the relative ease of formation of the intermediates ($I_B > I_H$), while the slopes (greater at lower pH) may reflect the relative ease of trapping of the two intermediates.

Acknowledgment. We are grateful to Professor Richard L. Schowen for reading the manuscript and providing valuable comment on the significance of the inhibitions.

Registry No. TEA, 121-44-8; NMP, 120-94-5; TEOA, 102-71-6; potassium ferricyanide, 13746-66-2; potassium ferrocyanide, 13943-58-3.

Reaction of Methoxide Ion with Dibenzo[*ce*]-1,2-dithiin 1,1-Dioxide: Surprising Behavior in the Reaction of an Aryl Thiolsulfonate with an Alkoxide

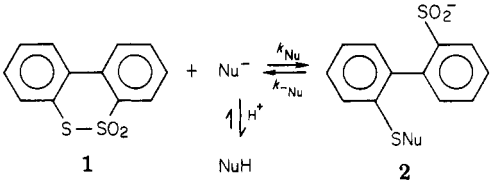
Bogdan Boduszek and John L. Kice*

Department of Chemistry, Texas Tech University, Lubbock, Texas 79409

Received August 30, 1982

Although the six-membered cyclic thiolsulfonate dibenzo[*ce*]-1,2-dithiin 1,1-dioxide (1) reacts with such nucleophiles as RS^-, CN^-, or SO_3^{2-} at a rate only slightly slower than they react with an acyclic aryl thiolsulfonate ($PhSSO_2Ph$), it reacts with methoxide ion *over 10^4 times slower* than does $PhSSO_2Ph$, and in methanol the equilibrium constant for the reaction of **1** with CH_3O^- to form the ring-opened sulfenate ester **2a** (eq 3) is so small that at equilibrium only a few percent of **1** is converted to **2a**, even at quite high methoxide concentrations. The equilibrium constant for the conversion of **1** to **2a** is, as might be expected, much larger in dimethyl sulfoxide (Me_2SO)–methanol, and the rate constants for both the forward and reverse steps of the equilibrium can be determined in 70–90% Me_2SO by stopped-flow spectrophotometry. The rate for the conversion of **1** to **2a** is found to increase markedly with an increase in the Me_2SO content of the medium, but the rate of the reverse reaction (**2a** → **1** + MeO^-) *is not significantly dependent* on solvent composition. It is shown that all these results can seemingly be satisfactorily explained only if the reaction of **1** with methoxide to form **2a** is assumed to take place by a stepwise mechanism (eq 8) in which a hypervalent sulfur species (**6a**) is present on the reaction coordinate as an intermediate which lies in a potential well of sufficient depth that there is a substantial $\Delta G^{\ddagger}$ for collapse of **6a** to **2a**. Because of the six-membered ring in **6a**, $\Delta G^{\ddagger}$ for **6a** going to **2a** is 5–6 kcal/mol larger than $\Delta G^{\ddagger}$ for the collapse of the equivalent intermediate (**6o**) to $PhSOCH_3$ plus $PhSO_2^-$ in the reaction of $PhSSO_2Ph$ with methoxide. In the reactions of RS^-, CN^-, or SO_3^{2-} with **1**, the free energy of **6b**, the intermediate analogous to **6a**, is substantially higher, so much so that $\Delta G^{\ddagger}$ for collapse of **6b** to ring-opened products is in no case more than 1–2 kcal/mol. For this reason there is little difference for these nucleophiles in the rates for **1** vs. $PhSSO_2Ph$. The preceding explanations are all in accord with expectations based on the findings of Martin and co-workers[10,11] regarding the relative stability of isolable hypervalent sulfur species containing apical ligands of differing electronegativity and the influence of a ring on the stability of such species.

The cyclic thiolsulfonate dibenzo[*ce*]-1,2-dithiin 1,1-dioxide (**1**) reacts readily in aqueous dioxane with such nucleophiles as cyanide, sulfite, or thiolate ions (step k_{Nu}, eq 1) to form ring-opened substitution products **2** (Nu = CN, SO_3^-, or SR).[1,2] The rate constants, k_{Nu}, at which **1** reacts with these nucleophiles are 2.5–8 times smaller than the rate constants[3] for the reactions of the same nucleophiles with the acyclic aryl thiolsulfonate $PhSSO_2Ph$. Acidification of the final reaction solutions with a carboxylic acid buffer sufficiently acidic to protonate the nucleophiles to their conjugate acids (NuH) causes **2** to revert (step k_{-Nu}, eq 1) rapidly and quantitatively to **1**, and the rate constants, k_{-Nu}, for these processes can also be measured.[1,2]



1 NuH 2 (1)

Another nucleophile that reacts readily with the acyclic thiolsulfonate $PhSSO_2Ph$ is methoxide ion (eq 2).[3] We

$$CH_3O^- + PhSSO_2Ph \xrightarrow[(\text{in } CH_3OH,\ k'_{MeO} = 400\ M^{-1}\ s^{-1})]{k'_{MeO}} PhSOCH_3 + PhSO_2^- \quad (2)$$

therefore anticipated that **1** should react readily with CH_3O^- in methanol (eq 1, $Nu^- = CH_3O^-$) to give **2a** (Nu = OCH_3) and that acidification of the final reaction solution would cause the reversion of the sulfenate ester **2a** to **1**. Surprisingly, **1** does not react readily in methanol with methoxide, even when the latter is present at high concentration (0.2 M), and acidification of the solution at the completion of the very slow reaction that does occur fails to regenerate **1**. On the other hand, in dimethyl sulfoxide (Me_2SO)–methanol mixtures containing at least 80% Me_2SO, **1** does react rapidly with methoxide ion, and, under appropriate conditions, prompt acidification of the final reaction solution leads to rapid regeneration of **1**.

