Positive Homotropic Allosteric Binding of Benzenediols in a Hydrindacene-based Exoditopic Receptor: Cooperativity in Amide Hydrogen Bonding

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Supporting Information

**General:** $^1$H and $^{13}$C NMR spectra were recorded on a JEOL ECP-300 ($^1$H/300 MHz, $^{13}$C/75 MHz) spectrometer in CDCl$_3$ unless otherwise indicated. IR spectra were taken on a Hitachi Model 215 grating spectrometer. Mass spectra were recorded on JEOL JMS-DX300 (EI) and JMS-01SG-2 (FD) spectrometers. Column and thin-layer chromatography (TLC) were performed on silica gel 60 (Merck) of particle size 63-200 and 5-20 µm, respectively. Elemental analyses were performed at the Center for Instrumental Analysis of Hokkaido University. 5-Chlororesorcinol 2Cl$^1$ and 1,4-Dibromo-2,3,5,6-tetrakis(bromomethyl)benzene 5$^2$ were prepared following the known procedures. Other reagents and solvents were obtained from commercial sources and purified prior to use.

**Scheme S1.** Preparation of exoditopic receptor $^1$

Reagents and conditions: (a) CH$_2$(CO$_2$Et)$_2$, EtONa, EtOH, reflux, 64%; (b) CuCN, HMPA, 150 °C, 60%; (c) t-BuOH, H$_2$SO$_4$, Ac$_2$O, AcOH, 65 °C, 90% for 1a; Ph$_3$COH, H$_2$SO$_4$, Ac$_2$O, AcOH, 60 °C, 50% for 1b; (d) H$_2$O$_2$, K$_2$CO$_3$, acetone/DMSO, rt, 80% for 1c (R = H); (e) Ph$_3$COH, H$_2$SO$_4$, Ac$_2$O, AcOH, 60 °C, 73% for 1b.

**Preparation of Tetraethyl 4,8-Dibromo-1,2,3,5,6,7-hexahydro-s-indacene-2,2,6,6-tetracarboxylate (6):** To a sodium ethoxide solution, which was prepared by dissolving sodium metal (14.2 g, 617 mmol) in absolute ethanol (1.0 L), were added diethyl
malonate (49.1 g, 306 mmol) and then 1,4-dibromo-2,3,5,6-tetrakis(bromomethyl)benzene 5 (62.3 g, 103 mmol). After heating the reaction mixture with stirring at reflux for 7 h under Ar, the solvent was removed under reduced pressure. The residue was neutralized with 0.5 M HCl (400 mL) and extracted with CHCl₃ (200 mL × 3). The extracts were combined, dried over MgSO₄, filtered, and the filtrate was concentrated under reduced pressure. The residue was recrystallized from CHCl₃/EtOH (1:1) to give pure 6 (39.7 g, 64%) as colorless crystals: mp 203.0-204.0 °C; ¹H NMR: δ 4.23 (q, J = 7.3 Hz, 8H), 3.64 (s, 8H), 1.27 (t, J = 7.3 Hz, 12H); ¹³C NMR: δ 170.97, 140.60, 114.78, 62.03, 58.53, 42.44, 14.00; IR (KBr) 2984, 1736, 1446, 1282, 1246, 1160, 1072, 862, 802 cm⁻¹; MS (FD) m/z (%): 602 (M⁺, 48), 604 (M⁺ + 2, 100), 606 (M⁺ + 2, 56); Anal. Calcd. for C₂₄H₂₈O₈Br₂: C, 47.70; H, 4.67; Found: C, 47.29; H, 4.63.

