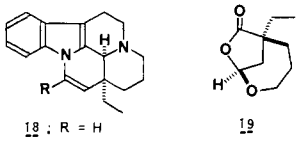
8a [mp 155–156 °C (AcOEt-MeOH); $[\alpha]^{22}_D$ – 70.4° (*c* 0.25, MeOH) [lit.[4m] mp 157–158 °C; $[\alpha]_D$ –62.37°]] and **8b** [mp 194.5–195.5 °C (AcOEt); $[\alpha]^{22}_D$ + 63.3° (*c* 0.07, MeOH) [lit.[4l] mp 193–194 °C; $[\alpha]_D$ + 61.14°]].

According to Kutney's procedure,[4c] quarternary ammonium salt **9** obtained on mesylation of a mixture of **8a** and **8b** was reduced with Na–EtOH in liquid ammonia to give crude (+)-quebrachamine (**1**). A single recrystallization from MeOH yielded optically pure (+)-quebrachamine [mp 144–146 °C; $[\alpha]^{22}_D$ + 117° (*c* 0.18, $CHCl_3$) [lit.[8] mp 147–149 °C; $[\alpha]_D$ + 111°]] in 53% overall yield from the lactam **7**. This revealed the absolute stereochemistry of **6**[7] to be *S*.

Hemiacetal **10** was obtained when reductive denitration of **6** with $TiCl_3$ was conducted in dimethoxyethane. Treatment of **10** with $NaBH_4$ followed by refluxing in aqueous 9% HCl afforded the lactone alcohol **11** in 75% overall yield from **6** (Scheme II). Conversion of **11** into the acetal **5** was accomplished in 76% overall yield through three steps involving the Jones oxidation and partial reduction with diisobutylaluminum hydride (DIBAH), followed by treatment with *p*-toluenesulfonic acid in methanol. Condensation of **5** with tryptamine proceeded in acetic acid to afford a 1:1 mixture of tetracyclic lactams **12a** and **12b** in 84% overall yield from **5** after hydrolysis. Enantiomeric enrichment of **12a** and **12b** was carried out after separation with short-path column chromatography on silica gel and gave optically pure lactams **12a** [mp 263–265 °C dec (aqueous MeOH); $[\alpha]^{22}_D$ –195.5° (*c* 0.16, MeOH)] and **12b** [mp 107–108.5 °C (aqueous MeOH); $[\alpha]^{22}_D$ +88.3° (*c* 0.13, MeOH)]. The Sarett oxidation of the optically pure lactam alcohol **12a** afforded dilactam **13** in 53% yield. (–)-Eburnamonine (**3**) [mp 171–172 °C (MeOH); $[\alpha]^{22}_D$ –88° (*c* 0.09, $CHCl_3$) [lit.[9] mp 173–174 °C; $[\alpha]_D$ –85°]] was obtained in 74% yield from **13** through reduction with $LiAlH_4$ followed by the Sarett oxidation.[10] This transformation confirmed the α-configuration of H(3) in **12a**. Since **12a** and **12b** were shown to establish an equilibrium in the approximate ratio of 1:1 in boron trifluoride–etherate at 35–40 °C after 10 h, the lactam **12a** necessary for the synthesis of (–)-eburnamonine (**3**) could be obtained from **12b**.

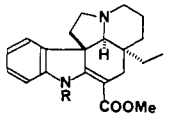
The behavior of **12a** against protic acids is totally different from boron trifluoride–etherate.[11] Thus, **12a** was converted into **14** in triflic acid at 100–110 °C for 45 min in 60% yield along with the eburnamine-type lactams **15a** (20%) and **15b** (12%). Reduction of **14** with $LiAlH_4$ afforded (–)-aspidospermidine (**2**), which was characterized as acetate **16** (81% from **14**) [$[\alpha]^{22}_D$ + 14.1° (*c* 0.31, $CHCl_3$) [lit.[12] $[\alpha]_D$ –15°]].

