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Stereochemistry in the Reaction of Alkylsulfinyl Phenylmethyl Carbanion with Electrophiles

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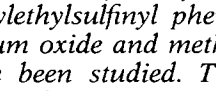
ABSTRACT

Stereochemistry of the reactions of methyl-, ethyl-, 2-propyl-, and 1,1-dimethylethylsulfinyl phenylmethyl carbanions with deuterium oxide and methyl iodide in tetrahydrofuran have been studied. The 2-propylsulfinyl phenylmethyl carbanion exerts abnormal behavior in the sense that the alkyl substituent herein has no ability to freeze the conformation of the carbanion. The results are interpreted in terms of hard and soft interactions. ^{7}Li and ^{17}O nuclear magnetic resonance (NMR) spectroscopy revealed that the carbanions derived from these sulfoxides behave as the oxylate form.

There have been numerous studies on the stereochemistry of α-sulfinyl carbanions [1, 2]. The stereochemistry is not only affected by the attacking electrophile [3] but is also influenced by the solvent [4]. In many cases, the stereochemistry observed was different from that proposed theoretically [5], which emphasizes the importance of the chelating countercation [6] as well as solvation [7] in controlling the stereochemistry of α-sulfinyl carbanions.

After Durst and his co-workers' pioneering report [3], it has been established that deuteriation of the carbanion from methyl (**1**) and 1,1-dimethylethyl (*t*-butyl) (**4**) phenylmethyl sulfoxides in tetrahydrofuran (THF) takes place with the same stereospecificity, whereas the methylation proceeds with different specificity [8, 9]. These results have been interpreted in terms of hard and soft interactions (HASAB principle) [9].



1: R=CH_3
2: R=C_2H_5
3: R=$(CH_3)_2CH$
4: R=$(CH_3)_3C$

The interpretation, however, was largely based on the proposed (and ambiguous) stable conformation of the starting sulfoxide in solution as well as that of the carbanion derived therefrom [10]. Although the conformation of **4** in solution has been established without doubt [11], that of **1** has had no concrete support [12].

Therefore, we have investigated the stereochemistry of the reactions of a series of alkyl phenylmethyl sulfoxides to elucidate the factor that controls which is the reacting face. In this report, we would like to report that the HASAB principle, in combination with the proposed conformations of the carbanions, can explain beautifully the stereochemical results of the reactions. The results also emphasize the important role of the countercation.

RESULTS AND DISCUSSION

The hard face of an α-sulfinyl carbanion has been defined as the face in which the carbanion-lone pair is located between the sulfinyl-oxygen and sulfinyl-lone pair. If either the sulfinyl-oxygen or sulfinyl-lone pair cannot come close to the carbanion-lone pair, then the carbanion-lone pair prefers to be adjacent to the sulfinyl-oxygen [13]. With this conformation, the electron density around the *carbanion* center is the highest, allowing maximum electrostatic interaction with the countercation. Indeed,

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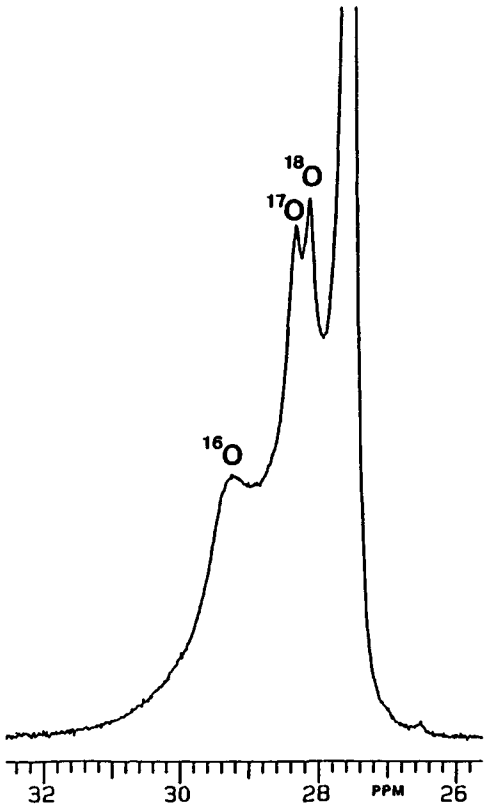


FIGURE 1 ^{7}Li NMR spectrum of $^{17/18}O$-enriched lithium 1,1-dimethylethyl sulfinyl phenylmethylide with the signals for ^{7}Li-^{16}O, ^{7}Li-^{17}O, and ^{7}Li-^{18}O bonds.

