Synthesis, Properties and Applications of Chalcogen-Containing Antioxidants

BY

JONAS MALMSTRÖM
Dissertation for the Degree of Doctor of Philosophy in Organic Chemistry Presented at Uppsala University in 2000

ABSTRACT

This thesis deals with the synthesis, properties, and applications of chalcogen-containing antioxidants.

In the first part, the preparation and properties of chalcogen-containing vitamin E analogues are described. The sulfur compound 3,3,4,6,7-pentamethyl-2,3-dihydrobenzo[b]thiophene-5-ol was prepared by two different routes using ionic and radical chemistry. Interesting rearrangements were observed in the two synthetic pathways.

A new methodology for the synthesis of dihydroselenophene and dihydrotellurophene derivatives is described. In the preparation of the vitamin E analogues 2,3-dihydrobenzo[b]selenophene-5-ol and 2,3-dihydrobenzo[b]tellurophene-5-ol a tellurium-mediated tandem $S_{RN1}/SH_i$ sequence was suggested to be operative. 2,3-Dihydrobenzo[b]thiophene-5-ol and the vitamin E-like selenide 2-methyl-2-(4,8,12-trimethyl-tridecyl)-selenochroman-6-ol were prepared via intramolecular homolytic substitution at sulfur and selenium, respectively. The first rate constant for intramolecular homolytic substitution at tellurium is also reported ($5 \times 10^8 \text{ s}^{-1}$ at 25 °C).

The antioxidant profile for 2,3-dihydrobenzo[b]furan-5-ol and its 1-thio, 1-seleno, and 1-telluro analogues is described. By means of pulse radiolysis, it was shown that the one-electron reduction potentials (ArO·/ArO$^-$) were independent of the chalcogen (0.49-0.52 V vs NHE). The O-H bond dissociation enthalpies for the compounds were also estimated to be similar (336-340 kJ mol$^{-1}$). The $pK_a$ values and the oxidation potentials were also determined for these compounds. For some compounds the rate of hydrogen atom donation to tert-butoxyl radicals was determined by means of laser flash photolysis. Using a two-phase lipid peroxidation model, it was demonstrated that the selenium and tellurium analogues could be regenerated in the presence of a stoichiometric amount of a reducing agent. The organotellurium analogue also acted as a good glutathione-peroxidase mimic and as a potent inhibitor of lipid peroxidation in liver microsomes.

In the second part of the thesis the stabilizing capacity of bis[4-(dimethylamino)phenyl]telluride was investigated in the thermoplastic elastomer PACREL®. It was demonstrated that the addition of 0.17-0.50% of the telluride significantly improved the tensile strength and elongation at break of the polymer. Chemiluminescence measurements showed that the organotellurium compound prolonged the induction period of thermo-oxidation and reduced the total luminescence intensity of the material.

Jonas Malmström, Department of Organic Chemistry, Institute of Chemistry, University of Uppsala, Box 531, SE-751 21 Uppsala, Sweden

© Jonas Malmström 2000

ISSN 1104-232X
ISBN 91-554-4863-1

Printed in Sweden by Eklundshofs Grafiska AB, Uppsala 2000
Det finns inga omöjliga drömmar - bara vår begränsade uppfattning om vad som är möjligt.
Beth Mende Conny

Till mina föräldrar och Ulrika
Papers included in this thesis

This thesis is based on the following papers and appendix, referred to in the text by their Roman numerals.


II. Toward Novel Antioxidants: Preparation of Dihydrotellurophenes and Selenophenes by Alkyltelluride-Mediated Tandem S<sub>RN1</sub>/S<sub>H1</sub> Reactions.  

III. The Antioxidant Profile of 2,3-Dihydrobenzo[b]furan-5-ol and its 1-Thio, 1-Seleno and 1-Telluro Analogues.  

IV. Synthesis of Novel Selenium-Containing Vitamin E Analogues via Intramolecular Homolytic Substitution (S<sub>H1</sub>) at Selenium.  

V. Stabilization of PACREL<sup>®</sup> by Organotellurium Compound.  

VI. Appendix: Supplementary material.  
Malmström, J.

Reprints were made with kind permission from the publishers.
CONTENTS

Abstract

Papers included in this thesis

List of abbreviations

1. INTRODUCTION ............................................................................................................ 1
   1.1 Oxygen in biological and polymeric systems ......................................................... 1
      1.1.1 General introduction ........................................................................................ 1
      1.1.2 Mechanism of autoxidation .............................................................................. 1
      1.1.3 Endogenous defense systems ............................................................................ 2
      1.1.4 Oxidative degradation and stabilization of polymers ...................................... 3
   1.2 Selenium and tellurium in organic chemistry ........................................................ 4
      1.2.1 Introduction ...................................................................................................... 4
      1.2.2 Nucleophilic selenium and tellurium and preparation of diselenides and
ditellurides 5
      1.2.3 Other applications ............................................................................................ 6
   1.3 Radical cyclizations in organic synthesis ............................................................... 7
      1.3.1 Introduction ...................................................................................................... 7
      1.3.2 Methods to conduct radical cyclizations .......................................................... 8
      1.3.3 Intramolecular homolytic substitution (SHi)..................................................... 11
2. CHALCOGEN ANALOGUES OF VITAMIN E .......................................................... 13
   2.1 Introduction .............................................................................................................. 13
   2.2 Synthesis of chalcogen-containing vitamin E analogues ...................................... 16
      2.2.1 Preparation of a sulfur analogue of vitamin E\textsuperscript{I} ..................................... 16
      2.2.2 Towards selenium and tellurium analogues of vitamin E\textsuperscript{II} ...................... 23
      2.2.3. Synthesis of 2,3-dihydrobenzo[b]furan-5-ol and its 1-thio analogue\textsuperscript{III} ....... 32
   2.3 The antioxidant profile of 2,3-Dihydrobenzo[b]furan-5-ol and its 1-thio,
1-seleno and 1-telluro analogues\textsuperscript{III} .......................................................... 33
      2.3.1 Introduction ...................................................................................................... 33
      2.3.2 Redox and thermochemical properties ............................................................. 33
      2.3.3 Reactivity towards tert-butoxyl radicals ........................................................... 35
      2.3.4 Inhibition of lipid peroxidation ....................................................................... 36
### List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>ADP</td>
<td>Adenosine 5’-diphosphate</td>
</tr>
<tr>
<td>AIBN</td>
<td>$\alpha,\alpha’$-Azobisisobutyronitrile</td>
</tr>
<tr>
<td>AMVN</td>
<td>2,2’-Azobis(2,4-dimethylvaleronitrile)</td>
</tr>
<tr>
<td>Ar</td>
<td>Aryl</td>
</tr>
<tr>
<td>BDE</td>
<td>Bond Dissociation Enthalpy</td>
</tr>
<tr>
<td>BHT</td>
<td>3,5-Di-$t$-butyl-4-hydroxytoluene</td>
</tr>
<tr>
<td>Bn</td>
<td>Benzyl</td>
</tr>
<tr>
<td>Bu</td>
<td>Butyl</td>
</tr>
<tr>
<td>CB-A</td>
<td>Chain-breaking accepting</td>
</tr>
<tr>
<td>CB-D</td>
<td>Chain-breaking donating</td>
</tr>
<tr>
<td>CL</td>
<td>Chemiluminescence</td>
</tr>
<tr>
<td>DMAP</td>
<td>4-Dimethylaminopyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>Et</td>
<td>Ethyl</td>
</tr>
<tr>
<td>Fc</td>
<td>Ferrocene</td>
</tr>
<tr>
<td>GSH</td>
<td>Glutathione</td>
</tr>
<tr>
<td>GSH-px</td>
<td>Glutathione peroxidase</td>
</tr>
<tr>
<td>GSSG</td>
<td>Glutathione disulfide</td>
</tr>
<tr>
<td>HPLC</td>
<td>High Performance Liquid Chromatography</td>
</tr>
<tr>
<td>In</td>
<td>Initiator</td>
</tr>
<tr>
<td>INEPT</td>
<td>Insensitive Nuclei Enhanced by Polarization Transfer</td>
</tr>
<tr>
<td>LFP</td>
<td>Laser flash photolysis</td>
</tr>
<tr>
<td>m-CPBA</td>
<td>meta-Chloroperbenzoic acid</td>
</tr>
<tr>
<td>MD</td>
<td>Machine direction</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>Ms</td>
<td>Methanesulfonyl</td>
</tr>
<tr>
<td>NAC</td>
<td>$N$-acetylcysteine</td>
</tr>
<tr>
<td>NADPH</td>
<td>Nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>NHE</td>
<td>Normal Hydrogen Electrode</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
</tr>
<tr>
<td>NOE</td>
<td>Nuclear Overhauser Enhancement</td>
</tr>
<tr>
<td>PD</td>
<td>Peroxide decomposer</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>PTOC</td>
<td>Pyridine-2-thione-$N$-oxycarbonyl</td>
</tr>
<tr>
<td>rt</td>
<td>Room temperature</td>
</tr>
<tr>
<td>SOMO</td>
<td>Singly Occupied Molecular Orbital</td>
</tr>
<tr>
<td>TBAF</td>
<td>Tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>TBAPO</td>
<td>Tetrabutylammonium perchlorate</td>
</tr>
<tr>
<td>TBARS</td>
<td>Thiobarbituric acid-reactive substances</td>
</tr>
<tr>
<td>TBDMS</td>
<td>tert-Butyldimethylsilyle</td>
</tr>
<tr>
<td>TD</td>
<td>Transverse direction</td>
</tr>
<tr>
<td>TEMPO</td>
<td>2,2,6,6-Tetramethyl-1-piperidinyloxy, free radical</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TLI</td>
<td>Total Luminescence Intensity</td>
</tr>
<tr>
<td>Ts</td>
<td>Toluenesulfonyl</td>
</tr>
<tr>
<td>TTMSS</td>
<td>Tris(trimethylsilyl)silane</td>
</tr>
</tbody>
</table>
1. Introduction

1.1 Oxygen in biological and polymeric systems

1.1.1 General introduction

Molecular oxygen is essential to the energy producing processes of aerobic organisms, but it is also detrimental in many cases.¹ All organic materials exposed to molecular oxygen undergo oxidative degradation (autoxidation). This process can be delayed by the involvement of antioxidants.² An antioxidant is generally defined as an inhibitor that is effective in preventing oxidation by molecular oxygen. Historically, de Saussure was the first to study autoxidation phenomena when in 1820 he measured the rate of walnut oil oxidation. A few years later, Berzelius suggested that the autoxidation of oil was initiated by atmospheric oxygen. In the 1920’s, Moureau and Dufraisse pioneered the study of antioxidants and the first approved antioxidant for food came in 1933. Today, antioxidants have great commercial interest in the preservation of various foods and in the prevention of oxidative degradation of petroleum products, rubber, and plastics. Medicinally, they are also interesting in the prevention of various diseases.³,⁴

1.1.2 Mechanism of autoxidation

The autoxidation process involves a radical chain reaction initiated by environmental stresses such as heat, irradiation or metal ions. Scott has proposed a general mechanism for autoxidation, consisting of two interlinked processes (Scheme 1).⁵ An alkyl radical, R·, formed as a result of environmental stress, is a common intermediate in the two cycles. The alkyl radical readily reacts with molecular oxygen to form the harmful peroxyl radicals, ROO·,⁶ which in turn can abstract a hydrogen atom, thus regenerating alkyl radicals and producing hydroperoxides. Hydroperoxides can easily

---

produce the reactive hydroxyl radicals (HO·) and alkoxyl radicals (RO·) in the presence of light, heat or a transition metal. Unless the autoxidation is terminated in some way, for example by combination of two radicals or by the involvement of antioxidants, the chain reaction will continue. Fortunately, aerobic organisms have developed several endogenous defense systems against the over-production of reactive oxygen species (oxidative stress, see Section 1.1.3).

![Scheme 1. General mechanism for autoxidation.](image)

### 1.1.3 Endogenous defense systems

Reactive oxygen species (for example ROO·, HO·, O₂· and H₂O₂) are produced continuously in our body as a consequence of normal metabolic processes as well as from environmental stresses. These species need to be inactivated, otherwise they might cause various diseases, including atherosclerosis, cancer, and an accelerated aging process.⁷ For example, lipids containing polyunsaturated fatty acids and their esters are readily oxidized by molecular oxygen in a process called lipid peroxidation.⁸ Normally, however, any over-production of reactive oxygen species can be controlled by enzymatic and non-enzymatic antioxidants. Antioxidants can be divided into two groups depending on their mode of action. Preventive antioxidants act primarily through attenuating the initiation step whereas chain-breaking

---

Antioxidants act through termination of the free radical chain reaction (Scheme 1). Peroxide decomposers (PD), UV absorbers and metal chelators belong to the group of preventive antioxidants. In biological systems, the enzymes catalase and the glutathione peroxidases (GSH-px) represent this kind of antioxidant. The chain-breaking antioxidants can be divided into two groups depending on their mechanism of action, chain-breaking donating antioxidants (CB-D) and chain-breaking accepting antioxidants (CB-A). Typical examples of CB-D type antioxidants are sterically hindered phenols, e.g. BHT (1), and aromatic amines, e.g. diphenylamine (2), which can donate a hydrogen atom. Nitroxyl radicals, e.g. TEMPO (3), which can trap short-lived free radicals by combining with them, are examples of the accepting type of antioxidants.

Unfortunately, our natural defense against reactive oxygen species is not perfect. It is therefore of great interest to design and synthesize new antioxidants with higher antioxidative capacity than the naturally occurring ones.

