

**Figure 1.** (A)  $^1\text{H}$  spectrum (200 MHz) of 1-dodecahedryl cation **2** in  $\text{SbF}_2/\text{SO}_2\text{ClF}$  at  $-70^\circ\text{C}$ . (B) Proton decoupled  $^{13}\text{C}$  NMR spectrum (50 MHz) of 1,16-dodecahedryl dication **4** in  $\text{SbF}_5/\text{SO}_2\text{ClF}$  at  $-70^\circ\text{C}$ . \* peaks due to lock solvent (acetone- $d_6$  containing some water).

the  $^1\text{H}$  spectrum at  $-70^\circ\text{C}$ . The three signals at 379.2 (s), 78.8 (d), and 59.8 (d) ppm that constitute the  $^{13}\text{C}$  spectrum are illustrated in Figure 1B.

These data allow the new species to be assigned as the symmetrical apical/apical 1,16-dodecahedryl dication (**4**). The formation of this unique species can be rationalized by protolytic ionization<sup>7</sup> of the C–H bond at position 16<sup>8</sup> involving an intermediate cation such as **3**. Independent generation of **4** was accomplished by ionization of the isomeric mixture of dibromododecahedranes (**6**) which is produced when **1** is brominated in the presence of  $\text{AlBr}_3$ . This mixture is constituted of three  $\text{C}_{20}\text{H}_{18}\text{Br}_2$  components (GC–MS analysis) in the ratio of 5:6:2 with the minor constituent being **11**. Since the only observable dication is **4**, 1,2-hydride shifts clearly occur readily once the system is charged.

The  $^{13}\text{C}$  chemical shifts of the positively charged centers in **2** (363.9 ppm) and **4** (379.2 ppm) happen to be the most deshielded ever observed for carbocationic species. Those previously recorded at the limit of the deshielding range include the 1-bicyclo[3.3.3]undecyl cation (**8**) and the 1,5-bicyclo[3.3.3]undecyldiyli



dication (**9**).<sup>9</sup> Application of the  $^{13}\text{C}$  chemical shift additivity criterion<sup>10</sup> reveals a net  $^{13}\text{C}$  chemical shift deshielding of 283 ppm for **2** and 610 ppm for **4** in accord with the progression from mono- to dication. The magnitude of deshielding per unit positive charge in both **2** and **4** is less than that observed in a typical tertiary carbocation such as 1-methyl-1-cyclopentyl cation ( $\Sigma\Delta = 374$ ).<sup>10</sup> This indicates the prevalence of some unique cage shielding effect in the cation whose origin is not yet clear.

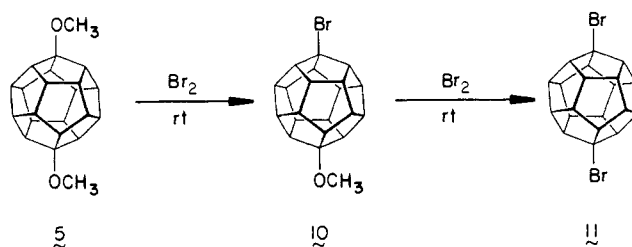
(7) Adventitious protic acid is invariably difficult to remove from such media.

(8) The independent conversion of **6** to **4** technically allows for ionization to occur initially at the other available sites. 1,2-Hydride migration would follow so as to position the positive charges as mutually distal as possible.

(9) Olah, G. A.; Liang, G.; Schleyer, P. v. R.; Parker, W.; Watt, C. I. F. *J. Am. Chem. Soc.* **1977**, *99*, 966.

(10) Schleyer, P. v. R.; Lenoir, D.; Mison, P.; Liang, G.; Prakash, G. K. S.; Olah, G. A. *J. Am. Chem. Soc.* **1980**, *102*, 683.

Dication **4** was found to be rather stable at  $0^\circ\text{C}$  for several days. Quenching of solutions of this ion in methanol gave 1,16-dimethoxydodecahedrane (**5**)<sup>11a</sup> in  $\geq 85\%$  yield. When stirred in



liquid bromine at room temperature, **5** is slowly transformed into **10**<sup>11b</sup> and ultimately into **11**.<sup>11c</sup> The isomeric purity of these products as determined by capillary GC is 100%. Therefore, the ready preparation of dication **4** makes available the capacity for effective regioselective functionalization of the dodecahedrane framework.

