Carbon Acids. 13. Acidifying Effects of Phenylthio Substituents

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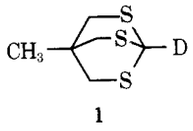
Replacement of a methyl group in $MeCH_2EWG$ parent carbon acids by a phenylthio group leads to an increase in equilibrium acidities in Me_2SO ranging from 4.9 to 11.5 pK units, depending on the nature of EWG (NO_2, F_3CSO_2, PhCO, CH_3CO, $PhSO_2$, CN). The progressively smaller effect observed as the acidity of the parent acid increases is attributed to a resonance saturation effect. The acidifying effects of PhS are comparable in magnitude to those of Ph, and change in the same way with changes in parent acid acidities. In more crowded systems Ph groups are subject to steric inhibition of resonance, but PhS groups are not. Separation of polar and resonance effects of PhS by using Me_3N^+ as a model for the polar effect suggests that strong conjugative interactions exist between PhS and an adjacent carbanion. Comparison of acidities of 2-phenyl-1,3-dithiane and of 4-methyl-2,6,7-trithiabicyclo[2.2.2]octane with those of open-chain analogues failed to reveal any stereoelectronic requirements for these conjugative interactions. Extrapolation indicates that the pK in Me_2SO is 44 for toluene.

There is a voluminous literature indicating that α-PhS (or, to a somewhat lesser degree, α-RS) groups increase the acidity of the adjacent C–H bond, and that this effect is associated with the ability of divalent sulfur to stabilize a negative charge on an adjacent carbon atom.[2] The evidence includes a demonstrated ability of one or more α-PhS (or α-RS) groups to facilitate (1) metalation of C–H, (2) deuterium exchange of C–H, (3) base-initiated β-elimination, (4) tautomerism, (5) Michael addition, and (6) decarboxylation.[2] Most experimentalists have attributed this C–H acidifying or carbanion stabilizing effect to conjugation of the incipient carbanion or the "free" carbanion with the adjacent sulfur atom, the d orbitals on sulfur presumably being involved.[2] From studies of deuterium exchange, or the like, in cyclic molecules containing two or three sulfur atoms several authors have drawn the conclusion that stereoelectronic factors may be important in deciding carbanion stabilities. For example, the fact that the base-initiated deuterium exchange of the bridgehead proton in 4-methyl-2,6,7-trithiabicyclo[2.2.2]-octane (**1**) is about 10^3 faster than that in an open-chain analogue (**2**) has been interpreted to mean that the incipient carbanion is stabilized by orbital overlap involving the carbanion and the three sulfur atoms.[3] Strong conjugative interactions involving d orbitals on two or more sulfur atoms and an adjacent carbanion have also been postulated to explain a number of related phenomena, such as the formation of a dilithium derivative of tetrathiadamantane (**3**).[4]



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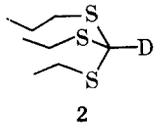

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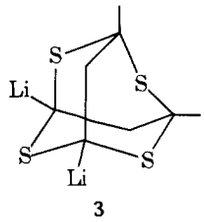

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There has also been considerable theoretical interest in the bonding characteristics of sulfur in all of its various oxidation states. The d orbitals of divalent sulfur have been described as being far too diffuse for bonding purposes, but theory predicts that attachment of electron-attracting ligands will contract the d orbitals and enhance their bonding properties.[5] In a recent review Coulson concluded that d orbitals are suitable for effecting polarization of p orbitals, but noted that little or no chemical relevance should be attached to the small d-orbital populations arising from this.[6] In considering the bonding in hypervalent molecules, such as SF_6, Musher concluded that "there is little need to introduce d orbitals . . . and that their inclusion is neither crucial nor qualitatively necessary."[7] Similar conclusions concerning the relative unimportance of d orbital participation has been arrived at by Florey and Cusachs for phosphorus and sulfur compounds.[8]

Recent ab initio calculations have indicated that d-orbital conjugation is irrelevant for stabilization of the $HSCH_2^-$ anion, and that the stabilizing effect of sulfur is due to its polarizability.[9] Similar conclusions have been drawn from calculations made on the $HSOCH_2^-$ and $HSO_2CH_2^-$ anions.[10]

The evidence in the literature for stabilization of a carbanion or an incipient carbanion by α-PhS (or α-RS) is compelling, but the magnitude of the effect, its nature, and the reality of the stereoelectronic effects that have been postulated are open to question. In making comparisons many of the earlier studies used α-PhO and α-RO groups as models. It was argued that, since the polar effect of PhO (or RO) is larger than that of PhS (or RS), the greater effects observed with α-PhS (or RS) than with their oxygen analogues must be due to some kind of special stabilizing effect (e.g., d-orbital conjugation). There is also evidence from deuterium exchange studies[11] and from equilibrium acidity measurements,[12] however, to indicate that MeO groups may *destabilize* adjacent carbanions. The question then becomes: how much of the observed difference in the apparent effect on carbanion stability of, say PhS vs. PhO, is caused by a destabilizing effect of oxygen, and how much is caused by a stabilizing effect of sulfur?

The reality of the postulated stereoelectronic effects of sulfur on carbanion stability is open to question because of the difficulty in interpreting some of the data. In some instances ion pair stability, rather than carbanion stability, may be involved. For example, the equatorial preference for the "carbanion" formed by deprotonation of 1,3-dithiane can be accounted for in terms of an equatorially held lithium ion,[13a] as well as by a stereoelectronically favorable p–d overlap,[3] or a "gauche effect".[13b] If carbanion stabilities are to be correctly judged from deuterium exchange studies, it is necessary that the exchange give a true measure of the rate of carbanion formation, which is not always the case.[14] It is also necessary that a good estimate of the size of the Bronsted coefficient be obtained; this too poses problems.[14] Equilibrium acidity measurements for weak acids in dimethyl sulfoxide (Me_2SO) solution provide a quantitative method of determining relative substituent effects. Assuming that the substituents are exerting their effects primarily by stabilizing the anion, as seems likely, in the systems being considered herein, this provides a quantitative measure of anion stabilities free of counterion influences.[15] In a preliminary report we showed that the