1.1.4 Oxidative degradation and stabilization of polymers

Polymers are also susceptible to attack by reactive oxygen species. Exposure to oxygen, ozone, high temperature, UV light, radiation, and chemical agents can degrade them. The thermo- and photo-oxidative aging of polymers causes a deterioration in their physical and mechanical properties. Poorer mechanical strength often results and properties such as stiffness, creep resistance, and brittleness are affected.

The differences between aging processes are often related to the nature of the initiating step of a free-radical chain reaction in which molecular oxygen is one of the

\[\text{Scheme 1} \]

Unfortunately, our natural defense against reactive oxygen species is not perfect. It is therefore of great interest to design and synthesize new antioxidants with higher antioxidative capacity than the naturally occurring ones.

1.1.4 Oxidative degradation and stabilization of polymers

Polymers are also susceptible to attack by reactive oxygen species. Exposure to oxygen, ozone, high temperature, UV light, radiation, and chemical agents can degrade them. The thermo- and photo-oxidative aging of polymers causes a deterioration in their physical and mechanical properties. Poorer mechanical strength often results and properties such as stiffness, creep resistance, and brittleness are affected.

The differences between aging processes are often related to the nature of the initiating step of a free-radical chain reaction in which molecular oxygen is one of the

\[\text{Scheme 1} \]

Unfortunately, our natural defense against reactive oxygen species is not perfect. It is therefore of great interest to design and synthesize new antioxidants with higher antioxidative capacity than the naturally occurring ones.

1.1.4 Oxidative degradation and stabilization of polymers

Polymers are also susceptible to attack by reactive oxygen species. Exposure to oxygen, ozone, high temperature, UV light, radiation, and chemical agents can degrade them. The thermo- and photo-oxidative aging of polymers causes a deterioration in their physical and mechanical properties. Poorer mechanical strength often results and properties such as stiffness, creep resistance, and brittleness are affected.

The differences between aging processes are often related to the nature of the initiating step of a free-radical chain reaction in which molecular oxygen is one of the

\[\text{Scheme 1} \]

Unfortunately, our natural defense against reactive oxygen species is not perfect. It is therefore of great interest to design and synthesize new antioxidants with higher antioxidative capacity than the naturally occurring ones.

1.1.4 Oxidative degradation and stabilization of polymers

Polymers are also susceptible to attack by reactive oxygen species. Exposure to oxygen, ozone, high temperature, UV light, radiation, and chemical agents can degrade them. The thermo- and photo-oxidative aging of polymers causes a deterioration in their physical and mechanical properties. Poorer mechanical strength often results and properties such as stiffness, creep resistance, and brittleness are affected.

The differences between aging processes are often related to the nature of the initiating step of a free-radical chain reaction in which molecular oxygen is one of the

\[\text{Scheme 1} \]

Unfortunately, our natural defense against reactive oxygen species is not perfect. It is therefore of great interest to design and synthesize new antioxidants with higher antioxidative capacity than the naturally occurring ones.

1.1.4 Oxidative degradation and stabilization of polymers

Polymers are also susceptible to attack by reactive oxygen species. Exposure to oxygen, ozone, high temperature, UV light, radiation, and chemical agents can degrade them. The thermo- and photo-oxidative aging of polymers causes a deterioration in their physical and mechanical properties. Poorer mechanical strength often results and properties such as stiffness, creep resistance, and brittleness are affected.

The differences between aging processes are often related to the nature of the initiating step of a free-radical chain reaction in which molecular oxygen is one of the

\[\text{Scheme 1} \]
reactants. Polyethylene for example, is degraded $10^5$ times more rapidly in oxygen atmosphere than in nitrogen at 260 °C.\textsuperscript{10} The autoxidation of simple low molecular weight compounds is relatively well understood, but the oxidation of polymers is more complex.\textsuperscript{11}

The free-radical chain reaction is initiated by thermal, photochemical or mechanical strain or by decomposition of peroxides or other impurities incorporated into the polymer during processing. The deleterious consequences of oxidative aging can be relieved by the addition of chain-breaking antioxidants, UV-absorbers, metal-complexing agents, and peroxide decomposers. However, commercial stabilizers sometimes suffer from poor efficiency and toxicity, so there is a great need for better antioxidants/stabilizers for polymeric materials.

1.2 Selenium and tellurium in organic chemistry

1.2.1 Introduction

Berzelius discovered elemental selenium in 1818 and the first organoselenium compounds were prepared a few years later by Löwig and Wöhler. These compounds were simple aliphatic selenols (RSeH), selenides (RSeR), and diselenides (RSeSeR). Von Reichenstein isolated elemental tellurium in 1782 and Wöhler prepared the first organotellurium compound, Et$_2$Te, in 1840. Although the fields of organoselenium and -tellurium chemistry date back to the 19th century, it was not until the 1970’s when selenium and tellurium came into practical use in organic chemistry. The apparent turning point was Sharpless use of the phenyl selenide anion as a mild reagent for converting epoxides into allylic alcohols (\textit{vide infra}).\textsuperscript{12} Ever since, there has been a growing interest in the development of organoselenium and -tellurium chemistry.

A full overview of the use of selenium and tellurium in organic chemistry will not be given here. A number of review articles\textsuperscript{13} and books\textsuperscript{14} have been published on this topic.

1.2.2 Nucleophilic selenium and tellurium and preparation of diselenides and ditellurides

Due to their importance in the synthetic work in this thesis, nucleophilic selenium and tellurium species and the preparation of diselenides and ditellurides will be discussed in some detail.

Selenide or telluride anions are often used to prepare organoselenium and organotellurium compounds. They are very powerful, soft nucleophiles, which react in an $S_N$2 fashion with a wide variety of substrates, including alkyl halides and epoxides. For example, Sharpless used the phenyl selenide anion to ring open the epoxide 4 to the alcohol 5 in excellent yield (Scheme 2). The anions can be formed by reduction of diselenides or ditellurides, respectively. The reduction is commonly carried out using NaBH$_4$ in ethanol, but other reductants can also be used.

\[
\begin{align*}
4 & \xrightarrow{\text{EtOH, 2 h, rt.}} 5 \\
\text{Scheme 2. Ring opening of an epoxide by the strongly nucleophilic phenyl selenide anion.}
\end{align*}
\]

The corresponding diorganyl diselenides and ditellurides can be prepared in various ways. Diselenides are generally prepared, as depicted in Scheme 3, by oxidation of selenols or selenolates, or by the reaction of Li$_2$Se$_2$ or Na$_2$Se$_2$ with alkyl or aryl halides. Aryl diselenides can also be obtained from the reaction of Na$_2$Se$_2$ with diazonium salts.

---


16 Selenolates and tellurolates are most commonly prepared by the reaction of Grignard reagents or alkyl- or aryl lithuims with elemental selenium or tellurium.

Ditellurides are generally prepared, as outlined in Scheme 4, by oxidation of tellurolate anion,\(^\text{16}\) alkylation or arylation of \(\text{Na}_2\text{Te}_2\), or by reduction of the corresponding organanyl tellurium trichlorides.


1.2.3 Other applications
Organoselenium and -tellurium compounds have also found several other applications in chemistry other than the purely synthetic uses. For example, they can be used as building blocks for organic conductors.\(^\text{17}\) Organoselenium compounds also play important biological roles. Thus, selenocysteine residues are incorporated in the glutathione peroxidase enzymes, which serve to reduce hydroperoxides without formation of toxic radical intermediates. Diaryl chalcogenides are a stable and odorless class of compounds, which have attracted a lot of interest in this research laboratory. It has recently been found that these compounds can act as selective inhibitors of thioredoxin reductase, and, thereby, act as potential antitumor agents.\(^\text{18}\)


They can also protect against peroxynitrite-mediated oxidation in our body.\textsuperscript{19} Diaryl tellurides also serve as effective antioxidants in polymeric systems.\textsuperscript{20,V} We have also demonstrated that various selenium and tellurium-containing compounds can act as chain-breaking antioxidants or peroxide decomposers in model systems.\textsuperscript{21,22} Apparently, new organoselenium and organotellurium compounds could find many uses.

1.3 Radical cyclizations in organic synthesis

1.3.1 Introduction

The development of radical chemistry started in the early twentieth century when Gomberg investigated the formation and reactions of the triphenylmethyl radical.\textsuperscript{23} In the 1920’s Paneth showed that less stabilized radicals also exist and he measured their lifetime in the gas phase.\textsuperscript{24} The use of radicals in organic synthesis began in the 1930’s when Kharasch recognized that the anti-Markovnikov addition of hydrogen bromide to alkenes proceeds via a radical chain process.\textsuperscript{25} At about the same time, Hey and Waters described the phenylation of aromatic compounds with benzoyl peroxide as a radical reaction.\textsuperscript{26}

The use of free radicals in organic synthesis has increased dramatically during the last twenty years, and radical-based methodology has become an important tool in organic synthesis.

\textsuperscript{26} Hey, D. H.; Waters, W. A. Chem. Rev. 1937, 21, 169.
synthesis, especially for natural product synthesis. The advantages of radical reactions are their high functional group tolerance and the use of mild reaction conditions combined with high levels of regio- and stereoselectivity. Radical cyclization reactions are a powerful and versatile method for the construction of mono- and polycyclic systems. This can be exemplified by the elegant one-pot synthesis of the taxane skeleton (6) reported by Pattenden (Scheme 5).

Scheme 5

1.3.2 Methods to conduct radical cyclizations

"Metal hydride" methods

Tri-n-butyltin hydride and tris(trimethylsilyl)silane (TTMSS) are commonly used reagents for effecting reductive radical carbon-carbon bond formation. The mechanism for radical cyclization using tin hydride as the promoter can be divided into three steps: initiation, propagation and termination, as exemplified in Figure 1. An analogous chain can be written for TTMSS. Initiation of the radical chain is usually accomplished by thermal decomposition of \( \alpha,\alpha'-\text{azobisisobutyronitrile} \) (AIBN) to generate a tin radical. When lower temperatures are needed, light or \( \text{Et}_3\text{B} \) in the presence of trace amounts of oxygen, are commonly used. In the propagating step, the initial radical is generated from a radical precursor by atom or group transfer to the tin radical formed in the initiation step. The radical can then undergo the desired intramolecular addition to the double bond to form the radical 9, which

---

finally undergoes an intermolecular reaction with the tin hydride to produce the cyclized product 10. A competing reaction is the reduction of radical 8 to form the reduced compound 11. If cyclization is slow it is necessary to use low concentrations of the hydride to minimize the undesired process. In this case it is also advisable to use TTMSS as a hydride donor, since it is about 10 times less reactive than \( n\text{-Bu}_3\text{SnH} \) toward alkyl radicals. There are also some other practical problems associated with the use of tin hydride.\textsuperscript{31,33} Tin reagents are toxic and they often make product isolation difficult.\textsuperscript{34} Therefore, a wide range of methods has been developed to avoid the use of tin.\textsuperscript{35} The most notable method is the Barton method, which will be discussed in the next section. A wide range of other methods has also been used for conducting radical cyclizations.\textsuperscript{28}

![Figure 1. Chain mechanism for radical cyclization mediated by trialkylstannyl radicals.](image)

Many radical precursors, including halogens, phenyl selenides or -sulfides, and xanthate esters, can be used. The reactivity of the carbon heteroatom bond (RX) towards stannyl radicals is generally in the order I > Br > SePh = OC(S)Me > Cl >


\textsuperscript{34} The desired product is often contaminated with tin compounds after flash chromatography.

The order of reactivity of various R· toward tin hydrides is aryl ≈ vinyl > alkyl > allyl ≈ benzyl.

Intramolecular cyclization to a double bond can occur in two different ways - exo or endo (Figure 2). Generally, the exo mode of cyclization is kinetically preferred.

[Diagram of exo and endo modes of cyclization]

Radical additions to C=C double bonds are usually irreversible and exothermic, with early, reactant-like transition states. Such kinetically controlled reactions often give rise to products that are unavailable by conventional ionic methods.27d

The free-radical methodology is most successful for the synthesis of 5-membered rings. There are several reasons for this: 1) The rate of cyclization for the formation of 5-membered rings is usually higher than the cyclization to give any other ring size. For example, the simple 5-hexenyl radical cyclizes 20 times faster than does the 6-heptenyl radical.38 2) The regioselectivity for 5-exo cyclizations is often outstanding.38,39 3) Cyclization giving 5-membered rings can be highly stereoselective.38,40

The thiohydroxamate method (Barton method)

The Barton41 method is one of the most important radical chain methods where tin is not involved (Scheme 6). This reaction provides a convenient way to generate alkyl

---

radicals from carboxylic acids. The radical chain is initiated by light or heat induced
decomposition of the radical precursor thiohydroxamate ester 12, which is normally
prepared in situ from carboxylic acids. The propagation steps involve cyclization,
addition of the cyclized radical to the thiohydroxamate moiety, and fragmentation
with the expulsion of carbon dioxide to generate the initial radical and the product
alkyl pyridyl sulfide 13. In contrast to the metal hydride based reactions, the chain-
transfer step is not hydrogen abstraction but transfer of a thiopyridyl group that can be
removed or employed for further transformations. In addition, if a suitable radical trap
is added, which can trap $R_2^\cdot$, then a wide variety of compounds can be prepared.

![Scheme 6. Schematic representation of the Barton method.]

The Barton method can be extended to involve PTOC oxalates (anhydrides of an
oxalic acid monoester and N-hydroxyperidine-thione), which can be used to generate
alkyl radicals from tertiary alcohols. This will be discussed in section 2.4.2.

