with the DNMR program[29] run on the CDC 6600 computer facilities of the University of Bologna.

The superposition of the experimental and simulated spectra in the temperatures range where the line shape was more sensitive to the value of the rate constants (k) afforded k values (in s^{-1}) with errors that, at worst, did not exceed ±10%. This gives an uncertainty of the $\Delta G^{\ddagger}$ values not larger than ±0.07 kcal mol^{-1}. Within this accuracy the $\Delta G^{\ddagger}$ values measured at various temperatures were found to be equal and therefore an averaged value is reported in Table I for each compound. The uncertainty of the measurement of the temperatures (±2 °C) introduced a second source of error that corresponds to ±0.08 kcal mol^{-1}; the combination of the two errors indicates that the $\Delta G^{\ddagger}$ values should be accurate within ±0.15 kcal mol^{-1}.

The ESR spectra of **1a** were recorded with a Varian E-4 spectrometer equipped with a standard cooling system. The radical was generated by irradiating (500-W high-pressure Hg lamp) a vacuum-degassed solution of **1** in cyclopropane: as expected[19,20] addition of hydrogen-donor substances greatly intensified the signal. In order to obtain the radical anion of **1a**, a sodium mirror was deposited under vacuum into one arm of the sample and a small amount of methanol was added to the cyclopropane solution of **1** in the second arm: when the vacuum-sealed sample was tipped an alkaline environment (sodium methylate) was produced, and UV irradiation thus yielded the radical $ArPh\dot{C}O^-$.

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Registry No. 1, 33574-11-7; **1a**, 99686-14-3; **2**, 99686-11-0; **3**, 99686-12-1; **4**, 99686-13-2; $(Pr\text{-}i)_3C_6H_2Br$, 21524-34-5; PhCN, 100-47-0; $(Pr\text{-}i)_3C_6H_2C(Ph)=NMgBr$, 99686-15-4; 2-[2,4,6-triisopropylphenyl]-2,3,3-triphenylthiirane, 99686-16-5; diphenyldiazomethane, 883-40-9.

Studies of Extended Quinone Methides. The Hydrolysis Mechanism of 1-Methyl-2-(bromomethyl)-4,7-dihydroxybenzimidazole

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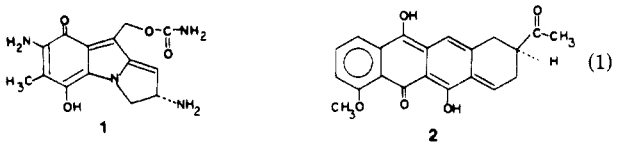
The hydrolysis of 1-methyl-2-(bromomethyl)-4,7-dihydroxybenzimidazole (**3**) was studied in anaerobic aqueous buffer to assess quinone methide formation and reactivity. Kinetic results, obtained over the pH range of 6.0–8.5 at 30.0 ± 0.2 °C, are consistent with rate-determining formation of the extended quinone methide **4**. The fate of **4** pertains to nucleophilic attack by added chloride and 2-hydroxyethyl mercaptide at the 2α-position to provide substituted hydroquinones. In a competing reaction, electrophilic trapping of the anionic form of **4** (4^-) occurs by 2α-protonation to provide 1,2-dimethylbenzimidazole-4,7-dione (**7**). Benzaldehyde was not observed to act as an electrophilic trap for 4^-, however. The following conclusions are drawn from these findings: **4** is an effective trap for nucleophiles, and 4^- is a poor trap for electrophiles. The facility of nucleophilic trapping is thought to pertain to the presence of nitrogen substitutions. These serve to make **4** electron deficient and thus promote nucleophilic trapping. Electrophilic trapping, on the other hand, will result in the formation of a high potential quinone.

It has been observed that many naturally occurring quinones are functionalized with a leaving group so as to permit quinone methide formation upon reduction.[1] Thus the reduction of mitomycin C and daunomycin would, upon 1,6-elimination of the leaving group, afford quinone methides **1** and **2** respectively (eq 1). As illustrated for



(1)

the quinone methide species in eq 2, the fate of these reactive species could pertain to both nucleophilic and electrophilic trapping. Nucleophilic trapping by a quinone methide may be responsible for the alkylation reactions exhibited by some naturally occurring quinones upon reduction.[2-4] Thus far the formation of **2** and its reactions with nucleophiles and electrophiles have been documented.[5,6] Yet to be studied are the myriad quinone systems which could form a quinone methide upon reduction. Nearly 200 naturally occurring quinones,[1] as well as many synthetic antitumor quinones,[7] fall into this category. Queries are thus posed concerning the formation of quinone methide intermediates from these structurally diverse systems and the relationship between structure and the relative facilities of nucleophilic and electrophilic trapping. Efforts in this laboratory have been directed toward studying quinone methide formation and reactivity

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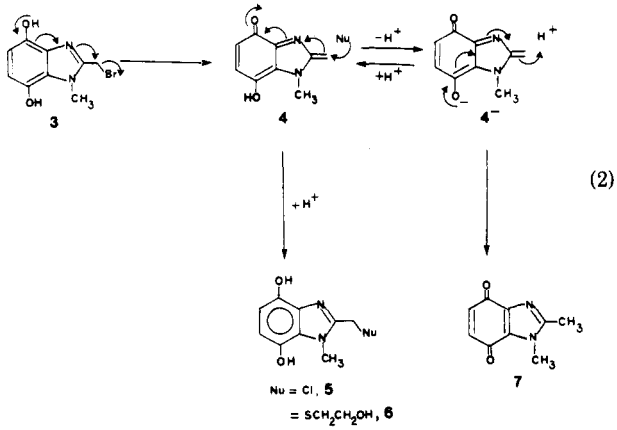
employing suitably functionalized model hydroquinones. The strategy is to synthesize and isolate hydroquinone systems that possess a leaving group placed so as to permit quinone methide formation. Kinetic and product studies on these systems in anaerobic buffer may then provide useful insights into the chemistry of these species. With this strategy, rather than generating the hydroquinone species in situ from the quinone, the complicating factors of rate-determining reduction and quinone–hydroquinone reactions are avoided.