Preparation of Tetraethyl 4,8-Dicyano-1,2,3,5,6,7-hexahydro-s-indacene-2,2,6,6-tetracarboxylate (7): A mixture of 6 (7.50 g, 12.4 mmol), copper(I) cyanide (3.57 g, 39.8 mmol), and hexamethylphosphoric triamide (10 mL) was heated with stirring at 150 °C for 8 h under Ar, and then poured into an aqueous iron(III) chloride solution (10.8 g, 40.1 mmol in H₂O 50 mL) to decompose the complex. The resulting solid was separated from the liquid layer by filtration and washed successively with water, aqueous sodium hydrogen sulfite, and water. The residue was dissolved in chloroform and washed with an aqueous iron(III) chloride solution, water, and brine, and dried over MgSO₄. The brown solid obtained by evaporation of the solvent was subjected to chromatography on silica gel eluted with chloroform. The resulting yellow solid (4.38 g) was recrystallized from CHCl₃/EtOH (1:2) to give pure 7 (3.77 g, 60%) as colorless crystals: mp 196.5-198.0 °C; ¹H NMR: δ 4.24 (q, J = 7.2 Hz, 8H), 3.75 (s, 8H), 1.28 (t, J = 7.2 Hz, 12H); ¹³C NMR: δ 170.12, 144.31, 114.63, 109.06, 62.47, 59.61, 39.87, 13.97; IR (KBr) 2984, 2228, 1732, 1304, 1250, 1192, 1074, 858 cm⁻¹; MS (FD) m/z (%): 496 (M⁺, 100); Anal. Calcd. for C₂₆H₂₈N₂O₈: C, 62.90; H, 5.68; N, 5.64. Found: C, 62.63; H, 5.55; N, 5.58.

Preparation of Tetraethyl 4,8-Bis(ß-buty lacarbamoyl)-1,2,3,5,6,7-hexahydro-s-indacene-2,2,6,6-tetracarboxylate (1a): To a mixture of 7 (200 mg, 0.40 mmol), t-bu tanol (386 µL, 4.0 mmol), acetic anhydride (380 µL, 4.0 mmol), and acetic acid (5.0 mL) was added H₂SO₄ (54 µL, 1.0 mmol). After stirring at 65 °C for 20 h, the reaction...
mixture was poured slowly into 5% aqueous NaHCO₃. The resulting suspension was extracted with EtOAc. The organic layer was washed with 5% aqueous NaHCO₃, water and brine, dried over MgSO₄, and then filtered. The white solid obtained by concentrating the filtrate was subjected to chromatography on silica gel eluted with EtOAc/hexane (4:6). The resulting white solid was recrystallized from EtOH to give pure 1a (233 mg, 90%) as colorless crystals: mp 242.0-242.5 °C; ¹H NMR: δ 5.56 (s, 2H), 4.20 (q, J = 7.2 Hz, 8H), 3.59 (s, 8H), 1.48 (s, 18H), 1.25 (t, J = 7.2 Hz, 12H); ¹³C NMR: δ 171.20, 166.76, 137.54, 131.35, 61.94, 60.52, 52.06, 39.14, 28.96, 14.01; IR (KBr) 3384, 2988, 1732, 1668, 1534, 1276, 1078, 860 cm⁻¹; MS (FD) m/z (%): 644 (M⁺, 100); Anal. Calcd. for C₃₄H₄₈N₂O₁₀: C, 63.34; H, 7.50; N, 4.34. Found: C, 63.17; H, 7.62; N, 4.33.

Preparation of Tetraethyl 4,8-Bis(tritylcarbamoyl)-1,2,3,5,6,7-hexahydros-indacene-2,2,6,6-tetracarboxylate (1b), Method A: To a mixture of 7 (200 mg, 0.40 mmol), triphenylmethanol (629 mg, 2.42 mmol), acetic anhydride (114 µL, 1.21 mmol), and acetic acid (5.0 mL) was added H₂SO₄ (43 µL, 0.81 mmol). After stirring at 60 °C for 12 h, the reaction mixture was poured slowly into 5% aqueous NaHCO₃. The resulting suspension was extracted with EtOAc, and the organic layer was washed with 5% aqueous NaHCO₃, water and brine, dried over MgSO₄, and then filtered. The white solid obtained by concentrating the filtrate was subjected to chromatography on silica gel eluted with CHCl₃/hexane (7:3). The resulting white solid was recrystallized from benzene to give 1b•(benzene)₂ (235 mg, 50%) as colorless crystals. Desolvated 1b was obtained by heating 1b•(benzene)₂ at 80°C in vacuo (0.1 mmHg). Analytical sample was obtained by recrystallization from CHCl₃/ether.

