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Chiral Sulfur-Containing Structures: Selected Synthetic and Structural Aspects

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ABSTRACT: *Synthetic procedures applied for the preparation of a new diastereomerically pure sulfinate and amidosulfite and a few enantiomerically pure sulfinyl derivatives, including sulfoxides functionalized with a perfluorocumyl substituent, are presented. Attempts to polymerize optically active 2-(3-thienyl)ethyl p-tolyl sulfoxide are also mentioned. Mechanistic and stereochemical aspects of the presented protocols are discussed. Structural studies, which include the X-ray, circular dichroism, and vibrational circular dichroism–based determinations of the absolute configurations at the stereogenic sulfur atoms and calculations of conformational equilibria for a few model sulfur-containing compounds are also described. The use of optically active t-butylphenylthiophosphinic acid as a chiral solvating agent is illustrated.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:527–536, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20335

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INTRODUCTION

For some years the main scientific interest of the Lodz group has been focused on studies of chiral sulfur-containing structures. Most of the studies have been concentrated on the synthesis and structural determinations of the family of optically active tetravalent, tricoordinated sulfinyl derivatives. Therefore in this article, in the part concerning synthetic aspects, we will discuss our most recent works on

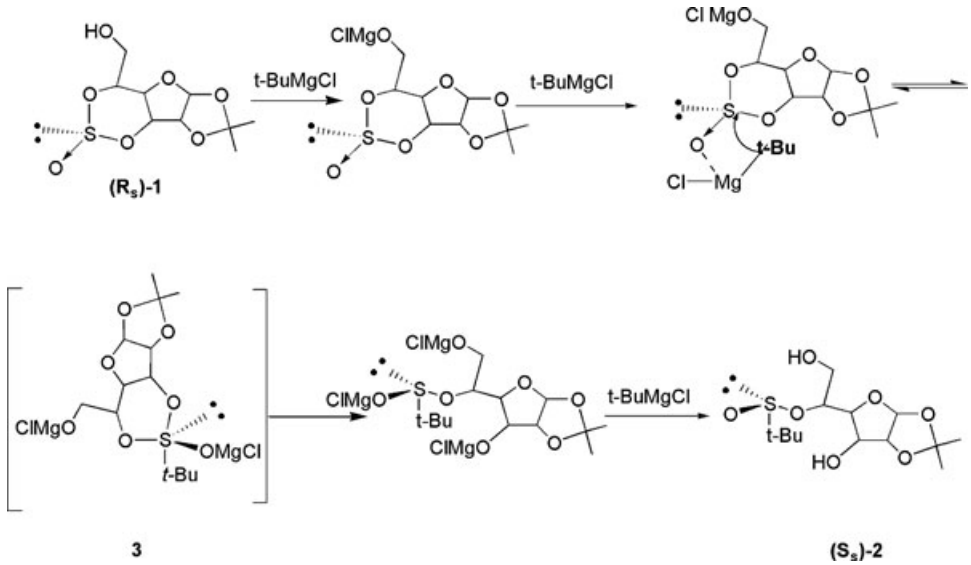
1. Reactivity of sulfites derived from α-D-glucofuranose.
2. Synthesis and reactivity of amidosulfites derived from diastereomerically pure 1-[α-*N*-1-phenylethyl]benzyl-2-naphthol.
3. Synthesis of optically active *p*-tolyl *o*-[(2-hydroxy-1,1,1,3,3,3-hexafluoro)propyl]phenyl sulfoxide and a possibility of its existence in an equilibrium with a sulfurane structure.
4. Synthesis of 3-sulfinylthiophenes and attempted polymerization.

The part presenting structural aspects will be focused on:

a. The first nonempirical circular dichroism (CD) determination of the absolute configuration of *N*-phthalimidosulfoximines based on exciton coupling mechanism and correlation with the absolute configuration of chiral sulfoxides.
b. Determination of absolute configurations, predominant conformations and tautomeric equilibrium of enantiomeric sulfoxides and *t*-butylphenylphosphinothioic acid based on vibrational circular dichroism (VCD) spectra.
c. The use of enantiomeric *t*-butylphenylphosphinothioic acid for enantiomeric excess determinations.

REACTIVITY OF SULFITES DERIVED FROM α-D-GLUCOFURANOSE

Among a few possible approaches to the preparation of optically active enantiomeric or diastereomeric sulfinates, asymmetric versions of the reaction of sulfites with organometallic reagents can also be included. The first report on this approach described the synthesis of enantiomeric *t*-butanesulfinates by the reaction of prochiral sulfites with *t*-butylmagnesium chloride carried out in the presence of optically active aminoalcohols as chiral complexing agents [1]. Later on, a few diastereomeric sulfinates were prepared by the reaction of a diastereomerically pure, cyclic sulfite derived from (*S*)-(–)-1,1-diphenyl-1,2-propanediol with Grignard reagents [2]. Having in hands diastereomerically pure (*R*)-1,2-*o*-isopropylidene-3,5-*O*-sulfinyl-α-D-glucofuranose (**1**) [3], we decided to check if its reaction with Grignard reagents could be stopped at the stage of the corresponding sulfinates. Preliminary experiments with a series of organomagnesium halides showed that only in the reaction with *t*-butylmagnesium chloride this conversion is stopped at the stage of the corresponding *t*-butanesulfinate. We were able to isolate, as a single reaction product, analytically pure sulfinic ester **2** whose structure and the *S* absolute configurations at the stereogenic sulfur atom were determined by an X-ray structural analysis. Comparison of absolute configurations of the starting sulfite **1** and the isolated sulfinate **2** clearly indicates that nucleophilic substitution at the stereogenic sulfur atom occurs with full inversion of configuration. This can be easily explained by the reaction sequence shown in Scheme 1 and by an assumption that the intermediate **3** has a trigonal bipyramidal structure in which both the entering and departing groups are located in apical positions.



