Total synthesis of high loading capacity PEG-based supports. Evaluation and improvement of the process by use of ultrafiltration and PEG as solvent.

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Supporting information

Examples of calculations
- One step transformation without recycling: preparation of 1
- One step transformation with solvent recycling: preparation of 19
- Multi-step transformation: Preparation of 15

Spectra
- Bis propargylated PEG₆₀₀₀ (1)
  ¹H NMR
  ¹³C NMR
  MALDI TOF
- Pentacyrthritol trially ether 6
  ¹H NMR
  ¹³C NMR
- Compound 9
  ¹H NMR
  ¹³C NMR
- Compound 10
  ¹H NMR
  ¹³C NMR
- Compound 11
  ¹H NMR
  ¹³C NMR
- Compound 12
  ¹H NMR
  ¹³C NMR
- PEG₆₀₀₀ with 6 allyl functions (13)
  ¹H NMR
  ¹³C NMR
  MALDI TOF
- PEG₆₀₀₀ with 6 alcohol functions (15)
  ¹H NMR
  ¹³C NMR
  MALDI TOF
- Compound 17
  ¹H NMR
  ¹³C NMR
- Compound 18
  ¹H NMR
  ¹³C NMR
- Compound 19
  ¹H NMR
  ¹³C NMR
- Compound 20
  ¹H NMR
  ¹³C NMR
- Compound 21
  ¹H NMR
  ¹³C NMR
- PEG₆₀₀₀ with 18 allyl functions (22)
  ¹H NMR
  ¹³C NMR
  MALDI TOF
- PEG₆₀₀₀ with 18 alcohol functions (23)
  ¹H NMR
  ¹³C NMR
  MALDI TOF
Examples of calculations

The determination of the green metrics can be done in a very easy way considering the mass of all the reagents and auxiliaries used in the reaction. Alternatively, we also show here how they can be calculated using the general formalism we developed. The results are presented here in tables, we generally used a spreadsheet application (Excel) to perform the calculations.

- One step transformation without recycling: Preparation of 1

\[ \text{PEG}_{6000} + 2 \text{NaOH} + 2 \text{BrPr} \rightarrow 1 \]

\[ \text{AE} = M_1/[M_{\text{PEG}}+2M_{\text{NaOH}}+2M_{\text{BrPr}}] = 0.962798251 \]

<table>
<thead>
<tr>
<th>Reaction</th>
<th>compound</th>
<th>M</th>
<th>volume mL</th>
<th>density</th>
<th>mass g</th>
<th>mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEG_{6000}</td>
<td>6185</td>
<td>40</td>
<td>0.006467259</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>THF</td>
<td>30</td>
<td>0.8892</td>
<td>26.676</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaOH</td>
<td>40</td>
<td>5.34</td>
<td>0.1335</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>H_{2}O</td>
<td>11</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BrPr 80%w in toluene</td>
<td>118.96</td>
<td>4.3</td>
<td>1.335</td>
<td>4.5924</td>
<td>0.03860457</td>
<td></td>
</tr>
</tbody>
</table>

stoichiometric ratio between NaOH and PEG \[ \varphi_1 = \text{mol NaOH}/2/\text{mol PEG} \]

ratio between the mass of the excess of NaOH and the mass of the reactants in a stoichiometric amount \[ b_1 = (\varphi_1 - 1) \times 2M_{\text{NaOH}}/[M_{\text{PEG}}+2M_{\text{NaOH}}+2M_{\text{BrPr}}] = 0.114671178 \]

stoichiometric ratio between BrPr and PEG \[ \varphi_2 = \text{mol BrPr}/2/\text{mol PEG} \]

ratio between the mass of the excess of BrPr and the mass of the reactants in a stoichiometric amount \[ b_2 = (\varphi_2 - 1) \times 2M_{\text{BrPr}}/[M_{\text{PEG}}+2M_{\text{NaOH}}+2M_{\text{BrPr}}] = 0.072610435 \]

