

Meyer, and T. R. Weaver, in "Extended Interactions between Metal Ions in Transition Metal Complexes", Vol. 5, L. V. Interrante, Ed., ACS Symposium Series, Washington, D.C., 1974.

- (4) $[\text{Ru}_3\text{O}(\text{CH}_3\text{CO}_2)_6(\text{py})_2(\text{pyz})](\text{PF}_6^-)$ analysis. Calcd for $\text{C}_{26}\text{H}_{32}\text{N}_4\text{O}_{13}\text{P}_2\text{F}_6\text{Ru}_3$: C, 29.55; H, 3.05; N, 5.30. Found: C, 29.41; H, 3.05; N, 4.90.
- (5) Potentials were measured by cyclic voltammetry (50–200 mV/sec) and stirred solution voltammetry in CH_3CN solution containing 0.1 M (*n*-butyl)₄NPF₆ as supporting electrolyte. A Pt bead electrode was used and potential values are referenced to the saturated sodium chloride calomel electrode at $25 \pm 2^\circ$. All cationic complexes were prepared as PF₆⁻ salts.
- (6) $\Delta E_p \approx 60$ mV and $i_{pa}/i_{pc} \approx 1$; see R. W. Murray and C. N. Reilley, "Electroanalytical Principles", Interscience, New York, N.Y., 1963.
- (7) (a) W. L. Jolly, *Coord. Chem. Rev.*, **13**, 47 (1974); (b) P. H. Citrin, *J. Am. Chem. Soc.*, **95**, 6472 (1973).
- (8) λ_{max} (ϵ) in CH_3CN : 775 nm (4300), 575 (3460), 312 (12,600). Anal. Calcd for $\text{C}_{27}\text{H}_{33}\text{N}_3\text{O}_{13}\text{F}_2\text{Ru}_3$: C, 27.01; H, 2.77; N, 3.50. Found: C, 26.89; H, 2.63; N, 3.46.
- (9) A. Spencer and G. Wilkinson, *J. Chem. Soc., Dalton Trans.*, 796 (1974).
- (10) $[\text{Ru}_3\text{O}(\text{pyz})\text{Ru}_3\text{O}]^{2+}$ has λ_{max} (ϵ) at 703 nm (14,500) and 420 (12,800). Calcd for $\text{C}_{48}\text{H}_{60}\text{N}_6\text{O}_{26}\text{P}_2\text{F}_{12}\text{Ru}_6$: C, 28.35; H, 2.97; N, 4.13. Found: C, 28.68; H, 2.96; N, 4.21. $[\text{Ru}_3\text{O}(\text{pyz})\text{Ru}_3\text{O}]$ has λ_{max} (ϵ) at 980 nm (20,400), 528 (14,800), 383 (15,400). Calcd for $\text{C}_{48}\text{H}_{60}\text{N}_6\text{O}_{26}\text{Ru}_3$: C, 33.07; H, 3.47; N, 4.82. Found: C, 32.90; H, 3.64; N, 4.84.
- (11) (a) G. M. Brown, Ph.D. Thesis, University of North Carolina, Chapel Hill, N.C., 1974. (b) G. M. Tom, C. Creutz, and H. Taube, *J. Am. Chem. Soc.*, **96**, 7829 (1974).
- (12) From cyclic voltammetry in CH_2Cl_2 (0.1 M (*n*-butyl)₄NPF₆) the equilibrium constant for the equilibrium (+2) + (0) = 2(+1) is 223. Using this value the equilibrium concentrations of the three species were calculated.
- (13) In CH_2Cl_2 solution in the region 400–1000 nm the electronic spectrum of $[\text{Ru}_3\text{O}(\text{CH}_3\text{CO}_2)_6(\text{py})_2(\text{pyz})]^+$ has λ_{max} (ϵ) 695 (6400) and $[\text{Ru}_3\text{O}(\text{CH}_3\text{CO}_2)_6(\text{py})_2(\text{pyz})]$ has λ_{max} (ϵ) 452 (8870), 910 (10,200).
- (14) N. S. Hush, *Prog. Inorg. Chem.*, **8**, 391 (1967).

