of stabilization as the conjugate with **1b**, but the α-chymotrypsin conjugate with the greatest distance between the anomeric center and the polymer backbone, **3c**-CPC(CT), reproducibly had 10–15% higher thermal stability at 50 °C than the conjugates of **1b** and **2b**. The native proteases also lost their activity in distilled water at 45 °C within 1 h while the CPC analogues retained greater than 80% of their activity over a 24-h period under identical conditions. Circular dichroism studies of **1c**-CPC(CT) confirm that the protein's tertiary structure is retained at temperatures up to 55 °C.[19]

We have immobilized an antibody that binds the pesticide aldrin [**1c**-CPC(M_{ab} 8H11)] and examined its stability in methanol, acetonitrile, and 2-propanol with an enzyme-linked immunoassay. We chose to study M_{ab} 8H11 because the current method of detection of aldrin is limited by the presence of organic solvents in the ELISA.[20,21] We found that **1c**-CPC(M_{ab} 8H11) was competent for 5 h in acetonitrile, methanol, and 2-propanol with 96, 60, and 57% of the original binding, respectively, while the native antibody retained no binding ability under identical conditions.[22]

We have also examined the use of CPC(proteases) and CPC(endonucleases) in reactions involving cleavage of proteins and nucleic acids. Unlike other methodologies for protein stabilization, the CPC materials are soluble in aqueous solutions and are active on large molecules. **1c**-CPC(Try) was incubated with BSA, and the proteolytic cleavage was compared to that of the native enzyme by SDS page electrophoresis.[23] As shown in Figure 1A, we found that **1c**-CPC(Try) and native trypsin gave identical proteolytic cleavage patterns. **1c**-CPC(*Eco*RI) was incubated with λ DNA or plasmid pBR322, and the cleavage patterns were compared to that of native *Eco*RI by gel electrophoresis.[24,25] We found identical cleavage patterns for both the native and the stabilized enzymes (Figure 1B).

These new carbohydrate-based materials provide structural stability and a water-like microenvironment for the protein and do not significantly alter the active site of the enzymes or the binding site of antibodies. We are continuing to explore the generality of the use of these carbohydrate-based macromolecules for the stabilization of enzymes and other proteins, the preparation of new carbohydrate-based macromolecules, and their applications.

Acknowledgment. We are grateful to Cargill, Incorporated (Minneapolis, MN), to the Director, Office of Energy Research, Office of Basic Energy Sciences, Divisions of Materials Sciences, and also to Energy Biosciences of the U.S. Department of Energy under Contract DE-AC03-76SF00098 to the Lawrence Berkeley Laboratory for their financial support of this work. We thank Dr. Paul Hager (University of California at San Francisco) for the generous donation of *Eco*RI. We also thank Dr. Alexander E. Karu and Mr. Douglas J. Schmidt (University of California at Berkeley Hybridoma Laboratory) for use of the aldrin antibody and their assistance.

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Supplementary Material Available: IR, NMR, and mass spectral data for **1a–3a**, **1b–3b**, and the products listed in Table I (4 pages). Ordering information is given on any current masthead page.

Macrocyclic Lewis Acid Host–Halide Ion Guest Species. Complexes of Iodide Ion

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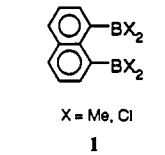
In contrast to the extraordinary achievements of cation complexation in host–guest chemistry,[1] only very recently has anion complexation by compounds containing electron-deficient atoms such as boron,[2] mercury,[3,4] tin,[5,6] and silicon[7] received attention, even though anion-inclusion complexes were reported as early as 1968.[8] Among the representative Lewis acid hosts, **1–3** are bidentate hosts that bind H^-,[2a] F^-,[2b,5] Cl^-,[2c,3-5] and Br^-.[3,4] We have recently reported the synthesis and structure of the very stable chloride ion complex of **4**.[9] Host **4** is the first member of a potential family of carborane-supported, cyclic and multidentate Lewis acids.