The present paper reports the details of a kinetic study of the reaction of **1** with methoxide ion in both methanol

(1) Chau, M. M.; Kice, J. L. *J. Org. Chem.* **1978**, *43*, 914.
(2) Boduszek, B.; Kice, J. L. *J. Org. Chem.* **1982**, *47*, 2055.
(3) (a) Kice, J. L.; Rogers, T. E.; Warheit, A. C. *J. Am. Chem. Soc.* **1974**, *96*, 8020. (b) Kice, J. L.; Liu, A. C.-C. *J. Org. Chem.* **1979**, *44*, 1918.

0022-3263/83/1948-0995$01.50/0

Table I. Rate of Disappearance of 1 in the Presence of Methoxide in Methanol at 25 °C[a]

$[CH_3O^-]$, M	10^4k_1, s^{-1}	$k_1/[CH_3O^-]$, M^{-1} s^{-1}
0.092	0.14	0.000 15
0.20	0.73	0.000 37
0.40	1.96	0.000 49
0.60	3.9	0.000 65

[a] $[1]_0 = 1.0 \times 10^{-4}$ M in all cases.

and Me_2SO–methanol solutions and of the reversion of **2a** (Nu = OCH_3) to 1 upon acidification of Me_2SO–methanol solutions with a carboxylic acid buffer. The results demonstrate that the reaction of 1 with CH_3O^- leading to **2a** is quite different in character from the reactions of 1 with such nucleophiles as CN^-, SO_3^{2-}, or RS^-, and they raise some interesting questions about the chemistry and reactivity of sulfenate esters.

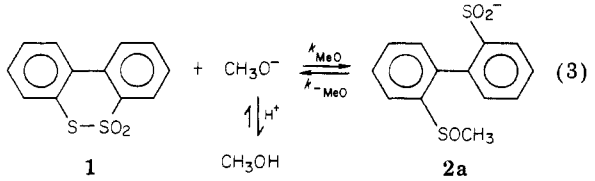
Results

Reaction of 1 with Methoxide Ion in Methanol. In methanol, with methoxide present in a large stoichiometric excess over 1, the disappearance of 1 (followed by monitoring the disappearance of the absorption maximum at 296 nm due to 1) follows good first-order kinetics. However, the rate of disappearance of 1 is *extremely* slow. Whereas the half-life for the disappearance of phenyl benzenethiolsulfonate ($PhSSO_2Ph$) in the presence of 0.092 M CH_3O^- at 25 °C in methanol is only 0.02 s,[3b] the half-life for the disappearance of 1 is over 13 h. This large difference in reaction rates is particularly noteworthy because in reactions with other nucleophiles (CN^-, SO_3^{2-}, RS^-) there is no large difference between the rate for 1 and that for $PhSSO_2Ph$.[1,2]

The experimental first-order rate constants, k_1, for the disappearance of 1 in the presence of various concentrations of methoxide in methanol are given in Table I. It is apparent that $k_1/[CH_3O^-]$ is not a constant but rather increases with increasing $[CH_3O^-]$.

Acidification of the 1–CH_3O^- reaction solutions with excess chloroacetic acid, either at the end of the reaction or when the reaction is approximately half complete, does not result in any regeneration of 1.

Reaction of 1 with Methoxide Ion in Me_2SO–Methanol. In 95% Me_2SO–5% methanol the nucleophilicity and basicity of methoxide ion are orders of magnitude larger than they are in methanol.[4] In 95% Me_2SO–5% methanol, the addition to 1 (1×10^{-4} M) of a slight molar excess of CH_3O^- led to the immediate disappearance of the absorption maximum of 1 at 296 nm. Subsequent prompt acidification of the solution with a chloroacetic acid–sodium chloroacetate buffer resulted in quantitative regeneration of 1 (as judged by the return of the absorption maximum at 296 nm to its original intensity). The 1–CH_3O^- system therefore behaves under these conditions in a manner consistent with the equilibrium in eq 3 being displaced completely to the right upon addition



1 2a (3)

of a slight molar excess of methoxide ion to 1 and with **2a** reverting back to 1 upon acidification of the solution with a chloroacetate buffer.

(4) Bowden, K. *Chem. Rev.* **1966**, *66*, 119.

In displacing the equilibrium in eq 3 to the right, it is important to use the minimum concentration of CH_3O^- adequate to give essentially complete conversion of 1 to **2a**. At higher methoxide concentrations, the rapid CH_3O^--promoted decomposition of **2a** is significant, and acidification of such solutions, particularly if they have been allowed to stand for some time before acidification, yields only a small amount of 1; i.e., most of the **2a** has undergone decomposition.

The rate of reversion of **2a** to 1 upon acidification of 95% Me_2SO–5% MeOH solutions of **2a** with carboxylic acid buffers can be measured by stopped-flow spectrophotometry by following the increase in the absorbance of the solution with time at 296 nm. The reaction follows good first-order kinetics; the experimental first-order rate constants (k_{-1}) under various conditions are shown in the first section of Table II.