The possibility also exists that monocation **2** and dication **4** can be deprotonated to form dodecahedrene and dodecahedradiene, respectively. These unsaturated molecules may be involved in deprotonative condensation or decomposition processes of the ions and may even prove isolable upon controlled deprotonation with hindered bases. Studies are continuing in this direction.

**Acknowledgment.** Support by the National Institutes of Health of the work at both USC and OSU is gratefully acknowledged. Professor F. A. L. Anet of UCLA is thanked for a 500 MHz  $^1\text{H}$  NMR spectrum.

(11) (a) **5**: mp  $247\text{--}248^\circ\text{C}$  (from hexane–benzene);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.50 (br s, 12 H), 3.42 (br s, 6 H), 3.24 (s, 6 H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ) ppm 122.28, 67.84, 65.51, 51.25; MS  $m/z$  ( $M^+$ ) calcd 320.1786, obsd 320.1781. (b) **10**: mp  $> 270^\circ\text{C}$  (from hexane);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.95–3.83 (m, 3 H), 3.75–3.35 (m, 15 H), 3.22 (s, 3 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) ppm 78.81, 68.10, 65.70, 65.04, 51.27 (two quaternary carbons not observed); MS  $m/z$  ( $M^+$ ) calcd 370.0756, obsd 370.0743. (c) **11**: mp  $> 270^\circ\text{C}$  (from hexane–benzene, 4:1);  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  3.93 (br s, 6 H), 3.60 (br s, 12 H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ) ppm 95.58, 79.09, 65.26; MS  $m/z$  ( $M^+$ ) calcd 417.9754, obsd 417.9727.

### Cyclopropanation of Spherical Hydrocarbons without Need for Prior Olefination. The Synthesis of Cyclopropadodecahedranes

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Carbocyclic ring systems are recognized to experience considerable structural distortion and concomitant enhancement of ground-state strain when fused to a cyclopropane ring across a key C–C bond. Notable examples include adamantane  $\rightarrow$  1,3-dehydroadamantane,<sup>3</sup> bicyclo[2.1.0]pentane  $\rightarrow$  [2.1.1]propellane,<sup>4</sup> and bicyclo[1.1.0]butane  $\rightarrow$  [1.1.1]propellane.<sup>5</sup> The synthetic protocol most commonly employed to produce such highly strained

(1) The Ohio State University Postdoctoral Fellow, 1986–1988.

(2) Author to whom inquiries should be addressed concerning the X-ray crystallographic analysis.

(3) (a) Synthesis: Pincock, R. E.; Torupka, E. J. *J. Am. Chem. Soc.* **1969**, *91*, 4593. (b) Structure: Gibbons, C. S.; Trotter, J. *Can. J. Chem.* **1973**, *51*, 87.

(4) Wiberg, K. B.; Walker, F. H.; Pratt, W. E.; Michl, J. *J. Am. Chem. Soc.* **1983**, *105*, 3638.

(5) (a) Synthesis: Wiberg, K. B.; Walker, F. H. *J. Am. Chem. Soc.* **1982**, *104*, 5239. (b) Structure: Honneger, E.; Huber, H.; Heilbronner, E.; Dailey, W. P.; Wiberg, K. B. *Ibid.* **1985**, *107*, 7172. (c) Wiberg, K. B.; Dailey, W. P.; Walker, F. H.; Waddell, S. T.; Crocker, L. S.; Newton, M. *Ibid.* **1985**, *107*, 7247.

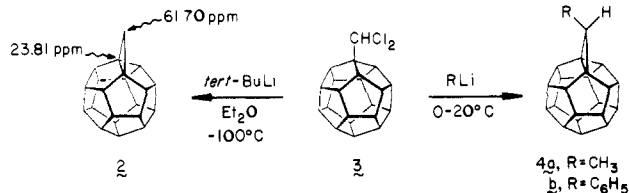
compounds involves reductive elimination of 1,3-bridgehead difunctionalized precursors.<sup>3-6</sup> When the progenitor molecules can tolerate a double bond, dichlorocarbene addition followed by dechlorination can be employed.<sup>7</sup>

Crystallographic definition of the exquisite structural symmetry of dodecahedrane (**1**)<sup>8,9</sup> has prompted us to consider the consequences on the spherical contour of cyclopropanation as in **2**.