1.3.3 Intramolecular homolytic substitution ($S_{\text{Hi}}$)

Generally, homolytic substitution results in the displacement of one radical by another
according to equation 1.

\[ R_1^\cdot + R_2 \rightarrow R_1^\cdot + R_2^\cdot \]

---

The reaction may either proceed via an $S_{H2}$ mechanism or, more rarely, via an $S_{H1}$ mechanism. The $S_{H2}$ reaction is a bimolecular process where $R \cdot$ attacks $AB$ with subsequent expulsion of $B \cdot$. Most commonly, $S_{H2}$ reactions involve attack on a univalent atom such as hydrogen or a halogen, but it can also occur at multivalent atoms. If the reaction is intramolecular it is denoted $S_{Hi}$ and it can be used to obtain various heterocycles.\(^{46}\) The reaction has frequently been used for the preparation of sulfur heterocycles,\(^{47}\) but it has recently been applied to the synthesis of selenium\(^{48}\) and tellurium\(^{49}\) heterocycles as well. For example, irradiation of radical precursor 14 leads to rapid and efficient intramolecular homolytic substitution at selenium to give substituted and saturated selenium-containing heterocycles 15 in good yield (Scheme 7).\(^{48a,b}\) Examples have also been reported where intramolecular homolytic substitution take place at oxygen,\(^{50}\) carbon,\(^{51}\) silicon,\(^{52}\) and boron\(^{53}\).

\[ \text{R} \cdot + \text{AB} \rightarrow \text{RA} + \text{B} \cdot \]


2. Chalcogen Analogues of Vitamin E

2.1 Introduction

Vitamin E is a well-known lipid-soluble antioxidant in biological systems. The term vitamin E refers to the structurally related phenolic compounds called tocopherols (compounds 16a-d), where α-tocopherol (16a) is the most active one.

![Image of tocopherol structures](image)

The tocopherols protect cell membranes from oxidative degradation by acting as chain-breaking donating antioxidants. Being phenolic compounds, they can act by trapping two peroxyl radicals according to equations 2 and 3.

\[
\text{ROO}^\cdot + \text{ArOH} \rightarrow \text{ROOH} + \text{ArO}^\cdot \quad (2)
\]

\[
\text{ROO}^\cdot + \text{ArO}^\cdot \rightarrow \text{Non-radical combination products} \quad (3)
\]

Since the pioneering work on vitamin E analogues by Ingold and co-workers in the 1980s, there has been a continuous search for compounds with a better antioxidative capacity than α-tocopherol. For example, Ingold and Barclay prepared oxygen

---

analogues 17 and 18, respectively. These analogues exhibited better antioxidant capacity than \( \alpha \)-tocopherol, mainly due to steric and stereoelectronic effects.\(^{55c,57a}\) Recently, Niki and co-workers prepared the tocopherol analogue 19 as a drug for inhibition of lipid peroxidation \textit{in vivo}.\(^58\) Certain requirements should be fulfilled for a good chain-breaking tocopherol: 1) the aromatic ring should be fully methylated; 2) the overlap between the phenoxy SOMO and a lone-pair on the chromane oxygen should be as good as possible. Thus, reducing the ring size of the non-aromatic ring from six atoms in \( \alpha \)-tocopherol to five atoms in the dihydrobenzofuran analogue increases the activity.\(^{54}\)

![Structures of 17, 18, and 19](image)

Although a wide range of lipophilic as well as hydrophilic\(^{59}\) chromanol systems have been studied, little effort has been made to change the heteroatom in the fused heterocyclic ring to see how that will affect the overall antioxidative capacity of the compounds. It is known that the sulfur atom is more effective than oxygen at stabilizing a neighbouring radical center.\(^60\) However, Ingold and co-workers have prepared 1-thio-\( \alpha \)-tocopherol (16e) and related 6-hydroxythiochromanes, and demonstrated that they were slightly less efficient than the structurally related 6-hydroxychromanes.\(^{55d-f}\) It has been referred that some phenolic compounds carrying sulfur para to the hydroxylic group, have shown high antioxidant capacity.\(^61\) As mentioned in Section 1.2.3, we have demonstrated that various selenium and tellurium-containing compounds show antioxidative properties in biological and


polymeric systems.\textsuperscript{20,21} For example, bis(4-hydroxyphenyl) telluride (20) was demonstrated to be a better inhibitor of azo-initiated peroxidation of linoleic acid than its corresponding sulfur analogue.\textsuperscript{21d} It is also known that tellurides react readily with hydroperoxides to form tellurium (IV) dihydroxides according to Scheme 8.\textsuperscript{21d,f} These species can be reduced back to the divalent state by mild stoichiometric reductants, such as thiols or ascorbate. In this way, the compound can act as a catalyst for reduction of hydroperoxides.

With this background we thought it would be of interest to synthesize chalcogen-containing vitamin E analogues, and to investigate if the selenium and tellurium-containing analogues, in addition to their chain-breaking properties, could be regenerated according to the mechanism depicted in Scheme 8.

\begin{center}
\textbf{Scheme 8.} Proposed catalytic mechanism for the hydroperoxide decomposing action of diorganyl tellurides in the presence of thiols.
\end{center}

\[\text{RSSR} \xrightarrow{\text{H}_2\text{O}_2 \text{ or ROOH}} \text{R-Te-R} \xrightarrow{\text{OH}} \text{R-Te-R} \xrightarrow{\text{OH}} \text{RSSR} \xrightarrow{2 \text{ RSH}} \]

2.2 Synthesis of chalcogen-containing vitamin E analogues

2.2.1 Preparation of a sulfur analogue of vitamin E

The target molecules of interest are the chalcogen-containing vitamin E analogues 21a-c, where the heteroatom X could be sulfur, selenium, or tellurium. Initially it was decided to synthesize 3,3,4,6,7-pentamethyl-2,3-dihydrobenzo[b]thiophene-5-ol (21a).

It is known that the 2,3-dihydrobenzothiophene as well as the 2H-1-benzothiopyran systems can be made by cyclodehydration of the corresponding aryl hydroxyalkyl sulfides. Preparation of the alcohol 25 required for such an approach was completed in a couple of steps starting from commercially available 2,3,6-trimethylphenol (22) (Scheme 9). Bromination of phenol 22 with bromine in acetic acid occurred, regiospecifically, in the 4-position to give the bromophenol 23, which was then protected as its TBDMS ether 24 in excellent yield. After protection, the bromide 24 was treated with tert-butyl lithium, elemental sulfur and isobutylene oxide in a one-pot procedure to obtain the desired alcohol 25 in an isolated yield of 74%. Finally, the alcohol was treated with neat concentrated sulfuric acid to obtain an inseparable 1:1 mixture of the desired product 21a and the by-product 26, in low yield. The low yield may be explained as a consequence of steric interactions between the gem-dimethyl group and the methyl group in the 4-position.

---

Scheme 9. (a) Br₂, AcOH, 20 °C, 97 %. (b) TBDMSI, imidazole, DMF, 20 °C, 95 %. (c) t-BuLi, THF, -78 °C. (d) Sulfur, THF, 20 °C. (e) Isobutylene oxide, THF, 20 °C, 74 % from 24. (f) Conc. H₂SO₄, 20 °C, 27 %.

To obtain separation of sulfides 21a and 26 by flash chromatography for characterization, the compounds were oxidized to their respective sulfoxides by m-CPBA.

Cyclodehydration of the alcohol 25 was found to be unsuccessful in polyphosphoric, perchloric, and formic acid. Various Lewis acids also failed to cause cyclization using either nitromethane or toluene as solvents.

The formation of the dibenzo[b]thiophene derivative 26 is mechanistically interesting. It could be proposed to occur via the carbocation and episulfonium ion intermediates, as outlined in Scheme 10, followed by both methyl and hydride shifts and finally oxidation. The driving force behind this rearrangement would be the aromatization of the molecule.

Since ionic chemistry did not work as well as expected, this led to the consideration of various radical cyclizations for the preparation of sulfide 21a. Cyclization of an aryl radical could be a convenient way for obtaining the target molecule. The radical precursors 28 and 29 were prepared as outlined in Scheme 11. Bromination of the alcohol 25 resulted not only in aromatic bromination, but partial substitution of the tertiary alcohol as well. The crude bromide was therefore hydrolyzed to afford the brominated alcohol 27 in a 67 % isolated yield from the alcohol 25. The acid-catalyzed dehydration of compound 27 afforded the terminal olefin 28 as the kinetic product and the vinylic sulfide 29 as the thermodynamic one, in good yields.

Scheme 11. (a) Br₂, AcOH, 20 °C. (b) Et₃N, THF, H₂O, 67 % from 25. (c) p-TsOH, toluene, reflux, 1 h, 68 %. (d) p-TsOH, toluene, reflux 24 h, 74 %.

The radical precursors were then subjected to radical cyclization (Scheme 12). Thus, the terminal olefin 28 was treated with tri-n-butyltin hydride and a catalytic amount of AIBN to afford a 3:1 mixture of the desired compound 30 and its constitutional isomer 31, in moderate yield. The reaction was also carried out using an excess of the hydride donor. With a 5-fold excess, compound 30 was isolated as the sole cyclized product in low (17 %) yield, probably due to suppression of the 6-endo mode of cyclization. In the cyclization of vinylic sulfide 29, the poorer hydride donor tris(trimethylsilyl)silane was added by syringe pump together with AIBN to keep the formation of reduced starting material 32 to a minimum. In addition to reduced starting material 32 (50 %), a 1:1 mixture of the desired compound 30 and isomer 31 was isolated in 41 % yield.
Scheme 12. (a) $n$-Bu$_3$SnH, AIBN, C$_6$H$_6$, reflux, 3.5 h, 40 %. (b) TTMSS, AIBN, C$_6$H$_6$, reflux, slow addition of reagents during 8 h followed by reflux for 15 h, 41 %.

It was possible to obtain the pure sulfide 30 by careful flash chromatography of the mixture, but unfortunately it was not possible to isolate pure compound 31. In order to characterize compound 31, the mixture was treated with $m$-CPBA to afford the corresponding sulfoxides. Compound 33 was then separable by flash chromatography. As indicated in Figure 3, the structural assignments were supported by NOE-difference experiments and were further corroborated by selective INEPT experiments.

Figure 3. Nuclear Overhauser Effects for compounds 30 and 33.

Finally, sulfide 30 was deprotected with tetra-$n$-butylammonium fluoride (TBAF) to obtain the desired product 21a in 79 % isolated yield (Scheme 13).
Despite the low yields in the cyclization reactions, the mechanisms for formation of the isomer 31 are interesting. The proposed mechanisms are outlined in Schemes 14 and 15. It could be proposed that the radical 34 can either undergo a 5-exo cyclization, followed by hydrogen abstraction to form the desired compound 30, or it can undergo a 6-endo cyclization to form the 6-membered radical 35. This species can then undergo β-scission to form the sulfur-centered radical 36. Subsequent 5-exo cyclization, followed by hydrogen abstraction, would then give the isomer 31.

Interestingly, the ratio between the two isomers was independent of the tin hydride concentration used (0.35 or 0.05 M). It is therefore unlikely that a neophyl rearrangement is involved in this reaction. Unless electron-withdrawing substituents are present in the aromatic ring, the neophyl rearrangement is normally slow.

The analogous mechanisms for formation of sulfides 30 and 31 from precursor 37 are more speculative (Scheme 15). It may be considered that the radical 37 can either

---

undergo a 5-endo cyclization, followed by hydrogen abstraction to form the desired compound 30, or it can undergo an unusual 4-exo cyclization to form the 4-membered heterocycle 38. A β-scission of this species to give radical 39, followed by 5-endo cyclization and hydrogen abstraction, would afford isomer 31. The 5-endo and 4-exo radical cyclizations are rarely seen. However, the products from 5-endo and 4-exo cyclization would both be stabilized; the former by interaction with the sulfur atom and the latter by being tertiary. This probably allows radical cyclization to compete more favorably with hydrogen abstraction.

Scheme 15. Proposed mechanisms for the formation of compounds 30 and 31 from radical 37.

The sulfide 41, unsubstituted in the allylic moiety, was also prepared in order to study the outcome of radical cyclization (Scheme 16). Lithiation of bromide 24, followed by sulfur insertion and alkylation with allyl bromide, afforded the allylic sulfide 40 in a 43% isolated yield from the bromide 24. Bromination followed by regeneration of the double bond by treatment with NaBH₄/bis(2-thienyl) ditelluride furnished the allylic sulfide 41 in a moderate yield. Under standard radical cyclization conditions, 5-[(tert-butyldimethylsilyl)oxy]-3,4,6,7-tetramethyl-2,3-dihydrobenzo[b]thiophene (42) was obtained as the sole product in a 55% isolated yield. As expected, 5-exo cyclization is

---


much more rapid than 6-endo cyclization in the case of an unsubstituted allylic moiety.\textsuperscript{67}

\textbf{Scheme 16.} (a) t-BuLi, THF, -78 °C. (b) Sulfur, THF, -78 °C. (c) Allyl bromide, THF, -78 °C – 20 °C, 43 % from 24. (d) Br2, AcOH, 20 °C. (e) NaBH4, bis(2-thienyl) ditelluride, EtOH, 50 % from 40. (f) n-Bu3SnH, AIBN, C6H6, reflux, 55 %.

An analogue of the vinylic sulfide 32, unsubstituted in the aromatic ring, has been reported to rearrange to 3,3-dimethyl-2,3-dihydrobenzo[\textit{b}]thiophene in dichloromethane in the presence of excess aluminium chloride.\textsuperscript{68} The analogous treatment of compound 32, resulted in desilylation but no cyclization occurred.

