1,8-Anthracenediethynylbis(catechol boronate): A Bidentate Lewis Acid on a Novel Framework

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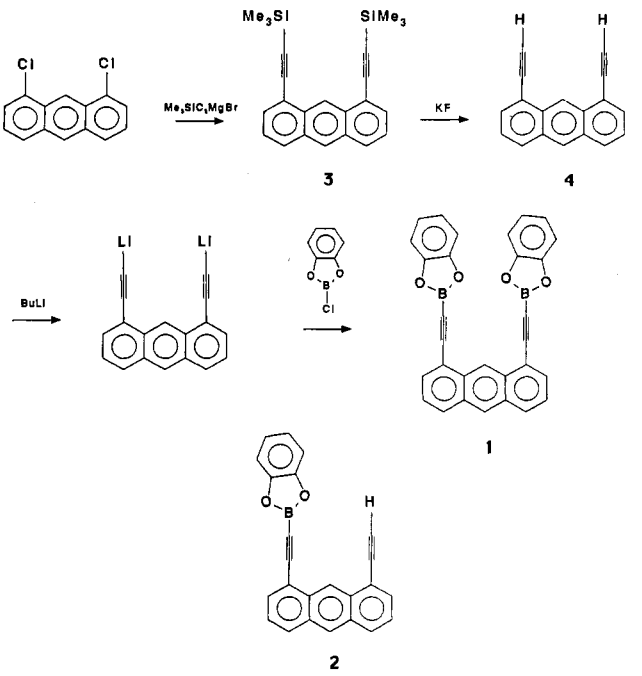
The high-yield synthesis of 1,8-diethynylanthracene (4) in two convenient steps from 1,8-dichloroanthracene is reported. Lithiation of 4 followed by boronation with catecholboron chloride affords the title compound 1. Adducts of 1 with Lewis basic heterocycles were observed in solution by NMR, and evidence for a bridged structure for the complex of 1 with 5-methylpyrimidine is presented. Compound 1 is the first rigid diboron receptor for dibasic guests.

The complexation of anions and Lewis bases by bidentate Lewis acids has progressed considerably since the prototypical complexes were first reported. Recent advances include the encapsulation of Cl^- in a bicyclic tin "cryptand",[1] the structural characterization of a "bis bidentate" macrocyclic organomercury compound,[2] and the observation of bridging between two different Lewis acid groups.[3] The recognition and activation of basic moieties by multiple hydrogen bonding has also become an established technique.[4-8] Application of the complexation phenomenon has extended to bifunctional catalysis of organic reactions,[4,8,9] design of drug receptors,[6] and transport of polar bases into apolar media.[7] A common theme of the latest efforts has been to maintain a degree of specificity in the hosts while designing larger cavities to accommodate correspondingly larger guests or assemblies of guests.

The 1,8-anthracenediethynyl group is a rigid framework for a bidentate ligand, offering a ca. 5 Å bridging distance with minimal steric interference from the anthracene ring, and thus should be useful in the synthesis of complexing agents for guests of considerable size. In principle, a wide variety of functionalities, Lewis acidic or otherwise, could be profitably attached to this framework in the construction of binding sites. Our specific interest in diboron Lewis acids[10] led to the exploration of the 1,8-anthracenediethynyl backbone in that context. Compared to the previously studied 1,8-naphthalenediylbisboranes,[10] the present system affords the opportunity to synthesize cyclic and oxygenated bisboron derivatives with much less steric repulsion of the substituents attached to boron and without filling the binding cavity with the substituent atoms. The formation of cyclic boronic and borinic anhydrides, which was a facile decomposition pathway in the naphthalene series,[10,11] is impossible in the anthracenediethynyl case, again owing to the longer distance between the boron atoms.