Method B: To a solution of 7 (555 mg, 1.12 mmol) in acetone/DMSO (1:1, 100 mL) were added successively 30% aqueous H₂O₂ (10 mL) and K₂CO₃ (250 mg, 1.81 mmol) at 0 °C. The reaction mixture was allowed to warm to 20 °C and stirred for 48 h. After evaporating of acetone, 0.1 M HCl (200 mL) was added and the resulting suspension was filtered to obtain a solid. The resulting white solid was washed with water and dried in vacuo to give primary amide 1c (477 mg, 80%): mp 261-263°C dec; ¹H NMR ((CD₃)₂CO): δ 7.04 (s, 2H), 6.90 (s, 2H), 4.18 (q, J = 7.2 Hz, 8H), 3.66 (s, 8H), 1.22 (t, J = 7.2 Hz, 12H); IR (KBr) 3372, 3188, 2928, 1734, 1658, 1390, 1282, 1192, 1068, 860, 688 cm⁻¹; MS (FD) m/z (%): 532 (M⁺, 100); Anal. Calcd. for C₂₆H₃₄N₂O₁₀: C, 58.42; H, 6.41; N, 5.24. Found: C, 58.27; H, 6.17; N, 5.16.
To a mixture of the above amide 1c (200 mg, 0.38 mmol), triphenylmethanol (391 mg, 1.50 mmol), acetic anhydride (142 µL, 1.50 mmol), and acetic acid (5.0 mL) was added H2SO4 (42 µL, 0.79 mmol). After stirring at 60 °C for 2.5 h, the reaction mixture was worked up as described in the method A to produce 1b (280 mg, 73%): mp 244.5-245.0 °C; 1H NMR: δ 7.36-7.25 (m, 30H), 6.89 (s, 2H), 4.16 (q, J = 7.1 Hz, 8H), 3.59 (s, 8H), 1.23 (t, J = 7.1 Hz, 12H); 13C NMR: δ 170.93, 166.38, 144.40, 138.36, 131.02, 128.73, 128.10, 127.22, 71.39, 61.84, 60.60, 39.58, 14.03; IR (KBr) 3412, 2928, 1730, 1684, 1492, 1282, 1240, 1070, 752, 700 cm -1; MS (FD) m/z (%): 1016 (M^+, 100); Anal. Calcd. for C_{64}H_{60}N_{2}O_{10}: C, 75.57; H, 5.95; N, 2.75. Found: C, 75.72; H, 6.07; N, 2.48.

Preparation of Crystalline Tritylamide–Resorcinol Complex (1b•2H): Crystals suitable for crystallography were obtained by slow vapor diffusion of hexane into a solution of 1b and 2H (1:10) in CHCl3/ether. mp 213-215 °C; IR (KBr) 3380, 2984, 1714, 1640, 1604, 1494, 1370, 1298, 1244, 1072, 832, 750, 702, 628 cm⁻¹; Anal. Calcd. for C_{76}H_{72}N_{2}O_{14}: C, 73.77; H, 5.86; N, 2.26. Found: C, 73.77; H, 6.03; N, 2.26.

1H NMR Titrations: A sample of receptor 1a or 1b was dissolved in CDCl₃ to give a solution with a concentration range of 1 – 4 mM. A portion (0.5 mL) of this solution was used as the host NMR sample, and the remainder was used to dissolve a sample of the guest 2 -4, so that the receptor concentration remains constant throughout the titration. Successive aliquots of the guest solution were added to the host NMR sample, and 1H NMR spectra were recorded after each addition at 298 K. The changes in chemical shift of all of the receptor signals as a function of guest concentration were then analyzed with a purpose-written software NMRTit HGG for the 1:2 complexation, kindly provided by Professor C. A. Hunter³. Titration data for two ± four different signals were used to determine the association constant in each experiment. Errors are quoted as twice the standard error from the weighted mean (weighting based on the observed change in chemical shift).

Job Plots: For each component of the complex, 5 mL solutions of accurately measured and identical concentrations (in the range 3-5 mM) were prepared. The two solutions were then combined to give a series of samples of identical total concentration but containing different mole fractions (χ) of the two components. The 1H NMR spectrum of each sample was then recorded, and these spectra were used to produce a graph of (Δδ × χ) against χ shown as the Job plot (Δδ = Δδ_{observed} - Δδ_{χ=1.0}).⁴
**Figure S1.** Complexation of receptor 1 with 2H. $^1$H NMR spectra (300 MHz, CDCl$_3$) from a titration experiment of 1a with equivalents of 2H added indicated on the right of the spectra. (a) Receptor 1a. (b) 1.2 equiv, (c) 2.2 equiv, and (d) 3.3 equiv of 2H was added. (e) Guest 2H.

