Conformational Preference of an α-Sulfinyl Carbanion

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Abstract: The rates of base-catalyzed H–D exchange of the protons α to a sulfoxide group have been measured in three conformationally fixed sulfoxides. Studies on the bridged biaryl sulfoxide (**1**) reveal rates which differ 1000-fold for two protons which differ by only 40° in their dihedral angular orientation with respect to the sulfoxide group. A striking effect of solvent is noted in that the proton trans to the lone pair on sulfur exchanges four times faster than that trans to the S–O bond in *tert*-butyl alcohol-*O-d*, but 250 times slower in CD_3OD. Studies on the exo and endo isomers of 2-thiabicyclo[2.2.1]heptane 2-oxide show that formation of the carbanion eclipsed with the lone pair on sulfur is much slower than that eclipsed with oxygen. The divergence of these results from predictions made on the basis of *ab initio* MO calculations is attributed to the inability of the calculations to include the effects of solvation.

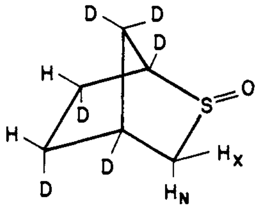
Interest in the stereochemical aspects of the reactivity of α-sulfinyl carbanions was initiated by the research of Cram and coworkers.[1] They studied the relative rates of exchange (k_e) *vs.* racemization (k_α) at the 2 position of 2-octyl phenyl sulfoxide in comparison with the corresponding sulfone and phosphine oxide as well as several other derivatives at the sulfur and phosphorus atoms. Their findings that sulfinyl sulfur provides only a slight tendency to maintain asymmetry at the α carbanion (k_e/k_α varied from 3.6 to 0.6 in two solvents) are in contrast with those of Rauk, Buncel, Moir, and Wolfe[2] on the behavior of benzyl methyl sulfoxide. The benzylic methylene protons were found to differ in their relative rates of base-catalyzed exchange by 16:1 in D_2O.[3] Other reports describing stereoselective exchanges in acyclic sulfoxides followed.[4] The cause of this stereoselectivity has been examined by carrying out extensive *ab initio* MO calculations[5] on the hypothetical model $^-CH_2S(O)H$. Calculation of the energy of this species as a function of rotation about the C–S bond led Wolfe, Rauk, and Csizmadia to conclude that the most stable conformation is the one in which the carbanion bisects the internal oxygen–sulfur–lone pair angle (see Figure 2, conformer A).

Several groups of workers[6–8] have tested the predictions of this theory by determining carbanion stabilities as a function of stereochemistry in conformationally fixed sulfoxides. In one of the studies[7] appreciable solvent effects were noted. Perhaps a more striking effect of solvent on the stereochemical course of the exchange was observed with benzyl methyl sulfoxide.[9] By conducting the exchange in *tert*-butyl alcohol-*O-d* (lithium *tert*-butoxide) the *RR* (*SS*) diastereoisomer, opposite in configuration to that produced in D_2O (NaOD), is formed more rapidly by a ratio of 4.5:1. This same diastereoisomer was produced stereoselectively in a ratio of 15:1 by treatment of the sulfoxide in THF with methyllithium followed by quenching with D_2O.

Already one practical application of this stereoselectivity has been demonstrated by Durst and coworkers[10] who have synthesized an optically active epoxide *via* the carbanion of optically pure benzyl methyl sulfoxide.

In this paper we will describe the extension of our previous work[6] on the exchange of the α protons in the biaryl sulfoxide **1** to include effects of solvent. In addition, results of exchange studies on two other rigid sulfoxides, the hexadeuterated exo (**2**) and endo (**3**), isomers of 2-thiabicyclo[2.2.1]heptane 2-oxide, will be presented.

