

Figure 1. Three-dimensional structure of CsA bound to cyclophilin.¹⁰ CsA/cyclophilin NOEs were observed from CsA protons attached to the filled and checkered carbon atoms.¹⁰ The protons attached to the jagged and checkered carbon atoms exhibited the largest change in relaxation rate [$R(5\text{mM})/R(0\text{mM}) \geq 2$] upon the addition of HyTEMPO.

Figure 1 depicts the three-dimensional structure of CsA when bound to cyclophilin that was recently determined by NMR.¹⁰ The protons attached to the filled and checkered carbon atoms were found to be in close proximity to cyclophilin, as evidenced by NOEs between these CsA protons and the protein.¹⁰ Most of these protons (e.g., $11\gamma^2$, $11\gamma^1$, 2γ , 11NCH_3 , 10α) were only marginally affected by the addition of HyTEMPO. However, some of the protons that displayed NOEs to cyclophilin (those attached to the checkered carbon atoms) also exhibited the largest changes in T_1 upon the addition of spin label (9NCH_3 , $9\delta^1$, 3α , $3\alpha'$, 1η , and 1ϵ). This suggests that these CsA protons are not as deeply buried within the protein. A possible explanation is that cyclophilin is located to one side of the CsA protons while the spin label is accessible to the other.

Large effects of the spin label were also observed for the protons attached to the jagged filled carbon atoms (Figure 1), indicating that these CsA residues (4, 6, 7, 8) are exposed to solvent. These results are consistent with the structure/activity relationships of CsA analogues¹¹⁻¹⁴ in which cyclophilin binding and immunosuppressant activity was found to be relatively insensitive to modifications of these CsA residues. Also consistent with the structure/activity relationships¹¹⁻¹⁴ was the finding that the CsA residues (1, 2, 9, 10, 11) important for cyclophilin binding and immunosuppressant activity are solvent shielded as indicated by the reduced effect of added HyTEMPO.

In summary, we have described an approach for identifying the solvent-exposed regions of enzyme-bound ligands. The methods are easy to implement and highly sensitive and can rapidly yield important structural information on enzyme/inhibitor complexes. The approach is expected to be especially useful in NMR studies of larger systems in which complete three-dimensional structures may be difficult to obtain.

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Registry No. HyTEMPO, 2226-96-2.

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Bis[(dimethoxyethane)lithium(I)] 1,2,4,5-Tetrakis(trimethylsilyl)benzenide. The First 6C-8 π Antiaromatic Benzene Dianion¹

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Cyclic conjugated polyenes exhibit aromaticity if the number of π electrons is $(4n + 2)$, whereas antiaromaticity is predicted for $4n\pi$ electron systems.² Thus anions such as cyclopentadienyl anion³ and cyclooctatetraenyl dianion⁴ are aromatic, while the benzene dianion bearing 8π electrons could be antiaromatic.⁵ However, a theoretical study on $\text{C}_6\text{H}_6^{2-}$ suggested that the benzene dianion could be stabilized by distorting the structure into a boat form.^{5b} The planar structures with D_{2h} or D_{6h} symmetry were calculated to be 20.2 and 36.6 kcal/mol higher in energy than the distorted one. Very recently, we reported bis[(tetrahydrofuran)lithium(I)] hexakis(trimethylsilyl)benzenide as the first example of such a benzene dianion distorted highly into a boat form with two lithium atoms located on the same side of the benzene ring.^{6,7} We report here the synthesis and characterization of bis[(dimethoxyethane)lithium(I)] 1,2,4,5-tetrakis(trimethylsilyl)benzenide as the first 6C-8 π antiaromatic system.

Reduction of 1,2,4,5-tetrakis(trimethylsilyl)benzene **1** (367 mg, 1.0 mmol) with lithium metal (60 mg, 8.6 mmol) in dry-oxygen-free dimethoxyethane (DME, 6 mL) at room temperature immediately led to a dark brown solution of the benzene dianion of **1**. The solvent was removed in vacuo, and then dry degassed hexane was introduced by vacuum transfer. Crystallization from hexane afforded dark brown crystals of bis[(dimethoxyethane)lithium(I)] 1,2,4,5-tetrakis(trimethylsilyl)benzenide **2**, $[\text{Li}(\text{dme})]_2[1,2,4,5\text{-(Me}_3\text{Si)}_4\text{C}_6\text{H}_2]$.⁸ Reduction of **1** in tetrahydrofuran similarly yielded the dianion; however, suitable crystals for X-ray crystallography were not obtained. The dianion **2** was extremely air- and moisture-sensitive.⁹

The structure of **2** was determined by X-ray crystallography.¹⁰

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(7) Distortion into the boat structure for hexakis(trimethylsilyl)benzene dianion is not due to the steric factor of the bulky trimethylsilyl group. (See footnote 12 of ref 6.)

