Electronic Supplementary Information

## Covalent Locking and Unlocking of an Atropisomeric Molecular Switch

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General. ^{1}H NMR and ^{13}C NMR spectra were performed on a Varian: Mercury 300 MHz spectrometer, Varian: Mercury 400 MHz NMR spectrometer, and a Varian: Inova 500 MHz NMR spectrometer. All reagents were purchased from commercial suppliers and used as received.

Synthesis

*anti-/syn-***1**
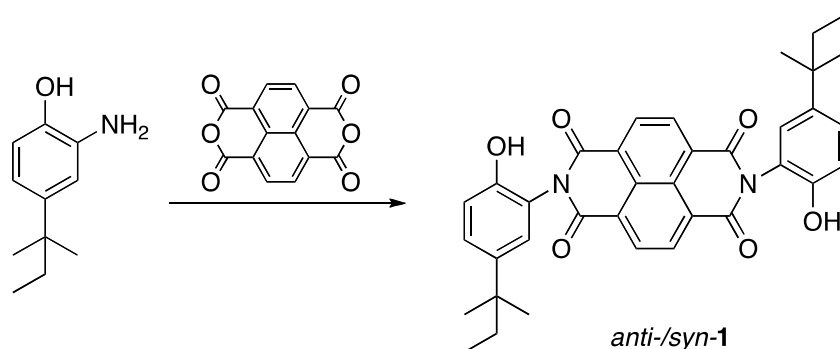
Diol-1. Was prepared as previously described.[1]

1. Y. S. Chong, M. D. Smith, K. D. Shimizu. *J. Am. Chem. Soc.* 2001, **123**, 7463.

syn-Enhanced Bis(benzylether) 2. To a solution of *syn-/anti-***1** (40 mg, 0.0677 mmol) in acetone (5 mL) was added 1 mL of silica gel 60 (230 – 400 mesh ASTM). The mixture was then dried *in vacuo* and allowed to stand for 3 h at room temperature. DMF (2 mL) chilled to 0 °C was used to wash off *syn-enriched* **1** from the silica gel into a round bottom flask containing 1 mL of DMF in an ice bath. Benzyl bromide (40.3 µl, 0.339 mmol) and K_2CO_3 (93.5 mg, 0.677 mmol) were added to the solution and stirred for 6 h. The reaction mixture was then diluted with 1 N HCl and extracted with ethyl acetate. The organic layer was dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The crude products were purified by flash chromatography on silica gel (33% ethyl acetate/ hexane) to give the title compound (37.2 mg, 71%). By ^{1}H NMR the *syn/anti* ratio of 2:1 was observed. FTIR (KBr) 2964, 2930, 2875, 1716, 1679, 1582, 1508, 1454, 1345, 1294, 1249, 1212, 1198, 1098, 1020, 1011, 981, 812, 769, 699, 419 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 8.34 (s, 4 H, *syn*), 8.33 (s, 4 H, *anti*), 7.51 (d, J = 2.2 Hz, 2 H, *anti*), 7.47 (d, J = 2.2 Hz, 2 H, *syn*), 7.29 - 7.19 (m, 12 H, *syn/anti*), 7.04 - 6.94 (m, 8 H, *syn/anti*), 6.92 - 6.84 (m, 4 H, *syn/anti*), 6.79 (d, J = 8.8 Hz, 2 H, *syn*), 6.79 (d, J = 8.8 Hz, 2 H, *anti*), 4.81 (s, 4 H, *syn*), 4.74 (s, 4 H, *anti*), 1.65 - 1.54 (m, 8 H, *syn/anti*), 1.27 (s, 12 H, *anti*), 1.23 (s, 12 H, *syn*), 0.82 (t, J = 7.4 Hz, 6 H, *anti*), 0.80 (t, J = 7.4 Hz, 6 H, *syn*); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.6, 151.6, 142.6, 136.8, 131.0, 129.0, 128.7, 128.4, 128.3, 127.9, 127.6, 127.5, 127.2, 127.0, 126.9, 123.0, 113.1, 70.5, 37.4, 37.0, 33.5, 28.3, 9.1; HRMS calcd. for $C_{50}H_{46}N_2O_6$: 770.3352, found: 770.3356.

