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# Intramolecular Cannizzaro desymmetrization of tetraethylene glycol assisted by a cation binding template

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Dedicated to Professor Henri Bouas-Laurent

**Abstract**—The synthesis of desymmetrized tetraethylene glycol possessing a benzyl alcohol and a benzoic acid end group via a Cannizzaro reaction is reported. The barium cation template used was found to be essential for a successful transformation.

Desymmetrization of macromolecules is an effective method for the preparation of functional nanoparticles for a variety of potential applications.[1] The development of efficient routes for the directed stepwise synthesis of desymmetrized functional oligoethylene glycols (OEG's) continues to be a major challenge in organic chemistry. Derivatization with a stoichiometric equivalent of a protecting group reagent generally yields a statistical proportion of the monosubstituted product in addition to unreacted and disubstituted starting material. Reported examples provide moderate yields of up to 50%.[2] Disubstitution can be avoided by using a vast excess of glycol relative to the reagent. This can be accomplished by using inexpensive, easily removed starting materials such as ethylene glycols of up to four units.[3]

A synthetic route for preparing OEG-terminated alkanethiol-amides was recently developed[4] that starts with the monomesylation of the OEG, followed by convertion into the corresponding monoazides and reduction of the azide function to the amine function by catalytic hydrogenolysis on Pd/C. The conversion of one of the hydroxyl groups in the OEG to the monomesylate derivative proved inefficient owing of the concomitant generation of the bismesylate product and small amounts of unprotected starting material. Separating the monomesylate derivative usually involves a time-consuming column chromatography procedure. Recently, this shortcoming has been circumvented by using a straightforward method with orthogonal end-functionalized OEG that yields a mono-*N*-protected diamino OEG directly in fewer steps.[5] OEG's are converted to bisazides via bismesyl derivatives, and the crucial monoreduction is accomplished by reacting the bisazide in a bilayer system ($PPh_3$, EtOAc/1 M HCl). Monoreduction of one of the azide groups is followed by rapid protonation; the water-soluble polar OEG-monoamine derivative migrates to the water layer and further reduction is thus hindered. However, purification of the compound involves passing the aqueous layer thorough a C-18 solid phase extraction column, which provides a 65% yield.

The synthesis and characterization of multivalent receptors for the binding of metal ions was recently reported by the authors.[6] One of the prerequisites for developing an effective synthetic approach here is the availability of practical methods for variably end-substituted tetraethylene glycol (TEG). Our primary interest was to obtain TEG's end-substituted with aromatic groups with a view to preparing chromophoric ditopic receptors.

The synthesis of compound **1**, the reference system for the ditopic receptors reported,[6] provided crystals suitable for X-ray structure analysis of their $Ba^{2+} \subset \mathbf{1}$ complex.[6a,c] Although the barium cation is 'wrapped up' by the TEG chain in a hexagonal fashion, both aromatic-end groups point in the same direction—but are not parallel.

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*Keywords*: Tetraethylene glycol; Desymmetrization; Cannizzaro reaction; Barium template.

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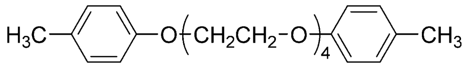


**1**

This led us into believing that dismutation (disproportionation) of appropriate functional groups (e.g., the aromatic-end groups of a symmetric podand such as **1**) might provide a method for controlled desymmetrization of skeletal remote positions that can be induced to adopt confined spatial vicinity by use of appropriate templates.

We chose the Cannizzaro reaction for disproportionating desymmetrization as in its simplest form, it involves the reaction of aromatic aldehydes (viz. aldehydes with no α-hydrogen in general) to form $RCH_2OH$ and $RCO_2H$ as major products.[7] The synthetic approach adopted starts from commercially available TEG and is shown in Scheme 1. Briefly, TEG is converted to the bistosyl derivative in 90% yield, using phase transfer catalysis.[8] Conversion of the bistosyl derivative to the bis-aryloxyaldehyde **2**,[9] in 96% yield, is achieved by reacting it with the sodium salt of 4-hydroxy benzaldehyde (4-HBA) in acetonitrile at reflux. Although comprehensive studies on the influence of $[HO^-]$ and nature of the cation are discussed later on the decisive desymmetrization reaction was best accomplished by reacting a 0.15 M solution of **2** with 1.5 M $Ba(OH)_2$ in boiling water for 22 h. Subsequent neutralization with 5% HCl to protonate the carboxyl group and extraction with $CH_2Cl_2$ gave **3** in almost quantitative yield.