Scheme I



This paper describes the synthesis of the title diboronate 1, in which a catecholboron group is attached to each triple bond of the anthracenediacetylene. Molecular models indicate that bridged complexes of 1 with guests containing two basic, sp^2-hybridized atoms in 1,3 relationships, such as in pyrimidine, are nearly strain-free. Such basic moieties occur in nucleotides as well as in many other biologically relevant compounds. Bis(organoborane) complexes of pyrimidines are unknown, although the $(BH_3)_2$ adduct of pyrimidine has been reported.[12] Methylene-linked distannyl complexes of pyrazine and pyridazine have been considered previously, but pyrimidine was not involved in those studies.[13] Pyrimidine has also rarely been utilized as a bridging ligand for transition metals.[14] Because of the potential interest in detection or selective reaction of 1,3-dibasic compounds, we explored the interaction of 1 with a simple 1,3-heterocycle, 5-methylpyrimidine (M5P). For comparison, the additional guests thiazole (T, containing only one significantly basic atom) and 4-methylpyrimidine (M4P, in which one of the basic atoms is sterically hindered) were also investigated. The

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presence of monodentate analogue 2 as an impurity in samples of 1 was exploited in order to observe the effect of the second boron atom on the complexation of 1 with guests.

Results

Synthesis of 1. Diboronate 1 was synthesized as illustrated in Scheme I. The preparation of 1,8-dichloroanthracene by reduction of 1,8-dichloroanthraquinone was carried out as before[15] except that 1,2-dichloroethane was used instead of dichloromethane to extract the crude dihydronaphthol intermediate. [(Trimethylsilyl)ethynyl]magnesium bromide[16] was employed as the nucleophile for the nickel-catalyzed substitution of 1,8-dichloroanthracene to give 3 under conditions similar to those in the previously reported syntheses of 1,8-diarylanthracenes.[15] Substitution of the second chlorine occurs much more slowly than that of the first, especially when the reflux temperature is lowered by the presence of ether in the reaction medium. An attempted alternative substitution reaction on 1,8-dichloroanthraquinone using lithium [(trimethylsilyl)ethynyl]cuprate[17] in THF at 0 °C–room temperature was not successful. Removal of the silyl groups from 3 to obtain 4 occurred under standard conditions.[18]

Conversion of 4 to a diboronate was attempted using several combinations of reagents. It was found that isolated, sublimed catecholboron chloride[19] was a superior boronating reagent compared to catecholboron chloride prepared in situ from either catechol and BCl_3 or catecholborane and HCl. The model reaction of (phenylethynyl)lithium with catecholboron chloride cleanly produced phenylethynyl catechol boronate, whereas (phenylethynyl)magnesium bromide in reaction with methyl catechol borate did not.[20-23] The use of hexane, in which the anthracene derivatives are sparingly soluble, as the lithiation solvent for 4 helped protect the dianion of 4 from decomposition pathways such as nucleophilic attack on the central ring. However, it was necessary to employ ether as cosolvent for the boronation of the dilithiate to ensure sufficient solubility for complete reaction. The addition of toluene to the medium had little effect on the boronation.

The precipitate obtained from the reaction of 4 contained 1 and 2 as well as the oxydimer of catecholboron, lithium salts, and unreacted 4. It was possible to remove 2 and 4 completely by vacuum sublimation at >80 °C; however, this caused extensive decomposition of the residue to an infusible material. Extraction of the precipitate with dichloromethane followed by reprecipitation of the concentrated extract from dichloromethane–ether removed virtually all of the impurities without decomposition. NMR and analytical data were consistent with the assigned structures of 1, 3, and 4.

Interaction of 1 with Heterocycles. Titrations of 1 dissolved in CD_2Cl_2 with T, M4P, and M5P were performed, and changes in the chemical shifts of the aryl protons were observed. Approximately 15 mol% of 2 was present in these solutions as well, and complexation of the heterocycles with 2 was monitored by observation of the acetylenic proton chemical shift. Plots of the chemical shift of H9 of 1 versus equivalents of heterocycle/equivalents of boron compounds are shown in Figure 1. While the curves for the T and M4P experiments smoothly approach asymptotic values for the chemical shifts at complete complexation, the trace for M5P changes slope drastically at the addition of ca. 1 equiv of guest and again, though less dramatically, at ca. 2.5 equiv addition. A plot of the acetylenic proton shift of 2 versus amount of M5P added, shown in Figure 2, resembles plots of 1 with T and M4P; plots of 2 verus added T and M4P were similarly