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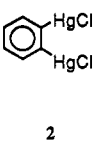

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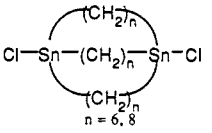

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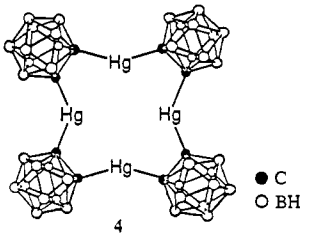

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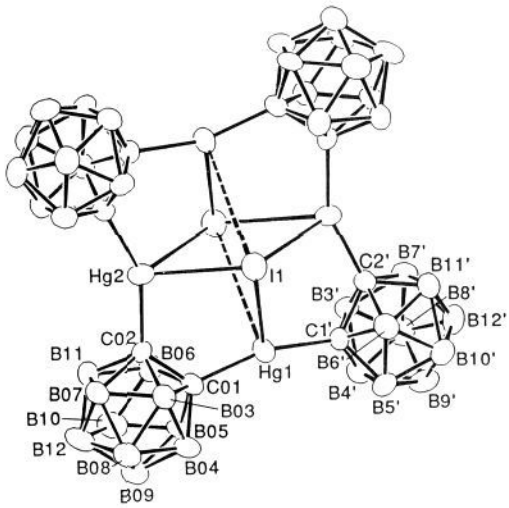


Figure 1. ORTEP representation of $4{\cdot}I_2^-$ with hydrogen atoms removed for clarity. Atoms labeled are in the x, y, and z positions; all other atoms are generated by the inversion symmetry of the tetramer. Some selected interatomic distances (Å) not given elsewhere are as follows: Hg1–C1′ = 2.099 (9), Hg1–C01 = 2.095 (9), Hg2–C2′ = 2.101 (9), Hg2–C02,2 = 2.101 (9). Some selected angles (degrees) are as follows: Hg2–I1–Hg1,2 = 74.02 (2), Hg2–I1–Hg2,2 = 106.19 (3), Hg1–I1–Hg2 = 66.87 (2), Hg1–I1–Hg2,2 = 67.71 (2), Hg2–I1,2–Hg1 = 73.14 (2), Hg1–I1–Hg1,2 = 111.92 (3). All atoms labeled with ",2" are in the positions related by the inversion symmetry of the tetramer.

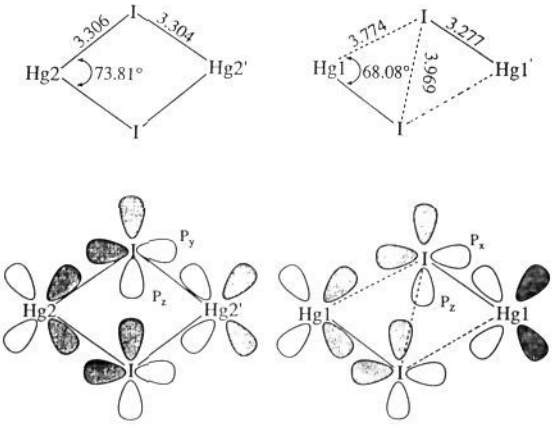
In this communication we report the first two examples of iodide ion complexes of Lewis acid hosts, $4{\cdot}I^-$ and $4{\cdot}I_2^{2-}$, as well as the structural characterization of $4{\cdot}I_2^{2-}$. The species **4**, 12-mercuracarborand-4, a charge-reversed analogue of the well-known 12-crown-4 macrocycle, has been demonstrated to be a reagent for binding chloride anion.[9]

The reaction of mercuric iodide with 1 molar equiv of *closo*-1,2-Li_2-1,2-$C_2B_{10}H_{10}$ in dry Et_2O at room temperature results in the formation of the cyclic tetramer, $Li_2[(HgC_2B_{10}H_{10})_4I_2]$, $4{\cdot}I_2Li_2$, as shown in eq 1. Complex $4{\cdot}I_2Li_2$ is a colorless, air-stable,

$$\textit{closo}\text{-}1,2\text{-}C_2B_{10}H_{12} \xrightarrow[-2\,n\text{-BuH}]{2\,n\text{-BuLi}} \textit{closo}\text{-}1,2\text{-}Li_2\text{-}1,2\text{-}C_2B_{10}H_{10} \xrightarrow{HgI_2} 4{\cdot}I_2Li_2 \quad (1)$$

crystalline solid isolated in 80% yield. Complex $4{\cdot}I_2Li_2$ was characterized by ^1H, ^{13}C, ^{11}B, and ^{199}Hg NMR.[10] The negative-ion FAB mass spectrum exhibited an anion with m/z = 1625, which corresponds to $4{\cdot}I_2^-$ and an anion of m/z = 1497 which corresponds to $4{\cdot}I^-$. **4**·ILi was similarly prepared in 70% yield by the reaction of HgI_2 with *closo*-1,2-Li_2-1,2-$C_2B_{10}H_{10}$ for 24 h.[11] **4**·ILi can be converted to $4{\cdot}I_2Li_2$ by reaction with I^-. The metathesis reaction of $4{\cdot}I_2Li_2$ with $[As(C_6H_5)_4]Cl$ gave $4{\cdot}I_2{\cdot}[As(C_6H_5)_4]_2$.[12] The ^1H NMR spectrum of $4{\cdot}I_2[As(C_6H_5)_4]_2$ displayed resonances due to $[As(C_6H_5)_4]^+$ and B–H in the ratio 1:1, which is consistent with the assigned formulation. The ^{199}Hg and ^{11}B NMR spectra of $4{\cdot}I_2[As(C_6H_5)_4]_2$ are identical to the corresponding spectra of $4{\cdot}I_2Li_2$. No halide ion exchange was observed during this metathesis reaction.