A palladium catalyzed tandem cyclization-anion capture process\textsuperscript{69} was also attempted for the cyclization. However, treatment of compound 29 (Scheme 12) with palladium(II) acetate, triphenylphosphine, sodium formate, and tetraethylammonium chloride in acetonitrile failed to give any product. This may be explained by catalyst poisoning caused by the sulfur. Recently, 3,3-dimethyl-2,3-dihydrobenzo[\textit{b}]thiophene was prepared by Crich\textsuperscript{47f} via an intramolecular homolytic substitution at sulfur and by Hillhouse\textsuperscript{70} via thiametallacycles. However, similar methods were not investigated for the preparation of compound 30.

\textbf{2.2.2 Towards selenium and tellurium analogues of vitamin E\textsuperscript{II}}

\textit{Introduction}

For the preparation of 3,3,4,6,7-pentamethyl-2,3-dihydrobenzo[b]selenophene-5-ol (21b), it was decided to try a radical cyclization approach analogous to the method described for the synthesis of the sulfur analogue 30. The first simplified target molecule was the selenide 44. Its attempted preparation is outlined in Scheme 17. Treatment of compound 24 with tert-butyl lithium, elemental selenium followed by addition of iodoethane in a one-pot procedure, gave the desired selenide 43 in a 76 % isolated yield. However, bromination using bromine in dichloromethane, chloroform, pentane or toluene at ambient temperature or reflux did not result in any formation of compound 44. Instead, formation of diorganyl selenium dibromide or organyl selenium tribromide products was observed. A different approach was therefore considered.

Except for the intramolecular homolytic substitution at selenium and tellurium, there are few ways described in the literature to construct the skeletons of 2,3-dihydrobenzo[b]selenophenes and tellurophenes and their respective 3,3-dimethyl analogues. In order to be able to study a series of simple chalcogen analogues of vitamin E, it was decided to try to construct the series 2,3-dihydrobenzo[b]furan-5-ol and its 1-thio, 1-seleno and 1-telluro analogues (45a-d) using intramolecular homolytic substitution at the chalcogen.

---

81 For some examples, see (a) Renson, M. *Chem. Scr.* **1975**, *8A*, 29. (b) Hanold, N.; Meier, H. *Chem. Ber.* **1985**, *118*, 198. (c) Ref. 70.
Schiesser and co-workers have recently paid considerable attention to intramolecular homolytic substitution at selenium for the preparation of a wide variety of selenium-containing heterocycles.\textsuperscript{48} Recently, the synthesis of benzo[\textit{b}]selenophenes via intramolecular homolytic substitution at selenium followed by aromatization was reported.\textsuperscript{48b,d} It was shown that the combination of an iodide radical precursor and a benzyl leaving group was ideal for ring closure using standard radical techniques (a “metal hydride” and AIBN in refluxing benzene). For example, the iodide \textit{46a} afforded an excellent yield of benzo[\textit{b}]selenophene \textit{47} upon treatment with tris(trimethylsilyl)silane under standard radical conditions, whereas the bromide \textit{46b} gave mainly the selenosilane \textit{48} under identical conditions (Scheme 18).

\begin{center}
\includegraphics[width=\textwidth]{image.png}
\end{center}

These observations are in accord with experimental studies,\textsuperscript{72} as well as \textit{ab initio} calculations,\textsuperscript{46} suggesting that the rate of homolytic substitution at halogen and chalcogen in a given row in the periodic table are very similar and it increases as one traverses the groups of halogen/chalcogen. However, both rate constants and computational data suggest that iodide precursors of type \textit{49} may only be expected to give about 50 \% of the cyclized and aromatized telluride \textit{50} together with the same quantity of the undesired tellurosilane \textit{51}.

Serendipity in action

Initially, it was decided to prepare 3-methyl benzo[b]tellurophene (55) in an analogous way to that used for benzo[b]selenophenes.\textsuperscript{48b,d} The aim was to prepare telluride 52 by treatment of epoxide 53\textsuperscript{48d} with a suitable ditelluride under reductive conditions. Initially, the di-\textit{n}-butyl ditelluride was tried because it is readily prepared from \textit{n}-butyllithium and elemental tellurium.\textsuperscript{73} In addition, the \textit{n}-butyl radical is a poorer leaving radical than the benzyl radical. This may direct the attack of the silyl radical on iodine rather than on tellurium. Accordingly, the oxirane 53\textsuperscript{48d} was reacted with 2 equivalents of sodium \textit{n}-butyltellurolate in THF/methanol (Scheme 20).\textsuperscript{74} To our surprise, none of the desired telluride 52 was formed. Instead the major product was the cyclized telluride 54, which was isolated in a 62 % yield. In the presence of a catalytic amount \textit{p}-toluenesulfonic acid, compound 54 could then be readily dehydrated to give the tellurophene 55.\textsuperscript{75}

The mechanism for the cyclization is probably an alkyltelluride-mediated S_\text{RN1}/S_\text{Hi} tandem reaction according to Scheme 21.\textsuperscript{49} It is believed that the telluride 52 is rapidly formed by nucleophilic substitution. This is then one-electron reduced via a

\textsuperscript{73}Cava, M. P.; Engman, L. Synth. Commun. 1982, 12, 163.
butyltelluride-mediated $S_{RN1}$ mechanism\textsuperscript{76} to give the aryl radical 56 after loss of iodide. The aryl radical can then undergo an intramolecular homolytic substitution at tellurium to form the desired cyclized telluride 54 and an $n$-butyl radical. The radical chain can then propagate with the $n$-dibutyl telluride radical anion serving as the chain-transfer agent. This reaction represents, to the best of our knowledge, the first example of an intramolecular homolytic substitution at tellurium. Interestingly, addition of more than 2 equivalents of the tellurolate gave no improvement in yield, whereas 1 equivalent resulted in a lower yield of compound 54. These observations are in accord with the mechanism proposed in Scheme 21, as 2 equivalents of $n$-butyltellurolate is required to generate 1 equivalent of compound 54 together with 1 equivalent of di-$n$-butyl telluride.

**Scheme 21.** Proposed mechanism for the formation of the cyclized telluride 54 via an alkyl-telluride mediated $S_{RN1}/S_{Hi}$ reaction.

In order to prove the involvement of aryl radicals, other iodides were examined (Scheme 22). Treatment of the selenium-containing iodide $^{57}$ with 1 equivalent of $n$-butyltellurolate in THF/MeOH for 24 h gave the cyclized selenide $^{58}$ in a 74 % isolated yield. However, the reaction of the iodide $^{59}$ was much slower under these conditions and was found to be only 50 % complete after 24 h. Due to the instability of the telluride $^{60}$ it could only be isolated in a yield of 17 % after flash chromatography. Crich and co-workers recently reported similar stability problems with some structurally related tellurides. $^{78}$ Notably, Beckwith and Palacios have reported similar intramolecular homolytic addition chemistry using PhS$^-$ and Ph$_2$P$^-$. $^{79}$ Similar chemistry using alkyne $^{61}$ gave a mixture of compounds, where the product $^{62}$ was observable by $^1$H NMR spectroscopy. However, its lability precluded its isolation and characterization. The formation of cyclized products in these reactions leaves no doubt about the involvement of aryl radicals. In addition, rate data provided further evidence for a radical pathway for the chemistry described (vide infra).

![Scheme 22](image)

Scheme 22. (a) di-$n$-butyl ditelluride, NaBH$_4$, THF and MeOH.

**The substituent on the tellurolate**

After having established that $n$-butyltellurolate can be used for the preparation of seleno- and tellurophenes, it was of interest to study the role of the alkyl group on

---

tellurium. Would the alkyl group play an important role in the overall transformation by changing the electron transfer properties of the tellurolate and the ease in which the aryl radical undergoes homolytic substitution? In order to answer these questions, the effect of other tellurolates was also investigated. Thus, the oxirane 53 was reacted with both s- and t-butyldellurolate. Whereas the s-butyldellurolate was prepared in the same manner as n-butyldellurolate, t-butyldellurolate was generated in situ from t-butyllithium and elemental tellurium. In order to exclude the involvement of borohydride in the chemistry described, n-butyldellurolate was also prepared analogously to t-butyldellurolate. Reactions involving s- and t-butyldellurolate appeared to proceed less cleanly than the reaction involving n-butyldellurolate (38 and 43 % yields, respectively for compound 54). The reaction with lithium n-butyldellurolate gave 50 % yield of the desired compound 54. Accordingly, the method of tellurolate generation does not seem to be a critical factor. It is concluded from these experiments that borohydride probably does not play an important role in the SRN1 process and that alkyl substitution has no significant effect either on the electron transfer properties of the tellurolate or the intramolecular homolytic substitution chemistry at tellurium.

Phenyltellurolate generated from both ditelluride by sodium borohydride and in situ from phenyllithium and elemental tellurium, afforded only starting material and diphenyl ditelluride. It is possible that the substrate undergoes rapid electron transfer from PhTe-, and the resulting phenyltellanyl radical then undergoes rapid recombination to afford diphenyl ditelluride.

Other tellurophenes

Having investigated the role of the substituent on the tellurolate, it was of similar interest to see if the substituent on the oxirane plays any significant role in the chemistry described. It was decided to try to synthesize benzo[b]tellurophene (66) and 3-phenyl benzo[b]tellurophene (67). When oxirane 63a, which is unsubstituted on the oxirane moiety, was treated with n-butyldellurolate, an inseparable mixture of the uncyclized alcohol 64 and the desired cyclized telluride 65 were obtained in a 1:1 ratio (Scheme 23). The mixture was then treated with p-toluenesulfonic acid in refluxing benzene to obtain the tellurophene 66 free from the alcohol 64 after flash chromatography. A probable explanation for the formation of the alcohol 64 would be
an attack by the tellurolate at the benzylic position followed by a reduction by the borohydride. This has previously been observed in the analogous selenium chemistry.\textsuperscript{48d} When compound 63b, with a phenyl group in the oxirane moiety, was treated with \textit{n}-butyltellurolate, none of the expected cyclized telluride 67 was observed. Instead, the aldehyde 68 was isolated in a 45\% yield. This compound is probably formed via a 1,2-hydride shift as depicted in Scheme 23. This can be explained by the lability of the oxirane, which has been shown to rearrange quantitatively to aldehyde 68 upon prolonged storage at ambient temperature.

\begin{equation}
\frac{d[54]}{d[70]} = \frac{k_C}{(k_H [THF])} \tag{4}
\end{equation}

\begin{equation}
\frac{[54]}{[70]} = \frac{k_C}{(k_H [THF])} \tag{5}
\end{equation}

\textit{Rate constant for intramolecular homolytic substitution at tellurium}

In addition to the cyclized telluride 54, a small amount of the reduced compound 70 was also isolated in a 7\% yield in the reaction of oxirane 53 with \textit{n}-butyltellurolate (Scheme 24). The product distribution can be used to estimate, for the first time, the rate of intramolecular homolytic substitution at tellurium. The integrated rate expression, equation 4,\textsuperscript{48d} which integrates to equation 5 under pseudo first order conditions in THF can be used.
If one assumes that the concentration of THF is 12 M,\textsuperscript{80} that $[54] / [70] = 57/7 = 8.14$ and that the rate constant for hydrogen abstraction of the aryl radical from THF ($k_H$) is $5.1 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$ at 25 °C,\textsuperscript{81} the rate constant for cyclization of $69$ ($k_C$) is estimated to be approximately $5 \times 10^8 \text{ s}^{-1}$ at 25 °C.

\[
\begin{align*}
&\text{TeOHR} \\
&\begin{array}{c}
\text{O} \\
\text{H}
\end{array}
\end{align*}
\]

\[
\begin{align*}
&\text{R} \\
&\begin{array}{c}
\text{OH} \\
\text{Te}
\end{array}
\end{align*}
\]

\[
\begin{align*}
&\text{TeOHR} \\
&\begin{array}{c}
\text{H} \\
\text{Te}
\end{array}
\end{align*}
\]

\[
\begin{align*}
&\text{R} \\
&\begin{array}{c}
\text{OH} \\
\text{Te}
\end{array}
\end{align*}
\]

This value can be compared with that of intramolecular homolytic substitution at selenium in selenide $71$ (expulsion of a benzyl radical), which has been estimated to be approximately $3 \times 10^7 \text{ s}^{-1}$ at 80 °C.\textsuperscript{48d} The larger rate constant of the telluride was expected on the basis of the trends observed in the rate constants for intermolecular homolytic substitution at selenium and tellurium and the relative leaving group abilities.\textsuperscript{46}

\[
\begin{align*}
&\text{SeCH}_2\text{Ph} \\
&\begin{array}{c}
\text{H} \\
\text{Se}
\end{array}
\end{align*}
\]

\textit{Synthesis of 2,3-dihydrobenzo[b]selenophene-5-ol and its 1-telluro analogue}

Having demonstrated that the alkyltelluride mediated $\text{SRN}_1/\text{SHi}$ tandem reaction can be used for the preparations of selenophenes and tellurophenes, this methodology was further employed in the synthesis of the selenium and tellurium-containing vitamin E analogues 2,3-dihydrobenzo[b]selenophene-5-ol (45c) and 2,3-dihydrobenzo[b]tellurophene-5-ol (45d). The compounds were prepared in several steps starting from the commercially available 3-hydroxyphenylacetic acid (72), as outlined

\textsuperscript{80} The concentration of THF is approximately 12 M based on a density of 0.886 (25 °C).  
in Scheme 25 and 26. After esterification of the starting material,\textsuperscript{82} the phenol was protected as a TBDMS ether 73 in good yield. Reduction of this material with lithium aluminium hydride afforded the primary alcohol 74 in excellent yield. Aromatic iodination with iodine and silver trifluoroacetate gave, regioselectively, the iodide 75 in almost quantitative yield. The alcohol function was further converted, via the mesylate, to afford the key intermediate tert-butylmethyisilyl 4-iodo-3-(2-iodoethyl)phenyl ether (76) in good yield. Treatment of the diiodide 76 with NaBH$_4$/Bn$_2$Se$_2$\textsuperscript{83} afforded the benzyl selenide 77 in an isolated yield of 84 %. The alkyltelluride mediated $S_{RN1}/S_{th}$ reaction described above could then be used to induce ring closure. Thus, treatment of the benzyl selenide with one equivalent of $n$-butyltellurolate (NaBH$_4$/di-$n$-butyl ditelluride\textsuperscript{73}) afforded the cyclized selenide 78 in a 65 % isolated yield.