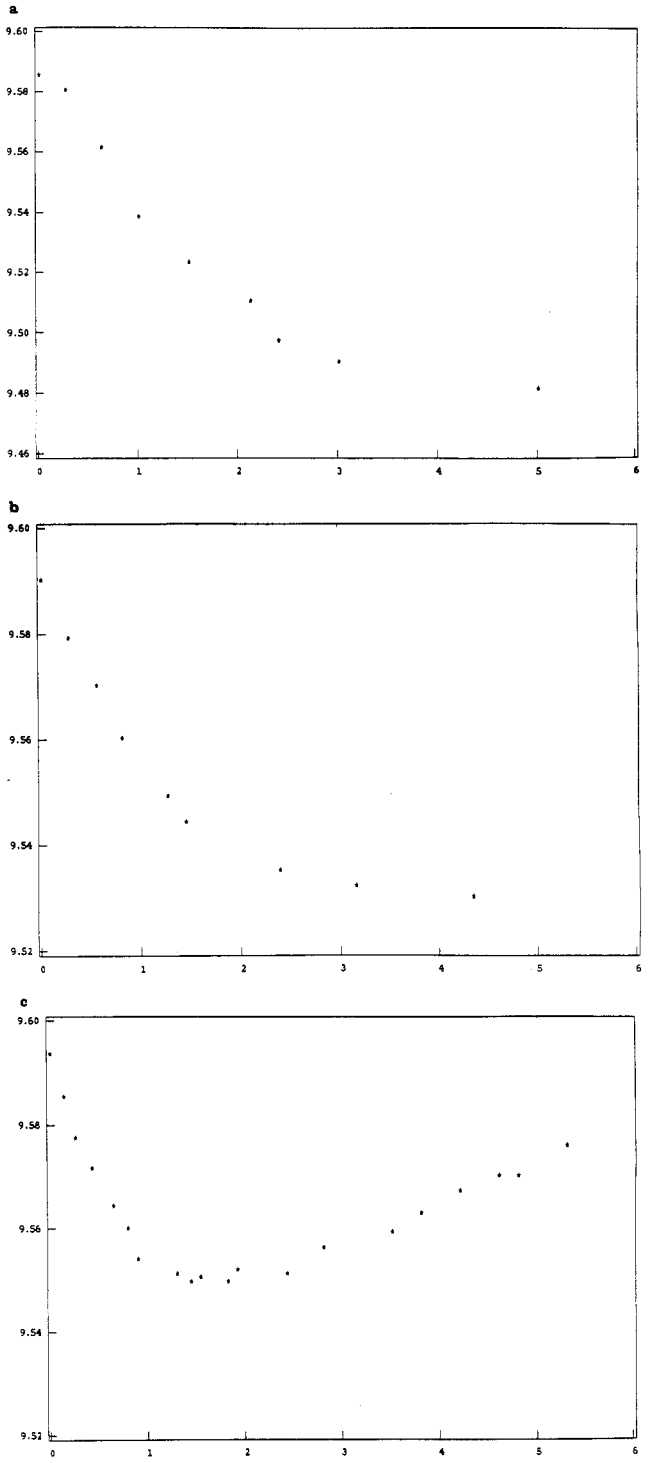

Figure 1. Chemical shift of H9 of 1 vs equivalents of heterocycle/equivalents of boron compound. Heterocycles are (a) T, (b) M4P, and (c) M5P.

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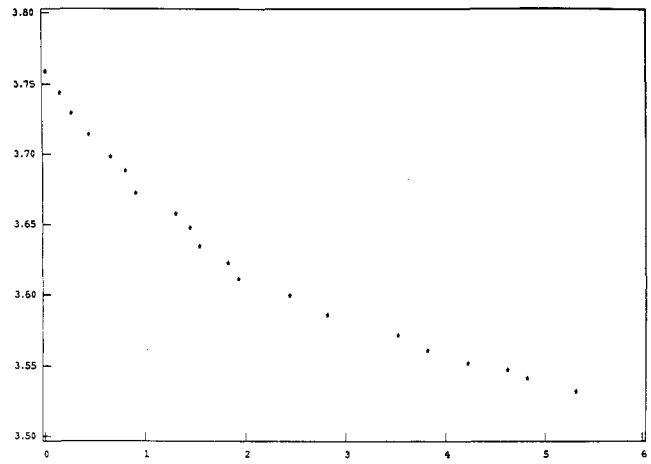

Figure 2. Chemical shift of the acetylenic proton of **2** vs equivalents of M5P/equivalents of boron compound.