Recently, (–)-eburnamonine (**3**), (+)-eburnamine (**17**), and (–)-eburnamenine (**18**) were synthesized via the optically active bicyclic acetal **19** as a key intermediate. The latter was prepared

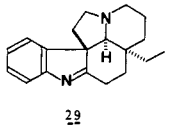


18 ; R = H
27 ; R = COOMe

19



24 ; R = H
25 ; R = Me



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in more than 10 steps and resulted in a 13% overall yield from L-glutaric acid.[6v] We prepared **19** [mp 89–90 °C (Et_2O); $[\alpha]^{22}_D$ + 5.4° (*c* 1.47, CH_2Cl_2) [lit.[6v] mp 82–85 °C, $[\alpha]_D$ + 6.7°]] from **6** in 74% yield with $TiCl_3$ in DME followed by treatment with *p*-toluenesulfonic acid in benzene. This completed an extremely short synthesis of these alkaloids in a formal sense. Since the quarternary salt **9** has been transformed into vincadine (**20**),[13] *epi*-vincadine (**21**),[13] vincaminoreine (**22**),[14] vincaminorine (**23**),[13] vincadifformine (**24**),[13] minovine (**25**),[13] vincamine (**26**),[15] and apovincamine (**27**),[16] the synthesis of optically active **9** constitutes the total syntheses of those alkaloids in optically active form though in a formal sense. Formal total syntheses of optically active isoeburnamine (**28**) and 1,2-dehydroaspidospermidine (**29**) could also be done, because these alkaloids had been derived from dilactam **13**[6a] and quebrachamine (**1**),[17] respectively.

Acknowledgment. We are grateful to Professor Seiichi Takano (Tohoku University, Japan) for providing us with ^{1}H NMR and IR spectra of (±)-quebrachamine and the authentic sample of optically active **19**. We are also grateful to Professor James P. Kutney (University of British Columbia, Canada) for sending us ^{1}H NMR and IR spectra of **8a** and **8b**.

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Assistance of Protodemercuration by Bis-Thiol Ligation and Nucleophilic Catalysis. A Model Study Which Relates to the Organomercurial Lyase Reaction

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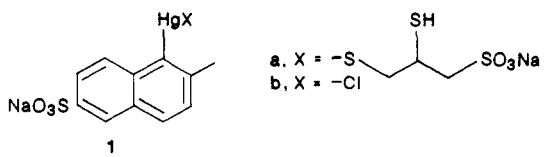
The first step in the microbial detoxification of organomercurial salts is the protonolytic cleavage of the carbon–mercury bond.[1] Organomercurial lyase enzymes that catalyze the protodemercuration of alkyl, aryl, allyl, and vinyl–mercury salts have been isolated from *Escherichia coli* and from *Pseudomonas*.[2-4] Neither enzyme possesses a cofactor. At least 2 × excess of thiol over substrate is required for activity. These enzymes show optimal activity at remarkably low [H^+]. The *E. coli* enzyme[2,3] shows optimal activity at pH 10 and the *Pseudomonas* enzyme[4] at pH 7. Aspects of the enzymatic reaction must, therefore, increase the susceptibility of the C–Hg bond to protonolysis. We establish in this preliminary report a plausible means by which the susceptibility of the C–Hg bond is enhanced in the organomercurial lyase reaction.

The water-soluble **1b** was obtained in >95% purity (^{1}H NMR, ^{13}CNMR, elemental analysis) by reacting sodium 2-methylnaphthalene 6-sulfonate (1 mM) with mercuric nitrate (1 mM)



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at 85 °C in 10 mL of 0.57 M HClO4 followed by reversed phase

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Table I. Constants Employed for the Fitting of Eq 3 to the Experimental Points of Figure 1b

buffer system	k_1	k_{-1}/k_2	K_a
formate	3.84×10^{-4}	6.06×10^{-6}	2.51×10^{-4}
acetate	1.17×10^{-3}	2.38×10^{-6}	2.45×10^{-5}
phosphate	1.58×10^{-2}	5.22×10^{-6}	2.51×10^{-7}

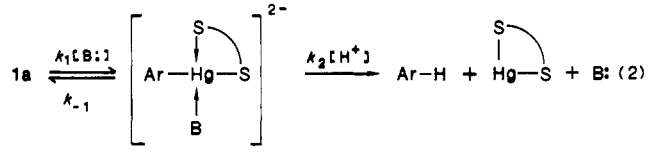
TLC separation and crystallization from ~0.5 M NaCl solution.

Since 2 equiv of mercaptan are required for enzymic protodemercuration, we have employed as substrate the dimercaptopropane sulfonate ligated organomercurial **1a**, which was generated in the stock solutions in situ by the addition of 100 equiv of dithiol. Pseudo-first-order rate constants (k_{obsd}) for protonolysis of **1a** in aqueous solution (30.4 °C, N_2 atmosphere) in the presence of excess dithiol and buffer were determined spectrophotometrically at constant pH (±0.03). The spectra of spent reaction solutions matched (at all pH's) spectra of solutions containing the requisite concentrations of the products Hg^{2+}, dithiol, and 2-methylnaphthalene 6-sulfonate.

