carboxylic esters.[27]





Some review of the research in this area is in order. Among the first lines of evidence for a concerted mech-

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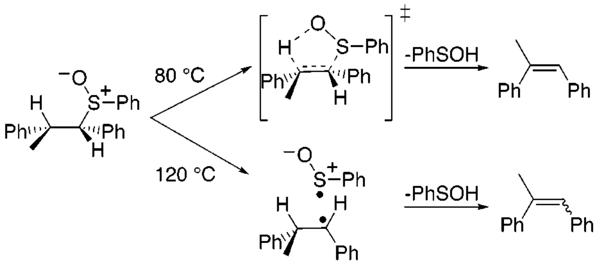
anism was the result that stereochemical integrity is usually maintained during sulfoxide elimination reactions. A particularly important example is the pyrolysis of *trans*-4-methylcyclohexyl *p*-tolyl sulfoxides, in which the two enantiomers of the sulfoxide lead largely to opposite enantiomers of 4-methylcyclohexene.[28]

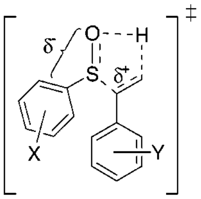
Pyrolysis of appropriately substituted sulfoxides in either the gas or solution phase usually displays first-order kinetics and is usually not affected by radical inhibitors, again consistent with a concerted mechanism. However, as far back as 1960, Kingsbury and Cram suggested there might exist a competing homolytic mechanism for 1,2-diphenylpropyl phenyl sulfoxides.[29] This was based on curved Eyring plots over the fairly narrow range of 70−110 °C and the loss of stereospecificity in the higher temperature regime. There has not been convincing evidence for a radical mechanism involving any other substrate, but this may depend on the presence of at least the α-phenyl group, which should stabilize the putative benzyl-type radical.



The effects of various structural parameters on the kinetics of the sulfoxide elimination have been investigated over the years. Emerson and co-workers examined the effect of alkyl branching and found that the overall rate for the formation of alkene was greater for the more branched carbon substituent.[30] For example, *sec*-butyl ethyl sulfoxide eliminated faster than *n*-butyl ethyl sulfoxide. Gas-phase activation enthalpies were near 30 kcal/mol, and the activation entropies were between −3.6 and −17 cal/K·mol. Walling and Bollyky investigated the pyrolysis of methyl 3-phenylpropyl sulfoxide in diglyme and got a similar activation energy of 31.6 ± 3 kcal/mol.[31]

The elimination of isobutylene from di-*tert*-butyl sulfoxide occurs faster than related but less sterically demanding systems. The barrier is below 30 kcal/mol, though some curvature in the data was observed.[32,33] Kwart attributed the lower barrier to a “corset effect” in which the starting material is destabilized by sterics more than is the transition state and the barrier for proton transfer is narrowed.[34] Kice and Campbell studied the effect of ring size on the rate of pyrolysis of cycloalkyl phenyl sulfoxides.[35] At 130 °C, the relative rates of cycloheptyl, cyclohexyl, and cyclopentyl phenyl sulfoxide were 120:1:25, respectively. The slowness of the cyclohexyl system was attributed to an awkward flattening of the ring required to achieve the proper transition state geometry. Similar results were later obtained by Yoshimura and co-workers.[36]

Scheme 1[37,38]



Phenyl sulfoxides are known from the synthetic literature to eliminate at lower temperatures than the corresponding methyl sulfoxides. Emerson and Korniski correlated substituent effects with the rate of reaction for a series of substituted-phenyl propyl sulfoxides.[37] At any given temperature, a Hammett plot gave a modestly positive ρ, meaning that electron-withdrawing groups accelerate the reaction. While the activation enthalpies (25.3 ± 2.6 to 27.9 ± 2.1 kcal/mol) follow this trend, the range is modest and they are only marginally outside of experimental error from one another. The $\Delta S^{\ddagger}$ values (−11.5 ± 6.7 to −16.0 ± 8.2 cal/mol·K) are similar in that the values are not widely beyond experimental uncertainty from one another. These results were rationalized in terms of negative charge buildup on sulfur in the transition state. A similar positive ρ value was found for the pyrolysis of substituted-phenyl *tert*-butyl sulfoxides by Shelton and Davis.[33]

In a related study, Yoshimura and co-workers studied the decomposition of substituted 1-phenylethyl phenyl sulfoxides in dioxane.[38] Hammett plots showed a positive ρ for the X position in agreement with Emerson and V-shaped Hammett plots for the Y-substituents. Scheme 1 illustrates the Emerson and Yoshimura structures. Activation data obtained over a 20 °C range were also generally consistent with Emerson's results. In addition, they found a kinetic isotope effect of $k_H/k_D = 4-6$ in the range of 80−100 °C. The authors suggested that electron-withdrawing groups on Y promoted a nearly synchronous reaction, but in other instances, an E1-like transition state was in force.

Despite the Hammett plot results in which the sign of ρ is opposite for the X substituent's effects on the elimination reaction and on sulfoxide basicity,[39] some authors have considered structural effects on the Ei reaction in terms of acid/base properties related to the proton abstraction by the oxygen atom. The acidity of the abstracted proton, unless controlled for with other adequate structural detail (see the Discussion), does not appear to have a consistently large effect. Elimination of the illustrated α- and β-carbethoxy-substituted sulfoxides affords the same products,[40] but the abstracted proton is substantially more acidic in the β-structure. At

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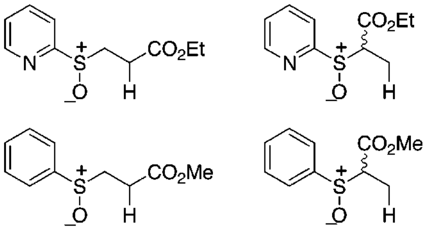
Table 1. Cope Elimination Reaction Activation Energies (E_a) at Various Levels of Theory for the Ei Reaction of Ethylamine Oxide

level of theory/basis set	E_a (kcal/mol)
HF/6-31G(d,p)	43.3
MP2/6-311++G(d,p)	26.3
B3LYP/6-311++G(d,p)	24.3
CCSD(T)(full)/6-311++G(d,p)[a]	28.8

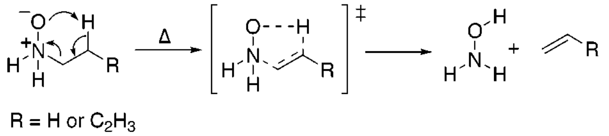
[a] Calculated at the MP4(SDQ)/6-311G(d,p) geometry.

70 °C, the rate of elimination of the β-carbethoxy pyridyl sulfoxide is higher by a factor of 1.5. Tsukurimichi and co-workers, however, found that, at 90 °C, the rate of decomposition of 2-carbomethoxyethyl phenyl sulfoxide was only about one-third that of 1-carbomethoxyethyl phenyl sulfoxide.[41]



We are aware of only a single computational study of the syn-elimination of sulfoxides.[42] Jursic compared the eliminations of a corresponding amine oxide, sulfoxide, and phosphine oxide and showed that the amine oxide elimination occurred with the lowest activation enthalpy regardless of level of theory applied, with the sulfoxide being the intermediate case.

The related Cope elimination[24,42,43] of amine oxides has been subject to computational study and is instructive. Reasonable agreement has been achieved between activation barriers for model compounds ethylamine oxide and 3-butenylamine oxide, calculated at the MP2 level of theory, and experimental data for related substrates.[21,22,24,43]



The barriers calculated by Tronchet and Komaromi at various levels of theory are shown in Table 1.[43] Since a good-quality gas-phase experimental value is not available for the parent case, we must accept the CCSD(T)-(full)/6-311++G(d,p) value as the standard for comparison to the other methods. It has long been known that HF barriers are too high for this type of reaction.[44] Despite its current popularity in the literature, B3LYP has its shortcomings, and one that is well-documented if not widely appreciated is in cases where proton transfers are involved.[45−47] Despite differences in the basis set in Table 1, it is a consistent observation that barriers are too low when calculated by B3LYP. The MP2 values are typically between CCSD(T) and B3LYP. A similar trend was observed in the sulfinyl elimination reaction calculated by Jursic:[42] BLYP/6-31G(d) < MP2/6-31G(d) < HF/6-31G(d).

Below, we present gas phase activation barriers for the thermolysis of several sulfoxides and related derivatives. A computational protocol is established that closely matches the experimental values. With these data in hand, extensions of the calculations to a number of molecules not studied experimentally is reasonable, and we are able to survey the structural effects on the sulfoxide elimination and analyze them in terms of both the elimination and the reverse addition reactions.

Results

Approach. Experimental and computational data were sought for a variety of sulfoxides and related derivatives in order to establish a reasonable computational protocol. The experimental systems needed to provide clean reactions and products that were easy to detect. Most sulfoxides were designed to give allylbenzene or an analogous product. On the other hand, for the calculations, the important electronic parts of the molecule must be retained, but any "excess" parts must be stripped off to make the calculations practical. As a result, the molecules calculated and run experimentally were not, in general, the same, though they were found to model each other very well. The molecules used in the study are shown in Chart 1. Where experimental data were collected, a related compound appears with an "e" appended to the number to denote the actual molecule used in the experimental studies. The proton that is transferred during the reaction is illustrated explicitly for each compound.

Once a reasonable computational protocol was established, the method was extended to a series of groups of compounds. Each of the groups contains compounds around which a particular structural question could be addressed. Though only illustrated in group 1, ethyl methyl sulfoxide (**1**) is taken as the benchmark against which the other compounds are judged.

The rationale for these various groups can be stated briefly. Group 1 was chosen to investigate the effect of substituents conjugated to the sulfinyl group. Group 2 stresses the electronegativity of the same "non reactive" substituent, while group 3 addresses the "corset effect" alluded to in the Introduction. Group 4 considers the effect of having the abstracted proton on an sp^2 carbon and the homologation of the reaction. Group 5 was designed to examine the effect of acidity of the proton or polarity of the reverse reaction with models of synthetically relevant systems. Group 6 provides data on endo- and exocyclic eliminations as a function of olefin ring size. Group 7 is designed to couple the effect of formation of double bonds with a heteroatom with another look at acidity. The compounds in group 8 were chosen to compare to literature results in which interactions between bond dipoles had been invoked to explain selectivity.

