Radical Ion Probes. 7. Behavior of a "Hypersensitive" Probe for Single Electron Transfer in Reactions *Not* Involving Electron Transfer

James M. Tanko* and Larry E. Brammer, Jr.

Department of Chemistry, Virginia Polytechnic Institute and State University, Blacksburg, Virginia 24061-0212

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1-Methyl-5,7-di-*tert*-butylspiro[2.5]octa-4,7-dien-6-one (**8**) and 1,1-dimethyl-5,7-di-*tert*-butylspiro-[2.5]octa-4,7-dien-6-one (**1**) react with thiophenoxide ion to produce cyclopropane ring-opened products. Thermodynamic considerations effectively rule out any possibility that single electron transfer is involved in theses reactions; the process $PhS^- +$ substrate $\rightarrow PhS^{\bullet} +$ substrate$^{\bullet -}$ is endothermic by over 50 kcal/mol! Nucleophilic attack occurs both at the least- and most-hindered carbons of the cyclopropyl group, and the product ratio (R(1°/2°) from **8** and R(1°/3°) from **1**, where 1°, 2°, and 3° refer to the regioisomeric phenyl sulfides formed from these substrates) is found to vary with solvent. In dipolar, aprotic solvents, nucleophilic attack occurs preferentially at the least-hindered carbon of the cyclopropyl group (R(1°/2°) and R(1°/3°) $\approx$ 4−5), consistent with an S_N2 mechanism. In protic solvents, products arising from nucleophilic attack at the more-substituted carbon of the cyclopropyl group become increasingly important, consistent with the onset of a carbocationic ($S_N2(C+)$) pathway. The strengths and weaknesses of **1** and **8** as probes for single electron transfer are discussed in the context of these results.

I. Introduction

Single electron transfer (SET) has emerged as an important mechanistic pathway for a number of organic transformations. Many processes previously believed to proceed solely via polar (two electron) pathways are now believed to involve some component of SET. Most experimental approaches for diagnosing whether electron transfer may be involved in a particular organic transformation exploit the unique properties of the paramagnetic intermediates (i.e., free radicals and radical ions) that are formed.

One very popular approach is to incorporate structural features into the reactants which serve as intramolecular traps for paramagnetic intermediates. Assuming that the rearrangement is a unique feature of the radical or radical ion, the detection of structurally rearranged products may infer that an electron transfer mechanism was involved. The problem with this approach is that rearranged products may *also* result from mechanisms other than SET. When such is the case, the differentiation between SET and polar pathways becomes a very knotty problem.

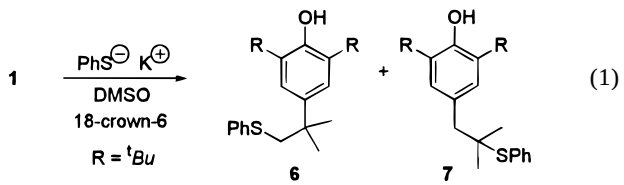
In 1994, we suggested that spiro[2.5]octa-3,6-dien-5-one **1** may be an excellent probe for the detection of SET in reactions of nucleophiles with carbonyl compounds.[1] The estimated reduction potential of **1** (−2.2 V vs SCE) is similar to that of aromatic ketones and enones. Moreover, the radical anion resulting from one-electron reduction of **1** undergoes ring opening (predominantly to 3° distonic radical ion **3**) with a rate constant $>10^7$ s^{-1}.

This system is especially intriguing because it may provide a means for differentiating between polar vs SET pathways based upon the observed regiochemistry of the reaction. The key elements of this hypothesis are highlighted in Scheme 1. If **1** reacts with a nucleophile via SET, rearrangement of the resulting radical anion (**2** → **3**) will lead to a product (**4**) in which the nucleophile is attached to the most-hindered carbon. In contrast, for the polar pathway nucleophilic attack is expected to occur preferentially at the least-hindered carbon, leading to **5**.[1]

By examining reactions of **1** with nucleophiles which have been shown independently to react with carbonyl compounds via SET, we were able to confirm the first half of Scheme 1, namely, the behavior of this system in bona fide SET processes.[2] However, in order to be generally useful as mechanistic probe for SET, it is equally important to understand how this compound behaves in reactions where SET is *not* occurring.

II. Results and Discussion

A. Initial Observations. Reaction of **1** (0.02 M) with thiophenoxide ion ($PhS^- K^+$) in DMSO (in the presence of 18-crown-6 to minimize ion-pair formation) led to formation of ring opened products, 1° and 3° sulfides **6** and **7** (eq 1). This reaction occurred in ≤5 min and in nearly quantitative yield. The product ratio **6**/**7** (R(1°/3°)) was unaffected by changes in the concentration of PhS^-: At both 0.02 and 0.2 M PhS^-, R(1°/3°) = 3.6.



(1)

[⊗] Abstract published in *Advance ACS Abstracts,* July 15, 1997.

(1) Tanko, J. M.; Brammer, L. E., Jr.; Hervas', M.; Campos, K. *J. Chem. Soc., Perkin Trans. 2* **1994**, 1407.

(2) Tanko, J. M.; Brammer, L. E., Jr. *J. Chem. Soc., Chem. Commun.* **1994**, 1165.