(8) Compound **2**: dark brown crystals; ¹H NMR (300 MHz, toluene-*d*₆, 233 K) δ 0.21 (s, 36 H, SiMe₃), 3.30 (s, 8 H, DME), 3.46 (s, 12 H, DME), 5.11 (s, 2 H, ArH); ¹³C NMR (75.5 MHz, toluene-*d*₆, 233 K) δ 2.74, (SiMe₃), 60.5 (DME, OMe), 70.7 (DME, OCH₂), 80.8 (C₆Si), 161.8 (C₆H); ²⁹Si NMR (59.6 MHz, toluene-*d*₆, 233 K) δ -19.2; ⁷Li NMR (116.6 MHz, toluene-*d*₆, 233 K) δ 10.7 ppm (from LiCl in MeOH).

(9) The dianion **2** readily reverted to **1** on exposure to air and reacted with H₂O to give 1,3,4,6-tetrakis(trimethylsilyl)cyclohexa-1,4-diene and 2,3,5,6-tetrakis(trimethylsilyl)cyclohexa-1,3-diene in 93 and 4% yield, respectively, in addition to a small amount of **1**.

(10) A single crystal (0.3 × 0.3 × 0.3 mm) of **2** was sealed in a capillary glass tube for data collection. Diffraction data were collected at 13 °C on a Rigaku Denki AFC-5R diffractometer with a rotating anode (45 kV, 200 mA) with graphite-monochromatized Mo K α radiation ($\lambda = 0.71069$ Å). A total of 5015 reflections with $2\theta = 3^\circ\text{-}45^\circ$ were collected. Crystal data: MF = Si₄O₄C₂₆Li₂H₅₈; MW = 560.97; monoclinic; $a = 10.801$ (10), $b = 11.087$ (6), $c = 31.971$ (10) Å, $\beta = 97.08^\circ$ (5); $V = 3799$ (8) Å³; space group $P2_1/c$; $Z = 4$; $D_c = 0.980$ g/cm³. The final R factor was 0.056 ($R_w = 0.052$) for 2375 reflections with $F_o > 3\sigma(F_o)$.