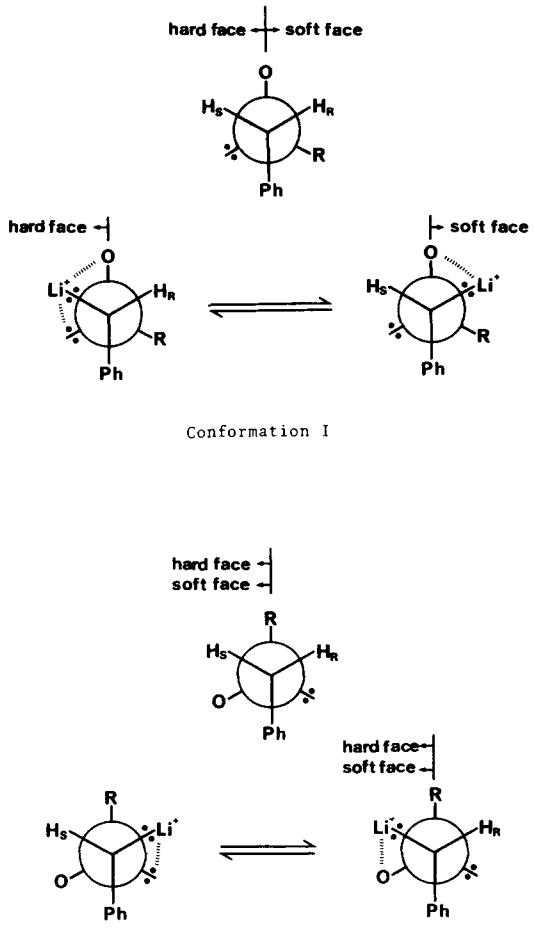
^{7}Li and ^{17}O nuclear magnetic resonance (NMR) spectroscopy revealed that the anionic species prepared by abstraction of a benzylic proton from an alkyl phenylmethyl sulfoxide behaved *not as a carbanion but as an oxylate anion* [10]; i.e., the oxygen-induced chemical shifts of Li were observed in the ^{7}Li NMR spectrum of lithium *t*-butylsulfinyl phenylmethylide (the carbanion derived from $^{17/18}O$-enriched-**4**) as shown in Figure 1, which strongly suggests that the sulfinyl-oxygen is bound to the lithium ion. At the same time, it was found that the ^{17}O-singlet at δ − 15.71 [15] from **4** in the ^{17}O NMR spectrum disappears completely when this sulfoxide is converted into the corresponding carbanion. Although this particular observation itself does not support positively the presence of an oxygen–lithium interaction, there remains no doubt that the electronic environment around the sulfinyl-oxygen has changed very much on the abstraction of the benzylic proton.

The sp^2-configuration and Li-O interaction for the carbanions of this class of compounds have been proposed previously without reasonable scientific evidence [2, 16]. The present results, on the other hand, provide strong support for the predominant oxylate structure of the anion derived from a sulfoxide [17].

The soft face of the carbanion is the face in which the carbanion-lone pair is located *anti* to the sulfinyl-lone pair. The antiperiplanar lone pair on the sulfur atom enhances the nucleophilic character of the carbanion-lone pair by the so-called α-effect [18], so that S_N2-type reactions proceed smoothly from this configuration.

Thus, when the alkyl group is sterically small enough to be adjacent to the phenyl group, the proposed most stable conformation predicts that the hard and soft faces exist on opposite sides of the molecule from each other, whereas when a sulfoxide has a large alkyl group, the stable conformer now has the alkyl group *anti* to the phenyl group. As a consequence, the hard and soft faces of the corresponding sulfinyl carbanion coincide with each other as shown in Scheme 1 [19].

Another conformation in which the phenyl group is located *syn* to both the oxygen and alkyl group need not be taken into consideration because the steric repulsion in this conformation is the highest.



SCHEME 1

TABLE 1 Products from the Reaction of Alkyl Phenylmethyl Sulfoxide with Electrophiles[a,b]

	H_S to H_R Ratio in the Substituted Product					
	Deuteriation		Chem. Yield	Methylation		Chem. Yield
Sulfoxide	H_S	H_R	(%)	H_S	H_R	(%)
1	95	5	55	5	95	67
2	92	8	74	18	82	89
3	95	5	83	42	58	99
4	>99	<1	91	>99	<1	99

[a] See Experimental for detailed reaction conditions.
[b] The sulfoxides that have the S_S-configuration (for **1** and **2**) or S_R-configuration (for **3** and **4**) are represented here for convenience of discussion. However, the experiments were carried out with racemic sulfoxides. For the sulfoxides with S_R-configurations (for **1** and **2**) or S_S-configurations (for **3** and **4**), H_S and H_R should be read as H_R and H_S, respectively.