Stereochemical Proton Assignments. In order to determine the stability of the α-sulfinyl carbanion as a function of its dihedral angular relation to the sulfoxide group, an unambiguous assignment for the signals due to each α proton is required. In **1** the assignments have been determined[11] by nuclear Overhauser effects in conjunction with the geminal coupling constant data. The dihedral angular relations of the four benzylic protons with respect to the sulfoxide group were measured on a Dreiding model and are depicted in Figure 1. The formulas for **2** and **3** depict the orientations of their α protons. Proton assignments were made on the basis of long-range couplings[12] and confirmed by



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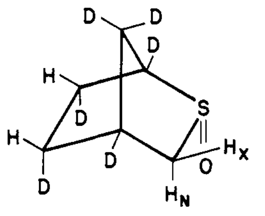

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(1) (a) D. J. Cram, R. D. Trepka, and P. St. Janiak, *J. Amer. Chem. Soc.*, **88**, 2749 (1966); (b) D. J. Cram and S. H. Pine, *ibid.*, **85**, 1096 (1963).

(2) A. Rauk, E. Buncel, R. Y. Moir, and S. Wolfe, *ibid.*, **87**, 5498 (1965).

(3) The stereochemistry of the more rapidly formed monodeuterated diastereoisomer has been shown to be *RS* (*SR*) by J. E. Baldwin, R. E. Hackler, and R. M. Scott, *Chem. Commun.*, 1415 (1969).

(4) (a) E. E. Bullock, J. M. W. Scott, and P. D. Golding, *ibid.*, 168 (1967); (b) M. Nishio, *ibid.*, 562 (1967).

(5) (a) S. Wolfe, A. Rauk, and I. G. Csizmadia, *Can. J. Chem.*, **47**, 113 (1969); (b) *J. Amer. Chem. Soc.*, **89**, 5710 (1967).

(6) R. R. Fraser and F. J. Schuber, *Chem. Commun.*, 397 (1969).

(7) B. J. Hutchinson, K. K. Andersen, and A. R. Katritzky, *J. Amer. Chem. Soc.*, **91**, 3839 (1969).

(8) R. Lett and A. Marquet, *Tetrahedron Lett.*, 2851, 2855, 3255 (1971).

(9) T. Durst, R. R. Fraser, M. R. McClory, R. B. Swingle, R. Viau, and Y. Y. Wigfield, *Can. J. Chem.*, **48**, 2148 (1970).

(10) T. Durst, R. Viau, R. Van den Elzen, and C. H. Nguyen, *Chem. Commun.*, 1334 (1971).

(11) R. R. Fraser and F. J. Schuber, *Can. J. Chem.*, **48**, 633 (1970). The proton assignments reported herein reversed the earlier tentative assignments[6] for H_1 *vs.* H_4 and H_2 *vs.* H_3.

(12) R. R. Fraser and Y. Y. Wigfield, *Chem. Commun.*, 1471 (1970).

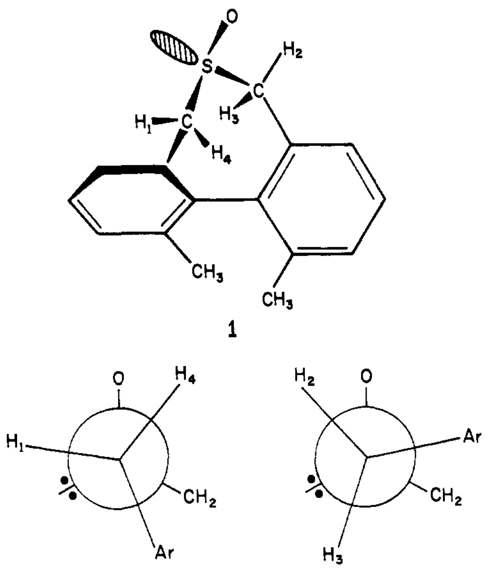

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Figure 1. A three-dimensional representation of 1,11-dimethyl-5,7-dihydrodibenz[*c,e*]thiepin 6-oxide (**1**). Below, the Newman projection formulas for the two C–S bonds in **1** show the orientations of the four benzylic protons.

solvent effects[13] and the effects of added shift reagent[12, 13] on the nmr spectra of **2** and **3**.