Table II indicates that an increase in the concentration of the buffer acid has no effect on k_{-1}; the reaction is therefore not general-acid catalyzed. Furthermore, although the pH of a 1:1 chloroacetic acid–chloroacetate buffer is lower than that of a 1:1 HCOOH–$HCOO^-$ buffer,[5] so that a_{H^+} is significantly higher in the chloroacetate buffer, k_{-1} is not correspondingly larger in the chloroacetate buffer; thus the reaction is not specific-hydrogen-ion catalyzed. In fact, k_{-1} is ~30% smaller in the chloroacetate buffer than in the formate buffer. This is presumably due to the fact that in the more acidic chloroacetate buffer a significant fraction of **2a** is present as the conjugate acid (SO_2H), and the SO_2H group is unreactive compared to SO_2^- as a nucleophile in the reversion reaction. This has been observed previously[1,2] in the reversion of other compounds 2 to 1 (step k_{-Nu}, eq 1) in carboxylic acid buffers. It means that the measured experimental rate constant k_{-1} is actually equal not to k_{-MeO} but rather to $k_{-MeO}(K_a^{2a}/K_a^{2a} + a_{H^+})$, where K_a^{2a} is the acid dissociation constant of the SO_2H group of the conjugate acid of **2a** and a_{H^+} is the hydrogen ion activity of the buffer.

The dependence of the rate of reversion of **2a** to 1 on solvent composition over the range 70–95% Me_2SO has also been investigated. Since the equilibrium constant for eq 3 in 70–85% Me_2SO is too small for 1 (10^{-4} M) to be converted essentially completely to **2a** if only a slight molar excess of CH_3O^- is used (as is required due to the sensitivity of **2a** to higher concentrations of methoxide), such measurements must be made by taking a solution of **2a** prepared by reacting 1 with a slight molar excess of methoxide in *95%* Me_2SO and mixing this in a stopped-flow spectrophotometer with an equal volume of a solution of a carboxylic acid buffer in a Me_2SO–methanol mixture containing the appropriate percentage of methanol to give the desired final methanol content after mixing. The rate constants obtained in this way (see the second section of Table II) appear to be reliable. All runs showed good first-order kinetics. Surprisingly, *k_{-1} is not significantly dependent on solvent composition* in the range 70–95% Me_2SO. This is in marked contrast to the behavior of the rate constant for the forward reaction of the 1 + CH_3O^- ⇄ **2a** equilibrium.

(5) The two buffers differ in pH by 0.90 pH units in water and 0.62 pH units in 60% dioxane.[1,2] A similar difference in 95% Me_2SO–5% MeOH would mean that a_{H^+} should be larger in the chloroacetate buffer by anywhere from a factor of 4 to a factor of 8. In view of the fact that Ritchie and Uschold[6] have shown that ρ for the ionization of substituted benzoic acids in Me_2SO is +2.6, rather than +1.0 as in water, it actually seems likely that ΔpK_a for chloroacetic and formic acids in 95% Me_2SO–5% MeOH will probably be significantly larger than the 0.90 unit difference found in water and that a_{H^+} for the chloroacetate buffer could be up to 50 times larger than that for the formate buffer.

(6) Ritchie, C. D.; Uschold, R. E. *J. Am. Chem. Soc.* **1968**, *90*, 2821.

Table II. Rate of Reversion of 2a to 1 upon Acidification of Me_2SO-Methanol Solutions with Carboxylic Acid Buffers[a]

solvent[b]	nature of carboxylic acid buffer	[RCOOH],[c] M	k_{-1}, s^{-1}
95% Me_2SO-5% MeOH (v/v)	1:1 $ClCH_2COOH$-$ClCH_2CO_2^-$	0.010	0.21
		0.005	0.21
	1:1 $HCOOH$-HCO_2^-	0.010	0.26
		0.005	0.29
90% Me_2SO-10% MeOH	1:1 $ClCH_2COOH$-$ClCH_2CO_2^-$	0.010	0.22
85% Me_2SO-15% MeOH	1:1 $ClCH_2COOH$-$ClCH_2CO_2^-$	0.010	0.21
80% Me_2SO-20% MeOH	1:1 $ClCH_2COOH$-$ClCH_2CO_2^-$	0.010	0.19
70% Me_2SO-30% MeOH	1:1 $ClCH_2COOH$-$ClCH_2CO_2^-$	0.010	0.16

[a] All runs were at 25 °C; 1 (1×10^{-4} M) was mixed with methoxide [($1.2-1.4) \times 10^{-4}$ M] in 95% Me_2SO-5% MeOH. For initiation of the reversion of 2a to 1, the solution was then acidified by being mixed in stopped-flow spectrophotometer with an equal volume of the indicated buffer in Me_2SO-methanol. [b] Composition of final reaction solution after mixing. [c] Concentration of carboxylic acid in final reaction solution.

Table III. Rate of Reaction of 1 with Methoxide Ion in Me_2SO-Methanol Solvent Mixtures[a]

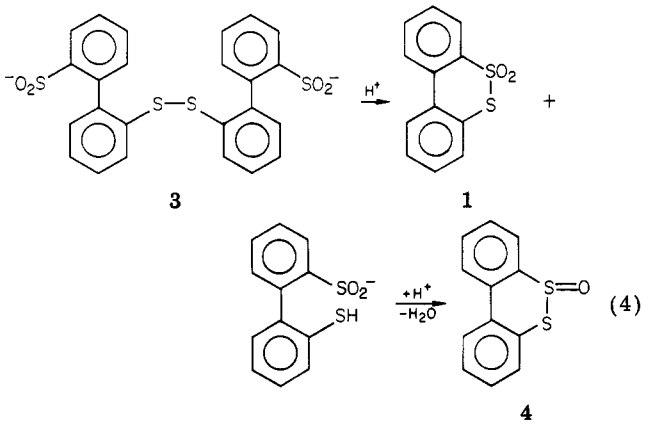
solvent	$[CH_3O^-]$, M	k_{exptl}, s^{-1}	k_{MeO},[b] M^{-1} s^{-1}
90% Me_2SO-10% MeOH (v/v)	0.0010	9.3	8.7×10^3
	0.0020	18.1	
85% Me_2SO-15% MeOH	0.0010	1.8	
	0.0020	3.2	1.5×10^3
	0.0030	4.9	
80% Me_2SO-20% MeOH	0.0010	0.50	
	0.0020	1.2	0.45×10^3
	0.0030	1.6	

[a] All runs were at 25 °C. $[1]_0 = 5 \times 10^{-5}$ M in all cases. [b] From plot of k_{exptl} vs. $[CH_3O^-]$.