Figure 1 illustrates the crucial role of the complexing cation. As can be seen in Figure 1a, using a $Ba(OH)_2$ concentration of 1.5 N ($[HO^-] = 3$ mol/L) or higher ensured quantitative yield in the intramolecular Cannizzaro desymmetrization reaction; also, lower concentrations (0.5 M $Ba(OH)_2$; $[HO^-] = 1$ mol/L) significantly decreased the reaction yield. However, this effect is appreciably displayed when the reaction is carried out with NaOH or KOH. Thus, quantitative transformation was only accomplished at a 12 M NaOH concentration, the yield decreasing to 84% at 6 M and the starting material being quantitatively recovered at lower NaOH concentrations. With KOH as the base, the yield barely reached 63%, even at such a high concentration as 12 M.

As can be seen from Figure 1b, the ability of the ethylene chain to bind the cation decisively influences the course of the Cannizzaro reaction. The reaction yield obtained with 0.5 M $Ba(OH)_2$ ($[HO^-] = 1$ mol/L), 22% (Fig. 1a), can be raised to 33% simply by adding $BaCl_2$ to a $[Ba^{2+}]$ concentration of 1.5 M. Significantly, at [NaOH] = 3 M, where the reaction does not occur and only the starting material is quantitatively recovered (Fig. 1a), the addition of $BaCl_2$ at a final concentration of 1.5 M increases the yield to 84%. The reaction can also be made quantitative by using a medium consisting of 1.5 M $BaCl_2$ and 6 M KOH. On the other hand, the reaction is completely inhibited in the absence of $Ba^{2+}$ (Fig. 1a).

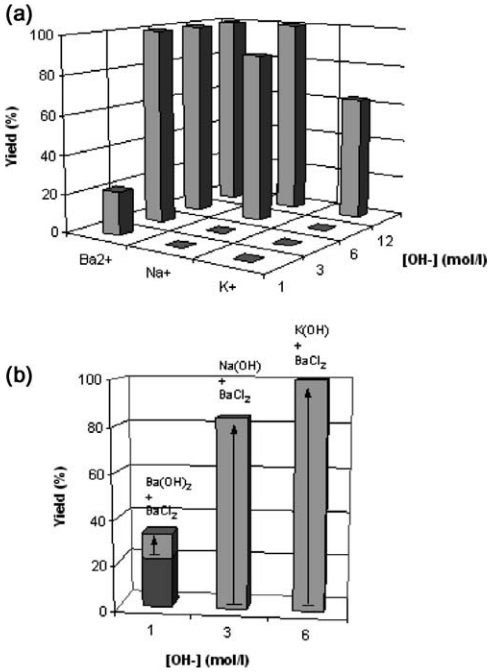
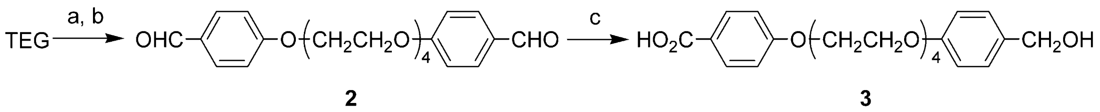


**Figure 1.** (a) Yields of the intramolecular Cannizzaro reaction of **2** to the desymmetrized **3** using $Ba(OH)_2$, NaOH and KOH as hydroxylic bases at different $[HO^-]$. (b) Increase in yields of the desymmetrization reaction resulting from the presence of a final $[Ba^{2+}]$ of 1.5 M for 0.5 M $Ba(OH)_2$, 3 M NaOH and 6 M KOH.

Therefore, the template provided by $Ba^{2+}$, which is perfectly bound by the TEG chain, allows the two aldehyde groups to be placed in a mutual spatial vicinity as reflected in the X-ray structure of the related compound **1**.[6c] This preferred conformation of the complex is even more crucial than the hydroxide concentration for effective hydride transfer in the Cannizzaro reaction. Thus, at $[HO^-] = 6$ mol/L (Fig. 1a) in the presence of $Ba^{2+}$, the reaction is quantitative; on the other hand, in the presence of $Na^+$ and $K^+$ the yield is 87% and zero, respectively. At the same $[HO^-]$ as provided for KOH, the yield is clearly increased by the presence of $Ba^{2+}$ (Fig. 1b). The reaction is efficient at lowers $[HO^-]$; although 3 M NaOH is inadequate for this purpose, the presence of 1.5 M $BaCl_2$ increases the yield to 84%. This reflects the ability of TEG to coordinate this



**Scheme 1.** Reagents and conditions: (a) TsCl, $CH_2Cl_2$, 30% NaOH, TEBA; (b) 4-HBA, NaOH, $CH_3CN$, 85 °C; (c) i. alkaline or alkaline earth hydroxide, $H_2O$, 100 °C; ii. 5% HCl.

cation and its efficiency in bringing the two aldehyde groups closes in the hydride transfer step.