Described herein is the hydrolysis of 1-methyl-2-(bromomethyl)-4,7-dihydroxybenzimidazole (**3**) in anaerobic aqueous buffer. As depicted in eq 2, the extended quinone methide **4** arises from **3** by the elimination of HBr and is subject to both electrophilic and nucleophilic attack. It



(2)

is concluded from this study that the presence of nitrogen atoms in **4** favor nucleophilic over electrophilic attack. Quinone methide **2**, on the other hand, does not possess nitrogen substitutions and thus is more susceptible to electrophilic attack.[5,6]

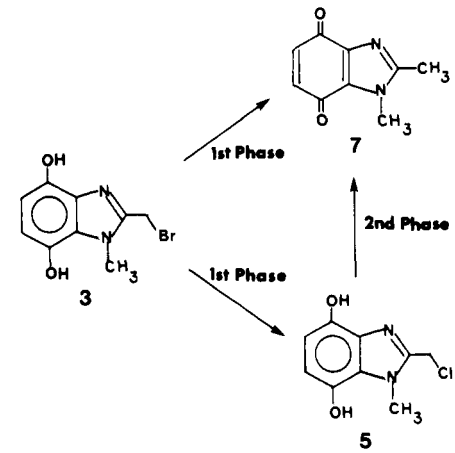
Results

The hydrolysis of **3** was studied under strictly anaerobic conditions in aqueous buffer (μ = 1.0, KCl) over the pH range of 6.0–8.5 at 30.0 ± 0.2 °C employing [**3**] + [**3**$^-$] = 5×10^{-5} M. Under the reaction conditions employed, **3** exists as a mixture of the free base and the 4-hydroxyl anion **3**$^-$ (vide infra). Likewise, the postulated hydrolysis intermediates could exist in more than one form in aqueous buffer. In the discussions which follow, the total concentrations of species are designated as such: $\mathbf{3}_T$ (=**3** + **3**$^-$).

The spectra of all completed reaction mixtures indicated that nearly quantitative (>90%) conversion of $\mathbf{3}_T$ to **7** had taken place. To verify that **7** was the final product, a preparative study of the hydrolysis of $\mathbf{3}_T$ was carried out at 2.95 mM in anaerobic pH 7.00 buffer (see Experimental Section). This reaction provided only a 25% isolated yield of **7** in addition to a trace amount of $\mathbf{3}_{ox}$ and a large amount of polymer. The presence of the latter two likely result from the high concentrations of $\mathbf{3}_T$ employed in the preparative study. Thus, the redox reaction between **7** and unreacted **3** will give rise to $\mathbf{3}_{ox}$ as shown in eq 3 without consideration of the ionic species present. By repetitive

(3)

scanning a reaction mixture initially consisting of 5×10^{-5} M $\mathbf{3}_T$ in anaerobic 0.2 M pH 7.00 phosphate buffer (μ = 1.0, KCl) at scan times of 300 s, a tight isobestic point at 244 nm can be observed (repetitive scan not shown). Thus, $\mathbf{3}_T$ is converted to **7** without any apparent buildup of intermediates. It was noted, however, that the buildup of **7** (λ_{max} = 400 nm) is associated with fast and slow bursts. This observation requires the formation of an intermediate which is slowly converted to **7**. To explain these observations the hydrolysis of $\mathbf{3}_T$ is proposed to occur in two phases. During the first phase $\mathbf{3}_T$ hydrolyses to **7** and an intermediate; during the second phase this intermediate is slowly converted to **7**. On the basis of kinetic studies to be described, the identity of this intermediate is 1-methyl-2-(chloromethyl)-4,7-dihydroxybenzimidazole $\mathbf{5}_T$ (=**5** + **5**$^-$). Inspection of UV–vis spectra found in the Experimental Section reveals that $\mathbf{5}_T$ possesses much lower extinction coefficients than **7** in neutral aqueous solutions which would account for the lack of obvious intermediate buildup in the repetitive scans. The sequence of product formation during the hydrolysis of $\mathbf{3}_T$ is summarized in eq 4 without consideration of the ionic species present.



(4)

Absorbance (400 nm) vs. time (s) plots were computer fit to the two consecutive first-order equation in eq 5,

$$OD_{400} = A \exp(-k_{obsd}t) + B \exp(-k_{obsd}'t) + C \quad (5)$$

where k_{obsd} and k_{obsd}' are the respective first-order rate constants associated with the first and second phases of **7** formation, A/B is the ratio of [**7**] formed during the first phase to [**7**] formed during the second phase, and **C** is the absorbance of **7** at $t = \infty$ (0.05 M^{-1} cm^{-1} when starting with 5×10^{-5} M $\mathbf{3}_T$). The effect of k_{obsd} and k_{obsd}' on the initial concentration of $\mathbf{3}_T$ was assessed by varying [$\mathbf{3}_T$] from 3×10^{-5} to 1×10^{-4} M. Plots of absorbance (400 nm) vs. time (s) were still two consecutive first order in nature and, upon fitting these data to eq 5, provided k_{obsd} and k_{obsd}' values which were unchanged over the concentration range studied. Thus, the process in eq 3 observed at low dilution does not contribute. To assess the role of buffer species in these reactions, 10-fold dilutions (0.2–0.02 M) of phosphate buffer were carried out at constant ionic strength (μ = 1.0 KCl) over the pH range studied. Changes in buffer concentration were observed to have no effect on k_{obsd}, k_{obsd}', and the A/B values. The value of A/B was observed to be 2.3 throughout the pH range studied.