\begin{align*}
\text{HO} & \quad \text{CO}_2\text{H} \\
\text{72} & \quad \xrightarrow{\text{a,b}} \quad \text{TBDMSO} \quad \text{CO}_2\text{Et} \\
& \quad \xrightarrow{\text{c}} \quad \text{TBDMSO} \quad \text{OH} \\
& \quad \xrightarrow{\text{d}} \quad \text{TBDMSO} \quad \text{OH} \\
& \quad \xrightarrow{\text{e,f}} \quad \text{TBDMSO} \quad \text{I} \\
& \quad \xrightarrow{\text{g}} \quad \text{TBDMSO} \quad \text{SeCH}_2\text{Ph} \\
& \quad \xrightarrow{\text{h or i}} \quad \text{TBDMSO} \quad \text{Se} \\
& \quad \xrightarrow{\text{j}} \quad \text{HO} \quad \text{Se} \\
\text{Scheme 25.} \quad (\text{a}) \text{EtOH, H}_2\text{SO}_4, \text{reflux, 94 \%.} \quad (\text{b}) \text{TBDMSCl, imidazole, DMF, 20 °C, 98 \%.} \quad (\text{c}) \text{LiAlH}_4, \text{Et}_2\text{O, 0 °C, 96 \%.} \quad (\text{d}) \text{I}_2, \text{CF}_3\text{CO}_2\text{Ag, 20 °C, 96 \%.} \quad (\text{e}) \text{MsCl, Et}_3\text{N, CH}_2\text{Cl}_2, 0 °\text{C, quantitative.} \quad (\text{f}) \text{NaI, acetone, reflux, 88 \%.} \quad (\text{g}) \text{Bn}_2\text{Se}_2, \text{NaBH}_4, \text{EtOH, 20 °C, 84 \%.} \quad (\text{h}) \text{n-Bu}_3\text{Te}_2, \text{NaBH}_4, \text{THF, MeOH, 20 °C, 65 \%.} \quad (\text{i}) \text{TTMSS, AIBN, benzene, reflux, 48 \%.} \quad (\text{j}) \text{TBAF, THF, 20 °C, 95 \%.}
\end{align*}

In a similar way, treatment of the diiodide 76 with two equivalents of $n$-butyltellurolate afforded the desired cyclized telluride 79 in an isolated yield of 47 % (Scheme 26). The cyclized selenide 78 could also be obtained from iodide 77 by silane mediated intramolecular homolytic substitution, but in a somewhat lower yield

\textsuperscript{82} Guanti, G.; Banfi, L.; Riva, R. \textit{Tetrahedron} \textbf{1994}, \textit{50}, 11945.
Finally, the cyclized selenide and telluride were deprotected with TBAF to obtain the desired products 45c and 45d in isolated yields of 95 % and 65 %, respectively.

![Scheme 26](image)

**Scheme 26.** (a) n-Bu₂Te₂, NaBH₄, THF, MeOH, 20 °C, 47 %. (b) TBAF, THF, 20 °C, 65 %.

### 2.2.3. Synthesis of 2,3-dihydrobenzo[b]furan-5-ol and its 1-thio analogue

In order to study the antioxidant properties of the series of unmethylated chalcogen compounds 45a-d, the oxygen and sulfur derivatives 2,3-dihydrobenzo[b]furan-5-ol (45a) and 2,3-dihydrobenzo[b]thiophene-5-ol (45b) were prepared. The oxygen analogue was synthesized according to a literature procedure. The sulfur analogue has been previously prepared, but an alternative procedure involving intramolecular homolytic substitution at sulfur has been developed (Scheme 27). The ester 73 was treated with bromine in acetic acid to obtain aryl bromide 80 in a high yield. The ester group was then reduced with lithium aluminium hydride, and the resulting alcohol 81 was treated with diphenyl disulfide and tri-n-butylphosphine in benzene to obtain sulfide 82 in a 76 % isolated yield. The sulfide together with tri-n-butyltin hydride and AIBN in refluxing benzene afforded the cyclized sulfide 83, via intramolecular homolytic substitution at sulfur. Due to an inseparable impurity, the sulfide 83 was deprotected with TBAF without isolation to give the desired product 45b in an isolated yield of 62 % from compound 82.

---

84 Alabaster, R. J.; Cottrell, I. F.; Marley, H.; Wright, S. H. B. *Synthesis* 1988, 950.
2.3 The antioxidant profile of 2,3-Dihydrobenzo[b]furan-5-ol and its 1-thio, 1-seleno and 1-telluro analogues{sup}III{sup}

2.3.1 Introduction
Prevention of autoxidation is an important task for antioxidants. Efficient phenolic antioxidants should have either a weaker O-H bond than the C-H bond in the material where oxidation should be prevented and/or the peroxyl radicals formed in the propagation step must easily oxidize the antioxidants. Thus, the redox and thermochemical properties of antioxidants are in crucial need of investigation. Therefore, we have determined the bond dissociation enthalpies, the redox properties and the hydrogen transfer capabilities for the series of antioxidants 45a-d. The capability of the compounds to inhibit stimulated lipid peroxidation, to catalyze decomposition of hydrogen peroxide in the presence of glutathione and their inhibiting effect on peroxidation in liver microsomes were also investigated.

2.3.2 Redox and thermochemical properties
Pulse radiolysis is a powerful technique for the determination of one-electron reduction potentials.86 This is the only method available for the measurement of thermodynamically correct potentials of solvated radicals. The technique is based on the formation of the radicals e_{aq}^{-}, H·, and HO· by radiolysis of water. These radicals can in turn be transformed into well defined reducing or oxidizing radicals via the use of suitable scavengers, such as N$_3$^{-}.
In order to determine the one-electron reduction potentials of the phenoxyl radicals, corresponding to phenols \textbf{45a-d}, primary oxidation of the phenolates \( \text{ArO}^- \) was achieved by azide radicals (\( \text{N}_3^\cdot \)). The azide radical \( \text{N}_3^\cdot \) was produced in the pulse radiolysis experiment by the reaction of \( \text{HO}^\cdot \) with \( \text{N}_3^- \). The reduction potential could then be determined from the redox equilibrium between the radical of interest and a redox couple with a known one-electron reduction potential (equation 6), using the Nernst equation (\( \Delta E^0 = 0.0591 \log K \) at 298 K).

\[
\text{ArO}^\cdot + \text{Ref} \rightleftharpoons \text{ArO}^- + \text{Ref}^{\text{**}} \quad (6)
\]

Having determined the \( pK_a \) values of the phenols spectrophotometrically, the O-H bond dissociation enthalpies in solution could then be calculated from equation 7, which is derived from Hess’ law.\(^{87,88}\) The results are summarized in Table 1.

\[
\text{BDE(O-H)} = 96.48 E^0 + 5.70 pK_a + C \quad (7)
\]

From these data one can see that the \( pK_a \) values as well as the reduction potentials do not differ dramatically within the series of compounds \( \textbf{45a-d} \). Consequently, the bond dissociation enthalpies are similar for all four compounds (336-340 kJmol\(^{-1}\)). These values are significantly higher than the value reported for \( \alpha \)-tocopherol (323 kJmol\(^{-1}\)).\(^{89}\)

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
 Compound & \( pK_a \) & \( \lambda_{\text{max}} \text{ ArO}^- \) & Reference substance & \( K_\text{E} \) & \( E^0 \) (ArO\(^\cdot\) / ArO\(^-\)) & BDE O-H (kJ mol\(^{-1}\)) \\
\hline
\textbf{45a} & 10.6 & 450 & \textbf{45b} & 1 & 0.49 & 340 \\
\textbf{45b} & 10.0 & 560 & 4-MeOC\(_6\)H\(_4\)OH & 7.86 & 0.49 & 337 \\
\textbf{45c} & 9.9 & 630 & \textbf{45a} & 1 & 0.49 & 336 \\
\textbf{45d} & 9.5 & 800 & 4-MeOC\(_6\)H\(_4\)OH & 2.53 & 0.52 & 337 \\
\hline
\end{tabular}
\caption{Acidity and redox properties of compounds 45 in aqueous solution}
\end{table}

Cyclic voltammetry is a versatile method for studying simple redox processes.\(^86\) The cyclovoltammetric oxidation potentials for compounds \textbf{45a-d} are given in Table 2.

---


The oxidation potential for the oxygen analogue (1.35 V vs NHE) is irreversible whereas it is quasireversible for the sulfur analogue (1.35 V vs NHE). For the selenide and telluride derivatives the oxidation potentials are fully reversible (1.13 and 0.74 V vs NHE, respectively), indicating the formation of stable radical cations in these cases.

<table>
<thead>
<tr>
<th>Compound</th>
<th>E (V vs Fc)</th>
<th>E (V vs NHE)</th>
<th>Solvent</th>
</tr>
</thead>
<tbody>
<tr>
<td>45a</td>
<td>0.66</td>
<td>1.35</td>
<td>MeCN</td>
</tr>
<tr>
<td>45b</td>
<td>0.66</td>
<td>1.35</td>
<td>MeCN</td>
</tr>
<tr>
<td>45c</td>
<td>0.44</td>
<td>1.13</td>
<td>MeCN</td>
</tr>
<tr>
<td>45d</td>
<td>0.05</td>
<td>0.74</td>
<td>MeCN</td>
</tr>
</tbody>
</table>

2.3.3 Reactivity towards tert-butoxyl radicals

It is known that tert-butoxyl radicals rapidly abstract phenolic hydrogen atoms in comparison with decomposition by β-scission. This can be used for studying the hydrogen donating ability of antioxidants. As demonstrated by Ingold and co-workers, such rapid processes are conveniently studied by laser flash photolysis. Photodecomposition of di-tert-butyl peroxide by 355-nm laser pulses gives rise to tert-butoxyl radicals within the duration of the pulse. These radicals will rapidly react with the antioxidants to generate phenoxy radicals, which can be directly monitored by UV-spectroscopy. The build-up of the signal follows pseudo-first order kinetics (equation 8) where \( k_{\text{obs}} \) is the observed rate constant and \( k \) is the absolute rate constant for the reaction of the tert-butoxyl radical with the phenolic compound (equation 9).

\[
\text{Me}_3\text{CO}^- + \text{ArOH} \quad \xrightarrow{k} \quad \text{Me}_3\text{COH}^- + \text{ArO}^-
\]

\[ k_{\text{obs}} = k_0 + k[\text{ArOH}] \quad (8) \]

The pseudo first order rate constant \( k_{\text{obs}} \) was determined from the build-up curves of the respective phenoxy radicals at their \( \lambda_{\text{max}} \) values (Table 1). The absolute rate constant \( k \) was then calculated by a least-square fitting of \( k_{\text{obs}} \) versus [ArOH] for five different concentrations. The rate constant values for the oxygen 45a and sulfur 45b...
analogues were both determined to be $2 \times 10^8$ M$^{-1}$s$^{-1}$. For the selenium and tellurium analogues, the corresponding rate constants could not be determined due to laser photo-excitation of the compounds. The rate constant for sulfide 21a was determined to be $4 \times 10^8$ M$^{-1}$s$^{-1}$. As compared with the unmethylated sulfide 45b, the better hydrogen donating ability of sulfide 21a is due to the more efficient stabilization of the phenoxyl radical by the electron releasing substituents on the aromatic ring. For comparison, the rate constant for $\alpha$-tocopherol was determined to be $6 \times 10^8$ M$^{-1}$s$^{-1}$, indicating that $\alpha$-tocopherol is a somewhat better hydrogen donor compared to compounds 45a, 45b, and 21a. With the limited rate data at hand, it seems that the reactivity of the tert-butoxyl radicals with the series of compounds 45 is reflected by the phenolic O-H bond dissociation enthalpies given in Table 1.

### 2.3.4 Inhibition of lipid peroxidation

Lipid peroxidation is a detrimental process, since it causes damage to lipids in biological membranes. The prevention of lipid peroxidation is therefore an important task for antioxidants. It has earlier been demonstrated that some organotellurium compounds retard lipid peroxidation.$^{21b-d}$ In order to study the ability to inhibit lipid peroxidation, azo-initiated peroxidation of linoleic acid or derivatives thereof have been used.$^{92}$ Recently a two-phase system for the assessment of antioxidant capacity was reported (Figure 4a).$^{21d}$ The aqueous phase contains N-acetylcysteine (NAC) as the stoichiometric reductant, which could regenerate any of the tellurium (IV) compounds (Scheme 8) or selenium (IV) compounds formed. The organic phase (chlorobenzene) contains linoleic acid, a radical initiator (AMVN) and the antioxidant to be studied.

In the figure, the time (h) and the concentration of LOOH (M) are plotted against each other. The concentration of LOOH increases with time, indicating the progress of lipid peroxidation. The antioxidant to be studied can effectively inhibit the peroxidation, as evidenced by the lower concentration of LOOH compared to the control without the antioxidant.

