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# Oligomerization of 1,2-Ethanedithiol: An Expedient Approach to Oligothiaethylenethioglycols

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**Abstract:** Reactions of ethylenedithioglycol (ETG) with $Na_2CO_3$, $K_2CO_3$, and $Cs_2CO_3$ provided the oligothiaethylenethioglycols (*n*ETG): di- (DETG), tri- (TrETG), tetra- (TETG), and pentathiaethylenethioglycol (PETG), along with higher polymers. The most efficient carbonate was $K_2CO_3$ and reactions using DETG and TrETG as starting materials—or their mixtures—were also found to afford similar species. This largely unknown oligomerization process was thoroughly explored and potential pathways were put forward. A convenient conversion of ETG to laboratory quantities of the otherwise scarce and/or expensive DETG, TrETG, TETG, and PETG oligomers, in organic or aqueous media was achieved. Notably, this straightforward reaction takes place without the addition of expensive or toxic metal catalysts and with pure water as the solvent, thereby highlighting its potential as a green chemical reaction. Moreover, the process opens up new approaches to dynamic combinatorial libraries (DCLs) of oligomers and macrocycles with manifolded *n*ETG $[(SCH_2CH_2)_nS]$ bridges.

**Keywords:** ethylenedithioglycol · green chemistry · macrocycles · microwave chemistry · oligomerization

## Introduction

In studies aimed to secure novel macrocyclic host systems with chiral core units, we used various known approaches of grafting polyheterochain bridges on the termini of chiral podands to produce 1+1, 2+2, 3+3, and larger macrocyclic products, as shown for the diacetal type (*cis*-1,3,5,7-tetraoxadecalin (TOD)) core system (Scheme 1, top).[1] In this framework we recently described[2] new classes of chiral macrocycles consisting of $(SCH_2CH_2)_nS$-bridged *cis*-1,3,5,7-tetraoxadecalin chiral core molecules. These have been prepared from the starting dibromide (**1**) with ethylenedithioglycol (ETG = HS-$CH_2$-$CH_2$-SH) or its (*n*ETG) oligomers: di- (DETG = HS-($CH_2$-$CH_2$-S$)_2$H), tri- (TrETG = HS-($CH_2$-$CH_2$-S$)_3$H), tetra- (TETG = HS-($CH_2$-$CH_2$-S$)_4$H), and pentathiaethylenethioglycol (PETG = HS-($CH_2$-$CH_2$-S$)_5$H).

Efforts to secure the latter, seemingly simple, reagents span a century of diverse, usually laborious synthetic work.[3,4] It should also be stressed that those available synthetic literature procedures usually require dihalogenated reagents, invariably giving rise to hazardous (e.g., vesicant, mustard agents) intermediates or byproducts. As to cost and commercial availability, when getting involved in processes in which the higher *n*ETG dithioglycols are needed, one realizes that their cost increases exponentially as *n* is augmented from 1 (ETG ≈ \$30 per 100 g) to 2 (DETG ≈ \$300 per 100 g) or 3 (TrETG: milligram quantities quoted only on demand), whereas the higher ones are not commercially available at all.

Crown thioethers are widely and well known[5] and recognized as excellent ligands for heavy- and transition-metal ions.[6] Most of the synthetic methods for such ligands are based on the chain flanking reaction of 1,2-dihalides with terminal dithiols[7] (e.g., ETG or its higher oligomers as sulfide- or $\alpha,\omega$-dithiolate salts, over a century old technique),[3] often using high-dilution techniques.[8] Although early in the game such reactions had yielded crown thioethers in low (up to 10%) yields, significant improvements have been made by Kellogg and co-workers by using $Cs_2CO_3$ as a base in DMF or sometimes $K_2CO_3$ in THF.[4] A large variety of

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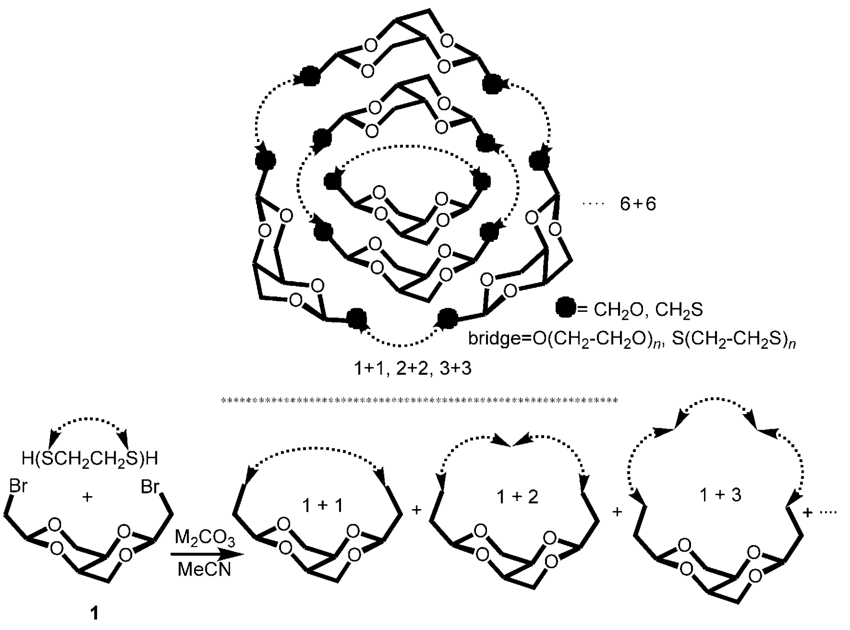


Scheme 1. Formation of ETG-bridged TOD macrocycles (M = Cs or K).

macrocyclic ligands have been synthesized using such techniques, as up to recently copiously reviewed,[5–7] and in most of those cases the dithiol starting materials were indeed ETG or some of the higher oligothiaethylenethioglycols.

