Electronic Supplementary Information

Efficient Multi-Click Approach to Well-Defined Two-Faced Octasilsesquioxanes: The First Perfect Janus Nanocube

Alberto Blázquez-Moraleja, M. Eugenia Pérez-Ojeda, Jose Ramón Suárez, M. Luisa Jimeno, and Jose Luis Chiara*
Table of Contents:

1. Synthesis and characterization data of compounds 2-5……..S3
2. NMR spectra and HPLC-MS data…………………………….S9
3. Dynamic NMR study of 5………………………………………S26
4. Molecular modeling calculations……………………………..S31
5. References……………………………………………………..S31
1. Synthesis and characterization data of compounds 2-5

**General.** Structural elucidation of the new compounds was accomplished by nuclear magnetic resonance spectroscopy (NMR). Proton and carbon-13 nuclear magnetic resonance ($^1$H NMR or $^{13}$C NMR) spectra were recorded on a BRUKER AVANCE-300 ($^1$H 300 MHz, $^{13}$C 75 MHz), a Varian INOVA 300 ($^1$H 300 MHz, $^{13}$C 75 MHz), a Varian INOVA 400 ($^1$H 400 MHz, $^{13}$C 100 MHz) or a Varian SYSTEM 500 NMR ($^1$H 500 MHz, $^{13}$C 125 MHz) equipped with a 5 mm HCN cold probe. Silicon-29 nuclear magnetic resonance spectra ($^{29}$Si NMR) were recorded on a Varian INOVA 400 (79.5 MHz) spectrometer using Wildmad’s PTFE-FEP (polytetra-fluoroethylene/fluorinated ethylene polypropylene copolymer) 5 mm tube liners. Chemical shifts of $^1$H ($\delta$H), $^{13}$C ($\delta$C) and $^{29}$Si in ppm were determined relative to tetramethylsilane (TMS). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, m = multiplet and/or multiple resonances, br = broad signal), integration, coupling constants in hertz (Hz), and assignment. One-dimensional NMR experiments ($^1$H, $^{13}$C, and $^{29}$Si) were performed using standard Varian pulse sequences. Two-dimensional (2D) $^1$H-$^1$H NMR experiments (gradient correlation spectroscopy gCOSY) were carried out with the following parameters: a delay time of 1 s, a spectral width of 3475.5 Hz in both dimensions, 2048 complex points in t2 and t4 transients for each of 128 time increments, and a linear prediction to 256. The data were zero-filled to 2048 x 2048 real points. 2D $^1$H-$^{13}$C NMR experiments (gradient heteronuclear single quantum coherence: gHSQC, and gradient heteronuclear multiple-bond correlation: gHMBC) used the same $^1$H spectral window, a $^{13}$C spectral window of 24132.7 Hz, a 1s relaxation delay, 1024 data points, and 128 time increments, with a linear prediction to 256. The data were zero-filled to 4096 x 4096 real points. Typical numbers of transients per increment were
4 and 16, respectively. Activation parameters for compound 5 were measured in CDCl$_3$
by lineshape analysis using gNMR, in the temperature range 223 to 323 °C. The
temperature was raised in steps of 5 °C, and 20 minutes were allowed for temperature
equilibration before shimming at each temperature. HPLC were recorded in an HPLC-
Alliance Waters 2695 coupled to a photodiode array from Waters 2996 and a mass
spectrometer Micromass ZQ provided with a ESI source in positive mode with a
quadrupole detector. A Sunfire C18 column (3.5 micron, 4.6×50 mm) was used. The
products were eluted with acetonitrile/water gradients using 0.1% formic acid. Yields
are given in relative area% of the absorbance measured at 287 nm (alkyl-azide
absorbance), as deduced from the MS analysis of the peak. High resolution mass spectra
(HRMS) were recorded on an Agilent 6520 Q-TOF instrument with a ESI source.
Anhydrous solvents were prepared according to standard methods by distillation over
drying agents or via elution through a PureSolv™ column drying system from
Innovative Technology, Inc. All other solvents were of HPLC grade and were used as
provided. All reactions were carried out with magnetic stirring and, if air or moisture
sensitive, in oven-dried glassware under argon. Copper(I) catalyst [Cu(C18$_6$tren)]Br
(C18$_6$tren = tris(2-dioctadecylaminoethyl)amine) was prepared according to a described
procedure.$^1$