**X-ray Analyses:** Crystal data for 1a: Crystals were obtained by recrystallizing from EtOH. C$_{34}$H$_{48}$N$_2$O$_{10}$, $M$ 644.75, colorless block, 0.5 × 0.4 × 0.4 mm$^3$, monoclinic $P2_1/c$, $a = 8.287(3)$ Å, $b = 20.037(8)$ Å, $c = 10.151(4)$ Å, $\beta = 95.856(6)^\circ$, $V = 1676(1)$ Å$^3$, $\rho(Z = 2) = 1.277$ g cm$^{-1}$. A total of 3779 unique data ($2\theta_{\text{max}} = 55^\circ$) were measured at $T = 153$ K by a Rigaku Mercury CCD apparatus (Mo K$\alpha$ radiation, $\lambda = 0.71069$ Å). Numerical absorption correction was applied ($\mu = 0.94$ cm$^{-1}$). The structure was solved by the direct method (SIR92) and refined by the full-matrix least-squares method on $F$ with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms were located in the D map and refined with isotropic temperature factors. The final $R$ and $R_w$ values are 0.037 and 0.048 for 2539 reflections with $I > 3\sigma I$ and 208 parameters. Estimated standard deviations are 0.002 Å for bond lengths and 0.1° for bond angles, respectively.

Crystal data for 1b: Crystals were obtained by slow vapor diffusion of hexane into a solution of 1b in ether. C$_{64}$H$_{60}$N$_2$O$_{10}$, $M$ 1017.17, colorless block, 0.35 × 0.15 × 0.1 mm$^3$, monoclinic $P2_1/n$, $a = 8.337(3)$ Å, $b = 19.963(7)$ Å, $c = 15.750(6)$ Å, $\beta = 102.408(7)^\circ$, $V = 2559(1)$ Å$^3$, $\rho(Z = 2) = 1.320$ g cm$^{-1}$. A total of 5652 unique data ($2\theta_{\text{max}} = 55^\circ$) were measured at $T = 173$ K by a Rigaku Mercury CCD apparatus (Mo K$\alpha$ radiation, $\lambda = 0.71069$ Å). Numerical absorption correction was applied ($\mu = 0.94$ cm$^{-1}$). The structure was solved by the direct method (SIR92) and refined by the full-matrix least-squares method on $F$ with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms were located in the D map and refined with isotropic temperature factors. The final $R$ and $R_w$ values are 0.037 and 0.048 for 2539 reflections with $I > 3\sigma I$ and 208 parameters. Estimated standard deviations are 0.002 Å for bond lengths and 0.1° for bond angles, respectively.
0.71069 Å). Numerical absorption correction was applied (μ = 0.89 cm⁻¹). The structure was solved by the direct method (SIR92) and refined by the full-matrix least-squares method on F with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms were located in the D map and refined with isotropic temperature factors. The final R and Rw values are 0.048 and 0.055 for 2765 reflections with I > 3σI and 343 parameters. Estimated standard deviations are 0.003-0.004 Å for bond lengths and 0.2-0.3° for bond angles, respectively.

Crystal data for 1b•(2H)₂: Crystals were obtained by the procedure described above. C₆₆H₆₀N₂O₁₀(C₆H₆O₂)₂, M 1237.41, colorless block, 0.3 × 0.3 × 0.15 mm³, monoclinic P2₁/c, a = 13.343(2) Å, b = 13.7657(7) Å, c = 18.3825(6) Å, β = 111.5078(7)°, V = 3141.2(5) Å³, ρ(Z = 2) = 1.308 g cm⁻¹. A total of 7205 unique data (2θmax = 55°) were measured at T = 110 K by a Rigaku Mercury CCD apparatus (Mo Kα radiation, λ = 0.71069 Å). Numerical absorption correction was applied (μ = 0.90 cm⁻¹). The structure was solved by the direct method (SIR92) and refined by the full-matrix least-squares method on F with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms were located in the D map and refined with isotropic temperature factors. The final R and Rw values are 0.054 and 0.073 for 4973 reflections with I > 3σI and 415 parameters. Estimated standard deviations are 0.002-0.003 Å for bond lengths and 0.1-0.3° for bond angles, respectively.