![Graph showing inhibition of lipid peroxidation](image)
The lipid peroxidation was initiated by the addition of the radical initiator and the solution was stirred vigorously at 42 °C. During the peroxidation, linoleic acid is converted to a conjugated lipid hydroperoxide, which can be monitored by HPLC with UV detection at 234 nm. A typical concentration-time plot for α-tocopherol is depicted in Figure 4b. Two parameters can be determined from the trace: the inhibited rate of peroxidation (R\textsubscript{inh}) and the inhibition time (T\textsubscript{inh}). The inhibited rate, R\textsubscript{inh}, is a measure of antioxidant efficiency, which is determined by least-square methods from the curve during the inhibited phase of peroxidation. The inhibition time, T\textsubscript{inh}, is a measure of the antioxidant’s lifetime and is determined graphically as the cross-point for the inhibited and uninhibited lines.

Values of R\textsubscript{inh} and T\textsubscript{inh} for compounds 45a-d are shown in Table 3 together with those recorded for α-tocopherol, sulfide 21a and telluride 20. For comparison, the values were also determined in the absence of a reducing agent.

It is clear from the inhibited rates of peroxidation that α-tocopherol is more efficient than any of the analogues tested, both in the presence and in the absence of N-acetylcysteine. In the absence of N-acetylcysteine the tellurides 45d and 20 do not inhibit peroxidation at all and the selenide 45c does so poorly. The tellurides 45d and 20 are probably oxidized immediately by the residual hydroperoxide contained in the linoleic acid, and thus inactivated. The oxygen and sulfur analogues 45a and 45b, have a longer induction time than α-tocopherol, but they are less efficient as antioxidants. When a reductant is present in the aqueous phase, the antioxidant efficiency increases in the series of compounds 45a-d as one traverse the periodic
The short inhibition time of telluride 45d can probably be explained by the decomposition of the telluride (or its corresponding telluroxide), since increasing the amount of thiol in the aqueous phase could not prolong the inhibition time. In the presence of NAC, all the inhibition times are increased, except for α-tocopherol and the sulfide 21a. This seems to indicate that the thiol is capable not only of regenerating selenides and tellurides from their oxides, but also some of the phenols at the aqueous lipid interphase. The latter process is apparently much less efficient for sterically hindered phenols. However, the presence of methyl groups in the sulfide 21a significantly increases antioxidant efficiency as compared with the unmethylated sulfide 45b. This was also reflected in their rate constants for hydrogen atom donation to tert-butoxyl radicals (vide supra).

In summary, it was demonstrated that the selenide 45b and the tellurides 45d and 20 could be regenerated in the presence of a stoichiometric reductant and thereby been able to act as catalytic antioxidants.

Table 3. Inhibited rate of peroxidation, \( R_{inh} \), and time of inhibition, \( T_{inh} \), for antioxidants tested in the presence and absence of N-acetylcysteine (NAC)

<table>
<thead>
<tr>
<th>Antioxidant</th>
<th>( R_{inh} ) and ( T_{inh} ) in the presence of NAC</th>
<th>( R_{inh} ) and ( T_{inh} ) in the absence of NAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( R_{inh} ) (( \mu M/h ))(^a)</td>
<td>( T_{inh} ) (min)(^b)</td>
</tr>
<tr>
<td>45a</td>
<td>44</td>
<td>140</td>
</tr>
<tr>
<td>45b</td>
<td>36</td>
<td>180</td>
</tr>
<tr>
<td>45c</td>
<td>36</td>
<td>&gt;300</td>
</tr>
<tr>
<td>45d</td>
<td>17</td>
<td>60</td>
</tr>
<tr>
<td>α-Tocopherol</td>
<td>11</td>
<td>90</td>
</tr>
<tr>
<td>Sulfide 21a</td>
<td>21</td>
<td>70</td>
</tr>
<tr>
<td>Telluride 20</td>
<td>34</td>
<td>160</td>
</tr>
</tbody>
</table>

\(^a\) Rate of peroxidation during the inhibited phase (uninhibited rate ~370 \( \mu M/h \)).

\(^b\) Duration of the inhibited phase of peroxidation.

The chain-breaking properties of phenolic aryl alkyl tellurides can be ascribed to their ability to reduce peroxyl radicals. In doing so, the diorganyl telluride will be oxidized to a tellurium (IV) dihydroxide. As illustrated in Scheme 28 for the telluride 45d several mechanisms must be considered for this transformation. Phenolic diorganyl tellurides can donate a hydrogen atom to form a resonance-stabilized phenoxy radical. Alternatively, there could also be an electron transfer from tellurium to give a radical cation. The formation of this species will result in an increase in the acidity of the phenolic hydrogen, which will readily be lost to give the resonance stabilized...
phenoxyl radical. Oxidation and hydrolysis of the resulting phenoxyl radical then affords the thiol reducible tellurium (IV) dihydroxide 84. Considering the observed reversible oxidation of the telluride 45d at 0.74 V vs NHE (vide supra), the chain-breaking mechanism probably involves an electron transfer from tellurium. Similar mechanisms are likely to be operative for the selenide 45c as well. A conclusion regarding the true chain-breaking mechanism has to await further mechanistic investigations.

\[
\text{Te}^\text{II} \underset{\text{Te}^\text{IV}}{\xrightarrow{\text{O} \cdot \text{H}^\text{+}}} \text{Te}^\text{II} \quad \text{(oxidation)}
\]

\[
\text{Te}^\text{II} + \text{H}_2\text{O} \underset{\text{Te}^\text{IV}}{\xrightarrow{\text{O} \cdot \text{H}^\text{+}}} \text{Te}^\text{II} \quad \text{(hydrolysis)}
\]

**Scheme 28.** Proposed chain-breaking mechanisms for telluride 45d.

### 2.3.5 Hydroperoxide decomposing capacity

In biological systems the selenium-containing glutathione peroxidases (GSH-px) catalyze’s the reduction of various hydroperoxides by reduced glutathione (eqn 10). The catalytic cycle relies on the redox cycling of selenium. Recently, much attention has been paid to the development of compounds that mimic the action of GSH-px. The selenium-containing heterocycle Ebselen (85) was the first compound found to exhibit this property.\(^{93}\)

\[
\begin{array}{c}
\text{Se} \quad \text{O} \\
\text{Ebselen (85)}
\end{array}
\]

In addition to Ebselen, a wide variety of selenium-containing compounds have been found to catalyze the reduction of hydroperoxides in the presence of thiols.\(^{93}\) It has been demonstrated that diorganyl tellurides and ditellurides are also glutathione

---

peroxidase mimics.\textsuperscript{21c-d,f} The catalytic mechanism for diaryl tellurides\textsuperscript{21d} and other organotelluriums\textsuperscript{94} rely on redox cycling at tellurium (Scheme 8).

The thiol peroxidase activity for the series of unmethylated vitamin E analogues 45a-d was assessed using a coupled reductase assay (equations 10 and 11).\textsuperscript{21a}

\[
\begin{align*}
2 \text{GSH} & + \text{ROOH} \quad \text{GSH-px or mimic} \quad \rightarrow \quad \text{GSSG} & + \text{ROH} & + \text{H}_2\text{O} \\
\text{GSSG} & \quad \text{GSSG-reductase} & \rightarrow & 2 \text{GSH}
\end{align*}
\] (10) (11)

In this assay, hydroperoxide, glutathione and the antioxidant to be evaluated are allowed to react at pH 7.4 in the presence of glutathione reductase and NADPH. When the glutathione has been oxidized to the corresponding disulfide, it will be enzymatically reduced by GSSG-reductase with NADPH acting as a co-factor and stoichiometric reductant. The reaction was followed spectrophotometrically by observing the consumption of NADPH at 340 nm and the catalytic activity was determined by recording the initial rate increase in comparison with the uncatalyzed process. The results are shown in Table 4. As expected, the oxygen and sulfur analogues 45a-b showed essentially no catalytic activity. The selenide 45c also did not show any catalytic activity, whereas the telluride 45d was a highly active catalyst. When hydrogen peroxide was used as the oxidant, NADPH was consumed almost 100 times faster than in the control experiment. To show that the telluride 45d acts in a catalytic fashion under the conditions used, additional NADPH, H\textsubscript{2}O\textsubscript{2} and glutathione were added to the incubation mixture and the consumption of NADPH was recorded again. After five repeated additions, no significant change in catalytic efficiency was observed. When tert-butyl hydroperoxide and cumene hydroperoxide were used as oxidants, the reaction was accelerated even more (333 and 213 times, respectively, as compared to the uncatalyzed reaction). This makes the telluride 45d one of the most efficient glutathione peroxidase mimics described.

### Table 4. Glutathione peroxidase-like activity of compounds 45a-d with various hydroperoxide substrates

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Hydroperoxide</th>
<th>NADPH consumption\textsuperscript{a} ((\mu\text{M/min}))</th>
<th>% Catalysis\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>H\textsubscript{2}O\textsubscript{2}</td>
<td>6.3±0.1</td>
<td>-</td>
</tr>
</tbody>
</table>

### 2.3.6 Lipid peroxidation in liver microsomes

Lipid peroxidation is accelerated in the presence of Fe(II) and Fe(III) salts and a reducing agent such as ascorbate. Thus, microsomal fractions prepared from animal tissues undergo lipid peroxidation in the presence of these substances. The metal dependent decomposition of lipid hydroperoxides results in the formation of carbonyl-containing products, some of which can react with thiobarbituric acid to give thiobarbituric reactive substances (TBARS) that can easily be quantified by UV-spectroscopy at 532 nm. By measuring the amount of TBARS formed, one can determine how efficient the antioxidants are to inhibit stimulated lipid peroxidation. This is expressed as the IC$_{50}$ value, which is the concentration that inhibits 50 % of the TBARS formation in the control experiment.

It has previously been demonstrated that diaryl tellurides retard lipid peroxidation in liver microsomes. The oxygen, sulfur and selenium compounds $45\text{a-c}$ showed only weak inhibiting activity (IC$_{50}$-values of ca 250, 25, 13 µM, respectively), whereas the organotellurium compound $45\text{d}$ was a potent inhibitor of lipid peroxidation in liver microsomes (IC$_{50}$-value of 0.13 µM). The outstanding performance of the telluride indicates that peroxide-decomposing capacity may be more important than the chain-breaking ability to inhibit lipid peroxidation in microsomes under the conditions used.


Ascorbate may also serve to amplify the protective effect by continuously regenerating the organotellurium compound from its corresponding oxidation products.

2.4 Towards a selenium-containing tocopherol

2.4.1 Introduction

Although Ingold showed that 1-thio-α-tocopherol (16e) and the related 6-hydroxythiochromanes are slightly less efficient antioxidants than their corresponding oxygen analogues, we believe that a selenium or tellurium containing α-tocopherol would show very interesting antioxidative properties as a consequence of their ability to undergo redox cycling. Initially, it was decided to develop a procedure for the synthesis of the selenium-containing tocopherol analogue 2-methyl-2-(4,8,12-trimethyltridecyl)-selenochroman-6-ol (86).

![Molecule 86]

2.4.2 Strategy

The crucial step in the preparation of compound 86 is the construction of the selenium-containing six-membered ring with a quaternary carbon next to selenium. A good way to do this is probably via an intramolecular homolytic substitution at the heteroatom. In order to investigate this methodology, we decided to use a method for radical generation developed by Barton, Crich, and co-workers in combination with intramolecular homolytic substitution at selenium (Figure 5). Tertiary radicals can be generated from tertiary alcohols by the use of PTOC oxalates (87) in the following way. Treatment of a tertiary alcohol with excess oxalyl chloride in benzene would convert the alcohol into the corresponding oxalyl monochloride alkyl ester (88). The crude material is then added to a suspension of N-hydroxypyridine-2-thione sodium salt and DMAP in benzene to obtain N-(alkoxyoxalyloxy)pyridine-2-thione (87), which readily undergoes decomposition on heating to generate a tertiary radical. It was envisaged that a free radical chain reaction would then produce the desired
selenide via an intramolecular homolytic substitution at selenium with the expulsion of a benzyl-leaving group (Figure 5, lower part).

Initiation:

\[ \text{Initiation:} \]

\[ 87 \xrightarrow{\Delta} \text{[initiator]} + 2\ CO_2 + \text{pyridyl radical} \]

Propagation:

\[ \text{Propagation:} \]

\[ \text{[propagating species]} + 2\ CO_2 + \text{pyridyl thioether} \]

\[ \text{[selenide] + \text{alkyl radical}} \]

Figure 5. Strategy for the construction of a six-membered selenium-containing heterocycle with a quaternary carbon-center \( \alpha \) to the selenium atom.

2.4.3 Synthesis of the model compound 2,2-dibutyl selenacyclohexane

To probe the versatility of the proposed strategy, the model compound 2,2-dibutyl selenacyclohexane (92) was synthesized from commercially available methyl 5-bromovalerate (89) as depicted in Scheme 29. Treatment of the bromide 89 with sodium benzylselenolate afforded the selenide 90 in high yield. The required tertiary alcohol 91 was then prepared in a 76% yield by treatment of the selenide 90 with two equivalents of \( n \)-butylmagnesium bromide. The alcohol 91 was then treated with

---

oxalyl chloride and pyridine, followed by the sodium salt of 2-mercaptopyridine N-oxide and DMAP to obtain the desired selenide 92 in a yield of 40 % from compound 91. This is, to our knowledge, the first example where a tertiary radical undergoes an intramolecular homolytic substitution at selenium to generate a selenium-containing heterocycle. Attempted intramolecular homolytic substitution using the tertiary iodide 93 under various standard radical conditions [tris(trimethylsilyl)silane and AIBN, n-Bu3SnH and AIBN, (n-BuSn)2 and hν], gave only low yields of the desired selenide 92. Elimination of hydriodic acid seems to be a severe competing reaction in these cases. The possibility of preparing the telluride 96 was also investigated. Thus, treatment of the ester 89 with n-butyltellurolate gave the telluride 94 in good yield. This compound was then treated with n-butylmagnesium bromide to afford the desired tertiary alcohol 95 in a 59 % isolated yield. However, treatment of the alcohol 95 under the Barton/Crich conditions did not result in any product formation. Thus, the methodology seems to be limited to the preparation of selenium-containing heterocycles.