Table I. Acidifying Effect in Dimethyl Sulfoxide Solution of the Phenylthio Group in Methane and Ethane Parent Carbon Acids

Registry no.	Parent acid	pK^a	p$K(\alpha$ − PhS)^a	Δp$K_H{}^b$	Registry no.	Parent acid	pK^a	Δp$K_{Me}{}^c$
75-05-8	CH_3CN	31.3	20.8	10.7	107-12-0	$MeCH_2CN$	~32.5[d]	~11.5[d]
3112-85-4	CH_3SO_2Ph	29.0	20.3	8.9	599-70-2	$MeCH_2SO_2Ph$	31.0	10.7
67-64-1	CH_3COCH_3	26.5	18.7	8.3	96-22-0	$(MeCH_2)_2CO$	27.1	8.7
98-86-2	CH_3COPh	24.7	17.1	7.8	93-55-0	$MeCH_2COPh$	24.4	7.3
421-82-9	$CH_3SO_2CF_3$	18.8	11.0	8.0	13003-57-1	$MeCH_2SO_2CF_3$	20.4	9.4
75-52-5	CH_3NO_2	17.2	11.8	5.6	79-24-3	$MeCH_2NO_2$	16.7	4.9
1070-92-4	$CH_2(SO_2Et)_2$	14.4	7.1	7.6	32341-85-8	$MeCH(SO_2Et)_2$	16.7	9.6
3406-02-8	$CH_2(SO_2Ph)_2$	12.2	5.6[e]	6.9	33419-26-0	$MeCH(SO_2Ph)_2$	14.3[5]	8.7

[a] Runs were made against at least two indicators; standard deviations within runs are generally less than ±0.05 pK unit and those for runs with different indicators are generally less than ±0.1 pK unit. [b] ΔpK_H = pK(HCH_2EWG) − pK($PhSCH_2EWG$); statistically corrected for the number of acidic hydrogen atoms. [c] ΔpK_{Me} = pK($MeCH_2EWG$) − pK($PhSCH_2EWG$). [d] Assuming that the methyl effect on CH_3CN is comparable to that on $PhCH_2CN$ and $CH_2(CN)_2$ as parent acids (ca. 1 pK unit).[16] [e] Measured only against a new indicator, 2,6-di-*tert*-butyl-4-nitrophenol (pK = 7.3). [A previous pK value of 7.6 was obtained potentiometrically by I. M. Koltoff, M. K. Chantooni, Jr., and S. Bhomik, *J. Am. Chem. Soc.*, **90**, 23 (1968).] Calculation of the pK value for the sulfone neglected the effects of self-ionization in Me_2SO which could lead to a greater uncertainty in the value obtained. Unpublished work from these laboratories and the work of Koltoff et al. cited above would indicate, however, that only a small amount of self-ionization should occur with an acid of this pK at these concentrations (≈10^{-3} M).

acidifying effect of an α-PhS substituent is large in four different carbon acid systems.[12] In the present paper we (a) report the acidifying effects of α-PhS on a variety of other carbon acid systems, (b) compare the effects with those of a phenyl group, (c) determine the size of the polar contribution to this acidifying effect by using the Me_3N^+ substituent as a model, and (d) examine the effect of incorporating the acidifying sulfur atoms into ring systems.

Results and Discussion

Acidifying Effects of the Phenylthio Group. In Table I the acidifying effect of the PhS group is compared to that of a hydrogen atom (ΔpK_H) or a methyl group (ΔpK_{Me}) for a variety of parent carbon acids, mostly of the type HCH_2EWG or $MeCH_2EWG$, where EWG is a strong electron-withdrawing group. Examination of Table I shows that the acidifying effects of PhS, as judged by either reference to a hydrogen atom, i.e., ΔpK_H = pK(HCH_2EWG) − pK($PhSCH_2EWG$) or a methyl group, i.e., ΔpK_{Me} = pK($MeCH_2EWG$) − pK($PhSCH_2EWG$), is large, ranging from 4.9 to 11.5 pK units. The magnitude of the effect varies somewhat depending on whether the methane or ethane carbon acid listed in Table I is used as a model. As was brought out in a previous paper,[12] neither H nor Me is a good model for PhS sterically or electronically, but methyl is no doubt the better model, and will be used in subsequent discussions.

Saturation of Phenylthio Effects. Examination of the ΔpK_{Me} column in Table I shows that, for $PhSCH_2EWG$ carbon acids, the acidifying effect of the PhS group, relative to Me, decreases from 11.5 for the weakest carbon acid, propionitrile, to 4.9 for the strongest carbon acid, nitroethane. The decrease is a progressive one, but not a regular one. A plot of ΔpK_{Me} for the PhS effect vs. pK for $MeCH_2EWG$ gives a smooth curve for the "planar" functions CN, CH_3CO, PhCO, and NO_2 (Figure 1). The $PhSO_2$ point deviated but little from this curve, but the SO_2CF_3 point deviated markedly. The question arose as to whether the F_3CSO_2 point is deviant or whether the points for sulfones in general are deviant, the $PhSO_2$ point happening to fall fortuitously near the curve for the "planar" functions. Inclusion of the points for $MeCH(SO_2Ph)_2$ and $MeCH(SO_2Et)_2$ as parent acids appears to answer this question unambiguously, the latter points falling near the line drawn between the $PhSO_2$ and F_3CSO_2 points, and deviating markedly from the curve. Therefore, the points for the "planar" functions fall on a curve, and the points for the (tetrahedral) sulfone functions fall on a different curve

