was removed under reduced pressure and the crude product recrystallized from methanol/diethyl ether to provide 2.16 g (92%) of the desired product as a white powder: mp 210-212 °C; ^{1}H NMR (CD_3OD, 200 MHz) ∂ 3.95 (s, 3 H), 3.97 (s, 2 H), 7.24 (dt, J = 7.8, 1.1 Hz, 1 H), 7.62 (dt, J = 8.0, 1.7 Hz, 1 H), 8.08 (dd, J = 8.0, 1.6 Hz, 1 H), 8.47 (dd, J = 7.8, 1.1 Hz, 1 H); IR (KBr pellet) 3200, 3140, 1720, 1700, 1250, 778 cm^{-1}; MS (CI/NH_3) calcd for $C_{10}H_{12}N_2O_3$, m/e 208, found 209 (M + 1).

(±)-*ab*,*cf*-Bis(ethylenediamine-*N*,*N'*)-*de*-(*N*-glycyl-2-(methoxycarbonyl)aniline)cobalt(3+) Trinitrate (4). To hydrobromide salt **23** (1.9 g, 6.57 mmol) dissolved in 10 mL of 95% ethanol was added *trans*-$[Co(en)_2Br_2]^+Br^-$ (2.15 g, 5.12 mmol) and then diethylamine (0.68 mL, 6.57 mmol) dropwise. The reaction mixture was stirred overnight at room temperature, chilled to precipitate a pink solid which was isolated on a medium frit, washed with ice-cold 96% ethanol, and dried in vacuo (yield 2.2 g). Silver nitrate (0.45 g, 2.6 mmol) was added to 500 mg of this solid dissolved in 3 mL of 10^{-4} M HNO_3, and the solution was vortexed and allowed to stand in the dark overnight before the silver salts were removed by filtration. Lithium nitrate (concentrated aqueous solution) was added dropwise at room temperature to the filtrate, which precipitated 78 mg (17%) of X-ray quality crystals: ^{1}H NMR (300 MHz, Me_2SO-d_6) ∂ 2.2-2.8 (m, 8 H + Me_2SO residue), 3.32 (HDO), 3.38 (s, 3 H), 4.07 (br s, 3 H), 4.48 (br s, 1 H), 5.13 (br s, 1 H), 5.34 (br s, 3 H), 5.65 (br s, 3 H), 5.80 (br s, 1 H), 7.42 (t, J = 7.3 Hz, 1 H), 7.6-7.8 (m, 2 H), 7.94 d, J = 7.7 Hz, 1 H), 9.06 (br s, 1 H); IR (Me_2SO-d_6 solution) 3500, 1720, 1616, 1261 cm^{-1}; UV-vis (0.5 mM solution in 0.1 M HCl) 487 (~100) nm. Anal. Calcd for $CoC_{14}H_{28}N_9O_{12}\cdot 2H_2O$ (found): Co, 9.67 (9.76); C, 27.59 (27.11); H, 5.29 (5.33); N, 20.69 (20.60). **(±)-*ab*-(2-Aminoacetanilide-*O*,*N*^{2})-*cf*,*de*-bis(ethylenediamine-*N*,*N'*)cobalt(3+) Trinitrate (6).** After centrifugation (discard pellet), the orange supernatant was chromatographed on G-10 Sephadex (0.5 M HCO_2H eluent) to remove excess soluble silver salts and then on Sephadex SP-25 (0.1-1.0 M gradient elution). The major 3$^+$ orange band was collected and evaporated to an orange glass which was recrystallized from dilute nitric acid to give a 42% yield of the desired product: ^{1}H NMR (Me_2SO-d_6, 300 MHz) ∂ 2.35-2.90 (br m, 8 H), 3.35 (s, HDO), 4.05 (br s, 3 H), 4.53 (br s, 1 H), 5.19 (br s, 1 H), 5.32 (br s, 2 H), 5.58 (br s, 3 H), 5.75 (br s, 2 H), 7.26 (t, J = 7 Hz, 1 H), 7.42 (t, J = 7 Hz, 2 H), 7.53 (d, J = 7 Hz, 2 H), 8.94 (br s, 1 H); IR (Me_2SO-d_6 solution) 3580, 1613, 1581, 1349, 829 cm^{-1}; UV-vis (0.5 mM solution in 0.1 M HCl) 490 (~100) nm. Anal. Calcd for $CoC_{12}H_{26}N_9O_{10}\cdot 1H_2O$ (found): Co, 11.05 (10.96); C, 27.02 (26.72); H, 5.29 (5.32); N, 23.64 (23.42).

Acknowledgment. This work was supported by the ONR. We thank Dr. Michael Chiang for the X-ray structure determination.

Supplementary Material Available: Table IV showing crystal data and structure analysis results (1 page). Ordering information is given on any current masthead page.

Metal Ion Catalyzed Reactions of Acrylonitrile, Acrylamide, and Ethyl Acrylate by way of Their Diels-Alder Cycloadducts

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Abstract: In this paper, we report our successful efforts in coupling a cycloaddition/cycloreversion sequence to the well-documented metal ion promotion of functional group conversion in the cases of acrylonitrile to acrylamide, acrylamide to ethyl acrylate, and ethyl acrylate to acrylic acid. With 9-(2-pyridyl)anthracene as the diene, cycloadducts were prepared that underwent metal-promoted nitrile hydration, ethyl ester hydrolysis, and amide alcoholysis reactions. In addition, we report the synthesis of 9,10-bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene, a diene capable of chelating to metal ions, as demonstrated by the successful synthesis of (9,10-bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene-*N*,*N'*,*N''*,*N'''*)dizinc tetrachloride.

"Molecular recognition" is an active area of chemical research that seeks to understand how to bind a "guest" molecule to a "host" molecule or material selectively, and its relevance to the rational design of catalysts is clear. The biomimetic origins of this field have, quite logically, focused attention on binding guests out of aqueous solution, and therefore enzyme-like binding mechanisms (e.g., hydrophobic binding, hydrogen bonding, ion pairing, and ion-dipole interactions) have been successfully exploited by the pioneering efforts of many groups.[1] Of course, not all guest molecules of importance are water soluble, and in these cases the general approach has been to couple a polar or intercalative binding mechanism onto a nonpolar, lyophilic backbone.[2] Occasionally, such complexations are also freely reversible, thereby meeting one of the least flexible tenets of true catalysis.

Many guest molecules do not possess the necessary "handle" with which to afford the transient associations available via precedented complexation mechanisms. Our work with acrylate-type substrates points this out clearly; few of the previously utilized methods of host-guest interaction seem practical in this case. We are, therefore, examining a mode of complexation that has not been utilized previously, *reversible cycloaddition*, that will effectively allow for the molecular recognition of dienophilic substrates. This idea is outlined in Figure 1 (cat. = catalytic group, f.g. = functional group), which is a highly generalized and versatile scheme for the formulation of Diels-Alder reaction based catalysts. Reversibility in the Diels-Alder reaction has substantial literature precedent,[3-5] and our own work learning to accelerate retro-Diels-Alder reaction rates is aimed at making such reversibility accessible at lower temperatures in the acrylate series.[6]

(1) The design of water-soluble compounds that catalyze reactions via mechanisms analogous to those of certain enzymes (often called "artificial enzymes", "synzymes", "synthetic enzymes", or "enzyme mimics") has been a fruitful area of research for about 25 years or so. The literature is by now so vast that it is not possible to list just a few key reviews that will provide lead references for most of what has been done.

(2) (a) Rebek, J., Jr.; Askew, B.; Islam, N.; Killoran, M.; Nemeth, D.; Wolak, R. *J. Am. Chem. Soc.* **1985**, *107*, 6736. (b) Rebek, J., Jr.; Nemeth, D. *J. Am. Chem. Soc.* **1985**, *107*, 6738. (c) Whitlock, B. J.; Whitlock, H. W., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 1325.

(3) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211, 230.

(4) Kiselev, V. D.; Konovalov, A. I.; Veisman, E. A.; Ustyugov, A. N. *Zh. Org. Khim.* **1978**, *14*, 128.

(5) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 150.

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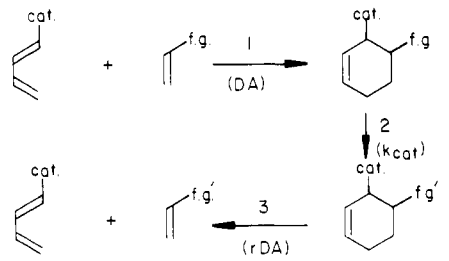

Figure 1.

