has only been observed from I and $Fe(CO)_5$. This may result from relative rates of various steps making the steady-state concentration of the corresponding species too low to detect for other metal carbonyls, but it is also conceivable that one or more of these reactions involve a different mechanism.
(10) Reactions under H_2 and mixed atmospheres were carried out in a Fischer–Porter pressure bottle at slightly above 1 atm; gas samples were removed by gas-tight syringe and analyzed using a Hewlett-Packard 5790 gas chromatograph, with a 4-ft, $\frac{1}{8}$-in. Porapak P (50–80 mesh) column and flame ionization detector. Isotopic labeling studies were achieved using a Du Pont DP-101 gas chromatograph–mass spectrometer, with a 5-ft, $\frac{1}{4}$-in Porapak Q (80–100 mesh) glass column, as well as an AEI MS-9 high-resolution mass spectrometer.
(11) Labeled chromium carbonyl (~70–80% ^{13}C by mass spectrometry) was prepared using the procedure recently reported by Darensbourg, wherein CO exchange is catalyzed by tributylphosphine oxide.[12] The mass spectrum of the gas phase after reaction of this labeled compound with I shows clearly that ^{13}CO has been reduced to ethane (peaks at *m/e* 32, 31; exact mass of former, 32.054; calcd for $^{13}C_2H_6^+$, 32.0535). Because the mass spectrum contains peaks at *m/e* 30, 29, . . . resulting from fragmentation of benzene (the solvent in the reaction; small amounts are present in the vapor phase) as well as fragments from the variously labeled ethanes, it is not possible to determine conclusively that *all* the ethane produced comes from CO reduction (note the formation of ethane from an alternate source in II, at higher temperature[5]); however, by making approximate corrections for the benzene-derived peaks we estimate that *at least* 75% of the ethane originates from CO.
(12) Darensbourg, D. J.; Walker, N.; Darensbourg, M. Y. *J. Am. Chem. Soc.* **1980**, *102*, 1213–4.
(13) Masters, C.; van der Woude, C.; van Doorn, J. A. *J. Am. Chem. Soc.* **1979**, *101*, 1633–4. Another mechanistic possibility is provided by the recent report (Wood, C. D.; Schrock, R. R. *J. Am. Chem. Soc.* **1979**, *101*, 5421–2) that reaction of CO with $(\eta^5\text{-}C_5Me_5)TaMe_4$ gives $[(\eta^5\text{-}C_5Me_5)MeTaO(OC\text{-}MeCMe_2)]_x$ via intermediate formation of an acetone complex. The similarities of this system (group 5 metal; exactly two carbons from CO in product; formation of metal oxide species) to that studied here are suggestive.
(14) These reactions were carried out in a vessel connected directly, via a bellows-type gas circulating pump and a gas sampling valve, to a Carle AGC-311 gas chromatograph, using an 8-ft, $\frac{1}{8}$-in Porapak column and FID.
(15) Under an atmosphere of 1:1 H_2-C_2H_4, CO reduction is inhibited: only traces of ethane and III, and *no* insoluble material, are formed; instead a clear solution of $(\eta^5\text{-}C_5H_5)_2Nb(C_2H_5)(C_2H_4)$[16] results. This also indicates that hydrogenation of C_2H_4 is not catalyzed by I under reaction conditions.
(16) Guggenberger, L. J.; Meakin, P.; Tebbe, F. N. *J. Am. Chem. Soc.* **1974**, 96, 5420-7.
(17) The possibility that these low levels of deuterium incorporation arise from prior exchange of I with D_2 is excluded by the observation (also reported previously[18]) that very little *reversible* exchange occurs at such mild temperatures; rather some decomposition of I with loss of H_2 is found. This may well be a partial cause of the relatively low yields of C_2H_6, since the reaction of I with $Cr(CO)_6$ is fairly slow. Similarly, the direct reaction of I with CO to give III[19] is too slow at these temperatures to account for the observed inhibition of ethane formation or the formation of III in good yield.
(18) Klabunde, U.; Parshall, G. W. *J. Am. Chem. Soc.* **1972**, *94*, 9081-7.
(19) Tebbe, F. N.; Parshall, G. W. *J. Am. Chem. Soc.* **1971**, *93*, 3793-5.
(20) ^1H NMR, IR and mass spectroscopy are consistent with the product from I and $Mo(CO)_6$ being $(\eta^5\text{-}C_5H_5)_2NbHMo(CO)_6$, isoelectronic (and presumably with a similar structure) to II.