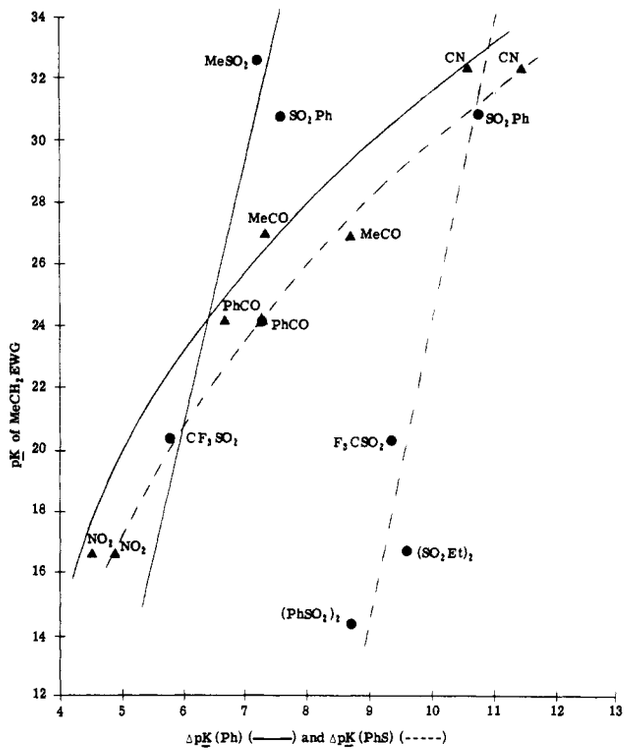


Figure 1. Comparison of phenyl (—) and phenylthio acidifying effects (- - - -) on parent ethane carbon acids, $MeCH_2EWG$, when EWG is a planar function (▲) and a tetrahedral (sulfone) function (●).

(or line). A similar observation has been made for the acidifying effect of a phenyl group on these two types of functions.[17] In fact, plotting ΔpK for the Ph and the PhS acidifying effects vs. the pK of the ethane carbon acids, $MeCH_2EWG$, gives parallel curves for the "planar" functions and roughly parallel lines for the tetrahedral functions (Figure 1). (The resonance to polar ratio for sulfoxide and sulfone functions apparently increases to a lesser degree with increasing acidity than is true for "planar" functions, causing the two types to fall on separate lines.[17])

In the previous paper in this series we assumed that for a series of methane carbon acids, HCH_2EWG, or ethane carbon acids, $MeCH_2EWG$, replacement of H or Me by Ph would cause relatively constant changes in solvation and steric effects.[17] The parallel behavior of Ph and PhS (Figure 1) sup-

Table II. Estimation of the Polar Effect (ΔpK_{calcd}) and Conjugative Effect ($\Delta\Delta pK$) for PhS using Me_3N^+ as a Model for the Polar Effect

Registry no.	G	σ_I[a]	ΔpK_{calcd}[f]	ΔpK_{obsd}[g]	$\Delta\Delta pK$[i]
	A. GCH_2CN Carbon Acids; $\rho_I = 14.5$[12]				
	Me	−0.04[b]	(0.0)	(0.0)	
6340-35-8	Me_3N^+	0.82[c]	(11.9)	11.9	
5219-61-4	PhS	0.30[d]	4.4	11.7	7.3
140-29-4	Ph	0.10	1.5	10.6	9.1
	B. GCH_2SO_2Ph Carbon Acids; $\rho_I = 14.1$[12]				
	Me	−0.04[b]	(0.0	(0.0)	
60595-13-3	Me_3N^+	0.82[c]	(11.6)	11.6	
15296-86-3	PhS	0.30[d]	4.2	10.5	6.3
3112-88-7	Ph	0.10	1.4	7.6	6.2
	C. GCH_2COPh Carbon Acids; $\rho_I = 11.9$[12]				
	Me	−0.04[b]	(0.0)	(0.0)	
16222-10-9	Me_3N^+	0.82[c]	(9.8)	9.8	
60595-14-4	PhS	0.30[d]	3.6	7.3	3.7
35050-01-2	PhSe	0.24[e]	2.9	5.8	2.9
451-40-1	Ph	0.10	1.2	6.7	5.5
	D. 9-G-Fluorene Carbon Acids; $\rho_I = 8.1$[h]				
17114-78-2	Me_3C	−0.07[b]	(0.0)		
6634-60-2	Me_3N^+	0.82[c]	(6.55)	6.55[h]	
	PhS	0.30[d]	2.4	6.9	4.5
	Ph	0.10	0.8	4.4	3.6

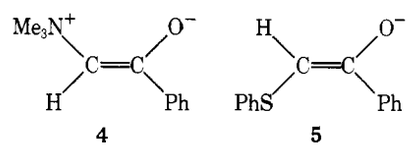
[a] From J. Hine, "Structural Effects on Equilibria in Organic Chemistry", Wiley-Interscience, New York, N.Y., 1975, unless otherwise noted. [b] Taken as 0.0. [c] An average value; see ref 12 for a discussion. [d] M. Charton, *J. Org. Chem.*, **29**, 1222 (1964). [e] Calculated from $\sigma^*CH_2SePh = 0.45$, obtained from the data of L. D. Pettit, A. Royston, C. Sherrington, and R. J. Whewell, *J. Chem. Soc. B*, 588 (1968). [f] From $\Delta pK = \sigma_I\rho_I$. [g] Relative to the p$K$ of $MeCH_2CN$ (32.5; series A), or $MeCH_2SO_2Ph$ (31.0; series B) or $MeCH_2COPh$ (24.4, series C), or 9-methylfluorene (22.3, series D). [h] Relative to 9-*tert*-butylfluorene (pK = 24.35). [i] $\Delta\Delta pK = \Delta pK_{obsd} - \Delta pK_{calcd}$.

ports this assumption. In particular, since, as will be brought out shortly, we have found that the Ph effect is highly sensitive to steric inhibition of resonance, whereas PhS is not, the parallel behavior of the two groups indicates that, for this series of carbon acids, steric inhibition of resonance is unimportant.

The Trimethylammonio Group as a Polar Model. In an earlier paper in this series the trimethylammonio group, Me_3N^+, was used as a model to deduce the size of the polar effect of the phenylthio group, as well as a number of other groups, in GCH_2EWG carbon acid systems. The difference in acidity between $MeCH_2EWG$ and $Me_3N^+CH_2EWG$ for EWG = CN, SO_2Ph, and COPh was used to calculate a ρ_I from the Taft equation, $\Delta pK = \sigma_I\rho_I$, and the σ_I for PhS was used to calculate the size of the polar effect.[12] The results of this analysis for the phenylthio group are shown in Table II, together with a similar analysis for the phenyl group.