Plots of log (k_{obsd}) and log (k_{obsd}') vs. pH are found in Figures 1 and 2, respectively. In both plots data were computer fit to eq 6, where k is an apparent first-order rate

$$k_{obsd} \text{ or } k_{obsd}' = \frac{kK_a}{a_H + K_a} \quad (6)$$

constant, K_a is an apparent acid dissociation constant, and a_H is the proton activity as determined with a pH meter. The solid line provided in Figure 1 was computer generated from eq 6 by employing k = 0.22 s^{-1} and pK_a = 8.13. Likewise, the solid line in Figure 2 was computer generated by employing $k = 3.3 \times 10^{-3}$ s^{-1} and pK_a = 7.86. Since $\mathbf{5}_T$

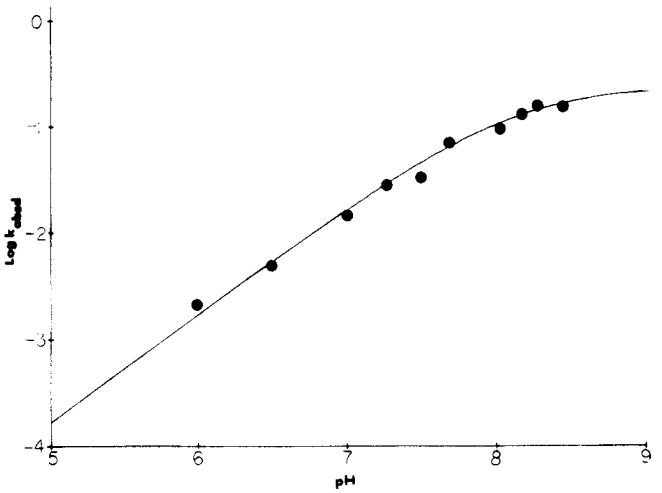


Figure 1. Plot of log k_{obsd} vs. pH for the first phase of 3_T hydrolysis (anaerobic conditions with μ = 1.0, KCl, at 30 °C).

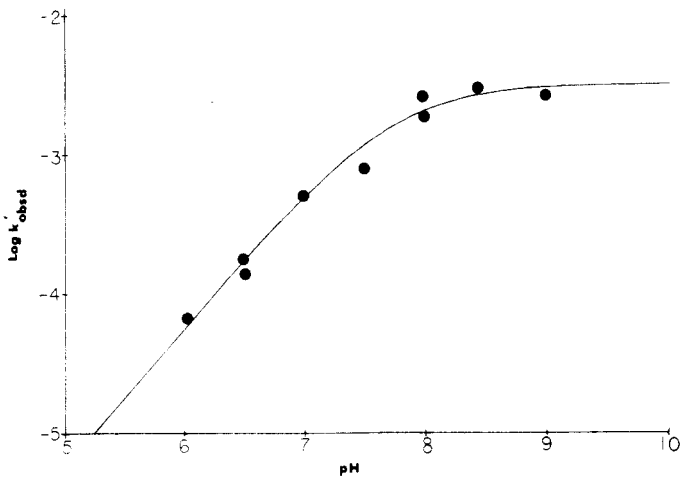
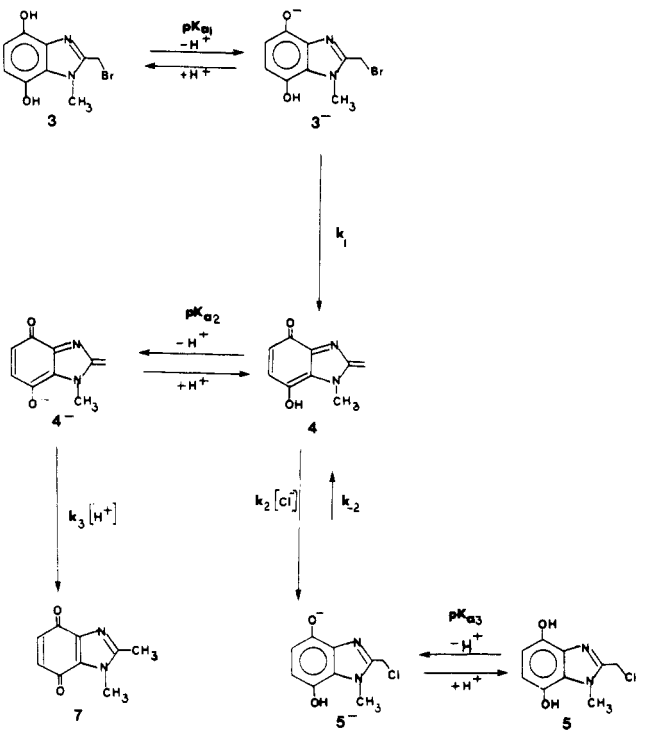


Figure 2. Plot of log k_{obsd}' vs. pH for the second phase of 3_T hydrolysis (anaerobic conditions with μ = 1.0, KCl, at 30 °C).

could not be isolated from reaction mixtures and identified, the kinetic data presented above were employed for the identification of this intermediate. It is proposed that the second phase pertained to $5_T \rightarrow 7$ (loc. cit.). Consistent with this postulate, authentic 5_T at 5×10^{-5} M was quantitatively converted to **7** by a first-order process with first-order rate constants identical with the k_{obsd}' values measured above. The kinetic findings cited above require that the rate-determining steps for $3_T \rightarrow 7 + 5_T$ and for $5_T \rightarrow 7$ occur from an anionic species formed by acid dissociation (apparent pK_a values for **3** and **5** are 8.13 and 7.86, respectively). Significantly, the acid dissociation of the 4-hydroxyl proton from **5** possesses a pK_a value of 8.4 ± 0.3 (see Experimental Section), which approximates the pK_a value obtained kinetically.

