

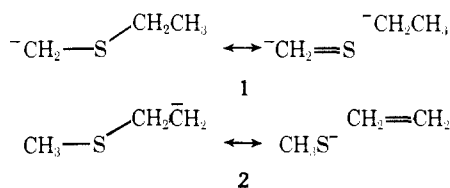
Regarding the Mechanism of C-H Bond Acidification by Sulfur

Sir:

Recent theoretical studies have presented convincing evidence for the unimportance of d-orbital participation in the acidification of C-H bonds α to sulfur atoms.^{1,2} In addressing the question of how an α sulfur atom stabilizes a carbanion, Streitwieser and Williams have emphasized the polarizability of sulfur.¹ Epitotis, Yates, Bernardi, and Wolfe, on the other hand, have developed a hyperconjugative model, involving delocalization of the unshared pair on carbon in $^-CH_2-S-R$ into the low lying S-R antibonding orbital.³ Lehn and Wipff have discussed both polarizability and hyperconjugation in the analysis of their SCF calculations on carbanions.⁴ However, since the hyperconjugative model so nicely rationalizes the preferred stereochemistry (antiperiplanar to the S-R bond) for carbanion formation adjacent to sulfur, the importance of the polarization effect in acidification of C-H bonds might be questioned. In this communication we present evidence, both experimental and theoretical, that polarization of the C-S σ bond is crucial in accounting for the *regiochemistry* of C-H acidification by sulfur.

Since carbon and sulfur are of comparable electronegativity, the hyperconjugative mechanism for carbanion stabilization implies that an R-S antibonding MO should be able to stabilize carbanions both α and β to sulfur. This is illustrated with resonance structures of the hyperconjugative type for the anions formed by deprotonation of the α (**1**) and β (**2**) methyl groups in methyl ethyl sulfide (Scheme I). A preference for deprotonation at the β methyl might even be suggested, based on the relative energies of the no-bond resonance contributors.

Scheme I



This prediction of the hyperconjugative model is not borne out by exchange studies on 2,2-dimethyl-1,3-dithiane (**3**),⁵ a system prejudiced in favor of forming carbanions β to sulfur. Dithiane **3** was equilibrated in partially deuterated diethylamine in THF using the lithium amide as the basic catalyst. Under these reaction conditions 1,3-dithiane equilibrates rapidly at C-2 and exists partially as the 2-lithio species at equilibrium (pK_a (C-2 H, 1,3-dithiane) = 30.7,⁶ pK_a (Et₂NH) = 30.4,⁶ relative to Ph₃CH, which is assigned a pK_a value of

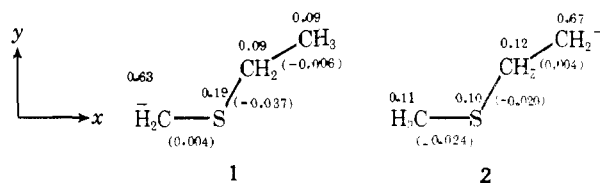


Figure 1. Differences between Mulliken atomic charges in methyl ethyl sulfide and anions **1** and **2**, for methyl groups, methylene groups, and sulfur atoms. Differences in total overlap populations between heavy atoms are shown in parentheses.

30.67). Dithiane **3**, which lacks hydrogens at C-2, exchanges only slowly under these conditions, and no dithianyllithium species were present, as judged from the lack of isotope ratio changes associated with H₃O⁺ vs D₃O⁺ quenching. Deuterium incorporation was determined by comparison of the NMR and mass spectra before and after equilibration (Table I). Greater than 94% of the D incorporation is at C-4 and C-6; <3% is at the C-2 methyl groups.

To confirm that preferred exchange α to sulfur is not a consequence of solvation or ion-pairing effects, we carried out ab initio SCF calculations at the STO-3G level on methyl ethyl sulfide and carbanions **1** and **2**. The same standard geometry⁸ was used for all three calculations and the proton antiperiplanar to the C-S bond was removed in **1** and **2**. The minimal basis set, the lack of CI, and the assumption of a standard geometry all represent approximations that mandate caution in taking the calculated energy difference between **1** and **2** as more than a semiquantitative indication of their relative energies in the gas phase. Nevertheless, the calculations show **1** to be more stable than **2** by 7.1 kcal/mol,⁹ in qualitative agreement with the experimental regioselectivity of exchange.