Examination of Table II shows that in the GCH_2CN system the acidifying effect of PhS observed is 7.3 pK units greater than that calculated for a polar effect. Somewhat smaller, but still large, differences are observed for the GCH_2SO_2Ph and GCH_2COPh systems ($\Delta\Delta pK$ = 6.3 and 3.7, respectively). These differences are presumably due to an effect other than an electrostatic effect. A conjugative effect of some type between the negatively charged carbon atom and the adjacent sulfur atom is indicated. The smaller effect observed for the GCH_2COPh system is probably the result of a steric effect of some kind. (In the previous paper we have presented evidence to show that this system is highly sensitive to steric effects.[17]) For example, if the structures of the enolate ions are **4** and **5**, respectively, the calculated polar effect would be enhanced by the proximity of the charged groups in **4**.

The magnitude of the acidifying effect of the PhS group is brought out further by a direct comparison of pK's:



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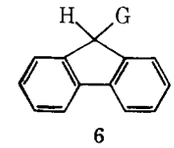

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$PhSCH_2CN$, 20.8 vs. $Me_3N^+CH_2CN$, 20.6, and $PhSCH_2SO_2Ph$, 20.3 vs. $Me_3N^+CH_2SO_2Ph$, 19.4. In the fluorene system (**6**) the PhS group produces a 2.4 pK unit *greater* acidifying effect than does Me_3N^+ (pK = 15.4 for **6** with G = PhS vs. 17.8 for G = Me_3N^+). Here, however, a steric effect is probably decreasing the effect of Me_3N^+, since 9-*tert*-butylfluorene is 2.2 pK units weaker than 9-methylfluorene. Nevertheless, here, as well as in the other instances, it is clear that the PhS group is producing a far greater acidifying effect than is expected from its polar effect, as judged by the Taft equation.

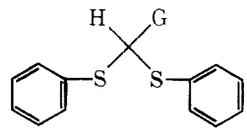
If $\Delta\Delta pK$ in Table II is taken as the size of the resonance effect, we see that for the first three carbon acid systems the resonance effect is appreciably larger for Ph than for PhS. The order is reversed for the fluorene system, but here the effect of Ph is subject to steric inhibition of resonance, whereas the PhS effect is not (see the next section). Nevertheless, even in this instance the resonance to polar ratio is much larger for Ph (4.9) than for PhS (1.9). For PhS the resonance to polar ratio ($\Delta\Delta pK/\Delta pK_{calcd}$ from Table II) is 1.6 for EWG = CN, 1.5 for EWG = $PhSO_2$, and 1.0 for EWG = COPh. These ratios are smaller than observed for Ph or CH_3CO, but are about the same size as those observed for NO_2, CN, or $PhSO_2$.[17] The resonance to polar ratio for the PhS group derived from the data in Table II is larger than 1.0, whereas the ratio of $\sigma_{R(A)}^-$ to σ_I is less than 1.0. This is typical of electron-withdrawing groups known to enter into conjugative interactions with anions, such as Ph, NO_2, CN, and $PhSO_2$.[17] The evidence is

consistent, then, with a conjugative interaction between PhS and the carbanion.[21]

A polarizability effect for PhS could also be involved to some extent since polarizability effects are known to fall off rapidly with distance. If the PhS effect is caused just by a polarizability effect, however, the larger and more polarizable selenium atom would be expected to have a still *larger* effect, but it does not. In the GCH_2COPh system $PhSeCH_2COPh$ has a pK of 18.6 as compared to 17.3 for $PhSCH_2COPh$. In terms of the analysis used in Table II, the PhSe group has a larger effect than expected from its σ_I constant, but the increase ($\Delta\Delta pK$) is smaller for PhSe than for PhS (2.9 vs. 3.7). The acidifying order PhS > PhSe is that expected for a conjugative effect, the orbitals of the larger selenium atom being less effective than sulfur in overlapping with the p orbital of the much smaller carbon atom in the anion.

Steric Demands of Phenylthio and Phenyl Groups. In the previous paper it was shown that, when a phenyl group is substituted for a hydrogen atom in a carbon acid already containing two substituents, as for $PhCH_2EWG \rightarrow Ph_2CHEWG$ or $PhCH_2Ph \rightarrow Ph_2CHPh$, the acidifying effect of the second phenyl group is greatly decreased.[17] This is in part due to a resonance saturation effect, but the major cause is steric inhibition of resonance. One would not anticipate that the acidifying effect of the phenylthio group would be subject to comparable steric restrictions since there is no reason to expect that the π system of its phenyl ring need adopt any particular orientation with respect to the p orbital of the carbanion. In agreement with this expectation it was found that, contrary to the behavior of the phenyl group, introduction of a PhS group into a disubstituted carbon acid caused a large acidifying effect. For example, whereas a 9-phenyl substituent increases the acidity of xanthene by only 2.4 pK units, a 9-phenylthio substituent causes a 7.5 pK unit increase in acidity. Table III provides a comparison of phenyl and phenylthio effects in a series of di- and trisubstituted carbon acids.