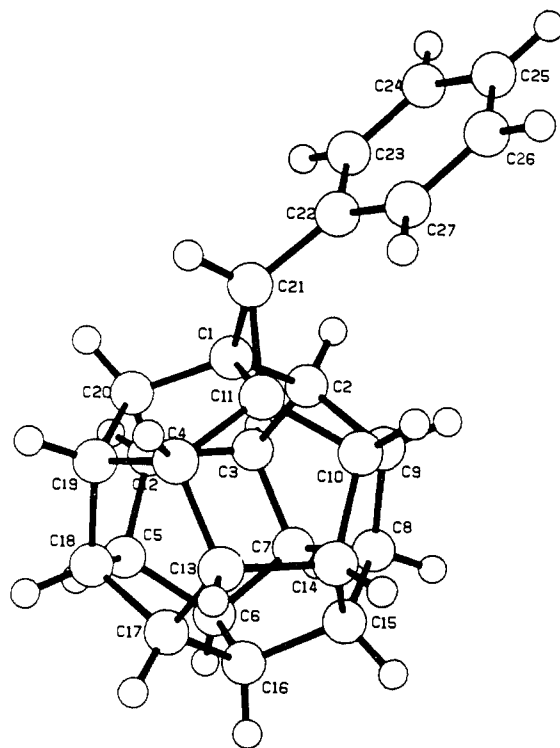
Since dodecahedrane is presently unknown and the feasibility of preparing 1,20-disubstituted homododecahedranes was deemed remote, arrival at **2** and its analogues required development of a new cyclopropanation procedure. Ideally, the route should make use of **1** as starting material in view of its availability.<sup>10</sup> We have developed, and report here, the first method for direct and systematic cyclopropanation of a saturated alicycle that is not dependent on prior introduction of a double bond.

Treatment of **1** (DDH) with dichlorocarbene, generated under phase-transfer conditions,<sup>11</sup> gave **3** in 59% yield.<sup>12</sup> When **3** was



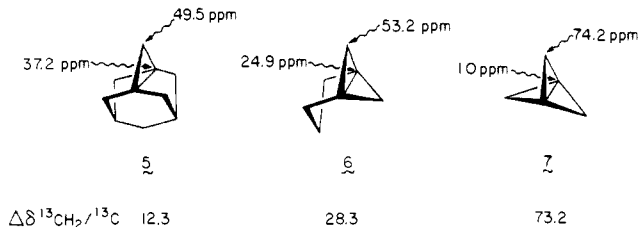
allowed to react with an excess of *tert*-butyllithium in ether at  $-100^{\circ}\text{C}$  for 1 h, there was produced a chromatographically separable mixture of **2** (50%) and (chloromethyl)dodecahedrane (19%).<sup>13</sup> The formation of **2** is believed to arise by initial conversion to a carbenoid such as DDH-CH(Li)Cl and/or DDH-C(Li)Cl<sub>2</sub>,<sup>14</sup> insertion into one of the three equivalent flanking C-H bonds, and (where possible) Cl/Li exchange prior to quenching.

Transient intervention of the  $\alpha$ -dichlorolithium intermediate was regarded to offer an opportunity for displacement of one Cl atom by a nucleophilic R group prior to three-membered ring formation. This phenomenon has been encountered in several structurally simpler carbenoids.<sup>15</sup> Indeed, the action of excess methylolithium on **3** in ether solution at  $0^{\circ}\text{C}$  gave rise to **4a** in 67% yield. Similarly, phenyllithium acts on **3** to furnish **4b** efficiently (81%).



**Figure 1.** An ORTEP drawing of **4b**. The non-hydrogen atoms are represented by 50% probability thermal ellipsoids. The hydrogen atoms are drawn with an artificial radius.

The [3.3.1]propellane substructure of **2** invited comparative <sup>13</sup>C NMR analysis with **5** and its lower homologs **6** and **7**.<sup>16</sup>



Notably, the  $\Delta\delta^{13}\text{CH}_2/^{13}\text{C}$  for the three-membered ring in this group revealed the chemical shift difference for cyclopropadodecahedrane (37.9) to be much larger than that of **5**. Its value, in fact, lies between those for **6** and **7**. This phenomenon may have its origin in the structural rigidity of **2** which enforces well defined C-C bond alignments in the immediate vicinity.

A single-crystal X-ray analysis of **4b** has been carried out to provide details of structure (Figure 1). The colorless rectangular rods belong to space group  $P4_2/n$  and exhibit cell constants of  $a = 17.528$  (3) Å and  $c = 10.752$  (2) Å, with  $Z = 8$ , and a calculated density of  $1.401\text{ g/cm}^3$ . The structure was solved by the direct methods program MITHRIL,<sup>17</sup> and the model converged at an  $R$  value of 0.12. The final refinement cycle for the 1773 intensities with  $F_0^2 > 1\sigma(F_0^2)$  and the 244 variables resulted in agreement indices of  $R = 0.0053$  and  $R_w = 0.052$ .