Kinetic Measurements. All the rate measurements reported herein have been determined by integration of the nmr absorptions of individual protons at given time intervals. In the studies of **1** in *tert*-butyl alcohol-*O-d*, the half-lives of the four benzylic protons were so different that under conditions where exchange of H_2, H_3, and H_4 could be monitored readily, the slow proton, H_1, exchanged too slowly for a convenient determination of its rate. In addition, curvature in the first-order plot of its exchange indicated the occurrence of a decrease in the concentration of base with time. This curvature was eliminated by determining the relative rate H_1/H_2 at a much higher concentration of base. For the studies in CD_3OD the ratio of the rates of exchange of H_2 *vs.* H_3 and H_4 were measured at 30° while the rates of exchange of H_1 and H_4 were determined at 60°. The observed rate ratios were adjusted to give the overall rates of exchange of H_2, H_3, and H_4 relative to H_1. In all cases good first-order plots were obtained for at least five measurements of each proton at appropriate time intervals.[14] The adjusted relative rates are recorded in Table I. Because of the interference by solvent in the region of H_1 as well as instrumental limitations, the nmr integration technique gives an accuracy of only ±10% in the determination of rate constants in *tert*-butyl alcohol-*O-d*,[16] and ±6% in CD_3OD.

Table I. Rates of Exchange of α Protons in **1**

Solvent system	Molarity of base	Rates[a] of exchange H1	H2	H3	H4
tert-Butyl alcohol-*O-d*	0.05	0.27		82	
($K^+\bar{O}$-*t*-Bu)	0.025		88	26	96
	0.005		6.8	2.3	7.9
	Relative rates	1	1100	300	1300
CD_3OD	1.0[b]	0.093[b]			2.6[b]
($CD_3\bar{O}Na^+$)	1.0		0.256	9.6	0.039
	Relative rates	1	200	7600	30

[a] Pseudo-first-order rate constants ($\times 10^5$ sec^{-1}). Exact rate constants cannot be obtained from these data as the order in base is not integral but is approximately 1.5. [b] This experiment was conducted at 60°. All others were conducted at 30°.

Exchange of the α protons in **2** and **3** could only be done in methanol-*O-d*, because decomposition occurred in *tert*-butyl alcohol-*O-d*. Since the reaction had to be conducted at a high temperature in a sealed tube, the relative rates were obtained from integral measurements on quenched samples. The relative rates of exchange of the α protons in **2** and **3** are presented in Table II.

Discussion

Proper evaluation of the results of exchange of **1** requires a comparison of H_1 *vs.* H_2 and H_3 *vs.* H_4 only. The protons in each of these pairs reside in identical environments with respect to the asymmetric biaryl system.[17] Thus the steric and electronic influences of the benzene rings on the rates of exchange of H_1 and H_2 (and H_3 and H_4) will be equal. Any difference in reactivity within either pair can only be attributed to the influence of the sulfoxide group on the stability of the transition states resulting from proton abstraction.[18] This difference is a reflection of the stereochemically dependent stabilizing effect of the sulfoxide group.

Before discussion of the experimental results it will be helpful to introduce a classification of the staggered conformations of the α-sulfinyl carbanion. As depicted in Figure 2, the electron pair may be oriented on the bisector of the oxygen–sulfur lone pair angle (A), trans to the oxygen atom (B), or trans to the lone pair

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[13] R. R. Fraser, T. Durst, M. R. McClory, R. Viau, and Y. Y. Wigfield, *Int. J. Sulfur Chem.*, **1**, 133 (1971).