In 95% Me_2SO the rate of reaction of CH_3O^- with 1 is too fast to be measurable by stopped-flow techniques, even at low methoxide ion concentrations. However, in media of lower Me_2SO content rates could be measured by stopped-flow techniques. When 1 (5×10^{-5} M) is mixed with excess methoxide (0.001–0.003 M) in Me_2SO–methanol, two consecutive reactions are observed. The first of these is the reaction of 1 with CH_3O^- to form **2a**; the second is the CH_3O^--promoted decomposition of **2a**. In 80–90% Me_2SO the rate of the first process is enough faster than the rate of the second that the infinity absorbance (A_∞^{init}) associated with the end of the 1 + CH_3O^- ⇄ **2a** reaction can be determined accurately enough to permit a study of the kinetics of this reaction. However, below 80% Me_2SO the equilibrium constant for eq 3 is small enough and the rate of the second reaction is fast enough that this is no longer possible. Thus we could only study the rate of the forward reaction of eq 3 in the range 80–90% Me_2SO. The experimental first-order rate constants (k_{exptl}) for the reaction of 1 with excess methoxide in these solvent media are given in Table III. Because of the difficulty in evaluating A_∞^{init} with high precision, these rate constants are of somewhat lower accuracy than those in Table II.

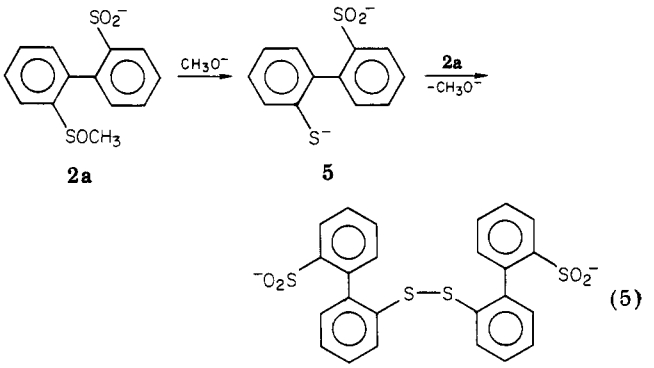
Since eq 3 is an equilibrium, k_{exptl} is equal to $k_{MeO^-}[CH_3O^-] + k_{-MeO}$.[7] Values of k_{MeO} for the different solvent media were obtained from the slopes of plots of k_{exptl} vs. $[CH_3O^-]$. They are shown in the last column of Table III and are seen to increase 20-fold with an increase in the Me_2SO content of the solvent from 80% to 90% Me_2SO. Thus k_{MeO}, unlike k_{-MeO}, is markedly dependent on solvent composition.

The decomposition of **2a** in the presence of methoxide in Me_2SO–methanol was also examined. Cyclic thiolsulfonate 1 (0.1 M) was treated with excess CH_3O^- (0.21 M) in 90% Me_2SO–10% MeOH, and the solution was allowed to stand for 15 min before the workup. The principal product was the disulfide–sulfinate **3**. Solutions of **3** upon acidification with HCl yielded an equimolar mixture of 1 and thiolsulfinate **4**, presumably as shown in eq 4. One reasonable path for the formation of **3** from



(4)

2a is shown in eq 5; this involves a CH_3O^--induced de-



(5)

composition of **2a** to give thiolate **5**, followed by reaction of **5** with **2a** to give **3**. For ease of workup and product identification this product study was conducted by using a much more concentrated solution of 1 (0.1 M) than those (5×10^{-5} M) used in the kinetic studies. Under the conditions of the kinetic runs it is possible that a bimolecular reaction of **5** with **2a** would not be competitive kinetically with the CH_3O^--promoted decomposition of **2a** and that, under these conditions, the reaction would proceed only to the formation of **5**. Earlier work[3b] has shown that methyl benzenesulfenate ($PhSOCH_3$) also decomposes readily in the presence of methoxide ion to give diphenyl disulfide (PhSSPh) as a major decomposition product.

Discussion

The behavior of the reaction of methoxide ion with 1 in methanol is dramatically different from the behavior

(7) Frost, A. A.; Pearson, R. E. "Kinetics and Mechanism", 2nd ed.; Wiley: New York, 1961; pp 186–187.

of the reactions of CN^-, SO_3^{2-}, and RS^- with **1**. These nucleophiles react with **1** only 2.5–8.0 times more slowly than they react with $PhSO_2SPh$ and give ring-opened substitution products **2** (eq 1; Nu = CN, SO_3^-, or RS).[1,2] Upon acidification of the final reaction solutions with a carboxylic acid buffer, **2** reverts readily and quantitatively to **1**.[1,2] On the other hand, the reaction of methoxide with **1** in methanol is $\sim 10^6$ slower than the reaction of methoxide with $PhSO_2SPh$ under the same conditions, and acidification of the final reaction solution does not lead to any regeneration of **1**. The slow disappearance of **1** in CH_3O^-/CH_3OH is approximately second-order in $[CH_3O^-]$ while the rapid reactions of CN^-, SO_3^{2-}, or RS^- with **1** to give **2** all show a first-order dependence on $[Nu^-]$.[1,2]