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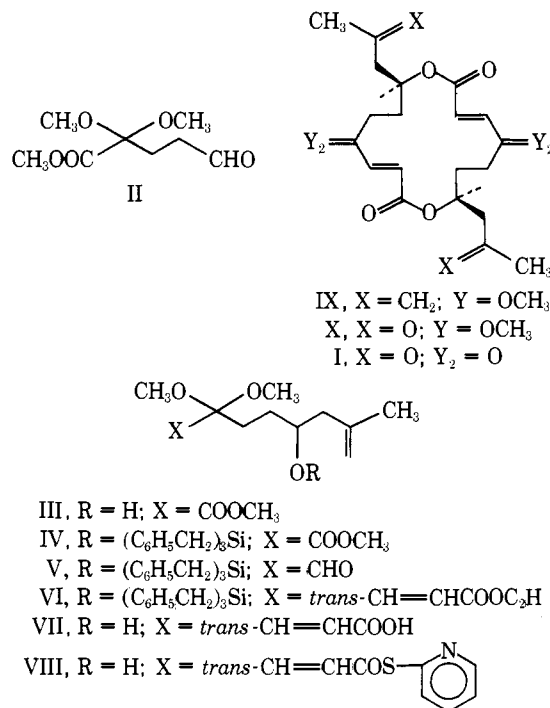
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Total Synthesis of (\pm)-Vermiculine

Sir:

The structure of the antibiotic vermiculine has recently been established as I on the basis of X-ray crystallographic analysis.^{1,2} The total synthesis of this substance in racemic form, undertaken as part of a program on the synthesis of biologically active macrocycles, is reported herein. The pathway of the synthesis, which involves only ten steps, features several noteworthy functionally selective reactions and the application of the previously described "double activation" method^{3,4} to generate *both* ester linkages of the macrocycle in a single operation.

The readily available dimethyl 2,2-dimethoxyglutarate,⁵ upon treatment with 1.4 equiv of diisobutylaluminum hydride in methylene chloride at -78° for 1 hr, afforded after workup⁶ the pure aldehyde ester II⁷ in 50% yield. Reaction of II with 1.5 equiv of dimethylcadmium⁸ in ether at -78° for 1 hr gave the alcohol III which without purification was treated with tribenzylchlorosilane (1.3 equiv) and imidazole (1.3 equiv) in dimethylformamide at 25° for 15 hr to form the corresponding silyl ether IV (70% from II). Reduction of IV with 1.2 equiv of diisobutylaluminum hydride in methylene chloride at -78° for 30 min produced the aldehyde V which was directly condensed with the sodium salt (from NaH) of diethyl ethoxycarbonylmethane-phosphonate (1.8 equiv) in tetrahydrofuran at 25° for 1 hr to give the *trans* α,β -unsaturated ester VI (94% overall from IV). The key intermediate for the synthesis of vermiculine, the hydroxy acid VII, was prepared from VI in 100% yield by hydrolysis with 0.17 N lithium hydroxide in methanol-water (2:1) at 25° for 24 hr. The 2-pyridinethiol ester VIII, prepared by reaction of the hydroxy acid VII with 1.5



equiv of 2,2'-dipyridyl disulfide and 1.5 equiv of triphenylphosphine in concentrated solution in xylene at 0° for 20 hr, was obtained in pure form in 77% yield after chromatography on silica gel. Heating of VIII in 0.1 M solution in xylene at reflux with 3 equiv of 2,6-lutidine⁹ for 24 hr produced in 30% yield a mixture (1:1) of the desired vermiculine derivative IX (methallyl groups *cis*) and the diastereomer of IX having a *trans* arrangement of the two methallyl groups.^{3,4,10} The mixture was converted without separation to the keto ketal lactone X by reaction with osmium tetroxide (0.1 equiv) and sodium periodate (6 equiv) in 50% aqueous *tert*-butyl alcohol at 25° for 1 hr (70% yield) and thence quantitatively to a mixture of (\pm)-vermiculine (I) and the *trans* (meso) diastereomer by exposure to acetic acid-water-tetrahydrofuran (3:1:1) at 45° for 1 hr. Chromatography of the mixture on silica gel using benzene-ethyl acetate (1:1) afforded racemic vermiculine (I), mp 143 – 144° , and the *trans* (meso) diastereomer, mp 131 – 132° (relative *R_f* values 0.24 and 0.15, respectively). The infrared (CHCl_3), ¹H NMR (CDCl_3), ultraviolet (EtOH), and mass spectra of synthetic (\pm)-I were identical with those of an authentic specimen of vermiculine.^{11–14}