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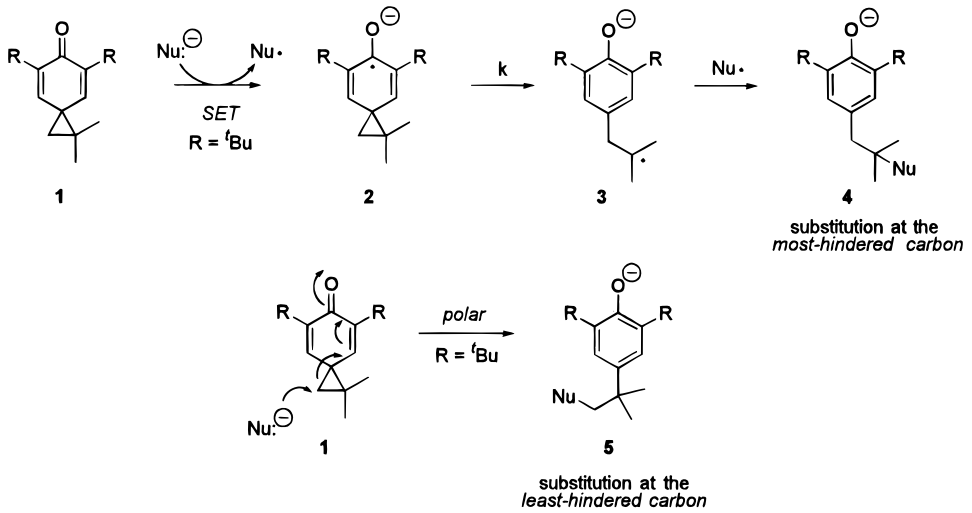
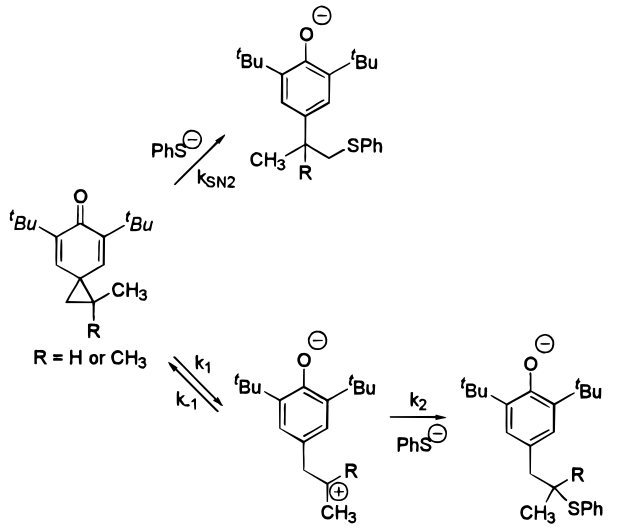
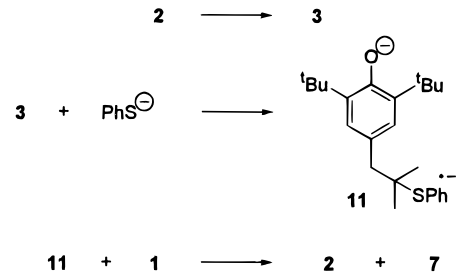
Scheme 1



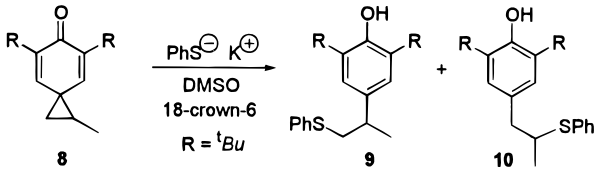
Scheme 2



Scheme 3



Similarly, reaction of monomethyl derivative **8** (under the same conditions) led to nearly the same ratio of 1° and 2° sulfides (**9** and **10**, eq 2): $R(1°/2°) = 3.8$.



(2)

B. Competing S_N2/S_N1 Pathways. It is likely that, for the reaction of both **1** and **8** with PhS^-, the primary sulfides are the result of direct nucleophilic attack at the least-hindered carbon of the cyclopropyl group (i.e., an S_N2 process). However, the origin of the products **7** and **10**, where PhS^- appeared to react at the more-hindered carbon was less obvious. Competing S_N1/S_N2 pathways (Scheme 2) appeared to be ruled out by two observations: (a) $R(1°/3°)$ and $R(1°/2°)$ were nearly identical (presumably $R(1°/3°)$ would be less than $R(1°/2°)$ because **1** can form a 3° carbocation, vs a 2° carbocation for **8**), and (b) the product ratio is unaffected by nucleophile concentration (higher nucleophile concentrations were expected to favor the S_N2 product).

C. Competing S_N2/SET Pathways? It is *very* unlikely that 3°-sulfide (from **1**) and 2°-sulfide (from **8**) are the result of direct electron transfer as outlined in Scheme 1. The redox potential of the $PhS^{\bullet}/PhS^-$ couple is reported to be 0.1 V (vs SCE).[3] The reduction potential of **1** is estimated to be −2.2 V vs SCE (also in DMSO). Thus, direct electron transfer between PhS^- and **1** (or **8**) is endothermic by over 50 kcal/mol!

We considered the possibility that **7** and **10** might be the result of a chain process involving radical anions, i.e., the $S_{RN}1$ reaction[4] (Scheme 3). Presumably this process could be initiated either fortuitously via action of laboratory light or, perhaps, via spontaneous electron transfer between PhS^- and substrate. (The fact that electron transfer from PhS^- to **1** is extremely sluggish might be overcome if the chain length were sufficiently long.)

However, the $S_{RN}1$ mechanism was ruled out for the reaction of **1** and PhS^- on the following grounds: The reaction is not photoinitiated and occurs readily in the dark resulting in the same ratio of products ($R(1°/3°) = 3.2$) in the same yield and in the same period of time. Furthermore, the reaction is not inhibited by O_2, PhSH, or PhSSPh, and the product ratios were nearly identical ($R(1°/3°) = 3.2$, 3.6, and 3.7, respectively) in the presence of these materials. (O_2,[5] PhSH,[6] and PhSSPh[7] react with

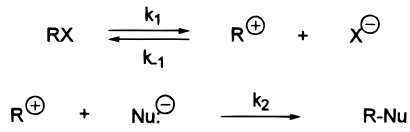
(3) Andrieux, C. P.; Hapiot, P.; Pinson, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1993**, *115*, 7783.

