Experimental Evidence for Negative Hyperconjugation as a Component of the Polar Effect: Variation of the Ease of α-Sulfonyl Carbanion Formation with the Orientation of a β-Alkoxy Substituent

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Abstract: We report evidence for a strongly geometry-dependent substituent effect. The rate constants for H−D exchange of the α-hydrogens, $(k_{exch})_{OR}$, in a set of 19 β-alkoxy sulfones of known, fixed (or strongly preferred) H−$C_α$−$C_β$−OR torsion angles have been measured. Those of corresponding model compounds lacking the alkoxy group, $(k_{exch})_{model}$, were also measured, thereby providing the ratio, $k_N = (k_{exch})_{OR}/(k_{exch})_{model}$; the k_N values so obtained range over more than 4 orders of magnitude. We show that when due allowance is made for steric and other influences, our observations are consistent with an equation of the form $\log k_N = a + b \cos^2 \theta$ (where $a = 1.70 \pm 0.17$ and $b = 2.62 \pm 0.20$). It is further shown that the observed rate constant ratios are not consistent with a substituent effect consisting only of the inductive effect and the field effect, and that they are fully consonant with the additional presence of a third effect, namely negative hyperconjugation or the generalized anomeric effect, specifically a torsion-angle-dependent donation of the partial negative charge of the incipient carbanion into the σ^*_{C-O} orbital. This effect is largest with torsion angles of 0 and 180° and at these torsion angles constitutes the major source of stabilization of the incipient carbanion by the β-alkoxy group. The present observation of a torsion-angle-dependent substituent effect may be combined with the known adherence of the specific rate of α-sulfonyl carbanion formation to the Taft equation, to provide an equation yielding torsion-angle-dependent Taft σ* constants for the alkoxy group: $(\sigma^*_\theta)_{OR} = 0.35 + 0.55 \cos^2\theta$. The idea of torsion angle dependence is usefully applied to the long-standing problem of the mechanisms of base-promoted elimination with 2-tosyloxycyclohexyl *p*-tolyl sulfones.

Introduction

A key procedure in the study of reaction mechanisms is the examination of the influence of a small perturbation in structure—a change of substituent—on properties and reactivity. For reactions of nonconjugated systems, the electronic effect of a substituent is customarily described as a *polar* effect, consisting of (a) an inductive (or electronegativity) effect in which the action of the substituent is propagated along the σ-bond array, and (b) a field (or Coulombic) effect in which the substituent acts directly through space; another effect, polarizability, may also be included.[1] Though a number of features of this description, including the independence[2] (or otherwise)[3] of these factors, their relative importance,[4] and methods of quantifying them,[5] have received attention, the overall picture has been accepted as sufficient for at least four decades by a great many chemists. It is in the full knowledge of this that we wish to present in this paper experimental evidence that the above explanation for substituent effects is not adequate, and that the *major* mechanism by which one substituent influences the reaction center in at least one reaction is by way of *negative hyperconjugation* or the *generalized anomeric effect*.[6−9]

In our study we have examined the rate of exchange of hydrogen atoms for deuterium atoms α to a sulfonyl group, a process known to take place by way of the α-sulfonyl carbanion, and the substituent examined is the alkoxy group placed on the β-carbon, i.e., on the carbon next to that undergoing H−D exchange. The choice of this system was dictated by two critical

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(1) (a) Hine, J. *Physical Organic Chemistry*, 2nd ed.; McGraw-Hill: New York, 1962; p 83. (b) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987; p 152n. (c) Topsom, R. D. *Prog. Phys. Org. Chem.* **1976**, *12*, 1−20. (d) Reynolds, W. F. *Prog. Phys. Org. Chem.* **1983**, *14*, 165−203. (e) Taft, R. W.; Topsom, R. D. *Prog. Phys. Org. Chem.* **1987**, *16*, 1−83.

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(5) Marriott, S.; Reynolds, W. F.; Taft, R. W.; Topsom, R. D. *J. Org. Chem.* **1984**, *49*, 959−965.

(6) (a) Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527−548. (b) Eliel, E. L. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 739−750. See also: (c) Thatcher, G. R. J. In *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series 539; American Chemical Society: Washington, DC, 1993; Chapter 2.

(7) The "anomeric effect" is a phenomenological effect which refers to the tendency for axial tetrahydropyranyl carbohydrates to be more stable than their equatorial anomers (contrary to the usual dictates of conformational analysis). The term "generalized anomeric effect" recognizes that the phenomenon found in pyranose sugars shows up in a wide variety of structures and has "been coined to describe the phenomenon in all its aspects".[8a] The theoretical basis of the "anomeric effect" has been subjected to much discussion but currently is regarded as arising (primarily) from $n \rightarrow \sigma^*$ (or analogous) delocalization;[9] i.e., it is identified as an expression of the theoretical concept of "negative (or anionic) hyperconjugation".

(8) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons: New York, 1994; (a) p 753; (b) pp 696−697; (c) pp 720−722; (d) p 707.

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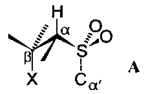
pieces of information. (a) First, the H−D exchange α to the sulfonyl group is known to have a well-defined stereochemistry, specifically, that the preferred orientation of the hydrogen atom in removal or addition has the hydrogen simultaneously gauche to both sulfonyl oxygens or, equivalently, an antiperiplanar arrangement of the H−C_α−S−$C_{\alpha'}$ bonds as shown in **A**.[10]

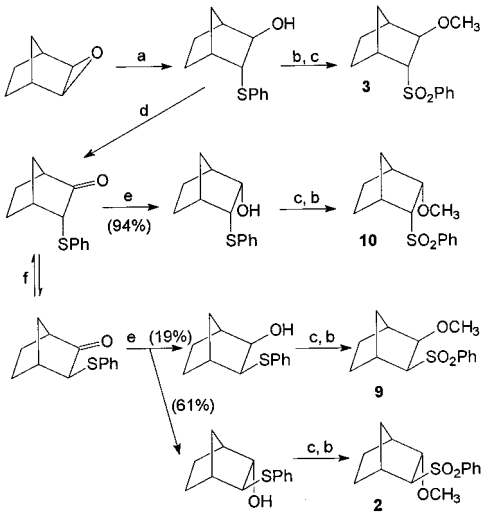


A

(b) Second, the exchange of hydrogen isotopes α to a sulfonyl group was known from the work of Thomas and Stirling[11a] on the detritiation of $PhSO_2CHTCH_2X$ to be very strongly dependent on X, showing a good correlation with σ^* (of CH_2X, $\rho^* = 4.89$); the effect of changing X from CH_3 to OPh, for example, was to increase the rate by 50 000-fold. This extremely high sensitivity to substituents seemed, in our view, too large to arise solely from the conventional polar effect, and it seemed possible that it might involve an additional phenomenon, e.g., negative hyperconjugation or the generalized anomeric effect.[7] Such an effect could readily arise given the arrangement in **A**, if the electrons of the incipient negative charge on C_α were to donate into the antibonding (σ^*_{C-X}) orbital which is antiperiplanar to the C−H bond. This would occur in addition to, and be entirely analogous to, the usual generalized anomeric stabilization of the α-sulfonyl carbanion involving H−C_α−S−$C_{\alpha'}$, as already mentioned above. The test of this hypothesis would be to make compounds with different, fixed H−C_α−C_β−X torsion angles and to see if, and how, the rate constant for H−D exchange varied with the torsion angle. Initially, we looked at a limited set of β-alkoxy sulfones (**A**, X = OR); our results, which have been published in preliminary form,[12] proved extremely promising and encouraged us to carry out the sizable task of studying the wider array of compounds described in this study.

Ideally, in this test one would find how the rate of α-hydrogen exchange varies in a series of β-alkoxy-substituted sulfones in which the only change in structure is the H−C−C−O torsion angle, and in which all steric effects are unchanged. In practice, this is impossible, and what we did was to synthesize a series of 19 β-alkoxy sulfones with (more or less) fixed H−C−C−O torsion angles, with the idea that the effect of the alkoxy group could be estimated by dividing the specific rate of the alkoxy-substituted compound by that of an ideal model compound, i.e., one which is identical in all respects with the β-substituted material except that the polar effect of the alkoxy group is replaced by that of a hydrogen atom. For those compounds in which steric factors are unimportant, a reasonable approximation for the above "ideal" model is one in which the alkoxy group is replaced by a hydrogen (the "hydrogen model"), or, where the oxygen is in a ring, by a methylene group, or in other instances, the methyl group (the "carbon model"). As will be apparent from what follows, some of the alkoxy-substituted and model compound pairs are acceptably close to the ideal, whereas others are not, usually because the introduction of the alkoxy group leads to steric effects not present in the model.

Scheme 1[a]



[a] Reagents: (a) PhSH, NaOH; (b) H_2O_2, HOAc; (c) MeI, KOH, DMSO; (d) Swern oxidation; (e) $LiAlH_4$; (f) KOH, EtOH, Δ (60% *exo*:40% *endo*).

Results and Discussion

Materials and Methods. Table 1 shows (a) the β-alkoxy-substituted sulfones, (b) the H−C−C−O torsion angle in each, as determined from PCModel calculations or from X-ray single-crystal structure determination, (c) the corresponding model compound(s), (d) k_{exch}, the rate constant for the H−D exchange with the specified medium and temperature for both the alkoxy compound ($(k_{exch})_{OR}$) and the model ($(k_{exch})_{model}$), and (e) finally, the key parameter, log k_N, where $k_N = (k_{exch})_{OR}/(k_{exch})_{model}$.

The syntheses of the previously unknown [2.2.1]bicycloheptyl alkoxy sulfones **2**, **3**, **9**, and **10** are summarized in Scheme 1, a route patterned on the earlier synthesis of the *p*-tolyl analogues by Kleinfelter et al.;[13] the [2.2.2]bicyclooctyl sulfones **1** and **11** were prepared similarly. *trans*-1,4-Oxathiadecalin 4,4-dioxide (**15**) was originally prepared as described by Rooney and Evans,[14a] but a more convenient procedure for obtaining both **14** and **15** from some of the same intermediates was developed in this work (see Scheme 2). Note that formation of **14**, which may be regarded as a Michael-type addition of the alkoxy anion onto the α,β-unsaturated sulfone, takes place with stereoselective formation of **14** with no sign of **15**; this is to be expected of an axial addition to the double bond with formation of the comparatively stable *cis*-α-sulfonyl carbanion with the favored orientation of the sulfonyl and alkoxy groups as in **A** (X = O). Other preparations are recorded in the Experimental Section.

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Table 1. Rate Constants for H−D Exchange in β-Alkoxy Sulfones with "Fixed" $H_\alpha-C_\alpha-C_\beta-O$ Torsion Angles (Plus Model Compounds)

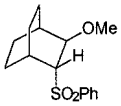
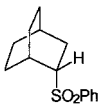
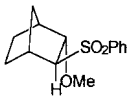
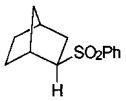
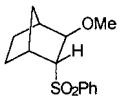
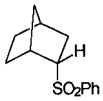
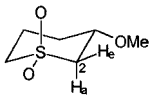
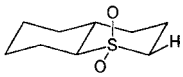
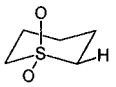
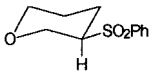
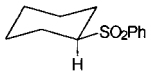
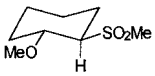
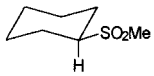
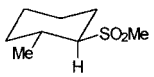
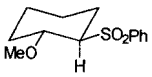
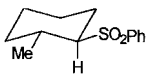
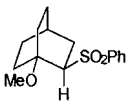
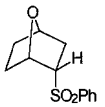
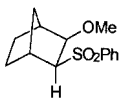
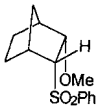
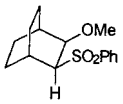
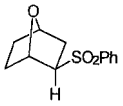
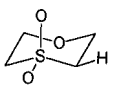
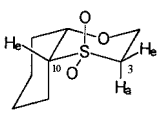
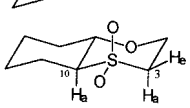
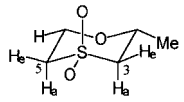
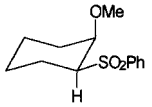
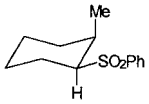
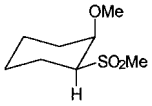
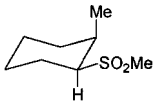
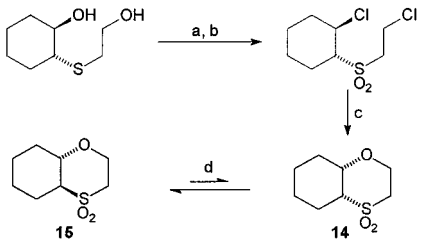
	alkoxy sulfone	θ^a (deg)	k_{exch} (M^{-1} s^{-1}) (conditions)[b]		model(s)	$(k_{exch})_{model}$ (M^{-1} s^{-1})	log k_N[c]
1		26.2 (6.2)	4.9×10^{-4} (A)	**18**		4.2×10^{-8} (A)	4.06
2		7.1 (6.4)	1.04×10^{-4} (A)	**19**		1.5×10^{-8} (A) 3.1×10^{-4} (B1)	3.84
3		13.9 (9.5)	1.14×10^{-3} (A)	**20**		$(4.5 \times 10^{-8})^d$ (A) 9.2×10^{-4} (B1)	(4.40)
4		59.3	C-2H_e: 4.5×10^{-4} (C) C-2H_a: $<1.8 \times 10^{-5}$ (C)	**21**		1.2×10^{-6} (C)	2.57
				(22)		$(\sim 2 \times 10^{-6})^e$ (C)	($\sim$2.35)
5		60.0	1.14×10^{-3} (B3)	**23b**		1.75×10^{-6} (B3)	2.81
6a		61.3	3.67×10^{-4} (B2)	**23a**		3.3×10^{-6} (B2)	2.04
				24a		1.1×10^{-6} (B2)	2.52
6b		61.9	1.12×10^{-4} (B3)	**23b**		1.75×10^{-6} (B3) 1.5×10^{-4} (B2)	1.81
				24b		$(5.25 \times 10^{-7})^f$ (B3) 4.4×10^{-5} (B2)	(2.33)
7		78.4 (63.9)	1.04×10^{-3} (B2)	**18**		2.24×10^{-4} (B2)	0.67
8		74.5	5.07×10^{-4} (B3)	**20**		$(2.07 \times 10^{-7})^g$ (B3) 9.2×10^{-4} (B1)	(3.42)
9		133.0 (128.4)	2.00×10^{-4} (A)	**19**		1.5×10^{-8} (A)	4.12
10		133.1 (130.3)	4.13×10^{-4} (A)	**20**		$(4.5 \times 10^{-8})^d$ (A)	(3.96)
11		145.0 (147.6)	1.36×10^{-3} (A)	**18**		4.2×10^{-8} (A)	4.51
12		152.4	1.07×10^{-3} (B3)	**19**		6.96×10^{-8} (B3) 3.1×10^{-4} (B1)	4.24
13		172.9	$(4.30 \times 10^{-2})^e$ (C)	**21** **(22)**		1.2×10^{-6} (C) $(\sim 2 \times 10^{-6})^e$ (C)	4.55 ($\sim$4.33)
14		173.5	C-3H_e: 4.8×10^{-2} (C) C-3H_a: 1.6×10^{-4} (C) C-10H_e: 3.3×10^{-5} (C)	**21**		1.2×10^{-6} (C)	4.60
15		173.5	C-3H_e: 3.2×10^{-2} (C) C-3H_a: 1.6×10^{-4} (C) C-10H_a: $<10^{-8}$ (C)	**21**		1.2×10^{-6} (C)	4.43

Table 1. (continued)

alkoxy sulfone		θ^a (deg)	k_{exch} (M^{-1} s^{-1}) (conditions)[b]	model(s)		(k_{exch})$_{model}$ (M^{-1} s^{-1})	log k_N[c]
16		174.0	C-3H$_e$: 1.6×10^{-2} (C) C-3H$_a$: $\sim 2 \times 10^{-4}$ (C)	**21**		1.2×10^{-6} (C)	4.12
		173.3	C-5H$_e$: 2.3×10^{-2} (C) C-5H$_a$: $\sim 2 \times 10^{-4}$ (C)				4.28
17b		178.0	3.90×10^{-4} (B3)	**23b**		1.75×10^{-6} (B3) 1.47×10^{-4} (B2)	2.73
				25b		$(8.96 \times 10^{-7})^h$ (B3) 7.5×10^{-5} (B2)	(3.02)
17a		179.4	2.35×10^{-4} (B3)	**23a**		4.2×10^{-8} (B3) 3.3×10^{-6} (B2)	3.75
				25a		$(1.67 \times 10^{-8})^i$ (B3) 1.3×10^{-6} (B2)	(4.16)

[a] The torsion angles (θ) were estimated by calculation using PCMODEL (PCM4), except those in parentheses, which were obtained from X-ray structure determination. [b]Reaction conditions: (A) CD_3CN-D_2O (1:1), 21 °C; (B1) dioxane-d_8-D_2O (1:1), 77 °C; (B2) dioxane-d_8-D_2O (1:1), 64 °C; (B3) dioxane-d_8-D_2O (1:1), 25 °C; (C) D_2O, 20 °C. Rate constants in parentheses are not directly measured values but are calculated as described in the accompanying footnote. [c] $k_N = k_{exch}/(k_{exch})_{model}$. [d] Value estimated at 21 °C by multiplying the rate constant, k_{exch}, for **19** at 21 °C by the rate constant ratio of **20**:**19** at 77 °C. [e] This rate constant is that for H−D exchange per H, and was obtained by multiplying the experimental value by 2 (see discussion in the text). [f] Value estimated at 25 °C by multiplying the rate constant, k_{exch}, for **23b** at 25 °C by the rate constant ratio of **24b**:**23b** at 64 °C. [g] Value estimated at 25 °C by multiplying the rate constant, k_{exch}, for **19** at 25 °C by the rate constant ratio of **20**:**19** at 77 °C. [h] Value estimated at 25 °C by multiplying the rate constant, k_{exch}, for **23a** at 25 °C by the rate constant ratio of **25a**:**23a** at 64 °C. [i] Value estimated at 25 °C by multiplying the rate constant, k_{exch}, for **23b** at 25 °C by the rate constant ratio of **25b**:**23b** at 64 °C.