Thus, when *rac*-**1** was reacted ($Cs_2CO_3$ or $K_2CO_3$ in MeCN heated to reflux) with equimolar quantities of ETG[2] (Scheme 1, bottom), the corresponding dithiacrown-TOD product (1+1) was indeed obtained, but surprisingly, consistent and rather intriguing occurrences of low yields of higher-order polythiacrown byproducts (1+2, 1+3, and traces of higher ones) were observed. Furthermore, processes starting with higher *n*ETGs turned out to suffer from analogous, inexplicable byproducts.[2] This frustrating, but also challenging behavior was taken to indicate that a concomitant reaction was occurring and raised the possibility of a potential dynamic combinatorial library (DCL) tool. Herein, we report the study of this intriguing reaction of ETG and carbonates in more detail.

## Results and Discussion

A search for existing related information indicated that, notwithstanding the vast literature on sulfur-containing macrocycles, oligomers, and polymers, one could find rather scarce or largely ignored observations on similar results. The most relevant are those of Newkome et al.,[9] who reported three instances of reactions of dihalo substrates with DETG, from which they isolated TrETG products in addition to the expected ones, with no further comments. In these processes, the bases/solvents ranged from NaH/xylene to tertiary amines.

Conjecturing that the process is one in which the starting dithiol reagents are affected by the reaction conditions before their interaction with their dihalo partners, we examined the basic reaction of ETG and $Cs^+$, $K^+$, and $Na^+$ carbonates in acetonitrile, with striking results. The primary process (i.e., the reaction of ETG itself with $Cs_2CO_3$, $K_2CO_3$, and $Na_2CO_3$ in boiling MeCN at diverse conditions), provided the higher *n*ETGs $H(SCH_2CH_2)_nSH$ ($n = 2$ (DETG), 3 (TrETG), 4 (TETG), 5 (PETG); Figure 1). These soluble and volatile products were separated, analyzed by GLC, and isolated accordingly, thereby leaving traces of hexathiaethylenethioglycol (HETG) and insoluble polymers in the residue.

It may be recalled that in the well-documented substitution reactions,[4] the $Cs^+$ ion reigned at the top, possibly due to the peerless character of the polarizable, poorly solvated, and tight-contact ion-pair-forming $Cs^+$ ion, as Kellogg and co-workers suggested[4] (see also ref. [10]). A closer look, however, at the time dependence of the conversion and formation of these dithiols (Figure 1) made it clear that the picture is more complicated and interesting, as is, for example, the relatively more attractive behavior of $K_2CO_3$ in the series. Here, the basicity of the alkali carbonates (vide infra) is clearly accompanied by extra features such as the significant difference between these bases with regard to their solubility in MeCN, with $Cs_2CO_3$ being more soluble in it than the other two,[10b] whereas the other processes are markedly heterogeneous, thereby making the exact end results dependent on crystal morphology, stirring efficiency, and so on.

And yet (Figure 1) the $Cs^{+2}$-induced process is "too good," being mainly plagued by enhanced formation of polymers with resultant yield impairment. These manifestly insoluble polymers were of less interest in this investigation's framework, because inter alia, in addition to the fact that they had been rather well looked into,[11] they provided no clues to our problem.

We have attributed the formation of the higher oligothiacrown byproducts (Scheme 1, bottom) from the reaction of **1** with ETG to a relatively slow thioetherification process, which consists of a thiolate-initiated oligothiachain formation. Recognizing the significant "carbon basicity" of thioalkoxide,[12a] and in some analogy with the Whitesides et al.[12] mechanism for the thiol–disulfide interchange, it was compelling to invoke the involvement of a primary thiolate anion: $HSCH_2CH_2S^-$ to start the entire chain of events (Scheme 2), which made available variable amounts of the higher oligothia-α,ω-dithiols products/reactants.

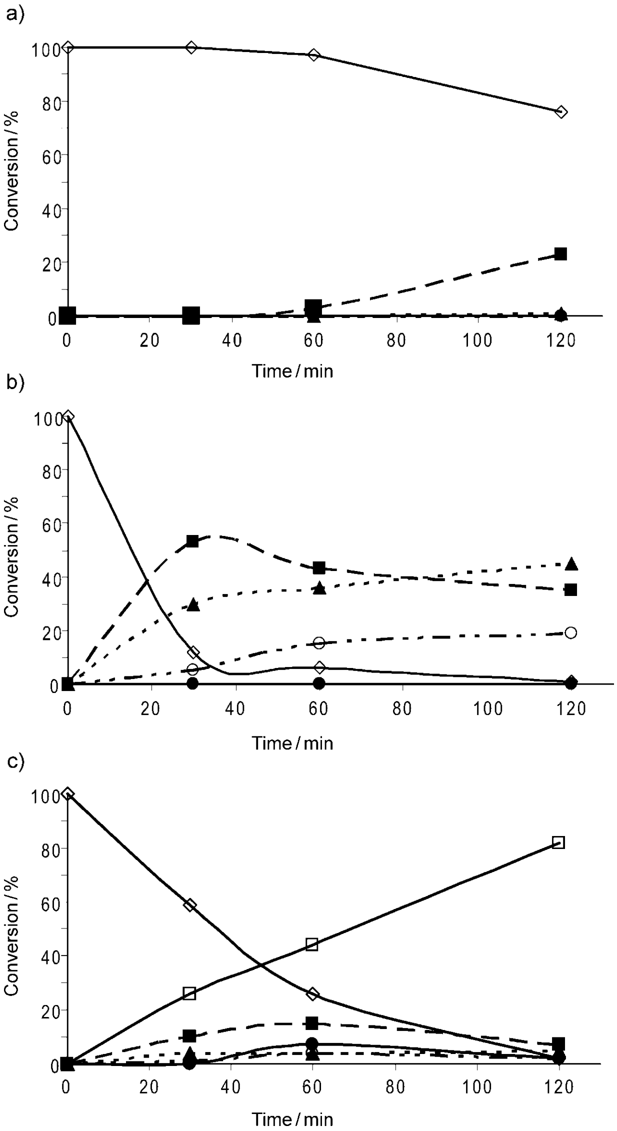
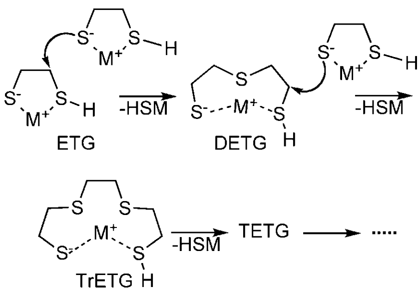


Figure 1. Reactions of ETG/$M_2CO_3$ in MeCN heated at reflux for a)$Na_2CO_3$, b) $K_2CO_3$, and c) $Cs_2CO_3$; the consumption/formation of ETG (◇), DETG (■), TrETG (▲), TETG (○), PETG (●), and polyETG (□) are shown. The sum of mole fractions may fall below 100 % due to either volatile products (e.g., dithiane, thiirane) and/or insoluble higher polythiaethylenethioglycols.