1,2-Bis(prop-2-yn-1-yloxy)benzene (2).$^2$ To a solution of pyrocathecol (500 mg, 4.54
mmol) in dry acetone (45 mL) under argon, was added finely powdered K$_2$CO$_3$ (2.51 g,
18.16 mmol) and the suspension was stirred at 60 °C for 30 min. To this mixture was
added a solution of propargyl bromide in toluene (80 wt.%, 1.52 mL, 13.62 mmol) in
portions during 1 h. After stirring at 60 °C for 20 h, the mixture was cooled and filtered,
and the filtrate was evaporated at reduced pressure. The resultant residue was purified
by flash chromatography to afford 2 as a light-orange thick oil (0.696 g, 82% yield). $^1$H
NMR (CD$_3$Cl, 300 MHz): $\delta$ 2.51 (t, 2H, $J = 2.3$ Hz, CCH), 4.76 (d, 4H, $J = 2.3$ Hz, ArOCH$_2$), 6.85-7.18 (m, 4H, Ar).

**4-tert-Butylcalix[4]arenetetrapropargyl ether (3).** To a flask containing 60% NaH in paraffin (370 mg, 9.24 mmol) under argon was added hexane (3 mL) and the resultant suspension was stirred for 5 min at room temperature and decanted. The resultant NaH solid was suspended in anhydrous DMF (3 mL) and a solution of 4-tert-butylcalix[4]arene (500 mg, 0.770 mmol) in DMF (2 mL + 1 mL rinse) was added dropwise at 0 °C under good stirring. Considerable frothing was observed at this stage. After stirring for 40 min at 0 °C, a solution of propargyl bromide in toluene (80 wt.%, 0.85 mL, 7.7 mmol) was added and the mixture was stirred at room temperature for 24 h. The reaction was quenched by adding MeOH (1 mL) dropwise and, after stirring for 15 min, water was added (40 mL) and the product was extracted EtOAc (3 × 50 mL). The combined organic extracts were dried and the resultant dark residue was purified by flash chromatography to afford 3 as a light brown solid (383 mg, 62% yield). $^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 1.09 (s, 36H, tBu), 2.48 (t, 4H, $J = 2.3$ Hz CH≡C), 3.18 (d, 4H, $J = 12.8$ Hz, Ar-CH$_2$-Ar), 4.62 (d, 4H, $J = 12.8$ Hz, Ar-CH$_2$-Ar), 4.81 (d, 8H, $J = 2.3$ Hz, CH$_3$O), 6.80 (s, 8H, Ar).

**CuAAC reaction of 1 and 2.** To a Schlenk flask fitted with a PTFE stopcock containing a solution of octakis(3-azidopropyl)octasilsesquioxane (1) (300 mg, 0.275 mmol) and di-O-propargyl-ε-cathecol (2) (11 mg, 0.055 mmol) in 16 mL of anhydrous toluene under argon was added [Cu(C$_{18}$tren)]Br (10 mg, 0.0055 mmol) and iPr$_2$NEt (60 mL, 0.385 mmol, 7.0 equiv). The stopcock was closed and the mixture was heated at 50 °C under stirring for 21 h. The solvent was removed at reduced pressure and the crude residue was purified by automatic flash chromatography in a silica gel cartridge.
using a toluene/MeOH (100:0 to 10:1 v/v gradient) to afford first 235 mg of unreacted octakis(3-azidopropyl)octasilsequioxane 1 (98% of the total excess used) followed by the click products (61 mg), as a pale yellow oil. The HPLC-MS analysis of the isolated product showed it to be a mixture of 4a (85.12%), 6 (8.87%), and an unidentified silsesquioxane dimer containing two bis-triazolyl tethers (tetra-triazolyl silsesquioxane dimers: TTSD, 6.01%). Characterization data for compound 4a: $^1$H NMR (CDCl$_3$, 500 MHz): 0.70-0.74 (m, 12H, SiCH$_2$CH$_2$CH$_2$N-triazole), 1.66-1.72 (m, 12H, SiCH$_2$CH$_2$CH$_2$N-triazole), 3.25-3.28 (m, 12H, CH$_2$-N$_3$), 4.37 (t, 4H, $J$ = 7.1 Hz, CH$_2$-triazole), 5.21 (s, 4H, CH$_2$-O), 7.00-7.02 (m, 2H Ar), 7.07-7.09 (m, 2H Ar), 7.80 (s, 2H, H-triazole). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 148.79, 144.37, 122.93, 122.52, 115.34, 63.96, 53.50, 52.58, 24.31, 22.56, 9.10, 8.99. $^{29}$Si NMR (CDCl$_3$, 79.5 MHz): d –67.00, –67.07, –67.52 (in 2:1:1 intensity ratio, respectively). HRMS-ESI: Calc. for C$_{36}$H$_{59}$N$_{24}$O$_{14}$Si$_8$ 1274.2718, found 1275.2748 [M+H]$^+$, 1297.2567 [M+Na]$^+$. 