Scheme 29. (a) Bn2Se2 or n-Bu2Te2, NaBH4, EtOH. (b) Mg, n-BuBr, Et2O. (c) Oxalyl chloride, pyridine, C6H6. (d) Sodium salt of 2-mercaptopyridine N-oxide, DMAP, C6H6.

2.4.4 Synthesis of a selenium-containing tocopherol analogue

The synthesis of 2-methyl-2-(4,8,12-trimethyltridecyl)-selenochroman-6-ol (86) was accomplished as outlined in Schemes 30 and 31. Bromination of the bromide 98
(obtained from alcohol 97 by a literature procedure\textsuperscript{98}) gave the dibromide 99 in high yield. Alkylation of the enolate of tert-butyl acetoacetate with this bromide gave the ester 100. Hydrolysis and decarboxylation furnished the desired ketone 101 quantitatively. The carbonyl functionality was protected as a 1,3-dioxalane (102). This material was lithiated, elemental selenium inserted and the resulting selenolate alkylated with benzyl bromide in a one-pot procedure. After workup, the crude material was subjected to deprotection with hydrochloric acid to furnish the key intermediate 2-(2-benzylselenenyl-5-methoxyphenyl)ethyl methyl ketone (103) in a 78% isolated yield from compound 102.

![Chemical structures and reactions]

**Scheme 30.** (a) PBr₃, Et₂O, 94%. (b) Br₂, CHCl₃, 97%. (c) tert-Butyl acetoacetate, NaN₃, THF, 71%. (d) HCl (6M). (e) Δ, quantitative from 100. (f) Ethylene glycol, p-TsOH, C₆H₆, 97%. (g) t-BuLi, THF. (h) Elemental Se. (i) Benzyl bromide. (j) HCl (3M), 78% from 102. (k) Mg, n-BuBr, Et₂O, 74%. (l) Oxalyl chloride, pyridine, C₆H₆. (m) Sodium salt of 2-mercaptopyridine N-oxide, DMAP, C₆H₆. (n) BBr₃, CH₂Cl₂, 28% from 104.

In order to test the methodology, an n-butyl group was first introduced as the lipophilic tail. Thus, treatment of the ketone 103 with n-butyllithium afforded the tertiary alcohol 104 in an isolated yield of 74%. The alcohol was then treated with oxalyl chloride and pyridine, followed by the sodium salt of 2-mercaptopyridine N-oxide and DMAP to obtain the desired cyclized selenide together with an inseparable impurity. The crude selenide was subjected to deprotection using

boron tribromide to furnish the desired selenochromane 105 in a 28 % isolated yield from compound 104.

Encouraged by this result, it was decided to introduce the racemic vitamin E side-chain. In order to do so, the bromide 106 was prepared in six steps from commercially available farnesol, according to literature procedures.

\[
\text{Br} \quad 106
\]

The Grignard reagent of the bromide 106 was treated with ketone 103 to afford the tertiary alcohol 107 in a 54 % isolated yield (Scheme 31). This compound was then subjected to the Barton/Crich procedure and deprotection, as described for the preparation of the selenide 105, to afford the final selenochromane 86 in a yield of 19 % from the compound 107 as a mixture of diastereomers.

\[
\begin{align*}
103 & \xrightarrow{\text{a}} \text{CH}_3\text{O} \quad \text{a} & \xrightarrow{\text{b,c,d}} \text{HO} \\
& \quad \text{SeCH}_2\text{Ph} & \quad \text{3} & \quad \text{3} \\
107 & \text{Se} & \text{HO} & \text{107} & \text{107} & \text{86}
\end{align*}
\]

Scheme 31. (a) Mg, bromide 106, Et_2O, 54 %. (b) Oxalyl chloride, pyridine, C_6H_6. (c) Sodium salt of 2-mercaptopyridine N-oxide, DMAP, C_6H_6. (d) BBr_3, CH_2Cl_2, 19 % from 107.

2.5 Conclusions and outlook

The fully methylated sulfide 21a was prepared by both ionic and radical chemistry and interesting rearrangements were observed in the two synthetic pathways. A new methodology for the synthesis of dihydroselenophene and dihydrotellurophene derivatives is described. In these reactions a tellurium-mediated tandem S_{RN1}/S_{Hi} sequence was suggested to be operative. The rate constant for intramolecular homolytic substitution at tellurium was also determined to be 5x10^8 s^{-1} at 25 °C.

A series of unmethylated antioxidants 45a-d were prepared in order to study their antioxidant capacity as a function of the chalcogen atom. The sulfur analogue 45b was

---

prepared by intramolecular homolytic substitution at sulfur. For the corresponding selenium and tellurium analogues (45c-d), intramolecular homolytic substitution via the $S_{RN1}/S_{Hi}$ mechanism was used. Pulse radiolysis experiments showed that the reduction potentials of the compounds as well as the O-H bond dissociation enthalpies were essentially independent of the chalcogen atom. In a two-phase lipid peroxidation model it was demonstrated that the selenium and tellurium containing antioxidants 45c-d could be regenerated in the presence of a stoichiometric reductant. As expected, introduction of methyl groups into the sulfur compound accelerated its hydrogen donating ability and thereby its antioxidant capacity. We also demonstrated that the tellurium-containing antioxidant 45d not only acted as a very efficient glutathione peroxidase mimic, but also as an efficient inhibitor of lipid peroxidation in liver microsomes.

A novel methodology for the synthesis of the selenium-containing vitamin E analogue 86 was also developed. The crucial step relied on formation of a tertiary radical from a PTOC oxalate in a system where intramolecular homolytic substitution could occur at selenium. Unfortunately, this methodology was limited to selenium-containing heterocycles. In the future it is hoped to develop procedures that can be used for making the corresponding tellurium analogue. It could also be worthwhile to prepare the fully methylated selenium and tellurium-containing analogues 21b-c by the $S_{RN1}/S_{Hi}$ tandem reaction developed. Provided that these materials show interesting antioxidative properties, the ultimate goal would then be to synthesize the “real” selenium and tellurium analogues of $\alpha$-tocopherol.
3. Organotellurium compounds as stabilizers for polymeric materials

3.1 Introduction

Inorganic tellurium compounds (e.g. elemental tellurium and its oxides and halides) have been shown to stabilize various polymers.\textsuperscript{100} However, organotellurium compounds have not been extensively studied for this purpose. It has previously been demonstrated that diaryl tellurides could stabilize natural rubber, polyethylene and polypropylene.\textsuperscript{20} As mentioned in Section 1.2.3, organic tellurides can act both as chain-breaking antioxidants and as peroxide decomposers. It has also been shown that diaryl tellurides act as quenchers of singlet oxygen ($\text{^1O_2}$),\textsuperscript{101} which is a contributor to the photo-oxidative degradation of various polymers.\textsuperscript{102} These results prompted us to carry out a more thorough investigation of the stabilizing effect of diaryl tellurides in polymers. Because of its thermal stability (up to 220°C) and its stabilizing effects in natural rubber at the 1-2% level,\textsuperscript{20} bis[4-(dimethylamino)phenyl] telluride (108) has been selected for these studies.

\[
\begin{array}{c}
\text{Me} \\
\text{Me} \\
\text{N} \\
\text{Me} \\
\text{Me}
\end{array}
\] 

108

The polymer chosen for this investigation was the thermoplastic elastomer PACREL\textsuperscript{®}, which is composed of a continuous polypropylene phase together with a lightly crosslinked polybutylacrylate phase.\textsuperscript{103} PACREL\textsuperscript{®} is prepared by a solid-state polymerization technique, which has been recently patented.\textsuperscript{104} Because of their


\textsuperscript{101} Sergueievski, P.; Detty, M. R. Organometallics 1997, 16, 4386.


interesting thermal characteristics, there is an enormous interest in thermoplastic elastomers in industry today.\textsuperscript{105}

3.2 Preparation of bis[4-(dimethylamino)phenyl] telluride

The diaryl telluride bis[4-(dimethylamino)phenyl] telluride (108) was prepared according to a literature procedure (Scheme 32).\textsuperscript{106} The complex 109 was prepared by the addition of aniline to a suspension of TeCl\textsubscript{4} in ether. This material was then reduced with Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5} and treated with NaHCO\textsubscript{3} to afford a mixture of the telluride 108 and its corresponding ditelluride. Treatment with activated copper in 1,4-dioxane effected detelluration of the ditelluride to give the desired monotelluride 108 in a fair yield.

\begin{equation}
\begin{align*}
2 \text{Me}_2\text{N} & \text{Me} \text{N} \text{Me} + \text{TeCl}_4 \\
& \xrightarrow{(a)} \text{2:1-Complex 109} \\
& \xrightarrow{(b)} \text{108} \\
\end{align*}
\end{equation}

Scheme 32. (a) Et\textsubscript{2}O, ambient temp., 92 %. (b) Na\textsubscript{2}S\textsubscript{2}O\textsubscript{5}, CH\textsubscript{2}Cl\textsubscript{2}, H\textsubscript{2}O followed by NaHCO\textsubscript{3} until neutral. (c) Activated copper (Cu(0)), 1,4-dioxane, reflux, 58 % from complex 109.

3.3 Autoxidation and mechanical properties in polymers

3.3.1 Chemiluminescence

The oxidation of most organic materials is accompanied by low intensity emission of light. This is called chemiluminescence (CL) if the light is the result of a chemical reaction. Russell has formulated the predominating mechanism behind CL, as outlined in Scheme 33.\textsuperscript{107} The low intensity emission of light is due to relaxation of excited molecules to their ground state. Emission of light from polymers has been studied since 1961,\textsuperscript{108} but not until recently has it been possible to measure it with high

\begin{footnotes}
\textsuperscript{105} Reish, M. S. C\&EN 1996 (August 5), 10.
\textsuperscript{106} Engman, L.; Persson J. Organometallics 1993, 12, 1068.
\end{footnotes}
accuracy. Nowadays, it is possible to detect a few photons per second. Therefore, the CL technique is a very sensitive method that can be used to study kinetics of polymer oxidation.\textsuperscript{109}

\[
\begin{align*}
\text{RO}_2^* + \text{RO} &\rightarrow \text{ROH} + \text{O}_2, \\
\text{RO}^* &\rightarrow \text{RO} + \text{h} \nu.
\end{align*}
\]

\textbf{Scheme 33.} The Russell mechanism for chemiluminescence

### 3.3.2 Mechanical properties

There are various methods available to study the mechanical properties of polymers.\textsuperscript{110} One way is to determine the modulus, which is defined as the ratio of the stress applied to a material to the strain produced. Tensile strength is another commonly used quantity for evaluating the strength of polymers. The tensile strength is a measure of the tension required for the material to break. Elongation at break, in percent, is also a measure of polymer strength. Since polymers may show anisotropy due to high shear rate during the shaping process, it may be relevant to determine these properties in two different directions, both in the flow (or machine) direction (MD) and in the transverse direction (TD). Dynamic mechanical tests represent other methods for evaluating the mechanical properties of polymers. These tests measure the response of a material to a sinusoidal stress. From these measurements one obtains a damping term, \(\tan \delta\), which is a measure of the mechanical losses in the material, originating from e.g. movements of chain segments in the polymer. \(\tan \delta\) is invaluable in the examination of relaxation processes and transitions in polymers.


3.4 Results and discussion

3.4.1 Mechanical properties

Mechanical properties for different PACREL® materials were studied with and without the addition of the diaryl telluride 108. The results are summarized in Tables 5-8.

Table 5. Mechanical properties of PACREL® 206 blends

<table>
<thead>
<tr>
<th>Aging time (weeks)</th>
<th>0</th>
<th>4</th>
<th>4</th>
<th>0</th>
<th>4</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging temp. (°C)</td>
<td>23</td>
<td>23</td>
<td>40</td>
<td>23</td>
<td>23</td>
<td>40</td>
</tr>
<tr>
<td>Hardness (%shore A)</td>
<td>74</td>
<td>75</td>
<td>76</td>
<td>74</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>Modulus (MPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>11 ± 0.5</td>
<td>11 ± 0.3</td>
<td>12 ± 0.5</td>
<td>9 ± 0.3</td>
<td>9 ± 0.3</td>
<td>10 ± 0.2</td>
</tr>
<tr>
<td>TD</td>
<td>8 ± 0.4</td>
<td>8 ± 0.2</td>
<td>8 ± 0.5</td>
<td>8 ± 1</td>
<td>8 ± 1</td>
<td>9 ± 0.3</td>
</tr>
<tr>
<td>Tensile strength (MPa)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>4 ± 0.1</td>
<td>4 ± 0.1</td>
<td>4 ± 0.1</td>
<td>4 ± 0.1</td>
<td>4 ± 0.1</td>
<td>4 ± 0.1</td>
</tr>
<tr>
<td>TD</td>
<td>3 ± 0.1</td>
<td>3 ± 0.1</td>
<td>3 ± 0.2</td>
<td>4 ± 0.2</td>
<td>4 ± 0.1</td>
<td>4 ± 0.1</td>
</tr>
<tr>
<td>Elongation at break (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MD</td>
<td>139 ± 7</td>
<td>147 ± 6</td>
<td>108 ± 8</td>
<td>185 ± 6</td>
<td>185 ± 4</td>
<td>181 ± 9</td>
</tr>
<tr>
<td>TD</td>
<td>221 ± 23</td>
<td>222 ± 24</td>
<td>222 ± 31</td>
<td>259 ± 19</td>
<td>258 ± 5</td>
<td>246 ± 12</td>
</tr>
</tbody>
</table>

MD, Machine direction; TD, Transverse direction.

