of unoccupied low energy σ-type orbitals on lithium,[18] which allow the additional α electron to occupy a bonding orbital. This should be contrasted with planar triplet ethylene ($^3B_{1u}$), where an electron occupies the π^* antibonding orbital.

We hope that these findings and the synthetic availability of closely analogous molecules such as 1,1-dilithio-2-methylpropene[19] will encourage experimental work on the determination of the structures and rotation barrier of ethylenes geminally substituted with electropositive groups.[20] Extension of our research to other polylithioethylenes, as well as to polylithiated methanes,[13] acetylenes, allenes, imines, and azo compounds has also revealed startling structural features, and these results will be presented in future publications.

Acknowledgments. We thank Professor Lionel Salem and Dr. P. Bruckmann for carrying out extensive series of 3 × 3 CI and intermediate Hamiltonian calculations and for their interest in this work. We would also like to thank Dr. Rolf Seeger for the use of his convergence program. Support was provided by National Science Foundation Grants GP-29078X (Princeton) and GP-9338 (Carnegie-Mellon) and by the generous donation of computer time by Princeton and Carnegie-Mellon Universities.

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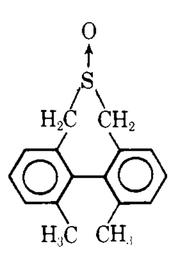
Evidence on Internal Return from Isotope Effects in the Hydrogen–Deuterium Exchange of Benzyl Sulfoxides. A Caveat re Interpretation of Isotopic Exchange Rates

Sir:

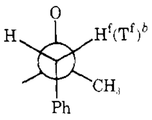
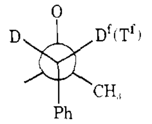
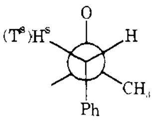
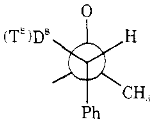
In 1965 the report by Rauk, Buncel, Moir, and Wolfe[1] describing a highly stereoselective hydrogen–deuterium exchange of the diastereotopic methylene protons of benzyl methyl sulfoxide, **1,** has stimulated extensive studies on the mechanism of this interesting reaction. Effects of orientation of the developing anion with respect to the asymmetric sulfur atom on selectivity have received wide attention[2] as have effects of solvent[2,3] and ion-pairing.[4] In addition, ab initio MO calculations of anion stability as a function of stereochemistry were carried out.[5] A comparison of the results of H–D exchange with those calculated (for the gas phase) led one of us[2f] to conclude that agreement was lacking "presumably because of strong solvation effects". At the same time it was pointed out that *internal return*,[6] which could invalidate the use of kinetic data to assess carbanion stability, remained to be examined. Recent additional studies on several thiolane *S*-oxide derivatives[2a] have produced results which the authors termed "difficult to organize in a unique coherent pattern". Such ambiguous accumulating data emphasize the need for knowing if internal return occurs during the exchange process. In this paper we provide evidence on internal return by measurement of the primary isotope effects k_H/k_T and k_D/k_T in the isotopic exchange of (a) each diastereotopic proton of benzyl methyl sulfoxide and (b) two of the benzylic protons of the bridged biaryl sulfoxide, **2.**[2f] The results show that internal return is negligible in the former case but dominant in the latter.



2

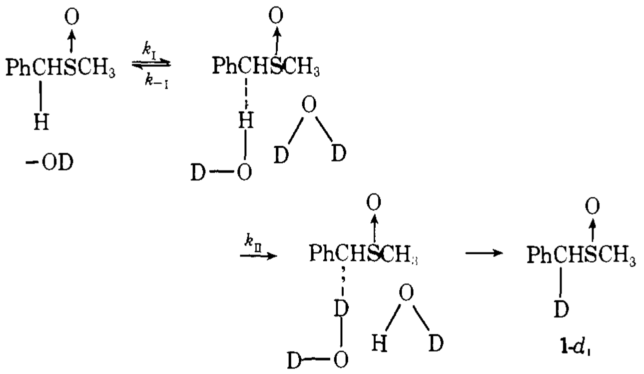
The pioneering research of Cram and co-workers first established the presence of internal return in an isotopic exchange reaction involving carbanion intermediates.[9] The pathway for