At pH 6.6 with 0.3 M phosphate buffer k_{obsd} for protonolysis of **1** is 10^{-7} s^{-1} (by initial rate method). In the presence of 100 equiv of the dithiol k_{obsd} is 1×10^{-4} s^{-1}. Most (90%) of this rate acceleration is observed on adding only 2 equiv of dithiol ($k_{obsd} = 9 \times 10^{-5}$ s^{-1}). Ligation of **1** is therefore complete under the reaction conditions, and the substrate is **1a**. At 10^{-2} M $HSCH_2CH_2SO_3^-Na^+$ there is seen only 0.5% of the rate acceleration observed with the dithiol at 2×10^{-4} M. Linear plots (Figure 1a) of k_{obsd} vs total buffer concentration (B_T) provide as slopes apparent second-order rate constants for buffer catalysis (k_{BT}) and apparent first-order rate constants for the buffer independent reaction (k_I) as intercepts. Plots of log k_BT vs pH describe "bell-shaped" curves for each buffer system (Figure 1b). The pH dependence of k_{BT} can be fitted by eq 1, where K_a is the

$$k_{BT} = \frac{k_1 K_a a_H}{(K_2 K_a + (K_2 + K_a)a_H + a_H^2)} \quad (1)$$

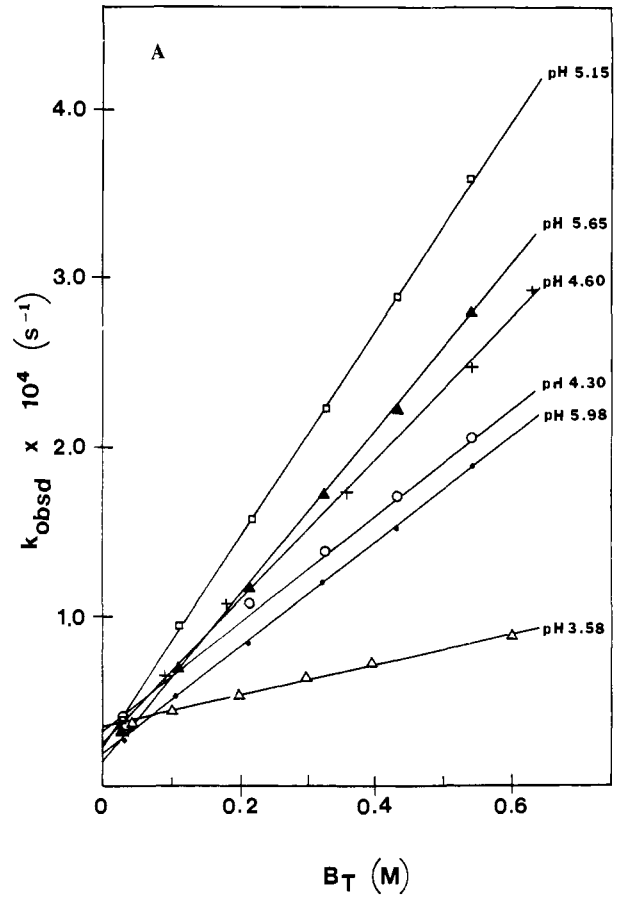
dissociation constant for the buffer acid. Inspection of eq 1 shows that k_{BT} is dependent upon buffer base concentration at lower pH's ($K_2/a_H \ll 1$) and upon buffer acid at higher pH's ($K_2/a_H \gg 1$). A change from apparent buffer base to buffer acid catalysis with increase in pH finds explanation in a sequential two-step mechanism with a pH-dependent change in the rate-determining step. The mechanism of eq 2 is kinetically competent. An assumption



of steady-state in the intermediate species provides eq 3 which has the same mathematical form as eq 1. The curves used to fit the experimental points of Figure 1b were computer-generaed from eq 3 with use of the constants of Table I.

$$k_{BT} = \frac{k_1 K_a a_H}{((k_{-1}/k_2)K_a + (k_{-1}/k_2 + K_a)a_H + a_H^2} \quad (3)$$

Our proposed mechanism has precedence in the I^- assistance of protodemercuration of allylmercuric iodide in $HClO_4$ solutions.[5,6] Assistance by less nucleophilic anions (Cl^-, RCO_2^-) was considered improbable.[7-10] The present study establishes car-