In Table 5 the mechanical properties of PACREL® 206 blends are shown. It was observed that the hardness of the polymer was unaffected by the addition of 0.3 % of the telluride 108 whereas the tensile modulus in the machine direction, but not in the transverse direction, was slightly lowered. Other interesting results are as follows: the tensile strength in the transverse direction was improved by 25 % by the addition of the stabilizer whereas the elongation at break was increased by about 11-17 %. Notably, the improvements in mechanical properties were already apparent before the aging of the polymer.

The results with PACREL® 632 are given in Table 6. With this polymer a lower amount of stabilizer was used (0.2 %), and the aging time was prolonged. The aging temperature was also increased to 80 °C as compared to 40 °C in Table 5. Again, the hardness of the polymer was unaffected by aging with the presence of the telluride 108. For the tensile modulus no trends were observed. Regarding the tensile strength in the machine direction, the stabilized material was outstanding in comparison with the unstabilized material after aging for 10 weeks at 80 °C. The tensile strength in the machine direction for the unstabilized material decreased by approximately 50 %,
<table>
<thead>
<tr>
<th>Aging time (weeks)</th>
<th>Unstabilized material</th>
<th>Stabilized material (0.2 % telluride)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>10</td>
<td>80</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>92</td>
<td>95</td>
</tr>
<tr>
<td>10</td>
<td>95</td>
<td>95</td>
</tr>
<tr>
<td>Hardness (° /shore A)</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Modulus (MPa) MD</td>
<td>176 ± 43</td>
<td>171 ± 15</td>
</tr>
<tr>
<td>TD</td>
<td>82 ± 14</td>
<td>112 ± 21</td>
</tr>
<tr>
<td>Modulus 100% (MPa) MD</td>
<td>9 ± 0.2</td>
<td>9 ± 0.2</td>
</tr>
<tr>
<td>TD</td>
<td>6 ± 0.3</td>
<td>6 ± 0.1</td>
</tr>
<tr>
<td>Tensile Strength (MPa) MD</td>
<td>9 ± 0.2</td>
<td>10 ± 0.1</td>
</tr>
<tr>
<td>TD</td>
<td>7 ± 0.3</td>
<td>8 ± 0.1</td>
</tr>
<tr>
<td>Elongation at break (%) MD</td>
<td>179 ± 20</td>
<td>187 ± 21</td>
</tr>
<tr>
<td>TD</td>
<td>266 ± 7</td>
<td>281 ± 19</td>
</tr>
</tbody>
</table>

MD. Machine direction; TD. Transverse direction.
whereas the tensile strength for the telluride stabilized material remained unchanged throughout the aging process.

There was also a significant difference between stabilized and unstabilized material after 10 weeks of aging at 80 °C for the elongation at break in the machine direction. In this case the stabilized material was unaffected after aging whereas the values for the unstabilized polymer were only about 10 % of those recorded for the stabilized material.

In Table 7 the corresponding results are summarized for PACREL® 632 blends compounded with oil and commercial stabilizers. Because this polymer contains oil, no direct comparison can be made with the results in Tables 5 and 6. However, it should be clear that the telluride increases the resistance to aging of PACREL® at least as much as conventional stabilizers.

<table>
<thead>
<tr>
<th>Table 7. Mechanical properties of PACREL® 632 blends compounded with oil and conventional antioxidants. No telluride present.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging time (weeks)</td>
</tr>
<tr>
<td>Aging temp. (°C)</td>
</tr>
<tr>
<td>Hardness (%/shore A)</td>
</tr>
<tr>
<td>Modulus (MPa)</td>
</tr>
<tr>
<td>MD</td>
</tr>
<tr>
<td>TD</td>
</tr>
<tr>
<td>Modulus 100% (MPa)</td>
</tr>
<tr>
<td>MD</td>
</tr>
<tr>
<td>TD</td>
</tr>
<tr>
<td>Tensile Strength (MPa)</td>
</tr>
<tr>
<td>MD</td>
</tr>
<tr>
<td>TD</td>
</tr>
<tr>
<td>Elongation at break (%)</td>
</tr>
<tr>
<td>MD</td>
</tr>
<tr>
<td>TD</td>
</tr>
</tbody>
</table>

MD, Machine direction; TD, Transverse direction.

In another series of experiments, the amount of stabilizer and the aging times were varied for PACREL 631®. The results are summarized in Table 8. These experiments were also complemented with chemiluminescence measurements (vide infra). Again, one could observe an improvement in the mechanical properties of the stabilized material as compared to the unstabilized. In the case of the stabilized polymer (0.17 % telluride), both the tensile strength and the elongation at break were almost unchanged.
after 9 weeks of aging at 70 °C. However, for the unstabilized material the corresponding values were reduced, the former by 40 % and the latter by 75 %.

From the above results there is no doubt that PACREL® needs to be stabilized in some way to withstand thermo-oxidative degradation. As compared to the unstabilized material, the diaryl telluride 108 (0.17-0.50 %) considerably improved elongation at break and tensile strength of the unaged as well as aged polymer. However, it is still not obvious why the diaryl telluride causes such an improvement in the mechanical properties of the unaged material. The known hydroperoxide decomposing capacity of the diaryl telluride 108 could be one contributing explanation to the observed effect.

### Table 8. Mechanical properties of PACREL® 631 blends

<table>
<thead>
<tr>
<th>Telluride 108 (%)</th>
<th>Aging Temp (°C)</th>
<th>Aging Time (weeks)</th>
<th>Tensile Strength (MPa)</th>
<th>Elongation at Break (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>23</td>
<td>0</td>
<td>3.8 ± 0.2</td>
<td>79 ± 22</td>
</tr>
<tr>
<td>0</td>
<td>70</td>
<td>4</td>
<td>2.6 ± 0.5</td>
<td>25 ± 9</td>
</tr>
<tr>
<td>0</td>
<td>70</td>
<td>9</td>
<td>2.3 ± 0.3</td>
<td>21 ± 4</td>
</tr>
<tr>
<td>0.17</td>
<td>23</td>
<td>0</td>
<td>7.1 ± 0.5</td>
<td>124</td>
</tr>
<tr>
<td>0.17</td>
<td>70</td>
<td>4</td>
<td>6.4 ± 0.8</td>
<td>84 ± 34</td>
</tr>
<tr>
<td>0.17</td>
<td>70</td>
<td>9</td>
<td>7.4 ± 0.6</td>
<td>130 ± 45</td>
</tr>
<tr>
<td>0.30</td>
<td>23</td>
<td>0</td>
<td>6.2 ± 0.1</td>
<td>197 ± 8</td>
</tr>
<tr>
<td>0.30</td>
<td>70</td>
<td>4</td>
<td>6.6 ± 0.5</td>
<td>168 ± 29</td>
</tr>
<tr>
<td>0.30</td>
<td>70</td>
<td>9</td>
<td>6.5 ± 0.7</td>
<td>146 ± 30</td>
</tr>
<tr>
<td>0.50</td>
<td>23</td>
<td>0</td>
<td>7.1 ± 0.7</td>
<td>200 ± 68</td>
</tr>
<tr>
<td>0.50</td>
<td>70</td>
<td>4</td>
<td>7.4 ± 0.3</td>
<td>167 ± 25</td>
</tr>
<tr>
<td>0.50</td>
<td>70</td>
<td>9</td>
<td>7.6 ± 0.5</td>
<td>184 ± 25</td>
</tr>
</tbody>
</table>

#### 3.4.2 Chemiluminescence

Chemiluminescence-time traces recorded in oxygen at 150 °C for PACREL 631® stabilized with 0.17-0.50 % of the diaryl telluride 108 showed significantly longer induction times (60-70 min) than the unstabilized material (30 min). This indicates that the antioxidative properties of tellurides previously observed in organic solvents can also be expressed in a polymeric matrix.

In another experiment the total luminiscence intensity (TLI) was measured as a function of the aging time at 70 °C (Figure 6) where PACREL 631® was stabilized with 0, 0.17, 0.30, and 0.50 % of the telluride. From these measurements one can observe that the initially low TLI for stabilized materials is only slightly increased (2-5 times) by aging. However, for the unstabilized material, the initial TLI is
approximately 10 times higher than that for the stabilized material and it increases by a factor of about 13 during aging. These studies clearly show that the diaryl telluride 108 considerably prolongs the induction period of oxygen-stimulated oxidation of the polymer and drastically reduces the total luminescence intensity of unaged and aged samples.

Figure 6. TLI as a function of aging time at 70 °C for samples of PACREL® 631 stabilized with 0, 0.17, 0.30, 0.50 % diaryl telluride 108. The right luminescence scale is for unstabilized material only.

3.4.3 Dynamic mechanical properties

The dynamic mechanical properties were studied as a function of temperature for the unstabilized and stabilized (0.3 % of the telluride 108) PACREL 631®. The results are shown in Figure 7 as a plot of tan δ versus temperature.
**Figure 7.** Tan δ as a function of temperature for PACREL® 631 stabilized with 0 % (normal line) and 0.30 % (bold line) of the diaryl telluride 108.

This figure clearly shows that the addition of the stabilizer suppresses the tan δ of the polybutylacrylate phase, resulting in a decreased flexibility of the polymer containing the telluride. However, the tensile modulus and the hardness are essentially unaffected by admixing of the telluride and swelling experiments gave no indication of increased crosslinking.

### 3.4.4 Stabilizer stability

The thermal stability of the diaryl telluride 108 was previously studied by thermogravimetric analysis. These measurements indicated that 5 % of the initial sample weight was lost at 220 °C in an atmosphere of nitrogen. To study the stability of the telluride under more userlike conditions, neat telluride was heated in air at various temperatures and 1H-NMR spectra were recorded. Heating of the telluride at 180 °C for 10 minutes gave a very slight decomposition of the material. At 215 °C, about 20 % of the telluride was decomposed within 15 minutes. So far, the decomposition products have not been further analyzed. However, no telluroxide corresponding to telluride 108 was formed under the conditions used.

### 3.5 Conclusions and outlook

It has been demonstrated, by different techniques, that bis[4-(dimethylamino)phenyl] telluride (108) acts as a multifunctional antioxidant/stabilizer in the thermoplastic elastomer PACREL®. Addition of the telluride 108 improved both the tensile strength and elongation at break of the polymer. Chemiluminescence measurements demonstrated that the telluride prolonged the induction period of thermo-oxidation and reduced the total luminescence intensity of the material.

This project will now be expanded to involve other tellurides as well as other polymers. It is also hoped that it will be possible to use diaryl tellurides in a catalytic fashion in polymers, according to Scheme 8.

It is also planned to use these compounds for the stabilization of other synthetic and man-made products such as oils, fluids and paper products.
5. Acknowledgements

I would like to express my sincere gratitude to:

My supervisor Prof. Lars Engman for accepting me as a graduate student, and for his great support, patience and enthusiasm during these years.

Past and present members of group Engman:
Dr. Vijay Gupta for your friendship, for taking care of me when I came to Uppsala and Melbourne and for sharing your knowledge in chalcogen and radical chemistry.
Fil. Lic. Magnus Beşev for your friendship, your eagerness to discuss chemistry and for introducing me to Raki.
Dr. Takahiro Kanda, Stefan Berlin, Cecilia Ericsson, Dr. Andrei Vasiliev, Fil. Lic. Per Eriksson, Dr. Nikolai Stuhr-Hansen, Dr. Nawaf Al-Maharik and Fredrik Lehmann for their friendship and stimulating co-operation.

Prof. Carl H. Schiesser for allowing me to work in his research group for three months and for making my stay at the University of Melbourne very pleasant.

Assoc. Prof. Mats Jonsson, Assoc. Prof. Ian A. Cotgreave, Assoc. Prof. Leif Hammarström and Martin Sjödin for stimulating collaborations concerning the vitamin E project.

Prof. Bengt Stenberg, Dr. Martin Bellander, Dr. Karin Jacobsson and Dr. Viveca Lönnberg, for fruitful collaborations concerning the polymer project.

Dr Nicholas Power and Ulrika Yngve for revision and linguistic corrections of this thesis.

Assoc. Prof. Adolf Gogoll for keeping all the instruments and computers in good shape and for his invaluable help concerning NMR and handling of instruments.

The technical and administrative staff Leffe, Gunnar, Wicke, Thomas and Tatti.

My first labmates Anders Persson and Andreas Palmgren, who took care of me when I started.
Per Ryberg for friendship and our hard games of badminton.
Stefan Modin for all help concerning HPLC, computers, etc.
All other past and present members of the department, especially Micke, Kattis, Sofia, Markus, Lotta, Catrin, Viviane, Tobias, Benita, Katarina, Pedro, Magnus E., Ludvig, Kalle and Jocke, for a pleasant time inside as well as outside Chemicum.

The Schiesser group and other people at the University of Melbourne who made my stay there great fun and memorable. I will never forget Melbourne and our trip to the Great Ocean road. A special thanks goes to Drs Melissa Laws and Lisa Zugaro for fruitful collaborations.

The Swedish Research Council for Engineering Sciences, Stiftelsen Bengt Lundqvist minne, Knut och Alice Wallenbergs stipendiefond, Stiftelsen Sigurd och Elsa Goljes minne and C. F. Liljewalchs resestipendiefond for financial support.

My friends from the south, especially Patrik, Fredrik, Christian, Staffan, Mats, Manne, Lasse, Magnus W. and Stefan for always being there.

My family for their great support.

My beloved Ulrika for all your love, your encouragement and for making my life more eventful and fun.