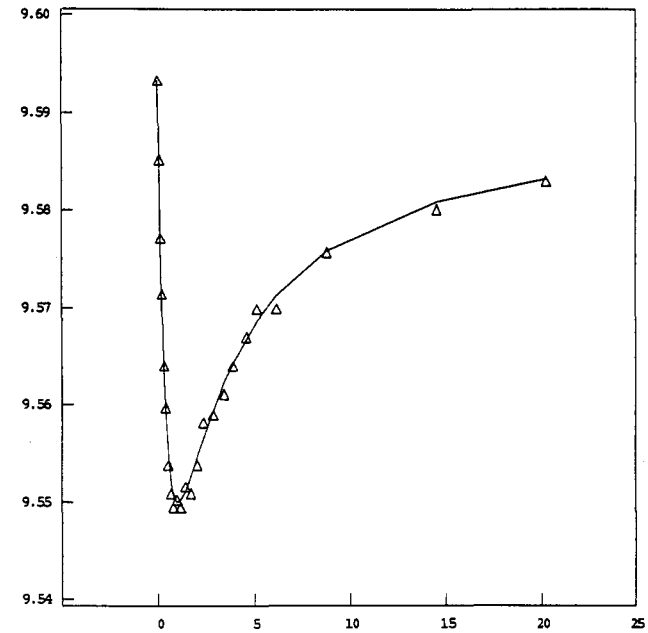

Figure 3. Chemical shift of H9 of **1** vs ratio of complexed to uncomplexed **2**. Triangles are experimental data; the curve is the calculated, optimized function.

unremarkable. Guest proton chemical shifts were invariably moved downfield upon complexation, although the degree of complexation could not be rigorously derived from them because the chemical shifts of the free guests varied by 10–20% of the difference between free and complexed shifts over the concentration range studied. π stacking equilibria, between hosts and guests, that are unrelated to the borons may have also perturbed the equilibrium constants, but should not have significantly altered their ratios.

Although the hosts could only be examined over a narrow concentration range, their chemical shifts were essentially constant from sample to sample. Both M5P and M4P displayed comparable affinities to **1**, and low-temperature NMR showed that the various species present in a solution of **1** and M5P were in rapid equilibrium at −100 °C. The acetylenic proton shift of **4**, also present as a minor contaminant, was unchanged throughout all of the titrations, eliminating interactions not involving boron as the cause of the chemical shift differences.

Data from the M5P experiment were used to estimate the equilibrium constants for the complexation of **1** and **2** with M5P, as indicated in Scheme II. Limiting chemical

Scheme II

$$D + G \rightleftharpoons DG; \quad [DG] = K_1[D][G]$$

$$DG + G \rightleftharpoons DG_2; \quad [DG_2] = K_2[DG][G] = K_2K_1[D][G]^2$$

$$M + G \rightleftharpoons MG; \quad [MG] = K_3[M][G]$$

$[D] = D_o - K_1[D][G] - K_2K_1[D][G]^2$, where subscript o indicates total concentration of the component.

$$[D] = \frac{D_o}{1 + K_1[G] + K_2K_1[G]^2}$$

$$\delta_1 = \frac{\delta_D[D]}{D_o} + \frac{\delta_{DG}[DG]}{D_o} + \frac{\delta_{DG_2}[DG_2]}{D_o}$$

$$\delta_1 = \frac{\delta_D + \delta_{DG}K_1[G] + \delta_{DG_2}K_2K_1[G]^2}{1 + K_1[G] + K_2K_1[G]^2}$$

$$[G] = \frac{[MG]}{[M]K_3} = \frac{\delta_M - \delta_2}{\delta_2 - \delta_{MG}} \cdot \frac{1}{K_3} = \frac{R}{K_3}$$

let $K_1 = yK_3$ and $K_2 = zK_3$

$$\delta_1 = \frac{\delta_D + \delta_{DG}yR + \delta_{DG_2}yzR^2}{1 + yR + yzR^2}$$

$\delta_D = 9.5933 \pm .002$

$\delta_{DG_2} = 9.5903 \pm .003$

$\delta_M = 3.7579 \pm .002$

$\delta_{MG} = 3.5052 \pm .02$

δ_1, R are measured and plotted

δ_{DG}, y, and z are adjusted to give a best fit:

