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Synthesis of a Diverse Library of *N,N*-Dimethylamino Containing Monomers Appropriate as Lipid Head Groups

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Abstract

We report on the synthesis of a diverse library of *N,N*-dimethylamino containing monomers. Subjecting these monomers to Chabrier reaction conditions would yield lipids with polymerizable head groups. This library of lipid head groups is equipped with a variety of arm lengths containing reduction-oxidation polymerizable groups at the terminus.

Keywords

Chabrier reaction; Lipid monomers; T-Rex Effect; Reduction-oxidation; *N,N*-dimethylamino containing monomers

Introduction

Our group has focused on the synthesis of lipid monomers containing UV-polymerizable units located within the fatty acid tail². We have recently published work describing the construction of long lived lipid bilayers³ and lipid bilayers for studying the interchannel protein alamethicin⁴. Future proteins of interest would be bleached during UV-polymerization. We have decided to design reduction-oxidation (redox) monomers appropriate for lipid head groups. Therefore, we have synthesized a diverse library of *N,N*-dimethylamino containing monomers that contain redox polymerizable moieties on arms of sufficient length.

Results and Discussion

Utilizing the Chabrier reaction, which involves the displacement on a cyclic phospholane by dimethylamine derivatives⁵, the known polymerizable lipid MA-DOPC **1**⁶ was synthesized and extruded into 200 nm vesicles. Verification by light scattering demonstrated that we did indeed form 200 nm vesicles. Yet, when the vesicles were subjected to standard reduction-oxidation polymerization conditions, we observed no enhanced mechanical stability⁷. When lipid **1** was subjected to MM2 energy minimization⁸, the polymerizable moiety was not observed to be in the correct orientation; it was pointed vertical to the plane of the vesicle. Since the polymerizable arm was too short to reach its nearest neighbor⁹, we have

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Supplemental Information: Details on MA-DOPC **1** vesicle formation, and representative synthesis and characterization are included for compounds **2**, **4**, **6**, **7**, and **11**.

whimsically referred to this observation as the “T-Rex Effect” (Figure 1). Work began with the design and synthesis of a symmetrical dimethylamine core with polymerizable moieties located at least 4.5 Å from the center of molecule. We were also interested in incorporating a degree of hydrophilicity by including amides and carbamides.

Reacting two equivalents of dimethyl methylmalonate with sodium ethoxide in ethanol followed by addition of 2-chloro-dimethylaminoethane hydrochloride produced diethylmalonate **2**¹⁰ with a yield of 35%. Addition of excess ethanolamine or 1,3-diaminopropane with a catalytic amount stannous (II) octoate followed by addition of acryloyl or methacryloyl chloride yielded polymerizable amides **3-6** with yields between 58-61% (Scheme 1). After purification, these materials spontaneously polymerized overnight to a colorless, rubbery material. Free radical inhibitor was necessary to store these amides for longer than 24 hrs.

Reduction of malonate **2** with lithium aluminum hydride in ether gave diol **7** in excellent yield. Addition of acryloyl and methacryloyl chloride yielded esters **8** and **9**, and addition of isocyanates yielded carbamides **10** and **11** (Scheme 2). These materials also spontaneously polymerized after purification.

Conclusion and Future Directions

With this diverse library of dimethylamino containing monomers, we plan to use the Chabrier reaction to yield new families of polymerizable lipids. Additionally, these head groups could produce lipids with orthogonal modes of polymerization with UV-tails and redox heads.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Cartoon Representation of Head Groups on a Lipid Bilayer

Scheme 1.
Synthesis of Dimethylamine Amide Monomers **3-6**

Scheme 2.
Synthesis of Dimethylamine Ester and Carbamide Monomers **8-11**