Table I. Isotopic Exchange Rates of Methylene Protons of Benzylmethyl Sulfoxide[a]

Substrate	Base/solvent	$k \pm 2$ (standard deviations), $M^{-1}\ min^{-1}$			Isotope effect	Internal return (a_H)
		H	D	T		
	NaOD (0.04 M) in D_2O	21.6 ± 0.3		7.22 ± 0.06	$k_H/k_T = 2.99$	0.03
	NaOH (0.04 M) in H_2O		5.41 ± 0.08	3.90 ± 0.03	$k_D/k_T = 1.39$	
	NaOD (0.48 M) in D_2O	0.942		0.330 ± 0.004	$k_H/k_T = 2.86$	
	NaOH (0.48 M) in H_2O		0.545	0.392 ± 0.004	$k_D/k_T = 1.39$	0.14

[a] All rate constants expressed as second-order rate constants measured at $29.8 \pm 0.1°$ and derived from least-squares treatment of the data. All correlation coefficients were 0.9998 or better. [b] Parentheses indicate the site of the tritium and the exchange process.

Scheme I



such exchanges is described in Scheme I. If the first step is the slow step, i.e., $k_{II} \gg k_{-I}$ there will be no internal return. As k_{-I} becomes more nearly equal to k_{II}, internal return becomes significant. A quantitative determination of internal return has recently been achieved by Streitwiesers' group[10] for several base-catalyzed exchange reactions. By measuring k_H/k_T in D_2O and k_D/k_T in H_2O it was possible to calculate $k_{-I}{}^H/k_{II}$ based on equations developed by Swain et al.[11] For example this ratio, defined as a_H, was found to have values of 0.6 and 0.2 in the exchanges of triphenylmethane and toluene, respectively (using lithium cyclohexylamide in cyclohexylamine[10a]).

The consistency of their results in several other cases[10b] indicated their approach to be reliable. We therefore decided to apply this method to the base-catalyzed exchange of each methylene proton of benzyl methyl sulfoxide in water and, for comparison, to the exchange of the biaryl sulfoxide, **2**, in *tert*-butyl alcohol-*O*-d.

Previous knowledge makes it possible to label benzyl methyl sulfoxide in a highly stereoselective manner. Base-catalyzed H-D exchange produces the *RS* (*SR*)[12] diastereomeric α-deuteriobenzyl methyl sulfoxide 16 times faster than the *SS* (*RR*) isomer.[1] In contrast the *SS* isomer is formed in large excess (94:6) by quenching the α-lithio derivative in THF at $-60°$ with D_2O.[3a] The requisite samples were labeled as follows: (Sample I) Replacement of the *pro R in S* or *fast* proton[13] by tritium was achieved by allowing the exchange of benzyl methyl sulfoxide in tritiated water[14] to proceed to only 3.3% of reaction; sample II, required for measurement of k_D/k_T for the "fast" proton, was produced by complete deuteration of the methylene group followed by back exchange in tritiated water to 3% of reaction. Sample III, containing tritium in place of the *slow* proton, was produced by quenching the lithiosulfoxide with tritiated water. Sample IV was deuterated and tritiated in the *slow* position by using D_2O containing 0.3% of tritiated water as the quenching solution.

All samples used in the kinetic measurements were subjected to NMR, low voltage MS and tritium assays to determine as accurately as possible both their isotope content and the proportions of diastereomers.[15] Rate constants were determined by monitoring gain or loss of deuterium using low voltage MS and loss of tritium by scintillation counting.[17] Table I summarizes the results.