Examination of Table III shows that the acidifying effect of phenyl is only 2 pK units for substitution into $PhCH_2Ph$, increases to 4.4 pK units for substitution into $PhCH_2SPh$, and to 8.1 pK units for substitution into $PhSCH_2SPh$. On the other hand, the acidifying effect of the PhS group is large (5.9–8.3 pK units) for substitution into any of these three substrates. Evidently there is appreciable steric inhibition of resonance of the phenyl groups in the Ph_2CSPh^- anion, but less so than in the Ph_3C^- anion. The acidifying effect of the PhS group does not appear to be subject to any appreciable steric inhibition of resonance. This is brought out further by the comparisons of pK's given under formulas **7–10.**



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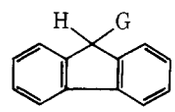

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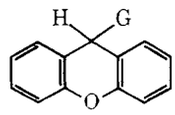

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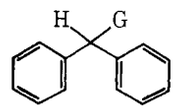

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G	pK	ΔpK	pK	ΔpK	pK	ΔpK	pK	ΔpK
H	30.8		22.6		30.0		32.3	
Ph	23.0	8.1	17.9	5.0	27.9	2.4	30.6	2.0
PhS	22.8	8.3	15.4	7.5	22.8	7.5	26.7	5.9

In the series **7, 8, 9, 10,** judging from the progressive decrease in the size of the acidifying effect of phenyl from ΔpK 8.1 in **7** to 2.0 in **10,** it is apparent that there is a progressive increase in steric hindrance as we proceed from **7** to **10.** The fact that the acidifying effect of PhS decreases but little in this series indicates that its steric demands are minimal. Even in the Ph_2CHG system (**10**), where the apparent PhS effect has decreased from 8.3 (for **7**) to 5.9 pK units, it is probably not a requirement for a particular orientation of the PhS group, relative to the p orbital of the carbanion, that causes the reduced effect, but rather a decrease in the overlap of the π systems of the phenyl groups with the p orbital of the carbanion resulting from increased crowding.

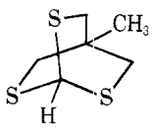
Table III. Comparison of the Acidifying Effects of Ph and PhS in $PhCH_2Ph$, $PhCH_2SPh$, and $PhSCH_2SPh$ Substrates

Acid	pK^a	ΔpK(Ph)[b]	ΔpK(PhS)[b]
$PhCH_2Ph$	32.3		
$PhCH_2SPh$	30.8		
$PhSCH_2SPh$	30.8		
Ph_2CHPh	30.6	2.0[c]	
Ph_2CHSPh	26.7	4.4[d]	5.9[c]
$PhCH(SPh)_2$	23.0	8.1[e]	8.1[d]
$PhSCH(SPh)_2$	22.8		8.3[e]

[a] Equilibrium acidity in Me_2SO;[15] not statistically corrected. [b] Statistically corrected for the number of acidic hydrogen atoms. [c] Relative to $PhCH_2Ph$. [d] Relative to $PhCH_2SPh$. [e] Relative to $PhSCH_2SPh$.

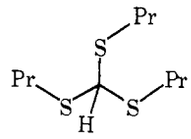
In the absence of steric effects we have suggested that, as a first approximation, the size of a substituent effect will be regulated by the negative charge density at the carbon atom in the anion to which the substituent is attached.[17,18] In view of the near constancy in the size of the PhS effect for carbon acid systems **7–10,** it would appear, then, that the negative charge density differs but little at the acidic site in the anions derived from these acids. For **7, 9,** and **10** this is not surprising since the acidities of the parent acids differ by only a few pK units. The fluorene system (**8**) differs sharply from the others, however. Note, for example, that the PhS effect is as large for **8** as for **9,** despite the 7.4 pK unit greater acidity of **8.** This suggests that a greater fraction of the negative charge in the fluorenyl anion remains at the 9 position, for aromaticity reasons, than is true for the xanthenyl anion. Delocalization of the negative charge in the $(PhS)_2CH^-$ anion to the benzene rings can occur only through the sulfur atoms. It is remarkable, then, that the charge density at the acidic site in the $(PhS)_2CH^-$ anion is no larger than at the 9 position in the fluorenyl or xanthenyl anions as judged by the PhS effect. It would appear that the sulfur atoms have been able to cause an effective decrease in the charge density in the anion, probably by some kind of conjugative interaction. This view is consistent with the observation that the acidifying effect is *smaller* for $CH_2(SPh)_2$ than for CH_3CN (ΔpK = 8.3 vs. 10.6). In the CH_2CN^- anion it seems clear that the charge density at carbon must be markedly decreased by delocalization to nitrogen;[22] it seems likely that the charge density in the $(PhS)_2CH^-$ ion is also decreased by delocalization.

The equilibrium acidities of **11,** the protio derivative of **1,** its acyclic analogue (**12**), 2-phenyl-1,3-dithiane (**13**), and an acyclic analogue (**14**) were examined in order to learn something of the stereoelectronic requirements, if any, of divalent sulfur. It has been suggested that sulfur atoms constrained in rings may provide more effective p–d overlap to carbanions in these ring systems.[3,4] For example, the approximately 10^3 faster rate for **11** than for an acyclic analogue, such as **12,**[3] could mean that the equilibrium acidity of **11** would be as much as 6 pK units greater than that for **12** (assuming a "normal" Bronsted coefficient of 0.5). The results of our equilibrium measurements show that **11** is more acidic than



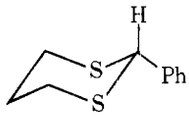
11

pK = 30.5



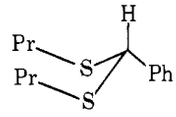
12

pK = 31.3



13

pK = 30.7



14

pK = 29.2

12, but the difference is small (0.8 pK unit). Examination of scalar molecular models shows that the p orbital of the carbanion derived from **12** may be completely shielded from the solvent by the alkyl groups. On the other hand, the pyramidal carbanion derived from **11** is open to solvation from the "front" side, but screened from solvation from the "back" side. It seems likely that these differences in solvation of the anions are the cause of the difference in acidities, and that no appreciable stereoelectronic effect is present.

No special stereoelectronic effect arising from incorporation of the sulfur atoms into a ring is apparent from the pK data for **13** and **14.** The ring compound is less acidic by 1.5 pK units, but again it seems likely that this relatively small difference is caused by a solvent effect of some kind.

