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Theoretical Study of Nucleophilic Substitution at Sulfur in Sulfinyl Derivatives

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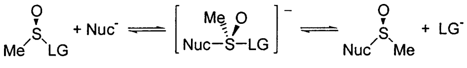

Nuc = LG = Cl, CN, PH_2, MeO, HO, NH_2

A series of gas-phase nucleophilic substitution reactions at sulfur of methanesulfinyl derivatives by small anions (chloride, cyanide, hydroxide, methoxide, amide, and phosphide, identical to the leaving group in each case) were examined by Hartree−Fock, MP2, and DFT computations. In most cases, substitution was found to follow an addition−elimination mechanism, resulting in a triple-well potential energy surface with small barriers of activation on either side of the central, tetracoordinate-sulfur minimum. The geometries of the central minima, as in the analogous methanesulfenyl cases, are unsymmetrical trigonal bipyramidal, with the nucleophiles and leaving groups occupying apical positions and the sulfur lone pair an equatorial position. The apparent exception, cyanide, may undergo an S_N2 displacement.

Introduction

Because nucleophilic substitution reactions play such a central role in organic chemistry, considerable effort has been devoted to the detailed study of their mechanistic pathways. Historically, much attention has focused on substitution at carbon,[1,2] but more recently attention has turned to the study of nucleophilic substitution reactions at heteroatoms in organic molecules,[3−15] arguably most importantly sulfur, which is frequently found in natural products in such an environment as to be subject to substitution reactions (e.g. as disulfides).

Previously, we examined[16−18] the mechanism of substitution at sulfur in di- and trisulfides by ab initio computations, where addition−elimination mechanisms were found to predominate. More surprisingly, not only divalent, 8-S-2, methanesulfenyl derivatives,[19,20] but also SCl_2 were predicted to undergo addition of nucleophiles to form intermediate, tricoordinate complexes along the reaction pathway; the latter case was confirmed experimentally in the gas phase.[21]

While the novelty of these findings was due in part to a relative dearth of previous studies, the same could not be said for the extension to analogous nucleophilic substitution reactions at sulfur in trivalent, 8-S-3 sulfinyl compounds. Because the sulfinyl sulfur is a potential chiral center[22] and because sulfinates are known to

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(1) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry*, 4 ed.; Kluwer Academic/Plenum: New York, 2000; Part A.

(2) Gronert, S. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jones, M., Jr., Eds.; Wiley-Interscience: Hoboken, NJ, 2004; pp 69−120.

(3) Beak, P.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 3834−3835.

(4) Bachrach, S. M. *J. Org. Chem.* **1990**, *55*, 1016−1019.

(5) Woods, K. W.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 6281−6283.

(6) Kurtzweil, M. L.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 3426−3434.

(7) Anderson, D. R.; Woods, K. W.; Beak, P. *Org. Lett.* **1999**, *1*, 1415−1417.

(8) Beak, P.; Li, J. *J. Am. Chem. Soc.* **1991**, *113*, 2796−2797.

(9) Bühl, M.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1993**, *115*, 364−365.

(10) Bühl, M.; Schaefer, H. F., III. *J. Am. Chem. Soc.* **1993**, *115*, 9143−9147.

(11) Li, J.; Beak, P. *J. Am. Chem. Soc.* **1992**, *114*, 9206−9207.

(12) Bachrach, S. M.; Mulhearn, D. C. *J. Phys. Chem.* **1993**, *97*, 12229−12231.

(13) Tollefson, M. B.; Li, J. J.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 9052−9061.

(14) Bachrach, S. M.; Demoin, D. W.; Luk, M.; Miller, J. V., Jr. *J. Phys. Chem. A* **2004**, *108*, 4040−4046.

(15) Lee, S. J.; Terrazas, M. S.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **2003**, *2003*, 7307−7312.

(16) Bachrach, S. M.; Mulhearn, D. C. *J. Phys. Chem.* **1996**, *100*, 3535−3540.

(17) Mulhearn, D. C.; Bachrach, S. M. *J. Am. Chem. Soc.* **1996**, *118*, 9415−9421.

(18) Bachrach, S. M.; Hayes, J. M.; Dao, T.; Mynar, J. L. *Theor. Chem. Acc.* **2002**, *107*, 266−271.

(19) Hogg, D. R. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Elsevier: New York, 1979; Vol. 3, pp 268−297.

(20) Bachrach, S. M.; Gailbreath, B. D. *J. Org. Chem.* **2001**, *66*, 2005−2010.

(21) Gailbreath, B. D.; Pommerening, C. A.; Bachrach, S. M.; Sunderlin, L. S. *J. Phys. Chem. A* **2000**, *104*, 2958−2961.

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undergo reaction with enolates and organometallics with inversion of configuration to form chiral sulfoxides, the reactions, and especially the stereochemical course of reactions, of sulfinates and related compounds have been studied extensively,[23,24] and their use in synthesis has been reviewed thoroughly.[25] Recent examples include the exploitation of sulfinates in the synthesis of chiral amines and amino alcohols.[26] Most of this work has focused on synthetic transformations, however, and details of the exact mechanism for any archetypal reaction have been mostly inferred by analogy, together with some data from kinetic and stereochemical studies.[27,28] Since our computational studies on substitution at divalent 8-S-2 (sulfenyl) sulfur for several nucleophiles and leaving groups had led to a considerable enhancement in mechanistic understanding, we decided to extend this study to several representative tetravalent 8-S-3 sulfinyl cases in the hope of shedding further light on the mechanism(s) involved in the reactions of these species.