Kwai Sam Wong, Jay A. Labinger*
Department of Chemistry, University of Notre Dame
Notre Dame, Indiana 46556
Received January 31, 1980

Evidence for an Intermediate in Nucleophilic Substitution of a Thiamin Analogue. Change from First- to Second-Order Kinetics in Sulfite Ion

Sir:

A hallmark reaction of thiamin (I) is nucleophilic substitution by sulfite ion. We recently provided kinetic evidence to show that this process takes place not by an S_N2 but rather by a multistep process:[1] sulfite ion adds to protonated substrate which then eliminates the leaving group (L = a thiazole) to give a resonance stabilized carbocation intermediate III.[2] Addition of a second sulfite ion to III followed by expulsion of the first gives product. For thiamin this sequence is first order in sulfite ion, reactions of the intermediate taking place after the rate limiting step (Scheme I).

Now we provide evidence to show that an analogue of thiamin undergoes nucleophilic substitution by a similar pathway and that reaction of the second sulfite ion may be rate limiting.

Scheme I

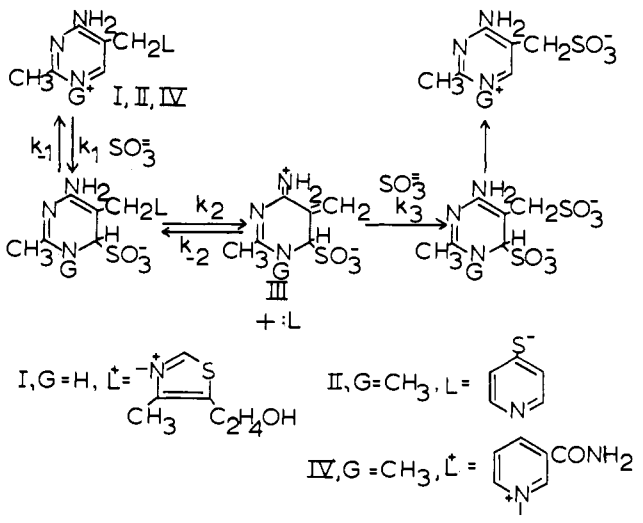

Table I. Apparent Second-Order Rate Constants for Substitution of II by Sulfite Ion at 25.0 °C and 1.0 Ionic Strength[a]

$10^4[II]_0$, M	$10^2[SO_3^{2-}]_{free}$,[b] M	10^4[4-thiopyridone]$_{tot}$,[c] M	10^3k, M^{-1} s^{-1}[d]
0.18	9.80	—	8.50
1.87	9.53	3.66	3.99
1.85	9.40	7.24	2.79
2.00	4.86	8.10	1.65

[a] At pH 9.41 ± 0.02. Reactions followed at 260 nm. [b] Calculated using $pK_a = 6.59$ (1.0 ionic strength). [c] May be converted into the concentration of anion using $pK_a = 8.66$ (1.0 ionic strength). [d] $k_{obsd}/[SO_3^{2-}]_{free}$.

Substrate II has a methyl group bonded to nitrogen (G = CH_3) instead of a proton.[3] The leaving group is the anion of 4-thiopyridone. At low substrate concentration (Table I), the rate of substitution is first order both in substrate and in sulfite ion. Either at high substrate concentrations or when leaving group is added at the start, the rate is retarded.[4] Adding more thiolate ion at the start leads to progressively larger retardations, as much as a 5.2-fold reduction in the apparent second-order rate constant, $k_{obsd}/[SO_3^{2-}]_{free}$ (Table I).[5]

The hetarenethiolate ion leaving group is a powerful nucleophile and competes with sulfite ion for intermediate. That is, formation of intermediate becomes reversible and its capture by a second sulfite ion becomes rate limiting. The equation expressing the pseudo-first-order rate constant for such a sequence may be rearranged to produce eq 1 which is linear.

$$\frac{[SO_3^{2-}]_f}{k_{obsd}} = \frac{k_{-1}k_{-2}[L]_f}{k_1k_2k_3[SO_3^{2-}]_f} + \frac{k_{-1} + k_2}{k_1k_2} \qquad (1)$$

