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Synthesis of Epoxy-Terminated Dialkyl Disulfides for Polymerizable Self-Assembled Monolayers

Laura J. Yeager, Dafni G. Amirsakis, Elan Newman, and Robin L. Garrell*†

Department of Chemistry and Biochemistry, University of California, Los Angeles, California USA 90095-1569

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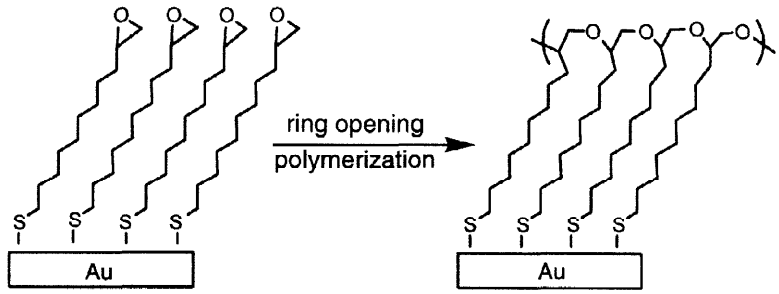
Abstract: The synthesis of epoxy-terminated dialkyl disulfides for incorporation into polymerizable self-asssembled monolayers is reported. The epoxide is installed by an indirect method in which the disulfide linkage is used as a built-in protecting group.

There is great interest in synthesizing novel organosulfur compounds that can be used to fabricate new types of self-assembled monolayers (SAMs) with prescribed structure and interfacial properties for applications such as chemical sensors. Conventional *n*-alkanethiolate SAMs on gold cannot withstand chronic exposure to organic solvents[1] or air ,[2, 3, 4] limiting their usefulness. One way to enhance the stability of alkanethiolate SAMs is to incorporate a polymerizable group into the alkane backbone, e.g., diacetylene,[5] vinyl,[6] pyrrole,[7] or boronic acid.[8] Once intermolecular crosslinks have been made,[5,9] even if a significant fraction of the adsorbed thiolate molecules oxidize to the more weakly adhering sulfinates and sulfonates, desorption and delamination are minimized. We have accomplished the convenient synthesis of epoxy-terminated dialkyl disulfides that can spontaneously self-assemble onto gold surfaces, and which can then undergo ring-opening polymerization (e. g., by cationic or anionic initiation)[10] to form novel thin-film polymers (**Scheme I**). While amphiphiles containing epoxides have been synthesized for polymerizable Langmuir Blodgett films,[11,12] and Löfäs et al. have desribed a method to modify hydroxyl terminated thiolates post-assembly to produce terminal epoxides,[13] this is the first synthesis of epoxy-terminated organosulfur compounds for self-assembly. Because epoxides are one of the most synthetically versatile organic intermediates,[14] these molecules also provide a convenient starting point for a wide range of chemically modified SAMs.



Scheme 1

The synthesis of the epoxy-terminated disulfides is built around two key transformations. One is installation of the epoxide ring in the last step by selectively converting a 1° alcohol of a terminal 1,2-diol to a tosylate group, and then effecting an intramolecular S_N2 reaction to close the three-membered ring. By installing the ring indirectly, the problems of (a) oxidizing an olefin in the presence of an electron-rich sulfur, and (b) of installing a thiol in the presence of the reactive epoxy ring are conveniently avoided. The second key transformation involves oxidizing the thiol to disulfide prior to the tosylation step. We have taken advantage of the fact that SAMs prepared from disulfides produce monolayers identical in structure to those prepared from the

† e-mail: garrell@chem.ucla.edu

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corresponding thiols. This protection (required in order to mask the nucleophilicity of the thiol) allows tosylation of the alcohol to proceed without interference. Protecting the thiols as disulfides also helps minimize any unwanted intra- or inter- molecular attack by the unprotected thiol on the epoxide ring once it has been installed.