Computational Methods

The reactions examined here (reactions 1−6) are all identity displacements, with equivalent nucleophile and leaving group. The ordering of these reactions is that of increasing gas-phase basicity of the nucleophile.[29]

$$Cl^- + CH_3S(O){-}Cl \rightarrow Cl{-}S(O)CH_3 + Cl^- \quad \text{(reaction 1a)}$$

$$Cl^- + HS(O){-}Cl \rightarrow Cl{-}S(O)H + Cl^- \quad \text{(reaction 1b)}$$

$$Cl^- + PhS(O){-}Cl \rightarrow Cl{-}S(O)Ph + Cl^- \quad \text{(reaction 1c)}$$

$$CN^- + CH_3S(O){-}CN \rightarrow NC{-}S(O)CH_3 + CN^- \quad \text{(reaction 2)}$$

$$PH_2^- + CH_3S(O){-}PH_2 \rightarrow H_2P{-}S(O)CH_3 + PH_2^- \quad \text{(reaction 3)}$$

$$CH_3O^- + CH_3S(O){-}OCH_3 \rightarrow CH_3O{-}S(O)CH_3 + CH_3O^- \quad \text{(reaction 4)}$$

$$HO^- + CH_3S(O){-}OH \rightarrow HO{-}S(O)CH_3 + HO^- \quad \text{(reaction 5)}$$

$$NH_2^- + CH_3S(O){-}NH_2 \rightarrow H_2N{-}S(O)CH_3 + NH_2^- \quad \text{(reaction 6)}$$

In searching for critical points, we considered only singlet species, as in our earlier studies. There is evidence for radical intermediates in some nucleophilic substitution reactions.[30] Sulfinyl derivatives, which carry an oxygen atom as well as one or more other electronegative substituents on sulfur, are expected to be better electron acceptors than the previously studied disulfides or sulfenyl derivatives, and thus we considered the possibility of single-electron transfer as an alternative initial step. With the best electron donor in this series, PH_2^-, the transfer of an electron to form the sulfinyl radical anion ($CH_3S(O)PH_2^-$) is very unfavorable; the energy for the vertical electron transfer is greater than 32 kcal mol^{-1} while the adiabatic electron transfer is endothermic by greater than 8.5 kcal mol^{-1} at MP2 or DFT. These studies do not rule out the possibility of single-electron transfer in either the gas or solution phase. No doubt appropriate structural variations in nucleophile, leaving group, and sulfinyl derivative could even lead to SET as the more favorable pathway, but it is unlikely to be competitive for reactions 1−6, and therefore we examined and report exclusively the two-electron pathways here.

While these reactions in the gas phase are of interest in assessing the nature of the mechanism of nucleophilic substitution at heteroatoms, their synthetic application is in the solution phase. Our initial study of solvation effects on substitution reactions of disulfides[18,31] and thionyl chloride[32] indicated that simple SCRF approaches may be problematic and that incorporation of explicit solvent molecules may be necessary. Therefore, we report only the gas-phase results here.

All structures of reactants and products, intermediates, and transition states were completely optimized using the HF, MP2, and B3LYP methods with the 6-31+G* basis set.[33] Optimizations were also performed at B3LYP with the slightly larger aug-cc-pVDZ basis set. As noted earlier,[16−18] adequate representation of the topology of the potential energy surface (PES) necessitates inclusion of electron correlation, with DFT methods giving a good combination of reliability and facility, and we anticipated a similar result here. In fact, the HF method proved to be inadequate for reactions 1−3, and therefore HF computations were not performed for the remaining reactions. The choice of a basis set with one set each of polarization and diffuse functions was also based on earlier explorations with various models.[16−18]

The nature of all structures was confirmed by analytical frequency calculations. Local minima had all real frequencies, and transition states had exactly one imaginary frequency. Zero-point vibrational energies (ZPE) were evaluated and used without scaling to compute the 298 K thermal contributions to the free energies using standard partition-function approximations.[33] All computations were performed with either Gaussian 98[34] or Gaussian 03.[35]

Results

As with the earlier sulfenyl examples, it was found that most of the sulfinyl derivatives studied here first undergo

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[22] Oae, S. *Organic Sulfur Chemistry: Structure and Mechanism*; CRC Press: Boca Raton, FL, 1991.

[23] Okuyama, T. In *The Chemistry of Sulphinic Acids, Esters and Their Derivatives*; Patai, S., Ed.; Wiley & Sons: Chichester, England, 1990; pp 623−637.

[24] Andersen, K. K. In *Comprehensive Organic Chemistry*; Jones, D. N., Ed.; Pergamon Press: Oxford, UK, 1979; Vol. 3, pp 317−329.

[25] Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651−3706.

[26] (a) Zhou, P.; Chen, B.-C.; Davis, F. A. *Tetrahedron* **2004**, *60*, 8003−8030. (b) Ellman, J. A. *Pure App. Chem.* **2003**, *75*, 39−46.

[27] Tillett, J. G. *Chem. Rev.* **1976**, *76*, 747−772.

[28] (a) Kice, J. L.; Large, G. B. *J. Am. Chem. Soc.* **1968**, *90*, 4069−4076. (b) Kice, J. L.; Rogers, T. E.; Warheit, A. C. *J. Am. Chem. Soc.* **1974**, *96*, 8020−8026. (c) Kice, J. I.; Rogers, T. E. *J. Org. Chem.* **1976**, *41*, 225−227. (d) Kice, J. I.; Liu, C.-C. *J. Org. Chem.* **1979**, *44*, 1918−1923.