Scheme 2[a]



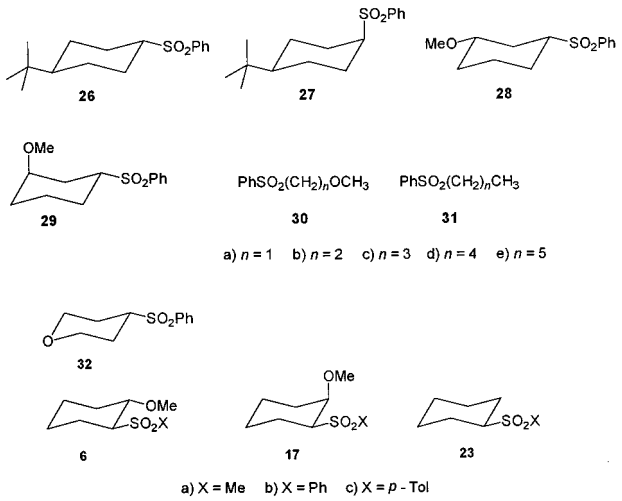
[a] Reagents: (a) HCl, DME; (b) H_2O_2, HOAc; (c) 5% aqueous KOH, DME; (d) KOH, H_2O−EtOH (3:1), 100 h reflux (9:1 *trans*:*cis*).

The structures of all new compounds are assigned by (a) the mode of synthesis, (b) full concurrence of the ^1H and ^{13}C NMR spectra and exact mass values with expectation, and (c) in the case of the [2.2.1]bicycloheptyl and [2.2.2]bicyclooctyl alkoxy sulfones, by single-crystal X-ray crystallography.[15] The H−C−C−O torsion angles so obtained (estimated error ±1°) are given in Table 1 in parentheses.

The rate constants shown in Table 1 were determined by observing the ^1H NMR spectrum under the specified conditions of medium and temperature as a function of time; see the Experimental Section. Normally the ^1H and ^{13}C NMR spectra taken during and upon completion of the exchange reaction showed only clean exchange, with no sign of products of elimination or isomerization; the significant exceptions are discussed below.

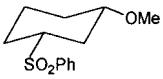
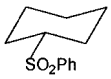
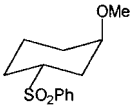
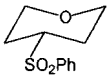
Geometric Effects. Relationship to the Sulfonyl Group. For the majority of the compounds in Table 1, there is only one hydrogen α to the sulfonyl group, and hence there is no ambiguity about which hydrogen is being exchanged. With the compounds carrying a methylsulfonyl group (**6a**, **17a**, **23a**−**25a**, Chart 1) the exchange of the methyl hydrogens was found to be very much faster than that of the methyne hydrogen on the other side of the sulfonyl group; this is in accord with the

Chart 1



(15) Diffraction data for compounds **1**, **2**, **3**, **9**, **10**, and **11** were collected from single crystals on either a Siemens P4 or an Enraf-Nonius CAD4 diffractometer. Structure solution and refinement was done using the SHELXTL suite of programs. Hydrogen atom parameters were refined for **1** and included in idealized positions in the other models. Torsion angles involving H atoms are probably accurate to 1°. Crystallographic data: **1**, $C_{15}H_{20}SO_3$, monoclinic, space group $P2_1/c$, Mo radiation $\lambda = 0.71069$ Å, $a = 8.483(2)$, $b = 10.359(1)$, and $c = 16.091(2)$ Å, $\beta = 101.53(1)°$ with $Z = 4$. Least-squares refinement of 253 variables on F^2 using 4249 unique data gave agreement factors $R_1 = 0.040$ and $R_2 = 0.038$. **2**, $C_{14}H_{18}SO_3$, monoclinic, space group $P2_1/n$, Mo radiation $\lambda = 0.71073$ Å, $a = 5.850(1)$, $b = 16.624(3)$, and $c = 13.500(3)$ Å, $\beta = 95.13(3)°$ with $Z = 4$. Least-squares refinement of 164 variables on F^2 using 2870 unique data gave agreement factors $R_1 = 0.043$ and $R_2 = 0.047$. **3**, $C_{14}H_{18}SO_3$, monoclinic, space group $P2_1/n$, Mo radiation $\lambda = 0.71073$ Å, $a = 11.056(2)$, $b = 9.560(2)$, and $c = 12.653(3)$ Å, $\beta = 90.84(3)°$ with $Z = 4$. Least-squares refinement of 165 variables on F^2 using 2408 unique data gave agreement factors $R_1 = 0.039$ and $R_2 = 0.054$. **9**, $C_{14}H_{18}SO_3$, monoclinic, space group $P2_1/c$, Mo radiation $\lambda = 0.71073$ Å, $a = 11.555(2)$, $b = 15.188(1)$, $c = 16.218(3)$ Å, $\beta = 108.20(1)°$ with $Z = 8$. Least-squares refinement of 186 variables on F^2 using 2403 unique data gave agreement factors $R_1 = 0.083$ and $R_2 = 0.076$. **10**, $C_{14}H_{18}SO_3$, monoclinic, space group $P2_1/n$, Mo radiation $\lambda = 0.71073$ Å, $a = 21.771(15)$, $b = 8.322(3)$, and $c = 30.856(23)$ Å, $\beta = 106.56(6)°$ with $Z = 16$. Least-squares refinement of 322 variables on F^2 using 3083 unique data gave agreement factors $R_1 = 0.075$ and $R_2 = 0.073$. **11**, $C_{15}H_{20}SO_3$, monoclinic, space group $P2_1/n$, Mo radiation $\lambda = 0.71073$ Å, $a = 8.822(2)$, $b = 15.746(3)$, and $c = 10.920(2)$ Å, $\beta = 110.17(3)°$ with $Z = 4$. Least-squares refinement of 174 variables on F^2 using 2486 unique data gave agreement factors $R_1 = 0.043$ and $R_2 = 0.058$. These analyses will be reported in detail elsewhere.

Table 2. H−D Exchange in β-Alkoxy Sulfones of Unfixed Conformation and γ-, δ-, ϵ-Alkoxy Sulfones [a]

	alkoxy sulfone	k_{exch} (M^{-1} s^{-1})		model(s)	$(k_{exch})_{model}$ (M^{-1} s^{-1})	k_N
28		1.83×10^{-3}	**23b**		1.47×10^{-4}	12.4
29		1.35×10^{-3}	**23b**		1.47×10^{-4}	9.2
30b	$PhSO_2(CH_2)_2OCH_3$ [b]	5.12×10^{-1}	**31a**	$PhSO_2CH_2CH_3$	4.14×10^{-4}	1.23×10^3
			31b	$PhSO_2(CH_2)_3CH_3$	2.3×10^{-4}	2.27×10^3
30c	$PhSO_2(CH_2)_3OCH_3$	1.68×10^{-3}	**31b**		2.3×10^{-4}	7.5
			31c	$PhSO_2(CH_2)_4CH_3$	2.03×10^{-4}	8.3
30d	$PhSO_2(CH_2)_4OCH_3$		**31c**		2.03×10^{-4}	2.0
			31d	$PhSO_2(CH_2)_5CH_3$	1.80×10^{-4}	2.2
30e	$PhSO_2(CH_2)_5OCH_3$		**31d**		1.80×10^{-4}	2.2
			31e	$PhSO_2(CH_2)_5CH_3$	1.80×10^{-4}	2.2
32		8.6×10^{-3}	**23b**		1.5×10^{-4}	49
	$CH_3SO_2(CH_2)_2OCH_3$ [b,c]	4.2×10^{-1}		$CH_3SO_2CH_2CH_3$	2.4×10^{-5}	1.79×10^4

[a] In D_2O-dioxane-d_8; cyclohexyl sulfones at 64 °C; alkyl sulfones at 25 °C. [b] For comparison: $PhSO_2CH_3$, $k_{exch} = 2.26 \times 10^{-2}$ M^{-1} s^{-1}; $CH_3SO_2CH_3$, $k_{exch} = 9.95 \times 10^{-4}$ M^{-1} s^{-1}. [c] Rates refer to the exchange of the methylene hydrogens; for the α-methyl group of ethyl methyl sulfone: $k_{exch} = 9.9 \times 10^{-4}$ M^{-1} s^{-1}.

general observation that (when otherwise equivalent) methyl groups form a carbanion more readily than a methylene group, which in turn reacts more readily than a methyne. With the substrates and conditions in this study, the results in Tables 1 and 2 indicate that the relative rates of hydrogen removal from methyl, methylene, and methyne groups are roughly 200:50:1.

Seven of the 19 alkoxy compounds of "fixed" geometry in Table 1 have the sulfonyl group in a six-membered ring and have at least one methylene group directly attached to the sulfonyl function. In most of these (**4**, **14**, **15**, **16**, and **21**) the methylene hydrogens are diastereotopic, but in two of them (**13** and **22**) the hydrogens of the methylene groups become equivalent by simple chair ⇌ chair interconversion; the members of this latter group present no problems in interpreting their spectra, but they do require inclusion of a statistical correction factor for comparison with other compounds in this study. The exchange reaction that is being followed is the replacement of all four α-hydrogens; at any time, however, only half of these hydrogens are in the (more reactive) equatorial position, and hence the measured rate constant must be multiplied by 2 for comparison with compounds in which the α-hydrogen is at all times in the favorable orientation.

In the group in which the individual hydrogens of the methylene group are diastereotopic (i.e., **4**, **14**, **15**, **16**, and **21**), the two hydrogens can be expected to exchange at different rates. The hydrogens are readily assigned as axial or equatorial (in the most stable conformation) by their ^1H NMR signals; the axial hydrogens show the typical large axial−axial coupling (10−15 Hz) with each vicinal axial hydrogen and a much smaller axial−equatorial coupling (2−4 Hz) with their vicinal equatorial neighbors, whereas the equatorial hydrogens show small couplings with both axial and equatorial neighbors. On observing the exchange reactions by ^1H NMR, it became evident that in all of the six-membered cyclic sulfones the equatorial hydrogen(s) exchange(s) faster than the epimeric axial hydrogen atom(s). With **21**, for example, the equatorial α-hydrogen (C-2_e) exchanges about 100 times faster than the axial hydrogen of the methylene group (C-2_a), and this in turn exchanges much faster than the axial methyne hydrogen (C-10_a). Similarly, in **4** it is the equatorial hydrogen which is exchanged more rapidly than the axial, by a factor of more than 25. These observations are, indeed, what was expected on the basis of the known preference for carbanion formation of the α-hydrogen with the antiperiplanar H−C−S−C torsion angle and would have required little comment had it not been that Katritzky and coworkers[16] reported that the equatorial:axial rate ratio in a model system of theirs (*cis*-3,5-diphenyl-*trans*-4-hydroxy-3,4,5-trideuteriotetrahydrothian 1,1-dioxide) was only 1.6. The origin of the difference between our results and Katritzky's is not obvious to us, but it is our contention that the comparative simplicity of our compounds indicates that our systems typify the general case and it is the Katritzky example which is the exception, perhaps because of perturbations due to the hydroxy and phenyl groups. This is also in agreement with the observation by Fuji et al.[17] that the equatorial α-hydrogens in 6-methyl-1,3-oxathiane 3,3-dioxide exchange 15−25 times more rapidly than the axial α-hydrogens (in $NaOCD_3-CD_3OD$ at 20 °C). It might be argued that most of our examples are also perturbed by the presence of an ether oxygen, and it is the basic point of this paper that this oxygen and its orientation strongly influence the rate of H−D exchange. In the two simple examples (**21** and **4**) noted above, however, one (**21**) has no ether oxygen at all and the other has the methoxy group (more or less) symmetrically disposed with respect to the two α-methylene hydrogen atoms, and hence it is most unlikely that the oxygen in **4** is directly responsible for the *difference* between the reactivities of the two hydrogens. In the other three compounds (**14**, **15**, and **16**) the oxygen accelerates the exchange reaction, but in our view it is the orientation of the hydrogen atom with respect to the $C_{\alpha'}-S$ bond that is the primary factor which determines which hydrogen is exchanged.

The evidence in the present study is fully consistent with the picture that, with the compounds and the conditions used in this investigation, at least, exchange of the α-hydrogens takes place *only* when the hydrogen has the antiperiplanar torsion angle around the $H-C_\alpha-S-C_{\alpha'}$ bond. The exchange of hydrogens lacking the favorable $H-C_\alpha-S-C_{\alpha'}$ torsion angle in the major conformation requires a conformational flip either to the alternative chair conformation (i.e., **4** with the methoxy group axial, **14** with the sulfonyl group axial to the cyclohexane

(16) Brown, M. D.; Cook, M. J.; Hutchinson, B. J.; Katritzky, A. R. *Tetrahedron* **1971**, *27*, 593−600.

(17) Fuji, K.; Usami, Y.; Sumi, K.; Ueda, M.; Kajiwara, K. *Chem. Lett.* **1986**, 1655−1658.

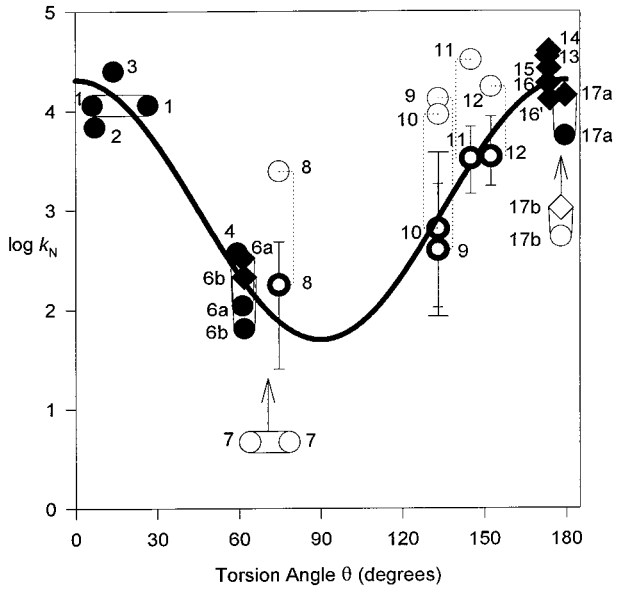


Figure 1. Plot of $k_N = (k_{exch})_{OR}/(k_{exch})_{model}$ for 18 of the 19 compounds listed in Table 1. Circles (filled or open) refer to k_N values determined using a hydrogen model, and the turned squares ("diamonds") refer to k_N values obtained using a carbon (methyl or methylene) model. The filled circles ("bullets") and filled turned squares ("black diamonds") are believed to represent the effect of the alkoxy group without requiring major correction for steric or other effects. The heavily outlined circles ("bulls-eyes") are values corrected for steric and γ effects as noted in the text. Compounds **1** and **7** are each represented by two horizontally yoked circles, reflecting the uncertainty resulting from discrepancies between the estimated (PCModel) and X-ray crystallographic torsion angles (see Table 1). Compounds **6a**, **6b**, **17a**, and **17b** are shown with vertically yoked points (circles and diamonds, from the hydrogen and carbon models, respectively). The curve was calculated from $\log k_N = (3.01 \pm 0.10) + (1.31 \pm 0.11)\cos 2\theta = (1.70 \pm 0.17) + (2.62 \pm 0.20)\cos^2 \theta$, which was obtained by a weighted nonlinear squares fit of the bullets and black diamonds with each of the yoked points given a weighting of 0.5; inclusion of the bulls-eyes with weightings corresponding to 1/(uncertainty)^2 did not affect the parameters in the above equations.

ring, or **16** with the methyl axial) or to the twist conformation of the heterocyclic ring in **15** or **21**. The very slow exchange of the (axial) methyne hydrogen in **15** could conceivably be an exception to this picture and could be taking place by way of a conformation in which the H−C$_\alpha$−S−C$_{\alpha'}$ torsion angle is not antiperiplanar; it should be noted, however, that even this hydrogen can come close to achieving the antiperiplanar arrangement when *both* rings are in twist conformations.

Geometric Effects. Relation to the Alkoxy Group. (a) Small Steric Effects. The experimental values of log k_N are shown in Figure 1 as either black filled or fully open circles (● or ○) or turned squares ("diamonds"). With those points shown as black filled circles ("bullets", ●) or black turned squares ("black diamonds", ◆) it is believed that the principal influence on log k_N is the electronic effect of the alkoxy group, i.e., steric factors have only a relatively small effect on log k_N; within the context of a range of k_N values spanning more than 4 orders of magnitude, "small" may be taken as a factor of 3 or (more usually) less. Some notion of the result of a small perturbation may be gained by examining the effect of replacing a β-hydrogen by a methyl group, i.e., by comparing the specific rates of H−D exchange either of (a) the α-hydrogens of **23** with those in **24** and **25** or (b) the C-3 and C-5 equatorial hydrogens in **16**. In the case of **24b** and **25b** vs **23b**, the effect of the methyl group is to slow the reaction by factors of 2.0 (with **25b**) and 3.33 (with **24b**). It is customary to assume that part of these rate reductions may arise from a small electronic effect of the methyl group (σ^* of CH_2X for X = H is 0.00 and for X = CH_3 is −0.1),[18a] and hence the steric effect of the methyl group (which must be only a part of the total effect) cannot be large. With **16** the effect of the 2-methyl group is to reduce the specific rate of H−D exchange from 3×10^{-2} to 1.6×10^{-2} M^{-1} s^{-1}. Again, in this more reactive system, the steric effect of the methyl group must be small; note that unless the steric effect of the methyl group is to accelerate the reaction (which seems unlikely in these cases), the *maximum* electronic effect of the methyl group is to slow the reaction by a factor of 2. Methyl and methoxy groups can often be regarded as of comparable "size", with a slightly larger Taft E_s value[18b] for OCH_3 vs CH_3 (respectively, for CH_2X, −0.19 and −0.07) and a distinctly lower *A* value[8b] for methoxy as compared with methyl (respectively, a range from 0.55 to 0.75 vs 1.74 kcal mol^{-1}). It is within this framework that the points in Figure 1 given as bullets or black diamonds are regarded as unlikely to be *strongly* influenced by steric factors; i.e., these points are the least perturbed by effects other than the electronic effect of the β-alkoxy group. The bullets and black diamonds clearly fall into three clusters, one at low torsion angles (0 to 20°), one around 60°, and finally, the largest, in the 170−180° range. The values of log k_N are around 4 for the first and last of these groups and are close to 2 for the 60° angle compounds. These results in themselves clearly show log k_N to be angle dependent. They are also not readily accounted for on the basis of the field effect; calculation of field effects using the Kirkwood−Westheimer approach (see below) cannot yield the variation shown by the bullets and black diamonds in Figure 1. Negative hyperconjugation or the generalized anomeric effect, which would lead to a torsion angle effect roughly corresponding to a cos 2θ (or $\cos^2 \theta$) dependence (as is discussed more fully below), presents itself as a most attractive possibility. We show in the next three subsections that when due allowance is made for either steric assistance or steric hindrance or the "γ-effect", we may, with the aid of arguments totally independent of the generalized anomeric effect, factor out the steric (and γ-effect) contributions to a number of these k_N values, leading to the "corrected" log k_N points shown as heavily outlined circles ("bulls-eyes") and leading to the cosine curve in Figure 1.