![Possible tetra-triazolyl silsesquioxane dimers (TTSD)](image_url)
Characterization data of the mixture of 4a, 6, and the minor TTSD products:

\[ ^1H\text{-NMR (CDCl}_3, 500 MHz): \delta 0.59-0.68 (m, 12H, SiCH}_2CH}_2CH}_2N}_3, 6/TTSD), 0.68-0.79 (m, 12H, SiCH}_2CH}_2CH}_2N}_3, 4a), 0.83-0.91 (m, 4H, SiCH}_2CH}_2CH}_2-triazole), 1.57-1.76 (m, 12H, SiCH}_2CH}_2CH}_2N}_3), 1.92-2.08 (m, 4H, SiCH}_2CH}_2CH}_2-triazole), 3.23-3.31 (m, 12H, CH}_2-N}_3), 4.33 (t, 4H, J = 7.1 Hz, CH}_2-triazole, 6/TTSD), 4.37 (t, 4H, J = 7.1 Hz, CH}_2-triazole, 4a and TTSD/6), 5.26, 5.27 and 5.28 (s, 4H, CH}_2-O, 6/TTSD, TTSD/6 and 4a), 6.89-6.94 (m, 2H, Ar, 6/TTSD), 6.95-6.98 (m, 2H Ar, 6/TTSD), 6.98-7.04 (m, 2H Ar, 4a), 7.04-7.06 (m, 2H Ar, TTSD/6), 7.06-7.12 (m, 2H Ar, 4a), 7.14-7.19 (m, 2H Ar, TTSD/6), 7.65 (s, 2H triazole, 6/TTSD), 7.67 (s, 2H, triazole, TTSD/6), 7.80 (s, 2H, 4a). \[ ^13C\text{-NMR (125 MHz, CDCl}_3): \delta 9.0, 9.1, 9.1 (SiCH}_2CH}_2CH}_2N}_3), 22.6, 22.6, 22.8 (SiCH}_2CH}_2CH}_2N}_3), 24.1, 24.3 (SiCH}_2CH}_2CH}_2-triazol), 52.6 (SiCH}_2CH}_2CH}_2-triazole), 53.5, 53.5 (SiCH}_2CH}_2CH}_2N}_3), 62.8, 63.6, 64.0 (CCH}_2O), 113.7, 115.3, 115.6, 121.8, 122.2 (CH Ar), 122.5 (CH triazole), 122.9 (CH triazole), 123.1 (CH triazole), 143.9 (C-triazole), 144.3 (C-triazole), 144.4 (C-triazole), 148.0 (CAR), 148.6 (CAR), 148.8 (CAR). HRMS: Calc. for C_{36}H_{59}N_{24}O_{14}Si_{8} 1274.2718, found 1275.2748 [M+H]^+, 1297.2567 [M+Na]^+. Calc. for C_{60}H_{106}N_{48}O_{26}Si_{16} 2362.4756, found 2362.4718 [M+H]^+. Calc. for C_{72}H_{116}N_{48}O_{26}Si_{16} 2548.5467, found 2549.5431 [M+H]^+, 2572.5151 [M+Na]^+. 