$\delta_{DG} = 9.505 \pm .005$; $y = 1.9 \pm 0.1$; $z = 0.55 \pm 0.05$

when $R = 1$, $K_3 = \frac{1}{[G]}$

$$[G]_{R=1} = G_o - [MG] - [DG] - 2[DG_2]$$

$$= G_o - \frac{M_o}{2} - \frac{yD_o}{1 + y + yz} - \frac{2yzD_o}{1 + y + yz}$$

$G_o = .032$ M, $D_o = .015$ M, $M_o = .003$ M

$$[G]_{R=1} = \frac{1}{K_3} = .014 \text{ M}; \quad K_3 = 70, \; K_1 = 130, \; K_2 = 40$$

shifts of fully complexed hosts were determined from solutions containing up to 20 equiv of guests; these determinations do not appear in Figures 1–3. The chemical shift of H9 of **1** (δ_1) is expressed as a function of the ratio of complexed to uncomplexed **2** [*R*, calculated in turn from the measured acetylenic shifts of **2** (δ_2)] and three adjustable parameters. The parameters were optimized both by use of a curve-fitting computer program and by trial-and-error minimization of the sum of the squares of the differences between δ_1 and the function, using Lotus 1,2,3. Both the experimental data and the optimized function are plotted in Figure 3; typical deviations of the data from

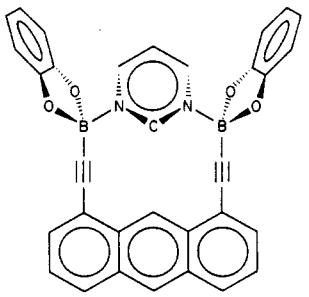

Figure 4. Molecular model based structure of the complex of 1 with pyrimidine.

the fitted curve are less than the error in the measurements. The experiment suggests that the first complexation constant of 1 with M5P (130 M^{-1}, ΔG = −2.9 kcal/mol) is almost double that of 2 with M5P (70 M^{-1}, ΔG = −2.5 kcal/mol), whereas the second binding constant of 1 with the same guest (40 M^{-1}, ΔG = −2.2 kcal/mol) is about half that of 2. In thermodynamic terms, the free-energy advantage in forming the bridged complex is about equal to the disadvantage in breaking the bridge bond to form 1·(M5P)$_2$. Also calculated is the unobservable chemical shift of 1·M5P, which is upfield of the corresponding resonances of 1·(M5P)$_2$ and 1·(M4P)$_2$.

Discussion

The synthesis of 4 is a great improvement over the one previously reported,[24] in which a mixture of diacetylanthracenes was prepared and separated and the 1,8 isomer was converted to 4 in 5–10% overall yield from anthracene. The anthracenediethynyl unit combines two of the rigid spacers, anthracene[25] and acetylene,[26] that have recently found utility in host–guest chemistry.

Although no direct structural information has yet been obtained, it is likely that 1·M5P is a bridged complex whose general structure may be represented by Figure 4. The gross difference between the shapes of curve 1c and curves 1a, 1b, and 2 indicates a phenomenon unique to the two-point binder M5P in combination with 1. An alternative interpretation is that the 1:1 complex of 1 with M5P is a linear polymer of the form ...1...M5P...1...M5P... which breaks up as the 2:1 complex is formed on the addition of excess M5P. This interpretation does not account for the thermodynamic stability of the 1:1 complex versus the 2:1 complex, nor does it explain the extremely upfield H9 shift calculated for the 1:1 complex or the surprising inflection in the chemical shift as the 2:1 complex appears. Invocation of bridging in these complexes might explain the unusual NMR behavior by virtue of the guest acting as a local "shift reagent" for H9. A modest chelate effect is observed in the competition between 1 and 2 for M5P, whereas no such effect is observable for T and M4P, in which only one sterically unencumbered, basic site is available for Lewis acid complex formation. A slightly larger effect had been noted in the distannacycle–Cl^- system.[27] It should be pointed out that bridging may occur even when there is no chelate effect at all, as was the case in the borylsilylnaphthalene F^- complex.[3]

Compound 1 is the first example of a diboron complexing partner for a dibasic heterocycle. The present discovery of a host geometry for pyrimidine might lead to the preparation of a new class of nucleotide receptors. The presence of an extended π system in the framework may lend intercalation activity to such a receptor or enable the sensing or further modification of its complexes by photochemical techniques. Although we found 1 itself to be too labile for anion complexation studies,[22,23] molecular models show that the positioning of its receptor groups is appropriate for anions such as acetate and phosphate, in addition to the neutral heterocyclic bases discussed here. The use of a non-boron Lewis acid, or else a spacer other than acetylene, might open this avenue for exploration as well.