The origin of the calculated preference for removal of a proton α , rather than β , to sulfur is apparent in the differences

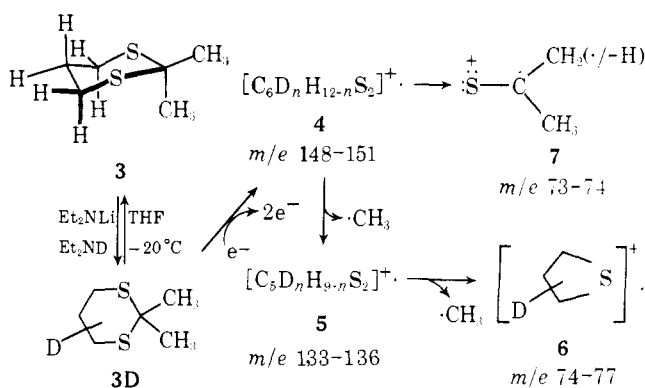


Table I. Equilibration of Dithiane **3** in Et₂ND-THF

Conditions ^a	NMR integrals for 3D , ^b Me: α -CH ₂ : β -CH ₂	Fragment	Isotope Distribution ^c			
			<i>d</i> ₀	<i>d</i> ₁	<i>d</i> ₂	<i>d</i> ₃
5.0, 5.0; 20 h, 50% residual NH	6.00:3.72:2.06	4	75	23	2	<2
6.4, 9.0; 115 h, 10% residual NH	6.00:2.83:2.16	5	75	21	4	<2
		4	24	40	30	6
		5	24	41	29	6
		6	<i>d</i>	<i>d</i>	~27	~9
3.2, 35; 115 h, ^{e,f}	6.00:2.25:2.13	4	10	30	43	16
10% residual NH		5	10	32	42	15
		6	<i>d</i>	<i>d</i>	~37	~22

^a All reactions were run at -20 °C for the time indicated. The amount of residual NH in Et₂ND is indicated. The millimoles of Et₂NLi and Et₂ND employed per millimole of **3** are indicated in the first two entries for each run. An additional four runs under various conditions give comparable results. ^b The Me resonance integral was assumed to represent six protons in each case, estimated error ± 0.1 H. ^c Estimated error $\pm 3\%$. ^d These cannot be determined accurately owing to contributions by both **6** and **7** at *m/e* 73, 74, and 75. ^e Exchange is slow; in this run the deuterium content is 52% of that expected at equilibrium. ^f Recovery of purified (column chromatography) dithiane **3** was >80%.

between the Mulliken atomic charges in methyl ethyl sulfide and in the anions **1** and **2** (see Figure 1).

The CH₂ group at the carbanionic center bears 0.04 less negative charge when it is α to sulfur than when it is β . This is surely a consequence of the fact that the sulfur atom next to the carbanionic center in **1** bears 0.07 more negative charge than the methylene group adjacent to this center in **2**. Nevertheless the hyperconjugative stabilization of the carbanion is also apparent, for the π bond order between the p_y orbitals on the carbanionic center and sulfur increases by 0.10, while the p_y-p_y bond order between sulfur and the methylene carbon decreases by 0.03 in **1**.

The hyperconjugative mechanism appears to be even more important for stabilization of **2**, where the bond order between the p_y orbital at the carbanionic center and p_y at the adjacent carbon increases by 0.17 on carbanion formation,¹⁰ 70% more than the corresponding π bond order in **1**. Since the C-C bond is shorter than the C-S bond, the π overlap integral for the C-C bond is greater (0.171 vs. 0.116) than that for C-S. Thus, the increase in π overlap population between carbanionic center and adjacent atom is nearly three times as large in **2** as in **1**. Nevertheless, it is clear from the relative energies computed for **1** and **2** that the apparently greater hyperconjugative stabilization of the latter anion is not sufficient to overcome the larger stabilization of the former by polarization of the C-S bond.¹¹ Therefore, we conclude that, while hyperconjugation accounts for the stereochemical aspects of C-H bond acidification by sulfur, the polarizability of the C-S σ bond at the carbanionic site accounts for the regiochemistry.