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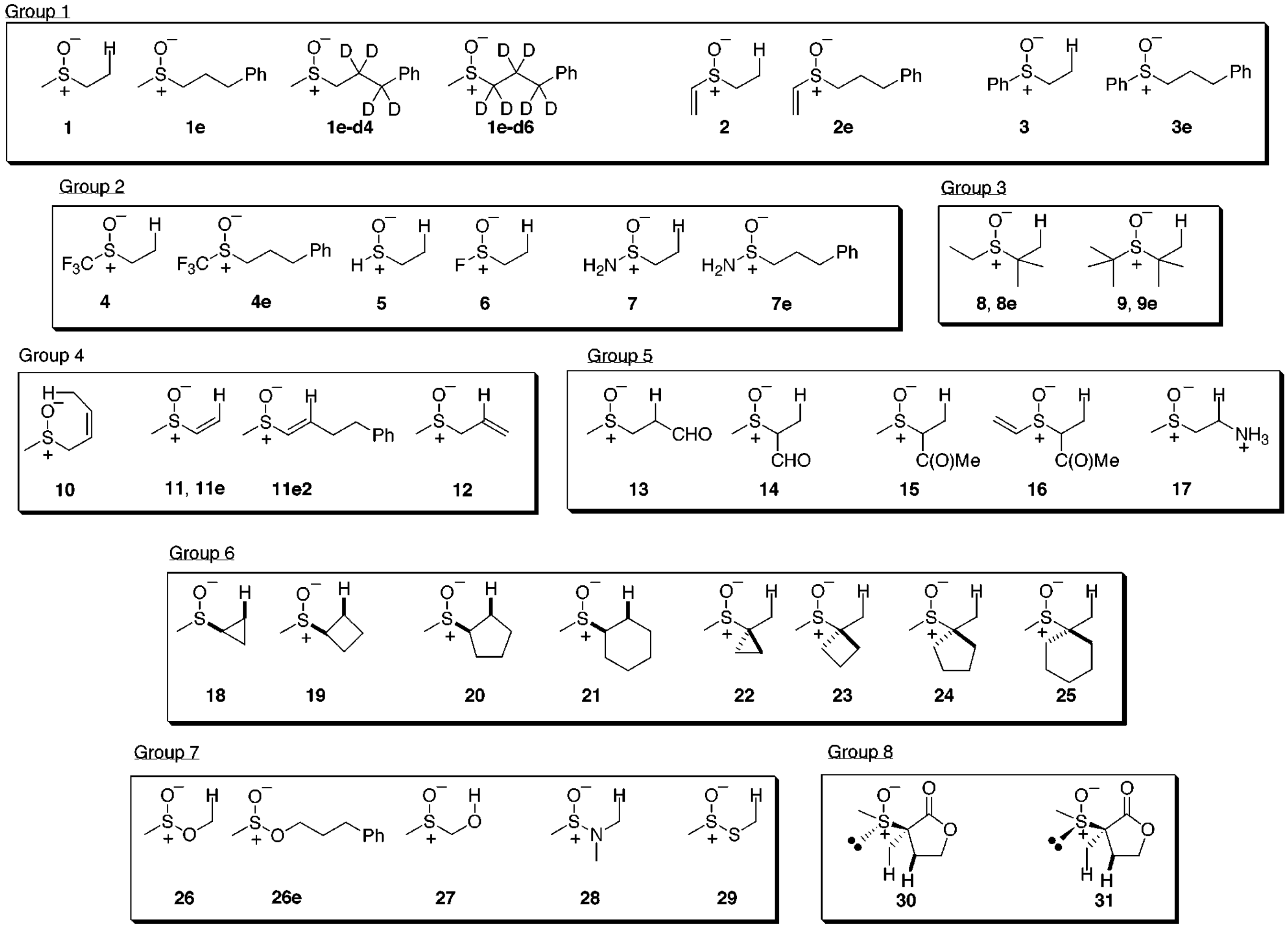
Chart 1



Experimental Results. The preparation of the sulfoxides was generally routine, and details are provided in the Experimental Section and Supporting Information. Several attempts were made to prepare sulfoxide **4e** from the corresponding sulfide without success.

Thermolyses were carried out in a pulsed stirred flow apparatus that uses a furnace area followed by an on-line GC to quantify starting materials and products.[48] Sulfoxide samples were injected as concentrated solutions in acetonitrile, and He was the carrier gas. Activation data are obtained by running the furnace at several different temperatures, but the range is limited by the need to quantify both starting materials and product. Useful data were only obtainable when activation enthalpies were about 30 kcal/mol or greater. The utility of the system is also limited by the need for the reaction to be very clean. A typical set of data is shown in Figure 1, and the activation data are given in Table 2. Plots for the other compounds are in the Supporting Information. All data reported here are for reactions in which only the expected olefinic product was observed. Formation of the sulfenic acids is inferred, since none of them survived GC analysis. However, their formation is well established by previous studies in solution. Though sulfenic acids are not generally stable in solution, they can be isolated as their anhydrides (thiosulfinates) or trapped with activated olefins.[49,50] There is also evidence, by means of deuterium incorporation, of sulfenic acid trapping by unactivated olefins in unimolecular cases, as in certain penicillin derivatives.[51]

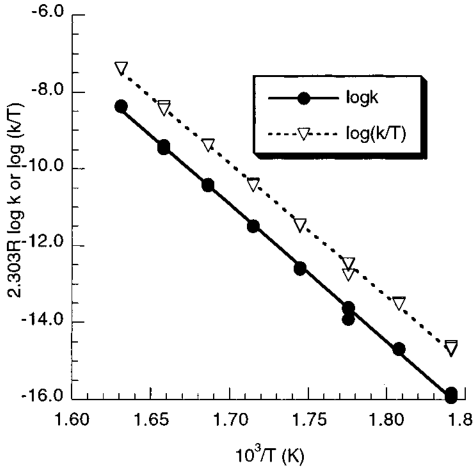


Figure 1. Arrhenius and Eyring plots for 3-phenylpropyl methanesulfinate (270−340 °C) elimination to give 3-phenylpropanal. Data points are from three runs at each temperature.

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Table 2. Activation Parameters for the Pulsed Stirred-Flow Thermolysis of 1e, 2e, 11e, and 26e[a]

sulfoxide	**1e**	**2e**	**11e**	**26e**
T range (°C)	240−300	225−270	340−400	270−340
log A (s^{-1})	12.5 ± 0.3	12.1 ± 0.8	13.1 ± 0.3	10.9 ± 0.2
E_a (kcal/mol)	34.0 ± 0.9	30.8 ± 0.8	42.9 ± 0.8	35.7 ± 0.6
$\Delta H^{‡}$ (kcal/mol)	32.9 ± 0.9	29.8 ± 0.8	41.6 ± 0.8	34.6 ± 0.6
$\Delta S^{‡}$ (cal/mol K)	−4.5 ± 0.8	−6.5 ± 0.8	−2.1 ± 1.2	−12.1 ± 1.0

[a] Errors are expressed as two standard deviations of the least-squares fit.

Table 3. Basis Set Evaluation at MP2 Level on the Elimination Reaction for Sulfoxide 1[a]

basis set	basis functions on **1**	$\Delta H^{‡\,b}$ (kcal/mol)	$\Delta H_{rxn}{}^{b}$ (kcal/mol)
6-31G(d,p)	119	32.9	16.6
6-31+G(d,p)	139	33.4	16.5
6-31++G(d,p)	147	33.2	16.7
6-31G(2d,p)	149	32.7	19.9
6-31G(2df,p)	199	33.9	23.8
6-31G(2df,2p)	223	33.8	23.9
6-31G(3df,2p)	253	36.3	27.3
6-31+G(3df,2p)	274	36.3	26.3
6-311G(d,p)	151	29.8	18.1
6-311++G(d,p)	179	31.2	15.6
6-311G(3d,p)	211	33.0	
6-311G(2df,p)	231	33.1	23.9
6-311G(3d,2p)	235	32.7	
6-311G(2df,2p)	255	33.3	23.4
6-311+G(3df,2p)	305	36.3	26.3
cc-PVDZ	119	25.1	
aug-cc-PVDZ	201	27.4	
cc-PVTZ	299	31.7	
aug-cc-PVTZ	479	32.4	
Experiment		33	

[a] Single-point calculations at various basis sets on the optimized MP2/6-31G(d,p) geometry. [b] No ZPEs are included. ZPE corrections lower $\Delta H^{‡}$ by about 3.0 kcal/mol and ΔH_{rxn} by about 3.7 kcal/mol.

Some compounds were run on the system, but proper activation data could not be obtained. Sulfoxide **3e** was on the margin of having too low of an activation barrier, and the temperatures required to get it through the GC made collecting good data impossible. Sulfinamide **6e** underwent the elimination reaction, but chromatographic conditions could not be found that allowed for accurate integration of the peak area of the starting material. A related *tert*-butylsulfinamide did not give clean chemistry. Similarly, **11e2** gave multiple products. However, the elimination to find the acetylene was an important experimental result to get. As a result, **11e** (same as **11**) was prepared. To give a detection window in the GC traces that avoided solvent, mesitylene was used as the solvent rather than acetonitrile.

Computational Results: Methodology. The work of Turecek[52] and others (including some of our own unpublished work) suggests that fairly large basis sets are required to correctly model sulfoxide energies relative to isomeric sulfenic esters (i.e., R−S−O−R′). Increasing the size of the basis set, in particular adding polarization functions on sulfur, stabilizes the sulfoxide relative to the sulfenate.

The effect of the basis set size on $\Delta H^{‡}_{elim}$ and ΔH_{rxn} for the Ei reaction of **1** are shown in Table 3 with both Pople-type and Dunning's correlation consistent basis sets. The MP2 level of theory was chosen for basis set evaluation after some initial experimentation with a modest basis set (6-31G(d,p)) gave answers in the right ballpark, compared to experiment.

The salient point to be gleaned from Table 4 is that while $\Delta H^{‡}_{elim}$ energies appear to have converged with respect to basis set, the convergence of ΔH_{rxn} is less clear. Among the Pople basis sets, addition of the diffuse functions is not a significant factor for $\Delta H^{‡}_{elim}$, nor is the doubling vs tripling in the 31 or 311 split valence. However, to have a balanced basis set,[53,54] we felt the need to have the triple split valence. Thus, adoption of 6-311+G(3df,2p) seemed like a reasonable approach, especially given the ambiguity over the ΔH_{rxn} value. Going to anything bigger would have been difficult for many of the relatively large systems (e.g., **3**), but as indicated below, good results were obtained for the systems in which both computational and experimental models were available. This and related[10] success suggest that this basis set gives data that are at least close to the infinite basis set limit for $\Delta H^{‡}_{elim}$. The Dunning basis sets were considered but rejected. Those sets that would have sufficient polarization functions (e.g., aug-cc-PVTV) would have so many basis functions overall that the computational resource needs would be prohibitive for all but the smaller systems.

Coupled with the choice of basis set was the choice of level of theory. We seriously considered three levels of theory: MP2, B3LYP, and MCSCF with perturbation theory correction (i.e., MRMP2). A modest test set that included most of the experimental compounds was used for evaluation. Activation energies from the MCSCF calculations (vide infra) were very similar to the HF values, so the multireference perturbation theory approach was not pursued further. Because the CCSD(T) calculations, which were being taken as the standard with regard to level of theory, would be impractical with the chosen basis set, the level-of-theory calculations were done with the 6-31G(d,p) basis. Table 4 shows the calculated values for several representative sulfoxides.