- Workup

by extraction/precipitation

<table>
<thead>
<tr>
<th>Compound</th>
<th>M</th>
<th>volume mL</th>
<th>density</th>
<th>mass g</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH_{2}Cl_{2}</td>
<td>200</td>
<td>1.3</td>
<td>260</td>
<td></td>
<td></td>
</tr>
<tr>
<td>aq. KH_{2}PO_{4}</td>
<td>80</td>
<td>1.1527</td>
<td>92.216</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H_{2}O</td>
<td>40</td>
<td>1</td>
<td>40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na_{2}SO_{4}</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et_{2}O (precipitation)</td>
<td>450</td>
<td>0.7134</td>
<td>321.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Et_{2}O (washing)</td>
<td>200</td>
<td>0.7134</td>
<td>142.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>product 1 (C_{286}H_{566}O_{141})</td>
<td>6261</td>
<td>39</td>
<td>0.96316483</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mass of reactants \[ = \text{m}_{\text{PEG}} + \text{m}_{\text{NaOH}} + \text{m}_{\text{BrPr}} \]

Mass of auxiliaries \[ = \text{m}_{\text{THF}} + \text{m}_{\text{H}_{2}\text{O}} + \text{m}_{\text{CH}_{2}\text{Cl}_{2}} + \text{m}_{\text{aq. KH}_{2}\text{PO}_{4}} + \text{m}_{\text{H}_{2}\text{O}} + \text{m}_{\text{aq. Na}_{2}\text{SO}_{4}} + \text{m}_{\text{Et}_{2}\text{O}} + \text{m}_{\text{toluene}} \]

### Reaction mass efficiency

$$RME = \frac{\text{mass of product}}{\text{mass of reactants}}$$

$$RME = \frac{\varepsilon AE}{1 + b_1 + b_2}$$

**Global mass efficiency**

$$GME = \frac{\text{mass of product}}{\text{mass of reactants} + \text{mass of auxiliaries}}$$

\[ E = \frac{\text{mass of waste}}{\text{mass of product}} \]

- **RME**
  - **H₂O Ultrafiltration 1**
    - M
    - Volume mL: 160
    - Density: 1.3
    - Mass g: 160
  - **H₂O Ultrafiltration 2**
    - M
    - Volume mL: 120
    - Density: 1
    - Mass g: 120
  - **H₂O Ultrafiltration 3**
    - M
    - Volume mL: 120
    - Density: 1
    - Mass g: 120
  - **Product 1 (C₂₈₆H₅₆₆O₁₄₁)**
    - M
    - Mass of reactants
    - Mass of auxiliaries
    - Mass of auxiliaries (without H₂O used in the workup)

- **E**
  - **E**
    - Volume mL
    - Density
    - Mass g
    - Yield

- **E** (without H₂O used in the workup)
  - **E**
    - Volume mL
    - Density
    - Mass g

- **One step transformation with solvent recycling: Preparation of 19**

\[ 18 + NaN_3 \rightarrow 19 \]

\[ AE = \frac{M_{19}}{M_{18} + M_{NaN_3}} = 0.931891148 \]

### Reaction compound

<table>
<thead>
<tr>
<th>Compound</th>
<th>M</th>
<th>Volume mL</th>
<th>Density</th>
<th>Mass g</th>
<th>Mol</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>1445.66</td>
<td>20</td>
<td>0.013834512</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PEG₄₀₀₀</td>
<td>16</td>
<td>1.128</td>
<td>18.048</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NaN₃</td>
<td>65.01</td>
<td>0.99</td>
<td>0.015228426</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
stochiometric ratio between NaN₃ and 18

$$\varphi = \text{mol}_{\text{NaN₃}} / \text{mol}_{18}$$

1.100756345

ratio between the mass of the excess of NaN₃ and the mass of the reactants in a stochiometric amount

$$b = (\varphi - 1) \times \frac{\text{M}_{\text{NaN₃}}}{[\text{M}_{18} + \text{M}_{\text{NaN₃}}]}$$

0.004335937

Workup

<table>
<thead>
<tr>
<th>M</th>
<th>volume mL</th>
<th>density</th>
<th>mass g</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Et₂O</td>
<td>40</td>
<td>0.7134</td>
<td>28.536</td>
<td></td>
</tr>
<tr>
<td>H₂O</td>
<td>20</td>
<td>1</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Na₂SO₄</td>
<td></td>
<td></td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>product 19 (C₇₂H₁₁₂N₁₂O₁₆)</td>
<td>1407.78</td>
<td>19.1</td>
<td>0.980696771</td>
<td></td>
</tr>
</tbody>
</table>