Scheme I



A single crystal of $4{\cdot}I_2[As(C_6H_5)_4]_2$ grown from acetone was selected for the X-ray diffraction study.[13] The structure of the anion $4{\cdot}I_2^{2-}$ is presented in Figure 1. The dianion possesses crystallographically imposed inversion symmetry and consists of four bivalent 1,2-$C_2B_{10}H_{10}$ cages linked by four Hg atoms in a cyclic tetramer with two iodide ions located above and below the tetramer plane of the four mercury atoms and 1.962 (1) Å from that plane, but not centered equidistant from the four Hg atoms. The iodide atoms are equidistant from the two Hg(2) (3.304 (1) and 3.306 (1) Å). Each of the iodide atoms is nearer to one of two remaining Hg atoms (3.277 (1) Å) than to the other (3.774 (1) Å). All distances are shorter than the van der Waals distance between Hg and I^- (3.89 Å).[14,15] The "sides" of the parallelogram formed by connecting the four Hg atoms are 3.921 (1) and 3.963 (1) Å, which are longer than the van der Waals separation (3.46 Å).[15] Angles about the Hg atoms to the two carborane carbon atoms are 152.6 (4) and 158.1 (4)°, which is the largest deviation from 180° yet observed in diorganomercurials.[9,16] The deviation from linear coordination of the mercury with carbon atoms in $4{\cdot}I_2^{2-}$ is induced by strain in the tetramer ring. The average Hg–C–C angle of 123.05 (6)° in $4{\cdot}I_2^{2-}$ is smaller than that required for a strainless planar eight-membered-ring model (135°), and this results in the displacement of the mercury centers toward the cavity of the cycle. The average Hg–C distance is 2.099 (9) Å, compared with the average Hg–C distances of 2.08 (3) and 2.10 (5) Å, respectively, for the monoclinic[17] and orthorhombic[18] crystals of the cyclic trimer of 1,2-phenylenemercury, $(1,2\text{-}C_6H_4Hg)_3$, which has a linear Hg environment.

The bonding of I^- to **4** in forming $4{\cdot}I_2^{2-}$ arises from the interaction of the filled p_x and p_y orbitals of both I^- ions with a total of eight empty Hg p orbitals with four directed 45° above and four below the plane of the host. Two of the resulting p_{Hg2}–p_I–$p_{Hg2'}$ three-center two-electron bonds are symmetrical while the remaining pair, p_{Hg1}–p_I–$p_{Hg1'}$, are unsymmetrical due to a lateral slippage of each guest I^- along its x axis. This distortion is thought to arise from trans–host repulsion of the filled p_z orbitals of each

(10) Spectroscopic data for $4{\cdot}I_2Li_2$: mp > 300 °C; ^1H NMR (200 MHz $(CD_3)_2CO$, 25 °C) δ = 1.0–3.6 ppm; ^{13}C NMR (90 MHz, $(CD_3)_2CO$, 25 °C, decoupled) δ = 95 ppm; ^{11}B NMR (160 MHz, $(CH_3)_2CO$, 25 °C, $BF_3{\cdot}Et_2O$ external, decoupled) δ = 0.3, –7.5 ppm (4:6); ^{199}Hg NMR (89.6 MHz, $(CD_3)_2CO$, 25 °C, 1.0 M PhHgCl in DMSO-d_6 as an external reference[20] at 1187 ppm upfield from neat Me_2Hg, decoupled) δ = –716 ppm; IR (KBr) ν (cm^{-1}) 2560 (B–H); negative-ion FAB, m/z 1625 ($4{\cdot}I_2^-$, 10), 1498 ($4{\cdot}I^-$, 100), 1299 ($4{\cdot}I^-$ – Hg, 95), 1157 ($4{\cdot}I^-$ – $HgC_2B_{10}H_{10}$, 30).