As with the Cope elimination, HF activation enthalpies are too high and B3LYP activation enthalpies are too low. The MP2 and CCSD(T) values are quite comparable in most cases and in the general vicinity of the experimental values. It remains unclear why there is such a large difference between the MP2 and CCSD(T) calculated ΔH for **10**. Nonetheless, general agreement between CCSD(T) and B3LYP is worse. A final test of B3LYP, with the larger basis set, was conducted, and the results are shown in Table 5. The $\Delta H^{‡}_{elim}$ values remain too small. Thus, MP2/6-311+G(3df,2p)//MP2/6-31G(d,p) was adopted as the general method.

Two sulfoxides (**1** and **11**, along with the respective transition states and products) were optimized at the MP2/6-311+G(3df,2p) level to see the effects on the energetics and geometries of re-optimizing rather than using MP2/6-31G(d,p) geometries for single-point calculations. The elimination activation enthalpies increased by 0.3 and 0.7 kcal/mol, respectively. The reaction enthalpies changed by 0.6 and 1.0 kcal/mol. This was deemed too insignificant to justify optimization in every case. As a result, the MP2 calculations cited below are MP2/6-311+G(3df,2p)//MP2/6-31G(d,p). Intrinsic reaction coor-

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(52) Turecek, F. *J. Phys. Chem. A* **1998**, *102*, 4703−13.

(53) Gordon, M. S.; Truhlar, D. G. *J. Am. Chem. Soc.* **1986**, *108*, 5412−9.

(54) Gordon, M. S.; Truhlar, D. G. *Int. J. Quantum Chem.* **1987**, *31*, 81−90.

Table 4. Activation Enthalpies and Heats of Reaction for Sulfoxides 1, 2–4, 10, and 11[a]

	1		**2**		**3**		**4**		**10**		**11**	
	$\Delta H^\ddagger$	ΔH	$\Delta H^\ddagger$	ΔH	$\Delta H^\ddagger$	ΔH	$\Delta H^\ddagger$	ΔH	$\Delta H^\ddagger$	ΔH	$\Delta H^\ddagger$	ΔH
HF	44.0	0.4	43.5	−2.1	42.7	0.5	41.2	−3.5	56.0	−5.2	50.1	15.0
MP2	28.9	12.8	28.6	9.6	28.5	14.5	27.4	9.8	53.7	16.6	37.9	20.4
CCSD(T)	29.6	8.5	29.3	7.8	29.2	9.5	27.6	5.0	49.4	6.3	39.4	19.5
B3LYP	23.5	9.0	22.5	8.4	22.3	8.5	21.9	6.8	41.4	6.4	34.4	22.9
expt[b]	33		30								42	

[a] All values are in kcal/mol and represent fully optimized structures at the specified level of theory with the 6-31G(d,p) basis set with ZPE corrections, save the CCSD(T) calculations, done at the MP2 geometry and corrected with the MP2 ZPEs. [b] Experimental $\Delta H^\ddagger$ are for compounds **1e**, **2e**, and **11** = **11e**.

Table 5. Activation Barriers[a] **at MP2/6-31+G(3df,2p)//MP2/6-31G(d,p) and B3LYP/6-31G+(3df,2p)//B3LYP/6-31G(d,p)**

	1	**2**	**3**	**4**	**11**
MP2	32.3	30.4	30.6	30.7	40.3
B3LYP	29.2	26.9	26.6	27.9	40.0
expt[b]	33	30			42

[a] Values are in kcal/mol and include ZPE. [b] For the corresponding "e" compounds.

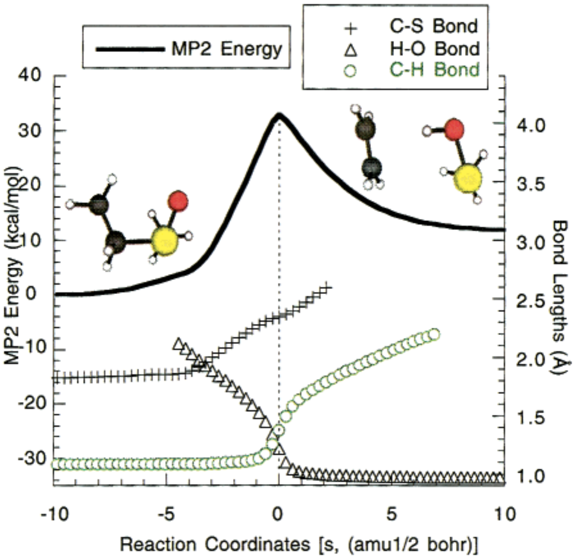

Figure 2. IRC calculation for the elimination reaction of **1** at MP2/6-31G(d,p).

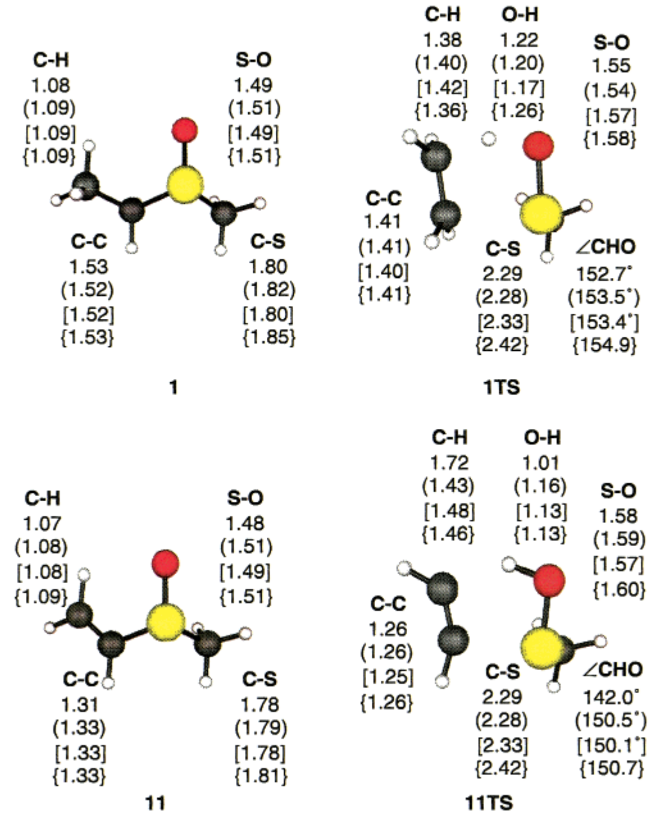

Figure 3. Geometry of **1**, **11**, and the respective transition states **1TS** and **11TS**. All bond distances are shown in Å. All bond distances and angles are shown in the following order: HF/6-31G(d,p), (MP2/6-31G(d,p)), [MP2/6-311+G(3df,2p)], and {B3LYP/6-31G(d,p)}.

dinate (IRC) calculations[55] were carried out on compounds **1**, **10**, **11**, and **26**–**29**. The transition states clearly connected to the starting materials and products. The IRC for **1** is shown as Figure 2. The others are in the Supporting Information.

Geometries for ethyl methyl sulfoxide (**1**), its transition state (**1TS**), and methyl vinyl sulfoxide (**11**) and its transition state (**11TS**) are shown in Figure 3. They are representative. The geometries, as expected, are all fairly similar with respect to method, with the exception of the HF geometry of **11TS**, where the C–H–O parameters are considerably out of agreement with any of the correlated models.[56] The result that HF/6-31G(d,p) bond lengths for **1** and **11** are very close to experiment[57] would appear to be due to fortuitous cancellation of errors from basis set (too long) and level of theory (too short). With the correlated methods, a large basis set is required to get the bond lengths right. The rest of the geometries, including those of the sulfenic acids and alkenes, are given in the Supporting Information.

CASSCF Analysis[58] **of Transition States.** To probe the nature of the transition states for diradical character and ensure that a single-reference description of the transition states was reasonable, complete active space self-consistent field (CASSCF) calculations were carried out on **1TS**–**4TS** and **11TS**. For **1TS**, **3TS**, and **4TS**, the choice of the active space, which consisted of six electrons in five orbitals, was guided by the illustrated orbital diagram. Initial orbitals were taken from localized orbitals obtained at the HF level and the final orbitals were well-behaved. Larger active spaces were tested on **1TS.** The starting orbitals included more lone pairs or the SO σ bond, for instance, but the results either did not provide

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(55) Gonzales, C.; Schlegel, H. B. *J. Chem. Phys.* **1989**, *90*, 2154–61.

(56) This justifies the use of the MP2/6-31G(d,p) geometries instead of the HF/6-31G(d,p) geometries, which are probably on the whole slightly more accurate for the sulfoxide reactants.

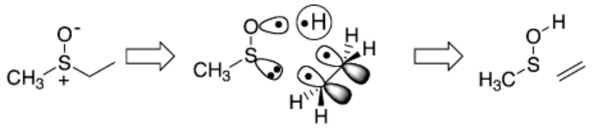
(57) Hargittai, I. In *The Chemistry of Sulfones and Sulfoxides*; Patai, S., Rappoport, Z., Stirling, C. J. M., Eds.; John Wiley & Sons Ltd.: New York, 1988; p 33–53.

Table 6. Calculated $\Delta H^{\ddagger}_{elim}$, ΔH_{rxn}, and $\Delta H^{\ddagger}_{addn}$[a]

compd	$\Delta H^{\ddagger}_{elim}$	ΔH_{rxn}	$\Delta H^{\ddagger}_{addn}$	compd	$\Delta H^{\ddagger}$	ΔH_{rxn}	$\Delta H^{\ddagger}_{addn}$
1	32.3 (33)	22.6	9.7	**18**	46.8	46.1	0.7
2	30.4 (30)	20.6	9.8	**19**	33.8	25.8	8.0
3	30.6 (26.3)[b]	15.7	14.9	**20**	28.0	20.9	7.1
4	30.7	18.0	12.7	**21**	33.4	21.2	12.2
5	30.0	20.1	9.9	**22**	39.6	35.5	4.1
6	42.7	42.6	0.1	**23**	33.5	27.1	6.4
7	35.1	28.9	6.2	**24**	31.2	23.4	7.8
8	29.1 (29)[c]	20.6	8.5	**25**	31.8	24.6	7.2
9	27.4 (25−30)[c]	16.6	9.8	**26**	32.7 (35)	12.6[d]	20.1
10	47.8	21.1	26.7	**27**	10.3	12.4[d]	3.5[f]
11	40.3 (42)	28.7	11.6	**28**	33.2	17.2[d]	16.0
12	42.8	29.9	12.9	**29**	21.3	26.4[c]	0.1[e]
13	22.0	18.8	3.2	**30 endo**[e]	25.0	15.6	9.4
14	25.2	21.0	4.2	**30 exo**[e]	24.2	23.7	0.5
15	25.3	21.0	4.3	**31 endo**[e]	23.2	17.3	5.9
16	23.6	19.9	3.7	**31 exo**[e]	29.8	25.3	4.5
17	19.3	16.9	2.4				

[a] MP2/6-311+G(3df,2p)//MP2/6-31G(d,p) calculations. All values in kcal/mol and data from experimental analogues are given in parentheses. [b] E_a, accompanied by surprisingly negative activation entropy. See ref 41 and text. [c] Experimental values are activation energies E_a. See refs 32 and 33 for experimental values. [d] See text. ΔH_{rxn} is for free products, not hydrogen-bonded complexes. [e] Endo and exo refer to endocyclic and exocyclic olefin formation. [f] $\Delta H^{\ddagger}_{addn}$ here refers to an intermolecular complex as starting material and ignores ZPE.

any new information or resulted in final orbitals that correlated electrons in obviously uninvolved parts of the molecule. The original [6,5] set was thus taken as the baseline from which to work on other molecules.