Table I. First-Order Rate Constants for the Metal Ion Promoted Hydration of Nitrile **3** to Amide **5** in Dioxane–Aqueous Buffer (1:1) at 100 °C[a]

metal	pH of buffer prior to mixing	10^5k_1, min^{-1}
Cu^{2+}	7.0	10.3
Zn^{2+}	7.0	6.1
Co^{2+}	7.0	4.6
Ni^{2+}	5.0	3.2
Ni^{2+}	6.0	5.4
Ni^{2+}	7.0	8.0
Ni^{2+}	8.0	13.4
Ni^{2+}	9.0	25.8
Na^+	7.0	<0.34

[a] [nitrile] = 3.2 mM, [M^{n+}] = 13 mM.

Anthracene forms cycloadducts with acrylate-type dienophiles that are kinetically stable at temperatures below about 150 °C; this stability allows us to examine the k_{cal} (functional group conversion) term separately from a K_{eq} (association) term. In this regard, we have examined the adducts of 9-(2-pyridyl)anthracene (**1**) and of 9,10-bis(((2-(dimethylamino)ethyl)methylamino)-methyl)anthracene (**16**), which are dienes carrying a donor atom in a position such that it may participate in metal ion chelation upon cycloaddition with donor atom bearing dienophiles.[11] In this paper, we report our efforts in coupling a cycloaddition/cycloreversion sequence to the well-documented metal ion promotion of functional group conversions[7-9] in the cases of acrylonitrile to acrylamide,[10] acrylamide to ethyl acrylate, and ethyl acrylate to acrylic acid.

Table II. First-Order Rate Constants for the Metal Ion Promoted Alcoholysis of Amide **5** to Ester **8** in Anhydrous Ethanol at 78 °C[a]

metal	10^4k_1, min^{-1}
Cu^{2+}	23
Ni^{2+}	14
Zn^{2+}	8.0
Co^{2+}	5.1
Na^+	<0.08

[a] [amide] = 3.1 mM, [M^{n+}] = 13 mM.

Table III. First-Order Rate Constants for the Metal Ion Promoted Hydrolysis of Ester **8** to Acid **11** in Dioxane–Aqueous Buffer (pH 8.0) at 100 °C[a]

metal	10^5k_1, min^{-1}
Cu^{2+}	25
Ni^{2+}	14
Zn^{2+}	9.2
Co^{2+}	5.6
Na^+	<0.84

[a] [ester] = 3.1 mM, [M^{n+}] = 13 mM.

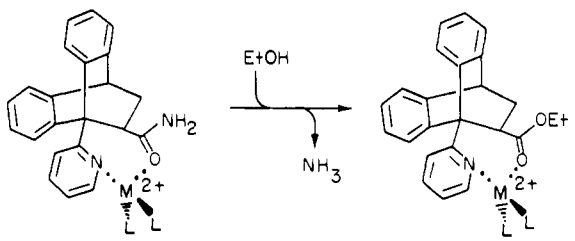

Figure 2.

Syntheses and Kinetic Studies of 9-(2-Pyridyl)anthracene Cycloadducts

Acrylonitrile to Acrylamide. The reaction of acrylonitrile (**2**) with anthracene **1** afforded a 5.4:1 mixture of adducts **3** and **4** in 64% combined yield (Scheme I), which could be easily separated by column chromatography. The isolated nitriles were then heated in a dioxane/H_2O solution (aqueous solution buffered to pH 7.0 before addition of the organic cosolvent) containing a 4-fold molar excess of a metal perchlorate, and the hydration of nitrile to amide was monitored by NMR spectroscopy as described in the Experimental Section. The efficient, metal ion catalyzed conversion of nitrile **3** to amide **5** was observed, and pseudo-first-order rate constants were obtained for this process both as a function of metal ion and of pH by using Ni^{2+}. As seen in Table I, all four divalent metal ions examined (Cu^{2+}, Zn^{2+}, Co^{2+}, and Ni^{2+}) facilitated the hydration at roughly the same rate. It is not yet established whether the small differences are due to inherent activating abilities of the metals or to differences in their association constants with the pyridine nitrogen. The importance of both metal ion participation and of correct geometry in this reaction is striking;

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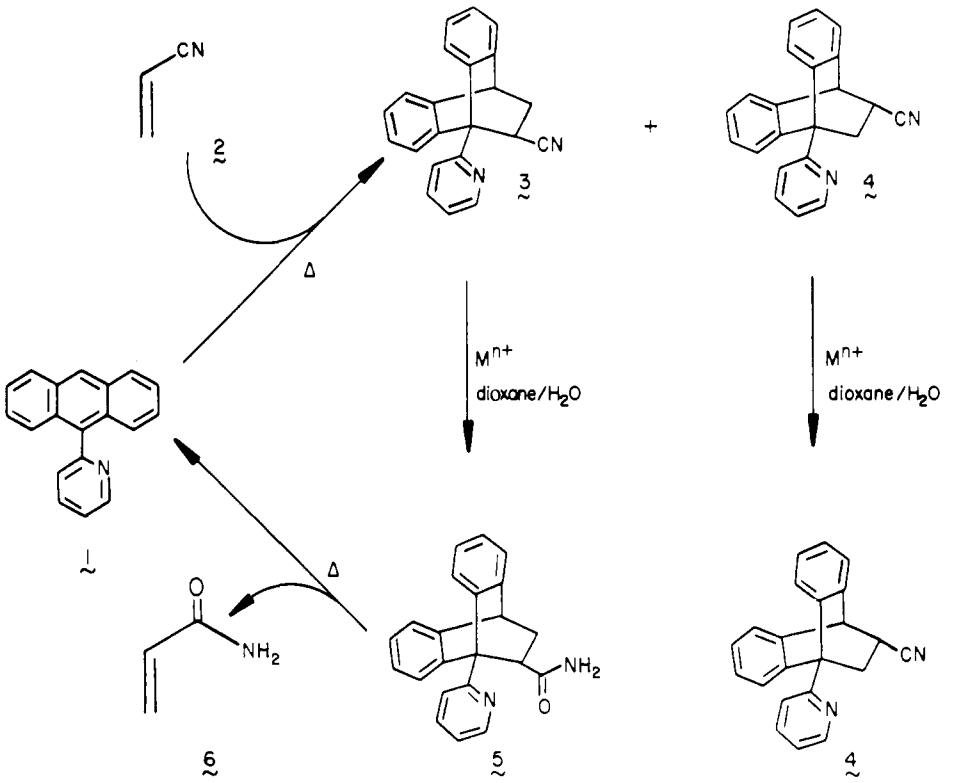
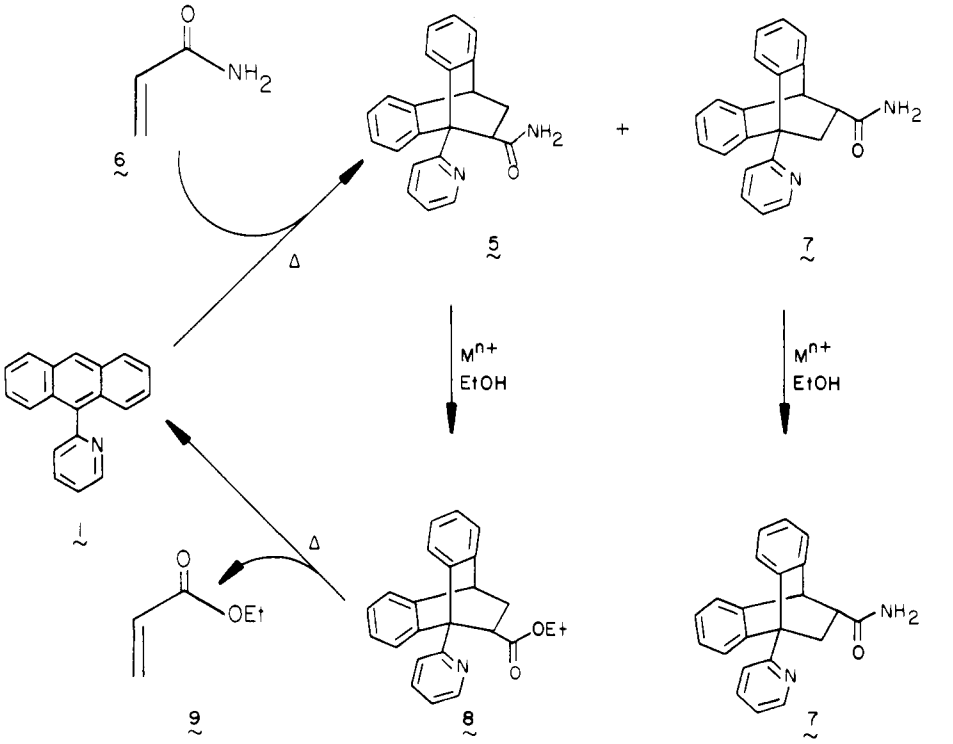
(7) Nitrile to amide: (a) Watanabe, K. *Bull. Chem. Soc. Jpn.* **1964**, *37*, 1325. (b) Watanabe, K.; Sakai, K. *Bull. Chem. Soc. Jpn.* **1966**, *39*, 8. (c) Breslow, R.; Fairweather, R.; Keana, J. *J. Am. Chem. Soc.* **1967**, *89*, 2135. (d) Sakai, K.; Ito, T.; Watanabe K. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 1660. (e) Barnard, J. *J. Chem. Soc. A* **1969**, 2140. (f) Breslow, R.; Schmir, M. *J. Am. Chem. Soc.* **1971**, *93*, 4960. (g) Komiyama, S.; Suzuki, S.; Watanabe, K. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1140. (h) Pinnell, D.; Wright, G. B.; Jordan, R. B. *J. Am. Chem. Soc.* **1972**, *94*, 6104. (i) Buckingham, D. A.; Keene, F. R.; Sargeson, A. M. *J. Am. Chem. Soc.* **1973**, *95*, 5649. (j) Bennett, M. A.; Yoshida, T. *J. Am. Chem. Soc.* **1973**, *95*, 3030. (k) Watanabe, K.; Komiya, S.; Suzuki, S. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 2792. (l) Quina, F. H.; Politi, M. J.; Cuccovia, I. M.; Baumgarten, E.; Martins-Franchetti, S. M.; Chalmovich, H. *J. Phys. Chem.* **1980**, *84*, 361. (m) Curtis, N. J.; Sargeson, A. M. *J. Am. Chem. Soc.* **1984**, *106*, 625. (n) Jensen, C. M.; Trogler, W. C. *J. Am. Chem. Soc.* **1986**, *108*, 723.
(8) Ester to acid: (a) Kroll, H. *J. Am. Chem. Soc.* **1952**, *74*, 2036. (b) Bender, M. L.; Turnquist, B. W. *J. Am. Chem. Soc.* **1957**, *79*, 1889. (c) Alexander, M. D.; Busch, D. H. *J. Am. Chem. Soc.* **1966**, *88*, 1130. (d) Buckingham, D. A.; Collman, J. P.; Happer, D. A. R.; Marzilli, L. G. *J. Am. Chem. Soc.* **1967**, *89*, 1082. (e) Buckingham, D. A.; Foster, D. M.; Sargeson, A. M. *J. Am. Chem. Soc.* **1968**, *90*, 6032. (f) Buckingham, D. A.; Foster, D. M.; Sargeson, A. M. *J. Am. Chem. Soc.* **1969**, *91*, 4102. (g) Wells, M. A.; Rogers, G. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1976**, *98*, 4336. (h) Wells, M. A.; Bruice, T. C. *J. Am. Chem. Soc.* **1977**, *99*, 5341. (i) Fife, T. H.; Squillacote, V. L. *J. Am. Chem. Soc.* **1978**, *100*, 4787. (j) Boreham, C. J.; Buckingham, D. A.; Keene, F. R. *J. Am. Chem. Soc.* **1979**, *101*, 1409. (k) Fife, T. H.; Przystas, T. J.; Squillacote, V. L. *J. Am. Chem. Soc.* **1979**, *101*, 3017.
(9) Amide to acid: (a) Collman, J. P.; Kimura, E. *J. Am. Chem. Soc.* **1967**, *89*, 6096. (b) Buckingham, D. A.; Foster, D. M.; Sargeson, A. M. *J. Am. Chem. Soc.* **1970**, *92*, 6151. (c) Reference 8j. (d) Buckingham, D. A.; Harrowfield, J. M.; Sargeson, A. M. *J. Am. Chem. Soc.* **1974**, *96*, 1726. (e) Boreham, C. J.; Buckingham, D. A.; Keene, F. R. *J. Am. Chem. Soc.* **1979**, *101*, 1409. (f) Boreham, C. J.; Buckingham, D. A.; Keene, F. R. *Inorg. Chem.* **1979**, *18*, 28. (g) Reference 7m. (h) Groves, J. T.; Chambers, R. R., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 630. (i) Buckingham, D. A.; Binney, G. S.; Clark, C. R.; Garnham, B.; Simpson, J. *Inorg. Chem.* **1985**, *24*, 135.

