Robert Mazzarese for his expert technical assistance.

Registry No. **2**, 77028-87-6; **3**, 77028-88-7; **4**, 77028-89-8; **5**, 77028-90-1; **6**, 77028-91-2; **7**, 77028-92-3; **8**, 5774-05-0; **9**, 77028-93-4; **10**, 64977-27-1; **11**, 77028-94-5; **12**, 135-02-4; **13**, 591-31-1; **14**, 123-11-5; *cis*-**15**, 77028-95-6; *trans*-**15**, 77028-96-7; *cis*-**16**, 77028-97-8; *trans*-**16**, 77028-98-9; *cis*-**17**, 77028-99-0; *trans*-**17**, 77029-00-6; **18**, 6398-50-1; **19**, 77029-01-7; **20**, 36112-61-5; **21**, 58149-89-6; **22**, 77029-02-8; **23**, 77029-03-9; *cis*-**24**, 77029-04-0; *trans*-**24**, 77029-05-1; **25**, 7035-02-1; **26**, 824-98-6; **27**, 824-94-2; **28**, 77029-06-2; **29**, 77029-07-3; **30**, 77029-08-4; **31**, 77029-09-5; **32**, 77029-10-8; **33**, 77029-11-9; *cis*-**34**, 77029-12-0; *trans*-**34**, 77029-13-1; *cis*-**35**, 77029-14-2; *trans*-**35**, 77029-15-3; *cis*-**36**, 77029-16-4; *trans*-**36**, 77029-17-5; benzyl chloride, 100-44-7; 1-acetylnaphthalene, 941-98-0; *p*-methoxybenzyl alcohol, 105-13-5; *o*-methoxybenzyl alcohol, 612-16-8; *m*-methoxybenzyl alcohol, 6971-51-3; 2-hydroxy-5-methylchrysene, 77029-18-6; 1-hydroxy-5-methylchrysene, 67411-85-2; 3-hydroxy-5-methylchrysene, 72427-02-2; 7-hydroxy-5-methylchrysene, 67411-84-1; 8-hydroxy-5-methylchrysene, 77029-19-7; 9-hydroxy-5-methylchrysene, 67411-83-0.

Nature of the Reaction of Thiamin in the Presence of Low Concentrations of Sulfite Ion. Competitive Trapping

John A. Zoltewicz* and Georg Uray

Department of Chemistry, University of Florida, Gainesville, Florida 32611

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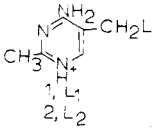
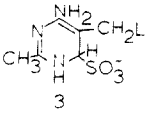
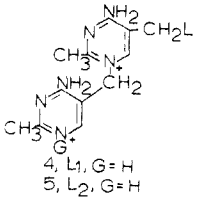
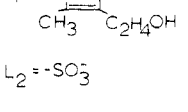
Nucleophilic substitution of thiamin (1), vitamin B_1, by sulfite ion gives pyrimidinium sulfonate **2** and the corresponding free thiazole.[1] Although this reaction was first reported in 1935 it was not until 1977 that a mechanism was advanced: one sulfite ion adds to the pyrimidinium ring, made electrophilic by protonation, to give intermediate **3**. A second sulfite ion, the one appearing in the observed product, then reacts either with **3** or with another intermediate formed from **3**, i.e., by loss of the leaving group (L) from **3**. Expulsion of the first sulfite gives product.[2]









Confirmation of the involvement of the second sulfite ion in this scheme was reported recently in a significant kinetic study.[3] Doerge and Ingraham demonstrated that at constant thiamin concentration reduction of the sulfite ion concentration leads to a change in kinetic order from one to two for sulfite ion.[3] However, the sigmoidal pH-dependent reactivity of the intermediate(s) detected when the second sulfite ion is kinetically important was not explained.

We provide an explanation for the observed pH-dependent reactivity of the intermediate observed by Doerge and Ingraham and isolate a product, not previously detected, which supports our interpretation.