Remarkably, the cyclopropane ring has all C-C bonds and internal angles essentially equal, and its geometry agrees very well with that of free cyclopropane in the gas phase.<sup>18</sup> The phenyl group is perpendicularly oriented relative to the cyclopropane ring, the two key torsion angles being equal to  $+92^{\circ}$  and  $-91^{\circ}$ . This

(16) Kalinowski, H.-O.; Berger, S.; Braun, S. *<sup>13</sup>C NMR Spektroskopie*; Georg Thieme Verlag: Stuttgart, 1984; p 109.

(17) Gilmore, C. J. MITHRIL: *A Computer Program for the Automatic Solution of Crystal Structures from X-ray Data*; University of Glasgow: Scotland, 1983.

(18) (a) Electron diffraction studies give a C-C distance of  $1.510$  (2) Å; Bastiansen, O.; Fritsch, F. N.; Hedberg, K. *Acta Crystallogr.* **1964**, *17*, 538. (b) Raman results show  $1.514$  (2) Å for the C-C bond; Jones, W. J.; Stochhoff, B. P. *Can. J. Phys.* **1964**, *42*, 2259. See, also: Butcher, R. J.; Jones, W. J. *J. Mol. Spectrosc.* **1973**, *47*, 64.

(6) For an additional example, see: Walker, F. H.; Wiberg, K. B.; Michl, J. *J. Am. Chem. Soc.* **1982**, *104*, 2056.

(7) E.g., 8,8-dichlorotricyclo[3.2.1.0<sup>1,5</sup>]octane: (a) Synthesis: Wiberg, K. B.; Lupton, E. C.; Burgmaier, G. J. *J. Am. Chem. Soc.* **1969**, *91*, 3372. (b) Structures: Wiberg, K. B.; Burgmaier, G. J.; Shen, K.; La Placa, S. J.; Hamilton, W. C.; Newton, M. D. *Ibid.* **1972**, *94*, 7402.

(8) Gallucci, J. C.; Doecke, C. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1986**, *108*, 1343.

(9) The  $D_{2d}$ -symmetric 1,16-dimethyl derivative of **1** has also been studied: (a) Paquette, L. A.; Balogh, D. W.; Usha, R.; Kountz, D.; Christoph, G. G. *Science (Washington, D.C.)* **1981**, *211*, 575. (b) Christoph, G. G.; Engel, P.; Usha, R.; Balogh, D. W.; Paquette, L. A. *J. Am. Chem. Soc.* **1982**, *104*, 784. (c) Allinger, N. L.; Geise, H. J.; Pyckhout, W.; Paquette, L. A.; Gallucci, J. C., submitted for publication.

(10) (a) Paquette, L. A.; Weber, J. C.; Kobayashi, T., accompanying communication in this issue. (b) Paquette, L. A.; Ternansky, R. J.; Balogh, D. W.; Kentgen, G. *J. Am. Chem. Soc.* **1983**, *105*, 5446. (c) Ternansky, R. J.; Balogh, D. W.; Paquette, L. A. *Ibid.* **1982**, *104*, 4503.

(11) (a) Tabushi, I.; Yoshida, Z.; Takahashi, N. *J. Am. Chem. Soc.* **1970**, *92*, 6670. (b) For the alternative use of mercury reagents, consult Seyferth and Cheng (Seyferth, D.; Cheng, Y.-M. *Synthesis* **1974**, 114).

(12) All new compounds exhibited compatible infrared, proton/carbon magnetic resonance, and mass spectrometric data.

(13) When this reaction was carried out at  $-78^{\circ}\text{C}$ , an inseparable mixture of **2** and **4** ( $R = t\text{-Bu}$ ) was produced in a 3:1 ratio (capillary GC analysis).

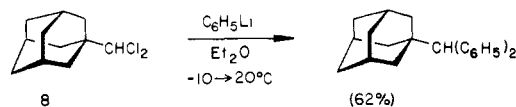
(14) Hine, J. *Divalent Carbon*; The Ronald Press Co.: New York, 1964; Chapter 3.