References and Notes

- (1) R. K. Boeckman, Jr., J. Fayos, and J. Clardy, *J. Am. Chem. Soc.*, **96**, 5954 (1974).
- (2) In an earlier paper a different structure had been assigned; see P. Sedmera, J. Vokoun, M. Podojil, Z. Vanek, J. Fuska, P. Nemeč, and I. Kuhr, *Tetrahedron Lett.*, 1347 (1973).
- (3) E. J. Corey and K. C. Nicolaou, *J. Am. Chem. Soc.*, **96**, 5614 (1974).
- (4) E. J. Corey, K. C. Nicolaou, and L. S. Melvin, Jr., *ibid.*, **97**, 653, 654 (1975).
- (5) H. Plieninger, L. Arnold, and W. Hoffmann, *Chem. Ber.*, **98**, 1761 (1965).
- (6) This involved quenching at -78° with methanol, washing with aqueous sodium potassium tartrate solution, and filtration through silica gel in ether—methylene chloride.
- (7) Satisfactory infrared, proton magnetic resonance, and mass spectral data were obtained for all synthetic intermediates.
- (8) Prepared from methallyl Grignard reagent and anhydrous cadmium bromide.
- (9) Added to the reaction mixture to prevent destruction of the dimethyl ketal unit by neutralization of any acidic material in the reaction mixture.
- (10) The formation of this *cis*–*trans* mixture is the expected consequence of using racemic hydroxy acid VII. Obviously, application of the cyclization process starting with the proper optically active form of VII would lead only to the vermiculine (*cis*) series.
- (11) We are indebted to Dr. J. Fuska for a sample of vermiculine.
- (12) The ¹H NMR spectra recorded by us for *both* authentic and synthetic

vermiculine lacked a previously reported² multiplet at δ 1.65 but otherwise agreed with the earlier² account. The mass spectra obtained by us also showed the expected molecular ion at m/e 392 (previously reported² to be absent). The infrared spectra of natural and racemic vermiculine in KBr pellet differ markedly.

- (13) For a synthesis using differing methodology of a simpler, related cyclic diester (pyrenophorin), see E. W. Colvin, T. A. Purcell, and R. A. Raphael, *J. Chem. Soc., Chem. Commun.*, 1031 (1972).
 (14) We are indebted to the National Institutes of Health for a grant in support of this research.

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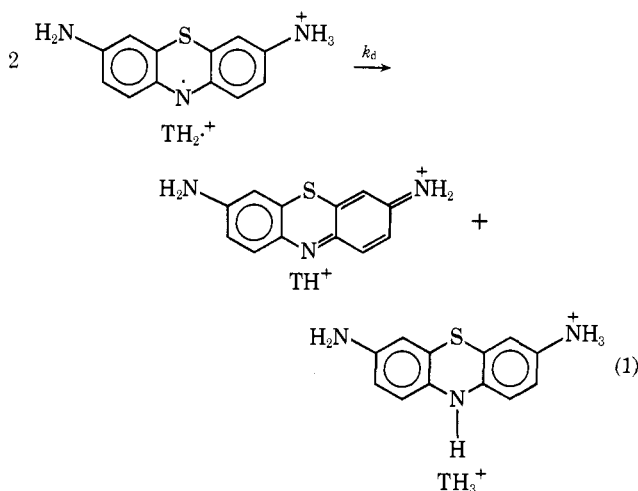
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Solvent Effects on the Electron-Transfer Disproportionation Rate Constant of Semithionine Radical Cation

Sir:

The radical cation semithionine, $\text{TH}_2^{\cdot+}$, undergoes rapid disproportionation to thionine, TH^+ , and leucothionine, TH_3^+ , in acidic aqueous solution (eq 1).¹⁻⁸ In 0.05 *M* aque-



ous sulfuric acid⁴ or 0.01–0.1 *M* aqueous trifluoromethylsulfonic acid (HTFMS) at 25°, $k_d = 2.4 \times 10^9 \text{ M}^{-1} \text{ sec}^{-1}$.

We have found that k_d is dramatically lower, in some cases by as much as a factor of 10^3 , in several aqueous organic solvent mixtures. Furthermore, in a wide variety of solvent mixtures, there is a fairly good linear relationship between $\log k_d$ and an empirical measure of solvent polarity, Kosower's *Z* parameter^{10,11} (Figure 1). Such a quantitative correlation of the specific rate of disproportionation of a charged radical with the *Z* parameter has not been previously reported.¹²

The linear variation of $\log k_d$ with solvent *Z* value can reasonably be expected if the rate-determining step in the disproportionation of $\text{TH}_2^{\cdot+}$ is electron transfer followed by a proton transfer (Scheme I) rather than H atom transfer.¹³⁻¹⁵ The partial electron-transfer characteristic of the difference between the reactants and the transition state in