(10) Alternatives to the sulfuric acid method for acrylonitrile to acrylamide conversion have been the focus of much study, which Professor Trogler has usefully summarized as part of his paper on this subject (ref 7n). It is worth noting that our proposed cycloaddition/cycloreversion scheme has the strong potential to select for nitrile hydration vs. olefin hydration in this reaction, a selectivity that has not been achieved to date with metal complexes that coordinate to the nitrile nitrogen.
(11) Chelation in 9-(2-pyridyl)anthracene adducts is possible with carbonyl functional groups, such as an amide or ester, but not with a nitrile group. We suggest that acceleration of the nitrile hydration observed in this system is the result of weak metal ion binding by a single pyridine nitrogen followed by a metal-promoted hydration mechanism (such as either the metal–hydroxide pathway or π-complexation with the nitrile in the transition state). The predicted instability of this nonchelated complex provided an impetus for the examination of 9,10-bis(((2-(dimethylamino)ethyl)methylamino)methyl)-anthracene as reported later in this paper.

Scheme I



Scheme II

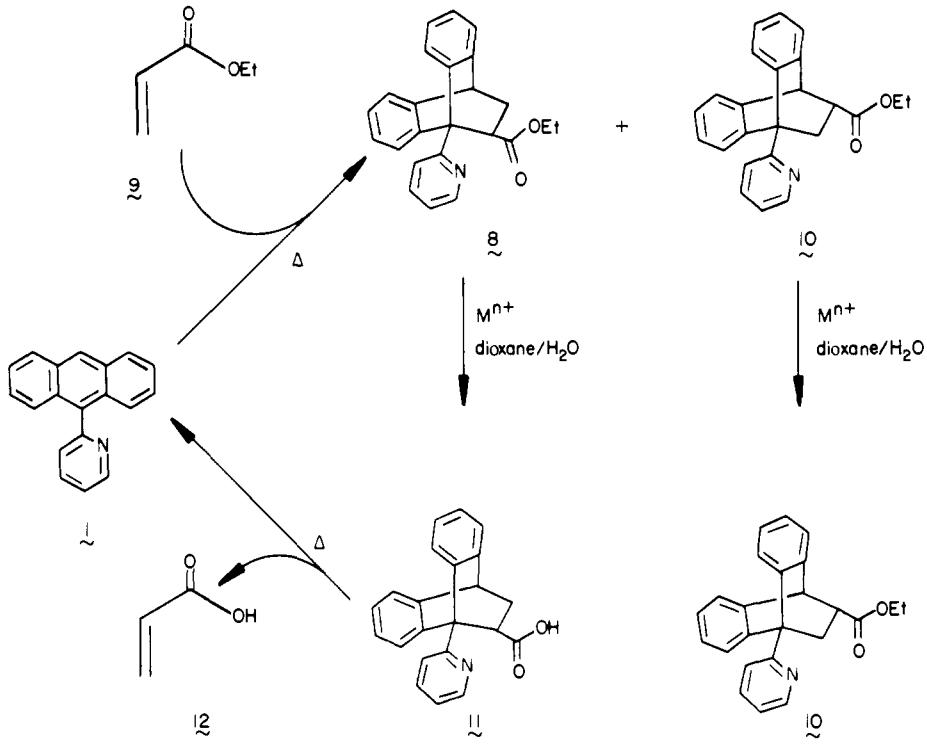


control reactions using nitrile **3** with sodium perchlorate or using nitrile **4** with Ni^{2+} or Cu^{2+} showed no amide formation even after heating under identical conditions for 250 h. As expected, the rate of hydration increases with increasing pH, and the Ni^{2+}-catalyzed reaction was 8 times faster at pH 9.0 than at pH 5.0; Ni^{2+} was chosen for the pH study owing to its solubility under basic conditions. Cycloreversion of amide **5** to regenerate anthracene **1** was accomplished by heating, thus completing the cycle suggested by Scheme I.