(4) For examples of ArS^- participating in $S_{RN}1$ reactions involving aliphatic radicals, see: (a) Meijs, G. F. *J. Org. Chem.* **1986**, *51*, 606. (b) Ahbala, M.; Hapiot, P.; Houmam, A.; Jouini, M.; Pinson, J.; Savéant, J.-M. *J. Am. Chem. Soc.* **1995**, *117*, 11488. For examples of ArS^- participation in the aromatic $S_{RN}1$ reaction, see: Bunnett, J. F.; Creary, X. *J. Org. Chem.* **1974**, *39*, 3174.

(5) Rate constants for reaction of alkyl radicals with O_2 in solution are greater than $10^9\ M^{-1}\ s^{-1}$, see: Maillard, B.; Ingold, K. U.; Scaiano, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 5095.

(6) Rate constants for $R^{\bullet} + PhSH \rightarrow RH + PhS^{\bullet}$ are ca. $10^8\ M^{-1}\ s^{-1}$ for R = 1°, 2°, or 3° alkyl. See: Franz, J. A.; Bushaw, B. A.; Alnajjar, M. S. *J. Am. Chem. Soc.* **1989**, *111*, 268.

Scheme 4



alkyl radicals efficiently and are expected to trap 3° distonic radical ion **3**, thereby inhibiting the reaction and diminishing the yield of 3° sulfide **7** and resulting in a larger observed R(1°/3°).) The observations that these reagents neither perturbed the product ratio nor inhibited the reaction is a good indication that competing S_N2/$S_{RN}1$ process is not involved.

D. Reevaluation of Results: The S_N2(C+) Mechanism. The general mechanism for nucleophilic substitution via carbocationic pathways is depicted in Scheme 4. Using the steady-state approximation, the overall rate law for this reaction is:

$$-\frac{\mathrm{d[RX]}}{\mathrm{d}t} = \frac{k_1 k_2 [\mathrm{RX}][\mathrm{Nu}^-]}{k_{-1}[\mathrm{X}^-] + k_2[\mathrm{Nu}^-]}$$

Typically, $k_{-1}[X^-]$ is small relative to $k_2[Nu^-]$, and the rate law reduces to k_1[RX], i.e., the *classic* S_N1 reactions. However, when the opposite situation prevails ($k_{-1}[X^-] > k_2[Nu^-]$), the rate law reduces to an overall second-order rate law: K_1k_2[RX][Nu:$^-$]. This latter situation is quite rare and is referred to as the S_N2(C+) process ("2" because the reaction is second-order overall, "C+" because a carbocation is involved).[8−10]

All of our observations for the reactions of **1**and **8** with PhS$^-$ are consistent with competing S_N2/S_N2(C+) pathways for product formation: (a) Both processes are first order in nucleophile, thus explaining why R(1°/2°) and R(1°/3°) are unaffected by changes in PhS$^-$ concentration. (b) The carbocation generated from **1** (**1**$^+$) is expected to be more stable than that generated from **8** (**8**$^+$). However, for the same reason, **1**$^+$ is also expected less reactive toward nucleophiles than **8**$^+$. Thus the more favorable equilibrium constant for carbocation formation from **1** (K_1) may be offset by a smaller rate constant for reaction with PhS$^-$ (k_2), thereby explaining why R(1°/2°) and R(1°/3°) are so similar.

Despite its rarity, it is not unreasonable to suspect that the S_N2(C+) mechanism might be operating in these systems. For "typical" substrates, external return (recombination of R$^+$ and X$^-$ to regenerate R−X) is a bimolecular process; $k_{-1}[X^-]$ is small relative to $k_2[Nu^-]$ because the concentration of X$^-$ in solution is small.[11] For our system however, k_{-1} (Scheme 2) is a *unimolecular* process...the leaving group is *still* attached to the carbocation. Thus it is not at all unreasonable to expect that intramolecular ring closure would be faster than intermolecular nucleophilic attack ($k_{-1} > k_2$[PhS$^-$], Scheme 2).

Table 1. Product Ratios and Yields for the Reaction of 1 and 8 with PhS$^-$ in Several Solvents

	reaction of **1**		reaction of **8**	
solvent	R(1°/3°)[a]	yield (%)	R(1°/2°)[b]	yield (%)
THF	5.34	84	4.81	63
EtOAc	3.91	84	4.77	87
acetone	4.68	96	4.17	97
pyridine	3.93	80	4.37	86
DMF	4.75	86	4.70	87
DMSO	3.05	80	3.75	80
t-BuOH	1.35	91	2.47	89
i-PrOH	0.96	84	2.30	90
EtOH	0.65	72	1.75	97
MeOH	0.43	56	1.46	95

[a] Ratio of 1° sulfide **6** to 3° sulfide **7**. [b] Ratio of 1° sulfide **9** to 2° sulfide **10**.

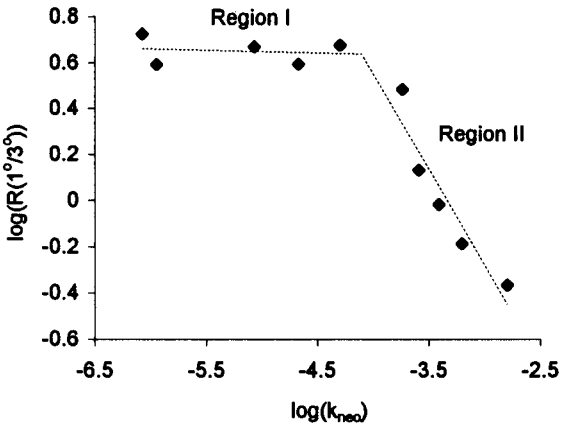
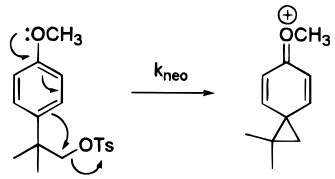


Figure 1. Variation in the log of the product ratio (**6**/**7**) for reaction of **1** with PhS$^-$ as a function of the ionizing power of the solvent.