[14] The equations necessary for exact analysis of this and similarly complex kinetic schemes are given by D. H. Hunter and R. W. Mair, *Can. J. Chem.*, **47**, 2370 (1969). From these equations it can be shown that the exchange of any proton H_A obeys the first-order law, $A = A_0e^{-k_At}$, if it is assumed that the secondary isotope effect, $i = 1$. The exact equations also provide a method for estimating i from the relative intensities of the two monodeuterio derivatives at a given time of reaction. From more accurate data on exchange of the sulfone related to **1** i was found to be 1.2 ± 0.2.[15] For the purpose of this paper the assumption of $i = 1$ will not alter the significance of the results.

[15] R. R. Fraser and F. J. Schuber, *Chem. Commun.*, 1474 (1969).

[16] The change in deuterium content of the isotope pool as the reaction progresses has a negligible effect, the *tert*-butyl alcohol-*O-d* being 99.3% d_1 at the start and 96.8% d_1 after complete exchange of all four benzylic protons.

[17] Proof of these relationships was obtained by reaction of selectively deuterated **1** with Meerwein's reagent, followed by hydrolysis to give the sulfoxide of inverted configuration at sulfur; see ref 11, p 636.

[18] If it is assumed that two carbanions are formed by abstraction of H_1 and H_2 and that the Brønsted relation $\log k/k_0 = \rho\Delta pK$, where ρ is estimated to be 0.7 (D. J. Cram and W. D. Kollmeyer, *J. Amer. Chem. Soc.*, **90**, 1791 (1968)), then the free energy differences in carbanion stabilities will be 1/0.7 or 1.4 times greater than the differences in transition state free energies. It has been suggested that the benzene ring in benzyl methyl sulfoxide ought to favor a carbanion having sp^2 hybridization.[3] Other considerations indicate this need not be so. The methyl protons of benzyl methyl sulfoxide underwent exchange at about $^1/_{1000}$th the rate of the methylene protons[2] (average value). At least half of the acceleration in kinetic acidity by a benzene ring is considered to be inductive in origin.[19] Thus a 30-fold enhancement in kinetic acidity by resonance with a benzene ring may not be sufficient to cause significant rehybridization of the carbanion. In the rigid sulfoxide **1** sp^2 hybridization is even less likely since the benzylic protons lack the proper orientation ($\theta = 0°$) for overlap with the adjacent π system. H_1 and H_2 are almost orthogonal to the π orbitals of the benzene ring ($\theta = 70°$) while H_3 and H_4 have $\theta = 50°$. As a result effective overlap cannot occur without an appreciable conformational change. Although direct evidence regarding carbanion hybridization is lacking it is logical to assume that, since the carbanion is in a totally asymmetric environment, it would be expected to be asymmetric (*i.e.*, not sp^2).

[19] A. Streitwieser, Jr., and D. E. Van Sickle, *J. Amer. Chem. Soc.*, **87**, 5250 (1965).

Table II. Relative Rates of Exchange of α Protons

Compound	Solvent, M^+	Result	Order	Ref
1	t-BuOD, K^+	$H_1/H_2 = 1/1100$		
		$H_3/H_4 = 1/4$	C > B	*a*
	CD_3OD, Na^+	$H_1/H_2 = 1/200$		*a*
		$H_3/H_4 = 250/1$	B > C	*a*
4-Phenylthiane *S*-oxides	CD_3OD, Na^+		B > A > C	7
	D_2O, Na^+		B > A > C	7
	DMSO-CD_3OD, Na^+		B ∼ C ∼ A	7
	t-BuOD, Na^+		B ∼ C ∼ A	7
Tetrahydrothiophene *S*-oxides	D_2O, Na^+		B > C, B > A	8
Benzyl alkyl sulfoxides	THF, Li^+		A > B > C	*b*
Theory	Gas phase		A > B > C	5
2	CD_3OD, Na^+	$H_X/H_N \geq 12/1$		*a*
3	CD_3OD, Na^+	$H_X/H_N = 1/2.5$		*a*

[a] This work. [b] Private communication, T. Durst and M. McClory.

(C). To a first approximation, the carbanions derived from abstraction of protons H_1 to H_4 can be classified as A (H_1 and H_2), B (H_3), and C (H_4) as is evident in Figure 1.