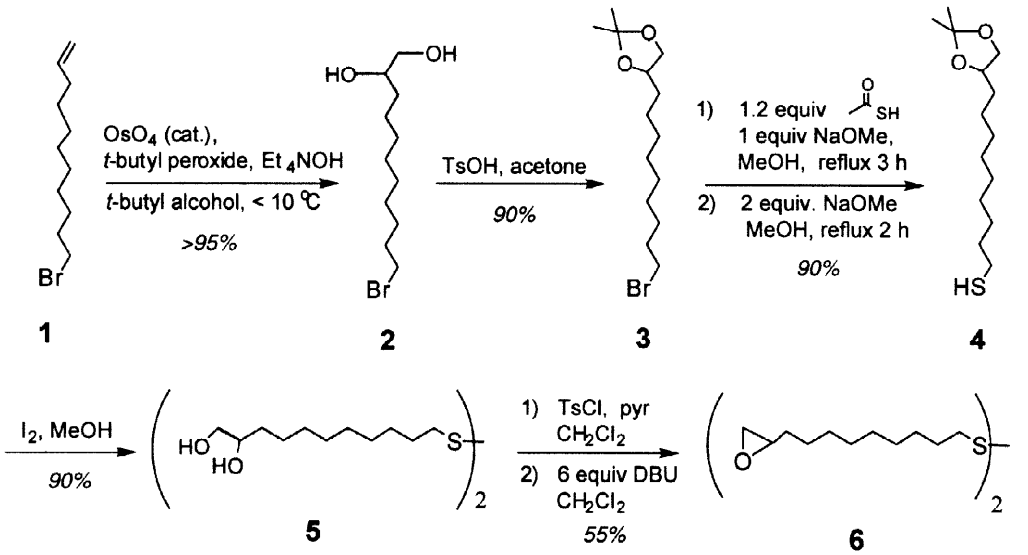

Figure 1

Figure 1 shows the synthetic route used to construct the epoxy-terminated symmetrical disulfides. The first step involves dihydroxylating bromoalkene **1**.[15,16] A racemic mixture of diol **2** is obtained in almost quantitative yield.[17] (Although one advantage of obtaining the racemic mixture is that racemic monolayers pack more densely and with fewer defects than monolayers composed purely of a single enantiomer,[18] the pure enantiomers may facilitate directed polymerization of the epoxides.) Protection of the 1,2-diol **2** is accomplished by dissolving it in dry acetone and adding TsOH in catalytic amounts to afford the acetonide **3**, in 90% yield.[19,20] Protection of the diol was found to be a necessary step. The subsequent transformation converts the 1° bromide into a thiol under extremely basic conditions. When carried out with an unprotected diol, a white insoluble polymer formed and the desired mercapto-diol was recovered in only ~30% yield. Polymerization presumably occurs through deprotonation of the alcohol followed by subsequent intermolecular attack on another bromide. To convert **3** to the thiol, the bromo-acetonide **3** is treated with thioacetic acid and excess sodium methoxide in a two-step procedure to give thiol **4** in 90% yield.[21,22] Thiol **4** is then oxidized with 0.1 M iodine to afford the deprotected disulfide **5** in 90% yield.[23] In this transformation, methanolic iodine was used because it not only selectively oxidized the thiol to the disulfide without over-oxidation, but it also deprotected the diol in the same step.[24] Disulfide **5** is dissolved in freshly distilled pyridine, treated with 2.5 eq TsCl to form the ditosylate, from which most of the pyridine is removed by aqueous extraction; the residue left after evaporation of the organic layer is taken up in CH_2Cl_2. Addition of 6 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) effects the intramolecular S_N2 ring-closure to yield epoxy-disulfide **6** in a 55% yield.[25] The remaining material has been determined to be a variable mixture of unreacted diol-disulfide and unsymmetrical disulfides of 10,11-diols and 10,11-epoxides, as well as 10,11-diols and 11-tosyl-10-ols. These compounds are easily separated from the target compound by flash chromatography. The six steps of this synthetic protocol produced the epoxy-terminated disulfide **6** in 40% overall yield.

This new synthetic route to symmetrical epoxy-terminated disulfides utilizes well-known reactions and common reagents, and can readily be extended to produce disulfides of varying chain lengths, affording control of the SAMs thickness. Another advantage of this approach is that the products have only carbon atoms in the backbone. Functional groups within SAMs can decrease the packing density and/or increase disorder in the SAM, or compromise the integrity of the film by introducing "weak-links" or reactive sites (e.g., a hydrolyzable ester linkage).[26,27] The epoxides can readily be converted to a number of more interesting and synthetically useful organic functionalities. Thus, these new disulfides provide the starting point for synthesizing new types of SAMs with novel interfacial properties.