For ethyl vinyl sulfoxide **2TS**, and methyl vinyl sulfoxide **11TS**, the active space contained eight electrons in seven orbitals. In addition to the same six electrons in five orbitals used previously, the π and π^* orbitals were added. For **3TS**, an active space of the same size was used. It included the same basic [6,5] active space, the highest lying benzene π orbital, and the lowest lying π^*.

An important result of these calculations is the natural orbital occupation numbers (NOONs). In systems that are reasonably described as closed shell, these are near 0 and 2. For example, the NOONs for ethylene at CASSCF[4,4]/6-31G(d,p) are 1.982 (C−C σ), 1.920 (C−C π), 0.079 (C−C π^*), and 0.018 (C−C σ^*). The NOONs obtained for the current transition states (0.020−0.092 and 1.911−1.998, see table in the Supporting Information) are all consistent with a dipolar and not diradical transition state. These results support the idea that a single reference method, such as MP2, may be sufficient to get meaningful results. The transition states **1TS** and **11TS** were reoptimized at the CASSCF level. Only insignificant changes were observed in the geometries, energies, and NOONs. Thus, the data in the Supporting Information are all from CASSCF/6-31G-(d,p)//MP26-31G(d,p) calculations.

Computational Results. The energies calculated for $\Delta H^{\ddagger}$ and ΔH_{rxn}, along with the experimental data for the analogues where available, are shown in Table 6. As justified in the previous paragraphs, the data are from MP2/6-311+G(3df,2p)//MP2/6-31G(d,p) calculations. The $\Delta H^{\ddagger}_{elim}$ values are the activation enthalpies for the elimination (the “forward” reaction), and the $\Delta H^{\ddagger}_{addn}$ values are those for the reverse reaction, i.e., the addition of the sulfenic ester to the olefin to form the sulfoxide.

The data for compounds **26**−**29** deserve special comment, particularly since **27** and **29** appear to have activation enthalpies that are lower than the total enthalpy change for the reaction. This is an artifact of having a transition state whose energy is very close to the initial product of the reactions, which is a hydrogen-bonded complex. The values for ΔH_{rxn} are taken not for such complexes, but for isolated olefin and sulfenic acids. IRC calculations were done starting from **26TS**−**29TS** at MP2/6-31G(d,p), and they led downward in energy to complexed products. The hydrogen bonded complex for **27** was reoptimized at MP2/6-311+G(3df,2p), along with the transition state and starting material. The $\Delta H^{\ddagger}_{elim}$ increased from 10.3 to 11.4 kcal/mol. The ΔH_{rxn}, counting the complex as products, is 7.9 kcal/mol at the MP2/6-311+G(3df,2p) level of theory. The complex is 5.8 kcal/mol more stable than the isolated products, methanesulfenic acid and formaldehyde, and the O−H hydrogen bond distance is calculated to be 1.90 Å. Because these structures were found by IRC methods rather than with the intention of finding the global minimum, the analogous hydrogen-bonded complex for **26** is a different “rotamer”, with an O−H distance of 1.94 Å. Similarly, a hydrogen-bonded structure for the products of thermolysis of **28** was located by IRC methods. Its N−H distance is 1.85 Å. Geometries are given in the Supporting Information.

A similar analysis was completed on **29**. The IRC (MP2/6-31G(d,p)) produced a complex associating thioformaldehyde and methanesulfenic acid. This was reoptimized at MP2/6-311+G(3df,2p) and found to be 4.6 kcal/mol more stable than the free products. The complex, whose geometry is very similar to the transition state, is only 0.1 kcal/mol below the transition state in the absence of vibrational ZPE corrections. When zero-point energies are added in, the transition state disappears as a maximum. In other words, methanesulfenic acid adds to thioformaldehyde to give the thiosulfinate without barrier when ZPE is included. A lower energy, hydrogen-bonded complex was also found. The overall calculated energetics of the thermolysis of **29** are summarized in Table 7.

Finally, a comment should be made about accuracy and precision. There is not a “random error” associated with

Table 7. Energetics[a] of 29 with TS, Free Products, the Initial Complex (29vdw), and the Hydrogen-Bonded Complex (29hb)

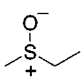
level	$\Delta H^‡$ no ZPE	$\Delta H^‡$ ZPE[c]	ΔH_{rxn} free[b]	ΔH_{rxn} free[b] w/ZPE	**29vdw**	**29vdw** w/ZPE	**29hb**	**29hb** w/ZPE
MP2/6-31G(d,p)	17.2	13.6	13.3	10.3			7.4	5.8
MP2/6-311+G(3df,2p)//MP2/6-31G(d,p)	25.6	22.0	30.4	27.4			24.5	22.9
MP2/6-311+G(3df,2p)	25.9	23.3	31.2	28.3	25.8	23.9	25.1	23.3

[a] All energies in kcal/mol and are stated relative to the lowest energy conformer of **29**. When not specified, ZPE is not included. [b] Free refers to separate calculations for thioformaldehyde and methanesulfenic acid. [d] ZPE energy used from the optimized geometry at the MP2/6-31G(d,p) level.

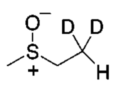
the calculations, meaning there are no "standard deviations." However, the degree of matching to experimental data and differences observed when using closely related protocols (e.g., optimizing at the biggest basis set or not) suggest limits below which the significance of the numbers is questionable. For purposes of discussion, we will look for differences of at least 2 kcal/mol in calculations to be confident of "real" variation from structure to structure. Comparison of very closely related systems may justify discussion of smaller differences, but a degree of realism is required.

Experimental and Computed Isotope Effects. Kinetic isotope effects (KIEs) were evaluated experimentally for **1e** by using **1e-d4** and **1e-d6** as substrates. The k_H/k_D was determined over the temperature range of 230−280 °C with three runs at each temperature at 10° intervals. The difference between the KIEs over this range was less than the scatter over the data, so the average was taken over the full temperature range. The k_H/k_D for **1e** vs **1e-d4** was found to be 2.5 ± 0.3. The k_H/k_D for **1e** vs **1e-d6** was found to be 2.8 ± 0.9, where the error limits are two standard deviations. There is no good chemical reason to expect a large difference in KIE between **1e-d4** and **1e-d6**; only a secondary KIE is expected. We interpret the experimental data for these two compounds, as being experimentally indistinguishable, given the large error bars.

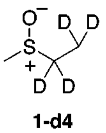
KIE computations were done on model compounds **1**, **1-d2**, and **1-d4** to attempt to model the KIE and further support the calculated transition-state model. The program ISOEFF98,[59,60] which uses vibrational frequencies from the substrates and respective transition states to solve for the KIE using the Bigeleisen equations,[61−63] was used in conjunction with the vibrational output from GAMESS. At 298 K, the calculated KIEs are 4.6 and 5.0 for **1-d2** and **1-d4**, respectively. This submaximal value is reflective of the somewhat bent geometry of the proton transfer. Over the temperature range of the experiments (503−553 K) both **1-d2** and **1-d4** have calculated KIEs that average to 2.5, in excellent agreement with the experiments.



1



1-d2



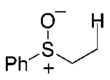
1-d4

Table 8. Comparison of Primary Kinetic Isotope Effects with Literature Measurements

k_H/k_D T (K)	k_H/k_D expt[64]	k_H/k_D **3/3-d1**	k_H/k_D T (K)	k_H/k_D expt[38]	k_H/k_D **3/3-d3**	k_H/k_D T (K)	k_H/k_D expt[32]	k_H/k_D **8/8-d9**
298		4.39	298		5.23	298	(15.6)[a]	5.81
403	3.17	3.07	353	5.15	4.14	385	5.4	3.97
423	2.94	2.92	363	4.97	3.99	393	4.5	3.86
443	2.77	2.80	373	4.77	3.85	400	3.8	3.78
463	2.63	2.68				408	3.4	3.68
483	2.49	2.58						
503	2.38	2.49						

[a] Extrapolated. See text.

KIE computations were also carried out to compare to experimental results reported by other workers (Table 8). Calculated isotope effects for **3-d1** and **3-d3** are shown at room temperature and the experimentally relevant temperatures. The calculations for **3-d1** nicely match Kwart's data for **3K**, collected in diglyme.[64] That conjugation in the transition state is important (vide infra) is demonstrated by comparing the KIEs calculated for **3-d3** to the compound **3Y**, studied in dioxane by Yoshimura.[38] The poor match clearly implies that data calculated for **3** are much less relevant to **3Y** than to systems without phenyls or other conjugating substituents.



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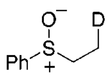
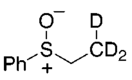
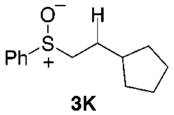


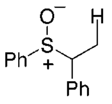
3-d1



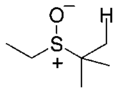
3-d3



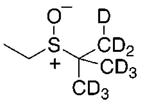
3K



3Y



8



8-d9

The experimental isotope effects[32] for **8** are somewhat unusual. Kwart interpreted[32,65] the A_H/A_D of 0.07 and ΔE_a of 3.2 kcal/mol as indicative of a mechanism that included a hydrogen atom tunneling component attributable to sterically induced narrowing of the barrier. Extrapolated to 298 K, the KIE for Kwart's compound is 15.6. The computational method used here explicitly excludes tunneling effects and cannot possibly duplicate these KIEs, regardless of the accuracy of the characteristics of the calculated transition states or whether tunneling is actually involved. It should be noted that the experimental and computed activation enthalpies for elimination by **8** are in excellent agreement (Table 6), though this does not eliminate the possibility of tunneling near the top of the barrier. For the sake of completeness, the computational data are included in Table 8.

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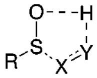
(63) Melander, L. *Isotope Effects on Reaction Rates*; Ronald Press: New York, 1960.

(64) Kwart, H.; George, T. J.; Louw, R.; Ultee, W. *J. Am. Chem. Soc.* **1978**, *100*, 3527−8.

(65) Kwart, H. *Acc. Chem. Res.* **1982**, *15*, 401−8.