A nucleophile trapping study was carried out by employing added 2-mercaptoethanol (RSH) in anaerobic pH 7.00 0.2 M phosphate buffer under the pseudo-first-order conditions of [RSH] = 5×10^{-4} to 5×10^{-3} M $\gg$ [3_T] = 5×10^{-5} M. Under these conditions, the disappearance of 3_T (followed at 240 nm) was simple first order in nature and rate constants were independent of [RSH]. These rate constants were identical with k_{obsd} obtained for the hydrolysis of 3_T in pH 7.00 buffer without added RSH. Spectra of completed reactions indicated that **7** had not formed and a preparative reaction (see Experimental Section) provided a 68% isolated yield of 1-methyl-2-[(2-hydroxyethylthio)methyl]-4,7-dihydroxybenzimidazole as its HCl salt (**6**·HCl). Considering these results and the

Scheme I



kinetic data, it is concluded that a reactive species arises from 3^- in a rate-determining step and that this species is then trapped in a fast step by 2-hydroxyethyl mercaptide (pK_a for RSH is 9.5) as well as by chloride and ketonization.

Discussion

Mechanistic aspects of the hydrolysis of 3_T are discussed in conjunction with Scheme I. 3^- eliminates bromide in a rate-determining step to provide an equilibrium mixture of **4** and 4^- ($=4_T$). Rapid nucleophilic trapping of **4** competes with the 2α-protonation of 4^- to provide a mixture of 5_T and **7**. The slow reversible elimination of chloride from 5^- reforms 4_T, which results in the formation of additional **7**.

In what follows is a detailed discussion of the mechanism of the first phase of hydrolysis. The pH–rate profile found in Figure 1 requires that the rate-determining step for this phase occurs from 3^-. That the kinetic pK_a value of 8.13 pertains to 4-hydroxyl group ionization was made after considering the following pK_a measurements (see Experimental Section). The acid dissociations $5 \rightleftharpoons 5^- + H^+$ and $8 \rightleftharpoons 8^- + H^+$ were measured spectrophotometrically as pK_a = 8.4 ± 0.3 and pK_a = 9.75 ± 0.10, respectively. Ionization of the 4-hydroxyl group results in an anion which could delocalize into the fused imidazo ring. Thus, the pK_a value for this ionization should be quite sensitive to the electron-withdrawing nature of the 2α-substituent. From the measurements provided it is seen that the 2α-bromo and -chloro derivatives possess nearly the same pK_a value reflecting the similar σ_m values for these substituents. The unsubstituted derivative (**8**), on the other hand, possesses a much higher pK_a value reflecting less inductive stabilization of the anion. Calculation of the rate law for the first phase of hydrolysis was carried out by employing material balance in 3_T (eq 7). The contribution of the N(3)-

$$K_{obsd} = \frac{k_1 K_{a1}}{a_H + K_{a1}} \qquad (7)$$

protonated species ($3 \cdot H^+$), pK_a = 3.99, need not be con-

sidered in the pH range studied. This rate law possesses the same form as the empirical rate law found in eq 6. Thus, 3^- eliminates bromide to form the reactive species at $k_1 = 0.22\ s^{-1}$.

Nucleophilic trapping and ketonization both follow the rate law in eq 6. The assessment is made that a reactive species able to undergo these reactions is formed in the rate-determining step. The best structure for this intermediate is an extended quinone methide, 4_T. That chloride is directly displacing bromide rather than attacking **4** is not considered. The use of the strong nucleophile 2-hydroxyethyl mercaptide did not result in direct displacement so neither should the weaker nucleophile chloride. Information about the mechanism of ketonization was obtained from the A/B ratio determined from eq 5. The ratio pertains to the relative amounts of **7** formed during the first and second phases or, alternatively, $[7]/[5_T]$ at the conclusion of the first phase. It was observed that this ratio was independent of pH and total buffer concentration. Thus, buffer species are not involved in ketonization and the pH–rate law for ketonization of the quinone methide is the same as nucleophilic attack on this species. The mechanism considered to explain these observations is water-catalyzed ketonization as seen in simple enol systems.[8] Thus, equilibrium formation of 4^- is followed by the protonation at the 2α-position. Kinetically, this is the same as **7** forming from **4**; only a proton is moved to a different location. With the rate constants found in Scheme I, the A/B ratio is expressed as found in eq 8. The

$$2.3 = \frac{A}{B} = \frac{[7]}{[5_T]} = \frac{k_3 K_{a2}}{[Cl]k_2} \qquad (8)$$

ratio in eq 8 does not contain proton activity terms, thus the pH independence of A/B. The concentration of chloride will influence the value of A/B; nearly constant values of $[Cl^-]$ (0.8–1.0 M) are maintained by adjusting the ionic strength to 1.0 with KCl. Measurement of the acid dissociation constant for **4** (K_{a2}) was not possible in this study. Kresge and co-workers have measured the acid dissociation constants of simple enols;[9a,b] for example, the pK_a determined for the enol of acetone is 10.96.[9b] Acid dissociation from **4** to provide the highly conjugated anion (4^-) likely possesses a much lower pK_a value. Without knowing the exact value of K_{a2}, it could be stated that $k_3 > k_2$. In the instance of added 2-hydroxyethyl mercaptide, however, $k_2 \gg k_3$ which results in only **6** as the final product.