Experimental Section

All reactions were performed on an argon–vacuum line. Boron compounds and heterocyclic bases were manipulated in an inert atmosphere. NMR spectra were obtained on a Bruker 360-MHz instrument. Proton and ^{13}C spectra are referenced to Me_4Si; ^{11}B spectra are referenced to $BF_3{\cdot}OEt_2$. Titrations were performed by adding 5-μL aliquots of stock solutions of heterocycles in CD_2Cl_2 by syringe to 1-mL solutions of 1 in CD_2Cl_2. Essentially identical results were obtained from 0.015 M and 0.019 M solutions of 1. Although examination of a wider concentration range might have been desirable, the relative insolubility of 1 precluded this. The quantity of added guest present at R = 1, used for the estimation of the binding constants, is taken from the point on Figure 2 where the chemical shift of 2 is midway between its free value and its asymptotic limit. All solvents were anhydrous reagent grade.

(1,8-Anthracenediyldiethynylene)bis(trimethylsilane) (3). To a suspension of 1,8-dichloroanthracene[15] (8.0 g, 0.033 mol), $Ni(acac)_2$ (16 mg), and PPh_3 (33 mg) in 60 mL of THF was added a solution of [(trimethylsilyl)ethynyl]magnesium bromide[16] [prepared from (trimethylsilyl)acetylene (23 mL, 16 g, 0.17 mol) and ethylmagnesium bromide (80 mL, 2 M in THF, 0.16 mol) in 180 mL of additional THF, 0 °C to room temperature, 45 min, with VIGOROUS gas evolution]. The mixture was heated at reflux for 3 days. An analytical sample was prepared by chromatography on silica gel, eluting with CH_2Cl_2–petroleum ether, obtaining a pale yellow solid: ^1H NMR ($CDCl_3$) δ 0.37 (s, 18, MeSi), 7.35 (B of ABC, 2, H3 and H6), 7.75 (C of ABC, 2, J = 9 Hz, H4 and H5), 7.95 (A of ABC, 2, J = 9 Hz, H2 and H7), 8.38 (s, 1, H10), 9.29 (s, 1, H9); mass spectrum (rel intensity) 370 (100, M^+), 267 (40), 73 (30). Anal. Calcd for $C_{24}H_{26}Si_2$: C, 77.77; H, 7.07. Found: C, 77.88; H, 7.07.

1,8-Diethynylanthracene (4). Crude 3 from above was treated with 6.0 g of KF in 500 mL of EtOH for 2 h at reflux. The solvent was removed and the residue taken up in 300 mL of H_2O and 200 mL of toluene. The aqueous layer was extracted with 100 mL of additional toluene. The combined toluene layers, including suspended solids, were concentrated to 6.2 g (85% overall yield from dichloroanthracene): ^1H NMR ($CDCl_3$) δ 3.60 (s, 2, ethynyl H), 7.44 (B of ABC, 2, H3 and H6), 7.74 (C of ABC, 2, J = 9 Hz, H4 and H5), 8.01 (A of ABC, 2, J = 9 Hz, H2 and H7), 8.44 (s, 1, H10), 9.42 (s, 1, H9); ^{13}C NMR ($CDCl_3$) δ 81.7 (quat ethynyl), 82.6 (tert ethynyl), 120.3 (C1 and C8), 123.7 (C9), 125.0 (C3 and C6), 127.5 (C4 and C5), 129.4 (C10), 131.3 (quat aryl), 131.5 (C2 and C7); mass spectrum 226 (M^+). A sample was recrystallized from toluene, and the resulting yellow plates melted at 150 °C with discoloration, in agreement with the literature.