[29] National Institute of Standards and Technology. NIST Chemistry Webbook. http://webbook.nist.gov/chemistry/ (released March 2003).

[30] Rossi, R. A.; Pierini, A. B.; Peñéñory, A. B. *Chem. Rev.* **2003**, *103*, 71−168.

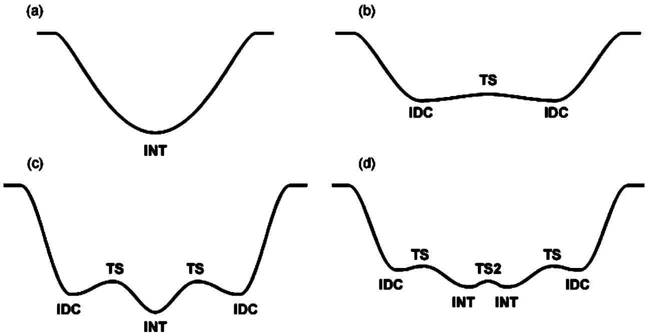
[31] Hayes, J. M.; Bachrach, S. M. *J. Phys. Chem. A* **2003**, *107*, 7952−7961.

[32] Moon, T. M.; Bachrach, S. M. In *Abstracts of Papers*, 229th American Chemical Society National Meeting, San Diego, CA, March 13-17, 2005; American Chemical Society: Washington, DC, 2005; CHED-931.

[33] Cramer, C. J. *Essentials of Computational Chemistry. Theories and Models*; Wiley: Chichester, UK, 2002.

[34] Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

SCHEME 1



addition to form an intermediate tetracoordinate complex, which then ejects the leaving group in a second mechanistic step. Low energy barriers usually were found to separate these complexes from ion−dipole complexes (IDCs) of reactants and products, giving a symmetrical triple-well reaction profile, indicative of the addition−elimination pathway (see Scheme 1c). With the strongly basic amide and hydroxide anions, the entrance/exit channel local minimum was with some models found to be the product of proton transfer (only at the DFT level for hydroxide, and only with DFT and a larger basis set for amide). In the case of cyanide, a more profound change in mechanism was observed, with the C_s symmetrical tetracoordinate species now being a low energy transition state for an S_N2 displacement, and a slightly unsymmetrical complex forming a local minimum on either side of it in the computed PES. With DFT, the PES for the cyanide case was also exceptional in that two local minima were found on each side of the central TS (Scheme 1d), the one ("inner") complex featuring a short contact between the cyanide carbon and the central sulfur atom, the other a short contact between the cyanide carbon and the α-hydrogen of the substrate ("H-bonded") complex.

Critical points along the reaction pathway for each individual reaction are displayed in Figures 1−6; details (bond lengths, angles) are given for the B3LYP/aug-cc-pVDZ optimized geometries in all cases. Bond distances and angles for the critical points computed at MP2/6-31+G* and B3LYP/6-31+G* differ little from the values reported in the figures. This is consistent with previous computations of analogous systems.[16−18] Relative energies (MP2/6-31+G* and B3LYP/aug-cc-pVDZ) of the critical points for all six reactions are listed in Table 1. Relative energies computed at HF/6-31+G* and B3LYP/6-31+G* are listed in Table S1.

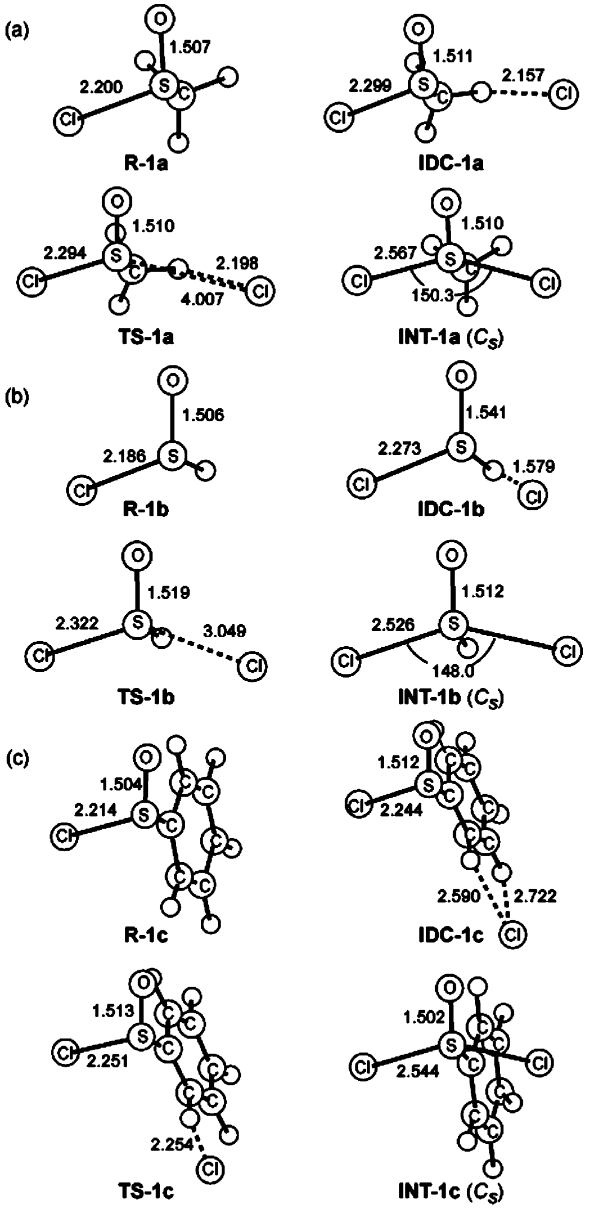


FIGURE 1. Geometries of critical points of reaction (a) 1a, (b) 1b, and (c) 1c. Distances are in Å, angles are in degrees.