The rate ratio for the exchange of protons H_3 and H_4 in **1** shows a very large solvent dependence. H_3/H_4 is less than one (B < C) in *tert*-butyl alcohol-*O-d* but is much greater than one (B ≫ C) in CD_3OD. These results are similar to those reported by Katritzky and coworkers[7] for the isomeric 4-phenylthiane S-oxides. They observed the same type of stereoselectivity to a lesser extent in CD_3OD[20] and in D_2O. However, in DMSO-CD_3OD and in *tert*-butyl alcohol-*O-d* no stereoselectivity was found. Our results are also in agreement with the qualitative findings of Lett and Marquet[8] who observed B > C or A in D_2O.

The observation of markedly different rates of exchange of H_1 and H_2 in **1** is particularly surprising. In spite of only a 40° difference in their orientations (both leading to type A carbanions) these two protons exchange with rate ratios of 200/1 and 1000/1, depending on solvent. Exchange which produces the carbanion closer to the lone pair on sulfur occurs much more slowly in both solvents. The results of our exchange experiments and those of other workers appear in Table II along with the predictions of theory.[5]

Exchange experiments on the bicyclic sulfoxides **2** and **3** require the consideration of both steric and electronic effects for proper interpretation. Since it is well known that attack at the exo face of a [2.2.1] system is sterically preferred,[22] it is not surprising that the only detectable exchange at C-3 in **2** occurred in the exo position, the limits of accuracy of the integration technique giving $k_{exo}/k_{endo} \geqslant 12$. The relative rates of exchange in **3** were $k_{exo}/k_{endo} = 0.4$. In this latter exchange the steric and electronic effects are in competition, the electronic effect being 2.5 times stronger. If we assume that both steric and electronic effects are equal in **2** and **3** then the results indicate $(k^{120°}/k^{0°})_{electronic} \geqslant 5.4$[23] and $(k_{exo}/k_{endo})_{steric} \geqslant 2.2$. That the electronic preference for abstraction of the proton syn to the S–O bond is very likely much greater than 5.4 is indicated by the small lower limit for the steric effect. In studies[24] on the isotopic exchange of four different bicyclo[2.2.1]-heptan-2-one derivatives, the lowest selectivity for abstraction of the exo *vs.* endo protons at C-3 was 20/1 in the case of camphor. In norbornanone exo abstraction was favored by 715 to 1. If we assume that exo abstraction is preferred in **2** and **3** more than in camphor, say by 100 to 1, then the electronic preference for abstraction of the proton cis to S–O is at least 250 to 1. This estimate, in conjunction with the ratio H_1/H_2 in **1**, indicates that the carbanion stability decreases rapidly as it approaches an eclipsing situation with the lone pair on sulfur.

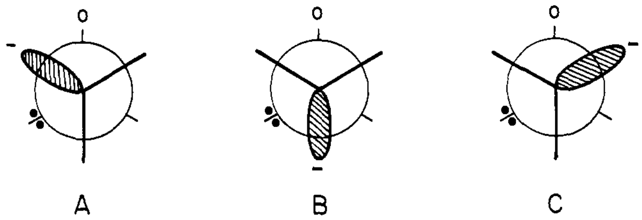

Figure 2. The Newman projection formulas representing the three staggered conformations of an α-sulfinyl carbanion.

The rates of exchange of the protons in **1**, **2**, and **3** show no correlation with the theoretical predictions based on *ab initio* MO calculations. The fact that a change in solvent can completely reverse the relative reactivities of H_3 and H_4 effectively demonstrates the role of solvent to dominate over the dihedral angular relation of carbanion to sulfoxide in determining the ultimate stereochemical influence on reactivity. The orders of reactivity of H_1/H_2 and H_{exo}/H_{endo} are both at odds with the theoretical predictions as well. The MO calculations do concur with experimental findings in the sense that a very large variation in carbanion stability (12.8 kcal/mol) *vs.* dihedral angle is found.