Figure 1 shows a plot of the results in Table I in the form of eq 1. As required by our mechanism, this plot indeed is linear. Moreover, the slope to intercept ratio is a quantity of some significance, being the ratio of the rate constants expressing the ability of thiolate and sulfite ions to compete for intermediate III. Thus, the anion of 4-thiopyridone traps intermediate 250 times faster than sulfite ion.[6]

The good fit of our results to eq 1 allows us to reach another conclusion: thiolate ion does not add in significant amounts to C_6 of II. Hence, thiolate ion successfully competes with sulfite ion for intermediate but not for aromatic substrate, reflecting a difference in kinetic and equilibrium affinities. Such an

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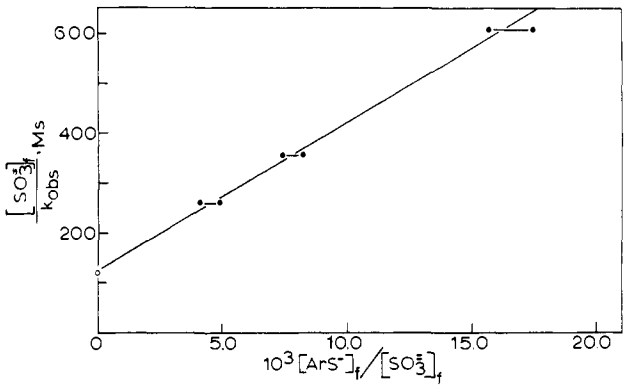


Figure 1. Nucleophilic substitution of II by sulfite ion in the presence and absence of added anion of 4-thiopyridone (ArS^-). Plot of the reciprocal of the apparent second-order rate constant vs. the ratio of 4-thiopyridone anion to sulfite ion concentrations. Horizontal bars indicate the contribution from substrate of ArS^- leaving group at 50 and 100% conversions. The open circle reflects the true second-order rate constant obtained in the absence of added ArS^-. The least-squares lines through the 50 and 100% points give slope to intercept ratios of 260 and 236, respectively. This ratio for the indicated line is 250.

outcome is not unprecedented: our first report on the substitution of thiamin contains such a contrast for azide and sulfite ions.[1] A similar "inversion" in rate and equilibrium constant ratios is found for an alkenethiolate ion and sulfite ion reacting with protonated quinazoline.[7]

As a check on the value of the rate constant ratio (Figure 1), competition experiments were performed using substrate IV to generate intermediate III. This material which has nicotinamide as a leaving group reacts ~280 times faster with sulfite ion than II.[8] Therefore IV may be converted into a mixture of II and sulfonic acid product in the presence of 4-thiopyridone and sulfite ion.[9] The product ratio was determined at 270 nm (pH 8.6, 25 °C) at three different concentrations of the two nucleophiles. A plot of the product ratio vs. the ratio of concentrations of the nucleophiles, corrected for the fraction present as reactive anion, is linear with a slope of 240. The remarkably good agreement between the rate constant ratios obtained from the two different types of experiments provides strong support for our analysis.[10]

Our results have considerable significance regarding the mechanism of nucleophilic substitution of thiamin and its analogues by thiaminase I.[11,12] In view of our demonstrations that substrates as diverse as I and II react by the common pathway given in Scheme I, we suggest that such a route may be followed by the enzymic reactions as well. Moreover, this pathway is reminiscent of that suggested for thymidylate synthetase.[13,14]

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

Supplementary Material Available: A listing of rate equations, a description of the competition experiments, and results (5 pages) is available. Ordering information is given on any current masthead page.