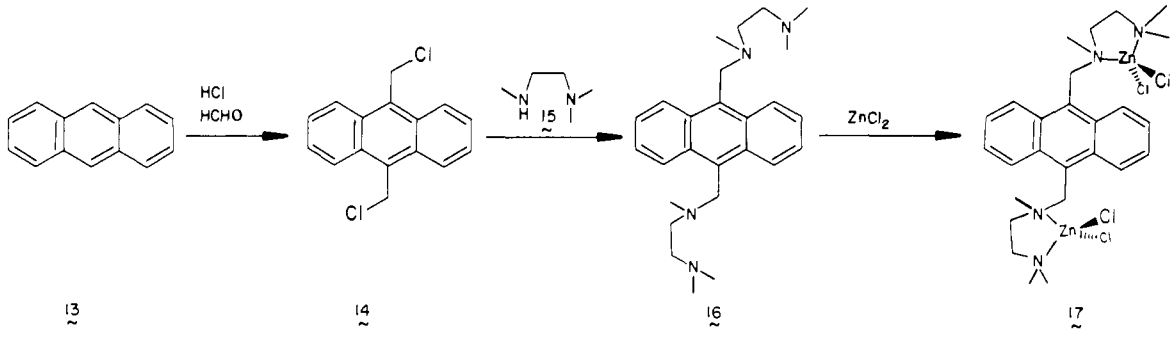
Acrylamide to Ethyl Acrylate. The Diels–Alder-mediated, metal ion catalyzed conversion of acrylamide to ethyl acrylate has already been described by this group in a preliminary form.[12] As shown in Scheme II, the cycloaddition reaction of anthracene **1** and acrylamide (**6**) was accomplished to afford ortho adduct **5** and meta adduct **7** in 18% and 29% yield, respectively, along with 22% recovered **1**. Solutions of **5** and **7** in anhydrous ethanol containing 20 mM metal ion were heated at gentle reflux under dry N_2, and the conversion of amide to ester could be followed conveniently by TLC analysis. In our earlier paper, we reported that after 100

(12) Czarnik, A. W. *Tetrahedron Lett.* **1984**, *25*, 4875.

Scheme III



Scheme IV



h with $NiCl_2$, amide **5** had been completely converted to the corresponding ester (**8**), while no observable conversion had taken place using amide **7**. A recent note that chloride ion may inhibit reactions of this type[13] prompted us to switch to perchlorate ion, and the kinetics of the amide to ester conversion in this system are shown in Table II. Alcoholysis catalyzed by Cu^{2+} occurs with a half-life of about 5 h, and the trend $Cu^{2+} > Ni^{2+} > Zn^{2+} > Co^{2+}$ is one seen often in metal ion promoted acyl-transfer reactions. As in the nitrile series, control reactions utilizing either amide **5** with sodium perchlorate or amide **7** with the divalent metal ions showed no conversion to ester even after 100 h. We propose that the rate acceleration occurs as a result of oxygen coordination in a seven-membered M^{2+} chelate (Figure 2); a complex of similar geometry has been reported by Blakely, Zerner, and co-workers.[14] Cycloreversion of ester **8** to anthracene **1** was readily achieved by simple heating, thus completing the reaction cycle.

Ethyl Acrylate to Acrylic Acid. Finally, we examined the ethyl acrylate to acrylic acid conversion using the 9-(2-pyridyl)-anthracene diene. The ease with which chelated esters of this kind have been reported to undergo hydrolysis[8a,b] led us to guess this should be a considerably faster process than either the nitrile to amide or the amide to ester reactions. In fact, hydrolysis occurred much more slowly, a result that reinforces a conclusion based on experiments by Groves[9h] in metal-promoted amide hydrolyses: a precise spatial orientation, as opposed to simple proximity, of metal ion to functional group is essential for large rate accelerations. Cycloaddition of anthracene **1** to ethyl acrylate (**9**) afforded a 1:1.1 mixture of esters **8** and **10** (Scheme III), which were separated by chromatography and hydrolyzed in dioxane/H_2O (pH 8.0) at 100 °C to afford the ortho acid (**11**) from **8** but not the corresponding meta acid from **10**. The kinetic results of varying the metal ion are shown in Table III. Even the best case in this series (Cu^{2+}) has a half-life of about 45 h, but control reactions as described before confirm that the reaction is both metal ion catalyzed and sensitive to the geometry of the intermediate chelate. Thermal cycloreversion of acid **11** completed the formal cycle.

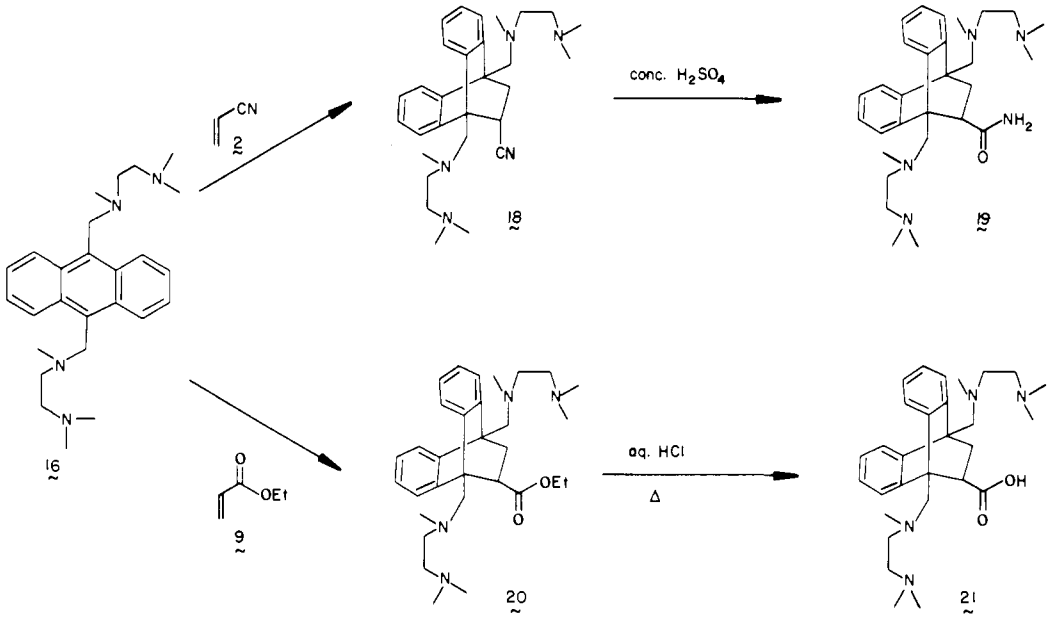
Syntheses and Kinetic Studies of 9,10-Bis(((2-(dimethylamino)ethyl)methylamino)methyl)-anthracene Cycloadducts

An obvious improvement to the idea shown in Schemes I–III would be to use a chelating ligand on the diene, so that the cycloadduct does not need to "find" a metal ion prior to the k_{cat} step. In that sense, such a metal-bearing diene would be quite similar to a metalloenzyme in that the chelated metal would be available immediately after binding of the substrate. We chose to examine the use of the *N,N,N',N'*-tetramethylethylenediamine (TMEDA) group as our chelating ligand for two reasons: (1) complexes of various metals with TMEDA have been used suc-

(13) Gellman, S. H.; Petter, R.; Breslow, R. *J. Am. Chem. Soc.* **1986**, *108*, 2388.

(14) Blakely, R. L.; Treston, A.; Andrews, R. K.; Zerner, B. Z. *J. Am. Chem. Soc.* **1982**, *104*, 612.

Scheme V

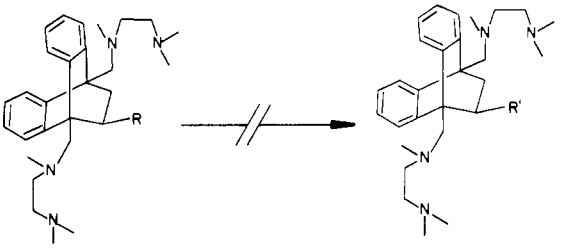


cessfully as catalysts in nitrile hydration reactions,[7k] and (2) in at least one reported case,[15] reaction of trien (a "bisTMEDA") with a divalent metal salt afforded the binuclear metal ion complex as opposed to the equally possible mononuclear complex.

Our synthesis of 9,10-bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene (**16**) began with the known[16] conversion of anthracene (**13**) to 9,10-bis(chloromethyl)anthracene (**14**) using HCl and formaldehyde (Scheme IV). Reaction of compound **14** with an excess of *N,N,N'*-trimethylethylenediamine (**15**) afforded the desired compound (**16**) as a low-melting yellow solid whose NMR, mass spectrum, and microanalysis are all consistent with the structure drawn. The relatively low yield (14%) in this 2-fold condensation reaction was deemed acceptable inasmuch as the reaction can be easily carried out on a large scale, and the bulk of the impurities can be removed by a simple extraction between water and hexane (which also removes residual DMF). Comixing of methanolic solutions of 9,10-bis(((2-dimethylamino)ethyl)methylamino)methyl)anthracene and zinc(II) chloride affords the binuclear complex **17** as a highly crystalline, high-melting solid whose ^{1}H NMR spectrum is consistent with a monomeric, symmetrical structure. Molecular models confirm that an intramolecular bridging interaction across the anthracene face would be highly strained, and the ability of **16** to chelate both metal atoms simultaneously was confirmed by the microanalytical data, which indicate a ratio of two zinc atoms per anthracene molecule.