It has been suggested[25] that results obtained by the kinetic exchange method fail to constitute a valid test of the stability of α-sulfinyl carbanions in that knowl-

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(20) Recalculation of the data given for the exchanges in CD_3OD[7] indicates the reported rate constants to be in error, the selectivity being substantially less than that quoted. We calculated B > A by 5:1 and A > C by 2:1 from both the tabulated and the graphical data on the exchange in methanol-*O-d*. The higher selectivity in **1** may be observable because of its completely rigid conformation[21] and slightly different carbanion orientations.

(21) K. Mislow, M. A. W. Glass, H. B. Hopps, E. Simon, and G. H. Wahl, Jr., *J. Amer. Chem. Soc.*, **86**, 1710 (1964).

(22) H. C. Brown and J. Muzzio, *ibid.*, **88**, 2811 (1966).

(23) The angle given in the superscript represents the dihedral angle between the carbanion and the lone pair on sulfur.

(24) T. T. Tidwell, *J. Amer. Chem. Soc.*, **92**, 1448 (1970).

(25) S. Wolfe, A. Rauk, L. M. Tel, and I. G. Csizmadia, *J. Chem. Soc. B*, 136 (1971).

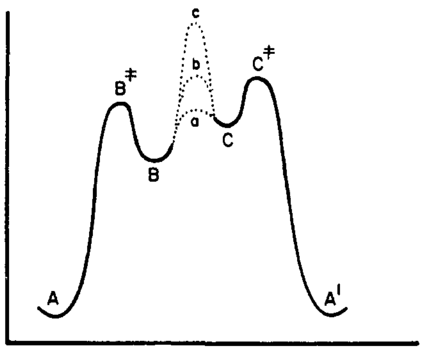

Figure 3. A free energy–reaction coordinate diagram representing the formation of two diastereotopic α-sulfinyl carbanions.

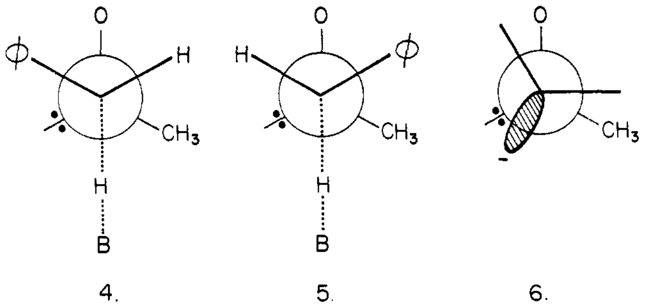

Figure 4. The Newman projection formulae of benzyl methyl sulfoxide showing abstraction of the "pro-*R* in *S*" proton (**4**), the "pro-*R* in *R*" proton (**5**), and the most stable α-sulfinyl carbanion (**6**).

edge of the stereochemical fate of the carbanion subsequent to its formation is lacking. The stereochemical fate of the carbanion is undoubtedly an important and interesting aspect of the mechanism of exchange. However, we wish to show by logical arguments that lack of such knowledge in no way invalidates the kinetic method of determining carbanion stabilities.

The assumption upon which the success of the kinetic method rests is adherence to the Brønsted equation, which in our case requires each transition state free energy to resemble that of the carbanion being formed. For a stereoselective exchange of protons in a methylene group the free-energy reaction coordinate diagram will appear as in Figure 3. In every stereoselective exchange process the more reactive proton *must exchange predominantly with retention.* If inversion were the course no stereoselectivity could be observed. The slower proton then has the possibility of exchanging (a) with inversion, (b) with racemization, or (c) with retention. These three possibilities will be determined simply by the height of the barrier to carbanion inversion as labeled for cases a, b, and c. In each instance, although the stereochemical pathways differ, the relative amounts of deuterated products will be determined solely by the relative heights of the two transition states $B^{\ddagger}$ and $C^{\ddagger}$ in Figure 3. This follows from a consideration of the steady-state rate equations which are given in the Appendix.