Deuteriation and Methylation

Table 1 lists the results from deuteriation with deuterium oxide and methylation with methyl iodide in a series of carbanions generated from **1**, ethyl phenylmethyl sulfoxide (**2**), 2-propyl phenylmethyl sulfoxide (**3**), and **4**, respectively, by treating them with butyllithium in THF.

Since the hard face of the carbanion is always the H_S-side, regardless of the conformation, the stereospecificity of the deuteriation is quite high for all of the sulfoxides. It is interesting, however, to note that the specificity decreases from methyl to ethyl, and then increases again (ethyl to 2-propyl to *t*-butyl) with the change in the bulkiness of the alkyl group. This phenomenon seems to reflect the bulkiness-dependent stability of the conformers (see above).

As shown in Scheme 1, conformation I predicts that the soft-soft interaction uses H_R for the substitution reaction, whereas the H_S-side is the reaction face in conformation II. Reflecting this difference, the stereochemistry of substitution with a methyl group takes place on opposite faces of **1** and **4**. Since steric repulsion between the phenyl and the ethyl groups in **2** is larger than that between the phenyl and the methyl groups in **1**, the contribution of conformation II becomes more important in **2** than in **1**. Consequently, opposite soft faces in the conformations I and II compete to decrease the specificity of the substitution on going from **1** to **2**. When a 2-propyl group is introduced on the phenylmethylsulfinyl group to form **3**, the two possible conformations contribute almost equally. Then the substitution occurs on both sides and the stereospecificity of the reaction of this sulfoxide disappears almost completely. Since there is no doubt that **4** is more stable in conformation II [11], the stereospecificity of the substitution is quite high and opposite to that of **1** and **2**.

^1H NMR Spectroscopy

The above discussion is based on the assumption that each of the sulfoxides **1**, **2**, and **4** can retain a certain stability in a particular conformation, whereas neither conformation I nor conformation II represent the stable form of **3**.

This proposal can be proved by use of ^1H NMR spectroscopy in $CDCl_3$; i.e., the signals from the methylene protons at the benzylic positions of **1**, **2**, and **4** appear to be an AB-quartet, indicating that the two protons are magnetically nonequivalent, and, therefore, that the conformations of these molecules are firmly fixed to a particular one within the time-scale of NMR spectroscopy. On the other hand, the two protons in **3** appear as a singlet, which indicates that no particular conformation can be assigned as the most stable one, in good agreement with the above proposal. Portions of the spectra are shown in Figure 2.

It should be noted that the chemical shifts of H_R and H_S in **1** and **2** are reversed from those in **4**, which represents an additional support for the difference in the stable conformations of these sulfoxides.

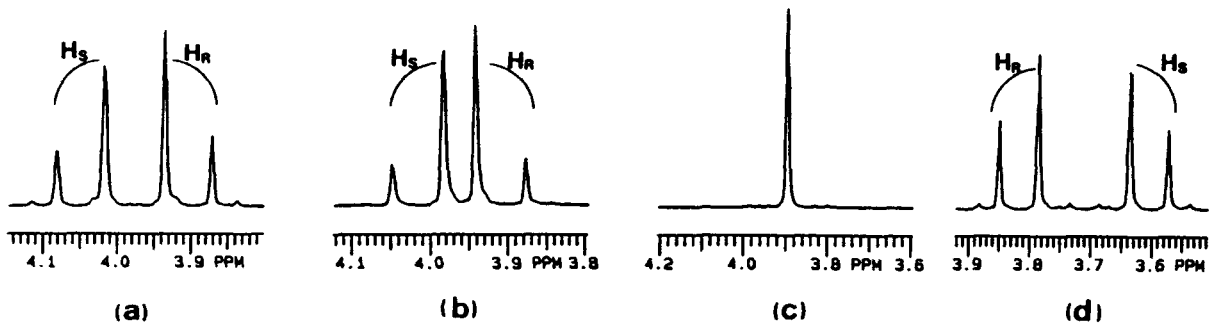


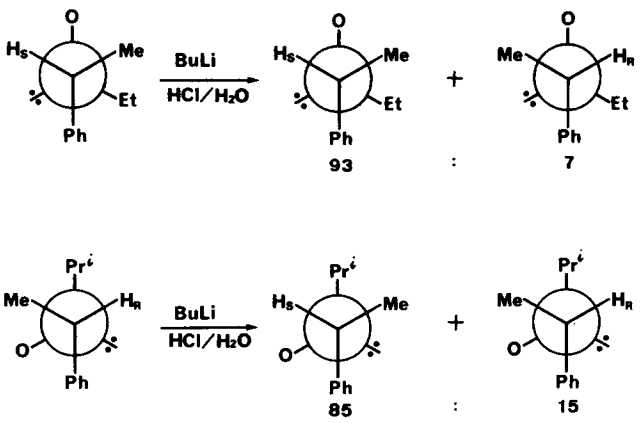
FIGURE 2 ^1H NMR spectra of benzylic protons in (**a**) **1**, (**b**) **2**, (**c**) **3**, and (**d**) **4**.