Reaction 1a. The addition of chloride ion to methanesulfinyl chloride is unusual in this series in that a single, symmetrical transition state with the standard gas-phase S_N2 PES (Scheme 1b), rather than a triple-well reaction profile (Scheme 1c), was found at the HF level. Both MP2 and DFT results predict the symmetrical complex to be a minimum, confirming again that HF is unsuitable for treating nucleophilic substitution at sulfur. However, the entering and exiting transition states could only be located for the DFT cases, and the energy barrier is extremely small. At B3LYP/6-311+G*, no barrier could be found. Altogether, these results suggest that reaction 1a proceeds without a barrier to produce **INT-1a** with the PES shown in Scheme 1a. We have observed this type of PES before in the reaction of thionyl chloride with chloride.[36] The geometry of the intermediate is trigonal bipyramidal, but strongly distorted from trigonal symmetry, with the angle between apical chlorine atoms only

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(35) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, J.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; C. Y. Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2003.

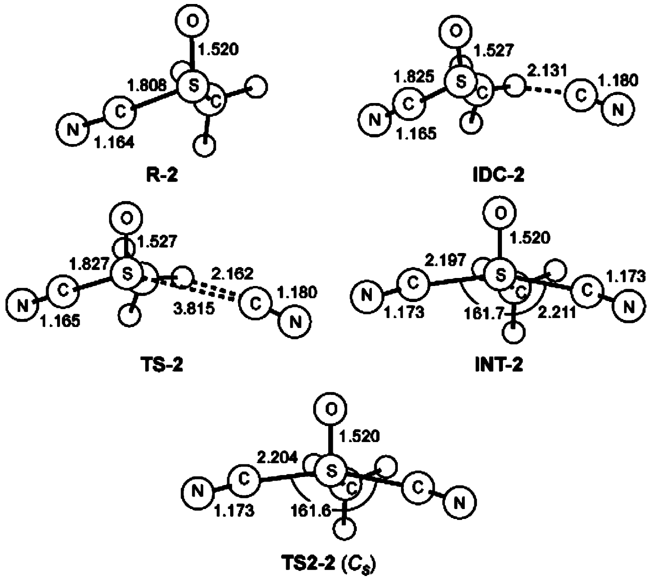

FIGURE 2. Geometries of critical points of reaction 2. Distances are in Å, angles are in degrees.

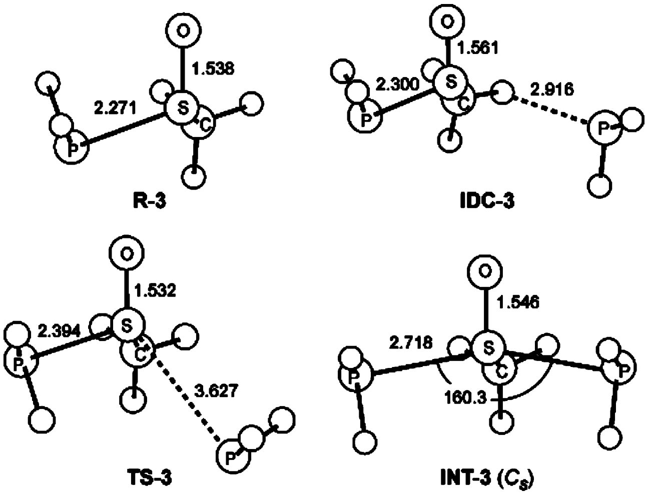

FIGURE 3. Geometries of critical points of reaction 3. Distances are in Å, angles are in degrees.

~150° (Figure 1a). This marked deviation from linearity was found in all cases in this study, and represents a contrast to the methanesulfenyl analogues studied earlier. There appears to be little correlation between the magnitude of the angular deviation and the nature of the nucleophile: OH^- and PH_2^-, for example, are associated with almost the same deviation from linearity in **INT-3** (Figure 3) and **INT-5** (Figure 5).

Reaction 1b. In an effort to gain further insight into the results of the previous case, we also examined the reaction of chloride ion with the lower (carbon-free) homologue HS(O)Cl (Figure 1b). This reaction was found to exhibit a triple-well reaction profile (Scheme 1c) with all theoretical models examined, although the well was very shallow in the HF case. This slightly greater reactivity at the HS(O) center versus $CH_3S(O)$ might be due to a combination of steric and electronic effects, somewhat analogous to the greater reactivity of aldehydes versus ketones, formate versus other carboxylates, and so forth,[1] where hyperconjugative donation of electron density by α-protons of the alkyl groups helps stabilize the partial positive charge of the carbonyl carbon, or as here, the sulfinyl sulfur. In addition, the hydrogen on sulfur in **IDC-1b** is more positively charged