Table 9. Bond Order Index Values[a] for Representative Sulfinyl Derivatives, Transition States, and Products



compd	S−O	O−H	H−Y	X−Y	X−S
1	1.36		0.96	0.97	0.86
1TS	1.06	0.41	0.43	1.33	0.46
CH_3SOH	0.82	0.86			
2TS	1.07	0.38	0.45	1.31	0.47
3TS	1.07	0.38	0.45	1.32	0.45
4TS	1.11	0.34	0.48	1.29	0.44
5TS	1.09	0.36	0.47	1.30	0.48
6	1.56		0.96	0.95	0.88
6TS	1.18	0.45	0.36	1.44	0.36
FSOH	0.92	0.84			
7TS	1.09	0.43	0.40	1.34	0.45
H_2NSOH	0.81	0.86			
8TS	1.04	0.39	0.45	1.29	0.47
9	1.24		0.96	0.98	0.86
9TS	1.03	0.37	0.47	1.28	0.45
11	1.37		0.95	1.93	0.88
11TS	1.04	0.47	0.38	2.38	0.50
12TS	1.04	0.43	0.39	1.37	0.43
13	1.36		0.94	0.95	0.86
13TS	1.05	0.45	0.38	1.17	0.61
acrolein				1.88	
14	1.35		0.97	0.95	0.86
14TS	1.11	0.36	0.48	1.24	0.52
15TS	1.06	0.40	0.42	1.32	0.43
16TS	1.08	0.37	0.46	1.30	0.43
17TS	0.96	0.62	0.23	1.34	0.52
18	1.39		0.97	0.93	0.88
18TS	0.97	0.56	0.28	1.44	0.38
19TS	1.06	0.40	0.43	1.31	0.48
20TS	1.05	0.39	0.45	1.30	0.48
21TS	1.08	0.35	0.48	1.27	0.50
22TS	1.03	0.49	0.35	1.39	0.48
23TS	1.05	0.42	0.41	1.31	0.48
24TS	1.04	0.39	0.44	1.31	0.44
25TS	1.05	0.39	0.44	1.30	0.47
26	1.50		0.96	0.81	0.77
26TS	1.08	0.48	0.34	1.41	0.31
27	1.26	0.08	0.79	0.92	0.87
27TS	1.06	0.43	0.35	1.20	0.70
28	1.41		0.96	0.90	0.83
28TS	1.09	0.40	0.44	1.29	0.43
29	1.50		0.94	0.94	0.83
29TS	1.03	0.49	0.33	1.44	0.41
30TS-endo	1.07	0.37	0.46	1.27	0.49
30TS-exo	1.07	0.39	0.43	1.35	0.41
31TS-endo	1.07	0.39	0.43	1.29	0.48
31TS-exo	1.08	0.38	0.44	1.34	0.42

[a] The minimum threshold to list a BOI is 0.05.

Transition States. With the exception of compound **10**, all of the transition states presented here are five-membered ring cycles and essentially planar. (Compound **10** was specifically included as a vinylogue of the main reaction and, therefore, has a seven-membered ring cyclic transition state.) This similarity suggests that comparison of some physical parameter might be made among all the transition states in order to examine which are "earlier" or "later" and the general synchronicity of the bond making and breaking. For example, Figure 2 suggests that, for **1**, the C−S bond is broken early in the reaction sequence, whereas the C−H bond breaking lags behind. Comparison of **1TS** and **11TS** in Figure 3 suggests that the proton transfer is closer to complete for **11TS**, whereas the C−S bond breaking is similar to the previous case. However, comparison of geometries such as this can be awkward and tenuous.

Instead, we report the MP2/6-31G(d,p) bond order indexes (BOIs)[66−68] for the transition states and certain representative sulfoxides in Table 9. Inspection of Table 9 will reveal that the BOIs for ordinary bonds are typically slightly less than 1.0. The C−H and C−C bonds in **1** are both over 0.95, while the C−S bond is 0.86, which is quite representative of most of the reactants. The S−O bond order of 1.36 reflects the additional "bonding" that results from the electrostatic attraction of the ylide but also points out that there is not a classic second bond between the two atoms. For purposes of further discussion, we will not consider differences in BOI significant unless they approach 0.05.

Discussion

Whither Pseudopericyclic. Overwhelming experimental and computational evidence shows that the elimination reaction of sulfoxides is concerted in the vast majority of cases. It has sometimes been characterized as pericyclic. However, there is little if any experimental evidence of a classic double bond between sulfur and oxygen.[69] A coordinate bond, which we have represented as an ylide, is more in line with experiment and theory. The most recent Atoms-in-Molecules analysis of the sulfoxide bond[16] sees it as essentially a single bond that is strengthened and shortened by electrostatic attraction. Localized molecular orbital views of the oxygen lone pairs show some distortion back toward the sulfur, consistent with this picture. If the essence of the enhanced single-bond view is accepted, then there is no longer reason to consider this reaction pericyclic, and the analogy to the Cope elimination holds.

The question of whether the reaction can be called pseudopericyclic is more interesting. Lemal's prototypical case[26] involved the automerization of a bicyclic sulfoxide and the interchange of the S lone pair with a C−S bonding orbital. Birney and co-workers have recently shown that many pseudopericyclic reactions occur through approximately planar transition states with lower barrier than a corresponding pericyclic, nonplanar transition state would have.[27] In this planarity, and in the exchange of lone pair and bonding orbitals, Birney's pseudopericyclic reactions have much in common with the current elimination reaction. In a sense, however, the important feature of a pseudopericyclic reaction it that it is *not* pericyclic, but merely is a concerted reaction in which a cyclic array of action occurs. In that sense, pseudopericyclic reactions are merely a subset of the many concerted unimolecular reactions that exist. The syn-elimination of sulfoxides is a concerted unimolecular reaction, but if we take seriously the idea of a coordinate, ylide-type sulfoxide bond, prudence suggests we not label the reaction pseudopericyclic because the oxygen is assigned the role of base, the sulfur acts as leaving group, and the bonding change between S and O is only marginal.

Adequacy of Modeling and the Nature of the Transition State. Gas-phase experimental data were collected here in order that computations could be done without reference to solvent modeling or other complica-

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(67) Mayer, I. *Chem. Phys. Lett.* **1983**, *97*, 270−4.

(68) Mayer, I. *Chem. Phys. Lett.* **1985**, *117*, 396.

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tions. As it turns out, the current experimental data are in line with previously reported results, both in solution and gas phase. The calculated activation enthalpies are all in good agreement where experimental values are available, and in the cases where only rates at single temperatures are known, the calculated activation enthalpies appear reasonable.

As established in Tables 3 and 4, it is a demanding problem to compare the energies of sulfoxides and their isomers, which, broadly speaking, includes the transition states. From Table 3, it appears that the basis set limit has been met for the transition state, relative to the sulfoxides, and the match of the MP2 calculations to the experimental data support that conclusion.

The use of MP2 calculations is clearly a compromise in methodology. CCSD(T) calculations were impractical given the large basis sets needed and the size of the molecules. However, the behavior of the CASSCF calculations and the NOONs obtained from them were at least consistent with MP2 being a reasonable method. Again, the performance of the MP2 calculations, including the accuracy of the calculated KIE for **1**, argues that the essence of the transition state is captured in the calculations.

The performance of the calculations is less clear for the calculated ΔH_{rxn} values (i.e., the sulfoxide compared to the sulfenic acid and olefin) because the convergence of the data with respect to basis sets is not demonstrated. However, since we are studying a series of closely related reactions, it is likely that any error would be systematic and result in an offset in the data that would be similar for all the compounds.

We were hampered in our efforts to critically evaluate ΔH_{rxn} because there are so few $\Delta H_f°$ data available for sulfenic acids. Neither are extensive data available for sulfoxides, but it is reasonable to use the Benson additivity method for simple alkyl derivatives to get estimates within a couple of kcal/mol.[70]

Turecek reported a value of -45.4 kcal/mol for the $\Delta H_f°(298\ \mathrm{K})$ of CH_3SOH.[71] Using this, the well-established experimental value for ethylene, and a Benson-type estimate for **1**, one obtains an estimate of $\Delta H_{\mathrm{rxn}} = 9$ kcal/mol. Perhaps coincidentally, this is approximately the value computed at all levels of theory using the 6-31G(d,p) basis set (Table 4). However, when the better MP2/6-311+(3df,2p) calculations were done, suddenly the MP2 computed value of 22.6 kcal/mol is in terrible disagreement with our "experimental" estimate of 9 kcal/mol.

This led us to reexamine the heat of formation of CH_3SOH using a G2 calculation.[72-74] Using either the atomization technique ($\Delta H°_f = -33.5$ kcal/mol) or isodesmic reactions (-33.6 kcal/mol), the G2 heat of formation at 298 K was 12 kcal/mol different than Turecek's experimental value. We are loathe to reject experimental values in favor of computational chemistry; however, the performance of G2 calculations for molecules of this size is excellent. Among the complete G2 test set, the single worst case is SO_2, whose calculated heat of formation is 5 kcal/mol different than the accepted experimental value. Methanesulfenic acid is the same size as SO_2 and has none of the complications of dative/hypervalent bonding. It is hard to believe that the G2 calculations would be so much worse for CH_3SOH than for any other molecule its size. When the G2 value for methanesulfenic acid is used as a surrogate for the experimental value, the new "experimental" estimate for ΔH_{rxn} (298 K) for **1** is 21 kcal/mol, much more in line with the 22.6 kcal/mol (O K) calculated value. It may reasonably be argued that this can be expected given the consistency of basis set in our calculations and the G2 calculation, but we suggest that the reported heat of formation for CH_3SOH be treated with caution.

General Interpretive Summary. The current data are all consistent with a concerted mechanism for the syn-elimination of sulfoxides and, thus, the addition of sulfenic esters to olefins. The concertedness of the elimination, however, does not imply the synchronicity of events. It is self-evident from Figure 2 that in the elimination reaction of **1** the breakage of the C−S bond begins earlier than does the breakage of the C−H bond. At the transition state itself, however, the BOI data in Table 9 show that the C−H and C−S bonds are broken to a similar extent. Given further that a BOI of 1.09 represents the halfway point for the transition of the S−O bond from sulfoxide to sulfenic ester, it can be concluded that the transition state for the Ei elimination of **1** is neither particularly early nor late and that it is roughly symmetrical with respect to bond making and breaking. Only the C−C BOI differs significantly from the middle of the starting and end points, suggesting that the π-bond formation is lagging.