The mechanism of the second phase of hydrolysis is now discussed. Formation of additional **7** during this phase of hydrolysis pertains to reversible elimination of chloride from 5^- (Scheme I). Calculation of the rate law for this process was carried out by employing material balance in 5_T and the steady-state approximation for 4_T (eq 9).

$$k_{obsd}' = \frac{\dfrac{k_{-2}K_{a3}}{1 + \dfrac{k_2[Cl]}{k_3 K_{a2}}}}{a_H + K_{a3}} \qquad (9)$$

Equation 9 possesses the same form as eq 6 with the apparent first-order rate constant ($k = 3.3 \times 10^{-3}\ s^{-1}$) represented by a complex mixture of terms. By considering $A/B = 2.3 = k_3 K_{a2}/[Cl]k_2$ (eq 8), the value of k_{-2} is calculated as $4.7 \times 10^{-3}\ s^{-1}$. The relative leaving ability of bromide and chloride in these reactions ($k_1/k_{-2} = 46$) reflects the relative leaving abilities observed in the S_N1 reaction with other systems.[10]

The conclusions are made that **4** acts as an effective trap for nucleophiles and that 4^- acts as a poor trap for electrophiles. Thus the trapping of **4** by 2-hydroxyethyl mercaptide and even chloride competes with 2α-carbon protonation of 4^-. Also suggestive of the poor electrophile trapping ability of 4^- is the lack of any trapping by added benzaldehyde. The quinone methide derived from daunomycin (**2** + anionic form), on the other hand, effectively traps electrophiles (protons and benzaldehyde) but reversibly traps nucleophiles.[5,6] The differences in reactivity between **2** and **4** may pertain to the presence of nitrogen substitutions in the latter. These electronegative substitutions will result in an electron-deficient quinone methide which would favor nucleophilic trapping. Electrophilic trapping of 4^-, on the other hand, will result in the formation of a quinone possessing a high free energy. Indeed, the electrophilic trapping product **7** has been shown to act as an effective oxidizing agent.[11]

The formation of **4** and its nucleophilic trapping reactions are significant to another ongoing project in this laboratory. We wish to design benzimidazole and imidazo[4,5-*g*]quinazoline-based reductive alkylators of purine-utilizing enzymes. Both of these systems have been shown to be purine mimics,[12,13] and their appropriate functionalization could result in redox-sensitive enzyme inhibitors.

Experimental Section

Elemental analyses were performed by MicAnal Laboratories, Tucson, AZ. IR spectra were taken as a thin film on a NaCl disk with a Nicolet MX-1 FT IR spectrophotometer. ^1H NMR spectra were taken on a Bruker WH-90, a Varian XL-100, or a Varian T-60A spectrometer. UV and visible spectra were obtained with a Perkin-Elmer 559 UV–vis spectrophotometer. Mass measurements were carried out in the electron impact mode with a Varian MAT 200 spectrometer. Measurements of pH were made with a Radiometer PHM84 pH meter equipped with a Radiometer GK2401C combination electrode. All kinetics were followed at 30 ± 0.2 °C with a Perkin-Elmer 559 spectrophotometer, a Perkin-Elmer Lambda 3 spectrophotometer, or a Gilford 2000 spectrophotometer. UV–vis spectra and spectrophotometric pK_a values were determined in aerobic aqueous buffers with $\mu = 1.0$ (KCl) at 30 °C; anaerobic conditions were employed when studying the hydroquinones. Kinetic studies were carried out in aqueous phosphate buffers ($\mu = 1.0$, KCl) at 30 °C under an argon atmosphere as previously described.[14]

The preparation of the hydrobromide salt of **3** (**3**·HBr) was carried out in six steps starting with 2-nitro-3,6-dimethoxyaniline (**9**).[15] The presence of the N(1)-methyl group in **3** precludes the loss of bromide by utilizing the N(1)-anion.[16] Trifluoroacetylation of **9** followed by treatment with methyl iodide in KOH/acetone afforded 2-nitro-3,6-dimethoxy-*N*-methylaniline (**10**). Catalytic reduction of **10** to 2-(methylamino)-3,6-dimethoxyaniline (**11**) was followed by ring closure to 1-methyl-2-(hydroxymethyl)-4,7-dimethoxybenzimidazole (**12**) with glycolic acid as described by Phillips.[17] Treatment of **12** with thionyl chloride[18] afforded the 2-chloromethyl derivative (**13**) which was converted to **3**·HBr by treatment with refluxing 48% HBr. The preparation of **5**·HCl

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was carried out by treating 3·HBr with anaerobic 1 M HCl at room temperature. The independent synthesis of 7 was carried out starting with 2-methyl-4,7-dimethoxybenzimidazole 14.[18] Treatment of 14 with methyl iodide in the KOH/acetone afforded 15, which upon treatment with refluxing 48% HBr afforded 1,2-dimethyl-4,7-dihydroxybenzimidazole hydrobromide (8·HBr). The oxidation of 8·HBr to 7 was carried out in water employing $FeCl_3$ as oxidant.

2-Nitro-3,6-dimethoxy-*N*-methylaniline (10). To a solution of 3.2 g (16.1 mmol) of 2-nitro-3,6-dimethoxyaniline (9)[15] in 20 mL of trifluoroacetic acid was added 2.2 mL of trifluoroacetic anhydride. The reaction mixture was stirred at room temperature for 1 h and then poured over cracked ice. Collection of the resulting precipitate by filtration followed by washing with water and drying in vacuo provided 4.8 g (~99%) of the N-trifluoroacetylated derivative of 9 as a yellow-white solid.