anti-Enhanced Bis(benzylether) 2. A solution of *syn-/anti-***1** (40 mg, 0.0677 mmol) in acetone (5 mL) was dried *in vacuo* and heated neat at 110 °C for 1 h in a round bottom flask. After cooling to room temperature, the flask was placed in an ice bath and DMF (3 mL) chilled to 0 °C

was added. While stirring benzyl bromide (40.3 μl, 0.339 mmol) and K_2CO_3 (93.5 mg, 0.677 mmol) were added and the solution was stirred for 6 h. See *syn*-enhanced bis(benzylether) **2** for work up procedures (41.2 mg, 79%). By ^{1}H NMR the *syn/anti* ratio of 1:4 was observed. FTIR (KBr) 2964, 2930, 2875, 1716, 1679, 1582, 1508, 1454, 1345, 1294, 1249, 1212, 1198, 1098, 1020, 1011, 981, 812, 769, 699, 419 cm^{-1}; ^{1}H NMR (300 MHz, C_6D_6) δ 8.34 (s, 4 H, *syn*), 8.33 (s, 4 H, *anti*), 7.51 (d, J = 2.2 Hz, 2 H, *anti*), 7.47 (d, J = 2.2 Hz, 2 H, *syn*), 7.29 - 7.19 (m, 12 H, *syn/anti*), 7.04 - 6.94 (m, 8 H, *syn/anti*), 6.92 - 6.84 (m, 4 H, *syn/anti*), 6.79 (d, J = 8.8 Hz, 2 H, *syn*), 6.79 (d, J = 8.8 Hz, 2 H, *anti*), 4.81 (s, 4 H, *syn*), 4.74 (s, 4 H, *anti*), 1.65 - 1.54 (m, 8 H, *syn/anti*), 1.27 (s, 12 H, *anti*), 1.23 (s, 12 H, *syn*), 0.82 (t, J = 7.4 Hz, 6 H, *anti*), 0.80 (t, J = 7.4 Hz, 6 H, *syn*); ^{13}C NMR (75 MHz, CDCl$_3$) δ 162.6, 151.6, 142.6, 136.8, 131.0, 129.0, 128.7, 128.4, 128.3, 127.9, 127.6, 127.5, 127.2, 127.0, 126.9, 123.0, 113.1, 70.5, 37.4, 37.0, 33.5, 28.3, 9.1; HRMS calcd. for $C_{50}H_{46}N_2O_6$: 770.3352, found: 770.3356.