CuAAC reaction of 1 and 3: Synthesis of Janus-silsesquioxane 5. To a Schlenk flask fitted with a PTFE stopcock containing a solution of 1 (520 mg, 0.477 mmol) and 3 (77 mg, 0.096 mmol) in 30 mL of anhydrous toluene under argon was added [Cu(C18tren)]Br (17 mg, 0.010 mmol) and iPr2NET (200 mL, 1.150 mmol). The stopcock was closed and the mixture was heated at 50 °C under stirring for 24 h. The solvent was removed at reduced pressure and the crude residue was purified by automatic flash chromatography in a silica gel cartridge using a toluene/MeOH (100:0
to 10:1) gradient to afford first 392 mg of unreacted octakis(3-azidopropyl)octasilsequioxane (99% of the total excess used) followed by compound 9 (148 mg, 82% yield), as a pale cream-colored solid. $^1$H NMR (CDCl$_3$, 500 MHz, –50 ºC): d 0.68-0.84 (br m, 16H, 8 SiCH$_2$), 0.77 (s, 18H, 2 t-Bu), 1.28 (s, 18H, 2 t-Bu), 1.65-1.71 (br m, 8H, 4 SiCH$_2$CH$_2$CH$_2$N$_3$), 1.87 (br m, 4H, 2 SiCH$_2$CH$_2$-triazole), 2.04 (br. m, 4H, 2 SiCH$_2$CH$_2$-triazole), 3.25 (d, 4H, $J$ = 12.7 Hz, CH$_2$-calixarene), 3.29 (t, 8H, $J$ = 6.7 Hz, 4 CH$_2$-N$_3$), 3.86 (br m, 4H, 2 SiCH$_2$CH$_2$-triazole), 4.36 (br m, 4H, 2 SiCH$_2$CH$_2$-triazole), 4.53 (d, 4H, $J$ = 12.7 Hz, CH$_2$-calixarene), 4.69 (s, 4H, 2 CH$_2$-O), 4.83 (s, 4H, 2 CH$_2$-O), 6.40 (s, 4H, 2 ArH-calixarene), 6.95 (s, 2H, 2 H-triazole), 7.07 (s, 4H, 2 ArH-calixarene), 8.69 (s, 2H, 2 H-triazole). $^1$H NMR (CDCl$_3$, 500 MHz, 55 ºC): d 0.67-0.71 (m, 8H, 4 SiC$_2$H$_2$CH$_2$N$_3$), 0.74-0.83 (m, 8H, 4 SiC$_2$H$_2$CH$_2$-triazole), 1.01 (br s, 36H, 4 t-Bu), 1.62-1.69 (m, 8H, 4 SiC$_2$H$_2$CH$_2$-triazole), 1.93-2.01 (br m, 8H, 4 SiC$_2$H$_2$CH$_2$-triazole), 3.18 (d, 4H, $J$ = 12.7 Hz, CH$_2$ -calixarene), 3.21 (t, 8H, $J$ = 6.7 Hz, 4 CH$_2$-N$_3$), 4.08 (br m, 8H, 4 SiC$_2$H$_2$CH$_2$-triazole), 4.55 (d, 4H, $J$ = 12.7 Hz, CH$_2$-calixarene), 4.74 (s, 8H, 4 CH$_2$-O), 6.70 (br s, 8H, 4 ArH), 7.81 (br s, 4H, 4 H-triazole). $^{13}$C NMR (125 MHz, CDCl$_3$, 25 ºC, based on HSQC and HMBC spectra): δ 8.9 (SiC$_2$H$_2$), 9.3 (SiC$_2$H$_2$), 22.7 (SiC$_2$H$_2$CH$_2$N$_3$), 24.6 (SiC$_2$H$_2$CH$_2$-triazole), 29.9 (this signal correlates with a singlet at 1.24 ppm in the $^1$H NMR spectrum, which seems to be an impurity in our sample), 31.6 (CH$_2$-calixarene), 31.8 (CH-t-Bu), 34.0 (Me$_3$C), 52.0 (SiC$_2$H$_2$CH$_2$-triazole), 53.6 (SiC$_2$H$_2$CH$_2$N$_3$), 66.5 (CH$_2$O), 125.3 (CH Ar), 125.4 (CH triazole), 133.8 (CH$_2$-CAr), 144.4 (tBu-CAr), 145.1 (C triazole), 153.2 (O-CAr). $^{29}$Si NMR (CDCl$_3$, 79.5 MHz, 25 ºC): d –66.67, –67.05. HRMS-ESI Calc. for C$_{80}$H$_{112}$N$_{24}$O$_{16}$Si$_8$ 1888.6842, found 1890.6931 [M+H]$^+$, 1912.6775 [M+Na]$^+$. 

S8
2. NMR spectra and HPLC-MS data
$^1$H NMR (CDCl$_3$, 300 MHz) of compound 2
$^1$H NMR (CDCl$_3$, 300 MHz) of compound 3
$^1$H NMR (CDCl$_3$, 500 MHz) of the click product isolated from the reaction of 1 and 2 (mainly 4a).
$^{13}$C NMR (CDCl$_3$, 125 MHz) of the click product isolated from the reaction of 1 and 2 (mainly 4a).
$^1$H-$^{13}$C HSQC (CDCl$_3$, 500 MHz) of the click product isolated from the reaction of 1 and 2 (mainly 4a).
$^1$H-$^{13}$C HMBC (CDCl$_3$, 500 MHz) of the click product isolated from the reaction of 1 and 2 (mainly 5a).
$^{29}$Si NMR (CDCl$_3$, 79.5 MHz) of the click product isolated from the reaction of 1 and 2 (mainly 5a).
HPLC-MS of the click products isolated from the reaction of 1 and 2 (TTSD: tetratriazolyl silsesquioxane dimer).
HRMS-ESI of the click products isolated from the reaction of 1 and 2 (TTSD: tetratriazolyl silsesquioxane dimer).