Mass of reactants = m₁₈ + m_{NaN₃}

20.99

Mass of auxiliaries = m_{PEG₄₀₀} + m_{Et₂O} + m_{H₂O} + m_{Na₂SO₄}

71.584

Mass of auxiliaries (1 recycling of PEG) = m_{PEG₄₀₀}/2 + m_{Et₂O} + m_{H₂O} + m_{Na₂SO₄}

62.56

Mass of auxiliaries (2 recycling of PEG) = m_{PEG₄₀₀}/3 + m_{Et₂O} + m_{H₂O} + m_{Na₂SO₄}

59.552

Mass of auxiliaries (3 recycling of PEG) = m_{PEG₄₀₀}/4 + m_{Et₂O} + m_{H₂O} + m_{Na₂SO₄}

58.048

Reaction mass efficiency

$$RME = \frac{\text{mass of product}}{\text{mass of reactants}}$$

0.909957122

$$RME = \frac{e \cdot AE}{1 + b}$$

Global mass efficiency

$$GME = \frac{\text{mass of product}}{\text{mass of reactants} + \text{mass of auxiliaries}}$$

0.206321429 (1st use of PEG₄₀₀)

0.228605625 (2nd use of PEG₄₀₀)

0.237143354 (3rd use of PEG₄₀₀)

0.241655912 (4th use of PEG₄₀₀)

E

$$E = \frac{\text{mass of waste}}{\text{mass of product}}$$

3.846806283 (1st use of PEG₄₀₀)

3.37434555 (2nd use of PEG₄₀₀)

3.216858639 (3rd use of PEG₄₀₀)

3.13815183 (4th use of PEG₄₀₀)

- Multi-step transformation: Preparation of 15

For a linear multi-step synthesis, the calculation of GME can be easy but for a multi-sequence convergent synthesis, the problem is more difficult and a general formalism allows for the calculation. The calculation of GRME (global reaction mass efficiency) of 15 is detailed below.
The global atom economy is:

\[
GAE = \frac{v_P M_P}{\sum M}
\]

were P refers to the product 15 and

\[
\sum M = v_{a1} M_{A1} + v_{a2} M_{A2} + \sum_{i=1}^{z} v_{b1,i} M_{B1,i} + \sum_{j=1}^{m} v_{b2,j} M_{B2,j}
\]

\[
2M_{\text{PEG}} + 2 M_i + 2 M_{\text{BrPr}} + 2 M_{\text{NaOH}} + 6 M_{\text{SHC(CH2)2OH}} + 6 M_{\text{AlBr}} + 6 M_{\text{NaOH}} + 2 M_{\text{Br(CH2)2Br}} + 2 M_{\text{NaOH}} + 2 M_{\text{Na3}}
\]

\[
GAE = M_{15} / \Sigma M = 7437/8851.758 = 0.840172088
\]

There are 2 branches in the synthesis of 15, and therefore two possibilities to carry out the calculation: Either considering the main branch starting from PEG (black branch) or by considering that the reference compound is pentaerythritol 3 (blue branch). As we have demonstrated,\(^1\) the final result is exactly the same. We chose here to consider that the black branch is the main branch.

Total yield from PEG (black branch): \(\Pi_{\text{PEG}} = \epsilon_{1,1,2,2} \epsilon_{1,3} = 0.845246869\)

Total yield from pentaerythritol 3 (blue branch):

For this calculation, we have to consider the stoichiometric ratio between 12 and 1:

\[
q_{1,2} = \text{mol}_{12}/\text{mol}_{12}/2 = 1.139607295
\]

\[
\Pi_{\text{PEG}} = \epsilon_{2,1,2,2,2,2,2,2,2}(\epsilon_{1,2}/\epsilon)_{1,3} = 0.418203894
\]

| number of moles of the reference molecule | = mol of PEG | 0.006467259 |
| number of moles of 3 necessary to give 15 from x mol of PEG | \(x = 2x_1 \Pi_{\text{PEG}}(\Pi_{\epsilon_{1,3}}) \) | 0.02614242 |
| 3/PEG (scale ratio) | \(\sigma = \sqrt{x} = \Pi_{\text{PEG}}(\Pi_{\epsilon_{1,3}}) \) | 2.021135818 |
| ratio between the mass of the excess of 3 and the mass of all the reactants in the ideal case* | \(a = (\sigma_{1,2} - 1) 2 M \Sigma M \) | 0.03144743 |

* Ideal case: All the yields (not necessary the last one) are 100% and all the reactions are carried out in the stoichiometric amount.