Analysis of the data involving exchange of the *fast* proton by Streitwieser's equations[10a] leads to the result that 3% of the anion undergoes internal return. Data for the exchange of the slow proton lead to a value for a_H of 0.14 (i.e., 12% internal return).[18] It is clear that in the exchange of each methylene proton the amount of internal return is small and will have a negligible effect on the calculated relative stabilities of the two transition states leading to anion formation. Thus, information obtained from kinetics regarding the stability of an anion intermediate is reliable in the case of benzyl methyl sulfoxide *in aqueous media.*

In contrast, in the exchange of protons H_1 and H_2 of the sulfoxide, **2**, in *tert*-butyl alcohol-*O-d*, a large amount of internal return occurs. Values for k_H/k_T of 1.21 and 1.41 were found for isotopic exchanges at H_1 and H_2 using stereoselectivity tritiated samples of **2**.[19] Such low primary isotope effects cannot possibly reflect values for $k_H{}^I/k_T{}^I$. For example, $k_H{}^I/k_T{}^I$ in benzyl methyl sulfoxide can be calculated to be 3.2 from a_H and the experimental value. The extremely small isotope effects observed for **2** can only logically be accounted for by the presence of large amounts of internal return. If one assumes a $k_H{}^I/k_T{}^I = 3.2$ in this sulfoxide exchange then from $(k_H/k_T)_{obsd}$ the percent internal return is calculated to be 80 ± 15 and $70 \pm 15\%$ for H_1 and H_2, respectively. It is of course consistent with the summary of Hunter,[8] that internal return is much larger in the less polar *tert*-butyl alcohol.

In conclusion, two points merit emphasis. Firstly, internal return does occur in the exchange reaction of **2** in *tert*-butyl alcohol-*O-d* to the extent that any resultant conclusions regarding anion stabilities based on its assumed absence may be erroneous. Secondly, and as a corollary, unless evidence establishing the absence of internal return is obtained, the derivation of anion stabilities from exchange rate data on any other sulfoxide is unwarranted. Fortunately, based on the recent studies of Cram and co-workers,[21] one can test for internal return, at least qualitatively, by examining the effects of adding crown ether on the rates of proton exchange. Such a test should be routinely applied to isotopic exchange studies.

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(14) The tritium content of the water used in the labeling techniques was adjusted in each case to provide sufficient specific activity in the resultant sample to give short (<10 min) scintillation counting times.

(15) In the preparation of sample 1 the selectivity in tritiation to only 3.3% of the tritium pool is assumed to be the same as in deuteration (i.e., the sample should contain 7% of T^s). Then detritiation kinetics were measured to only two half-lives of T^f assuming no change in $[T^s]$. The rate of deuteration, measured as $-dD_0/dt$, includes formation of both diastereomeric monodeuteriosulfoxides and requires the correction factor $k_H f = 0.94k^{obsd}$ be included. This correction factor (14.4/15.4) was measured to greater accuracy by Swingle[16] using mass spectral analyses to follow the exchange in D_2O at 24 °C. In the preparation of sample II three consecutive labeling experiments were required. Formation of the anion of **1** in THF at −95° using lithium diisopropyl amide (0.92 of an equivalent), allowing 100 min for equilibration of all possible anionic species then addition of D_2O gave 92% monodeuteriosulfoxide, whose D^s/D^f was shown in separate experiments to be >94/6 by NMR integration. Treatment of this sample with NaOD in D_2O gave mainly dideuteriosulfoxide with no deuterium in the methyl group (MS) and, by NMR, 90% D^s and 95% D^f. Subsequent tritiation in H_2O to 3% of the tritium pool gave selectively labeled sample II, containing 90% D^s and 86% D^f (by NMR). The selectivity in this labeling experiment is assumed to be identical with that measured (MS) separately on a dideuterated sample and found to be (14:1), the same as for deuteration in D_2O. Detritiation kinetics to two half-lives were corrected for the presence of 7% T_s. Loss of deuterium was measured as $-dD_2/dt$ with a correction for loss of D^s included. Sample III, prepared from quenching the anion with tritiated water in THF at −95° was also assumed to contain 6% T^f. Detritiation kinetics were measured after 18% loss of original tritium content (i.e., four half-lives of T^f). Deuteration over the same time period was measured as $-dD_1/dt$ (at beginning of which no undeuterated sample remained). Sample IV from quenching with D_2O + TOD was also assumed to contain 94% $D^s + T^s$. Loss of tritium and deuterium was measured for kinetics after 25% of total tritium had been lost. The assumption that the selectivity in tritiation is the same as in deuteration is verified by the observed kinetics of detritiation, in particular, by the fact that the largest standard deviation is less than 0.7% of the rate constant. The assumption is, of course, consistent with absence of internal return in the exchange process.