Cycloaddition of complex **17** with acrylonitrile does occur;[17] however, in order to evaluate the effect of metal ion substitution on the various functional group conversions, cycloaddition of anthracene **16** with acrylonitrile (**2**) was accomplished (Scheme V) to give the metal-free nitrile **18** in pure form after alumina and ion-exchange chromatography.[21] The adduct with ethyl acrylate was prepared similarly to give ester **20**. Authentic samples of the corresponding amide (**19**) and carboxylic acid (**21**) were prepared by using classical hydrolysis methods from **18** and **20**, respectively. For the kinetic studies, two solvent systems for

Scheme VI



Reaction A: 18 (R=CN) 19 (R'=$CONH_2$)
Reaction B: 19 (R=$CONH_2$) 20 (R'=CO_2Et)
Reaction C: 19 (R=$CONH_2$) 21 (R'=CO_2H)
Reaction D: 20 (R=CO_2Et) 21 (R'=CO_2H)

reverse-phase HPLC were found that permitted rapid quantitation of the concentrations of all four adducts (**18–21**; see Experimental Section).[18]

Kinetic studies of the conversions shown in Scheme VI were initiated, using aqueous solution buffered to pHs between 5.0 and 9.5 (reactions A, C, and D) or absolute ethanol (reaction B) as solvent. Unexpectedly (and unfortunately), none of these attempted reactions were observed to occur even under conditions more strenuous than those utilized in the 9-(2-pyridyl)anthracene study. Several possible explanations for this surprising lack of reactivity in adducts **18–21** exist. For example, it is conceivable that the binuclear complexes formed in methanolic solution are kinetic products and that in aqueous solution equilibration occurs to give complexes of one metal atom per two TMEDA units; such a species would be oligomeric and probably catalytically inactive owing to the lack of available metal ligand sites for either functional group or solvent. It is also possible that the TMEDA chelates formed are sufficiently "bulky" to prohibit metal interaction with the functional group within the adduct; this does not appear to be the case on the basis of an examination of CPK models but cannot be ruled out on this basis alone.

Conclusion

The catalytic step represented by k_{cat} in Figure 1 has been isolated from the association step and examined independently.

(15) Cristini, A.; Ponticelli, G. *J. Chem. Soc., Dalton Trans.* **1972**, 2602. While Zn(II) gave the binuclear complex in this case, Ni(II) and Cu(II) yielded mononuclear tetradentate complexes with the same ligand (Cristini, A.; Ponticelli, G.; Diaz, A. *J. Chem. Soc., Dalton Trans.* **1972** 1361).

(16) Miller, M. W.; Amidon, R. W.; Tawney, P. O. *J. Am. Chem. Soc.* **1955**, *77*, 2845.

(17) A mixture of metal complex **17** and BHT was heated in acrylonitrile at 160 °C for 22 h, the polymer was filtered, and the filtrate was evaporated to dryness. ^{1}H NMR indicates that the anthracene is consumed, and aromatic peaks corresponding to an adduct are observed. We will pursue cycloaddition reactions of metal ion bearing dienophiles using a more reactive system.

(18) A sense of fairness demands noting that the work described in this paragraph required an amount of effort greatly disproportionate to its space in this article.

Adducts of acrylonitrile, acrylamide, and ethyl acrylate all undergo metal ion catalyzed conversions to other acrylate-type products as their adducts in the 9-(2-pyridyl)anthracene system. An extension of this idea to the chelating diene 9,10-bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene has not demonstrated these types of rate accelerations to date. The cycloadducts we are working with are relatively rigid "host–guest" complexes and are therefore amenable to the kind of spatial fine-tuning of catalytic groups now recognized as essential in enzymes and successful enzyme models. Experiments designed to afford larger rate accelerations are currently in progress in this laboratory.

Experimental Section

General. Melting points were taken on an electrothermal melting point apparatus and are uncorrected. Microanalyses were carried out at Canadian Microanalytical Service, New Westminster, BC. Mass spectra were obtained by use of a Kratos-30 mass spectrometer. FT-NMR spectra at 11.75 (500 MHz) or 7.0 T (300 MHz) were obtained by using equipment funded in part by NIH Grant 1 S10 RR01458-01A1. We thank Richard Weisenberger and Dr. C. E. Cottrell for their assistance in obtaining mass and high-field ^{1}H NMR spectra, respectively, at The Ohio State University Chemical Instrumentation Center and Carl Engelman for other NMR assistance. Due to difficulties in the purification of polyamine adducts **18–21**, the yields reported reflect an attempt to obtain the purest sample possible, rather than the highest yield possible. Neutral alumina (70–230 mesh, activity 1) for chromatography was obtained from EM Reagents and was deactivated with 3% H_2O prior to use. The determination of first-order rate constants was accomplished by using the computer program LSTSQ, available from Serena Software, 489 Serena Lane, Bloomington, IN, 47401.

HPLC was carried out on an IBM LC/9533 system using an IBM C-18 reversed-phase column and a 20-μL injection loop. Elution was carried out at a flow rate of 2 mL/min with continuous UV detection of the eluant at 254 nm. Solvent systems were used as follows: a pH 2.0 aqueous buffer of 0.2 M potassium phosphate was made from phosphoric acid and KOH. A solution of buffer/methanol (7:4) gave base line separation of acid or amide (elute first) from nitrile or ester (elute later) within 5 min. A solution of buffer/methanol (7:2) gave base line separation of acid (elutes first) from amide (elutes second) within 10 min. This acidic eluant successfully decomposed all metal ion complexes and gave peaks with retention times identical with those obtained by using the corresponding free amines.

The buffer solutions used were 25 mM potassium hydrogen phthalate (KHP) for pH 5.0, 21 mM 2-(*N*-morpholino)ethanesulfonic acid (MES) for pH 6.0, 24 mM *N*-(2-hydroxyethyl)piperazine-*N*′-2-ethanesulfonic acid (HEPES) for pH 7.0 and 8.0, and 26 mM 2-(*N*-cyclohexylamino)ethanesulfonic acid (CHES) for pH 9.0. pH measurements were made with a Fisher Accumet pH meter, Model 810.

Cycloadducts of Acrylonitrile and 9-(2-Pyridyl)anthracene: 3 and 4. A solution of 9-(2-pyridyl)anthracene[19] (**1**; 1.0 g, 3.9 mmol), acrylonitrile (**2**; 10 mL), and hydroquinone (40 mg) was heated at 110 °C in a sealed tube for 20 h. Column chromatography on silica gel eluting with CH_2Cl_2 afforded the ortho adduct (**3**), which was recrystallized from methanol to afford a colorless solid (654 mg, 54%): mp 179–181 °C; ^{1}H NMR ($CDCl_3$) δ 2.07–2.17 (m, 1, C*H*CHCN cis to nitrile), 2.27–2.40 (m, 1, C*H*CHCN trans to nitrile), 3.72–3.80 (m, 1 CHCN), 4.50 (t, 1, J = 2.6 Hz, C*H*CH$_2$CHCN), 6.42–6.46 (m, 1, ArH), 6.95–7.95 (m, 10, ArH), 8.86–8.90 (m, 1, ArH); EI mass spectrum, m/e 308 (M^+).

Anal. Calcd for $C_{22}H_{16}N_2$: C, 85.69; H, 5.23; N, 9.08. Found: C, 85.50; H, 5.23; N, 9.10.

Continued elution of the column with 4% ethanol in CH_2Cl_2 gave the meta adduct (**4**), and recrystallization from methanol gave a colorless solid (124 mg, 10%): mp 244–246 °C; ^{1}H NMR ($CDCl_3$) δ 2.45–2.54 (m, 1, C*H*CHCN cis to nitrile), 2.70–2.82 (m, 1, C*H*CHCN trans to nitrile), 3.00–3.09 (m, 1, CHCN), 4.66 (d, 1, J = 2.4 Hz, C*H*CHCN), 6.79–7.96 (m, 11, ArH), 8.83–8.87 (m, 1, ArH); EI mass spectrum, m/e 308 (M^+).

Anal. Calcd for $C_{22}H_{16}N_2$: C, 85.69; H, 5.23; N, 9.08. Found: C, 85.49; H, 5.30; N, 9.07.