E. Evidence for Carbocations as Intermediates in the Reaction of 1 and 8 with PhS$^-$. To fully explore whether carbocations were involved in the reactions of **1** and **8** with PhS$^-$, these reactions were examined in several solvents. In all instances, PhSK was utilized in the presence of 18-crown-6 so as to complex K$^+$ and minimize ion-pairing effects. Mass balances in these experiments were typically >80%.[12] The results of these experiments are summarized in Table 1.

In Figures 1 and 2, log(R(1°/3°)) and log(R(1°/2°)) are plotted as a function of the ionizing power of the solvent, expressed in terms of log(k_{neo}), where k_{neo} is the rate constant for ionization of neophyl tosylate (**12**) in the same solvent (eq 3).[13]



(3)

There are several good reasons for selecting log(k_{neo}) as the solvent parameter to correlate these results: (a) Ionization of **12** proceeds with anchimeric assistance yielding spiro cation **13**. As a result, these solvent parameters are a good measure of a solvent's ionizing

(7) Undecyl radical reacts with PhSSPh with a rate constant of 2×10^5 M^{-1} s^{-1}, see: Curran, D. P.; Martin-Esker, A. A.; Ko, S.-B.; Newcomb, M. *J. Org. Chem.* **1993**, *58*, 4691.

(8) Gelles, E.; Hughes, E. D.; Ingold, C. K. *J. Chem. Soc.* **1954**, 2918.

(9) Hartshorn, S. R. *Aliphatic Nucleophilic Substitution*, Cambridge University Press: London, 1973; pp 12−13.

(10) Kinoshita, T.; Ueda, H.; Takeuchi, K. *J. Chem. Soc., Perkin Trans. 2* **1993**, 603.

(11) For a classical S_N1 process, the addition of X$^-$ to the solution results in a depression in reaction rate (i.e., the common-ion effect). See ref 9.

(12) Compound **1** has a tendency to polymerize in MeOH and EtOH, and as a consequence, the mass balances were only 56 and 72%, respectively, in these two solvents.

(13) Smith, S. G.; Fainberg, A. H.; Winstein, S. *J. Am. Chem. Soc.* **1961**, *83*, 618.

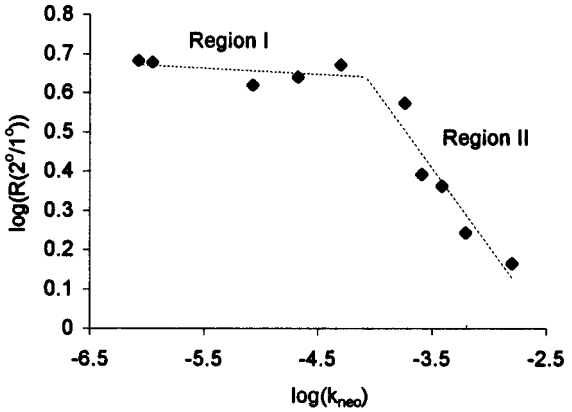


Figure 2. Variation in the log of the product ratio (**9**/**10**) for reaction of **8** with PhS^- as a function of the ionizing power of the solvent.

power and are not "contaminated" by the solvent's nucloephilicity (as is the case with parameters such as the *Y* scale). (b) $\log(k_{neo})$ values are available for a broader range of solvents (ranging from dipolar, aprotic to protic) than is the case for *Y* values,[14] which are limited mostly to protic solvents.[15]

As Figures 1 and 2 reveal, there are two regions in the plots of $\log(R)$ vs $\log(k_{neo})$. In region I (which is constituted by the dipolar aprotic solvents) the product ratio is *independent* of the ionizing power of the solvent. Using the results for THF, EtOAc, acetone, pyridine, and DMF, the slope of the plot of $\log(R)$ vs $\log(k_{neo})$ is −0.011 and −0.016 for **1** and **8**, respectively. In region II (constituting the more polar aprotic solvents and protic sovents), the product ratio varies *linearly* with the ionizing power of the solvent. Using the results for DMSO, *t*-BuOH, *i*-PrOH, EtOH, and MeOH, the slope of $\log(R)$ vs $\log(k_{neo})$ is −1.07 and −0.401 for **1** and **8**, respectively.

Because of the observed curvature in the $\log(R)$ vs $\log(k_{neo})$ plots for **1** and **8** (Figures 1 and 2), it seemed prudent to verify that the effect of PhS^- concentration on the product ratios was the same in both regions I and II. (The preliminary results discussed above were confined to DMSO solvent, which appears to be the break point in these plots.) Toward this end, the effect of PhS^- concentration on *R* was studied for both the reaction of **1** and **8** in representative solvents in both regions I and II (Table 2).

The results in Table 2 reveal that *R*(1°/2°) and *R*(1°/3°) are unaffected by $[PhS^-]$ in both regions I and II, consistent with the fact that the competing processes resulting in apparent nucleophilic attack at the least- and most-hindered postions of **1** and **8** were the same reaction order in PhS^- (presumably first order).

