Stereochemistry of organic sulfur compounds:more than 100 years of history, current state and further challenges

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#### Abstract.

In the paper presented are the author's subjective views on the most important achievements in the stereochemistry of organic sulfur compounds, which, as an object of research, has more than 100-year history. Prospects for further development are also mentioned.



#### Keywords

organosulfur derivatives; stereochemistry; optical activity; asymmetric synthesis, chiral auxiliaries

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#### **INTRODUCTION**

Research on the stereochemistry of organic sulfur compounds comprises more than a hundred years of history <sup>1,2</sup>. Its course can be easily divided into two periods. The first one, which lasted until the end of the seventies of the twentieth century, was associated with methodological studies, which were focused on the synthesis of optically active compounds with a stereogenic sulfur atom having various valency and/or coordination number, determination of their optical and chemical stability and reactivity, stereochemistry of the basic functional group interconversions and basic structural parameters including their chiraloptical properties. The second period, lasting until now, has been focused on research aimed at the use of the optically active derivatives with a stereogenic sulfur atom as chiral auxiliaries or catalysts in asymmetric synthesis and chiral substrates useful in the synthesis of new materials. At the same time, thorough research has been conducted on the biological activity of these types of organic sulfur compounds with the hope of discovering new pharmaceutically applicable ingredients.

#### **RESULTS AND DISCUSSION**

# Methodological studies focused on the synthesis of optically active compounds with a stereogenic sulfur atom having various valency and/or coordination number

The first period of research devoted into the stereochemistry of organic sulfur compounds, which opened in  $1900^3$  and lasted roughly until the end of the seventies of the twentieth century, was focused above all on:

 a) synthesis of model optically active compounds with a stereogenic sulfur and determination of their optical stability

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- b) determination of the absolute configurations and enantiomeric excesses of substrates and products of examined conversions
- c) description of the mechanisms of nucleophilic substitution at a stereogenic sulfur,
   including the determination of stereochemical consequences of nucleophilic substitution
   at the sulfur (similarities and differences in comparison with the reactions of nucleophilic
   substitution at the stereogenic carbon atom)

The pioneering report on successful optical resolution of sulfonium ion 2 (Scheme 1)<sup>3</sup> was of great contemporary importance in the development of the theory of optical activity based on the tetrhedral model (the role of a fourth substituent is played by the unshared pair of electronson the sulfur atom). It should be noted here that the isolation of the diasteromerically pure sulfonim salt **2a** or the diasteromerically pure sulfonim salt **2b** were possible only after very tedious fractional crystallization of starting salt **2** from a mixture of absolute alcohol and ether (some 40 to 50 times)<sup>3</sup>.

In recent years, enantiomeric sulfonium salts **3** have been frequently used<sup>4-6</sup> as precursors of the optically active sulfonium ylides **4**, useful chiral auxiliaries in the asymmetric synthesis of epoxides **5** formed according to Scheme 2.

The fundamental importance in stereochemistry of organosulfur compounds plays diastereomerically pure *O*-menthyl *p*-toluenesulfinate **8** obtained for the first time in 1926 by the reaction of *p*-toluenesulfinyl chloride **7** with (-) -- (1*R*, 2*S*, 5*R*)- menthol- **7** (Scheme 3).<sup>7</sup> Considering details of this procedure it is evident that it constitutes the first example of the reaction that now have been termed as dynamic kinetic resolution (DKR) process<sup>8</sup>. It should also be noted that recent modifications of this procedure<sup>9-10</sup>, including a base and solvent free reaction

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of *p*-toluenesulfinyl chloride with menthol<sup>11</sup>, allows the convenient isolation of  $(S_S)$ -8 diastereomer in a very high yield. This sulfinate was also used as a substrate in the first stereospecyfic synthesis of enantiomerically pure aryl alkyl and nonsymmetric diaryl sulfoxides. This procedure, now known as the Andersen's method, is ilustrated on Scheme 4 by the original reaction which afforded enantiomerically pure ethyl p-tolyl sufoxide **9** (Scheme 4)<sup>1-2,12</sup>. After this seminal paper of Andersen a number of diasteromerically pure sufinates have been prepared and used as precursors of enantomerically pure, nonfunctionalized and differently

functionalized aryl alkyl, diaryl and dialkyl sulfoxides<sup>1-2, 13-14</sup>.

The second methods for the preparation of enantiopure sulfoxides is asymmetric sulfide oxidation. Developing a novel oxidation method that involves reacting a sulfide **10** with an chiral oxidising agent (COA-**11**) to form the enantiopure (or enriched) sulfoxide **12** (Scheme 5) has been, and still is, a very hot research topic<sup>13-15</sup>. Key advances in this field are related to the use as oxidation reagents: a) Davis oxaziridines<sup>16</sup> b) oxidants based on an organometallic core<sup>17-19</sup> c) biological oxidants<sup>20-21</sup>.