^1H NMR Assignment of Stereochemistry of the Product

The configurations of the methylated and deuterated products from **1** and **4** were determined absolutely and reported in the previous work [8]. Those of the methylated products from **2** and **3** were assigned by comparing their ^1H NMR chemical shifts with the signals previously reported [20]. Since the stereoselectivity in the methylation of **3** is very small, it was necessary to confirm this result. This was done by comparing the solvent effect on the chemical shift of the benzylic protons in both diastereoisomers from the methylation: the $\delta(CCl_4)$-δ(benzene) values for the major and minor isomers were +0.378 (lit. [20] +0.37) and +0.187 (lit. [20] +0.18), respectively, which is in exact agreement with those reported for the compounds in which the H_R and H_S of **3** were substituted, respectively, by a methyl group. Thus, it has been confirmed that the methylation of **3** takes place mainly on its H_R-face, showing that conformation I is slightly predominant over conformation II when R is the 2-propyl group. In addition, the values for the major (H_R-substitution) and minor (H_S-substitution) isomers of **2** were found to be +0.492 ([20] +0.42) and +0.305 ([20] +0.25), respectively.

The assignment for the deuterated products are not so trivial as those for the methylated products. In order to confirm the stereochemistry, the major product isolated from the methylation of **2** was subjected to a deprotonation-protonation reaction, and it was found that the major product from this reaction retained the configuration of the starting material. On the other hand, the same reaction from the minor isomer of methylated **3** afforded the product with the opposite configuration from that of the starting material.

When the methylation and protonation take place on opposite faces, the methylation retains the hydrogen which can be subjected to the subsequent deprotonation-protonation, and the configuration of the benzylic carbon does not change during these procedures. However, when the methylation and protonation proceed on the same face, the methylation blocks the site of protonation, and the configuration on this carbon has to be reversed in order to introduce a proton into the methylated sulfoxide by the deprotonation-protonation procedure. Results of the deprotonation-protonation reactions on the methylated sulfoxides are shown in Scheme 2.



SCHEME 2

CONCLUSION

It has been demonstrated that our interpretations of the stereochemistry of a series of α-sulfinyl carbanions have wide applicability, and that the proposed stable conformations of sulfoxides in solution are feasible. The carbanion has a larger negative charge density on the sulfinyl-oxygen than on the carbanionic carbon.

EXPERIMENTAL

Instruments

Melting points were not corrected. NMR spectra were recorded at 200 and 400 MHz on Varian VXR-200 and JEOL GX400 Fourier Transform NMR spectrometers, respectively, in $CDCl_3$, CCl_4, C_6H_6, or dimethyl sulfoxide (DMSO)-d_6 with Me_4Si as an internal reference. Infrared spectra were recorded on a Hitachi EPI-S2 infrared (IR) spectrometer. Elemental analyses were performed with a Yanako MT-3 elemental analyzer.

Materials

THF was distilled over Na and benzophenone prior to its use. A hexane solution of butyllithium was obtained from a commercial source.

Preparation of Sulfoxides

Methyl, ethyl, 2-propyl, and 1,1-dimethylethyl phenylmethyl sulfides were prepared according to literature procedures [21]. Oxidation of the sulfides by *m*-chloroperbenzoic acid gave the corresponding sulfoxides.

General Procedure for the Deuteriation and Methylation of Sulfoxides

Into a 20-mL flask 1 mmol of a sulfoxide and 14 mL of THF were placed under an argon atmosphere. The mixture was cooled to −78°C and stirred. A solution of butyllithium in hexane (0.68 mL, 1 mmol) was added to this mixture by use of a syringe. The mixture was kept at −78°C for an additional 20 min. The resulting solution was quenched

with excess D_2O (D_2O/DCl in THF) or methyl iodide and allowed to stand for 15 min. The reaction mixture was further stirred without cooling. Saturated aqueous sodium chloride was added to the reaction mixture, and the organic portions were repeatedly extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate and the solvent was evaporated under reduced pressure. The H_S to H_R ratio in the substituted product was determined by ^1H NMR analysis of the crude reaction product by use of the intensities of the signals for the benzylic protons. The chemical yield was determined by ^1H NMR analysis using 1,1-diphenylethylene as an internal standard.

The products were isolated by subjecting the crude mixture to column chromatography on silica gel with ethyl acetate as an eluent. The results are summarized in Table 1.

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