The entire amount (16 mmol) of this product was added, along with 2.8 mL (44 mmol) of methyl iodide, to a suspension consisting of 2.5 g (44 mmol) of powdered KOH in 100 mL of acetone. This mixture was refluxed for 6.5 h after which the hot liquor was decanted from the solids. Concentration of this liquor in vacuo afforded a red oil, which was triturated with 50 mL of benzene. Precipitated solids were removed by filtration and discarded. Evaporation of the filtrate to ~5 mL followed by addition of 25 mL of hexane resulted in formation of a red oil, which slowly formed a crystalline mass. The yield of **10** upon filtration and drying was 2.18 g (64%). Recrystallization for analytical purposes was carried out from hexane/ether: ^1H NMR ($CDCl_3$) δ 6.13 and 6.64 (2 H, AB system, J = 8.4 Hz, Ar protons), 3.73 and 3.76 (6 H, 2 s, methoxy protons), 2.76 (3 H, s, *N*-methyl); mp 66–67 °C; IR (thin film) 3410 (N–H stretch), 2938, 1614, 1517, 1451, 1107 cm^{-1}; TLC (100% chloroform on silica gel), R_f 0.25. Anal. Calcd for $C_9H_{12}N_2O_4$: C, 50.94; H, 5.70; N, 13.19. Found: C, 50.75; H, 5.46; N, 13.05.

2-(Methylamino)-3,6-dimethoxyaniline (11). To a Parr bottle were added 1.0 g (4.7 mmol) of **10**, 0.2 g of 5% Pd on charcoal, and 10 mL of ethanol. Reduction was carried out for 1 h under 50 psi of H_2. The catalyst was removed by filtration and the filtrate acidified by addition of 1 mL of concentrated HCl. Concentration of the filtrate in vacuo afforded a white foam which was crystallized by addition of 1 mL of 95% ethanol followed by 5 mL of ethyl acetate. Yield of the hydrochloride salt of 11 upon filtration and drying was 0.74 g (68%): ^1H NMR (Me_2SO-d_6) δ 7.87 and 7.40 (2 H, AB system, J = 8 Hz, Ar protons), 4.82 and 4.78 (6 H, 2 s, methoxy), 3.78 (3 H, s, N-methyl). Anal. Calcd for $C_9H_{14}N_2O_2$·HCl·0.75H_2O: C, 46.55; H, 7.16; N, 12.06. Found: C, 46.70; H, 6.72; N, 11.94.

1-Methyl-2-(hydroxymethyl)-4,7-dimethoxybenzimidazole (12). Prepared from 11 and glycolic acid by the Phillips method.[17,18] Buffering the reaction mixture to pH 6 afforded 1.55 g (73%) of analytically pure 12: mp 145–146 °C; ^1H NMR ($CDCl_3$) δ 6.50 and 6.49 (2 H, d, Ar protons), 4.85 (2 H, s, hydroxymethyl), 4.02 and 3.94 (6 H, 2 s, methoxy groups), 3.85 (3 H, s, N(1)-methyl); IR (thin film) 3200, 2950, 1521, and 1263 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.44; H, 6.35; N, 12.60. Found: C, 59.16; H, 6.35; N, 12.51. TLC (10% ethanol in chloroform on silica gel), R_f 0.76. pK_a of the N(3)-protonated form is 5.24 ± 0.10; **12**·H^+ 226 (2.84 × 10^4), 270 nm (7700); **12** 218 (5.2 × 10^4), 258 (1.16 × 10^4), [280] nm (8200).

1-Methyl-2-(chloromethyl)-4,7-dimethoxybenzimidazole (13). Prepared in 60% yield by treating **12** with thionyl chloride; the procedure employed is found in ref 18. Purification of **13** for analytical purposes was carried out by recrystallization from chloroform/hexane: mp 114–116 °C (forms a gel-like material); TLC (10% ethanol in chloroform on silica gel), R_f 0.61; ^1H NMR ($CDCl_3$) δ 6.50 and 6.57 (2 H, AB system, J = 8.6 Hz, Ar protons), 4.80 (2 H, s, chloromethyl), 4.10 (3 H, s, N(1)-methyl), 3.95 and 3.89 (6 H, 2 s, methoxy groups); IR (thin film) 2959, 1525, 1460, 1280, 1086 cm^{-1}. Anal. Calcd for $C_{11}H_{13}ClN_2O_2$: C, 54.89; H, 5.44; N, 11.63. Found: C, 54.85; H, 5.46; N, 11.50. pK_a of the N-(3)-protonated form is 4.10 ± 0.10; **13**·H^+ 231 (1.4 × 10^4), 274 nm (2.8 × 10^3); **13** 226 (1.95 × 10^4), 264 nm (4.18 × 10^3).

1-Methyl-2-(bromomethyl)-4,7-dihydroxybenzimidazole Hydrobromide (3·HBr). A mixture of 0.09 g (0.37 mmol) of **13** and 2 mL of 48% HBr was heated at 120 °C for 3 h. Toward the end of the reaction time, 3·HBr began to crystallize from the reaction mixture. Crystallization was completed by chilling the reaction mixture for 3 h in the refrigerator. The product was removed by filtration and washed with ethyl acetate. Recrystallization was carried out by dissolution in 1 mL of ethanol and then diluting to 20 mL with ethyl acetate. Yield of 3·HBr upon filtration and drying was 0.09 g (79%): TLC (10% ethanol in chloroform on silica gel), R_f 0.34; ^1H NMR (Me_2SO-d_6) δ 6.76 (2 H, s, Ar), 5.23 (2, H, s, bromomethyl), 4.16 (3 H, s, N(1)-methyl); IR (KBr) 3200, 1509, 1300, 1278, 828, 760 cm^{-1}. Anal. Calcd for $C_9H_9BrN_2O_2$·HBr: C, 31.95; H, 2.98; N, 8.27. Found: C, 32.09; H, 2.91; N, 8.17. Mass spectrum; m/z 256 (free base − H), 258 (free base [^{81}Br] − H), 177 (free base − HBr). pK_a of the N-(3)-protonated form is 3.99 ± 0.20; **3**·H^+ 240 (2 × 10^4), 280 (3600), [380] nm (1800); **3** 240 (2 × 10^4), 380 nm (5200).