For the main branch (branch 1 in black): there are 3 steps, involving 2 reagents (step 1), no reagents (step 2) and 1 reagent (step 3). Hence, we have to calculate the ratios between the mass of the excess of every reactant and the mass of all the reactants used in the total synthesis, with respect to PEG. These ratios are \(b_{1,i} \) (branch 1, step 1, reactant 1), \(b_{1,i} \) (branch 1, step 1, reactant 2), \(b_{1,i} \) (branch 1, step 3, reactant 1). They are calculated using the formula given below.\(^1\)

\[
b_{1,i} = \left[ q_{1,i} (\epsilon_{1,2,2,2,2,2,2,2,2} - \epsilon_{1,1,1,1,1,1,1,1,1}) - 1 \right] \frac{v_{b1,i} M_{B1,i}}{\sum M}
\]

\[
q_{1,i} = \frac{\text{mol number of } B_{1,i}}{v_{b1,i}}
\]

\[
\text{yield} = \epsilon_{1,1,1} = \frac{0.950816563}{0.950816563} \text{ purification by UF}
\]

<table>
<thead>
<tr>
<th>Branch 1 step 1</th>
<th>PEG + 2 NaOH + 2 BrPr→1</th>
<th>yield = (\epsilon_{1,1,1} = 0.950816563) (purification by UF)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stoichiometric ratio between NaOH and PEG</td>
<td>(q_{1,1} = \text{mol NaOH}/2/\text{mol PEG} )</td>
<td>10.32121875</td>
</tr>
<tr>
<td>ratio between the mass of the excess of NaOH and the mass of the reactants in the ideal case, for the total synthesis with respect to PEG</td>
<td>(b_{1,1} = {q_{1,1} - 1} 2 M_{\text{NaOH}}/\Sigma M )</td>
<td>0.08424287</td>
</tr>
<tr>
<td>stoichiometric ratio between BrPr and PEG</td>
<td>(q_{1,1} = \text{mol BrPr}/2/\text{mol PEG} )</td>
<td>2.984616047</td>
</tr>
<tr>
<td>ratio between the mass of the excess of BrPr and the mass of the reactants in the ideal case, for the total synthesis with respect to PEG</td>
<td>(b_{1,1} = {q_{1,1} - 1} 2 M_{\text{BrPr}}/\Sigma M )</td>
<td>0.053343059</td>
</tr>
</tbody>
</table>
For the second branch (branch 2 in blue): there are 3 steps, involving 2 reagents (step 1 and step 2) and 1 reagent (step 3). Hence, we have to calculate the ratios between the mass of the excess of every reactant and the mass of all the reactants used in the total synthesis, with respect to PEG, in the ideal case; i.e., all the yields (not necessary the last one) are 100% and all the reactions are carried out in the stoichiometric amount. These ratios are $b_{2,1}$ (branch 2, step 1, reactant 1), $b_{2,1^*}$ (branch 2, step 1, reactant 2), $b_{2,2}$ (branch 2, step 2, reactant 1), $b_{2,2^*}$ (branch 2, step 2, reactant 2) and $b_{2,3}$ (branch 2, step 3, reactant 1). They are calculated using the formula given below.

$$b_{2,j} = \left( \frac{M_{b_{2,j}}}{M_{B_{2,j}}} \right) \left( \frac{\epsilon_{2,j}}{\epsilon_{2,1^*}} \right) \left( \frac{\epsilon_{2,1^*}}{\epsilon_{2,2}} \right) \left( \frac{\epsilon_{2,2}}{\epsilon_{2,3}} \right)$$

$$q_{2,j} = \frac{\text{mol number of } B_{2,j}}{\sum \text{mol number of } F_{2,j-1} / \sum \text{mol number of } F_{2,j}}$$