HRMS-ESI of compound 4a
HRMS-ESI of **TTSD** (**TTSD**: tetratriazolyl silsesquioxane dimer).
$^1$H NMR (CDCl$_3$, 400 MHz, 55 °C) of compound 5.
$^{13}$C NMR (CDCl$_3$, 125 MHz, 25 °C) of compound 5.
$^1$H-$^{13}$C HSQC (CDCl$_3$, 500 MHz, 55 °C) of compound 5.
$^{1}H-^{13}C$ HMBC (CDCl$_3$, 500 MHz, 55 ºC) of compound 5.
$^{29}$Si NMR (CDCl$_3$, 79.5 MHz, 25 °C) of compound 5 (relative intensities ca. 2:5; smaller signal shows larger broadening).
### Compound Table

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>RT</th>
<th>Mass</th>
<th>Abund</th>
<th>Formula</th>
<th>Tgt Mass</th>
<th>Diff (ppm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C80 H112 N24 O16 Si8</td>
<td>1.349</td>
<td>1888.6862</td>
<td>211196</td>
<td>C80 H112 N24 O16 Si8</td>
<td>1888.6842</td>
<td>1.07</td>
</tr>
</tbody>
</table>

### Compound Label

<table>
<thead>
<tr>
<th>Compound Label</th>
<th>RT</th>
<th>Algorithm</th>
<th>Mass</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cpd 1: C80 H112 N24 O16 Si8</td>
<td>1.349</td>
<td>Find By Formula</td>
<td>1888.6862</td>
</tr>
</tbody>
</table>

### MS Zoomed Spectrum

[Graph showing mass spectrum with peaks at 1912.6775 (M+Na)^+ and 1890.6931 (M+H)^+]

HRMS-ESI of compound 5
3. Dynamic NMR study of compound 5

In order to obtain the activation barrier for the conformational equilibrium of 5, rate constants were determined from the $^1$H NMR spectra over the temperature range 223-323 K by using the line shape method with the gNMR program$^5$ and considering a symmetric two-site exchange model. The enthalpy $\Delta H^\ddagger$ and entropy $\Delta S^\ddagger$ of activation were calculated using the Eyring equation. The resonance signal of the triazol proton ($\delta = 8.69, 6.94$) and of the phenyl protons ($\delta = 7.06, 6.38$) were used for the simulation.

The simulated spectra with different rate obtained were compared with experimental spectra at different temperatures.

$$R \ln \left( \frac{h \kappa T}{kT} \right) = -\Delta H^*/T + \Delta S^*$$

Eyring plot was obtained by plotting $R \ln \left( \frac{h \kappa T}{kT} \right)$ against inverse of temperature (1/T).
Figure 1S. Eyring plot for compound 5. $R^2 = 0.998$. $\Delta H^* = -A$ (slope) = 7.17 $\pm$ 0.07 kcal mol$^{-1}$. $\Delta S^* = (y\text{-intercept}) = -0.0196 \pm 2.5e^{-04}$ kcal K$^{-1}$ mol$^{-1}$. 
Figure 2S. $^1$H NMR (400 MHz) spectra of 5 at varying temperature in CDCl$_3$. 
Figure 2S. $^1$H NMR (400 MHz) spectra of 5 at varying temperature in CDCl₃.
Figure 2S. $^1$H NMR (400 MHz) spectra of 5 at varying temperature in CDCl$_3$. 
4. Molecular modeling calculations

We have carried out a simple molecular modeling study of 5 in vacuum. First, we have run extensive energy minimizations using the MMFF94 force field starting from a large set of different initial conformations of the calixarene system and the linking chains connecting it to the silsesquioxane cage. The starting conformations were both manually set or obtained during different molecular dynamics trajectories performed with the same force field. The minimum energy conformer thus obtained was fully re-optimized using the semiempirical PM3 method.

5. References

Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi,
J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi,
M. Cossi, N. Rega, N. J. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken,
C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin,
R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G.
Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D.
Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox,
Gaussian 09, Revision B.01, Gaussian, Inc., Wallingford CT, 2009.