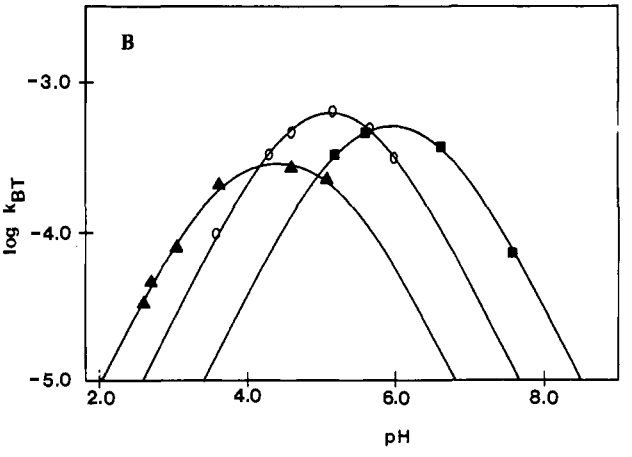


Figure 1. (A) Linear buffer dilution plots for acetate buffers. Pseudo-first-order rate constants (k_{obsd}) for the protodemercuration of **1a** were obtained by varying the buffer concentrations at constant pH (±0.03) values at 30 °C (±0.01 °C). Six values of k_{obsd} were determined for each buffer at a given pH under the pseudo-first-order condition of buffer concentration in great excess over substrate. Typically, the reaction mixtures were 0.6–0.018 M in total buffer, 10^{-2} M in dithiol, and 10^{-4} M in **1**. Ionic strength was maintained at 1 with K_2SO_4. Apparent second-order rate constants for buffer catalysis (k_{BT}) are obtained as slopes and apparent first-order rate constants for the buffer independent reactions (k_I) as intercepts. Values of k_I have only a small pH dependence ($\Delta \log k_I/pH = 0.16$) but are dependent on the concentration of dithiol. Values of k_{BT} are independent of dithiol concentration at >10-fold excess over **1** but are pH dependent (Figure 1b). (B) Plots of log k_{BT} vs pH in formate (▲), acetate (○), and phosphate (■) buffers. The values of k_{BT} (M^{-1} s^{-1}) were obtained from the slopes of buffer dilution plots, and the curves were generated from eq 3 by using the constants of Table I. Values of K_a were determined by half neutralization under experimental conditions.

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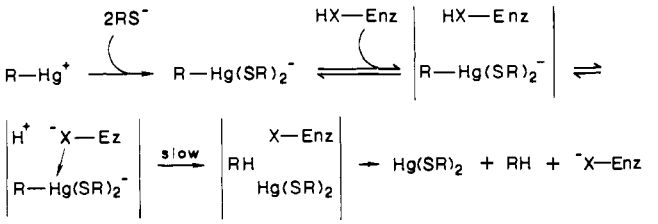
boxylate bases to be effective nucleophilic catalysts in protodemercuration when the mercury is bis-thiol ligated. Comparison of k_1 values shows HPO_4^{2-} is even better, while imidazole is found to be a much less effective catalyst.

Begley, Walts, and Walsh[2] have shown that the *E. coli* lyase does not possess an available sulfhydryl substituent at the active site (lack of reaction with ICH_2CONH_2). Bis ligation by thiol has been shown to be required to dissociate the Hg^{2+} product from the enzyme.[2] This study suggests that bis-thiol ligation is also required to create the actual substrate (eq 4). The mechanism



(4)

of eq 4 would predict activity to increase with pH until the pK_a of the functional group HX– is reached. Such behavior apparently pertains to the *E. coli* lyase.[2] If the proton dissociated from HX– is diffusable to solvent, a "bell-shaped" pH profile would be obtained as is apparently the case with the *Pseudomonas* enzyme and is seen in the present study.

Acknowledgment. This work was supported by a grant from the National Science Foundation.

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Aromatic Hydrocarbon Dianions: Super Bases. Anthracene Anion Radical and Dianion Conjugate Acid pK_a Values

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Although numerous mechanistic and product studies of the protonation reactions of anion radicals have been carried out,[1] information on the thermodynamic basicity of these reactive intermediates is still not available. Qualitatively, it is well known that the corresponding dianions react much more readily with proton donors.[2] Recently, detailed kinetic studies have shown that the mechanisms of these fundamentally important reactions, although complex, can be determined quantitatively.[3] Our goal to achieve a more complete understanding of these reactions led to the development of a method to evaluate pK_a values for the conjugate acids of anion radicals and the corresponding dianions.