References and Notes

(1) Zoltewicz, J. A.; Kauffman, G. M. *J. Am. Chem. Soc.* **1977**, *99*, 3134.
(2) Intermediate III may also be written as a sultone.
(3) Zoltewicz, J. A. *Synthesis*, in press.
(4) At low substrate concentrations and when large amounts of thiolate ion are present initially, pseudo-first-order plots are linear over at least 4 half-lives. Under intermediate conditions such plots show pronounced curvature in the beginning and then become almost linear. This approximately linear region (>50% conversion) was used to obtain the rate constant for the second run in Table I.
(5) The total absorbance change for the last three kinetic runs is essentially the same, after correcting for small variations in the concentration of II. This indicates that (a) substitution goes to completion and not to an equilibrium condition and (b) II and 4-thiopyridone do not react in the absence of sulfite ion.
(6) The rate expression associated with Scheme I can be integrated exactly. To fit concentration–time data to this equation, a correct value for the competition constant is required. Our value obtained from Figure 1 allows us to obtain linear kinetic plots. Moreover, the slope is the second-order rate constant in the absence of inhibition. It has a value which is not significantly different from that given by the first entry in Table I.
(7) Cho, M. J.; Pitman, I. H. *J. Am. Chem. Soc.* **1974**, *96*, 1843.
(8) Unpublished result of G. M. Kauffman.
(9) This conversion into II is effected in 64% isolated yield on a preparative scale.
(10) The competition constant has, in general, two limiting forms, i.e., k_{-2}/k_3 and $k_{-1}k_{-2}/k_2k_3$. A future publication will discuss these possibilities.
(11) Evans, W. C. *Vitamins Hormones* **1975**, *33*, 467.
(12) Lienhard, G. *Biochemistry* **1970**, *9*, 3011.
(13) Pogolotti, A. L.; Santi, D. V. *Bioorg. Chem.* **1977**, *1*, 277.

John A. Zoltewicz,* Georg Uray, Glenn M. Kauffman
Department of Chemistry, University of Florida
Gainesville, Florida 32611
Received February 15, 1980

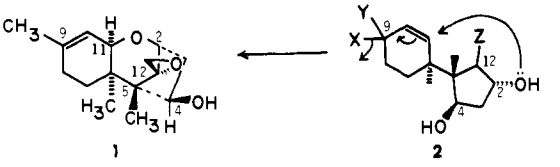
Total Synthesis of (±)-Trichodermol

Sir:

Trichodermol is a central member of the trichothecane group of terpenoid antibiotics and has been the subject of numerous synthetic investigations since its structure was revealed as **1** in 1964.[1] Although a total synthesis was reported in 1971 by Raphael and co-workers,[2] the failure of a certain key aldol cyclization to establish the C-4–C-5 bond in >10% yield made it clear that further work on trichothecane synthesis should be undertaken. The work that we describe here uses a different type of construction in which a preformed cyclopentanol (e.g., in **2**) cyclizes biomimetically along lines described previously[3] to produce the desired tricyclic system (see Scheme I). The synthetic problem thus effectively reduces to one in which a way must be found to relate the stereochemistry between the two isolated rings. As we will show, a cycloaddition–fragmentation sequence provides a mechanism for the desired stereocontrol and yields a novel pathway to (±)-trichodermol.

Our plan for the construction of an intermediate equivalent to **2** begins by the Diels–Alder addition of quinone to the cyclohexadienyl silyl ether **3**[4] (1 M in C_6H_6; 25 °C; 5 days). The highly crystalline adduct **4** (mp 73–73.5 °C) was readily obtained in 90% yield (Scheme II). Subsequent epoxidation (*t*-BuOOH, Triton B, THF; −20 °C; 82% yield) and Herz–Favorskii ring contraction[5] (NaOH, EtOH; 25 °C; 70% yield) proceeded regiospecifically to give the crystalline cyclopentenonecarboxylic ester **5** (mp 74.5–75.5 °C; IR (Nujol) 1720 cm^{-1}).[6] At this point, the C-4 hydroxyl was introduced stereospecifically by epoxidation (*t*-BuOOH, Triton B, THF; 25 °C; 92% yield) and dissolving metal reduction (Li, NH_3, EtOH, THF; 93% yield). The resulting triol (**6**, mp 116–117 °C) was monoacetylated (Ac_2O, C_5H_5N; 0 °C) and reduced photochemically[7] (deoxygenated HMPA, H_2O; 450-W medium-pressure Hanovia, quartz; 60–70% yield at 70% conversion) to the corresponding diol (**7**, mp 90–93 °C, NMR ($CDCl_3$) δ 1.10 (s, 3 H) and 1.12 (s, 3 H)). Although the less-hindered C-2 hydroxyl could not be directly derivatized for fragmentation, an alternative sequence ((1) PhCOCl,

Scheme I



1 **2**

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