If the elimination reaction is naturally pictured as using the sulfinyl oxygen acting as an internal base while the sulfinyl sulfur acts as leaving group, then the reverse addition can be seen as having the sulfur act as nucleophile while the sulfenic acid proton is removed by the π-bond acting as a Lewis Base. This is consistent with experimental results in which activated olefins or acetylenes have been used as traps for sulfenic acids. The regioselectivity of that addition reaction always favors the sulfoxide product that is formed when sulfur attacks the more electrophilic carbon of the olefin, i.e., with Markovnikov selectivity.[50]

There are several trends to be seen within the current data. For some compounds (e.g., **6**, **18**), the ΔH_{rxn} is much larger than the rest because of particularly unstable products. In those cases, the transition states are naturally product-like. However, among the more closely related sulfoxides, the variation in $\Delta H^{\ddagger}_{\mathrm{elim}}$ values is small. This observation is in line with previous more extensive experimental reports.[30,37,38] Moreover, at first glance, the variation in $\Delta H^{\ddagger}_{\mathrm{elim}}$ seems to track with ΔH_{rxn}. On closer inspection, though, there are interesting patterns among the $\Delta H^{\ddagger}_{\mathrm{addn}}$ data that may be more straightforward to interpret than the variations in $\Delta H^{\ddagger}_{\mathrm{elim}}$. For example, the compounds most closely related to the standard benchmark **1** have $\Delta H^{\ddagger}_{\mathrm{addn}}$ of approximately 10 kcal/mol. Even compounds **9**, **11**, and **12** are in this ballpark. This value appears to be characteristic of systems in which neither the olefin nor sulfenic acid are activated. In other words,

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variations in the $\Delta H^{\ddagger}_{\mathrm{elim}}$ within this group are mainly due to little more than changes in overall endothermicity.

Interpretation of the $\Delta H^{\ddagger}_{\mathrm{addn}}$ data can be taken further. When the sulfenic acid sulfur is made less nucleophilic, as in the product from compounds **3** and **4**, $\Delta H^{\ddagger}_{\mathrm{addn}}$ is higher. When the opposite is true, e.g., **7**, there is a decrease in $\Delta H^{\ddagger}_{\mathrm{addn}}$. (We presume that the α-effect of the nitrogen in **7** increases the sulfur nucleophilicity. The oxygens of sulfinamides are also known to be less basic than sulfoxides.[75−77]) With compound **17**, the olefin is activated by the ammonium substituent, making it more electrophilic and lowering $\Delta H^{\ddagger}_{\mathrm{addn}}$. In the forward direction, the ammonium substituent can be seen as increasing the acidity of the abstracted proton and is the only example in which additional conjugation in the transition state is not introduced along with the change in acidity.

Electron-withdrawing (and therefore electron-releasing) substituents might in principle exert effects in both favorable and unfavorable directions with respect to the elimination reaction. The oxygen atom acts as an internal base, and thus, electron-withdrawing substituents on the nonreactive side of the sulfoxide might be expected to raise the activation barrier by decreasing[39] basicity. However, there is a countervailing structural issue. The S−O charge separation is greater in the sulfoxide than in the sulfenic acid product. As a qualitative benchmark, the MP2/6-31G(d,p) Mulliken charges on sulfur for **1**, **1TS**, and CH_3SOH are 0.82, 0.57, and 0.38, respectively. Therefore, electron-withdrawing substituents might also preferentially destabilize the sulfoxide over the transition state and sulfenic acid, thus lowering the barrier.

We believe the Hammett plot results of Emerson and Yoshimura are interpretable within this context, using **4** as a model. The small Hammett ρ values are consistent with there being the two effects in opposite directions, especially given the relatively large ρ value of opposite sign known for acidity effects on aryl methyl sulfoxides.[39] Relative to **1**, the barrier for elimination is lower and the barrier for addition for **4** is higher. This is a consequence of the electron-withdrawing CF_3 substituent having a destabilization influence in the order sulfoxide > transition state > sulfenic acid, consistent with the charge argument. It thus must be the case that the decrease in basicity of the sulfoxide is more than made up for in the transition state by the presence of the electron-withdrawing group next to the partially positive sulfur. In more “chemical” language, we can speak of this being the drop in nucleophilicity of the sulfenic acid sulfur or the increased nucleofugacity of the sulfoxidic sulfur, with a smaller effect on the basicity of O. Both Emerson and Yoshimura showed a small decrease in activation enthalpy for nitrophenyl sulfoxides ($X = NO_2$ in Scheme 1), relative to the parent phenyl sulfoxide.

The opposite energetic effect would be expected for electron-rich substituents, that is, a differential stabilization in the order of sulfoxide > transition state > sulfenic acid. Again, the experimental Hammett results are in line with this interpretation. Unfortunately, carrying out a series of calculations at the MP2/6-311+G(3df,2p)//MP2/6-31G(d,p) level for substituted phenyl ethyl sulfoxides (i.e., derivatives of **3**) is still prohibitively demanding of computer resources.

The carbonyl-conjugated systems find in themselves a new group with small $\Delta H^{\ddagger}_{\mathrm{addn}}$ (3−5 kcal/mol), presumably due to conjugation in the transition state. Polarity matters, as with **13** vs **14**, but the effect is small, relative to the mere existence of a more delocalized transition state. Nonetheless, as Markovnikov-type selectivity is always observed experimentally, it is reassuring to see at least small differences in $\Delta H^{\ddagger}_{\mathrm{addn}}$ that favor the Markovnikov product. Carbonyl compounds themselves are obviously electrophilic and very strongly polarized. In the absence of extra conjugative effects, the polarization becomes very important, as, for example, the $\Delta H^{\ddagger}_{\mathrm{addn}}$ for **26** is larger than average and that of **27** is very small. Returning to the elimination direction, this can also be seen as an acidity effect, where the OH of **27** is quite acidic compared to the analogous protons in benchmark compounds.

Groups 1 and 2: Sulfoxides with Substituents on the Nonreactive Side. Given the prevailing wisdom in the synthetic use of the sulfoxide elimination that a phenyl substituent causes the reaction to go at lower temperature than a methyl, we chose phenyl ethyl sulfoxide (**3**) as a model experimental system to compare with **1**. The difficulty in getting data (and the relative size of the molecule for computational study) made **2** a logical compromise. The observed differences in activation barrier between **1** and **2** are relatively small, but in the end served as an important test for the computational method.

Experimental data are also available for phenyl ethyl sulfoxide **3**.[41] In dioxane solution, an activation energy (E_a) of 26.3 kcal/mol over an unspecified apparently 20 °C range was obtained, along with a very negative activation entropy of -18 ± 4 cal/mol·K that is the most negative reported in the study. It is at least coincidental that such a very negative activation entropy accompanies an activation energy that we apparently overestimate computationally, especially given our experimental data for **2e**. The reasons for this discrepancy are not clear.

The molecules in group 2 were chosen in an attempt to find a system where there might be a greater variation in $\Delta H^{\ddagger}_{\mathrm{elim}}$ and to test the ideas about countervailing effects of substituents on basicity and nucleofugacity of the sulfinyl group. As discussed above, the activation barrier for **4** is consistent with destabilization of the sulfur position being the predominant effect in the sulfoxide. This may be reflected in the comparatively incomplete proton transfer in the transition state as illustrated in the BOI values. Qualitative analysis of the BOIs in the addition direction is also ambiguous in that the proton of CF_3SOH is certainly more acidic than that of CH_3SOH, but the sulfur is less nucleophilic.

With **7**, analysis of the addition reaction is more straightforward. The electronegativity of the nitrogen, relative to carbon, should make H_2NSOH more acidic than methanesulfenic acid. However, the α-effect of the lone pair on N is also expected to contribute to the nucleophilicity of sulfur. Thus, as observed, a lower-than-benchmark $\Delta H^{\ddagger}_{\mathrm{addn}}$ is expected. This is a prime example of how the $\Delta H^{\ddagger}_{\mathrm{elim}}$ can be difficult to interpret in isolation from other data. It is higher than the benchmark value at least largely because of the high ΔH_{rxn}. The appearance of **7TS** is unremarkable, save for being behind in making

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(77) Ruostesuo, P. *Finn. Chem. Lett.* **1979**, 202−5.

the OH bond (in the elimination direction), consistent with the diminished basicity[75−77] of the oxygen in sulfinamides.

In compound **6**, there is a case in which the elimination is so endothermic (43 kcal/mol, compared to 23 for **1**) as to cause the transition state to be very late and productlike.[78] The lateness of **6TS** is reflected in the BOIs, but they are also more asymmetric with respect to bond making and breaking, with the fluorine reducing the basicity of oxygen and hindering proton transfer.

Group 3: Sterically Hindered Sulfoxides. Among these two sulfoxides, the greater effect is expected for di-*tert*-butyl sulfoxide **9**, in which greater steric crowding of the starting material is relieved by the elimination reaction.[33] As a gauge of the steric strain, the calculated C−S−C angle for **9** is 15° greater than the experimental value for DMSO.[57] Mulliken charge analysis points to a slightly more negative O than usual (−0.84 vs −0.80 for **1**), and this is accompanied by a notably smaller S−O BOI than usual (1.24 vs 1.36 for **1**).

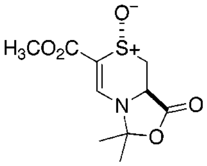
Shelton presumed that C−S bond cleavage would come early along the reaction pathway to relieve strain. Kwart suggested that the narrower barrier inherent in the steric crowding might lead to increased tunneling.[32,65] The simplest explanation consistent with the current data is that steric strain destabilizes the starting material without causing a major shift in the location of the transition state. The $\Delta H^{\ddagger}_{\mathrm{addn}}$ values for **8** and **9** are very similar to that for **1**, indicating that the majority of the strain in **8** and **9** is relieved in the transition state. The BOIs of the transition state for **9**, interestingly, are not biased toward greater than usual breakage of the C−S bond, but in fact is early with respect to O−H bond formation. Though we cannot model a transition state in which tunneling is significant, the greater O−H bond formation in the classical transition state is at least consistent with Kwart's proposal that tunneling is significant in these cases.[65]

Group 4: Sulfoxides with Double Bonds. The activation enthalpy for the vinylogous analogue **10** is higher than for the other compounds. The $\Delta H^{\ddagger}_{\mathrm{addn}}$ value is also higher than usual, meaning that this is not due to a simple endothermicity problem. (This substrate could not be studied experimentally because of the competing reversible rearrangement of allyl sulfoxides to allyl sulfenic esters.[79]) We attribute this to the strain inherent in the seven-membered ring transition state.[80] In Figure 4, it can be seen that although the general alignment of the five key atoms is about the same as usual, albeit with the orthogonal diene extension in the middle, there is a distinct distortion of those five atoms from planarity.

The other members of this group, **11** and **12**, test what happens when the abstracted proton is attached to an sp^2 carbon. The less negative experimental $\Delta S^{\ddagger}_{\mathrm{elim}}$ (Table 2) reflects the fewer degrees of freedom in the starting material because of the restricted rotation of the C−C bond. Aside from the excellent match between experiment and calculation in Table 6, the striking results are the very similar values of $\Delta H^{\ddagger}_{\mathrm{addn}}$ that **11** and **12** share with **1**. In other words, the addition is not particularly activated by the sp center, compared to the usual sp^2 center.

Figure 4. Top and side view of **10TS**.