F. Determination of the Reaction Order in PhS^-. Determination of the precise reaction order in PhS^- in reactions with **8** was accomplished by competition experments.[16] In these experiments, **8** was allowed to compete with CH_3CH_2Br for PhS^- in several solvents

Table 2. Effect of PhS^- Concentration on the Product Ratios Observed for Reactions of 1 and 8 in Representative Solvents

	reaction of **1**		reaction of **8**	
solvent	$[PhS^-]$, M[a]	*R*(1°/3°)[b]	$[PhS^-]$, M[c]	*R*(1°/2°)[d]
acetone	0.002	5.1	0.001	4.1
	0.02	4.9	0.005	4.2
			0.01	4.4
DMSO	0.02	3.6	0.001	3.9
	0.20	3.6	0.005	4.1
			0.01	4.1
i-PrOH			0.001	2.1
			0.005	3.1
			0.01	3.1
EtOH	0.02	0.60		
	0.20	0.62		

[a] 0.02 M **1**. [b] Ratio of 1° sulfide **6** to 3° sulfide **7**. [c] 0.10 M **8**. [d] Ratio of 1° sulfide **9** to 2° sulfide **10**.

Scheme 5

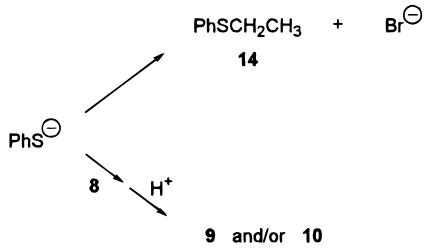


Table 3. Ratio of Products Formed in Competition Experiments Pitting 8 vs CH_3CH_2Br for PhS^- in Several Solvents

solvent	$[PhS^-]$, M[a]	product ratio **14**:**10**	product ratio **14**:**9**	*R*(1°/2°)
acetone	0.001	7.4	33	4.5
	0.005	7.8	41	5.2
	0.01	10.0	52	5.2
i-PrOH	0.001	0.49	0.94	2.1
	0.005	0.35	0.75	2.1
	0.01	0.42	0.88	2.1
DMSO	0.001	7.1	28	3.95
	0.005	6.7	27	4.1
	0.01	8.0	36	4.1

[a] For all experiments, [**14**] = $[CH_3CH_2Br]$ = 0.10 M.

(Scheme 5). The results of these experiments are summarized in Table 3. (These experiments also provide values of *R*(1°/2°), which are consistent with the data in Tables 1 and 2.)

The product ratios **9**:**14** and **10**:**14** remained constant over an order of magnitude variation in PhS^- concentration. Making the reasonable assumption that the reaction $CH_3CH_2Br + PhS^- \rightarrow CH_3CH_2SPh + Br^-$ is an S_N2 process in all solvents and, thus, first order in PhS^-, the results in Table 3 confirm that the processes leading to **9** and **10** are both first order in PhS^- in these solvents. By inference, the same presumably holds true for the formation of **6** and **7** from **1**.

G. Effect of Solvent/Counterion on the Structure of Dienone 8. The reactivity of **1** and **8** toward nucleophiles, either via direct displacement or carbocationic pathways, is attributable to direct conjugation between the cyclopropyl and carbonyl (Scheme 6). In these compounds, the cyclopropyl group is effectively locked in the bisected conformation, where this interaction is maximal.

Bond lengths and atomic charges for these spirohexadienones obtained by AM1 SCF-MO calculations[17] are

(14) Grunwald, E.; Winstein, S. *J. Am. Chem. Soc.* **1948**, *70*, 846. For a review, see: Bentley, T. W.; Llewellyn, G. In *Progress in Physical Organic Chemistry*, Vol. 17; Taft, R. W., Ed.; Wiley: New York, 1990; pp 121−158.

(15) $\log(k_{neo})$ values were not available for 2-propanol and *tert*-butyl alcohol. These values were extrapolated from the slope of a graph of *Y* values vs $\log(k_{neo})$ values.

(16) Attempts to directly study the kinetics of reaction between PhS^- and either **1** or **2** by UV proved troublesome because the reactions were over in less than 5 min, and the results were unacceptably erratic.

Scheme 6

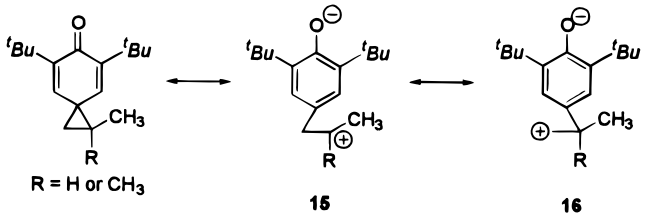


Table 4. AM1-Calculated Bond Lengths and Atomic Charges for Spiro[2.5]octa-4,7-dien-6-ones

	Atomic charges		Bond lengths (Å)		
	C2	C1	C2-C3	C1-C3	C1-C2
$R_1 = R_2 = H$	-0.177	-0.177	1.52	1.52	1.49
$R_1 = H$; $R_2 = CH_3$	-0.177	-0.120	1.52	1.53	1.49
$R_1 = R_2 = CH_3$	-0.173	-0.066	1.52	1.54	1.49

Table 5. Effect of Solvent and Counterion on ^{13}C NMR Shifts for the Cyclopropyl CH_2 and CH of 8

solvent/counterion	δ_{CH_2} (ppm vs TMS)	δ_{CH} (ppm vs TMS)	Δ (ppm)[a]
benzene-d_6	27.6	27.6	0.0
$CDCl_3$	28.1	27.9	−0.2
acetone-d_6	28.9	28.1	−0.8
DMSO-d_6	28.3	27.8	−0.5
DMSO-d_6 + $KClO_4$	28.3	27.8	−0.5
DMSO-d_6 + $KClO_4$ (18-crown-6)	28.4	27.8	−0.6
methanol-d_4	30.0	28.9	−1.1

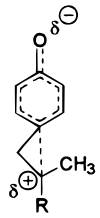
[a] $\Delta = \delta_{CH} - \delta_{CH_2}$.

summarized in Table 4. With increased methyl substitution at C1, the C1−C3 bond length becomes slightly longer than C2−C3, and the electron density becomes diminished at C1 compared to C2. These observations are consistent the resonance structures depicted in Scheme 6 and help explain why C1 and C2 are both reactive toward nucleophiles.