(b) Correction for Large Steric Assistance. In contrast to the examples considered in the previous section, in which steric factors are regarded as fairly small, a substantial steric effect was immediately evident from the observation in the reactions of the *cis*-methoxy sulfones, **9**, **10**, and **11**, not only of H−D exchange, but also of concomitant isomerization to the equilibration mixture; e.g., starting with **9** led to an equilibrium mixture of the α-D isotopomers of **9** and **3**, with the latter predominating. In deuterated media, the free energy changes accompanying equilibration ($\Delta G^\circ_C = G^\circ_{cis} - G^\circ_{trans}$) of the respective isotopomers were 2.5 ± 0.2 for **3** ⇌ **9**, 4 ± 1 for **2** ⇌ **10**, and 2.4 ± 0.2 kcal mol^{-1} for **1** ⇌ **11**. The likely source of the clear preference for the *trans* isomer is a strong nonbonding repulsion (probably both steric and Coulombic) between the eclipsed *cis* methoxy and arylsulfonyl groups. In addition to this, there is a difference between the ΔG° values for **3** ⇌ **9** vs **2** ⇌ **10** which is readily assigned to the well-known lower energy of *exo*- vs *endo*-[2.2.1]bicycloheptane systems. This was confirmed by treating **19** and **20** individually with strong base (at 77 °C) to give mixtures of **19** and **20**, indicating an equilibrium mixture with 86 ± 5% of **19** and 14

(18) Taft, R. W. In *Steric Effects in Organic Chemistry*; Newman, M. S., Ed.; John Wiley & Sons: New York, 1956, (a) p 595. (b) p 598.

± 5% of **20**, and corresponding to $\Delta G°_{endo} - \Delta G°_{exo} = \Delta G°_{NX} = 1.26 \pm 0.3$ kcal mol^{-1}. If we label the *cis* interaction energy difference in **9** vs **3** as $(\Delta G°_C)_X$ and that in **10** vs **2** as $(\Delta G°_C)_N$, and if we then assign the observed energy differences primarily to the *cis* and *endo* interaction energies, we may write the following:

$$G°_{\mathbf{20}} - G°_{\mathbf{19}} = \Delta G°_{NX} = 1.3 \pm 0.3 \text{ kcal mol}^{-1}$$

$$G°_{\mathbf{9}} - G°_{\mathbf{3}} = (\Delta G°_C)_X - \Delta G°_{NX} = 2.5 \pm 0.2 \text{ kcal mol}^{-1}$$

$$G°_{\mathbf{10}} - G°_{\mathbf{2}} = (\Delta G_C)_N + \Delta G°_{NX} = 4 \pm 1 \text{ kcal mol}^{-1}$$

From this we readily obtain $(\Delta G°_C)_X = 3.8 \pm 0.5$ kcal mol^{-1} and $(\Delta G°_C)_N = 2.7 \pm 1.3$ kcal mol^{-1}.

The *exo-cis* and *endo-cis* isomer interaction energies appear to be somewhat different, though the accumulated error in these estimates is large and precludes precise comparison. Inspection of the S- - -OMe interaction distances and the O−C−C−S torsion angles,[19] which indicate slightly shorter distances in the *exo* isomer, are in accord with an apparently higher energy for $(\Delta G°_C)_X$. The energy difference between the *cis*- and *trans*-[2.2.2]bicyclooctyl sulfones, $G°_{\mathbf{11}} - G°_{\mathbf{1}}$, was found to be 2.4 ± 0.2 kcal mol^{-1}, i.e., a value apparently smaller than the other *cis* interactions, in accord with the larger O−C−C−S torsion angle and S- - -OMe internuclear distance in **11** vs **10** and **9**.[19]

The abstraction of a proton to form the carbanion from **9**, **10**, or **11** must be accompanied by a change in the O−C−C−S torsion angle, and this in turn leads to a measure of relief of the ground-state strain noted above; this well-known phenomenon is often referred to[8c] as "steric assistance". The question that now arises is what proportion of the observed energies of the *cis* and *endo* interactions is expressed in the transition states leading to the carbanion; i.e., to what extent does ground-state strain affect the *rate* of carbanion formation (and hence of H−D exchange)?

To approach this problem, we have looked at the relationship between rates and equilibria in two simple sulfonyl systems, **19** ⇌ **20** and **26** ⇌ **27**. An energy diagram for **19** ⇌ **20** is shown in Figure 2. Note that $\Delta G^‡$ is 26.22 kcal mol^{-1} for **20** and 25.46 kcal mol^{-1} for **19**; the difference in free energy of activation, $\Delta\Delta G^‡ = \Delta G^‡_{\mathbf{20}} - \Delta G^‡_{\mathbf{19}} = 0.76$ kcal mol^{-1} is clearly ascribable to steric acceleration in the reaction of **19**. Of the original 1.26 kcal mol^{-1} of strain energy (in **19** vs **20**), 0.76 kcal mol^{-1}, or 60%, is released as steric assistance in the formation of the α-sulfonyl carbanion from the sulfone. In the other system **26** ⇌ **27** (Chart 1), the axial isomer was found to be higher in energy by 2.66 kcal mol^{-1}, and the difference in free energies of activation was 1.91 kcal mol^{-1}; the release of strain energy is therefore 1.91/2.66, or 72% of the total. The results from the two reactions are in reasonable accord (average 66%) and consistent with other work on steric assistance.[20]

Returning to the alkoxy systems, for example the reaction of **9**, we take 66% of 3.7 ± 1 = 2.44 ± 0.6 kcal mol^{-1} as the strain energy released in making the carbanion. To find the electronic effect of the methoxy group, we must correct the value of log k_N accordingly; i.e., we must reduce log k_N by the effect of the 2.44 kcal mol^{-1}, which is to say, by $2440/2.303RT = 1.52 \pm 0.2$ ($T = 77$ °C), and the value of log k_N for **9** corrected for steric acceleration becomes 2.60 ± 0.2, the value given by the bulls-eye (and error bars) in Figure 1. In the same way, the corrected (bulls-eye) values for log k_N for **10** and **11** (2.81 and 3.52) were also obtained.

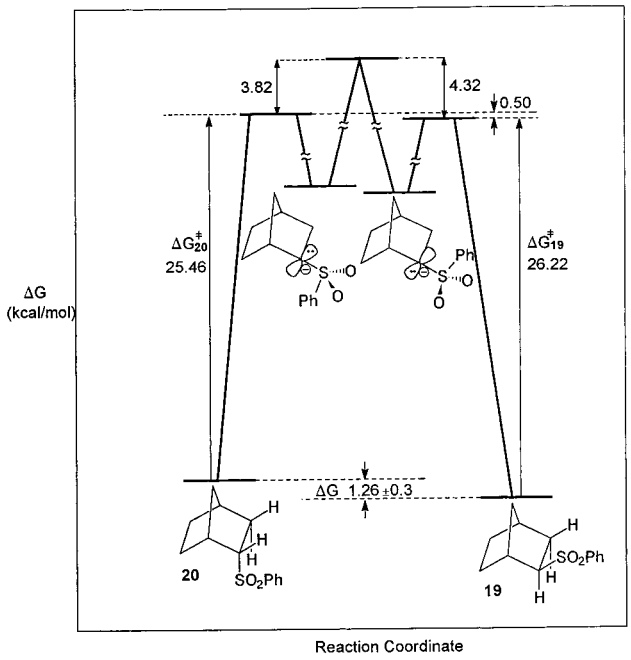


Figure 2. Free energy vs reaction coordinate diagram for carbanion formation and epimerization reactions of **20** and **19** (with sodium deuterioxide in dioxane-d_8−D_2O, 1:1, at 77 °C). The $\Delta G°$ value for **19** ⇌ **20** was obtained from the estimated equilibrium ratio (86:14); the $\Delta G^‡$ values are calculated from the k_{exch} values in Table 1 and from $k_{inv} = 3.8 \times 10^{-6}$ M^{-1} s^{-1} for **20** → **19** determined by Guo[44b] under these conditions.

(c) Correction for the γ-Effect. In light of our observation that an alkoxy substituent in the β position may accelerate the H−D exchange by more than 10^4-fold, it would appear prudent to take due account of an alkoxy interaction at the γ position and perhaps more distant locales as well. Table 2 includes the results of a brief look into γ and more distant effects. From this we see that an alkoxy group connected by a single three-carbon chain to the sulfonyl group increases the rate of H−D exchange by 7.5−12.4 times. With one oxygen connected to the α-carbon by two identical three-carbon chains, as in **32** (Chart 1), the effect of the oxygen is increased to 49-fold. By the same token, we must conclude that in the reactions of the two 7-oxabicyclo[2.2.1]heptyl sulfones (**8** and **12**) in which the oxygen is β to the sulfur by one route and γ by another, the observed rate must be influenced not only by the β interaction but also by the γ effect, and hence the magnitude of the γ effect must be accounted for if we are to estimate the magnitude of the β effect by itself in these compounds. An *upper* limit of roughly 12-fold for the γ effect may be set by the value for **28** (Chart 1) in Table 2. The lower limit is less clear because it would appear reasonable to expect that when one oxygen is

(19) The O−C−C−S torsion angles (as determined by X-ray crystallography) in **9** are 11.2 and 0.7° (two conformations), those in **10** are 13.9, 17.3, 6.2, and 10.9° (four conformations), and that in **11** is 30.8°; the S- - -OCH_3 internuclear distances are, respectively, in **9**, 2.830 and 2.900 Å; in **10**, 2.888, 2.971, 3.009, and 2.887 Å; and in **11**, 2.930 Å.

(20) Rüchardt and Beckhaus, for example, find slopes for plots of $\Delta G^‡$ vs strain enthalpy for thermal cleavage of hydrocarbons which point to about 40−67% of strain energy being released in the reaction.[20a] The effects of strain energy release are, however, known to be highly variable,[20b,20c] and estimates of these effects must be made with great caution. We emphasize that our approach in the present study is simply empirical: we have (a) taken two examples of the reactions under study (i.e., carbanion-mediated H−D exchange), (b) found that they show similar strain release factors, and (c) applied the average of these factors to obtain our estimate of the strain release correction. (a) Rüchardt, C.; Beckhaus, H. D. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 429−440. (b) Tonachini, G.; Bernardi, F.; Schlegel, H. B.; Stirling, C. J. M. *J. Chem. Soc., Perkin Trans. 2* **1988**, 705−709. (c) Sella, A.; Basch, H.; Hoz, S. *J. Am. Chem. Soc.* **1996**, *118*, 416−420.

interacting by two paths, the total effect will not be as large as if there were two separate oxygen atoms acting independently; i.e., to the extent that an oxygen atom acting by, for example, a β effect withdraws charge from the α-carbon in the transition state, then that same oxygen atom acquires an increased negative charge and can therefore be expected to be less electron-withdrawing by the other pathway than if this involved another, quite different, oxygen atom. In accord with this, we find that the "double γ effect" via the two pathways (in **32**, 49-fold) is less than that expected from two independent γ effects. In the absence of any straightforward basis for assigning the γ effect when the same oxygen also shows a β effect (as in **8** and **12**), we suggest that the value 5 ± 3 very likely covers the γ effect range in these substrates. The corrected point for **12** in Figure 1 has been obtained using this number; the large error bars reflect the uncertainty in the γ effect assignment. For **8**, an additional (steric) correction is required because the strain energy difference between **8** and **12** is 2.15 kcal mol^{-1} (or 0.9 kcal mol^{-1} greater than that observed for **19** vs **20**), and hence is not adequately accounted for with **20** as the model. Accordingly, a correction corresponding to 66% of the difference in strain energies (i.e., 0.66×0.9 kcal mol^{-1}) is applied to **8** in addition to the γ effect correction; the final corrected values of log k_N for **8** and **12** are, respectively, 2.25 and 3.54.

Table 2 also records examples of the effect of more distant alkoxy groups, i.e., those in the δ and ϵ positions from the sulfonyl group. It is interesting to note that even at the ϵ position the effect of the alkoxy group is detectably different (by a factor of 2) from that of the hydrogen; note that there is no effect on introducing a methyl group (**31e** vs **31d**). It is tempting to postulate direct donation from the α center into the σ^* orbital of the alkoxy-bearing carbon by way of a cyclic structure (three-membered for γ, four-membered for δ, and five-membered for ϵ).

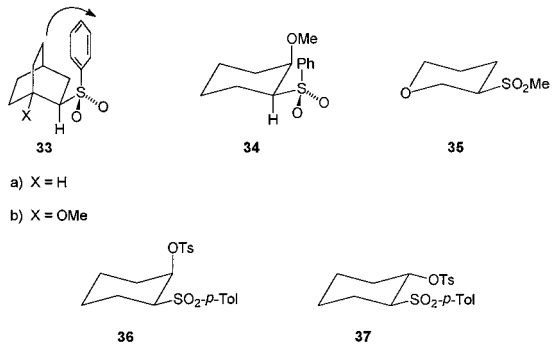
(d) Other Deviant Points. Even the most cursory examination of Figure 1 shows two points (unfilled circles) to be clearly removed from the others, those for (a) *cis*-2-methoxycyclohexyl phenyl sulfone (**17b**), and (b) the bridgehead methoxy sulfone **7**; the k_N value of the latter, 4.6 (log $k_N = 0.66$), is very low, being only about half that of the typical γ effect k_N values shown in Table 2! This, in itself, suggests a rate suppression factor of some kind. Each case is examined in footnote 21, and it is concluded that it is possible to assign a likely origin for the deviation from the pattern shown by the other points, but that we cannot derive quantitative corrections such as those discussed above. At this stage we regard the results with **7** and **17b** as neither contributing to nor detracting from the conclusions drawn from the bullets, black diamonds, and bulls-eyes in Figure 1.

Variation of log k_N with the H−C−C−O Torsion Angle. (a) Negative Hyperconjugation and the Generalized Anomeric Effect. Inspection of Figure 1 reveals a pattern consistent with variation of log k_N with cos 2θ (or cos^2 θ), where θ is the H−C−C−O torsion angle; the line corresponds to eq 1 derived from a nonlinear least-squares best fit.

$$\log k_N = (3.01 \pm 0.10) + (1.31 \pm 0.11) \cos 2\theta = (1.70 \pm 0.17) + (2.62 \pm 0.20) \cos^2 \theta \quad (1)$$

Of the three log k_N values not included in the least-squares treatment (those for **5**, **7**, and **17b**), the last two are discussed above and in footnote 21, while **5** is taken up in a later section. Experimental free energy relationships in chemistry are always subject to "noise", i.e., to minor deviations from perfect fit to the line. In addition, in the present case of log k_N, the problem

Chart 2



of imprecision is made worse by the fact noted already that k_N cannot, by its very nature, always be uniquely and precisely determined.[22] Within this framework we suggest that the results in Figure 1 constitute a strong case for eq 1. The variation of experimental log k_N values with θ ranges from log k_N of about 2 to about 4.6; i.e., there is a torsion-angle-dependent component

(21) Examination of molecular models suggests that two factors combine to slow the H−D exchange in **7** relative to its model (**18**). As was noted in the Introduction, the preferred (and in the present examples, probably the only) orientation of the α-sulfonyl system for carbanion formation is that shown in **A**. For **7** this would require the conformation shown in **33b** (Chart 2) with very strong nonbonding repulsions between the phenyl and the nearest methylene groups. In the model (**18** = **33a**) this can be alleviated in considerable measure by having the phenyl group move as shown by the arrow with concomitant twisting of the [2.2.2]bicyclooctyl system (which presumably also helps to minimize the eclipsing interactions in this array). With **7** (=**33b**), however, such motion leads to a shrinkage of the O−C−C−S torsion angle from its original value of about 60° in the untwisted bicyclo system to a value approaching 0°. This extreme would correspond to the eclipsed arrangement of the phenylsulfonyl and methoxy groups, which, as has already been seen with **9**, **10**, and **11**, above, would add extra energy of the order of ~2.5 kcal mol^{-1} or more. It would appear that the methoxy group in **7** introduces a steric-cum-electronic effect not adequately factored out by dividing by the rate constant for the model system (**18**), and hence a correction must be applied to increase k_N to find the purely electronic effect of the methoxy group in **7**. It should also be noted that any tendency to involve hyperconjugation in **7** (which would be expected to be small because of the unfavorable torsion angle) would probably be accompanied by at least a small change in hybridization (from sp^3 to sp^2) at C-1 and C-2. Such a change would generate angle strain in the bridged structure associated with Bredt's rule. The net result could be either (a) no hyperconjugation or (b) some hyperconjugation but with little or no energy release because of increased strain. The other unfilled circle well removed from the others is that due to **17b**. Examination of molecular models shows that the appropriate conformation of the H−D exchange is that shown in **34** (Chart 2). One immediately notes what appears to be a substantial "1,3-synaxial-like" interaction between the methoxy and phenyl groups. Interestingly (as has been noted earlier), however, when *cis*-2-methylcyclohexyl phenyl sulfone (**27a**) was examined, the effect of the "1,3-synaxial-like" *methyl*−phenyl interaction was found to be comparatively minor, with the rate constant for H−D exchange in **25b** about one-half of that of cyclohexyl phenyl sulfone (**23b**). One possibility raised by these results is that there is a substantial MeO- - -Ph interaction not mimicked by the methyl analogue, i.e., one presumably not primarily steric in origin. That there is something unusual about the "1,3-synaxial-like" MeO- - -Ph interaction is indicated by the following evidence which is quite apart from anything related to Figure 1. Note the effect on relative rates of H−D exchange of changing from a methyl sulfone to the corresponding phenyl sulfone: 23-fold from $CH_3SO_2CH_3$ to CH_3SO_2Ph, 45-fold from **23a** to **23b**, 26-fold from **6a** to **6b**, 58-fold from **25a** to **25b**, but only 4-fold from **17a** to **17b**. These results are consistent with a repulsive nonbonding MeO- - -Ph interaction in **17b** (=**34**) (and analogous compounds) not compensated for by models such as **23b** or **25b**. Without a clear picture of its origin, we are not in a position to make any estimate of its effect on rates of H−D exchange magnitude other than the roughly 1 order of magnitude change noted in the methyl vs phenyl sulfone series above, and we merely indicate, by an upward-pointing arrow in Figure 1, that it is likely that the points for both **7** and **17b**, when properly corrected, will likely have distinctly higher log k_N values.

(22) A similar problem of precise determination appears with some well-known chemical parameters, e.g. resonance (or delocalization) energy and effective molarity (alias effective concentration). Like these, log k_N can be useful, and absence of high precision is not in itself grounds for not making use of the idea.

of log k_N which appears to constitute more than half of the maximal value, and also a component (presumably the inductive and field effects) which appears to be (more or less) independent of θ (see below).