2,2′-(1,8-Anthracenediyldiethynylene)bis(2*H*-benzo[*d*]-1,3,2-dioxaborole) (1). A suspension of 4 (1.3 g, 5.8 mmol) in 100 mL of hexane was cooled to 0 °C. A slight excess of *n*-BuLi (13 mmol) was added, and the cooling bath was removed. After 1.5 h, the lithiate mixture was added to a solution of catecholboron chloride[19] (2.3 g, 15 mmol) in 75 mL of ether containing 1 mmol of *n*-BuLi. The combined mixtures were stirred overnight at ambient temperature and then allowed to settle. Some of the supernatant liquid (containing a small amount of unreacted 4) was removed directly by cannula and the rest by filtration under an inert atmosphere. The solids were extracted successively with

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20 mL, 15 mL, and 10 mL of CH_2Cl_2 and the combined extracts filtered, concentrated, and transferred to a dry box. The solid concentrate consisted mostly of 1, but contained significant amounts of 2, 4, and catecholborate impurities. A single reprecipitation from CH_2Cl_2–ether gave 250 mg of 1 as a yellow solid contaminated with 15% and 10% of 2 and 4, respectively. This sample was used for the NMR titration experiments. A second reprecipitation yielded an analytical sample. Calcd for $C_{30}H_{16}B_2O_4$: C, 77.98; H, 3.49; B, 4.68. Found: C, 74.76; H, 3.72; B, 5.01. The low value for C is probably due to retained CH_2Cl_2 (observable by NMR), which could not be removed because of the thermal instability of 1. As little as 0.25 equiv of retained CH_2Cl_2 would depress the C value to 75.17% while marginally affecting the data for H and B. The exact amount of the retained solvent could not be determined by NMR because of contamination of the only suitable NMR solvent, CD_2Cl_2, with protio solvent. ^1H NMR (CD_2Cl_2): δ 7.04 and 7.08 (AA'BB', 8, catechol H), 7.55 (B of ABC, 2, H3 and H6), 7.98 (C of ABC, 2, J = 7 Hz, 1 Hz, H4 and H5), 8.17 (A of ABC, 2, H2 and H7), 8.58 (s, 1, H10), 9.59 (s, 1, H9). ^{13}C NMR (CD_2Cl_2): δ 112.4 (catechol C2), 119.1 (C1 and C8), 123.0 (catechol C3), 123.2 (C9), 125.1 (C3 and C6), 130.8 (C4 and C5), 131.4 (C10), 133.0 (C2 and C7), 147.8 (catechol C1). ^{11}B NMR (CD_2Cl_2): δ 26 (phenylethynyl catechol boronate, prepared analogously to 1 from (phenylethynyl)lithium, had $\delta(^{11}B)$ = 24 ppm). Mass spectrum: 462 (M^+). Since phenylethynyl catechol boronate was only prepared while determining the feasibility of reaction, it was not further characterized.

Acknowledgment. I am grateful to A. M. Mujsce for obtaining the mass spectra. I also thank W. R. Reents, L. H. Dubois, C. W. Dirk, and M. F. Katz for help in plotting and fitting the equilibrium constant data and B. Askew for useful discussions.

Registry No. 1, 119818-99-4; 2, 119796-30-4; 3, 119796-31-5; 4, 78053-58-4; T, 288-47-1; M4P, 3438-46-8; M5P, 2036-41-1; $Ni(acac)_2$, 3264-82-2; Me_3SiC_2MgBr, 61210-52-4; 1,8-dichloroanthracene, 14381-66-9; catecholboron chloride, 55718-76-8.

Synthesis of Exogonic Acid and Related Compounds

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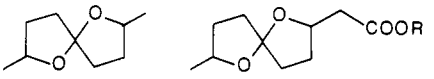
Hydroxymercuration, cyclization, and reduction of appropriate hydroxy ketones or enones carrying a suitably located α,β-unsaturated ester function is an efficient route to exogonic acid (2-(carboxymethyl)-7-methyl-1,6-dioxaspiro[4.4]nonane), a resin constituent of the Brazilian tree *Ipomoea operculata* (Martin), and related [4.5] and [5.5] spiroketal systems. Procedures incorporating stereocontrol at C-2 and C-7 of exogonic acid are also reported and involve sequential alkylation with epoxypropane and 1,2-epoxy-4-(tetrahydropyranyloxy)butane of anions (or dianions) derived from methyl acetoacetate or acetone dimethylhydrazone.