In a further, more detailed series of experiments, ETG as well as the higher dithiols DETG and TrETG were subjected to reactions with the choice base, $K_2CO_3$, in MeCN (stirred under Ar) with salient results, as shown in Tables 1, 2, 3, 4, and 5, along with the respective interpretative Schemes 3 and 4, in analogy with the mechanism proposed in Scheme 2.



Scheme 2. Proposed mechanism for the formation of *n*ETG oligomers.

Table 1. Reaction of ETG with $K_2CO_3$ in acetonitrile.

| Entry | *t* | ETG [%] | DETG [%] | TrETG [%] | TETG [%] |
|---|---|---|---|---|---|
| 1 | 30 min[a] | 18 | 63 | 18 | 1 |
| 2 | 60 min[a] | 1 | 58 | 33 | 8 |
| 3 | 120 min[a] | 0 | 53 | 36 | 11 |
| 4 | 96 min[b] | 73 | 27 | – | – |
| 5 | 168 min[b] | 53 | 46 | – | – |
| 6 | 288 min[b] | 59 | 41 | – | – |
| 7 | 3 weeks[b] | 0 | 45 | 55 % residue | |

Conversions include corresponding disulfides as minor byproducts. [a] Stirred during heating at reflux under argon: ETG (1.1 mmol) and $K_2CO_3$ (3 mmol) in MeCN (6 mL). [b] Stirred at RT under argon: ETG (1.8 mmol) and $K_2CO_3$ (5 mmol) in MeCN (10 mL).

Table 2. Reaction of DETG with $K_2CO_3$ in acetonitrile.

| Entry | *t* | DETG [%] | TrETG [%] | TETG [%] | PETG [%] |
|---|---|---|---|---|---|
| 1 | 30 min[a] | 99 | 0.5 | – | – |
| 2 | 30 min[b] | 100 | – | – | – |
| 3 | 60 min[a] | 97 | 2.5 | – | – |
| 4 | 60 min[b] | 98 | 2 | – | – |
| 5 | 120 min[a] | 93 | 7 | – | – |
| 6 | 120 min[b] | 89 | 11 | – | – |
| 7 | 240 min[b] | 78 | 22 | 0.5 | – |
| 8 | 24 h[a] | 16 | 39 | 36 | 9 |

Conversions include corresponding disulfides as minor byproducts. Stirred during heating at reflux under argon. [a] DETG (6 mmol) and $K_2CO_3$ (12 mmol) in MeCN (32 mL). [b] DETG (1.1 mmol) and $K_2CO_3$ (3.3 mmol) in MeCN (20 mL).

Table 3. Reaction of TrETG with $K_2CO_3$ in acetonitrile.

| Entry | *t* [min] | DETG [%] | TrETG [%] | TETG [%] |
|---|---|---|---|---|
| 1 | 60[a] | 6 | 93 | < 1 |
| 2 | 60[b] | 5 | 93 | 1.4 |
| 3 | 120[a] | 7 | 91 | 2 |
| 4 | 120[b] | 6 | 90 | 1.1 |
| 5 | 180[a,c] | 9 | 87 | 4 |
| 6 | 180[b] | 8 | 90 | 2 |
| 7 | 240[b] | 10 | 86 | 3 |
| 8 | 300[b,d] | 13 | 82 | 5 |

Conversions include corresponding disulfides as minor byproducts. Stirred during heating at reflux under argon. [a] TrETG (1 mmol) and $K_2CO_3$ (2.5 mmol) in MeCN (5 mL). [b] TrETG (0.8 mmol) and $K_2CO_3$ (2 mmol) in MeCN (5 mL). [c] At the end of the reaction, 58 % polymer was recovered. [d] At the end of the reaction, 17 % polymer was recovered.

In all the above analytical trials, the formation of higher *n*ETG products was our main concern, but variable amounts of byproducts that are not listed were detected in many cases, namely, small amounts of the well-known 1,4-dithiane (**2**), its less-known isomer 3,6-dithiahexene (**3**), and the $ETG_2$-, DETG-, $DETG_2$-, TrETG-, and $TrETG_2$-disulfides

Table 4. Soluble products from the reaction of ETG/DETG mixtures with $K_2CO_3$ in acetonitrile.[a]

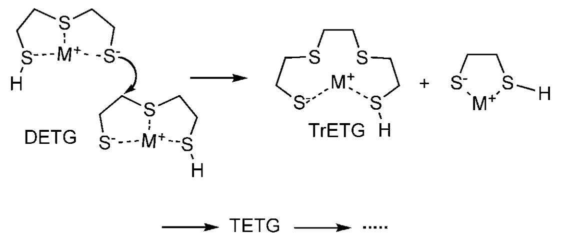
| Entry | *t* [min] | ETG [%] | DETG [%] | TrETG [%] | TETG [%] |
|---|---|---|---|---|---|
| 1 | 0 | 19 | 81 | – | – |
| 2 | 10 | 15 | 79 | 5 | – |
| 3 | 20 | 9 | 80 | 10 | – |
| 4 | 30 | 5 | 80 | 15 | – |
| 5 | 45 | 2 | 78 | 20 | <1 |
| 6 | 60 | 1 | 76 | 22 | 1 |
| 7 | 90 | – | 75 | 24 | 1.7 |
| 8 | 120 | – | 73 | 25 | 2.3 |
| 9 | 180 | – | 71 | 25 | 3 |

[a] Conversions include corresponding disulfides as minor byproducts. Stirred during heating at reflux under argon: ETG (1 mmol), DETG (2.5 mmol), and $K_2CO_3$ (5 mmol) in MeCN (5 mL).