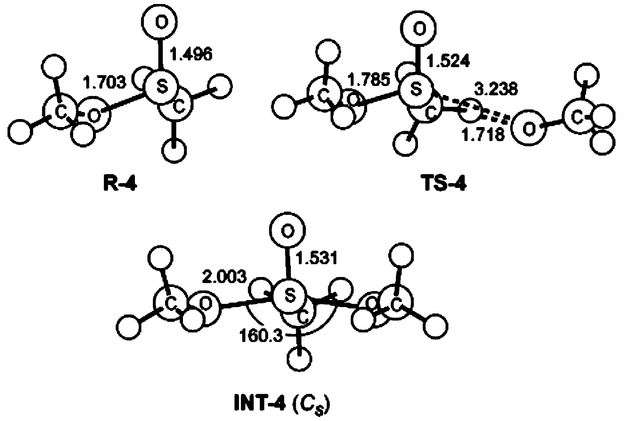

FIGURE 4. Geometries of critical points of reaction 4. Distances are in Å, angles are in degrees.

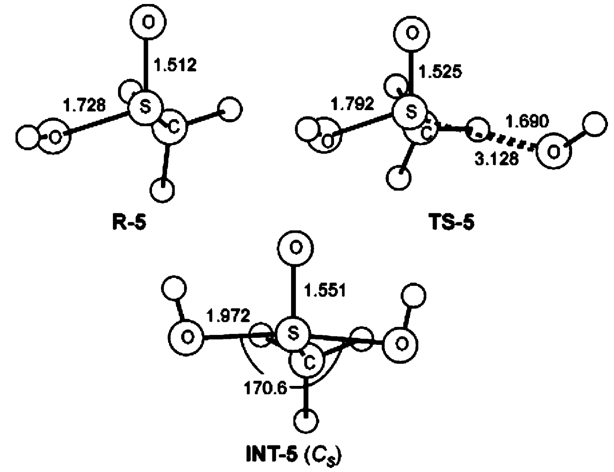

FIGURE 5. Geometries of critical points of reaction 5. Distances are in Å, angles are in degrees.

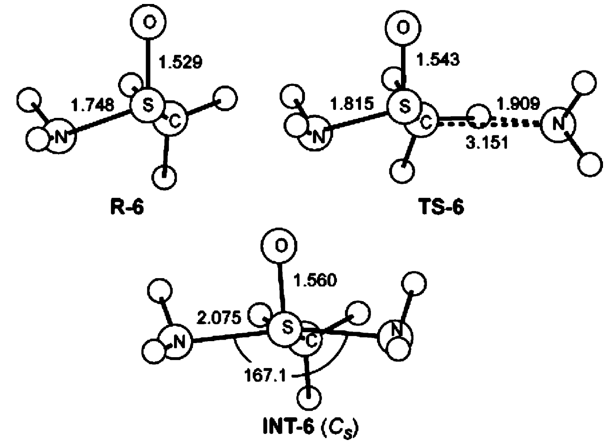

FIGURE 6. Geometries of critical points of reaction 6. Distances are in Å, angles are in degrees.

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(36) Lobring, K. C.; Hao, C.; Forbes, J. K.; Ivanov, M. R. J.; Bachrach, S. M.; Sunderlin, L. S. *J. Phys. Chem. A* **2003**, *107*, 11153–11160.

TABLE 1. Relative Energies (kcal mol^{-1}) of Critical Points on the PES for Reactions 1−6[a]

reaction 1a	R	IDC	TS	INT	TS2	reaction 3	R	IDC	TS	INT	TS2
MP2(FC)/6-31+G*	0.0	*b*	*b*	−24.76		MP2(FC)/6-31+G*	0.0	−17.81	−9.22	−13.96	
	0.0			*−17.68*			*0.0*	*−7.62*	*−1.46*	*−5.40*	
B3LYP/aug-cc-pVDZ	0.0	−17.36	−17.31	−26.43		B3LYP/aug-cc-pVDZ	0.0	−15.56	−10.77	−14.19	
	0.0	*−12.05*	*−10.86*	*−19.29*			*0.0*	*−6.24*	*−2.58*	*−5.85*	
reaction 1b						reaction 4					
MP2(FC)/6-31+G*	0.0	−25.84	−24.07	−28.54		MP2(FC)/6-31+G*	0.0	−18.97	−18.97	−33.23	
	0.0	*−20.22*	*−17.64*	*−21.61*			*0.0*	*−10.47*	*−9.50*	*−20.55*	
B3LYP/aug-cc-pVDZ	0.0	−29.60	−25.83	−31.53		B3LYP/aug-cc-pVDZ	0.0	*e*	−17.78	−29.16	
	0.0	*−24.99*	*−19.66*	*−24.42*			*0.0*		*−8.20*	*−16.50*	
reaction 1c						reaction 5					
MP2(FC)/6-31+G*	0.0	−17.81	−17.71	−24.48		MP2(FC)/6-31+G*	0.0	−22.13	−22.11	−34.35[d]	−34.10[f]
	0.0	*−10.80*	*−9.17*	*−17.53*			*0.0*	*−14.92*	*−13.83*	*−24.60*	*−23.73*[f]
B3LYP/aug-cc-pVDZ	0.0	−14.87	−14.38	−23.81		B3LYP/aug-cc-pVDZ	0.0	*e*	−21.53	−33.32[g]	*g*
	0.0	*−8.68*	*−7.45*	*−16.72*			*0.0*		*−13.86*	*−23.68*	
reaction 2						reaction 6					
MP2(FC)/6-31+G*	0.0	−18.29	*c*	*c*	−16.30	MP2(FC)/6-31+G*	0.0	−18.05	−17.54	−25.84	
	0.0	*−13.70*			*−10.45*		*0.0*	*−9.78*	*−7.53*	*−13.62*	
B3LYP/aug-cc-pVDZ	0.0	−17.16	−17.15	−20.21[d]	−20.21	B3LYP/aug-cc-pVDZ	0.0	*e*	−15.96	−23.69	
	0.0	*−10.33*	*−9.06*	*−12.84*	*−11.41*		*0.0*		*−6.89*	*−12.60*	