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16. 11-Bromo-1-undecene (Pfaltz and Bauer) was used as received.
17. **Synthesis of 11-bromoundecane-1,2-diol (2)** 10 mL of *tert*-butyl alcohol, 405 μL of tetraethylammonium hydroxide, (20% in water, 0.6 mmol), and 11-bromo-1-undecene **1** (1.26 g, 5.4 mmol) were added to the reaction flask placed in a salt/icebath. 960 μL (8.6 mmol) of *tert*-butylhydroperoxide (90% in water) followed by 100 μL (0.008 mmol) of osmium tetraoxide (2.5% in *tert*-butyl alcohol) were added. Upon addition of the OsO_4, the reaction turned deep purple. The mixture was allowed to stir at 0 °C for 3 h and stored at ~4 °C overnight. The reaction was quenched by adding 20 mL aqueous 5% sodium bisulfite, which caused the reaction mixture to turn orange-gray. Once warmed to R.T., the mixture was concentrated *in vacuo* to remove most of the *tert*-butyl alcohol and water. The residue was extracted with ether (2 × 20 mL) and the organic phase washed with brine. After drying over $MgSO_4$, filtration, and concentration, the organic phase yielded diol **2** as white crystals. (1.31 g, 99% yield). **^{1}H NMR ($CDCl_3$, 400 MHz)** δ: 3.67 (m, 1H), 3.41 (m, 2H), 3.38 (t, 2H)(C-Br), 1.81 (quin., 2H), 1.79 (broad s, 1H), 1.40 (m, 3H), 1.3 – 1.2 (m, 12H). **HRMS:** calcd for $C_{11}H_{23}O_2Br$ 267.0960 $(M+H)^+$ & 265.0803 $(M-H)^+$; found, 267.0960 $(M+H)^+$ and 265.0800 $(M-H)^+$.
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20. **Synthesis of 1-bromo-10,11-isopropylidene-undecane (3).** Adapted from a procedure reported by Lewbart et al.,[15] diol **2** (1.4 g, 5.4 mmol) was placed in a flame-dried 1 L flask, to which were added dry acetone (700 mL) and *p*-toluenesulfonic acid (0.362 g, 0.36 mmol). The reaction was allowed to stir overnight R.T., after which excess $NaHCO_3$ was added. Most of the acetone was removed *in vacuo* and the residue extracted by adding 20 mL of DI H_2O and 30 mL of CH_2Cl_2 (2×). The combined organic layer was washed with saturated brine solution (30 mL), dried over $MgSO_4$, and concentrated. The residue was purified by flash chromatography (65%:35% Hex/EtOAc) to afford **2** (1.31 g) as a pale yellow oil in 90% yield. **^{1}H NMR ($CDCl_3$, 400 MHz)** δ: 4.00 (m, 1H), 3.96 (m, 1H) 3.41 (t, 1H), 3.38 (t, 2H), 1.81 (quin., 2H), 1.42 (m, 2H), 1.34 (s, 3H), 1.29 (s, 3H), 1.3-1.2 (m, 12H). **HRMS:** calc'd for $C_{14}H_{27}O_2Br$ 307.1273 $(M+H)^+$; found, 307.1281 $(M+H)^+$
21. **Synthesis of 10,11-isopropylidene-undecane-1-thiol (4).** Modified from a procedure described by Bain et al.[18] 0.46 mL (1.5 equiv., 6.5 mmol) of thiolacetic acid (97%) was added to 20 mL of 0.25 M methanolic $NaOCH_3$, followed by 1.4 g (4.5 mmol) of **3**. The reaction was refluxed for 4 h under nitrogen and then cooled to R.T. An additional 0.48 g (8.9 mmol) of $NaOCH_3$ was added, and the reaction was refluxed for 2 h more. Upon addition of $NaOCH_3$, the reaction mixture turned from a light yellow to a peach color. Most of the CH_3OH was removed *in vacuo*. The reaction was quenched by addition of 30 mL of half-saturated aqueous NH_4Cl. The aqueous layer was extracted with 30 mL of $CHCl_3$ (2×); the combined organic phases were washed with water, dried over $MgSO_4$, and concentrated. Purification of the resulting crude yellow oil (1.09 g, 95%) by flash chromatography (1:1 EtOAc/Hexs) furnished **4** in 90% yield (1.05 g). **^{1}H NMR ($CDCl_3$, 400 MHz)** δ: 4.00 (m, 1H), 3.95 (m, 1H), 3.41 (t, 1H), 2.46 (q, J = 8 Hz, 2H), 1.41 (m, 4H), 1.34 (s, 3H), 1.30 (s, 3H), 1.3-1.2 (m, 14H). **HRMS:** calc'd for $C_{14}H_{28}SO_2$ 261.1888 $(M+H)^+$; found, 261.1884 $(M+H)^+$.
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23. **Synthesis of di(10,11-dihydroxyundecyl) disulfide (5).** 0.42 g (0.104 mmole) of **4** was dissolved in 2 mL of methanol and titrated with 0.1 M methanolic iodine until the reaction turned from colorless to a persistent yellow. The reaction was quenched with 2 mL of 5 % sodium bisulfite. Most of the solvent was evaporated to afford a white precipitate that was collected by vacuum filtration, thoroughly washed with cold 5% sodium bisulfite solution, then water. After drying, and recrystallization from CH_3OH and $CHCl_3$, white solid **5** was obtained in 90% yield (0.31 g). **^{1}H NMR ($CDCl_3$+ CD_3OD, 400 MHz)** δ: 3.60 (m, 1H), 3.55 (m, 1H), 3.39 (m, 1H), 2.67 (t, 2H), 1.61 (quin, 2H), 1.2-1.3 (m, 14H). **HRMS:** calcd for $C_{22}H_{46}S_2O_4$ 438.2838 $(M)^+$; found, 438.2837 $(M)^+$.
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