There is one situation for which the above analysis is not valid. This could occur when the rate of solvent reorganization necessary for exchange with retention (k_e) is very slow. Then inversion to a less stable carbanion (k_α) followed by deuteration could be a favored path for either proton.[26] This would cause the exchange rates for the two protons to be equal in spite of unequal carbanion ion stabilities. The probability for this taking place in protic solvents seems low in view of our results and those of Cram and Pine[1b] who found $k_e/k_\alpha > 1$ for exchange of both stereoisomeric 2-octyl phenyl sulfoxides in *tert*-butyl alcohol-*O-d*.

The most remarkable selectivity of all in sulfoxide exchanges is actually that observed for benzyl methyl sulfoxide in D_2O, the rate ratio being 16:1 for the benzylic protons in spite of the fact that the sulfoxide has no conformational rigidity. It is interesting to speculate on the reasons for this behavior.[27] According to the Curtin–Hammett principle,[28] the rates of exchange of the diastereotopic protons in benzyl methyl sulfoxide will be determined *solely* by the stabilities of the two transition states leading to the two carbanions and will be independent of the relative energies of the rapidly interconverting ground-state conformations. Let us assume that each proton is exchanged *via* a carbanion having the same dihedral angular relation to the sulfoxide group. Of the three possible staggered carbanion conformations only one predicts the observed preferential formation of the (*RS*)-monodeuterated sulfoxide (in D_2O). As shown in Figure 4 removal of the "pro-*R* in *S*" proton will be preferred due to the presence of fewer nonbonded interactions in the derived carbanion **4** than in the diastereomeric carbanion **5**. The difference in energies, *i.e.*, one gauche phenyl/methyl interaction, may be estimated from data on 2-phenyl-1,3-dithiane.[29] The preference of phenyl for the equatorial position was found to be 1.7 kcal/mol indicating one gauche phenyl/methyl interaction to be 0.85 kcal/mol. This estimated energy difference between **4** and **5** is not sufficient to account for the observed selectivity. In all probability a somewhat nonstaggered conformer such as **6** is involved. Although nonstaggered conformers other than **6** could account for a larger stereoselectivity, the involvement of **6** is supported as well by the fact that it has the same conformation as the carbanion derived from abstraction of H_3 in **1**, and H_3 is the most labile proton in the more polar solvent CD_3OD.

In summary, the rates of exchange of protons α to a sulfoxide group have been found to vary strongly depending upon their orientations relative to the sulfoxide group and upon the solvent used. Justification of the kinetic method of determining carbanion stabilities has been presented, which allows interpretation of these exchange rates in terms of carbanion stabilities. These carbanion stabilities do not coincide with those predicted by MO calculations, presumably because of strong solvation effects.

Experimental Section

The preparation of **1** has been described in an earlier paper.[11] Sulfoxides **2** and **3** were prepared as previously described.[12] All

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[26] It is also possible that internal return (ionization followed by collapse to starting material) is present, particularly in *tert*-butyl alcohol. Such an effect could influence the stereoselectivity.

[27] This rationale has resulted from numerous discussions of the problem with T. Durst and M. McClory.

[28] E. L. Eliel, N. L. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, p 28.

[29] (a) H. T. Kalff and E. Havinga, *Recl. Trav. Chim. Pays-Bas*, **85**, 467 (1966); (b) R. J. Abraham and A. W. Thomas, *J. Chem. Soc.*, 335 (1965).