[a] R: reactants; IDC: ion−dipole complex; TS: transition state; INT: intermediate (tetracoordinate) complex. Relative electronic energies are given in the first line, relative free energies are listed in italics in the second line. [b] Only an intermediate was found; there appear to be no other critical points. [c] A double-well PES with no tetracoordinate complex was found. [d] The intermediate complex in this case is not symmetrical (C_1); see Figure 2 and discussion in text. [e] Proton transfer occurs, IDC not found. [f] C_s TS for methyl group rotation. [g] The INT is C_s in this case, as in almost all others, so there is no TS for methyl group rotation along the reaction coordinate of interest.

than the hydrogen in the methyl group of **IDC-1a**, making the former more tightly hydrogen-bonded than the latter. This stronger interaction has to be broken during the course of the nucleophilic substitution, which gives rise to the barrier in reaction 1b that is not seen in reaction 1a.

Reaction 1c. To test the effect of a larger substituent on sulfur, we replaced the methyl group with a phenyl group, giving the archetype for the many known arylsulfinyl derivatives. The reaction profile in this case was very nearly the same as that for reactions 1a and 1b. The energy of formation of the intermediate **INT-1c** is slightly smaller than that for **INT-1a**. The well depths associated with both **INT-1a** and **INT-1c** are very similar, nearly 10 kcal mol^{-1}. The largest difference due to the phenyl group is in the relative energy of **IDC-1c**; it is much less negative than either **IDC-1a** or **IDC-1b**. These ion−dipole complexes are created primarily by the electrostatic attraction of the chloride anion for a partially positively charged hydrogen of the sulfinyl substrate. Since the hydrogen atoms of the phenyl group are much less acidic than either the methyl hydrogen atoms of $CH_3S(O)Cl$ or the hydrogen of $HS(O)Cl$, it is understandable that this C−H bond will be less polarized than the others, thereby forming a weaker complex with chloride. Thus neither the steric bulk of the phenyl group nor the possibility of sulfur-ligand π conjugation can be seen to exert an obvious influence on the mechanism in this case.

Reaction 2. Cyanide anion, although less basic than the other anions following, behaves as a strongly electron-withdrawing group. It might be expected that a sulfinyl sulfur carrying a cyano substituent might be particularly electron-deficient and hence coordinate strongly to incoming anions to form stable tetracoordinate complexes. It is somewhat surprising, therefore, that a C_s symmetric transition state was found for the identity displacement of cyanide ion with all theoretical models examined. The predicted topology of the PES is dependent on the computational method. At MP2/6-31+G*, the surface looks like that of Scheme 1b, having two mirror-image ion−dipole complexes separated by the single transition state. In contrast, the transition state located using B3LYP (**TS2-2**) connects two mirror-image, slightly unsymmetrical “inner” complexes with cyanide proximate to the partially positively charged sulfur. The PES is very flat in this region. An earlier TS (**TS-2**) was found to connect this species to the “hydrogen-bonded” complex, thus giving a quadruple-well reaction surface (Scheme 1d), with the C_s symmetric TS being only slightly higher in energy than the unsymmetrical “inner” complexes. The motion of the C−S−O fragment in the central TS is such that the entry and exit of the CN groups is coupled with the rotation of the methyl group, allowing the methyl group to be in a staggered conformation in the TS, consistent with C_s symmetry (Figure 2). This has some analogy with the displacements at methansulfenyl sulfur studied earlier,[16,20] in which the staggered orientation of the methyl group was found to correspond to a conformational TS, with very slightly unsymmetrical complexes lying very close in energy on either side.

Reaction 3. Examination of the PES associated with the phosphide case was complicated by the possibility of conformational isomerism about the S−P bond. It was found for the reactant, methanesulfinylphosphide (**R-3**), and intermediate (**INT-3**) that the energies of the conformers were only minimally different, with a very soft potential for bond rotation, causing the optimizations, even with tight cutoffs, to retain considerable uncertainty in the H−P−S−X dihedral angles. We show the reaction pathway involving the lowest energy conformer for each species along the way (Figure 3). As with chloride, the PES shows a symmetrical transition state at the HF level (Scheme 1a), but a more pronounced triple-well PES (Scheme 1c) with correlated methods. The well depth associated with **INT-3** is about 3−5 kcal mol^{-1}, with little variation due to the computational method.

Because P and H are very similar in electronegativity, the P−H bond dipole moments are much smaller than those for analogous N−H bonds. Their orientation is not expected to play a major role in determining the lowest energy geometries of the species involved in reaction 3, in contrast to more highly polar groups such as amide (reaction 6) or hydroxide (reaction 4). The relatively weak σ-bond between S and P (two third-row elements of only moderately dissimilar electronegativity) and relatively poor π overlap between 3p and 3d orbitals on S and P apparently contribute to making **INT-3** the weakest complex (relative to **IDC**) of those examined. Thus the analogy between amide and phosphide is poor, and phosphide in this reaction is more analogous to another third-row species, chloride, than to its own second-row congener, amide.