Scheme I

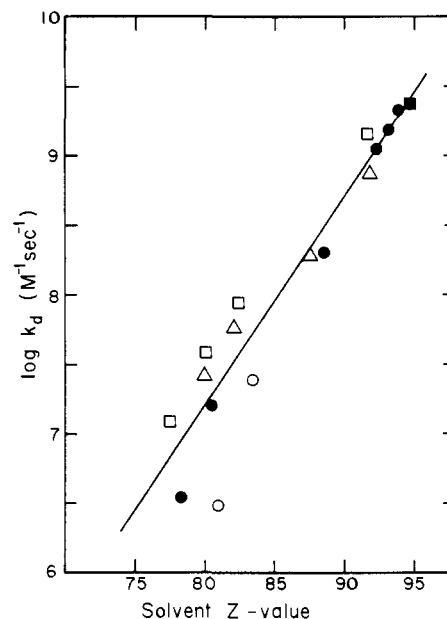
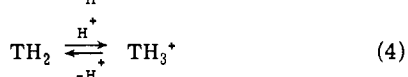
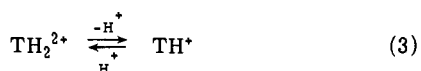
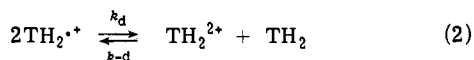
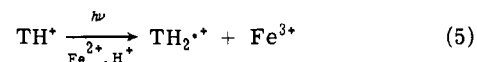


Figure 1. Effect of solvent on the rate constant for disproportionation of semithionine, k_d . (●) Aqueous *N,N*-dimethylacetamide (DMA); % v/v DMA in order of decreasing *Z* value: 10, 18, 25, 50, 75, 84%. (□) Aqueous 1,2-dimethoxyethane (DME); % v/v DME in order of decreasing *Z* value: 25, 50, 75, 95%. (Δ) Aqueous acetonitrile (AN); % v/v AN in order of decreasing *Z* value: 25, 50, 75, 92%. (○) Aqueous ethanol; % v/v ethanol in order of decreasing *Z* value: 75, 95%. (■) Water.

reaction 2 is analogous to the partial electron transfer which characterizes the difference between the ground and excited states of 4-carbomethoxy-1-ethylpyridinium iodide (CEPI), the transition which defines the solvent *Z* value.^{10,16} The linear correlation of $\log k_d$ with *Z* value also suggests that there is negligible change in the orientation of the solvent around the reactant molecules in going from the separated ions to the transition state of step 2, a condition which must be true in the transition from the ground to excited state of CEPI.

It should be noted that the variation in k_d is not related to such bulk solvent parameters as dielectric constant or viscosity. For example, in both 98% v/v *N*-methylpropionamide (MPA) ($\epsilon_{\text{MPA}}(30^\circ) = 164$, $\mu_{\text{MPA}}(25^\circ) = 4.568 \text{ cP}$)¹⁷ and in 92% v/v acetonitrile (AN) ($\epsilon_{\text{AN}}(25^\circ) = 37.5$, $\mu_{\text{AN}}(25^\circ) = 0.304 \text{ cP}$),¹⁴ k_d is much lower than in water ($\epsilon_{\text{water}}(25^\circ) = 78.54$, $\mu_{\text{water}}(25^\circ) = 0.89 \text{ cP}$).¹⁴ The measured *Z* value for 98% v/v MPA is ≈ 78 and $k_d < 2 \times 10^6 \text{ M}^{-1} \text{ sec}^{-1}$. Obviously k_d is influenced by specific solvent-solute interactions rather than by bulk solvent characteristics.

In the present experiments, $\text{TH}_2^{\cdot+}$ was generated according to reaction 5 by flash excitation of solutions containing



$2 \times 10^{-6} \text{ M}$ TH^+ , 0.03 *M* $\text{Fe}(\text{TFMS})_2$, and 0.01 *M* HTFMS. The temperature was maintained at $25 \pm 1^\circ$. The disappearance of $\text{TH}_2^{\cdot+}$ or the reappearance of TH^+ following flash excitation was followed by monitoring the absorbance at 730 and 580 nm, respectively. Where possible, *Z* values for the solvent mixtures in Figure 1 were determined by measuring the absorption spectrum of CEPI in those solvents. Using CEPI recrystallized twice from cold acetone, we obtained excellent agreement with the published *Z* values for ethanol-water mixtures.¹⁰ Since it has been shown that the presence of ions can markedly increase the *Z* value of some solvents,¹⁸ 0.1 *M* NaTFMS was added