Introduction

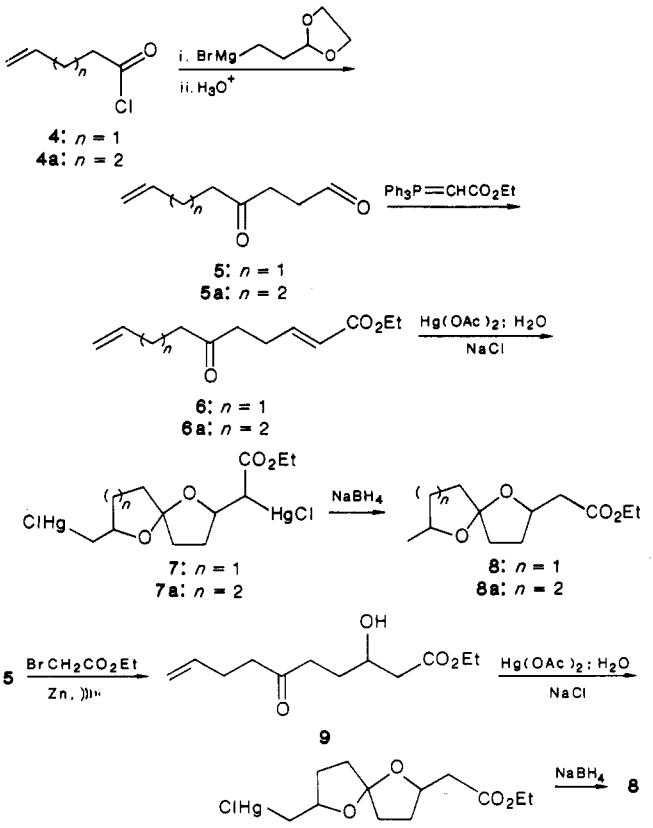
Spiroketals of relatively low molecular weight have been identified as grandular components in a variety of insect species,[1,2] and determinations of chirality, largely by capillary gas chromatography using chiral stationary phases, have been undertaken on some of these in the context of their anticipated pheromonal behavior.[3,4] Although the simple spiroketal, 2,7-dimethyl-1,6-dioxaspiro[4.4]nonane (1), is unknown as a natural product, its structural isomer,



1 2, R = H 3, R = CH_3

2-methyl-1,6-dioxaspiro[4.5]decane, has been identified in species of wasp[1a] and fruit fly.[5] 1 is structurally related to 2-(carboxymethyl)-7-methyl-1,6-dioxaspiro[4.4]nonane (exogonic acid) (2), a constituent of the resin of the Brazilian tree *Ipomoea operculata* (Martin).[6] Graf and

Scheme I



Dahlke[6] reported that methyl exogonate (3) was an optically active diastereomeric mixture, and we became interested in establishing some stereochemical detail for both

(1) See for example, (a) Francke, W.; Hindorf, G.; Reith, W. *Naturwissenschaften* **1979**, *66*, 618. (b) Bergström, G.; Tengö, J.; Reith, W.; Francke, W. *Z. Naturforsch.* **1982**, *37C*, 1124. (c) Baker, R.; Herbert, R.; Howse, P. E.; Jones, O. T.; Francke, W.; Reith, W. *J. Chem. Soc., Chem. Commun.* **1980**, 52. (d) Francke, W. *Les Médiateurs chimiques, INRA* Versailles, 1982, 81.

(2) Kitching, W.; Lewis, J. A.; Fletcher, M. T.; Drew, R. A. I.; Moore, C. J.; Francke, W. *J. Chem. Soc., Chem. Commun.* **1986**, 853.

(3) Haniotakis, G.; Francke, W.; Mor, K.; Redlich, H.; Schurig, V. *J. Chem. Ecol.* **1986**, *12*, 1559.

(4) Kitching, W.; Lewis, J. A.; Perkins, M. V.; Drew, R. A. I.; Moore, C. J.; Schurig, V.; König, W. A.; Francke, W. submitted to *J. Org. Chem.*

(5) Perkins, M. V.; Drew, R. A. I.; Kitching, W. unpublished results.

(6) Graf, E.; Dahlke, E. *Chem. Ber.* **1964**, *97*, 2785. Considerable additional information is contained in Dahlke, E., Dissertation, Univ. Tübingen, 1964.

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