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(17) Aliquots for tritium and deuterium assay were purified by TLC followed by sublimation. Deuterium analyses were made using an AEI Ms-902 mass spectrometer. Scintillation counts were made using a Beckmann LS-150 counter. NMR measurements on selectivity were made using a Varian HA-100 spectrometer equipped with an SD-100 deuterium spin-decoupler.

(18) Using the theoretical expressions relating $(k_H/k_T)_{obsd}$ and a_H to k_H/k_T for step I, Scheme I, one can calculate k_H/k_D for step I which turns out to be 2.2 for abstraction of either diastereotopic proton. This very low primary isotope effect is consistent with a highly endothermic proton abstraction process.

(19) Proton assignments for H_1 and H_2 in **2** have been made earlier.[2f] That selective tritiation is feasible at these two positions was shown by exchange studies in two solvents. Since H_1 exchanges 300 times slower than any other proton in *tert*-butyl alcohol-*O-d*, complete tritiation at all four benzylic positions, followed by detritiation at the three more labile positions gave the sample labeled with tritium in place of H_1. To obtain the tritium label at H_2, the above sample was inverted at sulfur.[20]

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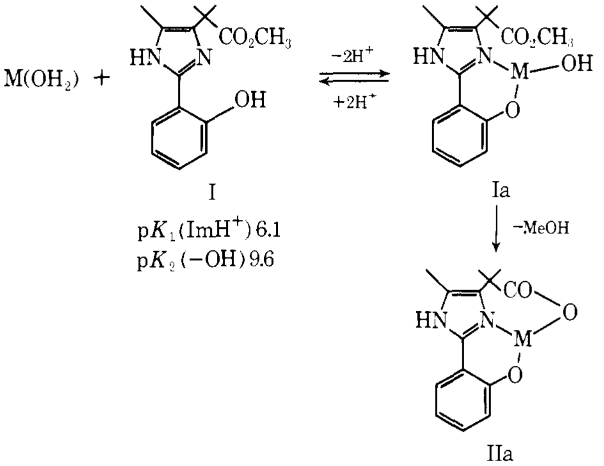
Intramolecular Hydrolysis of a Methyl Ester by Substrate Bound Metal Hydroxide

Sir:

The role of the metal ion in the mechanism of hydrolytic metalloenzymes continues to receive much attention. Interest in the role of metal bound hydroxides as nucleophiles has been stimulated by recent communications concerning the ability of these species to add to carbonyl compounds[1] and to effect the hydrolysis of carboxylic acid anhydrides.[2] An ideal model for a metallohydrate centered acyl transferase would be one that directed the attack of the metal bound hydroxyl group in either an intramolecular or an intracomplex reaction, involved the hydrolysis of an acyl function with a poor leaving group (aliphatic carboxylic acid ester or amide), and would allow the determination of all kinetic and thermodynamic constants. In



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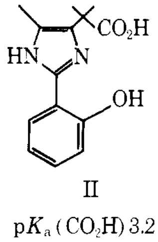

II

pK_a (CO_2H) 3.2
pK_b (ImH^+) 6.9
pK_c (−OH) 9.8