(15) (a) Dilling, W. L. *J. Org. Chem.* **1964**, *29*, 960. (b) Moss, R. A. *Ibid.* **1965**, *30*, 3261. (c) Closs, G. L.; Coyle, J. J. *Ibid.* **1966**, *31*, 2755. (d) Marquis, E. T.; Gardner, P. D. *Chem. Commun.* **1966**, 726. (e) Dilling, W. L.; Edamura, F. Y. *J. Org. Chem.* **1967**, *32*, 3492.

conformation is likely adopted to minimize steric interactions between the aromatic ring and dodecahedrane framework hydrogens. As a consequence, the noncrystallographic point symmetry of **4b** is  $C_3$  within experimental error.

While the three-membered ring is strikingly undistorted, those dodecahedrane bonds in the immediate vicinity of the C1-C11 fusion are extensively perturbed.<sup>19</sup> Thus, atoms C1 and C11 are involved in short C-C bonds ranging from 1.503 to 1.515 Å.<sup>20</sup> To compensate, the other C-C bonds within the two pentagonal rings which contain the C1-C11 bond are meaningfully lengthened (1.555-1.560 Å).<sup>21</sup> Furthermore, the interior C-C-C angles of these rings range from 106.0° to 109.8°. For the two pentagonal rings which contain either C1 or C11, but not both of these carbons, the range of internal angles is even greater: 104.5-113.7°. All the other cyclopentane rings have internal angles much closer to the ideal 108° (107.2-108.6°).

Finally, it remains to point out that the success of the intramolecular carbenoid insertion process described herein rests on the ability of the reaction center to eclipse a neighboring C-H bond. When this is not possible as in **8**,<sup>11a</sup> where the constrained molecular architecture forces the carbenoid carbon to bisect the H-C-H angle in all three directions, only substitution (and reduction) products are formed.<sup>22</sup>



**Acknowledgment.** We are grateful to the National Institutes of Health for their generous financial support of this research program (Grant AI-11490).

(19) For a theoretical assessment of the energy costs associated with distorting the dodecahedrane framework, consult Ermer (Ermer, O. *Angew. Chem., Int. Ed. Engl.* 1977, 16, 411).

(20) As a means of comparison, dodecahedrane itself has two types of framework bonds [1.541 (2) and 1.535 (5) Å] and three types of C-C-C bond angles [108.1 (1), 107.7 (2), and 107.9 (4)°]. See ref 8.

(21) All of the remaining C-C bonds lie in the range 1.536-1.552 Å and cannot be considered significantly different from the cyclopentane value of 1.546 Å (Adams, W. J.; Geise, H. J.; Bartell, L. S. *J. Am. Chem. Soc.* 1970, 92, 5013). Although no reduction to (chloromethyl)adamantane is seen with phenyllithium, this product does arise when methylithium is utilized.

(22) Although no reduction to (chloromethyl)adamantane is seen with phenyllithium, this product does arise when methylithium is utilized.

## Selective Binding of Imidazoles and Related Organic Molecules in an Organic Solvent

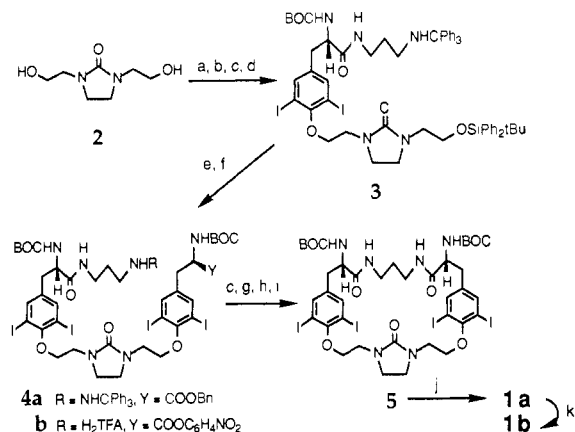
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To form molecular complexes between neutral molecules, a driving force is needed which is compatible with the medium in which the complexation is to operate. In water, removing lipid surfaces from contact with solvent is an effective way to stabilize a molecule or complex. In organic solvents, specific electrostatic effects become more important and may not only drive complexation but also orient a substrate within a ligand. Previous reports of binding in organic solvents have described several systems capable of the oriented binding of neutral substrates although a few of the ligands incorporate well-defined three-dimensional cavities possessing functionality actively involved in the substrate complexation.<sup>1</sup> We believe that such geometrical