Results and Discussion

We suggest that as the sulfite ion concentration is reduced in a series of experiments involving thiamin, another nucleophile begins to compete with sulfite ion for intermediate. This nucleophile under the conditions employed by Doerge and Ingraham is thiamin. In support of this are reports relating to other conditions: pyridine, a nucleophile similar in basicity to the conjugate base of **1**, can be made to compete with sulfite ion in the formation of substitution products to give a derivative of **1** having a pyridine ring as substituent L.[2,4]

Consideration of our suggestion that thiamin and sulfite ion both compete for intermediate leads to an explanation of the observed sigmoidal pH dependent reactivity of the intermediate, given by k_2/k_3 in ref 3. This apparent rate constant ratio contains pH-dependent terms to reflect the fractional amount of each nucleophile present in its reactive, basic form as the acidity of the reaction medium is varied. The fractional amount of nucleophile present as its reactive base is given by $K_a/([H] + K_a)$; appropriate pK_a values are 4.7 (HB) and 6.9 (HSO_3^-). Our eq 1 which

$$\frac{k_2}{k_3} = \left(\frac{k_B}{k_S}\right)\left(\frac{\text{fraction free 1}}{\text{fraction free } SO_3^{2-}}\right)[1]_0 \qquad (1)$$

has a linear form reproduces the previously unexplained observations and establishes a new rate constant ratio given by the slope which is pH independent (correlation coefficient 0.989). This slope, k_B/k_S, reflecting the relative abilities of the two competing nucleophiles to trap intermediate, is roughly 10^{-4}. Hence, only under conditions where **1** is present in large excess over sulfite ion is **1** able to compete with the strongly nucleophilic sulfite ion.

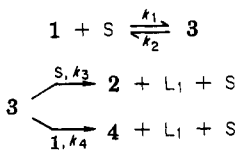
We sought support for our analysis of kinetic data by carrying out a product study. As a way to solve the practical problem of maintaining a very small concentration of sulfite ion in solution so that thiamin might successfully compete with it and yet achieve conversion to products in an amount suitable for isolation we elected to employ $CaSO_3$. This sparingly soluble salt ($K_{sp} = 1.1 \times 10^{-7}$ at 18 °C[5]) acts as a "buffer", keeping a low, roughly constant amount of sulfite ion in solution, compensating for the loss due to formation of sulfonic acid product.

A 2.4 M solution of **1** when briefly heated with $CaSO_3$ gives rise to **5** which we have isolated in very low yield. This material contains two pyrimidine rings. One of these is bonded to the methylene side chain of **1** in place of the thiazole leaving group. This new bond to the quaternized pyrimidine ring is logically produced in a trapping reaction because a control shows that no significant reaction takes place in the absence of sulfite ion. Although we would have liked to isolate bispyrimidine **4** where L is a thiazole ring instead of a sulfonato group as with **5**, this was not possible. Other studies making use of independently synthesized **4** and **5** (G = CH_3) show that **4** is much more reactive than **1**.[6] In other words, the product produced in a trapping

(1) Williams, R. R. *J. Am. Chem. Soc.* **1935**, *57*, 229.
(2) Zoltewicz, J. A.; Kauffman, G. M. *J. Am. Chem. Soc.* **1977**, *99*, 3134.
(3) Doerge, D. R.; Ingraham, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4828.
(4) Matsukawa, T.; Yurugi, S. *Yakugaku Zasshi* **1951**, *71*, 1423.
(5) "CRC Handbook of Chemistry and Physics", 61st ed.; Weast, R. C., Ed.; Boca Raton: FL, 1980; p B-89.
(6) Zoltewicz, J. A.; Uray, G.; Kauffman, G. M. *J. Am. Chem. Soc.*, in press.

0022-3263/81/1946-2398$01.25/0

Scheme I



reaction with thiamin acting as a nucleophile is more reactive than thiamin starting material.