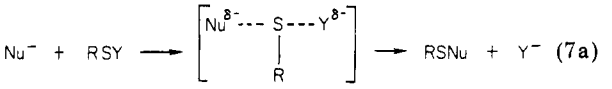
In contrast to the situation in methanol, treatment of **1** in 95% Me_2SO–5% MeOH with slightly more than 1 equiv of methoxide results in the rapid disappearance of **1**, and subsequent acidification of the final reaction solution leads to quantitative regeneration of **1**. Thus in 95% Me_2SO–5% MeOH the system **1** plus methoxide behaves in the same way as the other 1–nucleophile systems studied earlier.[1,2] In Me_2SO–methanol solutions containing 70–95% Me_2SO the methoxide–**1** system can be studied kinetically in the same manner as other Nu^-–**1** systems. The rate of reaction of MeO^- with **1** (Table III) is proportional to the first power of $[MeO^-]$, and k_{MeO} (eq 3) decreases markedly with increasing methanol content of the solvent in these Me_2SO–methanol mixtures. Kinetic measurements of the reversion of **2a** to **1** in Me_2SO–methanol solutions in the presence of carboxylic acid buffers (Table II) show that this process is not acid catalyzed. Therefore, the role of acid in promoting the reversion of **2a** to **1** is simply to remove CH_3O^- from the equilibrium in eq 3 by protonating it to CH_3OH. The measured rates of reversion, k_{-1} (Table II), therefore provide[8] k_{-MeO}, the rate at which **2a** gives **1**, and *not* the rate of an acid-catalyzed process having a different value of k_{-MeO} than would obtain in alkaline solutions of **2a** in Me_2SO–methanol. In the range 70–95% Me_2SO k_{-1} (and therefore k_{-MeO})[8] shows little dependence on solvent composition.

The equilibrium constant for eq 3, K_{eq}, is, of course, equal to k_{MeO}/k_{-MeO}. The data for k_{MeO} and k_{-MeO} in Tables II and III show that K_{eq} decreases by a factor of 20 (from 4×10^4 to 2×10^3) on going from 90% to 80% Me_2SO. This large decrease and the relatively modest magnitude of K_{eq} in 80% Me_2SO suggest that in pure methanol K_{eq} will be quite small,[9] small enough that even at high methoxide concentrations only a small fraction of **1** will be converted to **2a** at equilibrium. The unusual behavior of the 1–MeO^- system in pure methanol (i.e., very slow rate of disappearance of **1** and dependence of the rate of disappearance on approximately $[CH_3O^-]^2$) is consistent with the reaction sequence shown in eq 6. While this accounts

$$1 + MeO^- \rightleftharpoons 2a \xrightarrow[\text{rate-determining}]{MeO^-} \text{products} \qquad (6)$$

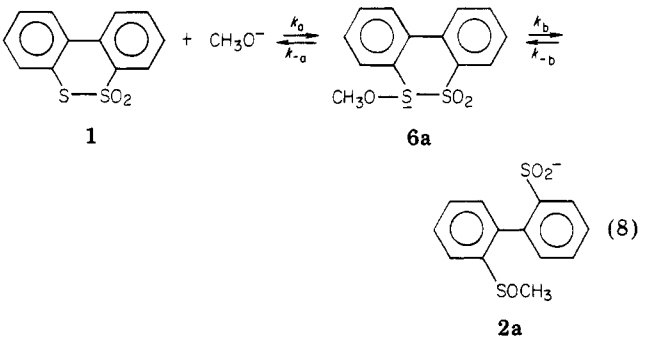
satisfactorily for the behavior of the 1–MeO^- system, it does not explain why the reaction of MeO^- with **1** is so different in its behavior from the reactions of CN^-, SO_3^{2-}, or RS^- with **1**. Any valid explanation should account for why k_{MeO} is, but k_{-MeO} is *not*, markedly dependent on solvent composition in Me_2SO–methanol mixtures.

In principle, nucleophilic substitution at dicoordinate sulfur can occur either by a mechanism in which bond making and bond breaking are synchronous (eq 7a) or by a stepwise mechanism (eq 7b) where bond making precedes bond breaking and an intermediate (**6**) is present on the reaction coordinate.



6

The observed dependence of the foward and reverse rates for eq 3 on solvent are consistent with a mechanism (eq 8) of the type shown in eq 7b where the second step



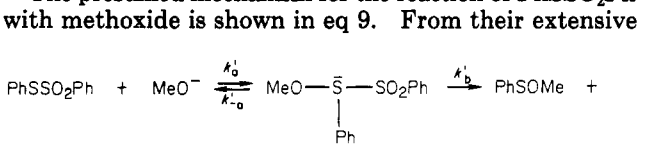
1 **6a** **2a**

$$k_b << k_{-a}$$

(interconversion of **6a** and **2a**) is rate determining. Under such circumstances the measured values of k_{MeO} will be equal to $k_b(k_a/k_{-a})$, while the measured values of k_{-MeO} will be equal to k_{-b}. Given the structures of **6a** and **2a**, it seems quite reasonable that k_b and k_{-b} might show little dependence on the methanol content of the solvent. On the other hand, k_a would be expected to increase markedly, and k_{-a} to decrease, with a decrease in methanol content. On this basis one can explain why k_{-MeO} shows practically no variation with solvent composition, while k_{MeO}, which is proportional to k_a/k_{-a}, increases markedly as the percentage of methanol is decreased.

Can the mechanism in eq 8 also explain why k_{MeO} is so much smaller in a given solvent medium that the rate constant (k'_{MeO}) for the reaction of MeO^- with $PhSO_2SPh$ (eq 2)? We believe that it can.