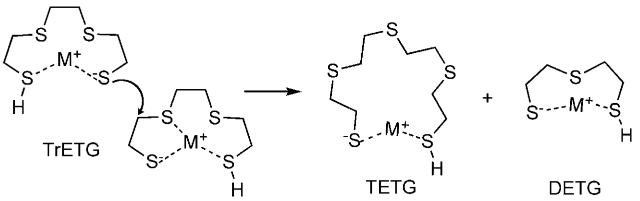
Table 5. Soluble products from the reaction of DETG/TrETG mixtures with $K_2CO_3$ in acetonitrile.[a]

| Entry | *t* [min] | ETG [%] | DETG [%] | TrETG [%] | TETG [%] |
|---|---|---|---|---|---|
| 2 | 0 | – | 28 | 70 | 1 |
| 4 | 15 | – | 27 | 72 | 1 |
| 7 | 30 | – | 28 | 71 | 1 |
| 10 | 60 | – | 28 | 70 | 2 |
| 12 | 90 | – | 28 | 69 | 2 |
| 14 | 120 | – | 31 | 66 | 3 |
| 16 | 180 | – | 29 | 68 | 3 |
| 17 | 300 | – | 32 | 64 | 4 |

[a] Conversions include corresponding disulfides as minor byproducts. Stirred during heating at reflux under argon: DETG (1.8 mmol), TrETG (3.2 mmol), and $K_2CO_3$ (5 mmol) in MeCN (5 mL).



Scheme 3. Proposed mechanism for the disproportionation of DETG.

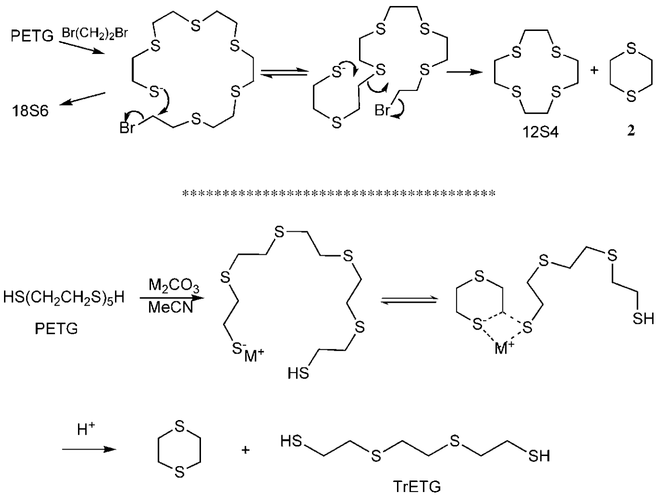


Scheme 4. Proposed mechanism for the disproportionation of TrETG.

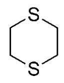
(**4**, **5**, **6**, **7**, **8**, and **9**, respectively). Although the detailed mechanisms of the above-described processes are not yet entirely solved, we observed (MS) signs of the -$SCH_2CH_2$-moiety, perhaps as thiirane (consistent with its known role in the transition-metal-[5j,13a–c] or acid[13d]-catalyzed buildup of polythiaethylene macrocycles), and of 1,2-dithietane, both easily rationalized in the above transformations as extrusion products along with $HS^-$.

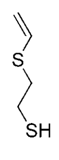
The disulfide species in the reaction products were actually anticipated, especially following earlier studies of their versatile formation and behavior,[12b] and more recent works including DCL formation.[14] They can be easily reduced to the parent dithiols by any of the known methods, as we did using $NaBH_4$.

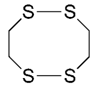
Concerning 1,4-dithiane (**2**), it should be noted that Ochrymowycz et al. had reported long ago[15] its isolation as a byproduct along with 12S4 (1,4,7,10-tetrathiacyclododecane) in the preparation of the 18S6 macrocycle from the reaction of the PETG salt with dibromoethane (Scheme 5, top) and had rationalized it by postulation of an initial chain lengthening to an intermediate terminal monohalide, followed by an intrachain thia displacement, accompanied by a thiolate-assisted C–S bond cleavage and 1,4-dithiane (**2**) formation. Our system differs by having no halogen–carbon-activated bond. However, in the course of the oligomerization process, PETG, for example, may follow a chain-shortening side reaction by displacement of an adjacent sulfide entity, thereby yielding TrETG + dithiane (Scheme 5, bottom). This



Scheme 5. Mechanistic explanation for the production of dithiane.


**2**


**3**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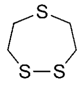
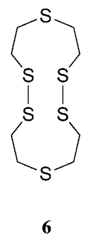