(s*yn-/anti*)-1 Prepared from the Hydrogenation of (s*yn-/anti*)-2. To a solution of *syn-/anti*-**2** (95.2 mg, 0.124 mmol) in THF (1 mL) and EtOH (4 mL) was added Pd/C (15 mg). The solution was placed under an atmosphere of H_2 and stirred for 12 h. The reaction mixture was then filtered through celite and concentrated *in vacuo* to give the title compound (64.2 mg, 87%) as a light brown solid. By ^{1}H NMR a mixture of *syn/anti* isomers was observed. FTIR (KBr) 2964, 1715, 1678, 1580, 1446, 1345, 1293, 1250, 1198, 1149, 1096, 1020, 981, 812, 769, 712, 640, 420 cm^{-1}; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.81 (s, 4 H), 8.54 (br s, 1 H), 8.50 (br s, 1 H), 7.36 - 7.29 (m, 4 H), 7.04 - 7.00 (m, 2 H), 1.65 (q, J = 7.4 Hz, 4 H), 1.29 (s, 12 H), 0.75 (t, J = 7.4 Hz, 6 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 162.7, 151.1, 140.7, 130.5, 127.7, 127.5, 122.2, 116.2, 116.1, 37.1, 36.8, 28.1, 8.6; HRMS calcd. for $C_{36}H_{34}N_2O_6$: 591.2495, found: 591.2508.
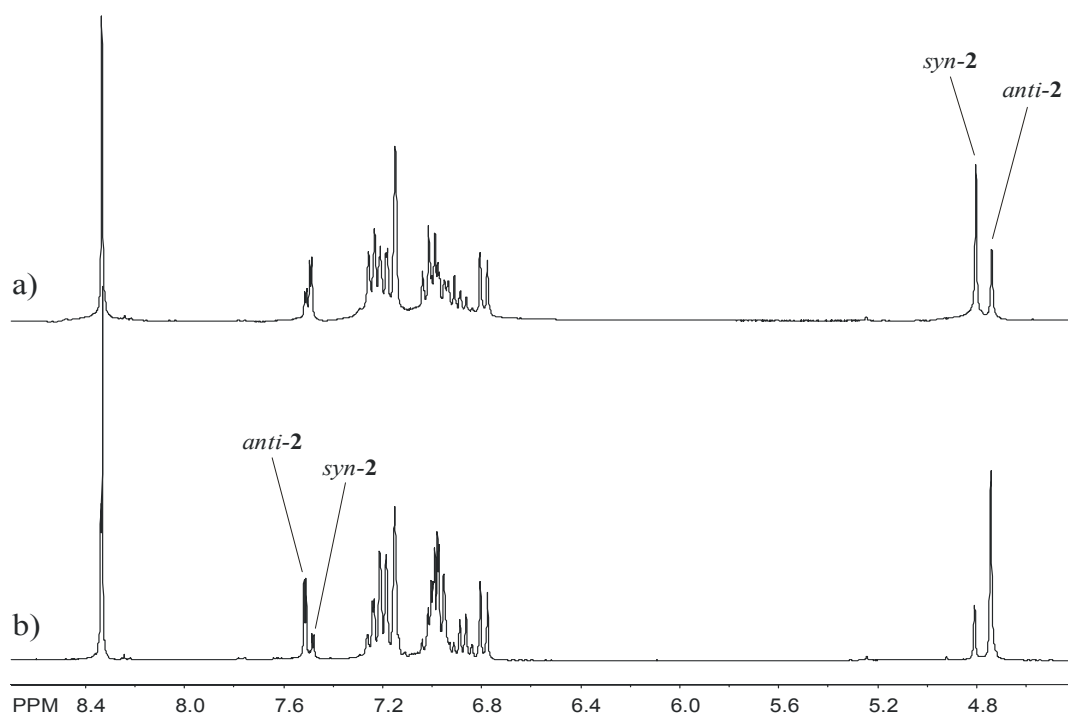
Figure S1. ^{1}H NMR spectra of a) *syn*-enhanced benzyl ether **2** and b) *anti*-enhanced benzyl ether **2**.
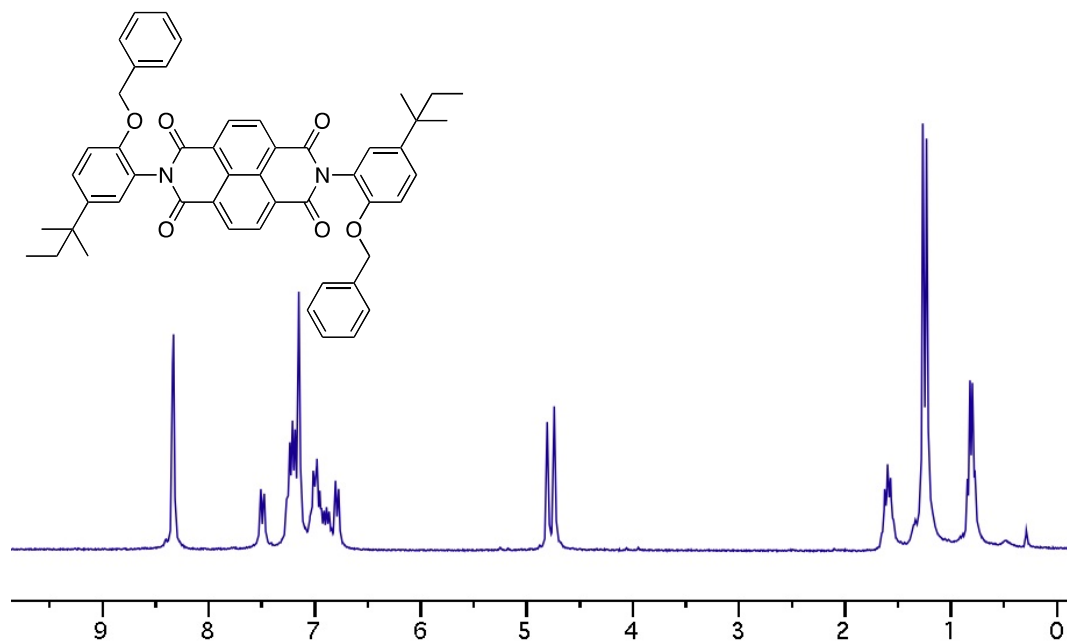