nmr integral measurements were performed using a Varian HA-100 instrument operating at 30°. The samples of **1** were kept in the probe throughout the reaction except for the determination of the exchange rates of H_1 *vs.* H_4 in CD_3OD. For these measurements the sample was kept in a constant-temperature bath at 60°, except for periodic determination of integrals. In the exchange reaction of **2**, a sample (50 mg) was dissolved in 0.5 ml of CD_3OD containing CD_3ONa (0.3 *M*) in a heavy-walled Pyrex tube. The tube was sealed and heated for 72 hr at 120°, cooled, and opened. The solvent was distilled off and the residue was sublimed to give a pure sample of **2** whose nmr spectrum showed that 58.5% exchange had occurred in the exo position while no endo exchange was detectable (<0.75%). Under similar conditions (110°, 48 hr in CD_3OD containing CD_3ONa (0.5 *M*)) an exchanged sample of **3** showed that 35% exchange in the endo position and 11% exchange in the exo position had occurred. The nmr spectra of **2** and **3** were measured during simultaneous irradiation of the deuterium atoms with an NMR Specialties SD-100 deuterium spin-decoupler.

Appendix

For a detailed consideration of the rate processes depicted in Figure 3, we can use the following scheme

$$A \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} B \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} C \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} A'$$

in which A and A′ represent the same initial substrate. H-D exchange *via* the step designated by k_3 will produce monodeuterated A′ which is a diastereomer of monodeuterated A resulting from the step designated by k_{-1}.

The differential equations for time-dependent behavior of intermediates B and C are

$$d[B]/dt = k_1[A] + k_{-2}[C] - k_{-1}[B] - k_2[B]$$

$$d[C]/dt = k_{-3}[A] + k_2[B] - k_3[C] - k_{-2}[C]$$

Since B and C are interconverted *via* the carbanion inversion barrier, $k_2[B] = k_{-2}[C]$

$$d[B]/dt = k_1[A] - k_{-1}[B]$$

$$d[C]/dt = k_{-3}[A] - k_3[C]$$

Also, assuming the steady-state equilibrium, then $d[B]/dt = d[C]/dt = 0$ and $k_{-1}[B] = k_1[A]$ and $k_3[C] = k_{-3}[A]$. Now

$$\frac{\text{rate of formation of A}}{\text{rate of formation of A}'} = \frac{k_{-1}[B]}{k_3[C]} = \frac{k_1}{k_{-3}}$$

i.e., since k_1 and k_{-3} involve the same ground states, the difference in the rates of formation of the deuterated species A and A′ is governed solely by the difference in the transition states $B^{\ddagger}$ and $C^{\ddagger}$.

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Conformational Dependence of the Electronic Energy Levels in Disulfides

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Abstract: The energies of extended Hückel molecular orbitals of model disulfides are studied as a function of dihedral angle about the S–S bond. Transition energies and oscillator strengths obtained in the virtual orbital approximation, but with exactly evaluated transition moment integrals, satisfactorily match experimental trends. Although the S 3d atomic orbitals are not highly occupied in the ground states of HSSH and H_3CSSCH_3, the inclusion of these orbitals in the basis set increases the number of low-lying excited states appropriate for uv absorption. The lowest energy transition of the disulfide chromophore involves an S–S σ^* virtual MO and lone-pair occupied MO's. Because of the conformational dependence of the latter MO's, the lowest energy transition red-shifts and loses intensity as the dihedral angle is twisted from 90 toward 0 or 180°. An explanation of the spectra of bulky dialkyl disulfides is based on the very weak intensity predicted for the lowest energy transition when the dihedral angle is opened beyond 90°. Calculated barriers to internal rotation are in fair agreement with microwave data on HSSH and H_3CSSCH_3. Insight into the origin of the rotational barrier is provided by population analyses, which show a repulsive interaction of the lone-pair electrons.

The conformation of a disulfide bridge in proteins and other biomolecules can often be deduced from the uv and CD spectra of these molecules. Molecules of known conformation and absolute configuration have been studied spectroscopically, and a correlation has been found between the energy of the lowest energy uv transition and the dihedral angle about the S–S bond. This correlation is exemplified by the data in Table I taken from the literature.[1–8] As the CSSC dihedral angle is opened from 0 to 90°, the absorption maximum of the first uv band shifts from near 370 to

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