However, the slightly increased yield obtained by adding $BaCl_2$ to a $[HO^-] = 1$ mol/L solution containing **2** (Fig. 1b) suggests that this $[HO^-]$ is inadequate for the Cannizzaro reaction to occur, even with the favourable spatial vicinity promoted by barium complexation.

Interestingly, no dialcohol—this compound was previously prepared by the authors, see Ref. 6c—or diacid resulting from an intermolecular process was formed under the conditions studied in this work. Only compound **3** (intramolecular process) or the starting material was detected.

The mechanism of the Cannizzaro reaction involves a hydride shift. First $HO^-$ adds to the C=O group to give a tetrahedral, tetravalent oxy-anion intermediate that can release a proton to the alkaline solution and give a *gem*-di(oxy-anion).[10] The strong electron-releasing character of $O^-$ is believed to greatly enhance the ability of the aldehyde hydrogen to leave with its electron pair. This effect is obviously stronger in the di(oxy-anion). When the hydride does leave, it attacks another aldehyde molecule. However, the spatial vicinity of the second aldehyde group appears decisive for the reaction. Although the two oxy-anions directly attached to the carbon atom increase the nucleofugal character of the hydride, only when the second electrophilic aldehyde group cooperates to enhance the nucleofugacity of the hydride does the disproportionation occur. Its location and distance from the site of nucleofugal reactivity are critical. With complexed barium cation, the optimum situation is a vicinal arrangement of the skeletal remote atoms involved.[11] Beyond these limits, the yield of the Cannizzaro reaction gradually decreases, or the reaction is inhibited, with increasing distance. The enhancement of the nucleofugal character of the hydride is crucial as the reaction fails at some $[HO^-]$ in a sodium or potassium environment unless barium is present. On the other hand, barium complexation makes the reaction possible at $[HO^-]$ too low to be efficient in its absence. Other hydroxides such as those of lithium and magnesium only provided the starting material, even at $[HO^-]$ as high as 12 M.

In conclusion, the proposed method is a simple, effective choice for the synthesis of desymmetrized diaryl-TEG, that avoids several protection–deprotection steps and tedious work-up while providing quantitative yields that facilitate isolation of the pure desired product. Experiments aimed at examining the effect of the OEG chain length on the binding efficiency of various cations that exploit the template effect in the desymmetrization process are currently underway and will be reported in the near future.

## Acknowledgements

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9. All compounds gave satisfactory spectral data. Selected spectral data for compounds **2** and **3** are given below. Compound **2**: mp 49–51 °C. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.68 (m, 8H), 3.85 (m, 4H), 4.17 (m, 4H), 6.98 (d, 4H, $J = 8.8$ Hz), 7.79 (d, 4H, $J = 8.8$ Hz), 9.84 (s, 2H). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 67.7, 69.4, 70.6, 70.8, 114.8, 130.0, 131.9, 163.7, 190.7. EI-MS *m/z* (%): 402 ($M^+$, 2), 149 (57), 121 (84), 77 (100), 65 (58). HRMS *m/z* calcd for $C_{22}H_{26}O_7$ ($M^+$) 402.1679, found 402.1690. Compound **3**: mp 76–78 °C. $^1H$ NMR (200 MHz, $CDCl_3$): $\delta$ 3.69 (m, 8H), 3.84 (m, 4H), 4.09 (m, 2H), 4.16 (m, 2H), 4.58 (s, 2H), 6.88 (m, 4H), 7.24 (m, 2H), 7.98 (d, 2H, $J = 9$ Hz). $^{13}C$ NMR (50 MHz, $CDCl_3$): $\delta$ 64.9, 67.4, 67.6, 69.5, 69.7, 70.6, 70.8, 114.2, 114.6, 121.8, 128.6, 132.2, 133.2, 158.3, 163.1, 170.8. EI-MS *m/z* (%): 420 ($M^+$, 10), 165 (70), 121 (100), 107 (50), 91 (50), 89 (90), 77 (90). HRMS *m/z* calcd for $C_{22}H_{28}O_8$ ($M^+$) 420.1784, found 420.1780.
10. Doubly deprotonated ions of *gem*-diols have been described as ligands in cobalt (II) clusters. Their formation can be accomplished by simply using a 4:1 ratio of $MeCO_2^-$, see: Tsohos, A.; Dionyssopoulou, S.; Raptopoulou, C. P.; Terzis, A.; Bakalbassis, E. G.; Perlepes, S. P. *Angew. Chem., Int. Ed.* **1999**, *38*, 983–985.
11. Desymmetrization of compound **2** has also been run under the reaction conditions described in the text in the presence of anisaldehyde and no cross-over product has been detected, proving evidence that the $Ba^{2+}$ ions haven only templating effect; this insight was provided by a referee.