Figure S2. ^{1}H NMR spectrum of (*syn/anti*-) bis(benzylether) **2** (CD$_3$COCD$_3$, 300 MHz).
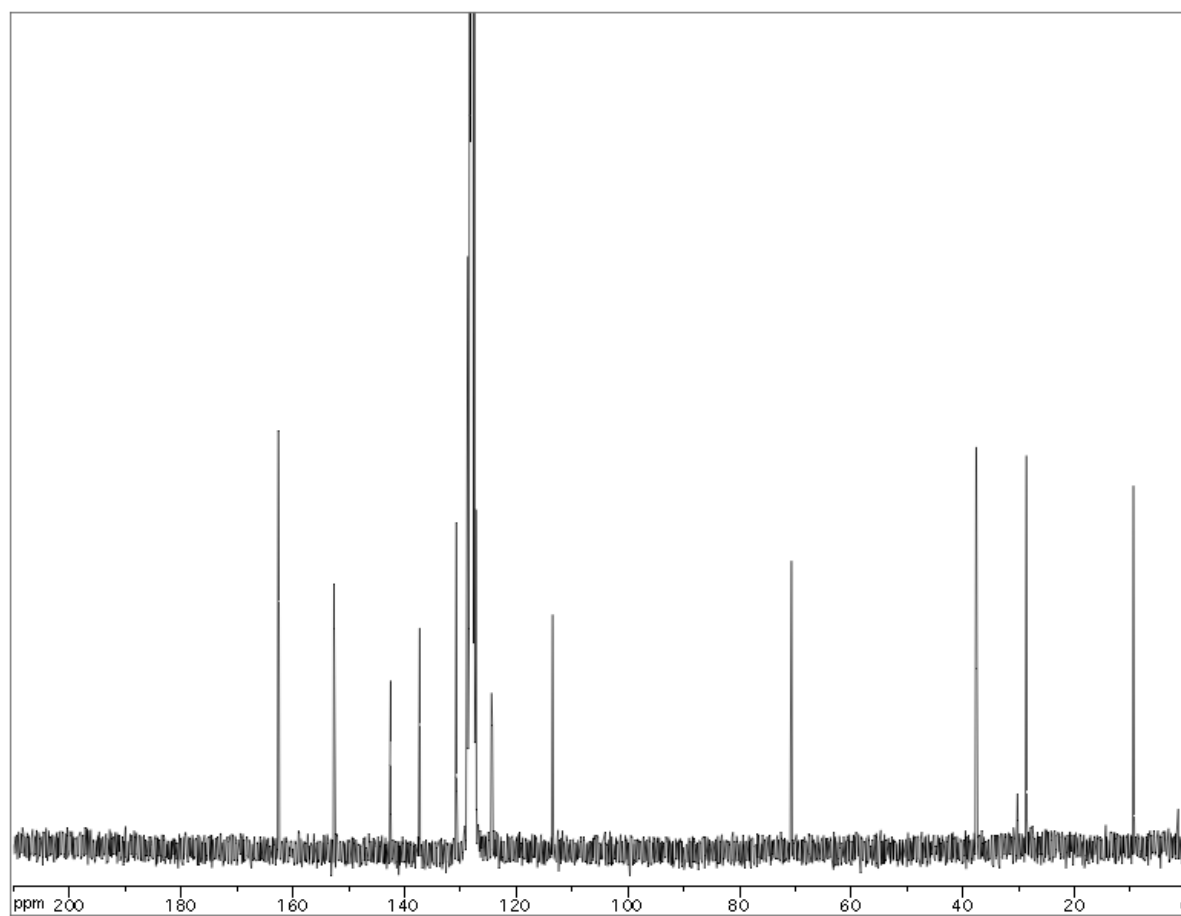
Figure S3. ^{13}C NMR spectra of (*syn/anti-*) bis(benzylether) **2** (CD$_3$COCD$_3$, 100 MHz).