Reactions 4 and 5. These two reactions were expected to be fairly comparable, with the methoxide ion being an alkylated homologue of hydroxide. The latter is more basic in the gas phase, however, and this raised the concern that the reaction pathway leading from the central well might progress not to the expected ion−dipole complex, but to the products of a proton transfer, specifically H_2O and $HOS(O)CH_2^-$. Such an endpoint in fact was found at the DFT level, but MP2 results show the more usual ion−dipole complex as the outer minima of the triple-well PES. Those structures that could be optimized with the B3LYP/cc-aug-pVDZ model are shown in Figure 5. Methoxide, a weaker base, showed the three-well profile with MP2 and B3LYP/6-31+G* but has the proton-transfer product instead of the ion−dipole with B3LYP/cc-aug-pVDZ. As in reaction 3, conformational isomerism was a complicating factor. Similar results were obtained for both conformers examined; only the lower energy one is included in Table 1 and Figure 4. The intermediates **INT-4** and **INT-5** both sit in rather deep wells of about 12 kcal mol^{-1}. This well depth is greater than that for the intermediates produced for reactions at 8-S-2 centers, which is usually no greater than 5 kcal mol^{-1}.[16−18,20] Again, we see little variation in the well depth of **INT-5** with computational method, but MP2 predicts a barrier out of **INT-4** that is 3 kcal mol^{-1} greater than with either DFT method. This is the largest difference among the reactions examined here.

Reaction 6. The reaction pathway associated with the extremely basic amide anion terminated, not unexpectedly, in the products of proton transfer (NH_3 and $H_2NS(O)CH_2^-$) but only when a larger basis set was used; otherwise, the more usual IDC could be located. Again, two conformers had to be considered, but the reaction profiles were not profoundly affected. Only results for the lower-energy conformer are given in Table 1 and Figure 6. As expected, an intermediate, with its associated entrance and exit transition states, was located at MP2 and B3LYP levels. The depth of the well associated with **INT-6** is computed to be about 8 kcal mol^{-1} with all three methods.

Discussion

The PES for gas-phase nucleophilic substitution at sulfinyl (8-S-3) sulfur is predicted to have three wells (Scheme 1c) for leaving groups only σ-bonded to sulfur. This PES corresponds to the addition−elimination mechanism. This is the same mechanism as that found in our previous studies of nucleophilic substitution at a variety of 8-S-2 centers, including acyclic mono-, di-, and trisulfides and larger cyclic disulfides.[16−18,20,37] The HF approximation incorrectly predicts the mechanism for many of the reactions examined here, again indicating that electron correlation must be included in any computational study of nucleophilic substitution at sulfur. The predicted structures of the intermediate 10-S-4 anionic complexes are found to be very similar to those of the 10-S-3 anionic complexes found earlier for displacements at sulfenyl sulfur. The entering nucleophile and leaving group occupy the apexes of a distorted trigonal bipyramid. The angle formed by the nucleophile, sulfur, and leaving group is farther from 180° in the 10-S-4 anions than in the 10-S-3 anions, placing the partial negative charges on the nucleophile and leaving group farther from the negative (oxygen) end of the sulfinyl S−O dipole, absent in the sulfenyl cases. This angle is relatively unaffected by the group occupying the apical positions; it ranges from 160°−170° except for the chloride case where the angle is 150.3°.

Even the variations in well depth and barrier height with the nature (particularly basicity) of the anion parallel those of the corresponding sulfenyl cases. The sulfenyl analogues of reactions 1−3 that we[20] previously computed at B3LYP/aug-cc-pVDZ (reaction 7−9) have well depths about their intermediates of 8.61, 0.86, and 10.16 kcal mol^{-1}, respectively. While the well for the phosphide adduct is much deeper in the sulfenyl than in the sulfinyl case, the well depths of the other two cases are remarkably similar. Regardless of the absolute agreement of the intermediate energies, the trends in their well depths are the same for the sulfinyl and sulfenyl reactions (i.e., $MeO^- > Cl^- > PH_2^-$). This trend correlates with the increasing softness of the nucleophile. All in all, it appears that the inclusion of an oxygen atom in the coordination sphere of sulfur, where a second lone pair would be present in the sulfenyl analogue, makes surprisingly little qualitative difference in the reaction profile of nucleophilic substitution, at least in the gas phase.

$$Cl^- + CH_3S{-}Cl \rightarrow Cl{-}SCH_3 + Cl^- \qquad \text{(reaction 7)}$$

$$PH_2^- + CH_3S{-}PH_2 \rightarrow H_2P{-}SCH_3 + PH_2^- \qquad \text{(reaction 8)}$$

$$CH_3O^- + (CH_3)_2CHS{-}OCH_3 \rightarrow CH_3O{-}SCH(CH_3)_2 + CH_3O^- \qquad \text{(reaction 9)}$$

Comparison of reactions 1a−c shows little effect due to substituent bulk. This may reflect, among other things, the relatively uncrowded environment around sulfur, which is known to accommodate up to six substituents (in SF6, etc.) and for which a number of tetravalent and pentavalent organic species have been characterized.[22] We would thus expect steric effects of bulky alkyl groups in place of methyl to be minimal; likewise, bulky leaving groups and/or nucleophiles should not perturb the basic reaction profiles as much as in analogous chemistry of first-row species. One further conclusion is that steric

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[37] Bachrach, S. M.; Woody, J. T.; Mulhearn, D. C. *J. Org. Chem.* **2002**, *67*, 8983−8990.

bulk is expected to play an even smaller role in the reactions of analogous selenium and tellurium species.