There are two likely routes to **5**: by conversion of **4** to **5** with sulfite ion and by trapping of intermediate by sulfonic acid product **2**. Our low-conversion conditions are designed to minimize the latter route.

Logically, bispyrimidine product **4** also might undergo substitution. It could give rise to another intermediate which might then be trapped by thiamin, forming a tris-pyrimidine product. This sequence of events could be repeated to form higher molecular weight oligomeric substitution products. Indeed, a pentameric oligomer has been isolated but under different conditions; i.e., the solvent is methanol instead of water and no sulfite ion is present.[8] Our own work shows that an oligomeric substitution product having more than two pyrimidine rings does indeed form in aqueous solution under conditions where sulfite ion is the limiting reagent. But because such oligomer is difficult to purify[8] we have established its presence by NMR and by its subsequent conversion to **2** with excess sulfite ion.[8]

The chemical shift of the methylene group bridging two pyrimidine rings as in **4**, **5**, and higher oligomer is unique and may be used to identify such products.[6,8] Under low-conversion conditions where concentrations are similar to those employed in the earlier kinetic study[3] we have observed that at least 6.5% of all intermediates may be trapped in a reaction where a pyrimidine ring rather than sulfite ion serves as a nucleophile.

Unfortunately the identity of the intermediate reacting with either sulfite ion or thiamin is not revealed by these studies. That is, there is no evidence to answer the question of whether the leaving group is present when the nucleophile attacks[3] or whether it has departed in a prior step. Only in one case has this question been firmly answered; common-ion retardation provides the informative clue.[7]

When a thiamin with the anion of 4-thiopyridone as group L is treated with sulfite ion common-ion rate retardation is observed. In this case as well as in the present one a nucleophile (anion of 4-thiopyridone or thiamin) competes with sulfite ion for intermediate. It is important to note that the transition to second-order kinetics in sulfite ion is a consequence of the successful competition by the other nucleophile. Although the two experiments[3,7] are similar in this regard the common-ion experiment is the more powerful one because it is more informative. Rate retardation by added leaving group (common ion) requires the presence of an intermediate without that leaving group.

The multistep mechanism of nucleophilic substitution of thiamin and its analogues by sulfite ion first proposed in 1977 now seems secure. But additional studies are required to determine whether the leaving group is present or absent when the second nucleophile attacks intermediate.

Experimental Section

Isolation of Product 5 by Competitive Trapping. To a solution of 4.0 g (12 mmol) of thiamin chloride hydrochloride in 5 mL of water containing a suspension of 0.40 g (3.3 mmol or 0.28 equiv) of $CaSO_3$ was added bicarbonate to raise the pH to 5.8. The mixture was heated on a steam cone for 15 min; the pH of the solution was unchanged. Unreacted sulfite was recovered (0.25 g, 62%) by filtration. NMR analysis (thiazole ring and methyl protons) showed approximately 50% liberated thiazole; most of this was removed by extraction with methylene chloride. Solid sodium perchlorate then was added to precipitate the remaining thiamin as its monoperchlorate. The filtrate was evaporated to a yellow oil containing some crystals. Addition of a small amount of absolute ethanol allowed solid to be removed by filtration. NMR ($DClO_4$) analysis showed this solid to be oligomer having the pyrimidine ring as a repeating unit.[8,9] It had multiple pyrimidine signals about δ 7.9, a bridging methylene at δ 5.25, and multiple methyl signals about δ 2.75. The ethanol mother liquor was replaced by acetonitrile; a crystalline product was isolated. It was recrystallized from 0.1 M perchloric acid to give 3 mg of product, mp darkens about 270 °C, decomposes >330 °C. anal. Calcd for $C_{12}H_{17}ClN_6O_7S$: C, 33.93; H, 4.03; N, 19.78. Found: C, 34.06; H, 4.06; N, 19.83. The compound is **5**, 4-amino-1-[(4-amino-2-methyl-5-pyrimidinio)methyl]-2-methyl-5-sulfonatomethylpyrimidinium perchlorate; NMR (pD 8) δ 8.1, 8.0 (CH), 5.3 (CH_2N), 4.2 ($CH_2SO_3^-$), 2.8, 2.5 (CH_3).