<table>
<thead>
<tr>
<th>Branch 2 step 2</th>
<th>6 + Br(CH$_2$)$_3$Br + NaOH$\rightarrow$7</th>
<th>yield = $\epsilon_{2,2}$ = 0.728932412 (method in water with recovery of dibromobutane)</th>
</tr>
</thead>
<tbody>
<tr>
<td>stoichiometric ratio between NaOH and 6</td>
<td>$q_{2,2} = \text{mol } \text{NaOH}/\text{mol } 6$</td>
<td>9.859230769</td>
</tr>
<tr>
<td>ratio between the mass of the excess of NaOH and the mass of the reactants, and the mass of the reactants in the ideal case, for the total synthesis with respect to PEG</td>
<td>$b_{2,2} = \left( \frac{\sigma_{2,2^<em>} \epsilon_{2,2^</em>}}{\sigma_{2,2} \epsilon_{2,2}} \cdot 1 \right) \text{mol } \text{NaOH}/\text{mol } 6$</td>
<td>0.125571404</td>
</tr>
<tr>
<td>stoichiometric ratio between Br(CH$_2$)$_3$Br and 4</td>
<td>$q_{2,2^*} = \text{mol } \text{Br(CH}_2\text{)}_4\text{Br}/\text{mol } 4$</td>
<td>1.250574159</td>
</tr>
<tr>
<td>ratio between the mass of the excess of Br(CH$_2$)$_3$Br and the mass of the reactants in the ideal case, for the total synthesis with respect to PEG</td>
<td>$b_{2,2^<em>} = \left( \frac{\sigma_{2,2^</em>} \epsilon_{2,2^<em>} \epsilon_{2,1^</em>}}{\sigma_{2,2^<em>} \epsilon_{2,2} \epsilon_{2,1^</em>}} \cdot 1 \right) \text{mol } \text{Br(CH}_2\text{)}_4\text{Br}/\text{mol } 4$</td>
<td>0.043378873</td>
</tr>
<tr>
<td>Branch 2 step 3</td>
<td>9 + NaN$_3$ $\rightarrow$ 12</td>
<td>yield = $\epsilon_{2,3}$ = 0.983996563 (method in PEG$_{400}$)</td>
</tr>
<tr>
<td>stoichiometric ratio between NaN$_3$ and 9</td>
<td>$q_{2,3} = \text{mol } \text{NaN}_3/\text{mol } 9$</td>
<td>1.098593293</td>
</tr>
<tr>
<td>ratio between the mass of the excess of NaN$_3$ and the mass of the reactants in the ideal case, for the total synthesis with respect to PEG</td>
<td>$b_{2,3} = \left( \frac{\sigma_{2,3^<em>} \epsilon_{2,3^</em>} \epsilon_{2,2} \epsilon_{2,1^<em>}}{\sigma_{2,3} \epsilon_{2,3} \epsilon_{2,2} \epsilon_{2,1^</em>}} \cdot 1 \right) \text{mol } \text{NaN}_3/\text{mol } 9$</td>
<td>0.0003080923</td>
</tr>
</tbody>
</table>
The general expression of GRME is:

$$\text{GRME} = \frac{GAE \prod_{i=1}^{z} f_{1,i}}{1 + a_2 + \sum_{i=1}^{z} h_{1,i} + \sum_{j=1}^{m} b_{2,j}}$$

Applied to the synthesis of 15 it becomes:

$$\text{GRME} = \frac{GAE \prod_{i=1}^{3} f_{1,i}}{1 + a_2 + \sum_{i=1}^{3} h_{1,i} + \sum_{j=1}^{3} b_{2,j}} = \frac{GAE_{1,1,2,3} F_{1,2,3}}{1 + a_2 + (b_{1,1} + b_{1,2} + b_{1,3}) + (b_{2,1} + b_{2,2} + b_{2,3}) + (b_{3,1} + b_{3,2} + b_{3,3})}$$

$$\text{GRME} = 0.41020332$$
Bis propargylated PEG$_{6000}$ (1)
Pentaerythritol triallyl ether 6
Compound 9
Compound 10
Compound 11
PEG₆₀₀₀ with 6 allyl functions (13)
PEG_{6000} with 6 alcohol functions (15)
Compound 18
 Compound 19
Compound 20
Compound 21
PEG₆₀₀₀ with 18 allyl functions (22)
PEG$_{6000}$ with 18 alcohol functions (23)