Group 5: Carbonyl-Conjugated Olefin Products. This group of compounds was used to examine the effect of a carbonyl-conjugated product, as found in the most common synthetic applications of this chemistry. Compounds **13**−**16** are marked by having unremarkable ΔH_{rxn} values that are a little lower than the parent compound **1** because of the conjugated carbonyl in the product. They have significantly lowered $\Delta H^{\ddagger}_{\mathrm{elim}}$ values, all in the range of 22−25 kcal/mol and correspondingly low $\Delta H^{\ddagger}_{\mathrm{addn}}$ values. The "vinyl effect" (comparing $\Delta H^{\ddagger}_{\mathrm{elim}}$ for **1** and **2**) of lowering activation enthalpy by about 2 kcal/mol is reproduced between **15** and **16**. As is reasonable, there is little difference between the aldehyde and ketone substituents used in **14** and **15**. These lower activation energies are at least qualitatively in line with experiment in that the polyfunctional sulfoxide shown below was shown to racemize in boiling chloroform by way of the reversible elimination reaction, whereas very similar sulfoxides without the carbonyl were stable.[81]



Compound **14** has the regiochemistry produced in the usual synthetic sequence when the sulfoxide is made from an enolate, but **13** is an isomer in which the sulfinyl oxygen is set up to remove the more acidic proton. Compound **13** is also the isomer that would be observed as the major product from addition of methanesulfenic acid to acrolein. The difference in ΔH_{rxn} between the two reflects a 2.2 kcal/mol greater stability of **14** and is reflected in a 1 kcal/mol lower barrier to form **14**. The clear message from the energetics is that the major part of the differences between these compounds and **1** is due to the carbonyl conjugation in the transition state, with the polarity/acidity playing a smaller part. These results are in line with the experimental observations of Crich, who used esters instead of aldehydes.[40]

Tsukurimichi came to the same conclusion that carbonyl conjugation in the transition state accelerated the rate of elimination, and the reported activation energies (E_a) for phenyl 1-carbomethoxy-1-methylethyl phenyl and 2-carbomethoxyethyl phenyl sulfoxides are both within experimental error of 26 kcal/mol.[41] In this same paper is reported the surprisingly low barrier for **3** (vide supra),

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(78) It should also be noted that computational modeling of the O−F bond is not straightforward and requires more sophisticated treatments than given here (e.g., CCSD(T)). We have not critically evaluated the F−S bonds calculated here, so some caution should be used in conjunction with the absolute energies given in the tables. Lee, T. J.; Rice, J. A.; Dateo, C. E. *Mol. Phys.* **1996**, *89*, 1359−1372.

(79) Tang, R.; Mislow, K. *J. Am. Chem. Soc.* **1970**, *92*, 2100−4.

(80) Beginning with S−O and going around the cycle of the transition state, the BOIs are 0.98 (S−O), 0.48 (O−H), 0.34 (H−C), 1.30 (C−C), 1.48 (C−C), 1.16 (C−C), 0.67 (C−S).

(81) Stoodley, R. J.; Wilkins, R. B. *J. Chem. Soc., Perkin Trans. 1* **1974**, 1572−9.

which if actually somewhat higher, would seem to be more consistent with their conclusion.

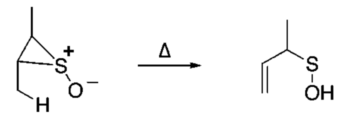
The complementary nature of structures **13** and **14** is reflected well in the corresponding transition-state structures. The structure of **13TS**, in which the partial conjugation is to the β-carbon whose proton is being abstracted, is considerably later than benchmark for O−H formation and C−H breaking, while it is rather early with respect to C−S breaking, where there is no conjugative advantage. Relative to **1**, **14TS** is early in every respect as measured by the BOIs. However, relative to **13TS**, it is late with respect to C−S dissociation, i.e., relatively speaking, the C−S bond, whose breakage is assisted by the conjugative effects of the carbonyl occurs before the proton abstraction. The C−S distance (see the Supporting Information) in **14TS** is fully 0.25 Å longer than that of **13TS**. These effects are in line with the suggestion of Yoshimura et al., based on rate data at fixed temperatures, that a β-electron-withdrawing group will encourage what they termed a "carbanion-like" mechanism in which the proton transfer proceeds in advance of C−S bond breaking.[82]

Hypothetical compound **17** demonstrates that the olefin polarity/proton acidity effect can be considerable in the absence of extended conjugation. Its $\Delta H^{\ddagger}_{\text{addn}}$ is among the very lowest in the whole group. The BOIs show the expected asymmetry if it is taken that the carbon acidity is responsible for the relative ease of elimination. The S−O, O−H, and C−H BOIs are extremely product-like in **17TS**, whereas the C−C BOI is unremarkable and the C−S BOI is, if anything, somewhat sulfoxide-like.

Group 6: Ring Strain and Endocyclic vs Exocyclic Olefin formation. Consistent with the experimental results of Kice[35] and Yoshimura,[36] we find a lower enthalpic barrier for the formation of cyclopentene (**20**) than for cyclohexene (**21**). The awkwardness of **21TS**, because of the need of the ring to flatten out, is confirmed by the relatively high $\Delta H^{\ddagger}_{\text{addn}}$ for **21** compared to **25**. The geometry can be obtained from the Supporting Information. However, the current models are not adequate to predict the experimental product mixture of 24:1 endo/exo methylcyclohexene obtained at 100 °C from the elimination of 1-methylcyclohexyl phenyl sulfoxide.[36] Yoshimura et al. also investigated the exo/endo selectivity for 4-*tert*-butyl-1-methylcyclohexyl phenyl sulfoxides,[83] in which the axial/equatorial position of the sulfoxide is locked, but molecules of this size are beyond the scope of the present investigation.

The formation of highly strained cyclopropene (**18**) or methylenecyclopropane (**22**) raise ΔH_{rxn}, and a correspondingly late transition state is observed. The cyclobutyl compounds show apparently ordinary $\Delta H^{\ddagger}_{\text{elim}}$ and ΔH_{rxn}, but closer inspection shows that some relief of ring strain is observed in the $\Delta H^{\ddagger}_{\text{addn}}$ values.

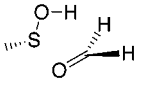
An additional alicyclic ring opening was calculated, for **32**, in which ring strain is relieved by the elimination reaction. The ΔH_{rxn} is only 0.5 kcal/mol and the $\Delta H^{\ddagger}$ was calculated to be 20.0 kcal/mol using the usual MP2/6-311+G(3df,2p)//MP2/6-31G(d,p) methodology. This value is quite reasonable, given Baldwin's half-life of 3 min at 35 °C for **32**.[84] If $\Delta H^{\ddagger}_{\text{elim}}$ is taken at the calculated value of 20 kcal/mol, the resulting $\Delta S^{\ddagger}_{\text{elim}}$ is −5 cal/mol·K. Greer and Foote found an experimental activation energy for the closely related 2-methyl-2-butene episulfoxide of 18 kcal/mol.[85]



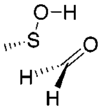
32

Group 7: Heteroatomic Sulfinyl Derivatives. The calculated activation enthalpy for **26** of 32.7 kcal/mol compares well with the experimental value of 34.6 ± 0.6 for **26e**. To the best of our knowledge, this is the first report of formation of an aldehyde by elimination from a sulfinic ester. The calculated ΔH_{rxn} for this reaction is 5 kcal/mol smaller than that for **1**. Given the very similar ΔH_{rxn} calculated for the isomeric sulfoxide **27**, the low ΔH_{rxn} value of 12.4 kcal/mol derives from the favorable formation of a carbonyl π system, rather than instability of the sulfinic ester.

The large difference in $\Delta H^{\ddagger}_{\text{elim}}$ between **26** and **27** is due to the energy difference between the transition states themselves. In fact, **27TS** is over 20 kcal/mol more stable than the isomeric **26TS**. This is easily understood by examining the addition reaction. The much larger barrier to addition in the sense that leads to **26** reflects the reversal of polarity of the carbonyl. The nucleophilic sulfur attacks the electrophilic carbon only on the path to **27** and the effect is quite substantial.



to **26**



to **27**

This analysis suggests that **27TS** ought to have a considerable C−S BOI, especially compared to the corresponding S−O BOI in **26**. This is borne out by the data. The C−S BOI of **27TS** is 0.70, the highest among all the transition states. The analogous C−S BOI for **26TS** is 0.31, which is the lowest.

The contrast between **26** and **27** can also be seen in the elimination reaction, using the idea of the acidity of the abstracted proton as being determining. The pK_a of the hydroxylic proton of **27** in water is obviously lower than the corresponding proton in the slower-reacting **26**, but gas-phase acidities are more relevant. A reasonable estimate of the gas-phase acidity of the hydroxylic proton in **27** of 370 kcal/mol ($\Delta H°$) can be made from data for a series of alcohols.[86] Data for sulfinic esters are not available, but the gas-phase acidity of the methyl protons in methyl formate is 391 kcal/mol.[87] The value for **26** should be similar. Clennan has proposed that α-hydroxysulfoxides are transient intermediates formed in the reaction between $^1O_2$ and alkyl sulfides.[88,89] The very

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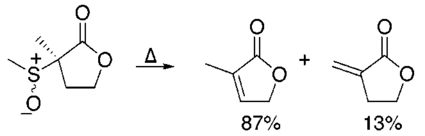
modest calculated barrier to elimination is consistent with the transient nature hypothesized there.

The elimination reaction energetics of **28** follow the pattern established by **26**, though there are obviously quantitative differences. Thiosulfinate **29** produces thioformaldehyde with a barrier of 21.3 kcal/mol. The weak S−S homolytic bond strength of **28** (ca. 45 kcal/mol[90]) certainly contributes to the low barrier in the forward direction, and the weak π-bond in the product contributes to the low barrier in the reverse direction. Most notable of this reaction is the flatness of the reaction potential in the vicinity of the transition state when the IRC is computed at MP2/6-311+G(3df,2p). (See the Supporting Information.) The transition state **28TS** is closer in BOIs to the benchmark **1TS** than to **27TS**, but this should be treated with caution, given the flatness of the potential. Although free products are higher in energy than the transition state, we found an initial van der Waals type complex and a hydrogen-bonded complex as described previously.

Elimination reactions of thiosulfinates have been demonstrated by Block in natural and model compounds.[4,5,90,91] A half-life of **29** of 7 min in neat thermolysis at 96 °C[91] can be used to verify that the calculations are at least in the right ballpark. Using the calculated $\Delta H^{\ddagger}_{\mathrm{elim}}$ of 21.3 kcal/mol, a $\Delta S^{\ddagger}$ of −14 cal/mol·K is obtained from the experimental half-life. If the calculated value is low by 1 kcal/mol, the newly implied $\Delta S^{\ddagger}$ is −11.4 cal/mol·K.

Group 8: Lactone Eliminations. Finally, the elimination reactions of the two diastereomers **30** and **31** deserve some comment. Three conformational minima were found for each diastereomer. As usual, we calculate the ΔH data by taking the lowest energy conformation as the starting material.[92] The lowest energy conformer is found for **31**, which is 1.6 kcal/mol lower than that of **30**.[93] These compounds were analyzed to compare to the work by Trost and co-workers[94,95] in which an unspecified mixture of the two diastereomers yielded mainly the endocyclic product.