(11) Spectroscopic data for **4**·ILi: mp > 300 °C; ^1H NMR (200 MHz, $(CD_3)_2CO$, 25 °C): δ = 1.0–3.6 ppm; ^{13}C NMR (90 MHz, $(CD_3)_2CO$, 25 °C, decoupled) δ = 94.5 ppm; ^{11}B NMR (160 MHz, $(CH_3)_2CO$, 25 °C, $BF_3{\cdot}Et_2O$ external, decoupled) δ = 0.2, –6.1, –8.4, –10.2 ppm (2:2:4:2); ^{199}Hg NMR (89.6 MHz, $(CD_3)_2CO$, 25 °C, 1.0 M PhHgCl in DMSO-d_6 as an external reference[20] at 1187 ppm upfield from neat Me_2Hg, decoupled) δ = –809 ppm; IR (KBr) ν (cm^{-1}) = 2562 (B–H); negative-ion FAB, m/z 1498 ($4{\cdot}I^-$, 100).

(12) Anal. For $4{\cdot}I_2[As(C_6H_5)_4]_2$. Calculated for $C_{56}H_{80}B_{40}As_2I_2Hg_4$: C, 28.12; H, 3.37; B, 18.08; I, 10.61; Hg, 33.55. Found: C, 27.86; H, 3.30; B, 17.92; I, 10.44; Hg, 33.70.

(13) Crystallographic data for $4{\cdot}I_2(AsPh_4)_2{\cdot}2CO(CH_3)_2$: $C_{62}H_{92}B_{40}O_2As_2I_2Hg_4$, monoclinic, space group $P2_1/n$, a = 9.518 (2) Å, b = 30.516 (6) Å, c = 15.531 (4) Å, β = 99.331 (6)°, V = 4451 Å^3, Z = 2 (four cations, two anions, four solvent molecules), ρ_{calcd} = 1.87 g·cm^{-3}. Data were collected on a Huber diffractometer, using Mo Kα radiation, to a maximum 2θ = 55°, giving 10 252 unique reflections, and the structure was solved by heavy atom methods. The final discrepancy index was R = 0.045, R_w = 0.053, for 5928 independent reflections with $I > 3\sigma(I)$.

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I^- guest as depicted in Scheme I since the $I^-\cdots I^-$ distance in $4\cdot I_2^{2-}$ (3.969 (1) Å) is shorter than the corresponding van der Waals distance (4.30 Å).

The host-guest chemistry of $4\cdot I_2Li_2$ has been investigated. The reaction of $4\cdot I_2Li_2$ with AgOAc in EtOH proceeded quantitatively to yield yellow AgI and a THF-soluble white solid **5**,[19] which has ^1H, ^{13}C, and ^{11}B NMR spectra similar to those of $4\cdot X_n^{n-}$ (X = Cl, n = 1; X = I, n = 1 or 2).[9-11] The ^1H and ^{13}C NMR spectra of **5** proved that **5** does not contain OAc^- ion. The ^{199}Hg NMR spectrum of **5** has a unique resonance at −1309 ppm in 50% THF-d_8, compared with those for $4\cdot I_2Li_2$ at −716 ppm, 4·ILi at −809 ppm, and 4·ClLi at −1077 ppm. A ^{199}Hg NMR experiment demonstrated that 4·ILi and $4\cdot I_2Li_2$ were formed upon the addition of 1 and 2 equiv of n-Bu_4NI, respectively, to **5** in acetone/THF solution, as shown in eq 2. Similar results were obtained when $AgNO_3$ was employed to remove the halide ions from the host.

$$4\cdot I_n^{n-} \underset{nI^-}{\overset{nAg^+}{\rightleftharpoons}} \mathbf{5} + nAgI\downarrow \qquad n = 1,2 \qquad (2)$$

A ^{199}Hg NMR experiment also established that $4\cdot Cl^-$ was converted to $4\cdot I_2^{2-}$ by the addition of n-Bu_4NI to an acetone solution of 4·ClLi.[9] These data strongly suggest that **5** is actually the host **4**. Determination of the equilibrium constants for the complexation of **4** to halide ions and a study of the catalytic potential of **4** are under active investigation.

Acknowledgment. We are grateful to the National Science Foundation (DMR-9014487) for support of this work and to Mr. Albert Calleros for the illustrations.

Supplementary Material Available: Tables of position and thermal parameters, bond lengths and angles, and crystallographic data (15 pages); listing of observed and calculated structure factors (35 pages). Ordering information is given on any current masthead page.