Cycloadducts of Acrylamide and 9-(2-Pyridyl)anthracene: 5 and 7. As reported previously,[12] reaction of anthracene **1** (2.0 g, 7.8 mmol) with acrylamide (**6**; 1.5 g, 22 mmol) and hydroquinone (100 mg) in chlorobenzene (10 mL) at 170 °C in a sealed tube for 53 h gave a mixture of the two products in solution plus polymerized acrylamide as an insoluble residue. The solvent was removed by evaporation, and column chromatography on silica gel eluting with $CHCl_3$ gave first the unreacted anthracene (**1**; 429 mg). Elution with 2% ethanol in chloroform gave the ortho adduct (**5**), which after recrystallization from benzene yielded a colorless solid (448 mg, 18%): mp 240–242 °C dec; ^{1}H NMR ($CDCl_3$) δ 2.00–2.10 (m, 1, C*H*CHCONH$_2$ cis to amide), 2.20–2.33 (m, 1, C*H*CHCONH$_2$ trans to amide), 3.49–3.57 (m, 1, C*H*CONH$_2$), 4.47 (t, 1, C*H*CH$_2$CHCONH$_2$), 5.00 (br s, 1, CONH*H*), 5.76 (br s, 1, CONH*H*), 6.90–6.98 (m, 1, ArH), 7.08–7.98 (m, 10, ArH), 8.79–8.83 (m, 1, ArH); FAB mass spectrum, m/e 327 (M^+ + 1).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.94; H, 5.57; N, 8.58. Found: C, 80.78; H, 5.70; N, 8.53.

Continued elution with 4% ethanol in chloroform gave the meta adduct (**7**), and recrystallization from benzene yielded a colorless, fibrous solid (731 mg, 29%): mp 248–249 °C; ^{1}H NMR ($CDCl_3$) δ 2.36–2.44 (m, 1, C*H*CHCONH$_2$ cis to amide), 2.61–2.73 (m, 1, C*H*CHCONH$_2$ trans to amide), 2.87–2.96 (m, 1, C*H*CONH$_2$), 4.69 (d, 1, J = 2.3 Hz, C*H*CHCONH$_2$), 4.98–5.18 (br s, 2, CONH$_2$), 6.76–6.84 (m, 1, ArH), 7.00–7.95 (m, 10, ArH), 8.84–8.88 (m, 1, ArH); FAB mass spectrum, m/e 327 (M^+ + 1).

Anal. Calcd for $C_{22}H_{18}N_2O$: C, 80.94; H, 5.57; N, 8.58. Found: C, 80.87; H, 5.64; N, 8.54.

Cycloadducts of Ethyl Acrylate and 9-(2-Pyridyl)anthracene: 8 and 10. A solution of 9-(2-pyridyl)anthracene (**1**; 5.0 g, 20 mmol), ethyl acrylate (**9**; 30 g), and hydroquinone (100 mg) was heated at 140 °C in a sealed tube for 40 h. Column chromatography on silica gel eluting with CH_2Cl_2 afforded the ortho adduct (**8**), which was recrystallized from methanol to afford a colorless solid (2.74 g, 39%): mp 130–150 °C; ^{1}H NMR ($CDCl_3$) δ 1.10 (t, 3, J = 3.5 Hz, CH_3), 1.56–1.85 (m, 1, C*H*CHCO$_2$CH$_2$CH$_3$ cis to ester), 2.22–2.54 (m, 1, C*H*CHCO$_2$CH$_2$CH$_3$ trans to ester), 3.30–3.51 (m, 1, C*H*CO$_2$CH$_2$CH$_3$), 3.77–4.17 (m, 2, CO$_2$C*H*$_2$CH$_3$), 4.43 (t, 1, C*H*CH$_2$CHCO$_2$CH$_2$CH$_3$), 6.43–6.54 (m, 1, ArH), 6.85–7.95 (m, 10, ArH), 8.68–8.76 (m, 1, ArH); EI mass spectrum, m/e 355 (M^+).

Anal. Calcd for $C_{24}H_{22}NO_2$: C, 80.86; H, 6.23; N, 3.93. Found: C, 81.16; H, 6.14; N, 3.94.

Continued elution of the column with $CH_2Cl_2/CHCl_3$ and then with $CHCl_3$ gave first unreacted **1** followed by the meta adduct (**4**). Recrystallization from methanol gave a colorless solid (2.93 g, 42%): mp 146–165 °C; ^{1}H NMR ($CDCl_3$) δ 1.06 (t, 3, J = 2.5 Hz, CH_3), 2.45–2.65 (m, 1, C*H*CHCO$_2$CH$_2$CH$_3$ cis to ester), 2.75–3.10 (m, 2, C*H*CHCO$_2$CH$_2$CH$_3$ trans to ester and C*H*CO$_2$CH$_2$CH$_3$), 3.85–4.18 (m, 2, CO$_2$C*H*$_2$CH$_3$), 4.78 (d, 1, J = 2.5 Hz, C*H*CHCO$_2$CH$_2$CH$_3$), 6.67–8.00 (m, 11, ArH), 8.81–8.91 (m, 1, ArH); EI mass spectrum, m/e 355 (M^+).

Anal. Calcd for $C_{24}H_{22}NO_2$: C, 80.86; H, 6.23; N, 3.93. Found: C, 80.42; H, 6.15; N, 3.91.

Cycloadducts of Acrylic Acid and 9-(2-Pyridyl)anthracene. The direct cycloaddition of acrylic acid to anthracene **1** was unsuccessful, so this adduct was made by hydrolysis of the corresponding ethyl ester. A solution of the ortho ester (**8**; 0.50 g, 0.14 mmol) in concentrated HCl (40 mL) was heated to reflux for 48 h. The reaction mixture was evaporated to 10 mL under reduced pressure and neutralized with dilute NH_4OH, and the remaining solvent was removed by evaporation. The colorless paste was purified by chromatography on silica gel eluting with 4% ethanol in chloroform and was crystallized from ethanol to afford the ortho acid (**11**) as a colorless solid (300 mg, 65%): mp 225–227 °C; ^{1}H NMR ($CDCl_3$) δ 1.99 (m, 1, C*H*CHCOOH cis to acid), 2.57 (m, 1, C*H*CHCOOH trans to acid), 3.69 (m, 1, C*H*COOH), 4.48 (t, 1, C*H*CH$_2$CHCOOH), 6.28 (m, 1, ArH), 6.94–7.61 (m, 9, ArH), 7.98 (m, 1, ArH), 8.78 (m, 1, ArH), 13.05 (br s, 1, COOH); FAB mass spectrum; m/e 328 [(M + 1)$^+$].

Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 80.20;[22] H, 5.28; N, 4.31.

The meta acid (structure not shown in text) was similarly hydrolyzed in concentrated HCl and then was diluted with H_2O, neutralized with NH_4OH, and extracted with $CHCl_3$ (2 × 25 mL). The crystalline solid obtained after evaporation was further purified by using silica gel chromatography, and elution with 4% ethanol in chloroform and recrystallization from ethanol afforded the meta acid in 54% yield: mp 248–250 °C; ^{1}H NMR ($CDCl_3$) δ 2.45 (m, 1, C*H*CHCOOH cis to acid), 2.59 (m, 1, C*H*CHCOOH trans to acid), 2.92 (m, 1, C*H*COOH), 4.50 (br s, 1, COOH), 4.75 (d, 1, J = 3.0 Hz, C*H*CHCOOH), 6.69–7.89 (m, 11, ArH), 8.84 (m, 1, ArH); FAB mass spectrum, m/e 328 [(M + 1)$^+$].

(19) Fields, D. L.; Regan, T. H.; Graves, R. E. *J. Org. Chem.* **1971**, *36*, 2995.

(20) Obtained from the Aldrich Chemical Company, Milwaukee, WI.

(21) A detailed, step-by-step outline for the first-time use of ion-exchange chromatography on a preparative scale is available from this laboratory (A.W.C.) upon written request.

(22) While this value for carbon is slightly less than the theoretical, all other indicators were supportive of our structure assignment.

Anal. Calcd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.23; N, 4.28. Found: C, 79.97;[22] H, 5.24; N, 4.27.

General Procedure for the Metal-Catalyzed Hydration of Nitriles to Amides. Solutions of nitrile adduct **3** (0.02 g, 0.063 mmol) and a metal perchlorate (0.26 mmol) in dioxane–buffer (1:1, v/v, 20-mL total volume) were heated in an oil bath maintained at 100 °C. At regular time intervals, a 5-mL aliquot of the reaction mixture was removed, diluted to 20 mL with water, extracted into $CHCl_3$ (2 × 25 mL), washed with water, and dried over Na_2SO_4. After removal of the solvent under diminished pressure, the colorless pasty mass was analyzed by ^1H NMR spectroscopy; the spectrum had several regions of cleanly separated peaks from either nitrile or amide. Pseudo-first-order rate constants were calculated in the usual way. A sample of the ortho amide (**5**) thusly prepared was identical in all respects with that obtained by the cycloaddition of acrylamide to anthracene **1**.