Such a cosine relationship is, of course, what is expected, as a first approximation, for electron donation of the $n \rightarrow \sigma^*$ type yielding a (full or partial) π-bond. In an ab initio study, Bors and Streitwieser[9d] describe the variation of the energy with rotation about the $C_\alpha-S$ bond in the $\bar{C}H_2SO_2CH_3$ anion; the variation is given as a function of cos θ, cos 2θ, and cos 3θ, but the actual coefficients are such as to make it primarily a function of cos 2θ.[9d] Schleyer and Kos[9b] similarly find a roughly sinusoidal dependence of relative energy with torsion angle accompanying rotation of the C−N bond in FCH_2NH_2. Of especial relevance to the present study are their results of calculations with $\bar{C}H_2CH_2OH$. The total interaction energy was calculated as the energy of the following reaction: $CH_3CH_2^- + HOCH_2CH_3 \rightarrow CH_3CH_3 + HOCH_2CH_2^-$. When the free electron pair and the C−O bond were antiperiplanar, the total interaction energy was found to be 23.5 kcal mol^{-1}, whereas when the torsion angle of the electron pair and the C−O bond was 90°, the interaction energy was 10.3 kcal mol^{-1}. They assigned the difference (13.2 kcal mol^{-1}) to negative hyperconjugation, i.e., the anomeric effect, with the residual 10.3 kcal mol^{-1} due to the inductive effect. Putting our experimental observations and arguments together with the calculations of Schleyer and Kos, the inescapable conclusion is that the effect of a β-alkoxy group on the ease of α-carbanion formation displays negative hyperconjugation or, alternatively, is an illustration of the generalized anomeric effect.

(b) The Synperiplanar Lone-Pair Stereoelectronic Effect. One notable feature of Figure 1 which warrants special mention is the powerful effect of synperiplanar alkoxy groups, as shown by the large log k_N values for **1**, **2**, and **3,** in which the effect on k_N is close to or as large as that of the antiperiplanar alkoxy groups (e.g., compounds **14**, **15**, and **16**). Padwa and Wannamaker[23] have proposed synperiplanar $n \rightarrow \sigma^*$ overlap in connection with carbanion formation from a substituted 2-methoxycyclopropyl *p*-tolyl sulfone. Experimental evidence for the synperiplanar lone-pair effect in the chemistry of acetals has been put forward by Deslongchamps and Kirby and co-workers[24] (who concluded that the synperiplanar effect is weaker than the antiperiplanar) and supported by calculations.[25] Notwithstanding a suggestion that "synperiplanar...overlap would be disfavored",[26] the case for a strong synperiplanar lone-pair effect appears established.

(c) Angle Dependence of σ^*. A New Parameter, σ^*_θ. The variation of log k_N with the torsion angle may be described in terms of the Taft parameter σ^* provided one adds a new feature, namely angle dependence; we shall symbolize the angle-dependent σ^* as σ^*_θ, where θ implies an unspecified angle and σ^*_{30}, for example, refers to the value at $\theta = 30°$. Under the conditions of our experiments (NaOD in D_2O-dioxane-d_8 at 25 °C), the rate constants for H−D exchange of $PhSO_2CH_2CH_2$-OMe (**30b**) and $PhSO_2CH_2CH_3$ (**31a**) (Chart 1) were found to be, respectively, 0.51 and 4.14×10^{-4} M^{-1} s^{-1} (ratio = k_N = 1.2×10^3). Thomas and Stirling[11a] report 0.44 and 3.7×10^{-4} M^{-1} s^{-1} (ratio 1.2×10^3) for their detritiations of $PHSO_2$-$CHTCH_2X$ (in EtO^-/EtOH at 25 °C), and it is clear that the two systems are very much alike. If we write eq 1 (log k_N = $3.01 + 1.31 \cos 2\theta = 1.70 + 2.62 \cos^2 \theta$) from our work and take log $k_N = 4.89\sigma^*_\theta$ from Thomas and Stirling's results, we get eq 2, which gives the σ^*_θ value of the CH_2OR group as a function of the torsion angle, θ: In this formulation, σ^*_θ for the

$$(\sigma*_\theta)_{OR} = 0.62 + 0.27 \cos 2\theta = 0.35 + 0.54 \cos^2 \theta \qquad (2)$$

CH_2OR group may vary from $\sigma^*_{90} = 0.35$ through $\sigma^*_{60} = 0.49$ to $\sigma^*_0 = \sigma^*_{180} = 0.89$. A plot of the "corrected" log k_N values (bullets, black diamonds, and bulls-eyes) vs σ^*_θ gives an approximately straight line with slope (ρ^*) of 4.88. Note that $\sigma^*_{180} = 0.89$ is distinctly larger than the value of σ^* for CH_2-OMe (0.64) used by Thomas and Stirling. This reflects the fact that the maximum value of log k_N in our study is taken as 4.3, whereas in Thomas and Stirling's work log(k_{OMe}/k_H) = 3.08; i.e., in these experiments we are seeing larger k_N values with alkoxy groups in fixed conformations than with the conformationally mobile species (**30b**). Such a situation arises in a conformationally mobile system whenever there is a mixture of conformations of differing reactivity and the system is subject to Winstein−Holness kinetics.[27] In the simplest case of two equimolar conformations, one of which is reactive and the other totally unreactive, for example, the measured k_{obs} is one-half of the specific rate of the reacting conformation. In the present case of $PhSO_2CH_2CH_2OMe$ (**30b**), the reacting conformer is arranged as in **A** (X = OMe, $C_{\alpha'}$ = Ph). From the discussion already given[21] in connection with the relatively low reactivity of **17b**, the arrangement as in **A** is expected to have high energy. The low value of log(k_{OMe}/k_H) is presumably a reflection of a relatively low concentration of the reacting conformer (**A**, X = OMe, $C_{\alpha'}$ = Ph).

This suggests that a rigorous treatment of a reaction of conformationally mobile species by the Taft equation would require a full conformational analysis with individual rate constants for conformers taken with a set of σ^*_θ values. Presumably, the success of simpler treatments suggests that (a) some systems are not complex, and (b) we often deal with averaging of conformational populations, rates, and σ^* values. Observation of experimental "noise" is not surprising.

(d) The Angle-Independent Term. As has been noted already, nearly half of the effect of alkoxy groups on log k_N appears to be more or less independent of the torsion angle, θ. This is readily reconciled with the presence of the inductive effect which operates by successive bond polarizations and is therefore uninfluenced by the torsion angle. The field effect, however, is expected to be controlled to some extent by geometry. The Coulombic interaction of a dipolar bond (the C−O bond in this instance) and charge (or partial charge in a transition state) may be calculated from the Kirkwood−Westheimer equation;[28] for a particular reaction and substituent (e.g., the alkoxy group) this equation may be written as $\Delta E = C(\cos \zeta)/r^2$, where with the system at hand, $RO-C_\beta-C_\alpha-H$, r is the distance from the hydrogen nucleus to the center of C−O bond, ζ is the angle that the hydrogen-to-mid-bond line makes with the C−O bond, and C is a constant in this system.[29] We

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obtained atomic coordinates with PCModel and then calculated $(\cos \zeta)/r^2$ as a function of θ, the O−C−C−H torsion angle, and obtained a smooth sigmoid curve varying from a low of 0.033 Å^{-2} with $\theta = 0°$ to a maximum of 0.11 Å^{-2} with $\theta = 180°$; i.e., the energy of the field effect is smallest with $\theta = 0°$ and is greatest (by about 3.3-fold) with $\theta = 180°$.

Note that the overall shape shown by the bullets, black diamonds, and bulls-eyes in Figure 1, and that for the field effect as described by Kirkwood and Westheimer, are qualitatively totally different. The field effect therefore cannot be responsible for the major features of Figure 1, but it is still possible that it could be making a detectable contribution. Inspection of Figure 1 suggests that the points around $\theta = 180°$ appear to be slightly higher than those around $\theta = 0°$, perhaps by as much as 0.5 log k_N units. One conceivable source of this difference—if it is real—could be the field effect.[30] More complete evaluation of the Kirkwood−Westheimer equation[29] requires the use of somewhat arbitrary parameters. Our calculations, which suggest that the field effect may make a contribution to log k_N of 0.22 at $\theta = 0°$ and 0.74 at $\theta = 180°$, were calculated by using $D_E = 4$ and a developing charge in the region originally occupied by the hydrogen of 0.75 of a negative charge; note that either a larger value for D_E or a smaller magnitude for the charge lowers the log k_N contributions due to the field effect estimated in this way.

The results and discussion to this point indicate that the polar effect of an alkoxy group may be qualitatively analyzed as follows: at $\theta = 0°$ and 180°, the polar effect comprises a negative hyperconjugative effect plus a smaller inductive effect plus a still smaller field effect. At other values of θ the hyperconjugative effect diminishes, until at $\theta = 90°$ it is zero and the polar effect consists of only the inductive effect and the field effect.

Reaction via a Less Stable Conformer: The Case of Compound 5. Although many reactions take place by way of the most stable conformer(s), one must keep in mind that exceptions to this generalization frequently occur when, as in the present study, stereoelectronic requirements are important.[31] It therefore seemed prudent to examine the substrates in Table 1 to see if any of these might react to a substantial extent via a conformation different from that shown. One likely example was, in fact, found.

Compound **5** in the most stable (equatorial) conformation (**5e**) clearly has the $PhSO_2$ group equatorial, with the H−C−C−O torsion angle (θ) close to 60°. The alternative axial conformation (**5a**) can be expected to have higher energy than **5e**, but θ in **5a** is close to 180°, and from eq 1 the rate constant for **5a** must be greater than that for **5e** by about 114 ± 5 times because of the angular dependence of the stereoelectronic effect. Using the Winstein−Holness equation,[27] we may write $k_{obs} = k_{eq}n_{eq} + k_{ax}n_{ax}$, where n is the number of mole fractions of the subscripted conformer and k is its rate constant. To estimate n for each of the conformers we note from an earlier section that $\Delta G°$ for **26** ⇌ **27** is 2.66 kcal mol^{-1} (at 64 °C) (a number in accord with the reported conformational energy 2.50 kcal mol^{-1} at −90 °C of the methylsulfonyl group attached to cyclohexane).[32] We also note, on the other hand, that García Ruano et al.[33] have estimated that $\Delta G_{ax} - \Delta G_{eq}$ for 3-methylsulfonyltetrahydropyran (**35**, Chart 2) is "in the 1.4 to 1.5 kcal mol^{-1} range", and have suggested that the most favorable axial arrangement is that with the methyl group pointing into the ring to avoid oxygen−oxygen repulsions (but unable to avoid a methyl−1,3-axial hydrogen interaction). The phenylsulfonyl group may be expected to show a stronger interaction with the 1,3-axial hydrogen, and hence $\Delta G_{ax} - \Delta G_{eq}$ for **5** may be expected to be >1.5 kcal mol^{-1}. We suggest that 2.0 ± 0.5 kcal mol^{-1} probably encompasses the likely range, and from this we estimate $n_{ax} \approx 0.03$ (range 0.01−0.09), from which, if we set $k_{ax} \approx 114\ k_{eq}$, then it is evident from the Winstein−Holness equation that about 80% (range 63−90%) of the reaction of **5** will proceed by way of the axial conformer (**5a**). We also find log $k_N = 4.2 \pm 0.3$ for **5a** and 2.14 ± 0.3 for **5e**, values of log k_N in good accord with expectation from eq 1 on the basis of torsion angles of, respectively, 180 and 60°; these values are not included in the array used for the best fit for eq 1, however, because they are not estimated independently of eq 1.

An Application. We now apply the results of this study to a question of mechanism dating back to the middle 1950s, when Bordwell and Pearson and co-workers[34] looked at *syn* and *anti* eliminations in a series of sulfones including **36** and **37** (Chart 2). These authors concluded initially that the *anti* elimination from **36** and the *syn* elimination from **37** (to form 1-cyclohexenyl *p*-tolyl sulfone in each case) both proceeded by way of concerted (*E*2) reactions. In 1962, Hine and Ramsay[35] questioned this conclusion and provided evidence that the *syn* elimination, contrary to the contention of Bordwell and Pearson, was not faster than could be expected for a carbanion process. Subsequently, Bordwell, Weinstock, and Sullivan[36] marshalled arguments and evidence to conclude that the *syn* and *anti* eliminations both take place by the carbanion mechanism. Their argument invoked two ideas, (a) internal return of the carbanion to account for the apparent difference between rates of H−D exchange and elimination reactions, and (b) a "retardation effect" in forming carbanions from 1,2-diequatorially disubstituted

(29) According to the Kirkwood−Westheimer equation $\Delta E = q\mu(\cos \zeta)/Dr^2$, where r is the distance from the hydrogen nucleus to the center of the C−O bond, q is the magnitude of the charge (which we took initially as that of the electron, 1.60×10^{-19} C, see below), μ is the bond moment of the dipolar bond, taken as 0.7 D where 1 D = 3.34×10^{-30} C·m, and $D = D_E(4\pi\epsilon_0)$, where D_E is the "effective dielectric constant" (see below) and ϵ_0 is the permittivity of free space (8.85×10^{-12} C^2 N^{-1} m^{-2}). From this (with Avogadro's number) we obtain $\Delta E = 2.03 \times 10^{-15}(\cos \zeta)/D_E r^2$ J mol^{-1}. As is discussed in the text, when θ is 0° then $(\cos \zeta)/r^2 = 0.033$ Å^{-2} ($=3.3 \times 10^{18}$ m^{-2}), and when θ is 180° then $(\cos \zeta)/r^2 = 0.11$ Å^{-2}. At this point we must make a choice of two parameters, D_E and the magnitude of the developing negative charge. Kirkwood and Westheimer[28] have suggested that the effective dielectric constant, D_E, for the space between the charge and a dipole should be in the range 3−10; we find that $D_E = 4$ gives a range of log k_N values consistent with Figure 1. The developing anionic charge must be less than 1, but, from the considerable sensitivity of the reaction to substituents (cf. $\rho^* = 4.89$) we find it difficult to imagine a charge less than 0.5; we used 0.75 in our calculations while noting that the results are not very sensitive to the precise number. These parameters (with 4.184 J/cal) gave ΔE values of 0.30 and 1.00 kcal mol^{-1} (for $\theta = 0°$ and 180°, respectively); division by $2.303RT$ gives log k_N field effect contributions of 0.22 (minimum) and 0.74 (maximum), respectively.

(30) Another possible source could be the choice of model compounds for **13**, **14**, **15**, and **16**; in all of these the alkoxy oxygen is modeled by a methylene group, which could (by its small polar effect) be slowing the reactions of the models, leading to slightly higher k_N values for these substrates.

(31) For purposes of illustration we note two examples: (a) the antiperiplanar preference over a synclinal arrangement in the *E*2 reaction which leads to reaction by way of the axially oriented leaving group on a cyclohexane ring, and (b) the formation (and opening) of cyclohexene oxides by way of the diaxial conformation of the chlorohydrin.

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cyclohexyl derivatives; in our view, both of these effects need at least a little modification.

Returning to Hine and Ramsay's paper,[35] the key piece of evidence was a plot of log *k* vs σ^* in which the reactions were (a) the H−D exchange reactions of cyclohexyl *p*-tolyl sulfone (**23c**) and 2-*cis*-methoxycyclohexyl *p*-tolyl sulfone (**17c**), and (b) the elimination reactions of **36**, **37**, and 2-*cis*-chloro- and 2-*cis*-fluorocyclohexyl *p*-tolyl sulfones. They commented as follows: "From the best straight line through the unsubstituted, *cis*-2-methoxy and *trans*-2-tosyloxy sulfones [i.e. **23c**, **17c** and **37**], it is seen that the rate of *cis* elimination of the *trans*-tosyloxy compound [**37**] is not faster but instead rather slower than would be predicted from the σ^*-constants of the groups used." The agreement between the points and "the best straight line" in the above quote is not very good, and the authors discussed possible steric factors for the observation that the point for **37** was below that expected from the σ^* value. Hine and Ramsay's plot included **36** and two *cis*-halo analogues; the points for the three were well above the best straight line through the other three points, consistent with the idea that these compounds react by an *E*2 reaction. Note that they used the same σ^* value for both the *cis*- and *trans*-tosylates (**36** and **37**).

We wish to point out that the notion of angle-dependent substituent effects automatically puts *all* of the points on the same straight line (modified) Taft plot. If we recall from the above discussion that $\sigma^*_{60} = 0.49$, i.e., roughly half of $\sigma^*_0 = \sigma^*_{180} = 0.88$, it is tempting, indeed, to simply assign to the *trans*-tosylate a σ^* value about half that of the *cis* isomer; immediately one sees all six points arrayed in a pattern remarkably close to a straight line! Obviously, a more rigorous treatment of these data in the light of the idea of angle-dependent σ^* values requires a set of independently determined σ^*_{180} values for the CH_3, CH_2F, CH_2Cl, CH_2OTs, and CH_2OMe groups and a σ^*_{60} value for the CH_2OTs function. We do not have such a set of experimental values, but a curve obtained using roughly estimated values gave an acceptable straight line.[37] Since two of the Hine−Ramsay reactions are carbanion formations, it is reasonable to infer that the eliminations also involve carbanions or, if not, that the transition states are extremely similar to those of carbanions. In other words, the reactions are either *E*1cB or very *E*1cB-like *E*2 processes.

In view of the complexity of some of the discussion in this paper to this point, it may be helpful to view this topic from a perspective requiring specifically neither σ^*_θ nor log k_N values. A simple plot of log *k* for the reactions of **23c** (H−D exchange), **36**, and **37** (both eliminations) (data as presented by Hine and Ramsay)[35] vs our results for H−D exchange in **23b**, **6b**, and **17b** is shown in Figure 3. The three points fit a straight line with a slope of 2.7, and we are immediately led to the same conclusions as those drawn in the previous paragraph. Note that the slope is expected to reflect the ratio of the σ^* values (1.31/0.52 = 2.5 if we take Hine and Ramsay's values). The point for the *cis*-tosylate (**36**) is slightly above the (projected) straight line joining **23c** and **37** (which has a slope of 2.5); this could conceivably permit an *E*1cB mechanism for **37** and an *E*1cB-like *E*2 reaction for **36**; it is also possible that the deviation could also arise from the factor responsible for the relatively low reactivity of **17b** noted[21] in connection with the deviation of this point from eq 1.

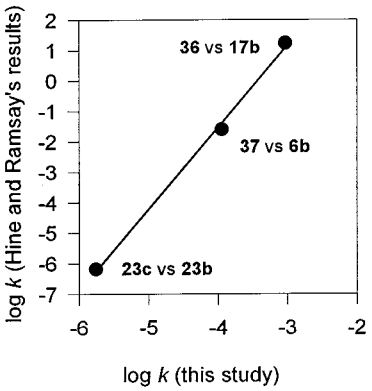

Figure 3. log−log plot of Hine and Ramsay's rate constants for H−D exchange in **23c** and for elimination in **37** and **36** vs our rate constants for H−D exchange in **23b**, **6b**, and **17b** (Table 1).