(19) Spectroscopic data for **5**: ^1H NMR (360 MHz, THF-d_6, 25 °C) δ = 1.0–3.6 ppm; ^{13}C NMR (90 MHz, THF-d_8, 25 °C, decoupled) δ = 94.5 ppm; ^{11}B NMR (160 MHz, THF, 25 °C, $BF_3\cdot Et_2O$ external, decoupled) δ = 1.4, −5.5 −8.5 ppm (2:2:6); ^{199}Hg NMR (89.6 MHz, 50% THF-d_8 25 °C, 1.0 M PhHgCl in DMSO-d_6 as an external reference[20] at 1187 ppm upfield from neat Me_2Hg, decoupled) δ = −1309 ppm; IR (KBr) ν (cm^{-1}) = 2560 (B–H).

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Biomimetic Synthesis of the Pentacyclic Alkaloid (±)-Nirurine and Possible Biogenetic Rearrangement of a Precursor into (±)-Norsecurinine

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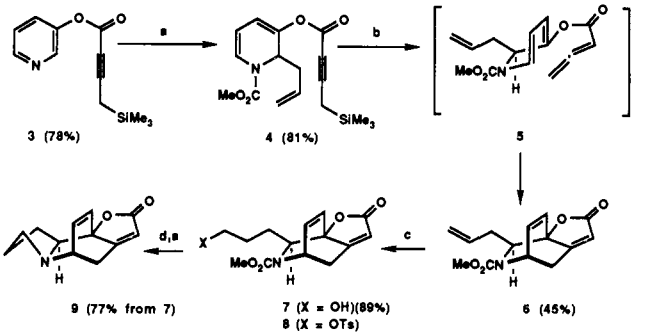
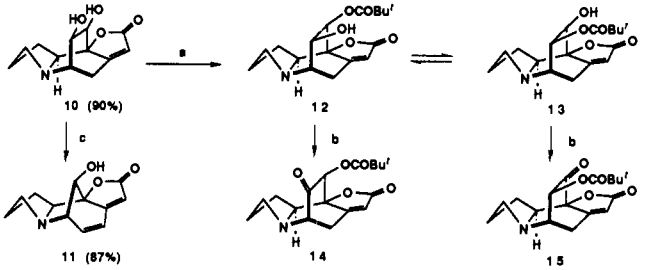
(+)-Nirurine (**1**) was isolated from *Phyllanthus niruri* L. and its pentacyclic structure elucidated by X-ray crystallography.[1] It appears that **1** is biogenetically related to norsecurinine (**2**) (also isolated from *Phyllanthus*). **2** has been synthesized;[2] however, there are no reported synthetic studies on **1**, nor is there a possible structural relationship between the two alkaloid skeleta.

Scheme I[a]



[a] (a) $ClCO_2Me/CH_2{=}CHCH_2SnBu_3$ (81%). (b) $KF\cdot 2H_2O$/MeOH/AcOH (45%). (c) Diisoamylborane/THF/−23 to 25 °C, $NaOH/H_2O_2$ (89%). (d) TsCl/py. (e) 30% HBr/AcOH/cyclohexene (77%).

Scheme II[a]



[a] (a) $Bu^tCOCl/DMAP/Et_3N/CH_2Cl_2$ (100%). (b) DMSO/$(ClCO)_2/Et_3N$. (c) Mitsunubo conditions (87%).

The strategy we have used to construct the azabicyclo-[2.2.2]octane (isoquinuclidine) core depends upon the generation of aza diene **5** and stereospecific intramolecular trapping by an allenyl ester to produce the core skeleton and the fused butenolide **6** in a single step, Scheme I.[3] Thus, 3-hydroxypyridine was treated with 4-(trimethylsilyl)-2-butynoic acid/DCC/CH_2Cl_2 to give the labile ester **3** (78%), which was immediately converted into **4** (81%).[4] Desilylation of **4** gave the azabicyclo[2.2.2]octane **6** (45%) as a single stereoisomer, presumably via the intermediate aza diene **5**. The structure and relative stereochemistry of **6** were established by single-crystal X-ray crystallography of a derivative of **6**.[5] Hydroboration of **6** gave, after oxidative workup, **7** (89%). The derived tosylate **8** was converted into **9** in 77% yield, Scheme I.

The disubstituted double bond in **9** proved to be extremely reluctant to undergo electrophilic addition, presumably because of the strongly inductively electron withdrawing allylic N and O substituents. The only useful functionalization was achieved by treatment of **9** with OsO_4(cat.)/NMNO/acetone–water to give the *cis*-diol **10** (90%).[6] Unfortunately, this compound has the

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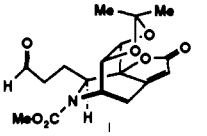

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