General Procedure for the Metal-Catalyzed Alcoholysis of Amides to Esters. A solution of amide adduct **5** (0.01 g, 0.031 mmol) and a metal perchlorate (0.13 mmol) in anhydrous ethanol (10 mL) was gently refluxed in an oil bath under nitrogen. At regular time intervals, an aliquot was removed for TLC analysis (silica gel, 4% ethanol in chloroform), which indicated the clean conversion of amide to ester. The half-life was estimated as the time point at which the two spots were of equal intensity, and the corresponding rate constant was derived from the equation $k = 0.693/t_{1/2}$. A sample of the ortho ester (**8**) thusly prepared was identical in all respects with that obtained by the cycloaddition of ethyl acrylate to anthracene **1**.

General Procedure for the Metal-Catalyzed Hydrolysis of Esters to Acids. A solution of ester adduct **8** (0.01 g, 0.031 mmol) and a metal perchlorate (0.13 mmol) in dioxane–buffer (1:1, v/v, 10-mL total volume) was heated in an oil bath at 100 °C. The progress of the reaction was monitored by TLC as above, which indicated the clean conversion of ester to acid, and the half-life and rate constants were estimated as done previously. A sample of the ortho acid (**11**) thusly prepared was identical in all respects with that obtained by the acid-catalyzed hydrolysis of the ortho ester from the cycloaddition of ethyl acrylate to anthracene **1**.

Kinetics of Cycloreversion in Adducts 3, 5, 8, and 11. The rates of cycloreversion in these adducts were determined in diphenyl ether at 200 °C and [adduct] = 7.5×10^{-5} M. By following the increase in the absorbance at 368 nm as a function of time, least-squares analyses gave the following rate constants (reported as 10^5k, s^{-1}): nitrile **3**, 1.5; amide **5**, 6.1; ester **8**, 5.2; and acid **11**, 17.7.

9,10-Bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene (16). A mixture of 9,10-bis(chloromethyl)anthracene[16] (**14**; 10 g, 36 mmol), anhydrous K_2CO_3 (10 g), dry DMF (100 mL), and *N,N,N'*-trimethylethylenediamine[20] (**15**; 10 g, 98 mmol) was desiccated and stirred at room temperature. After 20 h, the mixture was filtered, and the filtrate was reduced to a small volume on a vacuum pump equipped rotary evaporator and poured into water (300 mL). The aqueous solution was made strongly basic with KOH and extracted with hexane (3 × 250 mL) [note: the resulting emulsion was easily dispersed by using gravity filtration], and the pooled organic phase was dried over anhydrous K_2CO_3 and evaporated to dryness. Chromatography on 400 g of alumina (3% added H_2O) eluting with $CHCl_3$ gave the product as a yellow oil that crystallized on standing. The solid was dried in vacuo at 35 °C to afford an orange-yellow solid (2.0 g, 14%): mp 64–65 °C; TLC (chloroform/alumina) R_f 0.4; ^1H NMR ($CDCl_3$) δ 2.2 (s, 12, $N(CH_3)_2$), 2.3 (s, 6, NCH_3), 2.4–2.8 (m, 8, CH_2CH_2), 4.5 (s, 4, $ArCH_2$), 7.5 (dd, 4, ArH), 8.6 (dd, 4, ArH); field desorption mass spectrum, *m/e* 407 $(M + H)^+$.

Anal. Calcd for $C_{26}H_{38}N_4$: C, 76.80; H, 9.42; N, 13.78. Found: C, 76.59; H, 9.32; N, 13.79.

(9,10-Bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene-*N,N',N'',N'''*)dizinc Tetrachloride (17). To a hot, stirred solution of anhydrous $ZnCl_2$ (400 mg, 2.9 mmol) in methanol (60 mL) was added all at once a solution of 9,10-bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene (**16**; 500 mg, 1.2 mmol) in methanol (20 mL). Immediately after addition, stirring was stopped, and the product was allowed to crystallize as the solution cooled slowly to room temperature. The resulting solid was collected by filtration, washed with methanol (3 × 30 mL), and dried at 70 °C in vacuo overnight to afford a light-yellow solid (730 mg, 87%): mp dec above 280 °C; TLC (chloroform/alumina) R_f 0.4 (coelutes with **1**); ^1H NMR ($(CD_3)_2SO$) δ 2.3 (s, 18, $N(CH_3)_2$ and NCH_3), 2.5–3.0 (m, 8, CH_2CH_2), 4.7 (s, 4, $ArCH_2$), 7.7 (dd, 4, ArH), 8.7 (dd, 4, ArH).

Anal. Calcd for $C_{26}H_{38}Cl_4N_4Zn_2$: C, 45.98; H, 5.64; Cl, 20.88; N, 8.25; Zn, 19.25. Found: C, 45.93; H, 5.72; Cl, 20.61; N, 8.07; Zn, 19.4.

Cycloadduct of Acrylonitrile and 9,10-Bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene: 18. A solution of anthracene **16** (950 mg, 2.3 mmol) and BHT (40 mg) in acrylonitrile (30 mL) was heated in a sealed tube at 175 °C with stirring for 13 h. After cooling to room temperature, the resulting mixture was filtered and evaporated to yield a yellow syrup. Chromatography on a column of alumina (18 × 3 cm) eluting with $CHCl_3$ separated the product from BHT and a small amount of unreacted starting. Pooling the appropriate fractions and evaporation to dryness gave an almost colorless gum (600 mg, 57%): TLC (chloroform/alumina) R_f 0.8; ^1H NMR ($CDCl_3$) δ 2.1–3.4 [m, 29, all aliphatic H's except "benzylic" CH_2's; notable signals: 2.3 (s, 12, 2 $N(CH_3)_2$), 2.55 (s, 3, NCH_3), 2.6 (s, 3, NCH_3)], 3.55 (dd, 2, benzylic CH_2), 3.8 (dd, 2, benzylic CH_2), 7.0–7.6 (m, 8, ArH); FAB mass spectrum, *m/e* (relative intensity) 460 (100, $[M + 1]^+$), 415 (20, $[M - N(CH_3)_2]^+$), 401 (50, $[M - CH_2N(CH_3)_2]^+$).

A sample was purified further for microanalysis by using Sephadex CM-25 ion-exchange chromatography[21] and elution with 0–0.9 M NH_4HCO_3. Fractions were examined at 258 nm, pooled, and evaporated to dryness several times from water to afford an almost colorless gum.

Anal. Calcd for $C_{29}H_{41}N_5 + 0.5H_2O$: C, 74.32; H, 9.03; N, 14.92. Found: C, 74.54; H, 8.86; N, 15.18.

Cycloadduct of Acrylamide and 9,10-Bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene: 19. The direct cycloaddition of acrylamide to anthracene **16** was unsuccessful, so we prepared this adduct from the corresponding nitrile. A mixture of **18** (600 mg, 1.5 mmol) in concentrated H_2SO_4 was swirled at room temperature to obtain a homogeneous solution (about 1 h required), and then the resulting solution was heated at 60 °C for 2 h. The reaction mixture was poured onto ice (100 g), and the solution was adjusted to pH >10 with KOH and extracted with $CHCl_3$ (3 × 100 mL). The organic phase was dried over K_2CO_3 and evaporated to afford a light-yellow glass. Chromatography on a column of alumina (30 × 2.5 cm) was accomplished first with $CHCl_3$ (to remove unreacted starting material) and then with 3% methanol in $CHCl_3$ (to elute the product). Pooling the appropriate fractions and evaporation to dryness gave the crude product, which was dissolved in aqueous HCl, washed with $CHCl_3$, made basic with KOH, and extracted with $CHCl_3$. This organic phase was dried over K_2CO_3 and evaporated to dryness. Ion-exchange chromatography on Sephadex CM-25 with a linear gradient of 0–0.9 M NH_4HCO_3 and monitoring at 258 nm gave a single major peak void of absorptions above 300 nm. The fractions were pooled, evaporated several times from H_2O, and lyophilized to afford a colorless solid (82 mg, 11%): TLC (chloroform/alumina) R_f 0.2; ^1H NMR ($CDCl_3$) δ 2.2–3.2 [m, 29, all aliphatic H's except benzylic CH_2's; notable signals: 2.2 (s, 6, $N(CH_3)_2$), 2.3 (s, 6, $N(CH_3)_2$), 2.5 (s, 3, NCH_3), 2.6 (s, 3, NCH_3)], 3.6 (dd, 2, benzylic CH_2), 3.7 (s, 2, benzylic CH_2), 5.05 (br s, 0.6, one amide NH, exchangeable with D_2O), 7.0–7.6 (m, 8, ArH), 7.9 (br s, 0.6, one amide NH, exchangeable with D_2O); FAB mass spectrum, *m/e* (relative intensity) 478 (100, $[M + 1]^+$), 419 (30, $[M - CH_2N(CH_3)_2]^+$).