The fundamental importance in stereochemistry of organosulfur compounds plays also sulfoximines  $13^{1-2,22}$  (which show a very interesting biological activity)<sup>-23</sup>, sulfinamides  $14^{1-2,24}$  and N-alkylidenesulfinamides  $15^{1-2,25}$ . All three classes of compounds are very useful as chiral auxiliaries and / or precursors of other optically active sulfinyl derivatives<sup>26</sup>.

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#### Determination of optical stability and chiraloptical properties.

An advantage of using optically active compound with a stereogenic sulfur atom as chiral species in asymmetric reactions lies in their relatively high optical stability. This is especially evident for the sulfoxides, sulfoximines, sulfinamides and sulfonium salts<sup>1,2</sup>. Classic works of Mislow's team showed that for the majority of sulfoxides racemisation only occurs via pyramidal inversion with measurable speed at around 200 °C.<sup>27</sup> Exceptions constitute benzyl sulfoxides, which racemise *via* a homolitic scission mechanism at 130--150 °C, and allyl sulfoxides where [2,3]sigmatropic rearrangements occur before pyramidal inversion at temperatures of 50--70 °C.<sup>28-29</sup> In this context it should be noted that sulfoxides with a proton in the  $\beta$ -position may undergo elimination to generate olefins at temperatures of around 80 °C<sup>30</sup> the majority of sulfonium salts racemisation *via* pyramidal inversion with measurable speed at around 70 °C.<sup>31</sup>

Considering the possibilities of determination of the absolute configuration of compounds with stereogenic sulfur atom the importance of chiroptical properties should be stressed. The first empirical correlations between electronic circular dichroism (CD) and optical rotatory dispersion (ORD) spectra (210-265 nm) of several nonracemic sulfoxides and sulfinates and their absolute

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configurations were also reported by Mislow's team.<sup>32</sup> The detailed discussions of experimental ORD and CD spectra of chiral sulfur compounds is given by Laur<sup>33</sup> whereas nonempirical interpretations of CD spectra for several aryl alkyl sufoxides<sup>34</sup> aryl benzyl sufoxides<sup>35</sup> are discussed by Rosini et al. The first nonempirical circular dichroism determination of the absolute configuration of N-phthalimidosulfoximines based on excition coupling mechanism was found to allow simultaneous determination of the absolute configuration of parent sulfoxides.<sup>36</sup> Simultaneously, the nonempirical determination of the absolute configuration of chiral sulfoxides was found to be possible based on the comparison of experimental and ab initio predicted absorption and VCD spectra.<sup>37-38</sup>

#### **Further challenges**

a) Synthesis of optically active sulfurous acid derivatives 16 derived from achiral, unstable sulfurous acid 17 and optically active sulfoimidoyl derivatives 18



b) Synthesis of optically active hypervalent derivatives 19 and 20

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- c) studies devoted to stereochemical aspects of the flow process (for reactions carried out in microreactors)
- d) studies devoted to stereochemical aspects of the reaction carried out under high pressure
- e) studies devoted to the use optically active compounds containing a stereogenic sulfur atom in the chemistry of "new materials"

1. Synthesis of polymers functionalized with substituents containing

a stereogenic sulfur atom

2. Funtionalization of nanaocarbon materials with substituents containing

a stereogenic sulfur atom

- f) studies devoted to the use of optically active compounds containing a stereogenic sulfur matom as chiral auxiliaries in asymmetric synthesis including a search for greener and reusable analogues
- g) suplamolecular chemistry of optically active compounds containing a stereogenic sulfur atom
- h) search for optically active compounds containing a stereogenic sulfur atom as pharmaceutically useful substances

# 7 ACCEPTED MANUSCRIPT

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# <sup>8</sup> ACCEPTED MANUSCRIPT

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### 9 ACCEPTED MANUSCRIPT

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### <sup>11</sup> ACCEPTED MANUSCRIPT



Scheme 1 Optical resolution of sulfonium ion 2

# <sup>12</sup> ACCEPTED MANUSCRIPT



Scheme 2 Asymmetric synthesis of optically active epoxides 5 based on sulfonium ylide 4 as a chiral auxiliary

# <sup>13</sup> ACCEPTED MANUSCRIPT



Scheme 3 The first protocol for the preparation of diastereomerically pure *O*-menthyl *p*-toluenesulfinate 8

# <sup>14</sup> ACCEPTED MANUSCRIPT



Scheme 4. The first preparation of enantiomerically pure ethyl p-tolyl sulfoxide 9

# <sup>15</sup> ACCEPTED MANUSCRIPT



Scheme 5 Asymmetric oxidation of sulfides 10 to the corresponding sulfoxides 12

# <sup>16</sup> ACCEPTED MANUSCRIPT