It is possible that the relative contributions of resonance structures **15** and **16** may be affected by counterion and solvent. Moreover, it is also possible that if interaction between the **1** or **8** with the positively charged counter ion associated with PhS^- (K^+/18-crown-6) were sufficiently strong, this might lead to partial ionization of the substrate (manifested by lengthening of the C1−C3 bond and a buildup of positive charge at C1 relative to C2).

^{13}C NMR chemical shifts should be a sensitive measure of the extent that solvent and/or counterion affects the polarization of the cyclopropyl group in these compounds. Chemical shifts for the cyclopropyl CH and CH_2 of **8** (and the difference between them) were determined in several solvents and in the presence of K^+ and K^+/18-crown-6. The results are summarized in Table 5 and suggest that as solvent polarity increases, the chemical shifts move downfield (very slightly). These results are consistent with notion that the cyclopropyl carbons bear slightly more positive charge in more polar and protic solvents (i.e., the contributions of resonance forms **15** and **16** is slightly enhanced in these solvents).

However, the data also suggest that although the cyclopropyl group is bearing slightly more positive charge in polar/protic solvents, *both carbons are affected to nearly the same extent*. Moreover, when K^+ or K^+/18-crown-6 are present, the chemical shifts are virtually unaffected. Thus it appears unlikely that there is any bond-lengthening or partial ionization of the compound (i.e., **17**) in these solvents or in the presence of the positively charged counterion.[18]



17

III. Conclusions

A. Dipolar, Aprotic Solvents (Region I). In dipolar, aprotic solvents spiro[2.5]octa-3,6-dien-5-ones **1** and **8** react with PhS^- to produce ring-opened products via an S_N2 process. As expected, nucleophilic attack occurs preferentially at the least-hindered carbon (by a factor of approximately 4−5 for both **1** and **8**). The only "surprise" in these results is that there is any attack at the more-hindered carbon at all. To the extent that the numbers are believable (i.e., uncontaminated by the S_N1 reaction) 3° carbons are generally (at least) 1000*x* less reactive 1° in a classic S_N2 reaction.[9]

However, this result is not unprecedented. Boger has reported that **18** reacts via an S_N2 mechanism with CH_3OH (Scheme 7).[19] Nucleophilic attack occurs preferentially at the primary carbon relative to tertiary of the cyclopropyl group by a factor of 1.7:1. Compound **18** is a member of a class of compounds (the duocarmycins) which are potent antitumor antibiotics and which possess the identical structural feature (spiro[2.5]octa-4,7-dien-6-one moiety) as **1** and **8**. An X-ray crystal structure of **18** reveals that (like spiro[2.5]octa-3,6-dien-5-ones **1** and **8**), the cyclopropyl group is effectively locked in a near perfect bisected conformation.[19] Thus both cyclopropyl bonds are activated toward nucleophilic attack.[20]

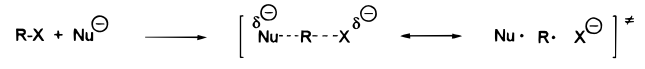
In terms of the utility of **1** or **8** as probes for single electron transfer, these results are consistent with our earlier hypothesis (Scheme 1)[1] regarding how these compounds would behave when reacting with a nucleophile via a polar pathway (S_N2) process—nucleophilic attack occurs preferentially at the least-hindered carbon yielding **5**. However, a fair amount of product also arises

(17) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.

(18) For both **1** and **8**, the bulky *tert*-butyl groups at the *ortho* position are expected to severely impede coordination of a Lewis acid with the carbonyl oxygen. We suspect that most of the observed changes in chemical shift observed for **8** are more a function of changes in the dielectric constant of the medium, rather than any close association of solvent or counterion with the oxygen.

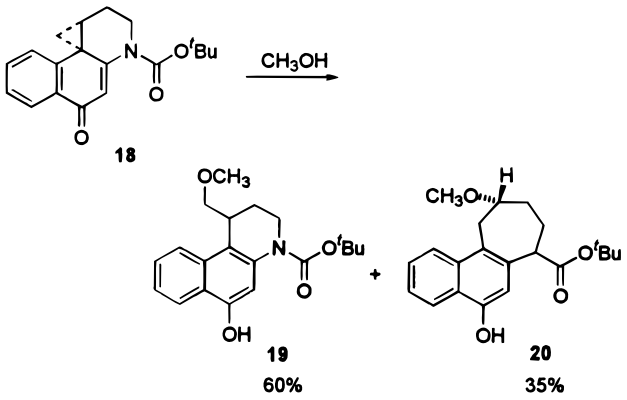
(19) Boger, D. L.; Johnson, D. S. *Angew. Chem., Int. Ed. Engl.* **1996**, *33*, 1438. See also: Boger, D. L. *Acc. Chem. Res.* **1995**, *28*, 20.

(20) An reviewer has suggested that this "S_N2" reaction may be occurring with significant electron-transfer character in the transition state, e.g.,



Increasing radical character at the cyclopropyl carbon favors attack at the more hindered carbon, while an increase in covalent character favors attack at the least hindered position. For an good discussion of the S_N2/ET mechanistic continuum, see: Pross, A. *Theoretical and Physical Principles of Organic Reactivity*; Wiley: New York, 1995; pp 222−232.

Scheme 7



from nucleophilic attack at the more-substituted carbon of the cyclopropyl group, albeit to a lesser extent, leading to **4**. Thus, the detection of a small quantity of compounds such as **4** does not mean that an electron transfer mechanism is operative. Thus compounds such as **1** or **8** are excellent probes for SET pathways, when the results are interpreted with caution.