The presumed mechanism for the reaction of $PhSSO_2Ph$ with methoxide is shown in eq 9. From their extensive



6o

$$k'_b \simeq k'_{-a}$$

study of isolable hypervalent sulfur species Martin and his collaborators[10] have concluded that a given compound

(8) As already noted in the Results, k_{-1} as measured in 1:1 chloroacetate buffers is somewhat smaller than k_{-MeO}, being equal to $k_{-MeO}(K_a^{2a}/K_a^{2a} + a_{H^+})$, where K_a^{2a} is the pK_a of the SO_2H group of the conjugate acid of **2a** and a_{H^+} is the hydrogen ion activity of the buffer. The data for 1:1 formate vs. 1:1 chloroacetate buffers in Table III show that $K_a^{2a}/K_a^{2a} + a_{H^+}$ for the chloroacetate buffer is no smaller than ~0.8. Therefore, for the purposes of our further discussion it does not introduce any serious error to take the k_{-1} values in Table II as equal to k_{-MeO} for the various reaction conditions.

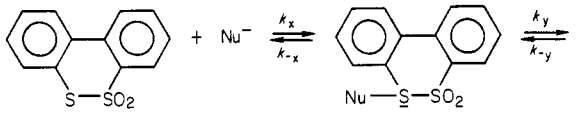
(9) If it is assumed that k_{-MeO} remains solvent independent and that the decrease in log k_{MeO} with an increasing percentage methanol roughly parallels the change[4] in H_ (as seems reasonable from the behavior of k_{MeO} in the range 80–90% Me_2SO), then K_{eq} for eq 3 in pure methanol is estimated to be ~0.07, with $k_{MeO} \simeq 0.014\ M^{-1}\ s^{-1}$ and $k_{-MeO} \simeq 0.2\ s^{-1}$.

where an apical ligand is part of a ring is often much less reactive in reactions involving the dissociation of that ligand than the equivalent compound where the same ligand is not part of a ring. Given their observations, it therefore seems reasonable to suggest that $\Delta G^{\ddagger}$ for step k_b for **6a** could be 5–6 kcal/mol greater than $\Delta G^{\ddagger}$ for step k'_b for **6o** and that, while $k_b \ll k_{-a}$, $k'_b \simeq k'_{-a}$. If this is true, then, provided that $k'_a \simeq k_a$, k'_{MeO} will be orders of magnitude larger than k_{MeO}.

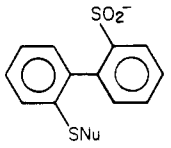
One can thus explain why the rate constant for the conversion of **1** to **2a** (k_{MeO}) is so much smaller under a given set of reaction conditions than the rate constant (k'_{MeO}) at which $PhSSO_2Ph$ reacts with the same nucleophile to give PhSOMe and $PhSO_2^-$.

What now remains is to explain why **1** and $PhSSO_2Ph$ differ by only a modest factor in their reactivity toward nucleophiles such as RS^-, CN^-, or SO_3^{2-} when the difference in their rate of reaction with methoxide is 10^4–10^5.

From the results of Martin et al.[10b,11] with other hypervalent sulfur species one can predict that the less electronegative the group Nu in **6** the less stable this intermediate will be. This means that intermediates **6b** (eq 10; Nu = RS, CN, or SO_3^-) should be significantly less



6b



(10)

Nu = RS, CN, or SO_3^-

stable (and considerably higher in energy) than intermediate **6a** (where Nu is the more electronegative CH_3O group). Indeed, intermediates **6b** might lie in such a shallow potential well that $\Delta G^{\ddagger}$ for step k_y might be no more than 1–2 kcal/mol (in contrast to $\Delta G^{\ddagger}$ for step k_b with **6a**, which our data suggest may be ~10–12 kcal/mol). If $\Delta G^{\ddagger}$ for step k_y is no more than 1–2 kcal/mol, then $k_y \simeq k_{-x}$, and k_{Nu} (eq 1) will be approximately equal to k_x. In that situation one will not see any large difference between the rates of reaction of **1** and $PhSSO_2Ph$ with such nucleophiles as RS^-, CN^-, or SO_3^{2-}. Large differences between **1** and $PhSSO_2Ph$ in rates of reaction with a nucleophile will be seen only in cases where the reacting nucleophile is one like CH_3O^- and where the resulting intermediate **6** is in a fairly deep potential well with a significant $\Delta G^{\ddagger}$ for collapse of the intermediate to products.

It is also possible that when Nu = RS, CN, or SO_3^-, the energy of **6b** may become so high that the concerted mechanism for substitution (eq 7a) will be a lower energy pathway than the stepwise mechanism (eq 7b) involving **6** as an intermediate. If that is the case, the experimental results could then be interpreted in the following manner: (a) the reactions involving methoxide proceed via eq 7b, with the very large difference in rates for **1** and $PhSSO_2Ph$ being explained as outlined previously; (b) the reactions involving RS^-, CN^-, or SO_3^{2-} proceed via eq 7a, and in such concerted substitutions the presence of the ring in **1** does *not* greatly lower the rate at which **1** will react with any nucleophile as compared to $PhSSO_2Ph$.[12]

In summary, then, the most economical explanation for the unusual behavior of the reaction of **1** with methoxide ion is to assume that hypervalent sulfur species **6a** occupies a position on the reaction coordinate as a reactive intermediate having significant stability relative to the stability of analogous intermediates (**6b**) from **1** and such less electronegative nucleophiles as RS^-, CN^-, etc. This is consistent with the observations by Martin and co-workers[11] that apical alkoxy ligands enhance the stability of hypervalent sulfur species. Since such an alkoxy ligand will perforce be present in any nucleophilic substitution at dicoordinate sulfur leading to or from a sulfenate ester, it does, however, suggest that one should not be surprised when substitutions involving sulfenates (R'SOR) exhibit significantly different behavior than substitutions of other sulfenyl derivatives (R'SNu) where the group Nu is *not* one that stabilizes the hypervalent sulfur intermediate (**6**).