Bordwell et al.[36] had already drawn the conclusion that the *anti* and *syn* elimination reactions are probably both carbanion processes, and it is now appropriate to see how the present results relate to their arguments, namely internal return and the retardation effect. First we note that Thomas and Stirling's results show the isotopic exchange reactions to be very sensitive to substituents ($\rho^* = 4.89$), and hence there is no longer any discrepancy between exchange and elimination to require an explanation in terms of internal return. In addition, the question of internal return had been considered by Thomas and Stirling,[11] who concluded from their observation of a sizable tritium isotope effect ($k_H/k_T = 7.1$) that internal return is probably not an important feature of this hydrogen isotope exchange reaction. The second effect postulated by Bordwell et al.[36] was the "retardation effect" in carbanion formation in six-membered cyclic compounds to account for the observation that *syn* eliminations in cyclohexyl compounds were apparently slow relative to either (a) the analogous *anti* eliminations in cyclohexyl or cyclopentyl substrates or (b) the corresponding *syn* eliminations in cyclopentyl species. If we now look at these results in the light of the present work, we note that the H−C−C−O torsion angle in the cyclohexyl substrates undergoing *syn* elimination (e.g., **37**) is around 60°, and these substrates are *expected* to form the carbanion more slowly than either the *trans*-cyclopentyl compounds (reacting by *syn* eliminations), in which the torsion angle can readily be close to 0°, or the *cis* substrates in either the cyclopentyl or cyclohexyl systems, in which the H−C−C−O torsion angle is close to 180°. The results of the present study *predict* that the *syn*-cyclohexyl ($\theta = 60°$) reactions will be slower than any of the other reactions (with 0 or 180° torsion angles). No further "retarding effect" is required to account for the results, though it is, of course, always possible that such an additional effect is operating in some measure.[38]

Finally, we note that the stereospecificity of the reactions of *threo*- and *erythro*-3-*p*-toluenesulfonyl-2-butyl brosylates, *p*-$TolSO_2$(Me)CHCH(Me)OBs,[36] also readily follows from the present work. The *threo* and *erythro* diastereomers each have three conformations about the C(2)−C(3) bond, but the kinetic

(37) Assuming that the ratio of σ^* to σ^*_{180} is probably much the same for all substituents. we readily get σ^*_{180} values of for the respective groups by multiplying the σ^* values (CH_3, 0.0; CH_2F, 1.16; CH_2Cl, 1.04; CH_2-OMe, 0.56; and CH_2OTs, 1.31) by $(\sigma^*_{180})_{OMe}/(\sigma^*)_{OMe} = 0.89/0.64 = 1.41$; the σ^*_{180} values so obtained were, respectively, 0.0, 1.64, 1.47, 0.79, and 1.85. The $(\sigma^*_{60})_{OTs} = 1.00$ was estimated from $(\sigma^*_{60})_{OMe} = 0.49$ (see above) by multiplying by the scaling factor 1.31/0.64. The linear least-squares line corresponded to the equation $\log k = -6.1 + 4.1\sigma^*_\theta$, with $r = 0.985$.

(38) We wish to point out that we fully concur with the *basis* of the skepticism of Bordwell et al., i.e., that "it does not seem possible to account for more than *ca.* 10^3 acceleration [in hydrogen exchange] on the basis of an inductive effect." It was precisely this difficulty that we experienced when faced with Thomas and Stirling's results and that led us to the present study, i.e., to look for another component of the polar effect in addition to the inductive and field effects.

acidity of the α-hydrogen in the one with the H−C−C−O torsion angle of 180° must be much greater than that in either of the other conformers (with $\theta = 60°$), and in each case that conformer reacts much faster than the others to give the olefin stereospecifically. This is perhaps the best place to point out explicitly that the stereospecificity (whether *syn* or *anti*) of *E*1cB and *E*2 reactions may be regarded as a *consequence* of the torsion angle dependence of the acidifying effect of the substituent-cum-nucleofuge, taken, of course, with any relevant accompanying factors such as conformational populations.

Relation to Other Work. (a) By Ahlberg and Thibblin. It is perhaps appropriate to point out here that hyperconjugative stabilization of transition states for carbanion-forming elimination reactions has been proposed by Ahlberg and Thibblin.[39] They have focused particularly on the borderline between *E*1cB and *E*2 processes, and though their picture and ours would appear to have a common feature at a fundamental level, their work is distinctly different from ours; they have proposed and applied a modified linear free energy relationship with two new parameters related to leaving group activity, whereas our studies have been primarily concerned with the experimental proof of torsion angle dependence and examining its consequences.

(b) By Rappoport and Apeloig. A somewhat different approach, involving substitution and addition reactions of electrophilic olefins, has led Apeloig and Rappoport[9e] to propose an ingenious rationalization involving negative hyperconjugative stabilization of an intermediate carbanion as an important factor influencing the stereochemistry of their reactions. In our view, their conclusions and ours are fully consistent and mutually supportive.

(c) By Lambert. A study related and in some ways complementary to ours of the effect of substituent torsion angles has been carried out by Lambert and co-workers[40] on the β-trimethylsilyl substituent and its effect on the ease of carbocation formation. In this admirable investigation, they find a very large angle dependence of the substituent fully compatible with (positive) hyperconjugation leading to stabilization of the carbocation. It is probably not coincidental that the influence of substituent hyperconjugation has first been most clearly shown in the reactions of carbocations or carbanions. For one thing, these are the reactions showing the greatest electron supply or demand, and which can be expected to show the greatest substituent dependency (highest absolute ρ^* values) and hence the most clearly evident hyperconjugative effect. In addition, the carbocation- and carbanion-forming reactions are processes strongly dependent on conjugative or hyperconjugative influences. With aromatic systems these are the reactions which lead to correlations with σ^+ or σ^-, greater through conjugation than in the reference reaction; similarly, with the analogous nonaromatic carbocation- or carbanion-forming systems positive or negative hyperconjugation may be expected to be more in evidence than in the reference process.

(d) By Sinnott. A vigorous criticism of the kinetic anomeric effect (the antiperiplanar lone-pair hypothesis, ALPH), has been put forward by Sinnott,[41] who has argued that the principle of least nuclear motion (PLNM) accounts well for observations interpreted by others in terms of the kinetic anomeric effect. We have noted in our preliminary communication[12] that our "results constitute a good case for a kinetic anomeric effect not readily accounted for by PLNM". In our view the further work reported in the present paper, notably the observation of both synperiplanar and antiperiplanar effects, adds further weight to our contention that the generalized anomeric effect (the periplanar lone-pair hypothesis, PLPH?) does, and PLNM does not, account for our results.

Generality. The present study, in our view, establishes that the effect of β-alkoxy substituents on the rate of H−D exchange via α-sulfonyl carbanions is subject to variation in rate correlating with the H−C−C−O torsion angle. The work of Thomas and Stirling also clearly showed that the reaction rate conforms well to the Taft equation (with $\rho^* = 4.89$ for their conditions) with a varied range of substituents. Since the anomeric effect and negative hyperconjugation are not confined to alkoxy groups, the only reasonable construction that we can make from these observations is that we must expect the torsion angle dependence to be a general phenomenon, capable of appearing to a greater or lesser measure with *all* substituents. The effect can be expected to be small or negligible with some substituents (e.g., alkyl groups), but with most heteroatomic substituents it must be significant. Obviously further experiments are required to determine the general importance of torsion angle dependence, and work on this problem is underway in our laboratory.[42]

Experimental Part

General. Melting points were determined on a Kofler Hot Stage or a Fisher Johns apparatus and are uncorrected. IR spectra were obtained with a Bruker IFS 32 FTIR spectrometer and ^{1}H NMR spectra with Varian XL-200 or XL-300 and Gemini 200 or 300 instruments; the Gemini 300 instrument was used in all kinetic determinations; ^{13}C NMR spectra were determined (at 75 Hz) with the 300-MHz instruments. Where not otherwise specified, spectra were run on $CDCl_3$ solutions referenced with TMS or the $CHCl_3$ signal; TMS was used as the reference for solutions in acetone-d_6, and sodium trimethylsilylpropanesulfonate (DSS) was used for D_2O solutions. Mass spectra were run on a Finnigan MAT311A spectrometer. A Waters model 510 and a Waters 490 programmable multiwavelength detector were used in HPLC analyses (columns, C18, $\lambda = 260$ nm; solvents, CH_3OH:H_2O 1:1). Most materials used for kinetic measurements and HRMS molecular weight determinations showed ^{1}H and ^{13}C NMR spectra appropriate to pure compounds; the two exceptions, **24a** and **24b**, were obtained as specimens contaminated with up to 25% of the *cis* isomer (**25**). The structural assignments for these latter compounds follow unambiguously from their their mode of synthesis and spectra; the signals due to the α-hydrogens were clearly visible, and their disappearance was readily followed.

Reagent grade chemicals and solvents were used without purification except where otherwise noted. Et_3N was distilled from CaH_2. CH_3CN, absolute EtOH, THF, and DMSO were dried over CaH_2 and distilled; CH_2Cl_2 was dried over P_2O_5 and Et_2O over $LiAlH_4$ before distillation. Workup, where not described, involves, minimally, extraction with CH_2Cl_2 (at least 3 times), washing of the CH_2Cl_2 layers with water and, as appropriate, with dilute aqueous acid (HCl or H_2SO_4) or base (NaOH or $NaHCO_3$), drying of the organic layer over anhydrous $MgSO_4$ or Na_2SO_4, and evaporation of the CH_2Cl_2 using a Büchi Rotovap attached to a water aspirator.

Materials and Spectra. 1,4-Oxathiane 4,4-dioxide (**13**) (Aldrich): mp 131−133 °C; ^{1}H NMR δ 3.13 (t, 4 H), 4.14 (t, 4 H); ^{13}C NMR ($CDCl_3$) δ 52.8, 66.1.

Thiane 1,1-dioxide (**22**) from oxidation of thiane (Aldrich) with MCPBA: mp 98−99 °C (reported[43] mp 98.5−99 °C); IR (KBr) ν_{max}

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(40) See, for example: Lambert, J. B.; Liu, X. *J. Organomet. Chem.* **1996**, *521*, 203−210. Lambert, J. B.; Zhao, Y.; Emblidge, R. W.; Salvador, L. A.; Liu, X.; So, J.-H.; Chelius, E. C. *Acc. Chem. Res.* **1999**, *32*, 183−190.

(41) Sinnott, M. L. *Adv. Phys. Org. Chem.* **1988**, *24*, 113−204.

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2940 (s), 2956 (m), 1446 (w), 1319 (m), 1281 (vs), 1196 (m), 1130 (vs) 1067 (w), 963 (w), 849 (m) cm^{-1}; ^1H NMR δ 1.58 (sym m, 2 H), 2.03 (m, 4 H), 2.97 (t, 4 H); ^{13}C NMR δ 23.8, 24.2, 52.1.

***trans*-1,4-Oxathiadecalin 4,4-dioxide (15):**[14] mp 120−121 °C; IR (KBr) ν_{max} 2942 (s), 2870 (s), 1456 (m), 1308 (vs), 1269 (vs), 1227 (w), 1183 (m), 1130 (vs), 1024 (m), 939 (w), 853 (w), 729 (m), 538 (s) cm^{-1}; ^1H NMR δ 0.97−2.45 (m, 8 H), 2.86 (dddd, 1 H, C-10H_a), 3.07 (d of t, J_{gem} = 13.6, J_{ea} = 2.83, J_{ee} = 2.6, 1 H, C-3H_e), 3.28 (d of q, J_{gem} = 13.6, J_{aa} = 10.9, J_{ae} = 5.3 Hz, 1 H, C-3H_a), 3.67 (quintet, 1 H, C-9H_a), 4.12 (d of t, J_{gem} = 12.8, J_{aa} = 10.9, J_{ae} = 2.83 Hz, 1 H, C-2H_a), 4.28 (d of q, J_{gem} = 12.8, J_{ee} = 2.6, J_{ea} = 5.3 Hz, 1 H, C-2H_e) (the chemical shifts of **15** were dependent on the solvent); ^{13}C NMR, see ref 14a; HRMS calcd for $C_8H_{14}O_3S$ 190.0664, found 190.0663. The three α-(α′-)monodeuterated, three α-(α′-)dideuterated, and the single α,α′-trideuterated isotopomers of **15** have been prepared by successive deuteration and dedeuteration; their ^1H and ^{13}C NMR spectra are recorded elsewhere.[44a]

3-Methoxythiane 1,1-dioxide (4):[45] mp 66−68 °C (lit.[45] mp 66−66.5 °C); ^1H NMR δ 1.27−1.48 (m, 1 H), 1.8−2.3 (m, 3 H), 2.76−2.93 (m, 2 H), 2.96−3.09 (m, 1 H), 3.39 (s, 3 H), 3.42 (sym m, 1 H), 3.69 (t of t, J = 10.7 and 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 19.4, 30.4, 50.9, 56.0, 56.6, 75.7.

***trans*-1-Thiadecalin 1,1-dioxide (21):**[14a] mp 114−115 °C (lit.[14a] mp 114−115.8 °C); ^1H NMR δ 1.0−2.25 (m, 13 H), 2.59 (ddd, J = 12.5, 10.0, 3.5 Hz, 1 H, C-9H_a), 2.91 (m, 1 H, C-2H_a), 3.10 (dddd, J = 13.5, 4.0, 3.5, 1.4 Hz, 1 H, C-2H_e); ^{13}C NMR, see ref 14a.

***cis*-1,4-Oxathiadecalin 4,4-Dioxide (14).** *trans*-2-(2-Hydroxyethylthio)cyclohexanol[14c] (5 g, 28.4 mmol) in DME (10 mL) with concentrated HCl (25 mL), on workup after standing overnight, gave the dichlorosulfide (6 g), which on oxidation with 30% H_2O_2 (10 mL) in HOAc (30 mL) and Ac_2O (10 mL) gave, after workup, the dichlorosulfone (6.3 g); this in turn was mixed with 5% KOH (50 mL) and DME (10 mL), and the mixture was refluxed for 3 h. Workup gave **14** as white crystals (4.5 g, 85%): mp (after recrystallization from ether−cyclohexane) 130−131 °C; IR (KBr) ν_{max} 2944 (s), 2869 (m), 1449 (w) 1393 (m), 1291 (vs), 1240 (s), 1136 (s), 1121 (s), 1094 (vs), 1021 (m), 959 (w), 855 (w), 527 (m); ^1H NMR δ 1.16−2.20 (m, 8 H), 2.79 (sym m, 2 H, C-3H_e, and C-10H_e), 3.25 (d of q, J_{gem} = 12.2, J_{aa} = 11.1, and J_{ae} = 4.9 Hz, 1 H, C-3H_a), 4.00 (d of t, J_{gem} = 12.4, J_{aa} = 11.1, and J_{ae} = 2.2 Hz, 1 H, C-2H_a), 4.20 (br m, 1 H, C-9H_a), 4.25 (d of q, J_{gem} = 12.5, J_{ee} = 4.9, J_{ea} = 2.5 Hz, 1 H, C-2H_e) (the chemical shifts were dependent on solvent); ^{13}C NMR δ 19.1, 22.5, 24.7, 31.7, 47.5, 62.4, 65.2, 74.0; HRMS calcd for $C_8H_{14}O_3S$ 190.0664, found 190.0660.

Equilibration. 15 (500 mg) in 10% KOH in H_2O−EtOH (3:1) (25 mL) was heated at 100 °C for ∼100 h. The cooled reaction mixture was acidified with 5% HCl solution and extracted with CH_2Cl_2. Evaporation of the solvent gave, in quantitative yield, a 9:1 mixture of **15** and **14**, as determined by ^1H and ^{13}C NMR spectra; similar treatment of **14** gave a mixture with the same NMR spectra as that from **15**.

3-(Phenylsulfonyl)tetrahydropyran (5). 3-(Phenylthio)tetrahydropyran[46] was oxidized by H_2O_2 (30%) in acetic acid and gave a quantitative yield of **5** as a colorless liquid: ^1H NMR δ 1.45−2.25 (m, 4 H), 3.05−3.23 (m, 1 H), 3.27 (t, J = 11.2 Hz, 1 H), 3.47 (t, J = 11.2 Hz, 1 H), 3.84 (d, J = 11.2 Hz, 1 H), 4.07 (d, J = 11.2 Hz, 1 H), 7.50−7.90 (m, 5 H); ^{13}C NMR δ 22.8, 24.6, 60.3, 66.0, 67.6, 128.7, 129.2, 133.9, 137.2; calcd exact mass for $C_{11}H_{15}O_3S$ (M + 1) 227.0742, found 227.0737.

***trans*-1-Methoxy-2-(methylsulfonyl)cyclohexane (6a):**[47] NMR, see ref 47.

***trans*-1-Methoxy-2-(phenylsulfonyl)cyclohexane (6b).** *trans*-1-Chloro-2-(phenylthio)cyclohexane[48] (4.5 g, 20 mmol) was refluxed in methanol for 10 h to give, after workup, *trans*-1-methoxy-2-(phenylthio)cyclohexane. Oxidation by hydrogen peroxide (30%) in acetic acid gave **6b** in good yield: mp 77−79 °C; ^1H NMR δ 1.0−2.4 (m, 8 H), 3.00−3.12 (m, 1 H), 3.09 (s, 3 H), 3.46 (m, 1 H), 7.4−7.9 (m, 5 H); ^{13}C NMR δ 23.4, 24.0, 24.6, 30.0, 55.6, 67.4, 127.8, 128.5, 132.9, 141.6; calcd exact mass for $C_{13}H_{18}O_3S$ 254.0977, found 254.0975.

***cis*-1-Methoxy-2-(methylsulfonyl)cyclohexane (17a).** *trans*-1-Bromo-2-methoxycyclohexane[49] (10 g, 0.0518 mol) and $NaSCH_3$ (4.0 g, 0.0571 mol) were dissolved in 2-butanol and refluxed for 24 h. Workup as usual gave *cis*-1-methoxy-2-(methylthio)cyclohexane (4.6 g, 55%), which was oxidized with H_2O_2 (30%) in acetic acid to give **17a** (80%). Recrystallization from ethyl acetate−hexane gave **17a** as colorless crystals: mp 44−47 °C; ^1H NMR δ 1.1−2.2 (m, 8 H), 2.73 (dt, J = 12.7 and 2.9 Hz, 1 H), 2.82 (s, 3 H), 3.30 (s, 3 H), 4.0 (m, $w_{1/2}$ = 6 Hz, 1 H); ^{13}C NMR δ 18.7, 22.0, 25.1, 27.1, 39.4, 55.9, 67.1, 73.4; calcd exact mass for $C_8H_{16}O_3S$ 192.0820, found 192.0823.