Trost attributed the mixture to the greater stability of a conformation in which the sulfinyl group and carbonyl dipoles opposed one another but recognized that other factors may play a role. We find that the exo product is slightly favored by about 1 kcal/mol from **30** but that the endo product is formed with a 6.6 kcal/mol lower barrier from **31** (Table 6)**.** The absolute energy of **31TS-exo** stands out as the highest of the four related transition states. In the two endo transition states, the S−O bond and carbonyl are pointed in essentially opposite directions, thus having approximately opposing dipoles. In the two exo transition states, the lactone dipole and sulfinyl dipole are disposed at roughly right angles. In both the endo and exo cases, the lower energy transition states (i.e., **30TS-exo** and **31TS-endo**) have the sulfinyl methyl over the carbonyl carbon, instead of over a methylene (**31TS-exo**) or the exocyclic methyl (**30TS-endo**), as can be seen in the Supporting Information. Thus, it would appear that the TS energy depends not only on the dipoles, but also on fairly subtle steric interactions.

Summary and Conclusions

The stirred-flow experiments have allowed access to activation parameters for a variety of sulfoxides and sulfinyl derivatives. The activation enthalpies are well modeled by an MP2 calculation with a sufficiently large basis set. Tests using CCSD(T) and CASSCF methods did not indicate that there was need for a multireference correlated method for the computations. B3LYP calculations performed poorly, consistently underestimating the barriers. With this settled, the MP2 calculations were extended to molecules whose activation data were not accessible.

These calculations demonstrate that substituent effects on the sulfoxide elimination reaction are much easier to understand if ΔH_{rxn} is known in addition to $\Delta H^{\ddagger}_{\mathrm{elim}}$. Sometimes it is easier to qualitatively predict the activation enthalpy of the reverse reaction, that is, the addition reaction. This is probably an artifact of the ΔH_{rxn} being positive in the direction of the elimination. For basically unactivated olefins and sulfenic acids, $\Delta H^{\ddagger}_{\mathrm{addn}}$ is approximately 10 kcal/mol. Activation of the sulfenic acid by making it more nucleophilic results in a lowering of the barrier. Activation of the olefin by conjugating it to a carbonyl also lowers the barrier. When the olefin is transformed into another simple π-bonded system (e.g., formaldehyde), the sense of electrophilicity becomes very important, such that in the “correct” orientation, addition barriers are virtually nonexistent, whereas they are higher than usual when the polarity is mismatched. In the direction of the elimination reaction, many of these same qualitative predictions on the value of $\Delta H^{\ddagger}_{\mathrm{addn}}$ can be drawn on the basis of basicity of the sulfinyl group and the acidity of the abstracted proton as long as ΔH_{rxn} is also known. The acidity of the abstracted proton, however, is a minor issue if comparing structures where the new π-bond will be conjugated with another π-system

Experimental Section

Computations. All computations, except the B3LYP,[96,97] G2 calculation on methanesulfenic acid and a few semiempirical conformational searches were carried out with the GAMESS suite of programs.[98] Results were visualized with MacMolPlt.[99] The Becke3LYP and G2 calculations were carried out using GAUSSIAN 94,[100] in which the default 6-311 basis

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[92] The barriers between the conformation are of course well below the energy defference between any of the conformers and either of the transition states.

[93] The four other conformers are within 5.5 kcal/mol of the lowest conformer of 31.

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set was made to conform with those in GAMESS, as developed by McLean and Chandler.[101] Low energy conformations of starting materials and products were determined using the PM3 model, and subsequent optimizations used those conformations as starting geometries. Hessians were obtained to confirm the nature of the stationary points. The Gonzales–Schlegel second-order method[55] was used for determining intrinsic reaction coordinate (IRC) paths. Except as noted, the products (usually an olefin and a sulfenic acid) were calculated independently and their energies summed. For each molecule, the coordinates, absolute energy in hartrees, and zero-point energies are given in the Supporting Information. Activation barriers and reaction enthalpies are all corrected with zero-point energies but do not contain any further corrections for thermal energy at temperatures above 0 K.

The temperature-dependent KIEs were calculated using the program ISOEFF98,[60] which uses vibrational frequencies from the substrate and TS to solve for the KIE using Bigeleisen equation.[61,63] The ISOEFF98 program uses Hessian matrixes obtained from GAMESS output.

Thermolysis Instrumentation. The stirred-flow reactor has a temperature-controlled furnace and is modeled very closely after the one that has been previously described.[48] It uses He as a carrier gas to bring the sample into a quartz reactor (clean, and silylated) whose volume controls the residence time, which is a few seconds. Samples were injected as concentrated solutions in acetonitrile, except where noted. After the furnace section, the gases are sent to a GC that operates at lower temperatures, where starting materials and products are separated and quantified. Rate constants are extracted from each run, and multiple injections were made at each temperature. Activation data are extracted from rate constants obtained over the range of temperatures where both starting material and product can be quantified. All sulfoxides thermalized were greater than 99% purity, as determined by the observation of a single peak by GC without thermolysis.

Compound Preparation. General Procedure. Unless otherwise noted, starting materials were obtained from Aldrich and used as received. Characterization was carried out on a Bruker Avance DXR NMR operating at 400 MHz for proton and 100 MHz for carbon. The ^{13}C signals for CD_2 carbons were generally not observed due to the low signal-to-noise and high multiplicity. Mass spectra were obtained on a Finnigan TSQ 700 operating in EI mode. IR spectra were obtained on a Mattson Galaxy Series FTIR 3000. Dry THF was freshly distilled from benzophenone ketyl. For the AB quartet in **1a** $\Delta\nu/J$ was calculated using: $\Delta\nu/J = (4C^2 - J^2)^{1/2}/J$; C = separation from first peak to third peak and J = separation from first to second peak in the quartet. Sulfoxides **2e** and **3e** were prepared as described in Guo's dissertation.[102] Synthetic details for other compounds that have appeared in the literature are in the Supporting Information.

General Procedure for Preparation of Sulfoxides from Sulfides. For a good general reference for the oxidation of sulfides to sulfoxides, see Mata's review.[103] In our hands, the low-temperature oxidation with 1 equiv of *m*-CPBA is the usual preferred method. The following is a general procedure. To an ice-cooled solution of 2–3 mmol of the sulfide in methylene chloride (15 mL) was dropwise added a solution of 1.0 equiv of *m*-CPBA in 25 mL of CH_2Cl_2. After 2 h, the mixture was poured in to aqueous NaOH (5%, 50 mL), and the layers were separated. The organic layer was washed with another portion of aqueous NaOH, dried with $MgSO_4$, and concentrated in vacuo. Further purification was carried out as noted. Unoptimized isolated yields in the range of 60–80% were typical, though near-quantitative yields are sometimes obtained. Alkyl sulfoxides can be prepared easily at lower temperature still, such as −78 °C.

Methyl 3-phenylpropyl sulfoxide (1e)[104] was prepared by oxidation of the corresponding sulfide:[10] ^{1}H NMR ($CDCl_3$) δ 7.33–7.27 (m, 2 H), 7.22–7.18 (m, 3 H) 2.80 (t, $J = 7.5$ Hz, 2 H), 2.61–2.73 (m, 2 H), 2.54 (s, 3 H), 2.09–2.17 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 140.4, 128.6, 128.5, 126.4, 53.8, 38.6, 34.2, 24.2; IR (thin film) 3024, 2922, 2859, 1453, 1044, 747, 700 cm^{-1}.

Methyl 2,2,3,3-tetradeutero-3-phenylpropyl sulfoxide (1e-d4) was prepared in quantitative yield by oxidation of methyl 2,2,3,3-tetradeutero-3-phenylpropyl sulfide (0.08 g, 0.05 mmol) with *m*-CPBA as described above.[10] It was further purified by recrystallization from ether at low temperature yielding white crystals (65% yield): ^{1}H NMR ($CDCl_3$) δ 7.29–7.26 (m, 2H), 7.21–7.15 (m, 3H), 2.95 (q_{AB}, $J = 13$ Hz, $\Delta\nu/J = 5.5$, 2H), 2.51 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 140.3, 128.8, 128.5, 126.6, 53.7, 38.6; EI-MS (*m*/*e*, relative abundance) 186 (27), 120 (100), 93 (48); IR (thin film) 3021, 2953, 2905, 2206, 2106, 2090, 1301, 1133, 1028, 744, 703 cm^{-1}.

Methyl 2,2,3,3,4,4-hexadeutero-3-phenylpropyl sulfoxide (1e-d6) was prepared from methyl 2,2,3,3,4,4-hexadeutero-3-phenylpropyl sulfide (0.08 g, 0.05 mmol) as described above in quantitative yield. It was further purified by recrystallization from ether at low-temperature yielding white crystals (65% yield): ^{1}H NMR ($CDCl_3$) δ 7.28–7.24 (m, 2H), 7.19–7.13 (m, 3H), 2.49 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 140.3, 128.6, 128.5, 126.4, 38.5; EI-MS (*m*/*e*, relative abundance) 188 (38), 123 (100), 93 (54); IR (thin film) 3021, 2983, 2213, 2111, 1448, 1107, 1040, 744, 703 cm^{-1}. Preparation of the sulfide is described in the Supporting Information.

3-Phenylpropyl Methanesulfinate (26e).[105] A solution of methanesulfinyl chloride (10.0 g, 0.10 mol)[106] in dry ether (80 mL) was added dropwise with stirring and cooling in an ice bath to a solution of distilled 3-phenylpropan-1-ol (12.6 g, 0.093 mol) and pyridine (8.1 g, 0.10 mol) in ether (20 mL). After the mixture was stirred overnight, the mixture was poured into ether (100 mL) and washed with cold water (20 mL), cold HCl (10%, 20 mL), cold saturated $NaHCO_3$ (20 mL), and cold water, in that order. The organic layer was dried ($MgSO_4$) and concentrated via rotary evaporator. The crude product (as needed in 2 mL to 3 mL aliquots) was purified using flash chromatography (CH_2Cl_2) affording a clear liquid: ^{1}H NMR ($CDCl_3$) δ 7.31–7.26 (m, 2H), 7.21–7.18 (m, 3H), 4.09–3.98 (m, 2H), 2.72 (t, $J = 4.0$ Hz, 2 H), 2.064–1.978 (m, 2H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 141.0, 128.5, 128.5, 126.2, 67.5, 44.2, 31.9, 31.9; EI-MS (*m*/*e*, relative abundance) 198 (3), 118 (100), 117 (56), 91 (76); IR (thin film) 3025, 2947, 2880, 1603, 1132, 1017, 907, 744, 701 cm^{-1}.

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Supporting Information Available: Further computational details including geometries, NOONs, absolute energies, and IRCs, along with preparation and spectroscopic characterization of a number of synthetic intermediates and **11e2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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