Experimental Section

Purification of Materials. Dibenzo[ce]-1,2-dithiin 1,1-dioxide[13] (1, mp 132–133 °C) was purified by recrystallization from chloroform–hexane. Anhydrous methanol was prepared from commercial absolute methanol by refluxing it with magnesium turnings, followed by distillation.[14] The dimethyl sulfoxide (Me_2SO) used was spectrophotometric grade solvent that was further purified in the manner described by Matthews et al.[15] Standard solutions of sodium methoxide in methanol were prepared by dissolving clean, freshly cut sodium in anhydrous methanol and, after preparation, were standardized by titration of an aliquot with standard acid. The formic and chloroacetic acids used to prepare buffers were of the highest degree of purity commercially available.

Procedure for Kinetic Runs. Reaction of 1 with Methoxide Ion in Anhydrous Methanol. A 3.5-mL aliquot of a solution of the desired concentration of methoxide ion in methanol was placed in a 1-cm spectrophotometer cell in the thermostated cell compartment of a Cary Model 17 spectrophotometer, and 35 μL of a 1×10^{-2} M solution of **1** in anhydrous dioxane was injected into the cell to initiate the reaction. The decrease in the optical density of the solution with time at 296 nm was then followed.

Acidification of the reaction solution by the addition of chloroacetate buffer, either at the end of the reaction or when it was only ~50% complete, did not lead to any regeneration of **1** (i.e., no increase in optical density at 296 nm, the wavelength where **1** has a strong absorption maximum).

Reaction of 1 with Methoxide Ion in Me_2SO–Methanol. A 1×10^{-4} M solution of **1** in Me_2SO–methanol was placed in one of the reservoir syringes of a Durrum-Gibson stopped-flow spectrophotometer. A solution containing the desired concentration of methoxide ion in the same Me_2SO–methanol mixture was placed in the other reservoir syringe. The reaction was

(10) (a) Martin, J. C.; Perrozzi, E. F. *J. Am. Chem. Soc.* **1974**, *96*, 3155. (b) Adzima, L. J.; Martin, J. C. *J. Org. Chem.* **1977**, *42*, 4006. (c) Michalak, R. S.; Martin, J. C. *J. Am. Chem. Soc.* **1980**, *102*, 5921. (d) Lam, W. Y.; Martin, J. C. *Ibid.* **1981**, *103*, 120. (e) Lam, W. Y.; Duesler, E. N.; Martin, J. C. *Ibid.* **1981**, *103*, 127. (f) Fisher, T. H.; Martin, J. C. *Ibid.* **1966**, *88*, 3382.

(11) (a) Adzima, L. J.; Duesler, E. N.; Martin, J. C. *J. Org. Chem.* **1977**, *42*, 4001. (b) Astrologes, G. W.; Martin, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 4390. (c) Livant, P.; Martin, J. C. *Ibid.* **1977**, *99*, 5761. (d) Martin, L. D.; Perrozzi, E. F.; Martin, J. C. *Ibid.* **1979**, *101*, 3595. (e) Lam, W. Y.; Duesler, E. N.; Martin, J. C. *Ibid.* **1981**, *103*, 127.

(12) Whether it is reasonable that the presence of the ring in **1** would have little effect on the rate of reaction of **1** vis-à-vis $PhSSO_2Ph$ for substitutions proceeding by the concerted mechanism (eq 7a) is certainly an open question, and some may feel that it is unlikely this would be true. However, until there is definitive evidence that in concerted substitutions at dicoordinate sulfur large rate retardations should be expected for cyclic six-membered substrates, we feel that the explanation for the results where RS^-, CN^- and SO_3^{2-} react with **1** via eq 7a while MeO^- reacts via eq 7b remains viable.

(13) Chau, M. M.; Kice, J. L. *J. Org. Chem.* **1977**, *42*, 3265.

(14) Vogel, A. I. "Practical Organic Chemistry", 2nd ed.; Longmans, Green and Co., Ltd.: London, 1951, p 168.

(15) Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

initiated by mixing the two solutions by using the stopped-flow device, and the decrease in the absorbance of the solution at 296 nm with time was then recorded on a storage oscilloscope. With the methoxide concentrations used (0.001–0.003 M) two consecutive reactions were observed. The first of these is the reaction of CH_3O^- with **1** to form **2a**; the second is the CH_3O^--promoted decomposition of **2a**. As long as the Me_2SO content of the solvent medium was 80% or greater the equilibrium constant for the first reaction was large enough, and its rate was fast enough compared to the rate of the second reaction, so that one could determine the value of the absorbance associated with the completion of the $1 + CH_3O^- \rightleftarrows$ **2a** reaction (A_∞^{init}) quite accurately. For solutions containing less than 80% Me_2SO this was no longer true.

Measurement of k_{-MeO}. A solution of a 1:1 buffer of either chloroacetic acid–sodium chloroacetate or formic acid–sodium formate in Me_2SO–methanol having the appropriate methanol content was placed in one of the reservoir syringes of the stopped-flow spectrophotometer. A 1×10^{-4} M solution of **2a** in 95% Me_2SO–5% methanol was prepared by adding $1.2–1.4 \times 10^{-4}$ M methoxide to a 1×10^{-4} M solution of **1** in 95% Me_2SO–5% methanol, and this solution of **2a** was then immediately placed in the other reservoir syringe of the stopped-flow spectrophotometer. Upon mixing the two solutions in the stopped-flow device the absorbance at 296 nm was observed to increase due to the regeneration of **1**. The rate of regeneration of **1** from **2a** was determined from the slope of a plot of log $(A_\infty - A)$ vs. time.