***cis*-1-Methoxy-2-(phenylsulfonyl)cyclohexane (17b).** *trans*-1-Bromo-2-methoxycyclohexane[49] (15 g, 0.0777 mol) and NaSPh (9.4 g, 0.0855 mol) were dissolved in 2-butanol and refluxed for 48 h. Workup as usual gave *cis*-1-methoxy-2-(phenylthio)cyclohexane (16 g, 93%). Oxidation of the sulfide by hydrogen peroxide (30%) in acetic acid gave **17b**: mp 98−98.5 °C; ^1H NMR δ 1.0−2.2 (m, 8 H), 2.95 (m, 1 H), 3.17 (s, 3 H), 3.95 (m, 1 H), 7.4−7.9 (m, 5 H); ^{13}C NMR δ 18.5, 21.6, 24.9, 27.3, 55.7, 67.9, 73.1, 128.3, 129.1, 133.1, 138.7; calcd exact mass for $C_{13}H_{18}O_3S$ 254.0977, found 254.0977.

Cyclohexyl methyl sulfone (23a):[32,50] NMR, see ref 32.

Cyclohexyl phenyl sulfone (23b):[51] NMR, see ref 52.

***cis*-2-Methyl-1-(phenylsulfonyl)cyclohexane (25b):**[53] mp 73−74 °C (lit.[53] mp 74−74.5 °C); ^1H NMR ($CDCl_3$) δ 1.00−2.00 (m, 8 H), 1.20 (d, J = 7.1 Hz, 3 H), 2.45 (symmetric m, 1 H), 2.99 (dt, J = 12, 3.8 Hz, 1 H), 7.48−7.93 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 13.3, 19.3, 20.2, 25.5, 27.7, 33.4, 66.3, 128.4, 129.0, 133.3, 138.8.

***trans*-2-Methyl-1-(phenylsulfonyl)cyclohexane (24b).**[53] *cis*-2-Methyl-1-(phenylsulfonyl)cyclohexane (**25b**, 1.0 g) was dissolved in dioxane (20 mL), and sodium hydroxide solution (1 M, 20 mL) was added. The resulting solution was refluxed for 5 days. Workup as usual gave a *cis*/*trans* mixture of the 2-methyl-1-(phenylsulfonyl)cyclohexanes. Several recrystallizations using different solvents gave a roughly 4:1 mixture of the *trans*/*cis* epimers. Thin-layer chromatography using different solvents did not effect separation; mp of the mixture was 86−87 °C. The mixture was used directly in the determination of the H−D exchange rate. Data for the *trans* epimer (**24b**): ^1H NMR ($CDCl_3$) 0.80−2.20 (m, 9 H), 1.22 (d, J = 7.1 Hz, 3 H), 2.71 (ddd, J = 11.3, 9.5, 3.4 Hz, 1 H), 7.45−7.95 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 21.4, 24.8, 25.0, 27.4, 32.3, 35.4, 69.1 (the ^{13}C NMR signals for the carbons of benzene ring for the *trans* epimer (**24b**) are not clear because of overlap with the signals of the *cis* epimer (**25b**)); calcd exact mass for $C_{13}H_{19}O_2S$ (M + 1) (the mixture) 239.1106, found 239.1100.

***cis*-2-Methyl-1-(methylsulfonyl)cyclohexane (25a).** Methyl iodide (1.1 g, 7 mmol) was added to a solution of 2-methylcyclohexanethiol[53] (0.30 g, 2.3 mmol) and NaOH (0.09 g) in aqueous ethanol (1:1, 2 mL). After the resulting mixture was stirred for 30 min, it was poured into water, and the sulfide was obtained by extraction with petroleum ether. Oxidation of the crude sulfide with 30% of H_2O_2 in acetic acid gave the crude sulfone (95% from the thiol) as a *cis*/*trans* mixture. Recrystallization from methanol gave pure **25a** (0.21 g): mp 86−88 °C; ^1H NMR ($CDCl_3$) δ 1.16 (d, J = 7.0 Hz, 3 H), 1.2−2.0 (m, 8 H), 2.57 (symmetric m, 1 H), 2.81 (3 H, s), 2.96 (dt, J = 11.9, 3.8 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.3, 19.3, 20.8, 25.5, 27.8, 33.3, 39.4, 65.5; calcd exact mass for $C_8H_{17}O_2S$ (M + 1) 177.0949, found 177.0943.

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***trans*-2-Methyl-1-(methylsulfonyl)cyclohexane (24a). 25a** (100 mg) in methanol containing sodium methoxide (5%) was refluxed for 2 days. Workup as usual gave a 3:1 mixture of **24a** and **25a** as a semisolid (100 mg); this mixture was used as such to obtain the rate constant for **24a**. Data for **24a**: ^{13}C NMR δ 21.1, 25.0, 25.1, 27.1, 32.8, 35.4, 39.1, 68.7; calcd exact mass for $C_8H_{17}O_2S$ (M + 1) 177.0949, found 177.0946.

***trans*-4-*tert*-Butylcyclohexyl phenyl sulfone (26) and *cis*-4-*tert*-butylcyclohexyl phenyl sulfone (27):**[54] NMR, see ref 55.

Phenyl ethyl sulfone (31a):[56] ^{1}H NMR, see ref 57; ^{13}C NMR, see ref 58.

Phenyl propyl sulfone (31b):[56] ^{13}C NMR δ 12.9, 16.5, 57.9, 128.0, 129.2, 133.6, 139.1; ^{1}H NMR, see ref 59.

Phenyl butyl sulfone (31c):[56] ^{1}H NMR, see ref 60.

Phenyl pentyl sulfone (31d):[60] ^{13}C NMR δ 13.6, 22.0, 22.2, 30.3, 56.2, 127.9, 129.2, 133.5, 139.1. ^{1}H NMR, see ref 61.

Phenyl hexyl sulfone (31e):[62] ^{13}C NMR δ 13.6, 22.2, 22.5, 27.9, 31.1, 56.3, 128.0, 129.2, 133.5, 139.1; ^{1}H NMR, see ref 59.

2-Methyl-1,4-oxathiane 4,4-Dioxide (16). Concentrated HCl (25 mL) was added slowly to a solution of $HOCH_2CH_2SCH_2CH(OH)CH_3$[14d] (5 g, 37 mmol) in DME (10 mL), and the mixture was left at room temperature overnight. Workup gave $ClCH_2CH_2SCH_2CHClCH_3$ as a clear oil (6.2 g, ~100%): ^{1}H NMR δ 1.56 (d, 3 H), 2.74−3.00 (m, 4 H), 3.62 (t, 2 H), 4.09 (sextet, 1 H); ^{13}C NMR δ 23.8, 35.0, 41.9, 42.9, 56.7. The dichlorosulfide (2 g, 11.8 mmol) on oxidation with MCPBA (4 g, 24 mmol), after workup, gave $ClCH_2CH_2SO_2CH_2CHClCH_3$ as a viscous liquid: IR (neat) ν_{max} 2984 (s), 2934 (m), 1451 (m), 1395 (s), 1318 (vs), 1125 (vs), 1034 (s), 868 (s), 735 (m) cm^{-1}; ^{1}H NMR δ 1.71 (d, 3 H), 3.34−3.79 (m, 4 H), 3.93 (t, 2 H), 4.56 (sym m, 1 H); ^{13}C NMR δ 25.2, 35.6, 49.7, 56.5, 62.9. The sulfone (2.5 g) in DME (5 mL) was refluxed for 5 h with 10% aqueous KOH (15 mL). Workup gave **16** (mp 110−111 °C from ether−petroleum ether): IR (KBr) ν_{max} 2974 (m), 2936 (m), 1375 (s), 1314 (s), 1287 (vs), 1256 (s), 1196 (s), 1127 (vs), 1082 (vs 509 (s) cm^{-1}; ^{1}H NMR δ 1.34 (d, 3 H), 2.83−3.23 (m, 4 H), 3.95−4.13 (m, 2 H), 4.30 (ddq, J = 12.7, 2.3, 4.7 Hz); ^{13}C NMR δ 21.2, 51.5, 58.4, 65.0, 72.7; HRMS calcd for $C_5H_{10}O_3S$ 150.0351, found 150.0352.

***endo*-3-(Phenylthio)-*exo*-2-norbornanol.** Thiophenol (13.00 g, 0.118 mol) and *exo*-norbornene oxide[63] (8.50 g, 0.077 mol) were added to a solution of sodium hydroxide (6.00 g, 0.15 mol) in 50% aqueous EtOH solution (v/v, 75 mL), and the mixture was refluxed for 100 h and then cooled to room temperature. Workup gave a brown oil which solidified on standing; recrystallization from toluene and petroleum ether gave *endo*-3-(phenylthio)-*exo*-2-norbornanol as white crystals (15.21 g, 0.069 mol, 89.7% yield): mp 64−65 °C; IR (KBr) ν_{max} 3291 (s), 3055 (s), 2940 (s), 2961 (s), 1582 (m), 1482 (m), 1437 (s), 1318 (m), 1117 (m), 1053 (s), 1005 (s), 814 (m), 737 (s), 688 (s); ^{1}H NMR δ 1.22 (m, 1 H), 1.39 (m, 2 H), 1.58 (m, 1 H), 1.78 (m, 3 H), 2.20 (d, 1 H), 2.42 (d, 1 H), 3.29 (m, 1 H), 3.56 (t, 1 H), 7.21−7.28 (m, 3 H), 7.42−7.46 (m, 2 H); ^{13}C NMR δ 22.3, 24.7, 35.6, 40.6, 44.9, 59.1, 81.9, 126.1, 128.9, 130.0, 136.6; HRMS calcd for $C_{13}H_{16}OS$ 220.0922, found 220.0924.

***endo*-3-(Phenylthio)-2-norbornanone.** Dimethyl sulfoxide (3.438 g, 44 mmol) was added dropwise over ca. 5 min to a solution of oxalyl chloride (2.539 g, 20 mmol) in dichloromethane (30 mL) at −78 °C. The reaction mixture was stirred for 15 min at −78 °C. *endo*-3-(Phenylthio)-*exo*-2-norborneol (3.50 g, 15.9 mmol) in dichloromethane (10 mL) was added dropwise over about 5 min, and the mixture was stirred for 30 min at −78 °C. Triethylamine (7.26 g, 71.7 mmol) was added dropwise over 5 min, and stirring was continued at −78 °C for 30 min. The cooling bath was removed, and water (30 mL) was added at room temperature. The mixture was stirred for ca. 10 min, and the organic layer was separated. Workup gave *endo*-3-(phenylthio)-2-norbornanone (3.47 g, 15.9 mmol, 99% yield), which was distilled at 245 °C (oil bath, 8 Torr) to give a slightly yellowish oil: IR (neat) ν_{max} 3478 (w), 3058 (m), 2967 (s), 2876 (m), 1746 (s), 1583 (m), 1480 (s), 1439 (m), 1316 (m), 1293 (m), 1157 (s), 1073 (s), 1026 (m), 941 (m), 742 (s), 693 (s) cm^{-1}; ^{1}H NMR δ 1.62−2.06 (m, 6 H), 2.73 (m, 2 H), 3.71 (dd, 1 H), 7.24 (m, 3 H), 7.43 (m, 2 H); ^{13}C NMR δ 21.8, 25.2, 36.2, 40.7, 49.8, 59.7, 126.9, 128.9, 131.0, 134.9, 213.4; HRMS calcd for $C_{13}H_{14}OS$ 218.0765, found 218.0769.

***endo*-3-(Phenylthio)-*endo*-2-norbornanol.** *endo*-3-Phenylthio-2-norbornanone (1.50 g, 6.87 mmol) in anhydrous diethyl ether (10 mL) was added dropwise over 6 min to a slurry of lithium aluminum hydride (0.508 g, 6.87 mmol) in anhydrous diethyl ether (20 mL) at 0 °C. The mixture was stirred for 0.5 h at 0 °C. Ethylene glycol (1.706 g, 27.48 mmol) was then added slowly at 0 °C. Stirring was continued for 5 min at 0 °C, and the mixture was filtered. The solid was washed with dichloromethane (3 × 30 mL). The combined filtrate was washed with water (3 × 30 mL), and the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated to give the product (1.42 g, 6.41 mmol, 94.2% yield) as a colorless liquid: IR (neat) ν_{max} 3443 (s), 3058 (w), 2957 (s), 2876 (s), 1586 (s), 1480 (s), 1452 (m), 1383 (m), 1320 (m), 1296 (m), 1125 (m), 1090 (s), 1063 (s), 1026 (s), 738 (s), 691 (s) cm^{-1}; ^{1}H NMR δ 1.47 (m, 4 H), 1.65 (m, 1 H), 1.87 (m, 1 H), 2.55 (d, 2 H), 2.96 (d, 1 H), 3.62 (dq, 1 H), 4.18 (m, 1 H), 7.27 (m, 5 H); ^{13}C NMR δ 19.49, 23.53, 36.09, 42.63, 42.68, 55.64, 69.68, 126.36, 129.02, 129.46, 136.38; HRMS calcd for $C_{13}H_{16}OS$ 220.0922, found 220.0920.

***endo*-3-(Phenylthio)-*endo*-2-methoxynorbornane.** *endo*-3-(Phenylthio)-*endo*-2-norbornanol (1.200 g, 5.45 mmol) in DMSO (3 mL) was added to a solution of potassium hydroxide (1.220 g, 21.8 mmol) in DMSO (7 mL) at room temperature. The mixture was stirred at room temperature for 1−2 min. Iodomethane (3.094 g, 21.8 mmol) was added, and stirring was continued for 15 min. Water (30 mL) and dichloromethane (40 mL) were added. Workup gave the product (1.263, 99% yield) as a slightly yellowish liquid: IR (neat) ν_{max} 3058 (w), 2955 (s), 2872 (s), 2824 (m), 1585 (m), 1480 (s), 1439 (s), 1360 (m), 1294 (w), 1190 (m), 1129 (s), 1109 (s), 957 (m), 909 (w) cm^{-1}; ^{1}H NMR δ 1.34 (m, 4 H), 1.78 (m, 1 H), 2.05 (m, 1 H), 2.30 (s, 1 H), 2.53 (s, 1 H), 3.33 (s, 3 H), 3.69 (dd, 1 H), 3.81 (dd, 1 H), 7.24 (m, 3 H), 7.35 (m, 2 H); ^{13}C NMR δ 19.9, 22.8, 35.8, 40.0, 41.1, 52.6, 57.9, 80.4, 125.8, 128.7, 130.2, 137.1; HRMS calcd for $C_{14}H_{18}OS$ 234.1078, found 234.1077.

***endo*-3-(Phenylsulfonyl)-*endo*-2-methoxynorbornane (10).** Hydrogen peroxide (30%, 8.5 mL) was added dropwise to a solution of *endo*-3-(phenylthio)-*endo*-2-methoxynorbornane (1.03 g, 4.4 mmol) in acetic acid (3 mL) at room temperature. The mixture was heated on a steam bath for 30 min. Workup gave the product **10** (1.12 g, 95% yield) as white crystals, which were recrystallized from 85% methanol: mp 96−98 °C; IR (KBr) ν_{max} 3058 (w), 2946 (s), 2874 (s), 2830 (m), 1447 (s), 1327 (s), 1310 (s), 1279 (s), 1248 (m), 1144 (s), 1113 (s), 1084 (s), 1073 (s), 720 (s), 693 (s) cm^{-1}; ^{1}H NMR δ 1.43 (m, 4 H), 2.06 (m, 1 H), 2.46 (m, 1 H), 2.60 (m, 2 H), 3.29 (s, 3 H), 3.45 (ddd, 1 H), 3.84 (ddd, 1 H), 7.56 (m, 3 H), 7.91 (m, 2 H); ^{13}C NMR δ 19.4, 22.6, 36.8, 40.1, 40.5, 58.1, 67.0, 80.0, 128.4, 128.8, 133.0, 141.4; HRMS calcd for $C_{14}H_{19}O_3S$ (M + H) 267.1055, found 267.1060.

***endo*-3-(Phenylsulfonyl)-*exo*-2-norbornanol.** Hydrogen peroxide (30%, 34 mL) was added dropwise to a solution of *endo*-3-(phenylthio)-*exo*-2-norbornanol (3.93 g, 17.8 mmol) in acetic acid (13 mL) as above to give the product (4.08 g, 91.0% yield) as a white solid, which was recrystallized from 60% ethanol: mp 114−115 °C; IR (KBr) ν_{max} 3453 (s), 3067 (w), 2940 (s), 2872 (m), 1304 (m), 1284 (s), 1269 (s), 1134 (s) 1086 (s), 1067 (s), 720 (s), 604 (s); ^{1}H NMR δ 1.39 (m, 2 H), 1.70 (m, 2 H), 2.13 (m, 2 H), 2.33 (d, 1 H), 2.51 (d, 1 H), 3.19 (dt, 1 H), 4.29 (m, 1 H), 7.61 (m, 3 H), 7.91 (m, 2 H); ^{13}C NMR δ 22.2, 24.3,

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37.0, 39.3, 45.2, 74.7, 76.2, 127.9, 129.3, 133.6, 140.2; HRMS calcd for $C_{13}H_{16}O_3S$ 252.0820, found 252.0822.

***endo*-3-(Phenylsulfonyl)-*exo*-2-methoxynorbornane (3).** *endo*-3-(Phenylsulfonyl)-*exo*-2-norborneol (0.25 g, 1.0 mmol) was added to a solution of potassium hydroxide (0.224 g, 4.0 mmol) in DMSO (2 mL) and treated with iodomethane (0.57 g, 4.0 mmol) as above. Workup gave the product (**3**) (0.238 g, 0.89 mmol, 89% yield) as a white solid, which was recrystallized from 60% methanol: mp 125−126 °C; IR (KBr) ν_{max} 3069 (w), 2976 (m), 2940 (m), 2880 (m), 1447 (s), 1363 (m), 1298 (s), 1269 (s), 1150 (s), 1130 (s), 1084 (s), 756 (s), 720 (s), 689 (s), 606 (s) cm^{-1}; ^1H NMR δ 1.27−1.41 (m, 3 H), 1.58−1.67 (m, 2 H), 2.20 (m, 1 H), 2.50 (m, 2 H), 3.16 (s, 3 H), 3.18 (m, 1 H), 3.67 (m, 1 H), 7.29 (m, 3 H), 7.63 (m, 2 H); ^{13}C NMR δ 22.9, 23.7, 37.0, 38.8, 41.3, 56.9, 74.0, 83.5, 127.8, 129.0, 133.3, 140.2; HRMS calcd for $C_{14}H_{19}O_3S$ (M + H) 267.1055, found 267.1059.