1-Methyl-2-(chloromethyl)-4,7-dihydroxybenzimidazole Hydrochloride (5·HCl). Dissolution of 50 mg (0.147 mmole) of 3·HBr in 25 mL of strictly anaerobic 1 M HCl was followed by incubation for 3 days at 30 °C. After removal from the anaerobic atmosphere, the reaction mixture was evaporated in vacuo to afford a solid residue. Recrystallization from ethyl acetate/methanol provided 36 mg (98%) of 5·HCl as a colorless crystalline solid: ^1H NMR (1 M DCl, TSP-d_4 as reference) δ 6.79 (2 H, s, Ar), 4.94 (2 H, s, chloromethyl), 4.18 (3 H, s, N(1)-methyl). Anal. Calcd for $C_9H_9ClN_2O_2$·HCl·0.3H_2O: C, 42.37; H, 4.21; N, 10.97. Found: C, 42.66; H, 3.98; N, 10.50. pK_a of N(3)-protonated form is 4.03 ± 0.18; **5**·H^+ 235 (1.9 × 10^4), 276 nm (2900); **5** 227 (1.6 × 10^4), 265 (4500), 290 nm (3100). pK_a for 4-hydroxyl ionization is 8.4 ± 0.3; 5^- 290 nm (3800).

1,2-Dimethyl-4,7-dimethoxybenzimidazole (15). A mixture consisting of 0.71 g (3.69 mmol) of **14**,[18] 0.44 g (7.85 mmol) of powdered KOH, and 10 mL of acetone was heated at reflux. After 5 min methyl iodide, 0.32 mL (5.07 mmol) was added and refluxing continued for 1 h. After the reaction mixture cooled to room temperature, the liquor was decanted from the precipitated solids and placed on a 100-g silica gel column (270–320 mesh) prepared with chloroform. Elution of the product was carried out with 10% ethanol in chloroform. Evaporation of eluants provided **15** as a white solid, which was pure by TLC (10% ethanol in chloroform on silica gel), R_f = 0.61. The yield was 0.41 g (54%). Recrystallization for analysis and characterization was carried out from water/ethanol: ^1H NMR ($CDCl_3$) δ 6.46 (2 H, s, Ar), 3.56 and 3.53 (6 H, 2 s, dimethoxy), 3.50 (3 H, s, N(1)-methyl), 2.46 (3 H, s, 2-methyl); IR (thin film) 2952, 1520, 1259, 1096, 1067 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_2$·0.2H_2O: C, 62.95; H, 6.91; N, 13.34. Found: C, 63.27; H, 6.88; N, 12.70. pK_a for N(3)-protonated form is 6.12 ± 0.08; **15**·H^+ 270 nm (9200); **15** 216 (5 × 10^4), 256 (1.27 × 10^4), [280]nm.

1,2-Dimethyl-4,7-dihydroxybenzimidazole Hydrobromide (8·HBr). Prepared in 98% yield by treating **15** with refluxing 48% HBr; the procedure employed is found in ref 18. Recrystallization was carried out by treating a concentrated solution of 8·HBr in 100% ethanol with activated carbon and then diluting with ethyl acetate. The colorless needles were filtered and dried in vacuo: ^1H NMR (Me_2SO-d_6) δ 6.69 (2 H, s, Ar protons), 4.04 (3 H, s, N(1)-methyl), 2.70 (3 H, s, 2-methyl); IR (thin film) 3100, 1539, 1292, 816 cm^{-1}; TLC (*n*-butanol, acetic acid, H_2O [5:2:3] on silica gel), R_f 0.62; mass spectrum, m/z 278 (parent peak). Anal. Calcd for $C_9H_{10}N_2O_2$·HBr·0.3H_2O:C, 40.85; H, 4.41; N, 10.58. Found: C, 40.73; H, 4.75; N, 10.22. pK_a for the N(3)-protonated form is 6.47 ± 0.09; **8**·H^+ 218 (4.9 × 10^4), 270 nm (8600); **8** 218 (4.8 × 10^4), 256 nm (9500). pK_a for 4-hydroxyl ionization is 9.75 ± 0.10: 8^- 218 (5 × 10^4), 290 nm (1 × 10^4).

1,2-Dimethylbenzimidazole-4,7-dione (7). A suspension of 100 mg (0.385 mmol) of 8·HBr in 5 mL of H_2O was treated with 0.5 g (1.92 mmol) of $FeCl_3$·6H_2O at room temperature for 5 min. The resulting homogeneous solution was extracted 5 × with 25-mL portions of chloroform. Extracts were combined and dried over $MgSO_4$ and then evaporated to afford crude 7 as a yellow solid, 34 mg (50%). Purification was carried out by column chromatography employing a 50-g silica gel column with 10% ethanol in chloroform as eluant. The purified 7 thus obtained was recrystallized from chloroform/hexane: TLC (10% ethanol in chloroform on silica gel), R_f 0.62; IR (KBr) 1659, 1518, 1472, 1060, 864 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.63 and 6.58 (2 H, AB pattern, J = 11 Hz), 3.91 (3 H, s, N(1)-methyl), 2.52 (3 H, s, 2-methyl); mass spectrum, m/z 176 (parent ion). Anal. Calcd for $C_9H_8N_2O_2$·

0.2H_2O: C, 60.13; H, 4.71; N, 15.57. Found: C, 60.38; H, 4.64; N, 15.23. UV-vis spectrum (pH 7.00 buffer) 252 (1.42×10^4), [290] (2200), 400 nm (1100).