Extrapolation to Obtain the pK of Toluene. Knowing the approximate magnitude of the acidifying effect of a PhS substituent and the approximate degree to which this acidifying effect is attenuated by delocalization of the charge in the system to which it is attached, we can make a rough estimate of the acidity of toluene, a hydrocarbon much too weakly acidic to be measured in Me_2SO solution. Since we can expect the negative charge in the $PhCH_2^-$ ion to be strongly delocalized into the benzene ring, the resonance saturation effect caused by Ph in this anion will be large, and the effect of substituting a group like PhS for an α-hydrogen atom into this anion will be strongly attenuated relative to that for substitution into an anion of comparable stability in which the charge is less delocalized. The Ph group in the $PhCH_2^-$ ion can be likened in this respect to the PhCO group in the $PhCOCH_2^-$ ion. As pointed out earlier, both groups have large resonance to polar ratios. Judging from the tangent of the PhS curve at the PhCO point (Figure 1), the attenuation in the size of the PhS acidifying effect caused by PhCO in the $PhCOCHSPh^-$ ion is about 3.5 pK units per 10 pK unit change in parent acid acidities. We can expect a proportional effect for Ph in $PhCH_2^-$, but since the parent acid ($PhCH_3$) in this instance has a pK roughly 20 pK units higher than that of $PhCOCH_3$, the total attenuation of the PhS effect due to resonance saturation will be about 7 pK units for substitution of PhS into toluene. The total PhS acidifying effect will then be this value plus the size of the acidifying effect of PhS on $PhCOCH_3$ (≈7.5 pK units). This places the pK of toluene about 14.5 pK units above that of $PhSCH_2Ph$ or ≈45. Similar extrapolations using the 14.4 pK unit acidifying effect of the CN group on $PhCOCH_3$,[12] or the 13.2 pK unit acidifying effect of the $PhSO_2$ group on $PhCOCH_3$,[12] give slightly lower values.

$$\underset{pK\ 30.8}{PhSCH_2Ph} \xrightarrow{+7.5 + 2(3.5)} \underset{(pK \cong 45)}{HCH_2Ph}$$

$$\underset{pK\ 21.9}{PhCH_2CN} \xrightarrow{+14.4 + 2(3.5)} \underset{(pK \cong 43)}{HCH_2Ph}$$

$$\underset{pK\ 23.4}{PhCH_2SO_2Ph} \xrightarrow{+13.2 + 2(3.5)} \underset{(pK \cong 44)}{HCH_2Ph}$$

These extrapolations are rough since they depend heavily on the value of 3.5 per 10 pK units chosen for the attenuation of the PhS effect, and since they assume that the same attenuation will apply for the CN and $PhSO_2$ groups. The average value of 44 ± 1 obtained agrees reasonably well, however, with the value of 41 arrived at for toluene by Streitwieser by extrapolation of a Bronsted plot.[22] (Our pK's in Me_2SO agree well with Streitwieser's ion pair pK's in cyclohexylamine for hydrocarbons forming highly delocalized anions.[15])

Conclusions Regarding Conjugation of Carbanions and Adjacent Sulfur Functions. In this paper we have shown that the acidifying effect of substituting PhS for Me in a variety of carbon acids, $MeCH_2EWG$, is comparable to that of a phenyl substituent in type and magnitude. The acidifying effect of PhS in a number of carbon acid systems has been shown to be almost as large as that of the much polar substituent, Me_3N^+. Arguments have been presented to support the conclusion that a large portion of this PhS effect is due to the ability of the sulfur atom to stabilize the charge on an adjacent negatively charged carbon atom by a conjugative effect, possibly utilizing d orbitals. According to our present estimates, substitution of PhS for a hydrogen atom in methane causes an increase in acidity in Me_2SO of a minimum of 17 pK units, equivalent at 25 °C to 23 kcal/mol stabilization of the carbanion. Increasing the oxidation state of sulfur, as in CH_3SO and CH_3SO_2, causes additional increases in acidity amounting to about 13 and 17 pK units, respectively. Evidence has been presented recently to show that sulfone functions exert strong conjugative interactions with adjacent carbanions.[24] We believe that conjugation is strong between, not only sulfone functions and adjacent carbanions, but also, to a lesser degree, between carbanions and adjacent sulfoxide and sulfide functions.

Two theoretical papers have appeared within the past few months each stressing the importance of stereoelectronic effects in stabilizing an adjacent carbanion and each denying the stabilizing effect of sulfur d orbitals.[46,47] Both papers cite comparisons of kinetic acidities, e.g., **11** with **12,**[3] as experimental support for stereoelectronic effects. In contrast, we find the differences in equilibrium acidities in Me_2SO solution between **11** and **12** to be small.

Experimental Section

The equilibrium acidity measurements were carried out as previously described.[15] Samples of methyl and ethyl trifluoromethyl sulfone were kindly provided by J. B. Hendrickson and P. L. Skipper of Brandeis University, while 2-phenyl-1,3-dithiane was provided by N. H. Andersen of the University of Washington. The syntheses and properties of 9-*tert*-butyl-, 9-phenylthio-, and 9-phenylfluorene and 9-phenylxanthene have been previously reported.[15] Other compounds listed in the text or tables are commercially available from the Aldrich or Parish Chemical Co. The remaining compounds are listed in Table IV, or below, with a reference to their method of preparation. All samples were 99+% pure as judged by the TLC or GLC analyses.

Phenylthiomethyl Trifluoromethyl Sulfone. Trifluoromethanesulfonyl chloride (5 g, 30 mmol, Aldrich Chemical Co.) was reduced with potassium iodide to potassium trifluoromethanesulfinate by the literature procedure.[40] To 4 g (23 mmol) of this salt in 30 ml of acetonitrile freshly distilled from P_2O_5 was added 3.9 ml (~23 mmol) of chloromethyl phenyl sulfide[41] and 0.35 g (2.1 mmol) of potassium iodide as catalyst. This mixture was refluxed overnight, then stirred for a further day at 25 °C, whereupon the resulting dark brown solution containing a yellowish-white precipitate was poured into water containing an excess of sodium thiosulfate. Extraction with dichloromethane, washing with water and brine, and drying ($MgSO_4$) gave 3.9 g of a brown oil after concentration in vacuo. Short-path vacuum distillation yielded 1.1 ml of a yellow oil as the major fraction, bp 100–115 °C (0.35–0.5 mm). This was purified by filtration through grade 1 alumina with dichloromethane as eluent, followed by repeated recrystallization from pentane at −78 °C to give white needles which melted below room temperature to a colorless oil. This oil was identified as pure phenylthiomethyl trifluoromethyl sulfone: NMR δ 4.39 (s, 2, $-CH_2-$) and 7.15–7.68 (m, 5, ArH); IR 1370 (s), 1120 (s) (sulfone),