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5. H. T. Kalf and E. Havinga, *Recl. Trav. Chim., Pays-Bas*, **81**, 282 (1962).
6. Unpublished results of N. H. Andersen and A. D. Denniston.
7. The pK_a value for Ph₃CH is for Me₂SO solutions with K⁺ as the counterion (F. G. Bordwell, J. E. Bares, J. E. Bartmess, G. E. Drucker, J. Gerhold, G. J. McCollum, M. VanDer Puy, N. R. Vanier, and W. S. Matthews, *J. Org. Chem.*, **42**, 326 (1977)); under these conditions the pK_a of 2-phenyl-1,3-dithiane is 30.7 but 1,3-dithiane cannot be measured (pK_a > 32.5). Streitwieser¹ reports the following for the Cs-C₆H₁₁NH₂ system: Ph₃CH, pK_a = 31.45; 2-phenyl-1,3-dithiane, pK_a = 29.6; and 1,3-dithiane, pK_a = 31.1.
8. The geometrical parameters were those used by Lehn and Wipff,⁴ including the 97.3° bond angle at sulfur.
9. When d orbitals were included on sulfur, the energy difference between **1** and **2** increased to 9.2 Kcal/mol. Without d orbitals the SCF energy of **1** was calculated to be -508.9250 hartrees. With the inclusion of d orbitals on sulfur it became -509.0056 hartrees. Exponents for d orbitals were taken from B. Roos and P. Siegbahn, *Theor. Chim. Acta*, **17**, 139 (1970).
10. Since these two carbons lie on a line that makes a 12.2° angle with a line parallel to the x axis, the p_y orbitals on these carbons do not overlap in a pure π fashion. The actual change in the π bond order (0.18) between these carbons is, therefore, slightly different from the change in the bond order between the p_y orbitals (0.17).
11. NOTE ADDED IN PROOF. Professor Lehn has pointed out (private communication) that the dominance of polarization over hyperconjugation in the stabilization of carbanions α to sulfur is implicit also in the proton affinities calculated⁴ for the 1-propyl carbanion and the two conformations of the carbanion formed by deprotonation of dimethyl sulfide.

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Lewis Acid Catalyzed Acyl Migration with Optically Active (*Z*)- and (*E*)-1,3-Diphenyl-2-buten-1-one Oxide. Evidence of a Concerted Pathway

Sir:

It is becoming increasingly evident that carbonyl migrations have assumed an important role in biosynthesis. It is now established that conversion of methylmalonyl-SCoA to succinyl-SCoA involves the intramolecular¹ migration of the carbonyl-SCoA group.² A nonenzymatic model for this reaction has been reported by Dowd.³ Similarly, Wemple⁴ has unequivocally proven the intramolecular 1,2 migration of a thiol ester in a biochemically patterned synthesis of tropic acid. We recently provided the first evidence that 1,2-carbonyl migration in the optically active epoxy ester ethyl (*E*)-3-methyl-3-phenylglycidate is a highly concerted process that occurs without loss of optical activity.⁵ Although it has been shown that carbonyl migration⁶ with epoxy ketones⁷ and esters⁸ is intramolecular, the more subtle features of the overall reaction mechanism remain obscure. The questions regarding the concertedness of these acyl rearrangements remain largely unresolved.^{5,8,9}

It was the purpose of the present study to probe for the intermedicity of a carbenium ion in the 1,2 migration of an acyl group by the use of diastereomerically related optically active epoxy ketones which are treated under identical reaction conditions. Two diastereomers, however, can afford a common long-lived cationic intermediate if carbon-carbon bond rotation is rapid resulting in a stereospecific 1,2 shift of a migrating group.¹⁰ If the rearrangement is concerted, different diastereomers need not necessarily give different diastereomeric products, although, if this does occur, then a freely rotating cation may be excluded.^{4c} The combined efforts of Collins,^{10a,11} Cram,¹² Winstein,¹³ and others¹⁴ all concur that concerted 1,2 migrations must be attended by complete stereospecificity. If a stereoselective reaction is observed, where even a minor amount of retention accompanies inversion, then a concerted pathway is not possible. We now report that Lewis acid catalyzed 1,2-benzoyl migration with both (*Z*)- and (*E*)-1,3-diphenyl-2-buten-1-one oxide (dypnone oxide) proceeds in nonpolar solvents with 100% inversion of configuration at the migration terminus excluding a long-lived freely rotating carbenium ion intermediate on the reaction pathway.

Because of the variety of methods available for the conversion of a carbonyl functional group to a ketone, we again intended to use optically pure sodium (+)-(2*S*,3*R*,*E*)-3-methyl-3-phenylglycidate (**1**)⁵ as the precursor to (*E*)-dypnone oxide (**3**). However, all known conversions¹⁵ failed to produce the acid- and base-sensitive epoxy ketone and we were required to develop a new reaction sequence that used a mixed carbonate functional group to activate the carbonyl group. Taking advantage of the water solubility of **1**, the sodium salt was dissolved in a buffered (NaHCO₃) aqueous solution and stirred at an interface with a second phase consisting of an excess of ethyl chloroformate dissolved in ethyl ether containing tri-*n*-propylamine. The resulting mixed carbonate **2** (93%) ([α]_D²⁵ 126.2° (*c* 1.63, CHCl₃); IR (neat)¹⁶ 1830, 1765 cm⁻¹; NMR