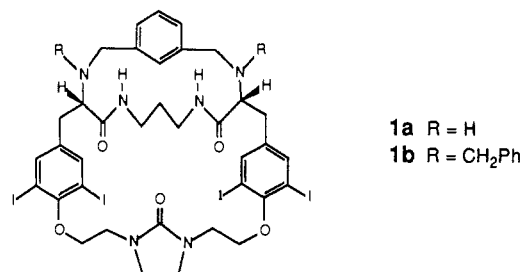
(1) Previous examples of oriented binding in organic solvents: Rebek, J.; Askew, B.; Islam, N.; Killoran, M.; Nemeth, D.; Wolak, R. *J. Am. Chem. Soc.* 1985, 107, 6736. Rebek, J.; Nemeth, D. *J. Am. Chem. Soc.* 1985, 107, 6738. Rebek, J.; Nemeth, D. *J. Am. Chem. Soc.* 1986, 108, 5637. Sheridan, R. E.; Whitlock, H. W. *J. Am. Chem. Soc.* 1986, 108, 7120. Rebek, J.; Askew, B.; Ballester, P.; Buhr, C.; Jones, S.; Nemeth, D.; Williams, K. *J. Am. Chem. Soc.* 1987, 109, 5033. Hamilton, A. D.; Van Engen, D. *J. Am. Chem. Soc.* 1987, 109, 5035. Kelly, T. R.; Maguire, M. P. *J. Am. Chem. Soc.* 1987, 109, 6549.

## Scheme I.



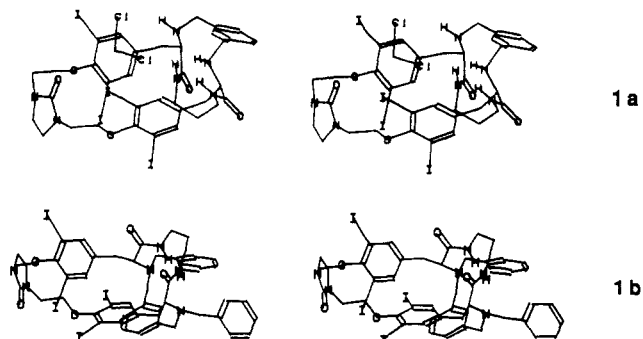
\* a. *t*-BuPh<sub>2</sub>SiCl (1 equiv), imidazole (45%); b. N-BOC O-Bn L-diodotyrosine, Ph<sub>3</sub>P, (*i*-PrO<sub>2</sub>CN)<sub>2</sub> (90%); c. LiOH, H<sub>2</sub>O, dioxane; d. Ph<sub>3</sub>CNH(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub>, DCC, HOBT (c. + d. 70%); e. Bu<sub>4</sub>NF, THF; f. N-BOC O-Bn D-diodotyrosine, Ph<sub>3</sub>P, (*i*-PrO<sub>2</sub>CN)<sub>2</sub> (e. + f. 70%); g. *p*-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>OH, DCC, HOBT; h. 0.7% TFA, CH<sub>2</sub>Cl<sub>2</sub> (c. + g. + h. 62%); i. high dilution, *i*-Pr<sub>2</sub>NEt, CH<sub>3</sub>CN (35-45%); j. (a) 35% TFA, (b) high dilution, *m*-C<sub>6</sub>H<sub>4</sub>(CH<sub>2</sub>Br)<sub>2</sub>, *i*-Pr<sub>2</sub>NEt, CH<sub>3</sub>CN (25-35%); k. excess BnBr, *i*-Pr<sub>2</sub>NEt (70%).

features are important for selective binding and have prepared a new ligand (**1**) incorporating an enforced cavity lined with convergent but spatially separated hydrogen bond donor and acceptor functionalities. These acidic and basic sites cannot easily associate with one another either inter- or intramolecularly but should bind to organic substrates having complementary functionality and size. Here we describe the synthesis and structure of **1** and summarize the highly selective binding of **1a** to certain organic molecules having appropriately oriented hydrogen bond donor and acceptor functionalities.



The synthesis of **1** is outlined in Scheme I and begins with cyclic urea **2**.<sup>2</sup> The transformations were generally straightforward, and we note only that the macrocyclization steps proceeded in <50% yield. The mediocre yields for these steps probably reflect the size and flexibility of the ring (28 members, 16 low barrier rotatable bonds) in the monocyclization of **4** to **5** (35-45%) and the requirement of both inter- and intramolecular steps in the cyclization of **5** to **1a** (25-35%).

Ligand **1a** was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>, and its structure was determined by X-ray crystallography. As shown below, the



(2) Steele, A. B. U.S. Patent no. 2847418, 1958; *Chem. Abstr.* 1959, 53, 1382i.