Undoubtedly, solvent will affect the energetics and perhaps the mechanism of these reactions. In particular, we anticipate that the ion−dipole complexes may not persist in aqueous and other solvent environments. For example, in Jorgenson's classic study of the S_N2 reaction of chloride with chloromethane, the ion−dipole complexes, which are 10 kcal mol^{-1} more stable than isolated reactants, disappear entirely in the solution-phase simulations.[38] Given that the energy differences between the IDCs and the TSs for many of the reactions examined here are small, a gross change in the topology of the potential energy surface for these reactions may occur in the solution phase. We did observe a change in mechanism between the gas (addition−elimination) and solution (S_N2) phases for the reaction of HS^- with CH_3SSH.[18,31] Caution is advised in attempting to extrapolate gas-phase results to the solution phase.

The one example in which a significant departure from the usual mode of reaction was observed is the cyanide anion/sulfinyl cyanide reaction. This combination of nucleophile and leaving group was not examined in our previous study of the sulfenyl reactions.[20] Cyanide differs from the other leaving groups considered in that it lacks any lone pairs α to S in the reactant. Thus, cyanide does not function as a π-donor; indeed, it functions as a π-acceptor, pulling electron density from the lone pair on sulfur into its π^*-orbital. Addition of a nucleophile to the S(O) center presumably diminishes this potentially stabilizing S−C π-interaction, raising the energetic cost sufficiently to place the energy of the tetracoordinate complex above the energy of the ion−dipole complex and indeed giving a transition state in place of a local minimum for the C_s geometry.

The mechanism for reaction 2 is not completely resolved. At MP2/6-31+G*, its PES is characterized by having an entrance and exit ion−dipole complex sandwiching a single symmetrical transition state. This is indicative of a classic S_N2 mechanism. The two B3LYP computations add mirror image intermediates (**INT-2**) on either side of and very near the C_s transition state (**TS2-2**). This necessitates the existence of a transition state connecting **IDC-2** with **INT-2**, that being **TS-2**. This creates a quadruple-well PES (Scheme 1d). However, the electronic energy difference between **INT-2** and **TS2-2** is very small. One might question whether **INT-2** is not simply an artifact of the DFT method. Furthermore, inclusion of zero-point vibrational energy actually makes **INT-2** higher in energy than **TS2-2**. Effectively, the surface about **TS2-2** is flat. Since **TS-2** lies only slightly above **IDC-2**, the entire surface resembles the PES shown in Scheme 1b, an example of an extreme addition−elimination mechanism. We cannot, therefore, conclusively determine what the nature of the mechanism is for reaction 2. Further examinations of nucleophilic substitution at sulfur where the nucleophile either lacks lone pairs or is a delocalized anion are currently underway in our laboratory.

The most common function of sulfinyl derivatives in synthesis is as chiral auxiliaries. The sulfinyl group is often introduced via nucleophilic substitution on sulfinate esters, amides, etc. that occurs with inversion of stereochemistry at the sulfur center. This observation has led many chemists to consider such a reaction to proceed according to the S_N2 mechanism, which invokes stereoinversion. Our computations indicate an S_N2 pathway (perhaps) only for the cyanide case. The other reactions, where the nucleophile is a localized anion possessing a lone pair, follow an addition−elimination pathway. Strict stereoinversion along this route demands that the intermediate avoid pseudorotation. This can result if the barrier for pseudorotation is higher than the barrier for dissociation of the leaving group or if the lifetime of the intermediate is short. Studies of these issues are ongoing and will be reported in due course.

Conclusions

Nucleophilic substitution at sulfur in sulfinyl derivatives proceeds through an addition−elimination pathway when the nucleophile and leaving group is a localized anion possessing a lone pair (reactions 1, 3−6). This is in accord with previously predicted pathways for substitution at sulfur in sulfides, disulfides, and trisulfides. In fact, the oxidation state of sulfur has little effect on the PES or geometry of the intermediate. The depths of the wells associated with the intermediates for reactions of sulfenyl and sulfinyl analogues are very similar. Both systems have intermediates that are trigonal bipyramidal with the nucleophile and leaving group in apical positions. The mechanism for the reaction where the nucleophile and leaving group is cyanide is unclear: MP2 predicts an S_N2 mechanism while DFT predicts an addition−elimination mechanism with no barrier toward formation of the tetracoordinate intermediate. Further studies are proceeding to attempt to generalize the conditions necessary for the S_N2 mechanism to operate for nucleophilic substitution at sulfur.

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Supporting Information Available: Relative energies of the critical points for reactions 1−6 at HF/6-31+G*, MP2/6-31G*, B3LYP/6-31G*, and B3LYP/aug-cc-pVDZ (Table S1) along with the coordinates of all optimized structures, their absolute energies, and number of imaginary frequencies. This material is available free of charge via the Internet at http://pubs.acs.org.

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[38] Chandrasekhar, J.; Smith, S. F.; Jorgenson, W. L. *J. Am. Chem. Soc.* **1984**, *106*, 3049−3050.