Isomerization Barrier Study

The isomerization barrier of the diol **1** and bis(benzylether) **2**, were measured in acetone-d_6 at 25 °C and in 20% acetonitrile-d_3 80% benzene-d_6 at 70 °C, respectively, by monitoring the change in the *syn/anti* ratios over time of isomerically enriched samples via ^{1}H NMR. The change in the *syn/anti* ratios as measured by $\ln[(R - R_e)/(R + 1)]$, where R = *syn/anti* ratio and R_e = equilibrium ratio, were plotted versus time (Figure S4), the slope thereof is the observed isomerization rate. From the isomerization rate it is possible to calculate the isomerization barrier, employing the Eyring equation, and the half-life of the diol **1** and bis(benzylether) **2**.
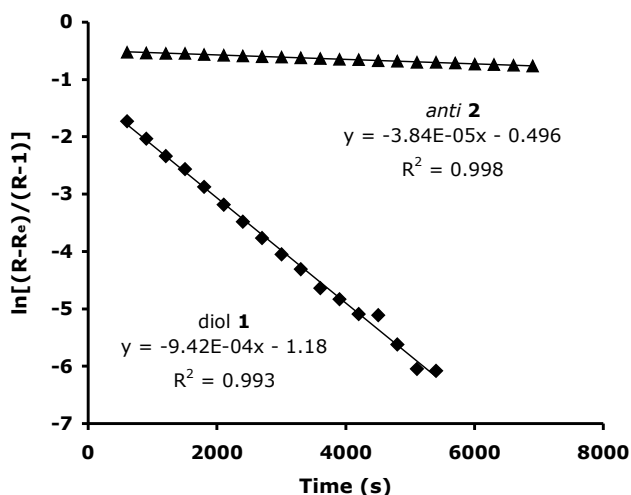
Figure S4. Isomerization rate study of diol **1** (k_{isom} = -9.42 x 10^{-4} s^{-1}, circles) and *anti*-**2** (k_{isom} = -3.84 x 10^{-5} s^{-1}, squares) at 25 °C and 70 °C, respectively. R is the *syn/anti* ratio and R_e is the equilibrium *syn/anti* ratio.

Crystal Structures

## X-Ray Structure Determination, $C_{36}H_{34}N_2O_6$, diol 1

An orange block of approximate dimensions 0.32 x 0.20 x 0.18 mm^3 was epoxied onto the end of a thin glass fiber. X-ray intensity data were measured at 293 K on a Bruker SMART

APEX CCD-based diffractometer system (Mo Kα radiation, λ = 0.71073 Å).[1] The raw data frames were integrated into reflection intensity files using SAINT+,[1] which also applied corrections for Lorentz and polarization effects. The final unit cell parameters are based on the least-squares refinement of 2117 reflections from the data set with I > 5(σ)I. Analysis of the data showed negligible crystal decay during data collection. No correction for absorption was applied.