***exo*-3-(Phenylthio)-2-norbornanone.** *endo*-3-(Phenylthio)-2-norbornanone (3.80 g, 17.4 mmol) was added to a solution of potassium hydroxide (1.95 g, 34.8 mmol) in methanol (70 mL) and water (10 mL). The mixture was refluxed for 2 h, and water (20 mL) was added. Most of the methanol was removed on a rotary evaporator, and the residue was worked up as usual to give a yellowish liquid (3.59 g, 16.5 mmol, 95% yield). The ^1H NMR spectrum showed the product to consist of *endo*-3-(phenylthio)-2-norbornanone (40%) and *exo*-3-phenylthio-2-norbornanone (60%), which were separated by column chromatography on silica gel using diethyl ether−petroleum ether, 20:80. The *exo* isomer eluted first; this was distilled in a coldfinger apparatus at 235−237 °C (oil bath, 8 Torr) to give a colorless oil: IR (neat) ν_{max} 3476 (w), 3058 (w), 2963 (s), 2876 (s), 1748 (s), 1581 (m), 1480 (s), 1439 (s), 1304 (s), 1172 (s), 1073 (s), 1026 (m), 937 (m), 911 (m), 747 (s), 691 (s) cm^{-1}; ^1H NMR δ 1.55 (m, 3 H), 1.86 (m, 2 H), 2.17 (d, 1 H), 2.61 (s, 1 H), 2.69 (s, 1 H), 3.31 (d, 1 H), 7.30 (m, 3 H), 7.45 (m, 2 H); ^{13}C NMR δ 24.3, 27.2, 35.1, 42.0, 49.3, 56.5, 127.2, 129.0, 131.3, 134.4, 213.3; HRMS calcd for $C_{13}H_{14}OS$ 218.0765, found 218.0765.

***exo*-3-(Phenylthio)-*endo*-2-norbornanol.** *exo*-3-(Phenylthio)-2-norbornanone (1.330 g, 6.09 mmol) in THF (10 mL) was added dropwise to a slurry of lithium aluminum hydride (0.300 g, 4.06 mmol) in THF (15 mL) at 0 °C, and after the mixture was stirred at 0 °C for 1.5 h, it was worked up to give a mixture (24:76 by ^1H NMR) of *exo*-3-(phenylthio)-*exo*-2-norbornanol and *exo*-3-(phenylthhio)-*endo*-norbornanol (1.070 g, 4.86 mmol, 79.7% yield) as a colorless oil which gave white crystals on standing. The solid was recrystallized from petroleum ether (60−80 °C) to give pure *exo*-3-(phenylthio)-*endo*-2-norbornanol as white crystals: mp 69−70 °C; IR (KBr) ν_{max} 3237 (s), 2957 (s), 2943 (s), 2869 (s), 1584 (m), 1480 (s), 1437 (m), 1337 (m), 1318 (w), 1157 (m), 1067 (s), 1053 (s), 740 (s), 700 (m), 689 (s) cm^{-1}; ^1H NMR δ 1.31−1.46 (m, 3 H), 1.61−1.80 (m, 4 H), 2.23 (m, 1 H), 2.36 (m, 1 H), 2.85 (m, 1 H), 4.05 (m, 1 H), 7.18−7.34 (m, 5 H); ^{13}C NMR δ 19.5, 29.4, 35.3, 43.0, 43.7, 57.4, 80.2, 126.1, 129.0, 129.6, 136.6; HRMS calcd for $C_{13}H_{16}OS$ 220.0922, found 220.0924.

***exo*-3-(Phenylthio)-*endo*-2-methoxynorbornane.** A mixture of DMSO (6.5 mL) and powdered potassium hydroxide (0.759 g, 13.5 mmol) was stirred for 5 min at room temperature. *exo*-3-(Phenylthio)-*endo*-2-norbornanol (0.745 g, 3.38 mmol) was treated with iodomethane (2.399 g, 16.9 mmol) as above; workup gave the product (0.750 g, 3.2 mmol, 94.7% yield) as a slightly yellowish liquid: ^1H NMR δ 1.37 (m, 3 H), 1.79 (m, 3 H), 2.22 (m, 1 H), 2.51 (m, 1 H), 2.89 (t, 1 H), 3.30 (s, 3 H), 3.55 (m, 1 H), 7.30 (m, 5 H); ^{13}C NMR δ 20.7, 30.1, 35.8, 40.9, 44.0, 55.6, 58.2, 89.3, 126.7, 129.7, 130.2, 138.0.

***exo*-3-(Phenylsulfonyl)-*endo*-2-methoxynorbornane (2).** Hydrogen peroxide (30%, 8.0 mL) was added dropwise to a solution of *exo*-3-(phenylthio)-*endo*-2-methoxynorbornane (0.75 g, 3.20 mmol) in acetic acid (3 mL) as above to give *exo*-3-(phenylsulfonyl)-*endo*-methoxynorbornane (**2**) (0.814 g, 95.5% yield) as white crystals, which were recrystallized from 50% MeOH: mp 87−88 °C; IR (KBr) ν_{max} 2979 (m), 2959 (s), 2876 (s), 2836 (m), 1451 (m), 1304 (s), 1291 (s), 1215 (m), 1148 (s), 1111 (s), 1084 (s), 903 (m), 760 (m), 725 (s), 693 (s), 606 (s), 550 (s) cm^{-1}; ^1H NMR δ 1.30 (m, 3 H), 1.63 (m, 2 H), 1.94 (d, 1 H), 2.59 (d, 2 H), 2.73 (dd, 1 H), 3.17 (s, 3 H), 4.05 (t, 1 H), 7.59 (m, 3 H), 7.91 (d, 2 H); ^{13}C NMR δ 19.5, 29.8, 34.9, 39.0, 39.1, 57.4, 72.9, 81.9, 128.4, 129.1, 133.5, 138.8; HRMS calcd for $C_{14}H_{19}O_3S$ (M + H) 267.1055, found 267.1057.

***exo*-3-(Phenylthio)-*exo*-2-norbornanol** was partially separated from the above mixture of the *exo*−*exo* and *exo*−*endo* isomers by column chromatography on silica gel: ^1H NMR δ 1.15−1.77 (m, 4 H), 2.35 (m, 2 H), 2.85 (m, 2 H), 3.35 (dd, 1 H), 3.92 (dd, 1 H), 7.21−7.38 (m, 5 H); ^{13}C NMR δ 25.2, 30.0, 34.5, 44.4, 45.3, 59.8, 76.0, 127.2, 130.1, 130.4, 137.7.

***exo*-3-(Phenylthio)-*exo*-2-methoxynorbornane.** Powdered potassium hydroxide (0.20 g, 3.6 mmol) was added to a solution of a mixture of *exo*-3-(phenylthio)-*exo*-2-norbornanol (80%) and *exo*-3-(phenylthio)-*endo*-2-norbornanol (20%) (0.115 g, 0.52 mmol) in DMSO (2 mL). This mixture was stirred for 2 min and treated with iodomethane (0.74 g, 5.2 mmol) as above, giving a mixture of *exo*−*exo* (80%) and *exo*−*endo* ethers (20%) as a yellowish oil (0.114 g, 0.49 mmol, 94% yield). Spectral data of *exo*-3-(phenylthio)-*exo*-2-methoxynorbornane: ^1H NMR δ 1.40−1.70 (m, 4 H), 1.92 (m, 2 H), 2.22 (m, 1 H), 2.57 (m, 1 H), 3.39 (s, 3 H), 3.41 (m, 1 H), 3.45 (m, 1 H), 7.29 (m, 3 H), 7.51 (m, 2 H); ^{13}C NMR δ 24.8, 34.0, 39.8, 41.5, 43.5, 56.6, 59.9, 86.7, 126.4, 129.8, 130.2, 138.9.

***exo*-3-(Phenylsulfonyl)-*exo*-2-methoxynorbornane (9).** Hydrogen peroxide (30%, 2 mL) was added dropwise to a solution of a mixture of *exo*-3-(phenylthio)-*exo*-2-methoxynorbornane (80%) and the *exo*−*endo* isomer (20%) (0.114 g, 0.49 mmol) in acetic acid (1 mL) as above to give a mixture (0.125 g, 0.47 mmol, 95.9% yield) of *exo*-3-(phenylsulfonyl)-*exo*-2-methoxynorbornane (**9**) (major) and *exo*-3-(phenylsulfonyl)-*endo*-2-methoxynorbornane (**2**) as a colorless oil which solidified slowly on standing. **9** was separated from the mixture by column chromatography using ethyl acetate (20%) and petroleum ether (80%) as the eluate and recrystallized from ethyl acetate and petroleum ether: mp 98−99 °C; IR (KBr) ν_{max} 2980 (s), 2877 (s), 1450 (m), 1303 (s), 1124 (s), 1103 (s), 719 (m), 691 (m) cm^{-1}; ^1H NMR δ 0.97 (m, 1 H), 1.14−1.1.20 (m, 2 H), 1.58 (m, 2 H), 1.95 (m, 1 H), 2.38 (s, 1 H), 2.78 (s, 1 H), 3.23 (s, 3 H), 3.29 (m, 1 H), 3.47 (m, 1 H), 7.52 (m, 3 H), 7.93 (m, 2 H); ^{13}C NMR δ 23.4, 29.6, 34.2, 38.5, 40.1, 58.4, 72.0, 85.2, 128.6, 128.7, 132.9, 141.4; HRMS calcd for $C_{14}H_{19}O_3S$ (M + H) 267.1055, found 267.1057.

***exo*-2-(Phenylsulfonyl)norbornane (19).** Thiophenol (3.51 g, 31.9 mmol) was added in small portions to norbornene (3.0 g, 31.9 mmol) at room temperature. The temperature rose to 60 °C about 5 min after the first portion was added. The remainder of the thiophenol was added at such a rate that the temperature remained between 60 and 70 °C. After all of the thiophenol was added, the mixture was heated at 75−80 °C for 30 min with stirring. This was then subjected to vacuum distillation. The product was collected at 128−130 °C (5 Torr) to give *exo*-(phenylthio)norbornane as a colorless oil (5.50 g, 84.4% yield): IR (neat) ν_{max} 3059 (w), 2955 (s), 2869 (s), 1586 (s), 1480 (s), 1451 (s), 1439 (s), 1313 (s), 1239 (m), 1269 (m), 1138 (m), 1068 (m), 1091 (s), 1026 (s), 953 (m), 736 (s), 690 (s) cm^{-1}; ^1H NMR δ 1.18−1.84 (m, 8 H), 2.27 (m, 2 H), 3.17 (m, 1 H), 7.11−7.32 (m, 5 H); ^{13}C NMR δ 31.3, 31.5, 38.2, 39.1, 41.2, 44.9, 50.7, 128.1, 131.4, 131.5, 140.4. Hydrogen peroxide (30%, 20 mL) was added dropwise to a solution of the *exo*-thioether (3.0 g, 14.7 mmol) in acetic acid (10 mL) as above to give white crystals of **19** (3.456 g, 99.5% yield), which were recrystallized from methanol: mp 80−81 °C; IR (KBr) ν_{max} 3063 (w), 2965 (s), 2872 (m), 1445 (m), 1325 (m), 1298 (s), 1271 (s), 1242 (m), 1146 (s), 1086 (s), 721 (s), 696 (s), 612 (s) cm^{-1}; ^1H NMR δ 1.18 (m, 3 H), 1.80 (m, 1 H), 2.01 (m, 1 H), 2.40 (dd, 1 H), 2.68 (dd, 1 H), 3.00 (ddd, 1 H), 7.60 (m, 3 H), 7.88 (m, 2 H); ^{13}C NMR δ 28.1, 29.8, 32.6, 36.1, 38.8, 66.7, 128.4, 129.1, 133.4, 139.1; HRMS calcd for $C_{13}H_{16}O_2S$ (M + 1) 237.0949, found 237.0949.

***endo*-2-(Phenylsulfonyl)norbornane (20).** A mixture of formic acid (3.05 g, 66.3 mmol), 10% palladium-on-charcoal catalyst (Pd−C) (0.35 g), and *endo*-2-(phenylsulfonyl)-5-norbornene[64] (0.49 g, 2.1 mmol) in absolute ethanol (80 mL) was refluxed for 2 h. The Pd−C was filtered off, and the solvent was removed to give a colorless liquid (0.40 g, 81% yield), which solidified on standing; **20** was recrystallized from 50% aqueous methanol: mp 61−62 °C; IR (KBr) ν_{max} 2975 (m), 2883

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(w), 1445 (m), 1276 (s), 1152 (s), 1086 (s), 722 (s), 703 (s), 603 (s); ^{1}H NMR δ 1.37 (m, 5 H), 1.77 (m, 2 H), 2.38 (m, 2 H), 2.52 (m, 1 H), 3.32 (m, 1 H), 7.52 (m, 3 H), 7.86 (m, 2 H); ^{13}C NMR δ 23.6, 28.9, 31.2, 37.3, 39.8, 40.4, 65.8, 127.9, 129.2, 133.3, 140.6; HRMS calcd for $C_{13}H_{16}O_2S$ 236.0871, found 236.0874.

***trans*-3-(Phenylthio)-2-bicyclo[2.2.2]octanol.** Thiophenol (3.42 g, 31.0 mmol) and 2,3-epoxybicyclo[2.2.2]octane[63] (2.80 g, 25.5 mmol) were added to a solution of potassium hydroxide (2.5 g, 44.6 mmol) in 50% aqueous ethanol (25 mL), and the solution was refluxed for 120 h with stirring. Workup gave the product (4.736 g, 20.2 mmol, 89.6% yield) as a slightly yellowish oil, which was distilled from a coldfinger apparatus at 235−240 °C (oil bath, 8 Torr) to give a colorless oil: IR (neat) υ_{max} 3393 (s), 3057 (w), 2940 (s), 2864 (s), 1583 (m), 1479 (s), 1454 (m), 1061 (m), 1026 (s), 738 (s), 691 (s) cm^{-1}; ^{1}H NMR δ 1.38 (m, 2 H), 1.69 (m, 6 H), 1.84 (m, 2 H), 2.28 (s, 1 H), 3.24 (m, 1 H), 3.73 (m, 1 H), 7.27 (m, 3 H), 7.40 (m, 2 H); ^{13}C NMR δ 18.1, 19.7, 23.4, 26.1, 29.9, 32.6, 56.3, 76.0, 126.5, 128.9, 130.9, 135.7; HRMS calcd for $C_{14}H_{18}OS$ 234.1078, found 234.1077.

3-(Phenylthio)-2-bicyclo[2.2.2]octanone. Swern oxidation (DMSO, oxalyl chloride, Et_3N, as above) of *trans*-3-(phenylthio)-2-bicyclo[2.2.2]-octanol (4.00 g, 17.2 mmol) gave the product (3.950 g, 99.5% yield) as a yellowish oil: IR (neat) υ_{max} 3060 (w), 2946 (s), 2870 (s), 1742 (s), 1581 (m), 1480 (s), 1455 (s), 1325 (w), 1111 (m), 1062 (s), 1026 (m), 741 (s), 691 (s), 666 (s) cm^{-1}; ^{1}H NMR δ 1.58 (m, 3 H), 1.84 (m, 4 H), 2.15 (m, 2 H), 2.38 (m, 1 H), 3.74 (t, 1 H), 7.27 (m, 3 H), 7.47 (m, 2 H); ^{13}C NMR δ 20.0, 22.7, 23.5, 25.3, 33.1, 42.5, 57.6, 127.2, 129.0, 131.8, 134.4, 213.5; HRMS calcd for $C_{14}H_{16}OS$ 232.0922, found 232.0923.

***cis*-3-(Phenylthio)-2-bicyclo[2.2.2]octanol.** 3-(Phenylthio)bicyclo-[2.2.2]octan-2-one (4.50 g, 19.4 mmol) in 2-propanol (15 mL) was added dropwise to a solution of sodium borohydride (0.733 g, 19.4 mmol) in 2-propanol (95 mL). The mixture was stirred overnight at room temperature. Concentrated hydrochloric acid (6 mL) was added, and the 2-propanol was removed on a rotary evaporator. Workup gave a mixture of the *cis* and *trans* alcohols as an oil (4.31 g, 18.4 mmol, 94.8% yield). The ^{1}H NMR spectrum showed the mixture to contain the *cis* isomer (78%) and the *trans* isomer (22%), which were separated by column chromatography on silica gel using a mixture of diethyl ether (20%) and petroleum ether (80%) as the eluent, with the *cis* isomer eluting first from the column; this was distilled in a coldfinger apparatus at 225−228 °C (oil bath, 8 Torr): IR (neat) υ_{max} 3440 (s), 3058 (w), 2936 (s), 2865 (s), 1584 (m), 1480 (s), 1456 (m), 1439 (s), 1067 (s), 1044 (s), 1026 (m), 738 (s), 691 (s) cm^{-1}; ^{1}H NMR δ 1.36 (m, 2 H), 1.60 (m, 4 H), 1.88 (m, 4 H), 3.07 (s, 1 H), 3.62 (dt, 1 H), 4.01 (dt, 1 H), 7.27 (m, 3 H), 7.37 (m, 3 H); ^{13}C NMR δ 18.1, 20.7, 23.0, 25.9, 31.3, 31.4, 55.0, 68.2, 126.4, 129.0, 129.9, 136.3; HRMS calcd for $C_{14}H_{18}OS$ 234.1078, found 234.1074.

***cis*-3-(Phenylthio)-2-methoxybicyclo[2.2.2]octane.** *cis*-3-(Phenylthio)-2-bicyclo[2.2.2]octanol (4.10 g, 17.5 mmol) was methylated with MeI in KOH/DMSO as above to give a yellow oil (4.169 g, 95.9% yield). The ^{1}H NMR spectrum showed that the product contained the *cis* isomer (86%) and the *trans* isomer (14%). Chromatography on silica gel gave the pure *cis* product as a colorless liquid: IR (neat) υ_{max} 3057 (w), 2938 (s), 2865 (s), 1584 (m), 1482 (m), 1439 (m), 1102 (s), 739 (s), 691 (s); ^{1}H NMR δ 1.27−1.42 (m, 4 H), 1.51−1.68 (m, 4 H), 1.85−1.94 (m, 2 H), 3.37 (s, 3 H), 3.65 (s, 2 H), 7.20−7.28 (m, 3 H), 7.33−7.40 (m, 2 H); ^{13}C NMR δ 18.7, 20.3, 22.6, 25.6, 27.8, 29.0, 51.5, 58.1, 79.2, 125.9, 128.8, 130.6, 136.5.