Detection and Isolation of 3_{ox} and 7 during the Solvolysis of 3 in pH 7.00 0.2 M Phosphate Buffer. A solution of 50 mg (0.148 mmol) of 3·HBr in 60 mL of pH 7.00 0.20 M phosphate buffer (μ = 1.0, KCl) was prepared under strictly anaerobic conditions and then stirred for 1.5 h at 30 °C. Opening of the reaction to the air was followed by extraction 5x with 50-mL portions of chloroform. These extracts were dried over $MgSO_4$, filtered, and concentrated to afford a green-yellow solid, 6.6-mg yield. TLC in 10% ethanol in chloroform indicated 7 as the major product with a trace amount of 3_{ox}. Thus, the crude product represents ~25% yield based on 3·HBr. Separation of the two quinones was carried out by using a 25-g silica gel column prepared with chloroform. Elution with chloroform removed 3_{ox} followed by 7. The identity of 7 was determined by ^1H NMR and mass spectral comparison with those of authentic material. The identity of 2-(bromomethyl)-1-methylbenzimidazole-4,7-dione (3_{ox}) was established by spectral means: ^1H NMR ($CDCl_3$) δ 6.69 and 6.68 (2 H, d, 5-H and 6-H), 4.58 (2 H, s, CH_2Br), 4.04 (3 H, s, N-(1)-methyl); mass spectrum; m/z 254 ($M^+ - H$), 256 ($M^+ + 2H$), 175 ($M^+ - Br$).

Isolation of 6 from the Reaction of 3 and 2-Mercaptoethanol in pH 7.00 Phosphate Buffer. A solution consisting of 50 mg (0.174 mmol) of 3-HBr in 2 mL of methanol was combined with 5 mL of pH 7.00 0.2 M phosphate buffer (μ = 1.0, KCl) and 135 μL (1.74 mmol) of 2-mercaptoethanol under strictly anaerobic conditions. After a 5-min reaction time the reaction mixture was opened to the air and immediately acidified by addition of concentrated HCl. Evaporation in vacuo afforded a mixture of buffer salts and the product. To remove the latter, solids were extracted with ethanol, and the insoluble material was discarded. Crystallization of the product from the filtrate was facilitated by concentration to ~1 mL and then dilution to ~5 mL with ethyl acetate: yield; 33.8 mg (67%) of 6·HCl; ^1H NMR (Me_2SO-d_6) δ 6.78 (2 H, s, Ar), 4.30 (2 H, s, 2-methyl), 4.14 (3 H, s, N(1)-methyl), 3.52 and 2.70 (4 H, 2 t, J = 6 Hz, SCH_2CH_2O). Anal. Calcd for $C_{11}H_{14}N_2O_3S$·HCl·$2H_2O$: C, 40.42; H, 5.86; N, 8.56. Anal. Found: C, 40.26; H, 4.65; N, 8.26.

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Registry No. 3, 99922-37-9; 3·HBr, 99922-30-2; 3_{ox}, 99922-35-7; 5·HCl, 99922-31-3; 6·HCl, 99922-36-8; 7, 97042-58-5; 8·HBr, 99922-34-6; 9, 26002-57-3; 9 trifluoroacetate, 99922-26-6; 10, 56741-28-7; 11, 99922-27-7; 12, 99922-28-8; 13, 99922-29-9; 14, 99922-32-4; 15, 99922-33-5; $(CF_3C(O))_2O$, 407-25-0; $HS(CH_2)_2OH$, 60-24-2; glycolic acid, 79-14-1.

Deprotonation/Alkylation Reactions of Monoalkyl 9,10-Dihydroanthracenes and 7,12-Dihydropleiadenes. Stereochemical Outcome and Anion Models

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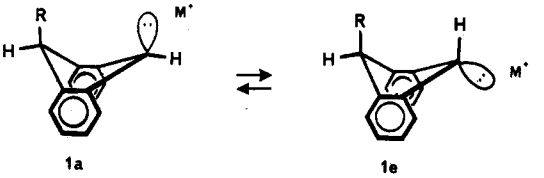
The alkylation stereochemistry of 9-alkyl-10-lithio-9,10-dihydroanthracene has often been explained on the basis of inverting, boat-shaped anion models. Recent carbon-13 NMR data for these anions has led to the suggestion of a flattened, sp^2-hybridized model, and alkylation studies herein are presented in support of this model. Since recent molecular mechanics calculations have indicated a wide range of central ring folding for 9,10-dihydroanthracenes (DHA's), alkylation studies with a system of known, reliable geometry were desirable. Hence, results are presented for a series of 7-alkyl-12-lithio-7,12-dihydropleiadenes (DHP's), and it is concluded that the neutral precursor geometries do not serve as good models for the anions. Substituent preferences in DHP's are examined by molecular mechanics calculations.

The alkylation of 9-alkyl-10-metallo-9,10-dihydroanthracene has attracted a considerable amount of attention.[1] From NMR studies, the neutral precursors (9,10-dihydroanthracenes) have been regarded as rapidly inverting boat structures with substituents preferentially located at the pseudoaxial position.[2] This concept, together with the stereochemical outcome of early alkylation studies, led to the model shown as **1a** ⇌ **1e**. An alkylation



1a **1e**

with small alkyl halides (R′X) was considered to give cis products via **1a**, whereas larger R′X (and R) produced trans products presumably via faster alkylation of **1e**. In the latter case, reaction was expected to be slower with **1a** due to a transannular steric effect between the substituent R and the alkylating agent R′X.[3]

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