Anal. Calcd for $C_{29}H_{43}N_5O + 1.1H_2O$: C, 70.01; H, 9.16; N, 14.08. Found: C, 69.66; H, 8.74; N, 13.96.

(Note: In one preparation of this compound we eliminated the alumina column purification step; this gave a much higher yield of the amide (50%), but the sample was not subjected to microanalysis. In addition, HPLC analysis indicates about 10% of a UV impurity that is not compound **4**; if this is an anthracene, it probably represents less than a 1% material impurity.)

Cycloadduct of Ethyl Acrylate and 9,10-Bis(((2-(dimethylamino)ethyl)methylamino)methyl)anthracene: 20. A solution of **16** (3.0 g, 7.4 mmol) and hydroquinone (20 mg) in ethyl acrylate (100 mL) was heated in a sealed tube at 145 °C with stirring for 72 h. After cooling to room temperature, the resulting solution was evaporated to yield a yellow syrup. The crude product was dissolved in aqueous HCl (150 mL, pH <2), washed with $CHCl_3$ (2 × 100 mL), adjusted to pH >10 with KOH, and extracted with $CHCl_3$ (2 × 150 mL); the organic phase was dried over K_2CO_3 and evaporated to give a yellow gum. Chromatography on a column of alumina (11 × 5.5 cm) eluting with $CHCl_3$ separated the product from a small amount of unreacted starting material. Pooling the appropriate fractions and evaporation to dryness gave a light-yellow gum (2.7 g, 73%): TLC (chloroform/alumina) R_f 0.6; ^1H NMR ($CDCl_3$) δ 1.1 (t, 3, CH_2CH_3), 1.6–4.1 [m, 31, all aliphatic H's except ethyl CH_3; notable signals: 2.25 (s, 6, $N(CH_3)_2$), 2.3 (s, 6, $N(CH_3)_2$), 2.45 (s, 3, NCH_3), 2.55 (s, 3, NCH_3)], 7.0–7.7 (m, 8, ArH); FAB mass spectrum, *m/e* (relative intensity) 507 (40, $[M + H]^+$), 505 (100, $[M - H]^+$), 448 (50, $[M - CH_2N(CH_3)_2]^+$).

A sample for microanalysis was further purified as follows: CM-25 Sephadex ion-exchange chromatography afforded three peaks with absorptions at 254 nm. The middle peak (the only one without a 400-nm absorption) was evaporated to afford a colorless solid, which was dissolved in acetonitrile (10 mL) and added to 40 mL of water. After swirling to homogeneity, the milky solution stood at room temperature for 24 h, during which time a colorless solid crystallized. The solid was collected by filtration, washed with water (3 × 5 mL), and dried in vacuo at room temperature to afford a colorless crystalline product: mp 84–86

°C; ^{1}H NMR identical with that of the uncrystallized sample.

Anal. Calcd for $C_{31}H_{46}N_4O_2$: C, 73.48; H, 9.15; N, 11.06. Found: C, 73.27; H, 9.02; N, 11.01.

Cycloadduct of Acrylic Acid and 9,10-Bis(((2-(dimethylamino)-ethyl)methylamino)methyl)anthracene: 21. The direct cycloaddition of acrylic acid to anthracene **16** was unsuccessful, so we prepared this adduct from the corresponding ester. A solution of ester **20** (408 mg, 0.8 mmol) in concentrated HCl (50 mL) was heated to reflux for 20 h. The resulting light-green solution was evaporated to dryness, and the residue was chromatographed on a column of Sephadex CM-25 cation-exchange resin by eluting with a linear gradient of 0-0.9 M NH_4HCO_3. Fractions were monitored at 258 nm, and the major peak was pooled, evaporated several times from H_2O, and finally lyophilized from H_2O to afford a hygroscopic colorless solid (180 mg, 48%): ^{1}H NMR (D_2O) δ 1.7 (dd, 1, C*H*CHCOOH cis to acid), 2.3-3.9 [m, 29, aliphatic H's except that from C*H*CHCOOH cis to acid; notable signals: 2.35 (s, 6, $N(CH_3)_2$), 2.4 (s, 3, NCH_3), 2.5 (s, 3, NCH_3), 2.65 (s, 6, $N(CH_3)_2$)], 7.0-7.5 (m, 8, ArH).

Anal. Calcd for $C_{29}H_{42}N_4O_2 + 1.5H_2O$: C, 68.88; H, 8.97; N, 11.08. Found: C, 69.15; H, 8.61; N, 11.10.

Kinetic Measurements in the Attempted Conversion of Nitrile 18 to Amide 19 (Reaction A, Scheme VI). The attempted conversion of **18** to **19** was monitored conveniently by HPLC as described in the general Experimental Section with the 7:4 solvent system. Typical retention times at a flow rate of 2 mL/min are nitrile **4**, 6 min; amide **5**, 3 min; and acid **11**, 2 min. A solution of Na-HEPES buffer (pH 9.5, 66.67 mM) containing nitrile **4** (1.67 mM) and metal perchlorate (20 mM) was heated at 94 °C in a pressure tube, and aliquots were withdrawn at various times for HPLC analysis. The control reaction was identical, except that there was no added metal ion. The formation of amide was not observed in any of these reactions, though even a few percent conversion would have been detectable.

Attempted Conversions of Amide 19 to Ester 20, Amide 19 to Acid 21, and Ester 20 to Acid 21 (Reactions B, C, and D, Scheme VI). Each attempted conversion was carried out similarly to that described above by using Cu^{2+}, Ni^{2+}, Zn^{2+}, and Co^{2+}, a variety of pHs between 5 and 9.5, and temperatures as high as 95 °C. The formation of the expected product was not observed in any of these reactions, though even a few percent conversion would have been detectable.

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Mechanistic Studies on the Mode of Reaction of Mitomycin C under Catalytic and Electrochemical Reductive Conditions[1]

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Abstract: The catalytic and electrochemical reduction of select mitosene derivatives and mitomycin C (**1**) are described. Treatment of *trans*- (**11**) and *cis*-1-hydroxy-2,7-diaminomitosene (**13**) with PtO_2 and H_2 led to the formation of the novel carbon-10 methyl products **12** and **14**, respectively. The corresponding 1-methoxy-2,7-diaminomitosene carbon-10 methyl adducts **19** and **20** were obtained from the controlled potential reduction of **1** at mercury (-1.5 V vs. SCE) or platinum (-1.0 or -1.2 V vs. SCE) electrodes in methanol. At a lower applied voltage (mercury electrode, -0.8 V), reduction of **1** in methanol gave predominantly *trans*- (**17**) and *cis*-1-methoxy-2,7-diaminomitosenes (**18**). The product profile of **1** in aqueous buffered solutions (pH 5.0, 6.5, 8.0) has also been elucidated. At pH 5.0, 2,7-diaminomitosene (**30**) and 10-decarbamoyl-2,7-diaminomitosene (**31**) were produced in high yields; while at pH 8.0, the major compounds isolated were *trans*- (**11**) and *cis*-1-hydroxy-2,7-diaminomitosene (**13**) and *cis*-2-acetamido-1-hydroxy-7-aminomitosene (**32**). The electroreduction of mitomycin C and *trans*- (**17**) and *cis*-1-methoxy-2,7-diaminomitosenes (**18**) were also investigated by cyclic voltammetry and ESR spectroscopy. These data were used in conjunction with the observed product profiles to postulate probable pathways in both the methanol and aqueous reduction experiments. Significantly, loss of methanol and aziridine ring-opening in **1** proceeds from the quinone anion radical stage. The isolation of the carbon-10 methyl products (**12**, **14**, **19**, and **20**) in the methanol-based experiments provides evidence that reaction at this site funnels through an iminium ion.

Mitomycin C (1) is a clinically significant antineoplastic antibiotic in which several key functional groups are exquisitely deployed within the drug.[2] Recent studies[3-15] have begun to unmask the chemical role of many of these groups and have contributed to the contention that mitomycin C functions as a bioreductive alkylating agent where both carbons-1 and -10 are likely DNA binding sites. Consideration of these points led Moore to propose the general mechanism in Scheme I.[16]

(1) This paper has been presented in part. See: *Abstracts of Papers*; The 191st National Meeting of the American Chemical Society, New York, NY, April 13-18, 1986; American Chemical Society: Washington, D.C., 1986; Abstr. Orgn. 184.

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