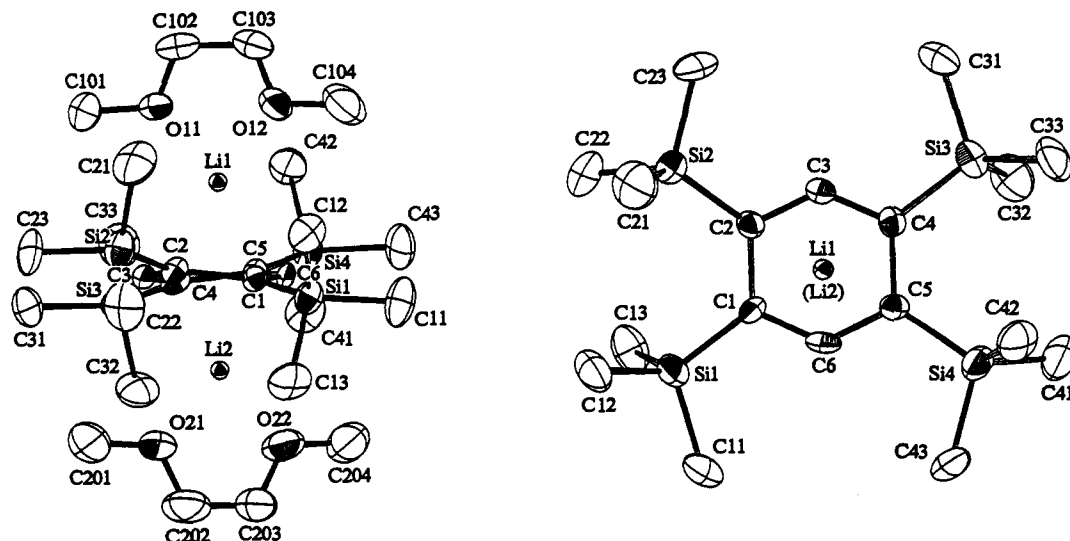


Figure 1. Molecular structure of $[\text{Li}(\text{dme})]_2[1,2,4,5-(\text{Me}_3\text{Si})_4\text{C}_6\text{H}_2]$ **2**: left, side view; right, top view (DME is omitted for the clarity). Selected bond lengths (Å) are as follows: C(1)–C(2) 1.558 (10), C(2)–C(3) 1.415 (11), C(3)–C(4) 1.392 (11), C(4)–C(5) 1.549 (11), C(5)–C(6) 1.411 (11), C(6)–C(1) 1.416 (11), C(1)–Si(1) 1.828 (8), C(2)–Si(2) 1.807 (8), C(4)–Si(3) 1.839 (8), C(5)–Si(4) 1.821 (8). Selected bond angles (deg) are as follows: C(6)–C(1)–C(2) 115.3 (6), C(1)–C(2)–C(3) 113.5 (6), C(2)–C(3)–C(4) 130.2 (6), C(3)–C(4)–C(5) 115.2 (6), C(4)–C(5)–C(6) 114.4 (6), C(5)–C(6)–C(1) 128.9 (7). Dihedral angle (deg) is as follows: C(1)–C(6)–C(5)/C(2)–C(3)–C(4) 8.0.

The ORTEP drawing of the molecular geometry of **2** is shown in Figure 1. The two lithium atoms are perfectly located above and below the center of the benzene ring, and each lithium atom is coordinated by one DME as a bidentate ligand. The distances between lithium atoms and the mean plane of the benzene ring are 1.870 (Li1) and 1.868 Å (Li2), and the distances between benzene carbons and lithium atoms are approximately equal (av 2.366 Å). The benzene ring is nearly planar as determined by the dihedral angle of 8° between C(1)–C(6)–C(5)/C(2)–C(3)–C(4) planes. The bond lengths of $\text{C}_{\text{ar}}\text{--Si}$ (av 1.824 Å) are shortened due to the increased bond order (cf. $\text{C}_{\text{ar}}\text{--Si}$ in Ph_4Si , 1.872 Å). The bond lengths of C(2)–C(3) (1.415 Å), C(3)–C(4) (1.392 Å), C(5)–C(6) (1.411 Å), and C(6)–C(1) (1.416 Å) are almost the same to average aromatic C–C bond distances (1.40 Å), whereas the bond lengths of C(1)–C(2) (1.558 Å) and C(4)–C(5) (1.549 Å) are appreciably elongated. The internal bond angles at C(1), C(2), C(4), and C(5) carbons range from 113.5 to 115.3°. However, the bond angles of both C(2)–C(3)–C(4) (130.2°) and C(5)–C(6)–C(1) (128.9°) are widened considerably. The molecular structure is in good accordance with that of the calculated (D_{2h}) form of $\text{C}_6\text{H}_6^{2-}$.^{5a} Thus the geometry of **2** reflects the nature of the ψ_{8s} LUMO of **1**.¹¹

In ^1H NMR spectrum of **2** in toluene- d_8 at 233 K, the signals due to the trimethylsilyl groups and aryl protons appear at 0.21 (36 H) and 5.11 ppm (2 H) together with the signals due to DME. In ^{13}C NMR, the aromatic carbons attached to the trimethylsilyl group can be observed at 80.8 ppm (1, 144.8 ppm), and the aromatic CH carbons can be seen at 161.8 ppm (1, 141.9 ppm). The former carbons exhibit a remarkable high field shift due to the location of the negative charge. ^{29}Si NMR resonances of the trimethylsilyl groups also shift to higher field (–19.2 ppm) compared to **1** (–3.3 ppm).

Of particular interest is ^7Li resonance at 10.7 ppm, being observed at the lowest magnetic field among the organolithium compounds reported so far.¹² The appreciable downfield shift is caused by the strong deshielding effect on the lithium atoms by the paratropic ring current resulting from 8π antiaromatic

system. On the basis of these spectroscopic properties, the molecular structure of **2** found in the crystals is retained in solution. Thus, the benzene dianion **2** has nearly the planar antiaromatic character with the anionic charge stabilized by the four silyl groups.

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Supplementary Material Available: X-ray experimental details and tables of positional parameters, thermal parameters, bond lengths, and angles (7 pages); table of observed and calculated structure factors (12 pages). Ordering information is given on any current masthead page.

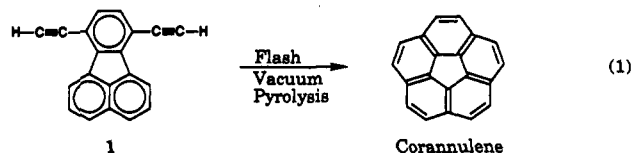
Corannulene. A Convenient New Synthesis¹

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We are pleased to report that corannulene, the marvelous bowl-shaped polycyclic aromatic hydrocarbon first prepared a quarter century ago by Barth and Lawton in a stunning tour de force,² is now readily accessible by a remarkably simple procedure (eq 1).



Our investigation of this high-temperature cyclization reaction was inspired by the pioneering work of R. F. C. Brown, who first

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