***cis*-3-(Phenylsulfonyl)-2-methoxybicyclo[2.2.2]octane (11).** Hydrogen peroxide (30%, 20 mL) was added to a solution of *cis*-3-(phenylthio)-2-methoxybicyclo[2.2.2]octane (2.0 g, 8.0 mmol) in acetic acid (8.5 mL) as above. Workup gave **11** (2.15 g, 96.3% yield) as a colorless oil which solidified on standing; recrystallization from ethyl acetate (10%) and petroleum ether (90%) gave **11**: mp 127−128 °C; IR (KBr) υ_{max} 3065 (w), 2984 (s), 2818 (s), 2924 (s), 2864 (s), 1448 (s), 1316 (s), 1302 (s), 1269 (s), 1284 (s), 1234 (m), 1144 (s), 1103 (s), 1086 (s), 995 (w), 762 (s), 721 (s), 692 (s) cm^{-1}; ^{1}H NMR δ 3.19 (s, 3 H), 3.39 (dt, 1 H), 3.53 (dd, 1 H), 7.57 (m, 3 H), 7.93 (m, 2 H); ^{13}C NMR δ 18.4, 20.9, 21.6, 25.4, 26.6, 27.0, 57.4, 66.4, 76.9, 128.6, 128.8, 133.0, 141.0; HRMS calcd for $C_{15}H_{21}O_3S$ (M + 1) 281.1211, found 281.1207.

***trans*-3-(Phenylthio)-2-methoxybicyclo[2.2.2]octane.** A mixture of DMSO (15 mL) and powdered potassium hydroxide (1.50 g, 26.7 mmol) was stirred for 5 min at room temperature. *trans*-3-(Phenylthio)-2-bicyclo[2.2.2]octanol (1.50 g, 6.4 mmol) (the minor product of reduction of the ketone, above) was added, followed immediately by iodomethane (4.54 g, 32 mmol), as above. Workup gave the product (1.45 g, 90.6% yield) as a colorless oil: ^{1}H NMR δ 1.03−1.40 (m, 4 H), 1.50−1.70 (m, 4 H), 1.80−1.85 (m, 2 H), 2.97 (m, 2 H), 3.06 (s, 3 H), 7.15−7.26 (m, 3 H), 7.35−7.45 (m, 2 H); ^{13}C NMR δ 19.3, 21.0, 24.1, 27.2, 29.4, 30.5, 54.6, 57.7, 85.9, 127.4, 129.9, 131.8, 137.0.

***trans*-3-(Phenylsulfonyl)-2-methoxybicyclo[2.2.2]octane (1).** Hydrogen peroxide (30%, 12 mL) was added dropwise to a solution of *trans*-3-(phenylthio)-2-methoxybicyclo[2.2.2]octane (1.20 g, 4.8 mmol) in acetic acid (5.0 mL), as above. Workup gave the product (**1**) (1.15 g, 85.4% yield) as a white solid which was recrystallized from 60% methanol to give white crystals: mp 84−86 °C; IR (KBr) υ_{max} 3061 (w), 2948 (s), 2863 (s), 2824 (m), 1447 (s), 1337 (m), 1306 (s), 1289 (s), 1246 (w), 1148 (s), 1107 (m), 1086 (s), 758 (m), 723 (s) cm^{-1}; ^{1}H NMR δ 1.37−1.69 (m, 7 H), 1.97 (m, 1 H), 2.23 (m, 2 H), 3.03 (s, 3 H), 3.05 (m, 1 H), 3.77 (m, 1 H), 7.60 (m, 3 H), 7.91 (m, 2 H); ^{13}C NMR δ 17.9, 20.6, 22.6, 25.6, 26.9, 27.3, 56.3, 70.7, 77.8,128.4, 129.0, 133.4, 139.2; HRMS calcd for $C_{15}H_{21}O_3S$ (M + 1) 281.1211, found 218.1212.

2-(Phenylthio)bicyclo[2.2.2]octane. Thiophenol (1.22 g, 11.1 mmol) was added in small portions to bicyclo[2.2.2]oct-2-ene (1.20 g, 11.1 mmol) as in the preparation of 2-(phenylthio)bicyclo[2.2.1]heptane, above. The product was vacuum distilled at 185−190 °C (oil bath, 8 Torr) to give the product (2.07 g, 85.6% yield) as a colorless oil: IR (neat) υ_{max} 3073 (w), 2934 (s), 2863 (s), 1586 (m), 1479 (s), 1439 (s), 1267 (w), 1092 (m), 1026 (m), 739 (s), 691 (s) cm^{-1}; ^{1}H NMR δ 1.62 (m, 10 H), 2.10 (m, 2 H), 3.50 (m, 1 H), 7.26 (m, 5 H); ^{13}C NMR δ 20.5, 24.7, 24.9, 25.5, 26.4, 28.3, 34.4, 45.3, 126.0, 128.8, 130.3, 136.7; HRMS calcd for $C_{14}H_{18}S$ 218.1129, found 218.1125.

2-(Phenylsulfonyl)bicyclo[2.2.2]octane (18). Hydrogen peroxide (30%, 16 mL) was added dropwise with stirring to a solution of 2-(phenylthio)bicyclo[2.2.2]octane (2.00 g, 9.17 mmol) in glacial acetic acid (6 mL) at room temperature, as above. Workup gave the product (2.15 g, 93.7% yield) as a colorless oil which solidified on standing. This was recrystallized from 60% methanol: mp 61−63 °C (lit.[65] mp 58−59 °C for 2-(phenylsulfonyl)bicyclo[2.2.2]octane-*5,6-d*$_2$); IR (KBr) υ_{max} 3073 (w), 2942 (s), 2867 (s), 1451 (m), 1306 (s), 1275 (s), 1148 (s), 1086 (m), 767 (m), 723 (s), 702 (m) cm^{-1}; ^{1}H NMR δ 1.39−1.78 (m, 9 H), 2.10 (m, 2 H), 2.27 (m, 1 H), 3.16 (m, 1 H), 7.59 (m, 3 H), 7.88 (m, 2 H); ^{13}C NMR δ 20.9, 24.1, 24.3, 24.6, 24.9, 26.8, 27.0, 62.5, 128.4, 129.1, 133.3, 139.1.

1-Methoxy-2-(phenylsulfonyl)bicyclo[2.2.2]octane (7). Hydrogenation of 1-methoxy-6-*endo*-(phenylsulfonyl)bicyclo[2.2.2]oct-2-ene[66] (0.20 g, 0.72 mmol) in chloroform and Pt/C (10%, 0.015 g) under 1 atm of H_2 gave a quantitative yield of **7**: mp 91.5−94.0 °C; ^{1}H NMR δ 1.3−2.5 (m, 11 H), 2.63 (s, 3 H), 3.47 (m, 1 H), 7.3−8.0 (m, 5 H); ^{13}C NMR δ 24.2, 25.1, 26.0, 26.3, 28.5, 30.0, 48.4, 63.6, 75.0, 128.4, 128.8, 132.8, 141.6; calcd exact mass for $C_{15}H_{20}O_3S$ 280.1133, found 280.1137.

2-*exo*-(Phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane (12). Hydrogenation of 2-*exo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene[67] (mp 63.5−65 °C, reported[67] to be a liquid) in $CHCl_3$ and Pt/C (10%) under H_2 (1 atm) gave a quantitative yield of **12**: mp 100−101.5 °C; ^{1}H NMR δ 1.0−2.3 (m, 6 H), 3.29 (m, 1 H), 4.63 (t, J = 4.8 Hz, 1 H), 4.94 (d, J = 5.0 Hz, 1 H), 7.45−8.00; ^{13}C NMR ($CDCl_3$) δ 29.0, 29.9, 33.7, 67.8, 76.4, 76.6, 128.8, 129.2, 133.7, 138.0; calcd exact mass for $C_{12}H_{14}O_3S$ 238.0666, found 238.0664.

2-*endo*-(Phenylsulfonyl)-7-oxabicyclo[2.2.1]heptane (8). Separation by TLC (CH_2Cl_2) of the mixture of 2-*endo*- and 2-*exo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-enes[67] gave 2-*endo*-(phenylsulfonyl)-7-oxabicyclo[2.2.1]hept-5-ene: mp 52−53 °C; ^{1}H NMR δ 1.6−2.3 (m,

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2 H), 3.70 (m, 1 H), 5.04 (m, 2 H), 6.50 (m, 2 H), 7.4−8.1 (m, 5 H); ^{13}C NMR δ 28.7, 62.6, 78.2, 79.6, 127.6, 129.4, 131.5, 133.7, 137.2, 140.3; calcd exact mass for $C_{12}H_{13}O_3S$ (M + 1) 237.0585, found 237.0588. Hydrogenation of the alkene in $CHCl_3$ and Pt/C (10%) under H_2 (1 atm) gave a quantitative yield of **8**: mp 75.7−77 °C; ^{1}H NMR δ 1.6−2.7 (m, 6 H), 3.5−3.63 (m, 1 H), 4.60−4.70 (m, 2 H), 7.5−7.9 (m, 5 H); ^{13}C NMR δ 26.0, 29.9, 32.9, 65.8, 77.2, 78.3, 127.6, 129.4, 133.7, 140.5; calcd exact mass for $C_{12}H_{14}O_3S$ 238.0664, found 238.0668.

***cis*-3-Methoxy-1-(phenylsulfonyl)cyclohexane (28) and *trans*-3-Methoxy-1-(phenylsulfonyl)cyclohexane (29) (Chart 1).** A mixture of 3-(phenylthio)cyclohexanone[68,69] (6.9 g, 0.0334 mol) and sodium borohydride (4.88 g, 12.9 mmol) in methanol (200 mL) was stirred for 2 h at 0 °C, and then hydrolyzed with water and acidified with sulfuric acid (10%). Workup gave 3-(phenylthio)cyclohexanol (6.0 g, 86%, *cis*−*trans* mixture). This alcohol (4.84 g, 23.2 mmol) in DMSO (10 mL) was added to KOH (5.2 g, 93 mmol) in DMSO (40 mL) at room temperature, and the resulting mixture was stirred for 2 min. Iodomethane (13.2 g, 0.093 mol) was added and stirred 30 min. Workup gave 3-methoxy-1-(phenylthio)cyclohexane (4.8 g, 93%, *cis*−*trans* mixture). The sulfide was oxidized by H_2O_2 (30%) in acetic acid, giving a quantitative yield of 3-methoxy-1-(phenylsulfonyl)cyclohexane. Thick layer chromatography (ether−hexane, 3:2) gave **28** and **29** separately. Compound **28**: mp 95.5−97.5 °C; ^{1}H NMR δ 1.0−2.5 (m, 8 H), 2.90 (tt, J = 12.4 and 3.4 Hz, 1 H), 3.07 (tt, J = 11.0 and 4.1 Hz, 1 H), 3.30 (s, 3 H), 7.5−7.9 (m, 5 H); ^{13}C NMR ($CDCl_3$) δ 22.6, 25.1, 31.0 (double intensity), 56.0, 62.0, 78.0, 129.1 (double intensity), 133.7, 136.8; calcd exact mass for $C_{13}H_{19}O_3S$ (M + 1) 255.1055, found 255.1056. Compound **29**: mp 63.5−64.5 °C; ^{1}H NMR δ 1.0−2.4 (m, 8 H), 3.17 (s, 3 H), 3.22 (tt, J = 12.2 and 3.5 Hz, 1 H), 3.58 (m, 1 H), 7.40−8.0 (m, 5 H); ^{13}C NMR δ 18.8, 24.8, 28.1, 28.4, 55.7, 58.4, 73.8, 128.8, 128.9, 133.5, 137.2; calcd exact mass for $C_{13}H_{19}O_3S$ (M + 1) 255.1055, found 255.1053.

Phenyl 2-methoxyethyl sulfone (30b):[11c,70] ^{1}H NMR, see ref 11c; ^{13}C NMR δ 55.7, 58.3, 65.3, 127.6, 128.8, 133.5, 139.3.

Phenyl 3-Methoxypropyl Sulfone (30c). Phenyl 3-hydroxypropyl sulfide[71] (5.0 g, 30 mmol) was added to KOH (6.7 g, 120 mmol) in DMSO (50 mL) and stirred for 2 min at room temperature. CH_3I (16.7 g, 118 mmol) was added, and the resulting solution was stirred for 15 min. Workup gave a quantitative yield of phenyl 3-methoxypropyl sulfide, which was then oxidized by H_2O_2 (30%) in acetic acid to give **30c** (100%) as a colorless oil: ^{1}H NMR δ 1.70−2.00 (m, 2 H), 3.05−3.15 (m, 2 H), 3.16 (s, 3 H), 3.32 (t, J = 6.0 Hz, 2 H), 7.30−8.00 (m, 5 H); ^{13}C NMR δ 22.9, 53.2, 58.3, 69.8, 127.7, 129.1, 133.5, 138.9; calcd exact mass for $C_{10}H_{14}O_3S$: 215.0742, found 215.0748.

Phenyl 4-Methoxybutyl Sulfone (30d). Phenyl 4-methoxybutyl sulfide[71] was oxidized with H_2O_2 (30%) in acetic acid and gave a quantitative yield of **30d** as a colorless oil: ^{1}H NMR δ 1.50−1.85 (m, 4 H), 3.05−3.15 (m, 2 H), 3.23 (s, 3 H), 3.30 (t, J = 6.0 Hz, 2 H), 7.45−7.95 (m, 5 H); ^{13}C NMR δ 19.9, 28.1, 56.0, 58.5, 71.7, 128.0, 129.2, 133.6, 139.0; calcd exact mass for $C_{11}H_{16}O_3S$ 229.0899, found 229.0898.

Phenyl 5-Methoxypentyl Sulfone (30e). Phenyl 5-methoxypentyl sulfide[71] was oxidized with H_2O_2 (30%) in acetic acid to give a quantitative yield of **30e** as a colorless oil: ^{1}H NMR δ 1.30−1.75 (m, 6 H), 2.98−3.1 0 (m, 2 H), 3.24 (s, 3 H), 3.28 (t, J = 6.0 Hz, 2 H), 7.45−7.95 (m, 5 H); ^{13}C NMR δ 22.4, 24.9, 28.9, 56.1, 58.5, 72.0, 127.9, 129.2, 133.6, 139.0; calcd exact mass for $C_{12}H_{19}O_3S$ (M + 1) 243.1055, found 243.1056.

Methyl 2-Methoxyethyl Sulfone. Oxidation of $MeOCH_2CH_2SMe$[72] with H_2O_2−HOAc as above gave the sulfone: ^{1}H NMR δ 2.93 (s, 3 H), 3.16 (t, J = 5.2 Hz, 2 H), 3.34 (s, 3 H), 3.77 (t, 2 H); ^{13}C NMR δ 43.0, 55.1, 58.9, 66.1.

4-(Phenylsulfonyl)tetrahydropyran (32). Tetrahydro-4*H*-pyran-4-ol (Aldrich) was converted into **32** by the method of Eliel and Ro for preparing **27**:[54] mp 87−89 °C; ^{1}H NMR δ 1.6−1.9 (m, 4 H), 3.11 (tt, J = 11.8 and 4.1 Hz, 1 H), 3.30 (ddd, J = 11.8, 11.8, and 2.6 Hz, 2 H), 4.02 (ddd, J = 11.8, 4.8, and 1.2 Hz, 2 H), 7.5−7.9 (m, 5 H); ^{13}C NMR δ 25.6, 60.6, 66.5, 129.1, 129.2, 133.9; calcd exact mass for $C_{11}H_{14}O_3S$ 226.0664, found 226.0666.

Determination of the Rates of H−D Exchange and Epimerization Equilibria Compositions. Solutions of NaOD in D_2O (0.10−0.50 M) were prepared by dissolving Na metal in D_2O under N_2. The solutions were titrated using 0.01 M HCl. Buffer solutions were prepared from (a) solid Na_2CO_3 in D_2O adjusted to the appropriate pD (pH meter reading + 0.37) with 37% DCl in D_2O, or (b) $Na_3PO_4 \cdot 12H_2O$ previously dried overnight in an oven at 200 °C, cooled in a desiccator, and dissolved in D_2O, and the pD was adjusted using 37% DCl. A typical run was carried out by dissolving a 9 mg sample of the substrate in CD_3CN (0.35 mL) in an NMR tube. NaOH solution (0.35 mL) was added using a 0.5-mL syringe, and the NMR tube was flame-sealed immediately. The concentration of the starting material was measured by determining the integral of the changing α-hydrogen signal relative to that of a convenient unchanging signal; the time for each measurement was taken as the average of the start and stop of data collection. Faster reactions were followed by taking a series of NMR spectra at the temperature of the NMR probe (21 ± 2 °C); with slower reactions the sample tube was placed in a water or oil bath maintained at the specified temperatures (±0.5 °C or better), with ^{1}H NMR spectra run at appropriate intervals. The value of k_{obs} was obtained from the slope of the plot of ln(% concentration of starting material at time t) vs t (in seconds); normally a plot of k_{obs} vs [OD^-] for reactions at two to four different NaOD concentrations gave k_{exch}. Standard deviations in k_{obs} were normally much less than ±5%, but in some instances, either because of overlapping NMR signals, or with very slow reactions (k_{obs} < 2 × 10^{-6} s^{-1} at 25 °C) apparently accompanied by slow decomposition processes, the errors may approach ±10%; for these and some compounds determined at only one concentration of OD^- (**4**, **13**, **14**, **15**, and **16** and their models) the k_{exch} values are expressed by two significant figures. The log k_N points are drawn in Figure 1 with heights of 0.1 log unit corresponding to errors in k_N of ±10%. Equilibrium constants for **1** ⇌ **11**, **2** ⇌ **10**, and **3** ⇌ **9** were determined by heating a sample of **1**, **2**, or **3** (9 mg) in NaOD (0.30 M) in methanol-d_4−D_2O (1:1) (0.7 mL) for 15 days at 77 °C in a sealed NMR tube. The solutions were neutralized with concentrated HCl, and the mixture was analyzed directly by HPLC; the equilibrium ratios were, respectively, **1** ⇌ **11**, 97.1:2.9; **2** ⇌ **10**, 99.7:0.3; and **3** ⇌ **9**, 97.6:2.4. Samples of **19** and **20** (10 mg of each in 0.70 mL of 0.30 M NaOD in dioxane-d_8−D_2O, 1:1) were heated in a sealed tube for 70 days at 77 °C (H−D exchange was complete in 1 day). The ^{1}H NMR spectrum of the product from **19** showed it to consist of the α-deuterated isotopomers of **19** and **20** in the ratio 57.2:42.8. In the product from **20** the ratio was 93.2:6.8; the equilibrium mixture ratio was estimated to be 86:14. Equilibrium constants for **28** ⇌ **27** and **12** ⇌ **8** were determined on solutions in dioxane-d_8−D_2O at 64 °C for at least 45 days until the ^{1}H NMR spectra from each direction indicated that equilibrium had been reached; careful integration gave the respective equilibrium constants, 0.019 and 0.040 (est. ± 0.01). Further details are available elsewhere.[44]

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