B. Protic Solvents (Region II). In protic solvents, spiro[2.5]octa-3,6-dien-5-ones **1** and **8** react via competing $S_N2/S_N2(C+)$ pathways. The contribution of the carbocationic pathway becomes increasingly important as the ionizing power of the solvent increases. To our knowledge, these systems provide the first example of the $S_N2(C+)$ mechanism under "normal" reaction conditions (i.e., without highly hindered nucleophiles or highly resonance-stabilized carbocations).

In protic solvents, the outlook for use of these compounds as SET probes is grim. With regard to Scheme 1, because in protic solvents a competing carbocationic pathway provides another means for forming **4**, simple product studies will lead to a false conclusion regarding the importance of SET pathways.

Experimental Section

General Methods. Melting points were determined using a Thomas-Hoover capillary melting point apparatus and are uncorrected. High-pressure liquid chromatography (preparative and analytical scale) was performed using a Beckman System Gold Model 128 solvent pump system and Model 166 UV−vis detector interfaced to an MS-DOS computer. Samples were analyzed and separated using Beckman C-19 reverse phase columns (analytical, 4.6 mm × 250 mm; preparative, 21.2 mm × 150 mm) using acetonitrile/water solvent mixtures. Gas chromatographic analyses were performed on a Hewlett-Packard HP 5890 instrument equipped with FID detectors, a HP 3393A integrator, and either an Alltech SE-54 capillary column (30 m × 0.25 mm) or a Supelco SE-30 capillary column (15 m × 0.25 mm). Ultraviolet spectra were acquired through the use of a Hewlett-Packard HP 8452A Diode Array UV−vis spectrophotometer. Infrared (IR) spectroscopy was performed on a Perkin-Elmer 1600 Series FT-IR spectrophotometer. Nuclear magnetic resonance (NMR) spectra were obtained in $CDCl_3$ using either a Bruker WP-200 or WP-270 spectrometer and are reported in units vs TMS. Low-resolution GC-MS was performed on a Hewlett-Packard HP 5890 gas chromatograph utilizing an HP 1% methyl phenyl silicone gum column (12.5 m × 0.2 mm) interfaced to a HP 5970 mass spectrometer. High- and low-resolution MS was performed on a VG-7070E mass spectrometer, employing EI ionization at 70 EV. Flash chromatography[21] was performed on silica gel (Aldrich Grade 60, 630−400 mesh) using ethyl acetate/hexane mixtures. Thin layer chromatography (TLC) was performed on precoated polyester silica gel plates (Whatman) with a fluorescent background.

Materials. Acetone (JT Baker HPLC Grade), ethyl acetate (Mallinckrodt), pyridine (Fisher), *tert*-butyl alcohol (Aldrich 99+%), 2-propanol (EM Scientific), ethanol (AAPER 100%), and methanol (JT Baker HPLC Grade) were used as received. THF (Mallinckrodt) was distilled from lithium aluminum hydride before use. DMSO (Fisher) was distilled from CaH_2 before use. DMF (EM Scientific) was stirred over anhydrous copper(II) sulfate and activated neutral alumina under argon for 3 days and then distilled prior to use. 1,1-Dimethyl-5,7-di-*tert*-butylspiro[2.5]octa-4,7-dien-6-one (**1**) and 1-methyl-5,7-di-*tert*-butylspiro[2.5]octa-4,7-dien-6-one (**8**) were prepared according to published procedures.[22]

Potassium Thiophenoxide. To a solution of 50 mL of 100% ethanol and 1.12 g of potassium hydroxide (20.0 mmol) was added with stirring 2.05 mL (20.0 mmol) of thiophenol (Aldrich 97%). The solution was allowed to stir for an additional 3 h after which the solvent was removed in vacuo. The resulting white solid was stirred with 4 × 50 mL aliquots of diethyl ether, cannulating the ether off each time. Removal of the ether yielded pure potassium thiophenoxide.

Ethyl Phenyl Sulfide (14). Iodoethane (5.6 g, 36.0 mmol) (Aldrich 99%) was added to 10 mL of dry acetone. Potassium thiophenoxide (5.36 g, 36.0 mmol) was added to the reaction mixture with stirring. The reaction mixture was monitored via HPLC. After disappearance of the starting material the solvent was removed leaving a light yellow liquid. This liquid was distilled (bp 50 °C, 2.0 mmHg consistent with lit.[23] bp 204 °C) yielding 4 g (80%) of colorless liquid.

General Procedure for the Reaction of 1 and 8 with Potassium Thiophenoxide. In a typical reaction 2.5×10^{-2} mmol of substrate was dissolved in 5 mL of dry solvent that had been thoroughly purged with argon. The resulting solution was added to potassium thiophenoxide (0.0045 g, 3.0×10^{-2} mmol) and 18-crown-6 (Aldrich, 99.5%) (0.0085 g, 3.0×10^{-2} mmol) dissolved in 5 mL of the same solvent at room temperature. The reaction mixture was allowed to stir for 1 h after which it was acidified with 1% H_2SO_4. The mixture was subsequently extracted with 3× with ether. The combined ether extracts were washed 3× with water, dried ($MgSO_4$), and evaporated. Yields were determined by HPLC and/or GC analysis. (The concentrations of reagents used and the results of specific experiments are summarized in the text and in Tables 1, 2, and 3.)

Authentic samples of products were obtained by preparative HPLC.

2,6-Bis(1,1-dimethylethyl)-4-(1,1-dimethyl-2-(phenylthio)ethyl)phenol (6): mp 85.0−85.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 18H), 1.44 (s, 6H), 3.20 (s, 2H), 5.07 (s, 1H), 7.19−7.20 (m, 7H); ^{13}C NMR ($CDCl_3$) δ 28.25 (q), 30.34 (q), 34.54 (s), 39.03 (s), 49.83 (t), 162.46 (d), 125.40 (d), 128.59 (d), 129.36 (d), 135.20 (s) and 138.11 (s), 138.38 (s), 151.89 (s); UV−vis (ethanol) λ_{max} (log ϵ) 206 nm (4.80), 258 (3.95); IR (neat) cm^{-1} 3640, 3059, 3000, 2963, 2871, 1583, 1479, 1437, 1382, 1363, 1320, 1637, 1158, 1120, 1025, 877, 809, 690, 668; MS *m*/*e* (relative intensity) 370 (M^+, 1), 339 (1), 262 (3), 247 (100), 631 (20), 217 (10), 163 (25), 83 (20), 57 (80); HRMS for $C_{24}H_{34}OS$ calcd 370.633038, obsd 370.636330, error 1.9 ppm.