**5**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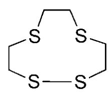
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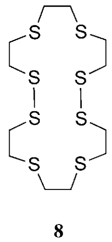
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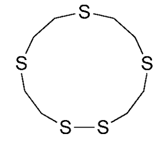
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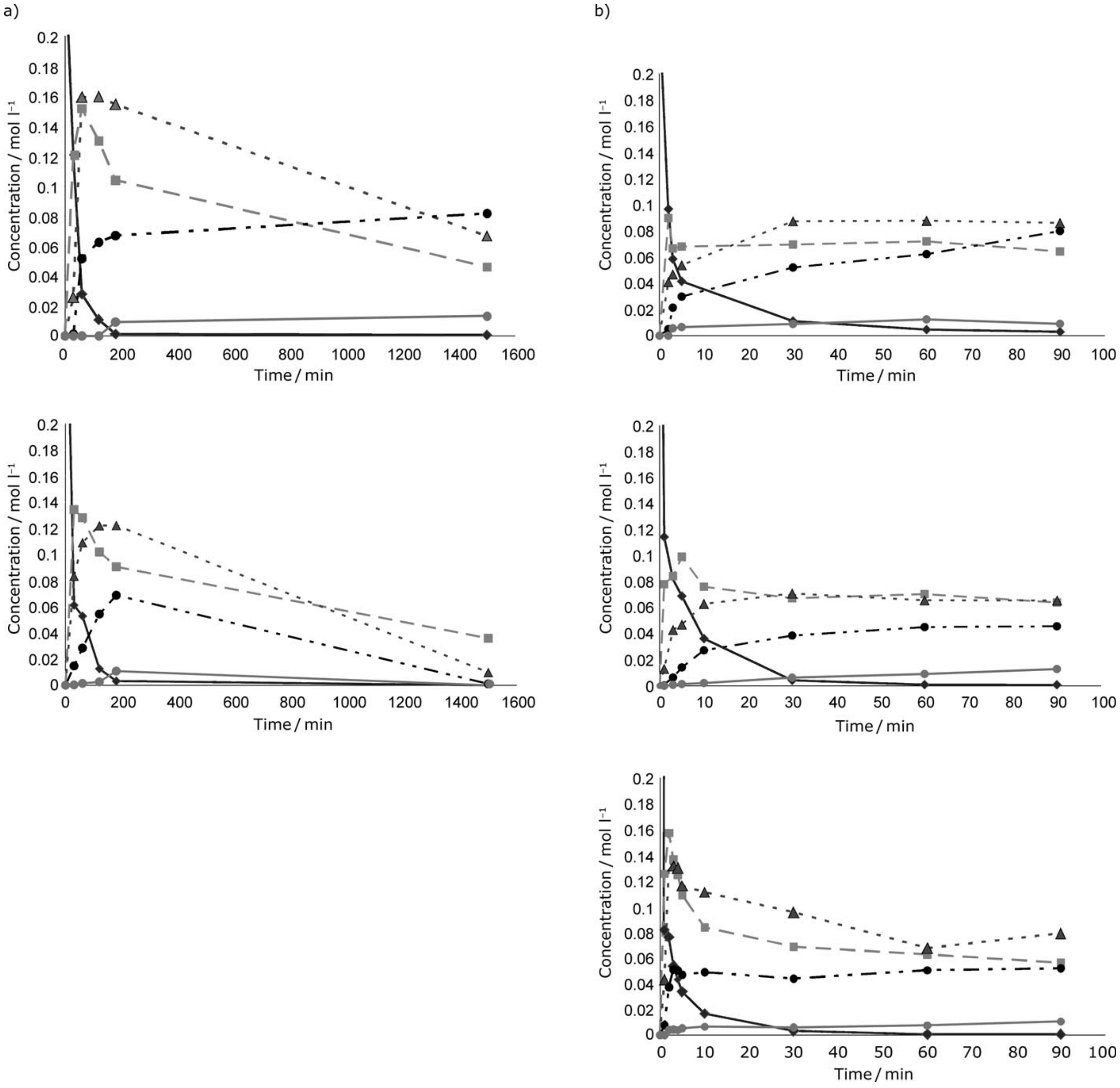


Figure 2. Reactions of ETG/$M_2CO_3$ in water a) heated at reflux (top: $K_2CO_3$, bottom: $Cs_2CO_3$) and b) MW (105 °C) (top: $Na_2CO_3$, middle: $K_2CO_3$, bottom: $Cs_2CO_3$). The consumption or formation of ETG (◆), DETG (■), TrETG (▲), TETG (●), and PETG (●) is presented. Initial ETG concentration 0.4 mol $L^{-1}$. Shown products analyzed by GC–MS.

is also how we interpreted the peculiar absence of $(SCH_2CH_2)_n$ macrocycles in all these processes.

At this point, juxtaposition and interpretation of the data in all the tables above is called for, in conjunction with the accompanying schemes. It is clear that in the canonic ETG/$K_2CO_3$ reactions (Table 1 and Figure 1, middle, and Scheme 2) the decay of ETG is the most rapid in the series. It is only when it is depleted that the produced DETG starts decaying itself, thus resupplying some ETG for its part. TrETG and TETG show much slower buildups, but they are steady and much less harmed. The straight DETG/$K_2CO_3$ reaction (Table 2, Scheme 3) is indeed much slower, both in its decay and in the higher products formation (it is probable that ETG is initially created, albeit unseen because it is used up faster than its formation). Similarly, the TrETG/$K_2CO_3$ reaction (Table 3, Scheme 4) is no less sluggish in its disproportionation process to DETG and TETG and the two intermixed runs, ETG+DETG and DETG+TrETG/$K_2CO_3$, (Tables 4 and 5) nicely corroborate all of the above.

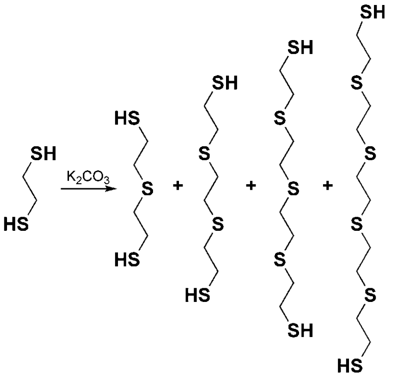
In the course of checking various variables in our above investigation, small amounts of water were added to the reaction medium (MeCN) and found not to harm or alter appreciably the outcome of the experiments. Due to the obvious benefits, we decided to investigate the effects of running the reactions in pure water as the solvent. Fortunately, we found that the entire process occurs equally well in water, in homogeneous carbonate solutions heated at reflux (Figure 2a) and, even better, with microwave (MW) acceleration[16] of the reaction (Figure 2b).

To be sure, the picture obtained in water (Figure 2) is to some extent different, but instructive. First, the fact that all three carbonates behave with only slight variations (viz., $Cs_2CO_3$ not rushing off and $Na_2CO_3$ not falling behind excessively) is in line with the above-suggested thiolate intermediacy, the p$K_a$ of dithiols, for example, ETG (p$K_{a1} = 8.85$ and p$K_{a2} = 10.43$) matching closely those of the carbonates (p$K_{a1} = 6.35$ and p$K_{a2} = 10.33$).[17]

In this context, it should be noted that this combination bestows buffer conditions to the aqueous medium, but the behavior under the two conditions is influenced also by the fact that, contrary to the MW experiment, when heated at reflux the $CO_2$ formed is continuously carried off, which may clarify the sometimes random ratios of *n*ETG products (cf. the Experimental Section). Furthermore, attempts to use alkali hydroxide bases in these reactions were largely unsuccessful, which conforms to this line of reasoning and strengthens the above-suggested pathway, since a double thiolate anion should be inert towards its neighbors. Moreover, practically no polymers were isolated in these conditions.