$C_{36}H_{34}N_2O_6$ crystallizes in the trigonal (rhombohedral) system. Systematic absences in the intensity data positively ruled out a c-glide operation. The space group R $\overline{3}$ was eventually confirmed by successful solution and refinement of the data. The structure was solved by a combination of direct methods and difference Fourier syntheses, and refined by full-matrix least-squares against F^2, using the SHELXTL software package.[2] The molecule resides on a crystallographic inversion center at the C3 – C3* midpoint; the defined contents of the asymmetric unit consists of half the molecule. The packing of the molecules creates three equivalent channels per unit cell, which run along the unique c-axis direction. The channels are roughly cylindrical with a diameter of 8.9 Å. The channels are filled with severely disordered solvent molecules. No reasonable model could be obtained for these diffusely scattering species despite much effort, and were therefore accounted for with the SQUEEZE program in PLATON.[3] The total solvent-accessible volume calculated by SQUEEZE was 1665.6 Å^3, corresponding to 484 e Å^{-3}. The contribution of these solvents was then removed from the structure factor calculations. Note that the calculated FW, density and F(000) reflect known unit cell contents only. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atoms were placed in geometrically idealized positions (C_{arene}-H = 0.930 Å, C_{alkyl}-H = 0.970 Å (methylene H) or 0.960 (methyl H)) and refined using a riding model with isotropic

displacement parameters 1.2 (arene and methylene H) or 1.5 (methyl H) times the U_{eq} value of the parent carbon. The hydroxyl proton H3 attached to O3 was located in the plane of the (C_6O) ring by Fourier difference synthesis and refined with an isotropic displacement parameter subject to an O-H = 0.90(2) distance restraint. Attempts to place this proton out-of-plane in a position more likely for intermolecular hydrogen bonding resulted in immediate shifting of H3 back to its located in-plane position.
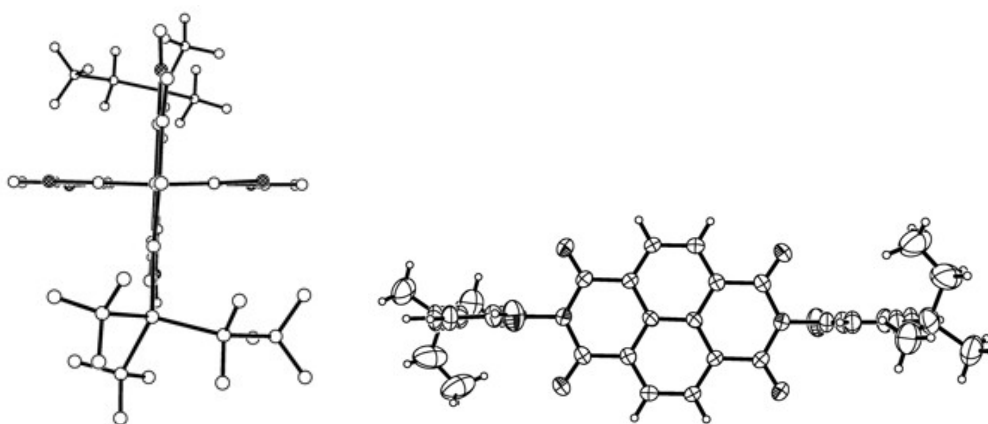
Figure S5. Side and edge-views of the crystal structure of diol **1**.

(1) SMART Version 5.624 and SAINT+ Version 6.02a. Bruker Analytical X-ray Systems, Inc., Madison, Wisconsin, USA, 1998.

(2) Sheldrick, G. M. SHELXTL Version 5.1; Bruker Analytical X-ray Systems, Inc., Madison, Wisconsin, USA, 1997.

(3) PLATON, A Multipurpose Crystallographic Tool, Utrecht University, Utrecht, The Netherlands, Spek, A. L. 1998.

Table 1. Crystal data and structure refinement for diol **1**.