Table IV. Physical Properties of Acids Listed in the Text

Compd	Mp or bp, °C	Lit. value, °C
Phenylthiomethyl phenyl sulfone	61–62	62[25]
Bis(ethylsulfonyl)methane	102.5–103.5	103–104[26]
1,1-Bis(ethylsulfonyl)ethane	74–75	75–76[26]
1,1-Bis(phenylsulfonyl)ethane	102–103	101–102[27]
Benzhydryl phenyl sulfide	78	78[28]
α,α'-Bis(*n*-propylthio)toluene (**14**)	114 (0.5 mm)	Not reported[29]
Tris(*n*-propylthio)methane (**12**)	83 (0.05 mm)	158–60 (12 mm)[30]
Tris(phenylthio)methane	42–42.5	39[31]
α,α'-Bis(phenylthio)toluene	50.5–51.5	48.5–51[32]
9-(Phenylthio)xanthene	77	78–79[33]
4-Methyl-2,6,7-trithiabicyclo-[2.2.2]octane (**11**)	130	130.5–131[34]
Bis(ethylsulfonyl)phenylthio-methane	83–83.5	86[35]
Bis(phenylsulfonyl)phenyl-thiomethane	178.5–179.5	179–180[36]
(9-Fluorenyl)trimethylammo-nium bromide	189–190 dec	189–190 dec[37]
(Cyanomethyltrimethylam-monium chloride	180 dec	186–189[38]
2,6-Di-*tert*-butyl-4-nitrophenol	156–157	156[39]

and 1210 cm^{-1} (br, s) cm^{-1} (CF_3). Anal. Calcd for $C_8H_7F_3O_2S_2$: C, 37.49; H, 2.75. Found: C, 37.43; H, 2.78.

Phenylthionitromethane. Following the general procedure of Mukaiyama,[42] ethyl nitroacetate (3.9 g, 38 mmol) and 4-(phenylthio)morpholine[43] (6.5 g, 38 mmol) were placed in 50 ml of dichloromethane. After the solution had stood at room temperature for 3 h, removal of solvent under reduced pressure gave a tan salt which was taken up in a solution of 8.6 g of potassium hydroxide in 75 ml of water and 50 ml of ethanol and heated for 0.75 h on a steam bath. The ethanol was removed under reduced pressure, and the aqueous mixture was acidified to pH 7 with 10% HCl. Then 10 g (140 mmol) of hydroxylamine hydrochloride in 20 ml of water was added to the aqueous solution at 0 °C over 10 min. Extraction with three 100-ml portions of ether afforded, upon workup, 5 ml of yellow oil, 92% pure by GC and NMR. Column chromatography on silica with CCl_4 as eluent gave a pale yellow material 99+% pure by GLC: n^{23} D 1.5785; NMR ($CDCl_3$) δ 5.38 (s, 2, $-CH_2-$) and 7.1–7.5 (m, 5, ArH); ir 1550 and 1350 cm^{-1} ($-NO_2$). Anal. Calcd for $C_7H_7NO_2S$; C, 49.69; H, 4.17; S, 18.95. Found: C, 49.64; H, 4.23; S, 18.79.

(Phenylsulfonylmethyl)trimethylammonium Chloride. Crude (phenylthiomethyl)trimethylammonium chloride (0.7 g, 3.2 mmol), prepared from chloromethyl phenyl sulfide[41] and anhydrous trimethylamine in ethanol, was dissolved in 50 ml of HOAc. To this solution was added 2 ml of 30% aqueous H_2O_2 and the mixture was heated upon a steam bath for 12 h. Aqueous workup followed by extraction with ethyl acetate and evaporation of the aqueous layer resulted in an oil which showed spectral characteristics of a sulfoxide. This material was then dissolved in 20 ml of HOAc and oxidized further by 5 ml of 30% H_2O_2 by the above procedure for another 18 h with workup as above. The oily residue was triturated with $CHCl_3$, resulting in crystals which were filtered and washed with $CHCl_3$. Recrystallization from CH_3CN–EtOH gave crystals: mp 181.5–183.5 °C; NMR (Me_2SO-d_6 and D_2O) δ 3.30 (s, 9, CH_3), 5.28 (s, 2, CH_2), and 7.6–8.2 (m, 5, ArH); IR (KBr) 1325 (s) and 1160 cm^{-1} (s) (sulfone).

Anal. Calcd for $C_{19}H_{16}ClNO_2S$: C, 48.09; H, 6.46. Found: C, 47.85; H, 6.50.

α-Phenylselenoacetophenone. A sample of α-acetoxystyrene (1.62 g, 0.01 mol, prepared by the method of Noyce and Pollack[44]) added dropwise, with stirring to a solution of benzeneselenyl chloride (1.9 g, 0.01 mol, prepared by the method of Behaghel and Seibert[45]) in CH_2Cl_2 (10 ml). The red color of the selenyl chloride disappeared during the addition. The mixture was washed with saturated $NaHCO_3$, dried (Na_2SO_4), and evaporated, leaving the crude phenylselenoacetophenone as a thick yellow oil. Twelve recrystallizations from ether/pentane at −78 °C produced the pure material as white platelets: mp 40–41 °C; NMR ($CDCl_3$) δ 4.15 (s, 2, CH_2), 7.1–8.0 (m, 10, aryl H); ir (mull) 1667 cm^{-1} (C=O).

(Phenacyl)trimethylammonium Chloride. Phenacyl chloride (3.1 g, 20 mmol) and 2 ml of trimethylamine were dissolved in 20 ml of EtOH and refluxed for 3.5 h. After cooling to room temperature, 100 ml of ether was added, followed by filtration of the resulting white crystals. Recrystallization from acetonitrile gave white crystals: mp 203–205 °C; NMR (Me_2SO-d_6) δ 3.35 (s, 9, CH_3), 5.55 (s, 2, CH_2), 7.4–8.1 (m, 5, ArH).