This peculiar reactivity provided the most valuable results of our study in preparative runs by securing from the simple and readily available ETG its higher, rare, and pricey *n*ETG oligomers in straightforward reactions, as shown in Scheme 6.

Such procedures were performed repeatedly in up to 50 g runs in acetonitrile or in water (see the Experimental Section) with largely comparable results, thereby making readily available substantial quantities of these oligo-ETG starting materials for the synthesis of a variety of thioether macrocycles.[2] Moreover, one can direct the proportionality of the reaction products by judicious choice of carbonate, temperature, or reaction time.



| | ETG | DETG | TrETG | TETG | PETG |
|---|---|---|---|---|---|
| in acetonitrile | ≈ 3% | ≈ 50% | ≈ 35% | ≈ 9% | < 1 |
| in water | ≈ 1% | ≈ 18% | ≈ 40% | ≈ 33% | < 6 |

Scheme 6. Preparative reactions in water and acetonitrile heated to reflux. Yields include respective disulfides.

The full significance of the above approach and its results are bound to be greatly appreciated by those actively involved in processes in which the *n*ETG dithioglycols are needed. It is then realized how these costly or altogether unprocurable reagents become readily accessible, not to mention the avoidance of health hazards in the available experimental procedures for their preparation (imputable to the dangerous—vesicant mustard agents—intermediates or byproducts). Admittedly, the ostensible simplicity and attractiveness of the above-described approach to hitherto expensive or laboriously made *n*ETG oligomers is not tallied by the clarity of its mechanistic pathway. The exact mechanism of this variegated reaction along with the reactivity of the homologous dithiols is expected to lead to highly interesting consequences. These, along with ion-templating effects, the addition of other thiol-containing molecules, and the potential of applying this new approach to DCLs containing $(SCH_2CH_2)_nS$ units will be reported in due course. It is also anticipated that the ready availability of such high *n*ETG oligomers will spur the conception of further interesting polythiamacrocyclic systems.

## Conclusion

The vexing byproducts in the preparation of polythiomacrocycles were found to be due to alkali-carbonate-catalyzed thioetherifying oligomerization reactions of ethylenedithioglycol (ETG) to higher polythiaethylenethioglycols. In targeted reactions, $M_2CO_3$-induced oligomerization of ETG was established, the most practical being $K_2CO_3$; similar catalyzed chain increases of DETG and TrETG—or their mixtures—were also found to occur. Thus, ETG could be used in facile and inexpensive preparations of laboratory quantities of the otherwise scarce and/or expensive DETG, TrETG, TETG, and PETG oligomers, thus also avoiding hazardous intermediates in the process. The use of only water as a solvent coincides with the safer procedures and opens the doorway to clean 'green' chemistry protocols for the synthesis of the thiaoligomers and their subproducts.

## Experimental Section

**General**: The NMR spectra were obtained using Bruker AMX 360, ARX 500, or DPX 500 spectrometers. All $^1H$ chemical shifts are in ppm and $\delta$ values are relative to TMS as internal standard. $^{13}C$ chemical shifts are reported in ppm relative to $CDCl_3$ (center of triplet $\delta = 77.0$ ppm), except for those taken in $D_2O$, which are reported in ppm relative to TMS salt as internal standard. Mass spectra (desorption electron ionization (DEI), desorption chemical ionization (DCI), and fast atom bombardment (FAB)) were recorded using a VG Autospec 250 mass spectrometer. UV spectra were taken using a Uvikon 931 spectrophotometer. Chromatographic analyses of experiments in MeCN were run using a Varian 3400 instrument with Megabor column 15 m × 0.53 mm, phase DB5, He gas flow 30 $mL\,min^{-1}$, column temperature from 50 to 300 °C with initial hold time 1.5 min, gradient 20° $min^{-1}$, and hold time 5 min. In experiments in water the GC–MS columns were alternately: 1) Agilent HP5-MS, column temperature from 80 to 300 °C; 2) Restek Rxi-5ms column, column temperature from 80 to 300 °C. All *n*ETG yields include those of their respective disulfide byproducts (which could easily be reduced to their dithiol precursors; see below).

**Analytical runs**

*In acetonitrile (Figure 1, Table 1)*: $M_2CO_3$ (2.8 mmol) was suspended in a solution of ETG (0.096 g, 1 mmol) in acetonitrile (5 mL) and the mixture was heated at reflux under Ar. At given intervals, chloroform (5 mL) and 1 N HCl (10 mL) were added to each individual reaction mixture, and the organic phase underwent GLC analysis (Megabore column 15 m × 0.53 mm, DB5, He gas flow 30 $mL\,min^{-1}$, column temperature from 50 to 300 °C). Retention times: ETG 1.5 min, DETG 5.7 min, TrETG 8.7 min, TETG 11.2 min, and PETG 13.5 min. Mass balance calculations were based on calibration curves. Starting relationships between peak areas $S$ and reagent concentrations $C$ in acetonitrile were in the range of $9\times10^{-3}$ to 0.2 $mol\,L^{-1}$. For ETG it was $C=(5.53\pm0.09)\times10^{-7}\times S$, $r=0.999$, $n=12$; for DETG it was $C=(3.47\pm0.04)\times10^{-7}\times S$, $r=0.999$, $n=14$; for TrETG it was $C=(3.05\pm0.14)\times10^{-7}\times S$, $r=0.994$, $n=8$.