Crystal data for 1b•(3)₂: Crystals were obtained by slow vapor diffusion of hexane into a solution of 1b and 3 in CHCl₃/ether. C₆₆H₆₀N₂O₁₀(C₆H₆O₂)₂, M 1237.41, colorless rod, 0.4 × 0.2 × 0.2 mm³, monoclinic P-1, a = 11.4515(9) Å, b = 12.187(1) Å, c = 12.550(1) Å, α = 85.201(3)°, β = 79.058(2)°, γ = 69.252(1)°, V = 1607.9(3) Å³, ρ(Z = 1) = 1.278 g cm⁻¹. A total of 6530 unique data (2θmax = 55°) were measured at T = 173 K by a Rigaku Mercury CCD apparatus (Mo Kα radiation, λ = 0.71069 Å). Numerical absorption correction was applied (μ = 0.88 cm⁻¹). The structure was solved by the direct method (SIR92) and refined by the full-matrix least-squares method on F with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms were located in the D map and refined with isotropic temperature factors. The final R and Rw values are 0.055 and 0.077 for 4262 reflections with I > 3σI and 424 parameters. Estimated standard deviations are 0.002-0.005 Å for bond lengths and 0.1-0.3° for bond angles, respectively.

Crystal data for 1b•acetone: Crystals were obtained by slow vapor diffusion of hexane into a
solution of 1b in acetone. \(\text{C}_{64}\text{H}_{60}\text{N}_{2}\text{O}_{10}\cdot\text{C}_{3}\text{H}_{6}\text{O}\), \(M\) 1075.27, colorless plate, \(0.40 \times 0.20 \times 0.05\) mm\(^3\), monoclinic \(P\)-, \(a = 8.889(1)\) Å, \(b = 17.022(1)\) Å, \(c = 19.613(3)\) Å, \(\alpha = 80.493(3)^{\circ}\), \(\beta = 84.133(1)^{\circ}\), \(\gamma = 77.093(1)^{\circ}\), \(V = 2846.5(7)\) Å\(^3\), \(\rho(Z = 2) = 1.254\) g cm\(^{-1}\). A total of 11509 unique data (\(2\theta_{\text{max}} = 55^{\circ}\)) were measured at \(T = 123\) K by a Rigaku Mercury CCD apparatus (Mo K\(\alpha\) radiation, \(\lambda = 0.71069\) Å). Numerical absorption correction was applied (\(\mu = 0.083\) cm\(^{-1}\)). The structure was solved by the direct method (SIR92) and refined by the full-matrix least-squares method on \(F\) with anisotropic temperature factors for non-hydrogen atoms. All the hydrogen atoms were located in the D map and refined with isotropic temperature factors. The final \(R\) and \(R_w\) values are 0.049 and 0.061 for 6953 reflections with \(I > 3\sigma\) and 721 parameters. Estimated standard deviations are 0.003-0.004 Å for bond lengths and 0.2-0.3° for bond angles, respectively.

**Figure S2.** X-ray crystal structures of complex 1a (left) and 1b (right). ORTEP representation with 50% probability. Hydrogen atoms except amide NH are omitted for clarity.

**Figure S3.** X-ray crystal structure of complex 1b\(\cdot(3)\). ORTEP representation with 50% probability. Hydrogen atoms not involved in hydrogen bonds are omitted for clarity.
Figure S4. X-ray crystal structures of 1b-acetone solvate, which contains two independent molecules A (left) and B (right).

ORTEP representation with 50% probability. Hydrogen atoms except amide NH are omitted for clarity.

Table S1. Hydrogen Bonding Partners D and A with Amide Groups, Amide Bond Lengths $R$ (Å), and Rotation Angles $\phi$ (°) toward Aromatic Plane in Crystals.

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<th>$1b^b$ (molecule B)</th>
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<th>$1b^{\text{(2H)}}^b$</th>
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$^a$ From crystals of 1b only. $^b$ From crystals of 1b-acetone solvate.

References