A control having identical composition but without calcium sulfite shows that thiamin decomposition is insignificant under the same conditions.

Measure of the Minimum Extent of Trapping by Thiamin. A 40 mM solution of thiamin in a 0.02 M acetate buffer at pH 5.4 containing 1 equiv of $CaSO_3$ was stirred at room temperature for 21 h. (A control having the same composition but without the sulfite salt showed by ultraviolet analysis no significant reaction.) Solid material was removed and dried at 140 °C; in order to determine whether this solid consisted of a mixture of $CaSO_3$ and sulfonic acid substitution product the sulfite was titrated iodometrically. The precipitate was pure calcium sulfite (61%), showing that no substitution product was removed by filtration. The mixture then was freeze-dried. A small amount of D_2O was added to the resultant powder, and the mixture was filtered, removing most of the pyrimidinylmethylsulfonic acid **2** substitution product. NMR analysis of the filtrate shows it contains thiamin, free thiazole, **2**, and oligomer.[8] The signal at δ 5.3, associated with the methylene group bridging two pyrimidine rings of oligomer stands in an 0.13 area ratio (corrected for the number of protons) with respect to the aromatic proton of free thiazole.

This ratio provides a measure of the minimum amount of trapping of intermediate by thiamin to produce oligomer. Free thiazole provides a measure of the total amount of substitution due to trapping by both thiamin and sulfite ion. But oligomer may be degraded by subsequent reaction with sulfite ion, making the significance of the ratio less certain. Moreover, if only oligomer forms, the ratio ranges in value between 0.5 and 1, the smaller value resulting when a product is produced having two pyrimidine rings and one sulfonic acid group. The ratio tends to the value of one as chain length increases. Thus, at least 13/2 or 6.5% of the intermediates were trapped by reaction with a pyrimidine ring. The conditions employed in our work are similar to those used in a kinetic study except that under initial rate conditions little high molecular weight oligomer should form.[3]

Acknowledgment. This work was kindly supported by Grant AM-17442 from the National Institutes of Arthritis, Metabolism and Digestive Diseases.

Appendix. Kinetic Derivation

Rate constants in Scheme I apply to the same steps as given in ref 3. However, another pathway, k_4, has been added to indicate that intermediate may also be trapped by thiamin. The data[3] do not distinguish between two

(7) Zoltewicz, J. A.; Uray, G.; Kauffman, G. M. *J. Am. Chem. Soc.* **1980**, *102*, 3653.

(8) Shimahara, N.; Asakawa, H.; Kanamatsu, Y.; Hirano, H. *Chem. Pharm. Bull.* **1974**, *22*, 2086.

(9) This high molecular weight product also is likely to be formed in a trapping reaction with thiamin serving as a nucleophile.[6]

mechanisms: (a) intermediate **3** or (b) another intermediate formed from **3** by loss of the leaving group is trapped by reaction with sulfite ion or thiamin. Consequently, simpler mechanism a is given in Scheme I. Incorporation of an additional step as required by pathway b does not change the kinetic form, only the collection of rate constants.