We now report a simple method to determine (pK(DA) – pK(AR)), the difference in pK_a of the conjugate acids of the dianion (DA) and the anion radical (AR), involving the measurement of electrode potentials without the necessity to rely on theoretical or experimental data for any other equilibria. The experimental data necessary for the thermodynamic cycle[4] (Scheme I) consists of the reversible electrode potentials for the reduction of the anion radical (eq 1) and that for the oxidation of the carbanion (eq 2). The equilibrium constants for the reactions completing the thermodynamic cycle (eq 3 and 4) correspond to the relative values that we wish to determine.

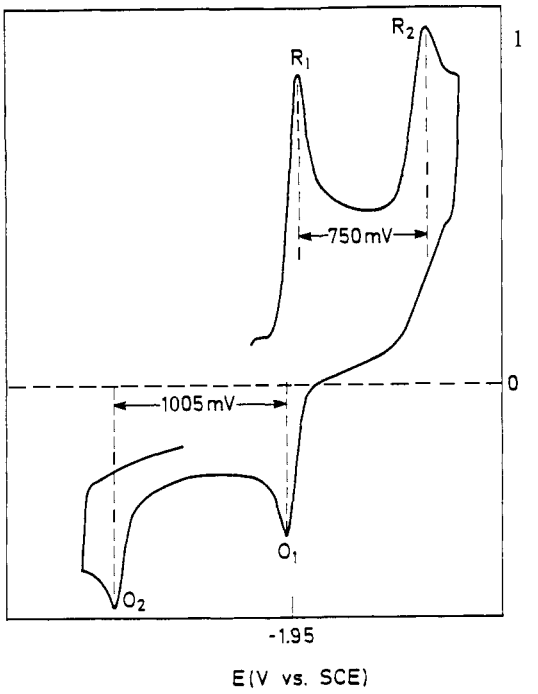

Figure 1. Cyclic voltammogram for the reduction of anthracene (1 mM) in DMSO/Bu_4NBF_4 (0.1 M) at 100 V/s and 20 °C.

Scheme I

	$\Delta G°$	
$A^{\cdot-} + e^- \rightleftarrows A^{2-}$	$-FE_1°$	(1)
$AH^- \rightleftarrows AH^{\cdot} + e^-$	$FE_2°$	(2)
$A^{2-} + H^+ \rightleftarrows AH^-$	$RT \ln K$(DA)	(3)
$AH^{\cdot} \rightleftarrows A^{\cdot-} + H^+$	$-RT \ln K$(AR)	(4)

$$pK(DA) - pK(AR) = F(E_2° - E_1°)/2.303RT \quad (5)$$

Scheme II

	$\Delta G°$	
$A + H_2 \rightleftarrows AH_2$	$-RT \ln K_6$	(6)
$AH_2 \rightleftarrows AH^- + H^+$	$-RT \ln K(AH_2)$	(7)
$A^{\cdot-} \rightleftarrows A + e^-$	$FE_8°$	(8)
$AH^- \rightleftarrows AH^{\cdot} + e^-$	$FE_9°$	(9)
$2H^+ + 2e^- \rightleftarrows H_2$	0	(10)
$AH^{\cdot} \rightleftarrows A^{\cdot-} + H^+$	$-RT \ln K$(AR)	(11)

$$pK(AR) = -pK(AH_2) - pK(6) - F(E_8° + E_9°)/2.303RT \quad (12)$$

Table I. Thermodynamic and Electrode Potential Data for the Determination of pK(AR) of Anthracene Anion Radical

reaction	data	remarks
$AH_2 \rightleftarrows AH^- + H^+$	$pK(AH_2) = 27$	*a*
$AH^- \rightleftarrows AH^{\cdot} + e^-$	$-E_2 = 730$ mV	*b*
$A^{\cdot-} \rightleftarrows A + e^-$	$-E_8 = 1730$ mV	*b*
$A + H_2 \rightleftarrows AH_2$	$\Delta G° = -11$ kcal/mol	*c*
$AH^{\cdot} \rightleftarrows A^{\cdot-} + H^+$	$pK(AR) = 23$	

[a] The difference in pK_a for triphenylmethane and 9,10-dihydroanthracene is 1 pK_a unit in cyclohexylamine and in dimethoxyethane and is assumed to be the same in DMSO. The pK_a of triphenylmethane is 28 in DMSO.[15] [b] The reversible electrode potential vs the standard hydrogen electrode. [c] From data in ref 16.

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(4) Thermodynamic cycles using electrode potential data give access to thermodynamic quantities such as pK_a values for hydrocarbons[5] and pK_a values for cation radicals.[6,7]

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