Product concentrations were based on relationships between reagent concentrations $C_r$ in MeCN, in the range $3\times10^{-3}$ to 0.2 $mol\,L^{-1}$, and peak areas $S_r$ from the GLC analysis of the organic phases after workup as above. For ETG it was $C_r=(4.41\pm0.16)\times10^{-7}\times S_r$, $r=0.992$, $n=14$; for DETG it was $C_r=(2.73\pm0.04)\times10^{-7}\times S_r$, $r=0.999$, $n=11$; for TrETG it was $C_r=(2.59\pm0.09)\times10^{-7}\times S_r$, $r=0.999$, $n=11$. For TETG and PETG, $C_r/S_r$ was estimated to be $2.5\times10^{-7}$. All other analytical runs (Tables 2, 3, 4, and 5, and respective schemes; vide supra) were run similarly and repeatedly, sometimes using also NMR spectroscopic techniques for analysis, with proper calibration curves. The formation of $H_2S$ was proven on $N_2$ bubbling of the initial crude reaction product mixture after acidification.

*In water (Figure 2)*: A mixture consisting of a suspension of $M_2CO_3$ (6 mmol) in a solution of ETG (168 µL, 2 mmol) in deionized water (5 mL) was purged with $N_2$ for 10 min. The mixture then underwent either microwave radiation at 105 °C (Discover equipped with Explorer robot, CEM corporation, 200 W, maximum pressure of 249 psi) or heating to reflux under $N_2$. At given intervals, HCl (600 µL, 32 %) was added to each individual reaction mixture and the neutralized solution was extracted 3 times with $CH_2Cl_2$ (2.5 mL). The organic phase underwent GC–MS analysis (Agilent 6850 GC equipped with an Agilent 5973 MSD and an Agilent HP5-MS column, heated from 80 to 300 °C). Retention times: ETG 2.5 min, DETG 6 min, TrETG 8.2 min, TETG 10 min, and PETG 12.6 min. Mass balance calculations were based on diglyme, which was used as an internal standard. Thus, for the MW reaction with 3 equiv $K_2CO_3$ (pH 10.61), a statistical analysis of 14 samples gave mean yields [%] of (standard errors are given in parentheses): DETG 20.57 (1.34), TrETG 53.5 (1.29), TETG 26.0 (1.44), PETG < 1. As the $K_2CO_3$ increased, the yields become rather erratic, and for 15 equiv of $K_2CO_3$ (pH 12.56) the results become (3 samples; means) ETG 6, DETG 90, TrETG 4. Similar runs at reflux were conducted at the same concentrations but different volumes, for example, in Figure 2a, a 25 mL sample of water was taken.

**Preparative runs**: The yields shown in Scheme 6 are approximate because they are quite dependent on the reaction and isolation conditions, namely, time and temperature (see below).

*In acetonitrile, process 1*: A mixture of fresh ETG (11.2 g, 0.12 mol) and $K_2CO_3$ (34.3 g, 0.25 mol) in $CH_3CN$ (100 mL) was mechanically stirred and swept with Ar for 20 min, after which it was heated at reflux under Ar for 4 h. GLC aliquot sampling showed the following after 1 h: 55 % ETG, 44 % DETG + disulfides, 1 % TrETG; and after 2 h: 20 % ETG, 66 % DETG + disulfides, 12 % TrETG, and 1 % TETG. After cooling the mixture and the addition of chloroform (100 mL) and HCl (2.5 M, 200 mL) with stirring, the organic layer was separated, washed, and dried, and showed a composition (GLC) of 1 % ETG, 70 % DETG + disulfides, 26 % TrETG + disulfide, and 3 % TETG. After removal of the solvent and low fractions at atmospheric pressure, a yellowish oil (8.7 g) was obtained. This was thoroughly triturated with diethyl ether (3 × 30 mL) and filtered to provide TETG (1.3 g, 15 %) as a white solid. The solvent was evaporated and the residue was distilled under high vacuum, at 0.02 millibar: the first fraction (60 °C) consisted of DETG (3.3 g, 29 %), whereas the second fraction (68 °C) was a mixture (0.34 g) and the residual white semisolid consisted of TrETG (3.0 g, 25 %) including approximately 5 % of its cyclic disulfide. The first, low fractions consisted of small amounts of ETG and the following byproducts: 0.01 % dithiane (**9**) and approximately 1 % of 3,6-dithiahexene. The solid residue contained variable amounts of PETG. Such procedures were performed repeatedly in up to fivefold-scaled-up runs with similar results.

*In acetonitrile, process 2*: After 4 h in the initial product mixture, a scale-up experiment starting with ETG (47 g) provided (GC–MS): 3.5 % ETG, 51 % DETG, 35 % TrETG, 9% TETG, and 0.3 % PETG (including the respective disulfides); and after isolation as described above: 34 % DETG, 27 % TrETG, and 12 % TETG (and disulfides). Isolation of the residue at higher temperatures provided variable small amounts of PETG and HETG. Part of the 1,4-dithiane and 3,6-dithiahexene formed in the reaction, as well as ETG, are removed in the first, aqueous washing step of the workup (from which they can be recovered by chloroform extraction). The rest are obtained in the preliminary distillation step at 134 °C/21 millibar.

*In water*: A mixture of fresh ETG (9.67 g, 0.103 mol) and $K_2CO_3$ (28.44 g, 0.206 mol) in deionized water (86 mL) was swept with Ar for 20 min, after which it underwent microwave radiation for 45 min at 105 °C (Discover equipped with Explorer robot, CEM corporation, 200 W, maximum pressure of 249 psi), by a sequence of 6 microwave tubes, each containing the reaction mixture (14.3 mL). After cooling the mixture, combining the tubes, and the addition of chloroform (100 mL) and HCl (2.5 M, 200 mL) with stirring, the organic layer was separated. Additional chloroform (50 mL) was added and again separated, and the combined organic phases were washed, dried, and showed a composition (GC–MS) of 1.2 % ETG, 18.4 % DETG + disulfide, 40.6 % TrETG + disulfide, 32.7 % TETG + disulfide, and 6.6 % PETG disulfide. After removal of the solvent and low fractions (mainly ETG) at atmospheric pressure by distillation at 61 °C under nitrogen, a white oil (7 g, 94 % yield) was obtained. This was thoroughly triturated with diethyl ether (3 × 30 mL), to provide a mixture (3.5 g) that contained 15 % DETG, 47.3 % TrETG, 35 % TETG, and 2.6 % PETG disulfide as a white solid. The filtrate was evaporated and the residue (46.5 % DETG, 53.5 % TrETG) was distilled under high vacuum, at 0.05 mmHg: one fraction was distilled at 66 °C and consisted of DETG with almost no disulfide (0.3 g,) as a clear oil, and the residual white semisolid consisted of TrETG with approximately 5 % of its disulfide (0.75 g).