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Registry No.—**7** (G = H), 3561-67-9; **7** (G = Ph), 7695-69-4; **7** (G = PhS), 4832-52-4; **8** (G = H), 86-73-7; **8** (G = Ph), 789-24-2; **8** (G = PhS), 28114-92-3; **9** (G = H), 92-83-1; **9** (G = Ph), 3246-80-8; **9** (G = PhS), 35595-00-7; **10** (G = H), 101-81-5; **10** (G = Ph), 519-73-3; **10** (G = PhS), 21122-20-3; **11**, 39137-60-5; **13**, 5425-44-5; **14**, 60595-12-2; phenylthiomethyl trifluoromethyl sulfone, 60595-15-5; trifluoromethanesulfonyl chloride, 421-83-0; chloromethyl phenyl sulfide, 7205-91-6; phenylthionitromethane, 60595-16-6; ethyl nitroacetate, 626-35-7; 4-(phenylthio)morpholine, 4837-31-4; (phenylthiomethyl)trimethylammonium chloride, 25803-80-9; α-acetoxystyrene, 2206-94-2; benzeneselenyl chloride, 5707-04-0; phenacyl chloride, 532-27-4; trimethylamine, 75-50-3; dimethyl sulfoxide, 67-68-5.

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Rates of Thiol–Disulfide Interchange Reactions between Mono- and Dithiols and Ellman's Reagent[1]

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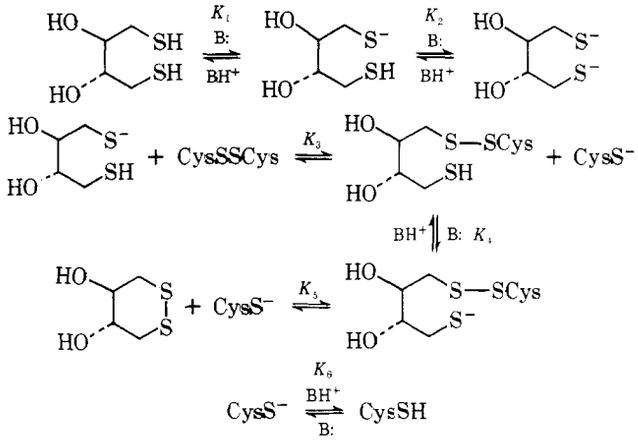
The rate constants for thiol–disulfide interchange between 21 mono- and dithiols and Ellman's reagent correlate with the pK_a's of the thiol groups with a Bronsted coefficient of $\beta = 0.36$. The maximum rates of reduction are observed for thiols having pK_a values close to the pH of the solution in which the reactions were carried out. In the dilute solutions examined (10^{-4}–10^{-6} M in each reagent), the rate of the second, intramolecular interchange step in reactions of dithiols was faster than that of the first, intermolecular interchange, regardless of the size of the cyclic disulfide formed. A convenient synthesis of a mixture of diastereomers of 1,4-dimercapto-2,3-butanediol (i.e., of a mixture of dithiothreitol, DTT, and dithioerythritol, DTE) has been developed from 1,2:,4-diepoxybutane and thiolacetic acid.

Oxidation of cysteine sulfhydryl groups during isolation, storage, and use of proteins is often an important contributor to their deactivation.[2] Although the rate of oxidation can be decreased by limiting access of oxygen to the enzyme, it is usually impractical to exclude oxygen completely, particularly in practical synthetic and analytical applications. The most effective and widely used reagents for protecting the cysteine moieties of enzymes against oxidation by adventitious oxygen, and for activating partially oxidized and deactivated enzymes by reduction, are thiols, particularly dithiothreitol (DTT, Cleland's reagent)[3] and β-mercaptoethanol. Each has its advantages and disadvantages: DTT reduces protein disulfide groups rapidly and completely and is convenient to handle, but is exorbitantly expensive; β-mercaptoethanol is readily available and inexpensive, but reacts less rapidly and completely.

As part of a project designed to develop techniques to permit the use of enzymes as catalysts in large-scale organic synthesis, we required an agent that would reduce disulfide moieties more rapidly and completely than β-mercaptoethanol but which would be less expensive than DTT. The design of an appropriate reagent is not straightforward for several reasons. First, the mechanism of reduction (illustrated in Scheme I for DTT) involves multiple acid–base and sulfhydryl–disulfide interchange equilibria, and the dependence of the overall rate and equilibrium position on the structure of the reducing agent (and possibly of the protein) is difficult to predict. An important part of the difference in reactivity between DTT and β-mercaptoethanol can, however, plausibly be attributed to the rate of release of the second equivalent of $CysS^-$ (or CysSH) from initially formed mixed disulfides: since β-mercaptoethanol is commonly used in enzymology at concentrations of ca. 10 mM, the rate of the intermolecular reaction involved in its release of CysSH from $CysSSCH_2CH_2OH$ should be approximately 10^{-3}–10^{-4} the rate of the corresponding intramolecular release from $CysSSCH_2CHOHCHOHCH_2SH$. Second, a useful reducing reagent, in addition to high reactivity and ready availability, should also have good water solubility, tolerable odor, and low toxicity. These requirements seriously limit the range of possible thiols.

Scheme I. Mechanism of Reduction of a Cystine Moiety CysS–SCys by DTT



Here we describe an examination of the rates of reaction of a number of mono- and dithiols with 5,5′-dithiobis(2-nitrobenzoic acid) (Ellman's reagent, EllS-SEll).[4] This study represents the first phase of an effort to understand the kinetics and equilibria of biochemically relevant thiol–disulfide interchange reactions in sufficient detail to be able to rationalize the exceptionally useful properties of DTT in terms of its structure, and to design alternative, effective reducing agents. Ellman's reagent was chosen as the disulfide for initial examination for several reasons. First, since the S–S bond is weak, its reduction by most thiols should be complete: it should thus be possible to examine the influence of the structure of a reducing thiol on its rate of reaction with the disulfide bond of Ellman's reagent without complications by