Products of the Decomposition of 1 in the Presence of Excess Sodium Methoxide. To 0.248 g (1.0 mmol) of **1** in 10 mL of Me_2SO was added 1.0 mL of 2.4 M CH_3ONa in methanol, and the solution was allowed to stand for 15 min. Water (5 mL) was then added, and the solvents were removed by evaporation under an oil pump vacuum at a temperature of 35–40 °C. The residue was treated with a little methanol and filtered, and the methanol was removed under reduced pressure. The resulting residue was insoluble in benzene but quite soluble in water. A portion of the residue was dissolved in methanol and several milliliters of benzene was added to the methanol solution. This led to the precipitation of a quite hygroscopic solid whose IR spectrum showed strong bands at 1010 and 960 cm^{-1} [as would be expected for a sulfinate ion (SO_2^-) functionality] but no absorption bands in either of the regions where sulfonyl groups have strong absorption. The remainder of the residue was dissolved in 10 mL of water, and 8 mL of 1 N hydrochloric acid was added. A white solid precipitated almost immediately. The resulting suspension was extracted several times with chloroform–benzene, the extracts were dried ($MgSO_4$), and the solvent was removed under reduced pressure; TLC of the residue showed that it was an approximately equimolar mixture of **1** and the corresponding thiolsulfinate **4**, dibenzo[*ce*]-1,2-dithiin 1-oxide,[16]

Acknowledgment. The support of this research by the Robert A. Welch Foundation (Grant D-650) is gratefully acknowledged.

Registry No. 1, 25331-82-2; **2a**, 84810-85-5; methoxide ion, 3315-60-4.

(16) Boduszek, B.; Kice, J. L. *J. Org. Chem.* **1982**, *47*, 3199.

Synthesis of an Alleged Constituent of New Brunswick Cranberry Leaves: The So-Called Cannivonine

Alan P. Kozikowski* and Richard J. Schmiesing

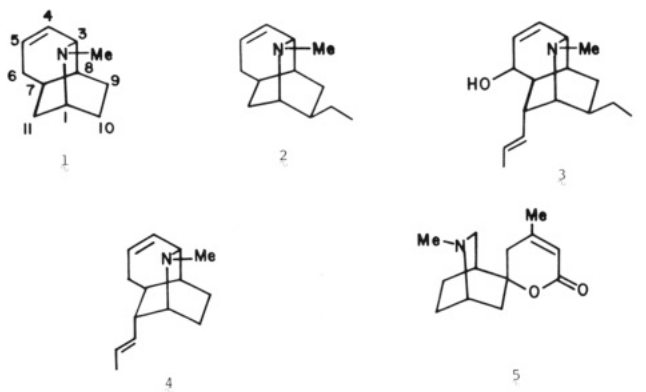
Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

Received July 7, 1982

An unambiguous ten-step synthesis of the compound possessing the reputed structure of the cranberry alkaloid cannivonine (**1**) is presented. Stereoselective reductive amination of the known *cis*-$\Delta^{5,6}$-2-octalone, protection of the nitrogen substituent, epoxidation, and N-deprotection with concomitant transannular ring closure provide a product possessing the desired 2-azatricyclo[5.3.1.$0^{3,8}$]undecane skeleton. Subsequent dehydration then yields the alleged cannivonine. Since the spectral data of the synthetic material fail to match those reported for cannivonine, a complete reinterpretation of the published data (and probably reisolation as well) and a reassignment of the structure of cannivonine appear to be in order.

Extracts from cranberry leaves (especially European) have found application in "naive" cancer therapy as well as traditional folklore medicine. In 1971, Jankowski and co-workers began a study into the basic constituents of extracts of cranberry leaves (*Viccinium oxycoccus*) native to New Brunswick. Their efforts resulted in a series of disclosures detailing the isolation and characterization of *N*-methylindolic and *N*-methylazatricyclic alkaloids believed to be the physiologically active ingredients of this plant.[1]

Of a minimum of 19 different basic substances detected by thin-layer chromatography, the structures of 8 of the alkaloids have thus far been communicated, 4 from the indole family, the cannagunine series, and 4 from the azatricyclic family, the cannivonine series (**1–4**). Unlike the four indole alkaloids, the cannivonines are a biogenetically interesting group because of their heretofore unknown 2-azatricyclo[5.3.1.$0^{3,8}$]undecane skeleton. Their architectural similarity to dioscorine (**5**), a natural product of known biogenetic origin, has, however, been alluded to.[2]



1 2 3 4 5

(1) (a) Jankowski, K.; Boudreau, J.; Jankowska, I. *Experentia* **1971**, *27*, 1141. (b) Jankowski, K.; Jankowska, I. *Ibid.* **1971**, *27*, 1383. (c) Jankowski, K. *Ibid.* **1973**, *29*, 519. (d) Jankowski, K. *Ibid.* **1973**, *29*, 1334. (e) Jankowski, K.; Godin, S.; Cundasawmy, N. E. *Can. J. Chem.* **1974**, *52*, 2064.

(2) Snieckus, V. A. "The Alkaloids-Specialist Periodical Reports"; The Chemical Society: Burlington House, London, 1973; Vol. 3, p 323.

0022-3263/83/1948-1000$01.50/0