2,6-Bis(1,1-dimethylethyl)-4-(2,2-dimethyl-2-(phenylthio)ethyl)phenol (7): mp 87.0−88.0 °C; ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 6H), 1.42 (s, 18H), 2.80 (s, 2H), 5.08 (s, 1H), 6.95 (s, 2H), 7.33 (m, 3H), 7.39 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.07 (q), 30.38 (q), 34.20 (s), 48.94 (t), 49.60 (s), 127.25 (d), 128.45 (d), 128.64 (d), 137.68 (d), 128.63 (s), 132.35 (s), 135.08 (s), 152.33 (s); UV−vis (ethanol) λ_{max} (log ϵ) 202 nm (4.67), 274 (3.23); IR (neat) cm^{-1} 3640, 3003, 2960, 2872, 1472, 1435, 1363, 1316,1635,

(21) Still, W.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(22) (a) Portnykh, N. V.; Volod'kin, A. A.; Ershov, V. V *Bull. Acad. Chem. Sci. USSR, Div. Chem. Sci.* **1966**, 2181. (b) Portnykh, N. V.; Volod'kin, A. A.; Ershov, V. V. *Bull. Acad. Chem. Sci. USSR, Div. Chem. Sci.* **1967**, 1328. (c) Portnykh, N. V.; Volod'kin, A. A.; Volod'kina, V. I. *Bull. Acad. Chem. Sci. USSR, Div. Chem. Sci.* **1970**, 688. (d) Schwartz, L. H.; Flor, R. V.; Gullo, V. P. *J. Org. Chem.* **1974**, *39*, 219.

(23) *Aldrich Handbook of Fine Chemicals*; Aldrich Chemical Company; Milwaukee, WI, 1993; p 604.

1159, 1120, 1024, 884, 705, 694; MS *m/e* (relative intensity) 370 (M^+, 5), 262 (40), 245 (20), 620 (35), 151 (100), 57 (95); HRMS for $C_{24}H_{34}OS$ calcd 370.633038, obsd 370.632864, error 0.5 ppm.

2,6-Bis(1,1-dimethylethyl)-4-(1-methyl-2-(phenylthio-)ethyl)phenol (9): mp 80.0−80.5 °C, ^{1}H NMR ($CDCl_3$) δ 1.37 (d, 3H, J = 7 Hz), 1.43 (s, 18H), 2.92 (m, 1H), 3.10 (dd, 1H, J_{AB} = 11 Hz, J_{AX} = 5.3 Hz), 3.23 (dd, 1H, J_{AB} =11 Hz, J_{AX} = 8.8 Hz), 5.08 (s, 1H), 6.99 (s, 2H), 7.62 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 20.84 (q), 30.38 (q), 34.41 (s), 39.44 (d), 42.51 (t), 163.42 (d), 125.63 (d), 128.79 (d), 163.94 (d), 135.72 (s), 136.15 (s), 137.62 (s), 152.30 (s); UV−vis (ethanol) λ_{max} (log ϵ) 210 nm (4.18), 258 (3.87); IR (neat) cm^{-1} 3637, 3057, 2957, 2871, 1583, 1480, 1436, 1390, 1372, 1313, 1635, 1213, 1152, 1120, 1025, 882, 737, 690; MS *m/e* (relative intensity) 365 (M^+, 7), 633 (100), 217 (10), 163 (20), 57 (25); HRMS for $C_{23}H_{32}OS$ calcd 356.217388, found 356.216949, error 1.2 ppm.

2,6-Bis(1,1-dimethylethyl)-4-(2-methyl-2-(phenylthio-)ethyl)phenol (10): ^{1}H NMR ($CDCl_3$) δ 1.25 (d, 3H, J = 7.0 Hz), 1.41 (s, 18H), 2.58 (dd, 1H, J_{AB} = 13.6 Hz, J_{AX} = 5.1 Hz), 2.92 (dd, 1H, J_{AB} = 13.6 Hz, J_{BX} = 8.6 Hz), 3.40 (m, 1H), 5.05 (s, 1H), 6.94 (s, 2H), 7.29 (m, 5H); ^{13}C NMR ($CDCl_3$) 20.48 (q), 30.34 (q), 34.24 (s), 43.62 (t), 44.77 (d), 125.08 (d), 125.71 (d), 128.74 (d), 126.27 (d), 129.05 (s), 135.62 (s), 152.63 (s), 139.26 (s); UV−vis (ethanol) λ_{max} (log ϵ) 210 nm (4.57), 260 (3.22); IR (neat) cm^{-1} 3640, 3072, 2957, 2871, 1583, 1479, 1434, 1390, 1374, 1362, 1315, 1634, 1212, 1154, 1121, 1025, 1011, 890, 879, 789, 769, 745, 692; MS *m/e* (relative intensity) 356 (M^+, 12), 346 (2), 247 (20), 620 (100), 137 (20), 109 (10), 57 (20); HRMS for $C_{23}H_{32}OS$ calcd 356.217388, obsd 356.216949, error 1.2 ppm.

Acknowledgment. Financial support from the National Science Foundation (CHE-9412814) is acknowledged and appreciated.

Supporting Information Available: ^{1}H NMR spectra for compounds **6**, **7**, **9**, and **10** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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