**Reduction of oxidized species**: An equimolar amount of sodium borohydride was added to a mixture of DETG, TrETG, and TETG with their oxidized species in water, and the mixture was stirred at 80 °C for 1 h. After acidification (HCl) and extraction ($CH_2Cl_2$), only the dithiols and no oxidized species were observed by GC–MS.

In situ acidification using a Dowex-50W-X2 instrument and $CH_3CN$ (no need for extraction) gave similarly good results.

Tables 6 and 7 provide the NMR spectroscopic and MS data of the products. ETG, DETG, and 1,4-dithiane (**2**) are commercial and well documented, but were included for the sake of comparison. All the others are either unknown or scarcely reported.

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Table 6. $^1$H and $^{13}$C NMR spectral data of *n*ETG oligomers and disulfides (ds).[a]

| *n*ETG | | 2,2′ δ [ppm] | 3,3′ δ [ppm] | 5,5′ δ [ppm] | 6,6′ δ [ppm] | SH δ [ppm] |
|---|---|---|---|---|---|---|
| ETG | $^1$H | 2.76 (m, 4H) | – | – | – | 1.76 (t) |
| | $^{13}$C | 27.7 | – | – | – | – |
| DETG | $^1$H | 2.77 (br m, 8H) | – | – | – | 1.74 (t) |
| | $^{13}$C | 24.7 | 36.0 | – | – | – |
| TrETG[b] | $^1$H | 2.77 (br m, 12H) | – | – | – | 1.74 (t) |
| | $^{13}$C | 24.6 | 36.1 | 32.1 | – | – |
| TETG[c] | $^1$H | 2.75 (br m, 16H) | – | – | – | 1.73 (t) |
| | $^{13}$C | 24.6 | 36.2 | 32.2 | – | – |
| **2** | $^1$H | 2.9 (m, 8H) | – | – | – | – |
| | $^{13}$C | 29.1 | – | – | – | – |
| **3** | $^1$H | 2.62 (m) | 2.90 (m) | 6.33 (m) | 4.90, 5.25 | 1.70 (t) |
| **4** | $^1$H | 3.17 (br m, 8H) | – | – | – | – |
| **5** | $^1$H | 3.20 (br m, 8H) | – | – | – | – |
| | $^{13}$C | 41.1 | 30.7 | – | – | – |
| **6** | $^1$H | 3.20 (br m, 8H) | – | – | – | – |
| | $^{13}$C | 34.7 | 250.7 | – | – | – |
| **7** | $^1$H | 2.85 (br m, 12H) | – | – | – | – |
| | $^{13}$C | 39.3 | 32.3 | 31.6 | – | – |
| **8** | $^1$H | 2.8, 2.9 (br m, 12H) | – | – | – | – |
| | $^{13}$C | 38.7 | 32.4 | 31.8 | – | – |

[a] $CDCl_3$, δ [ppm]; the primed atoms are related by $C_2$ symmetry; t = triplet, m = multiplet. [b] Also cf. ref. [18].

Table 7. MS data of *n*ETG oligomers, their cyclic disulfides (*n*ETGds), and other products.

| Molecule | Peaks (relative abundance [%])[a] | $M_r$ | Formula |
|---|---|---|---|
| ETG | 94 (82), 61 (50), 60 (77), 47 (100), 45 (50) | 94.20 | $C_2H_6S_2$ |
| DETG | 154 (18), 152 (45), 120 (16), 94 (32), 61(100), 60 (25) | 154.32 | $C_4H_{10}S_3$ |
| TrETG | 214 (100), 180 (20), 154 (50), 152 (47), 120 (15), 61 (76);<br>CI: 215 (55), 181 (10), 153 (23), 121 (100) | 214.44 | $C_6H_{14}S_4$ |
| TETG | 274 (4), 154 (30), 120 (46), 61 (100) | 274.55 | $C_8H_{18}S_5$ |
| PETG | 334 (5), 214 (30), 120 (40), 61 (100) | 334.67 | $C_{10}H_{22}S_6$ |
| HETG | 394 (8) | 394.79 | $C_{12}H_{26}S_7$ |
| **2** | 120 (100), 92 (22), 61 (70), 60 (20), 47 (80) | 120.24 | $C_4H_8S_2$ |
| **3**[b] | 120 (80); CI: 121 (90) | 120.24 | $C_4H_8S_2$ |
| **4**[c] | 184 (100), 124 (55), 92 (25), 87 (35), 60 (40) | 184.37 | $C_4H_8S_4$ |
| **5**[c] | 152 (100), 124 (26), 106 (18), 87 (33), 78 (20), 60 (42) | 152.30 | $C_4H_8S_3$ |
| **6** | 304 (12) | 304.60 | $C_8H_{16}S_6$ |
| **7** | 212 (56), 184 (15), 152 (100), 124 (98), 87 (38), 60 (58) | 212.42 | $C_6H_{12}S_4$ |
| **8** | CI: 425 (10), 269 (20), 213 (90), 153 (95), 121 (100) | 424.84 | $C_{12}H_{24}S_8$ |
| **9** | 272 (12); CI: 273 (12), 215 (20), 153 (36), 74 (100) | 272.54 | $C_8H_{16}S_5$ |
| PETGds | 332 (12), 272 (15), 212 (20), 184 (18), 152 (28), 124 (100) | 332.66 | $C_{10}H_{20}S_6$ |
| HETGds | 392 (28), 332 (85), 272 (65), 244 (26), 212 (100), 184 (86) | 392.77 | $C_{12}H_{24}S_7$ |

[a] Main fragments are listed; isotopic distribution was ascertained and is not exhibited; the higher systems often carry lower homologue impurities. [b] Also cf. ref. [19] [c] Also cf. ref. [20].

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