Identification code	sqz2
Empirical formula	C36 H34 N2 O6
Formula weight	590.65
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Trigonal
Space group	R-3
Unit cell dimensions	$a = 31.419(5)$ Å $\alpha = 90.000(5)°$.
	$b = 31.419(5)$ Å $\beta = 90.000(5)°$.
	$c = 9.403(5)$ Å $\gamma = 120.000(5)°$.
Volume	8039(5) Å^3
Z	9
Density (calculated)	1.098 Mg/m^3
Absorption coefficient	0.075 mm^{-1}
F(000)	2808
Crystal size	0.32 x 0.18 x 0.12 mm^3
Theta range for data collection	1.30 to 22.54°.
Index ranges	-33<=h<=33, -33<=k<=33, -10<=l<=9
Reflections collected	11935
Independent reflections	2353 [R(int) = 0.0605]
Completeness to theta = 22.54°	100.0 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2353 / 1 / 206
Goodness-of-fit on F^2	1.020
Final R indices [I>2sigma(I)]	R1 = 0.0707, wR2 = 0.1779
R indices (all data)	R1 = 0.1249, wR2 = 0.1973
Largest diff. peak and hole	0.246 and -0.163 e.Å^{-3}

Crystal structure data of bis(benzylether) 2.
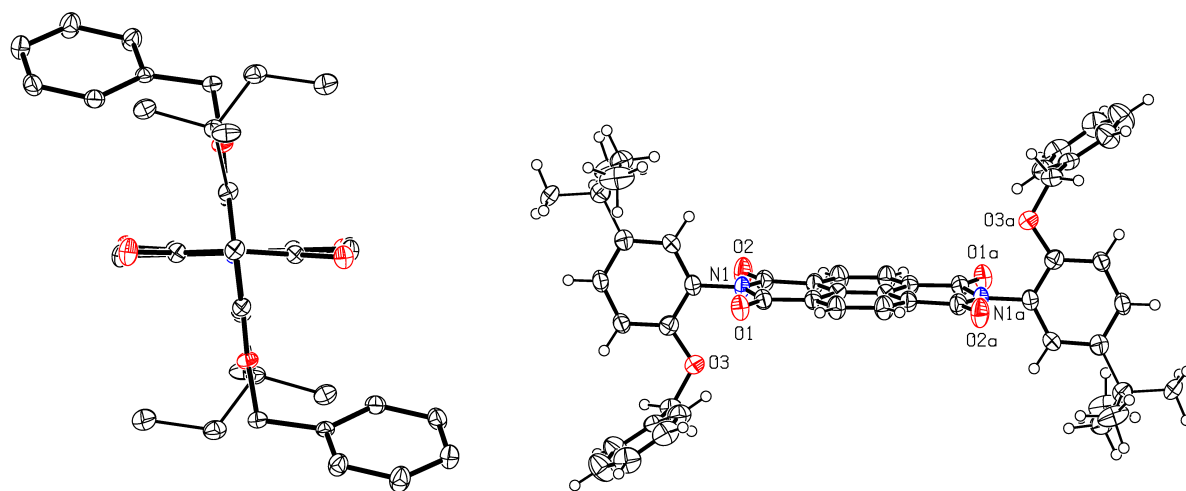
Figure S6. Side and edge-views of the crystal structure of bis(benzylether) **2**.

Table 1. Crystal data and structure refinement for bis(benzylether) **2**.

Identification code	gbbbm
Empirical formula	C50 H46 N2 O6
Formula weight	770.89
Temperature	150(1) K
Wavelength	0.71073 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 11.2972(8) Å α= 89.1900(10)°.
	b = 13.2286(9) Å β= 70.0700(10)°.
	c = 14.8485(10) Å γ = 76.7010(10)°.
Volume	2025.2(2) Å^3
Z	2
Density (calculated)	1.264 Mg/m^3
Absorption coefficient	0.083 mm^{-1}
F(000)	816
Crystal size	0.48 x 0.18 x 0.10 mm^3
Theta range for data collection	1.59 to 23.26°.
Index ranges	-12<=h<=12, -14<=k<=14, -16<=l<=16
Reflections collected	12391
Independent reflections	5790 [R(int) = 0.0376]
Completeness to theta = 23.26°	99.7 %
Absorption correction	None
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5790 / 17 / 571
Goodness-of-fit on F^2	1.018
Final R indices [I>2sigma(I)]	R1 = 0.0583, wR2 = 0.1542
R indices (all data)	R1 = 0.0805, wR2 = 0.1657
Largest diff. peak and hole	0.930 and -0.233 e.Å^{-3}