The derivation pertains to experimental conditions[3] where sulfite ion S is the limiting reagent under initial rate conditions and **1** is present in excess. The pH dependence is not expressed but it is to be understood that the conjugate acid of thiamin reacts with free sulfite ion while thiamin base is a nucleophile. Step k_3 is not included in the rate expression because one S is consumed and another is liberated. Note that S is liberated in step k_4 in which thiamin traps intermediate; the formation of oligomer is *catalyzed* by S, and so step k_4 must be included in the rate expression. Applying a steady-state assumption for **3** gives eq 2. This has the form of eq 1 in ref 3, $k_2 + k_4[1]$ being an apparent constant.

$$R = -\mathrm{d}[S]/\mathrm{d}t = k_1[1][S] - [3](k_2 + k_4[1])$$

$$R = \frac{k_1k_3[S]^2[1]}{k_2 + k_3[S] + k_4[1]} \qquad (2)$$

The k_2/k_3 ratio in ref 3 now becomes $(k_2 + k_4[1])/k_3$ and reduces to $k_4[1]/k_3$ if $k_2 < k_4[1]$. We actually prefer a scheme in which the two nucleophiles compete for an intermediate which already has lost the leaving group and therefore use different symbols k_B/k_S in eq 1 to express the competition. In this case no assumption needs to be made about the relative magnitudes of k_2 and $k_4[1]$.

Highly instructive is a consideration of the case where $k_4[1] > k_3[S]$; i.e., intermediate is trapped preferentially by **1**. As eq 3 shows, the rate of disappearance of sulfite ion now is second order in sulfite ion.

$$R = \frac{k_1k_3[S]^2[1]}{k_2 + k_4[1]} \qquad (3)$$

By use of our value for k_B/k_S and the concentrations given in ref 3 calculations show that sulfonate ion **2** is the major product at high pH. But as the acidity is lowered and the ratio of thiamin base to sulfite ion concentrations increases the major product becomes bispyrimidine **4** as the reaction becomes second order in sulfite ion.[10]

Registry No. 1·HCl, 67-03-8; **5**, 77028-14-9; sulfite ion, 14265-45-3.

(10) Buffer base also could trap intermediate, three being employed.[3] The good fit given by eq 1 suggests this process is not significant.

Vinylsilane-Mediated Spiroannulation. Synthesis of Spiro[4.5]decadienones

Steven D. Burke,* Charles William Murtiashaw, Meera S. Dike, Sharon M. Smith Strickland, and Jeffrey O. Saunders

Department of Chemistry, University of South Carolina, Columbia, South Carolina 29208

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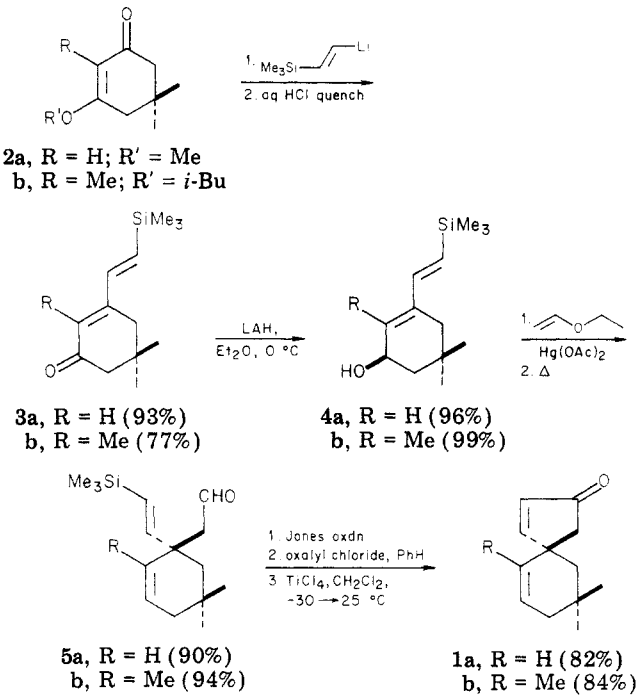
The efficient construction of quaternary carbon centers remains as a fundamental test of synthetic methodology.[1] A popular arena for the probation of such technology is the construction of spiroannulated bicyclic carbon frameworks.[2] In connection with ongoing synthetic efforts in these laboratories, we required an efficient entry to spiro[4.5]decadienones of general structure **1**. The known and readily accessible dimedone derivatives **2** were seen as particularly attractive starting materials.[3] We report herein a vinylsilane-mediated spiroannulation sequence which effects the desired overall transformation of the vinylogous esters **2** to the spirodienones **1** in excellent yield.[4]

Scheme I[6]



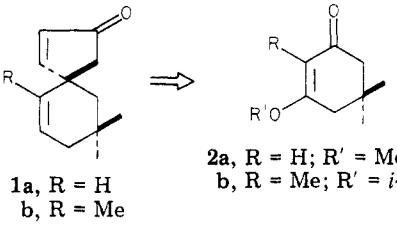
2a, R = H; R′ = Me
b, R = Me; R′ = *i*-Bu

3a, R = H (93%)
b, R = Me (77%)

4a, R = H (96%)
b, R = Me (99%)

5a, R = H (90%)
b, R = Me (94%)

1a, R = H (82%)
b, R = Me (84%)



1a, R = H
b, R = Me

2a, R = H; R′ = Me
b, R = Me; R′ = *i*-Bu

Treatment of dimedone methyl ether (**2a**) with *trans*-β-(trimethylsilyl)vinyllithium[5] (−78→25 °C) followed by a quench with 5% aqueous HCl provided the crystalline

(1) For a recent review of this topic, see: Martin, S. F. *Tetrahedron* **1980**, *36*, 419.

(2) The synthetic pursuit of a large variety of sesquiterpenes possessing a spiro[4.5]decane carbon skeleton has spawned much of this work. For a representative selection of papers describing various spiroannulation strategies, see: (a) Dauben, W. G.; Hart, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 7307; (b) Corey, E. J.; Boger, D. L. *Tetrahedron Lett.* **1978**, 13; (c) Trost, B. M.; Hiroi, K.; Holy, N. *J. Am. Chem. Soc.* **1975**, *97*, 5873; (d) Semmelhack, M. F.; Yamashita, A. *Ibid.* **1980**, *102*, 5924; (e) Stork, G.; Danheiser, R. L.; Ganem, B. *Ibid.* **1973**, *95*, 3414; (f) Büchi, G.; Berthet, D.; Decorzant, R.; Grieder, A.; Hauser, A. *J. Org. Chem.* **1976**, *41*, 3208; (g) Martin, S. F. *Ibid.* **1976**, *41*, 3337; (h) Marx, J. N.; Norman, L. R. *Ibid.* **1975**, *40*, 1602; (i) Oppolzer, W.; Mahalanabis, K. K.; Battig, K. *Helv. Chim. Acta* **1977**, *60*, 2388; (j) Ruppert, J. F.; Avery, M. A.; White, J. D. *J. Chem. Soc., Chem. Commun.* **1976**, 978; (k) Altenbach, H.-J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 940. For a review on the chemistry of spirosesquiterpenes, see: Marshall, J. A.; Brady, S. F.; Anderson, N. H. *Fortschr. Chem. Org. Naturst.* 1974, *31*, 283. For general reviews on spirocycle synthesis, see: Krapcho, A. P. *Synthesis* **1978**, 77; *Ibid.* **1976**, 425; *Ibid.* **1974**, 383.

(3) Clark, R. D.; Ellis, J. E.; Heathcock, C. H. *Synth. Commun.* **1973**, *3*, 347.

(4) For applications of vinylsilanes in intermolecular acylation–cyclopentenone annulation sequences, see: (a) Cooke, F.; Moerck, R.; Schwindeman, J.; Magnus, P. *J. Org. Chem.* **1980**, *45*, 1046; (b) Paquette, L. A.; Fristad, W. E.; Dime, D. S.; Bailey, T. R. *Ibid.* **1980**, *45*, 3017.

(5) Prepared from the corresponding vinylstannane: Cunico, R. F.; Clayton, F. J. *J. Org. Chem.* **1976**, *41*, 1980.

0022-3263/81/1946-2400$01.25/0