SCHEME 1

SYNTHESIS AND REACTIVITY OF AMIDOSULFITES DERIVED FROM DIASTEROMERICALLY PURE 1-[N-1-PHENYLETHYL]BENZYL-2-NAPHTHOL

A highly stereoselective cleavage of the S—O bond in cyclic diastereomeric amidosulfites by Grignard reagents, followed by highly stereoselective cleavage of the S—N bond with lithium reagents in the resulting chiral sulfinamide, are the key steps in the stereospecific synthesis of chiral sulfoxides [4]. This methodology has already been applied for amidosulfites derived from ephedrine [5] and an optically active phenol derivative [6] and 1,2-aminohydroxyindole [7]. Since diastereomerically pure 1-[α-*N*-1-phenylethyl]benzyl-2-naphthol (**4**) has recently become very easily available starting from 2-naphthol, benzaldehyde, and enantiomers of [α]-phenylethylamine [8], we decided to use it as a substrate for the preparation of a new diastereomerically pure amidosulfite with a hope that it would serve (if it is easily available) as a precursor for other diastereomeric and enantiomeric sulfinyl derivatives such as sulfinamides and sulfoxides. Preliminary, small-scale reactions of thionyl chloride with the aminonaphthol **4** or its in situ generated sodium salt in the presence of a tertiary amine at temperatures from −70°C to room temperature in diethyl ether gave in yields above 90% the expected amidosulfite **5** as a mixture of diastereomers having diastereomeric excess value in a narrow range between 30% and 40%. All attempts to isolate from these mixtures the pure diastereomers (or a mixture strongly enriched in a particular diastereomer) by typical crystallization have until now been unsuccessful. In this context it is interesting to note that it was possible, in some experiments, to isolate the pure diastereomers by partition of the diastereomers in petroleum ether occurring effectively during a few hours of stirring of their suspensions in this solvent. The results of a single, fully successful experiment are shown in Scheme 2. The partition progress was very easily followed by taking the ^{1}H NMR spectra of the isolated samples in which two well-resolved singlets and quartets appear at 6.01 ppm and 5.80 ppm (for singlets) and at 5.28 ppm and 4.42 ppm (for quartets), respectively. In this context, it is interesting to note that the partition progress could not be followed by polarimetric measurements since the samples having substantially different *de* values have very close optical rotations (J. Drabowicz, unpublished data).

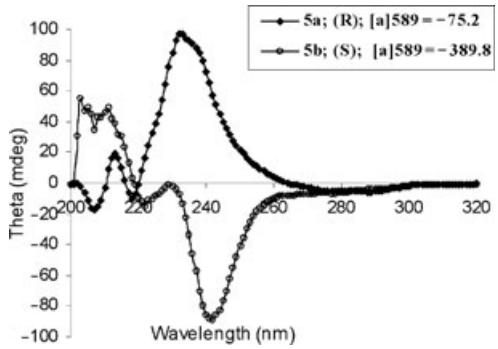
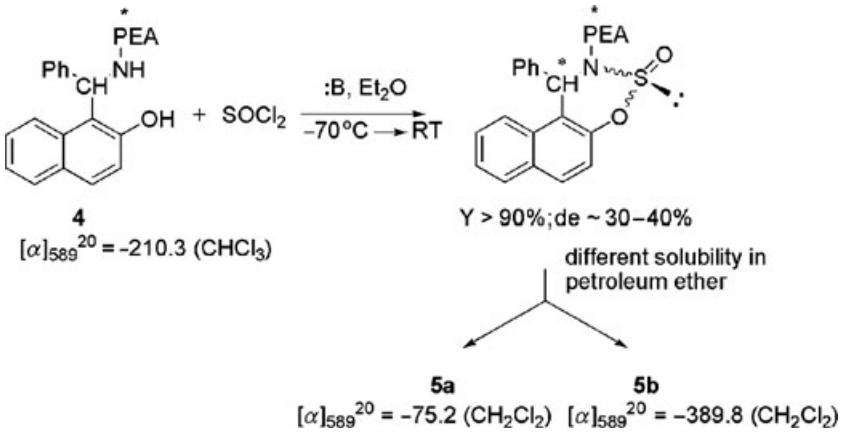


FIGURE 1 CD spectra of the diastereomeric amidosulfites **5a** and **5b**.

We were able to carry out an X-ray structural analysis for the pure diastereomer having optical rotation equal to $[\alpha] = -75.2(CH_2Cl_2)$ (J. Drabowicz et al., unpublished data). It showed a slightly distorted tetrahedral rearrangement of the substituents (two oxygens, a nitrogen, and a lone electron pair) and the (*R*) absolute configuration around the central sulfur atom. For both pure diastereomers of the amidosulfite **5**, we measured circular dichroism (CD) spectra, which are shown in Fig. 1. The analysis



SCHEME 2

of the spectra of the particular diastereomers shows interesting optical rotatory power in the region of 200–280 nm.

First of all, the recorded spectra show almost mirror-image shape. It means that the sign of the observed Cotton effects, related obviously to aromatic transitions, can be directly related with the absolute configuration at the stereogenic sulfur atom. Moreover, comparison of the result of the X-ray analysis for the pure diastereomer having optical rotation equal to $[\alpha]_D = -75.2(CH_2Cl_2)$ and its CD spectrum clearly indicates that the positive Cotton effect corresponds to the (*R*) absolute configuration at the stereogenic sulfur atom.

Having in hands the samples of diastereomeric amidosulfites **5**, we were able to begin the preliminary experiments on their reactivity with Grignard reagents hoping this would open a new way to diastereomerically pure sulfinamides. The model experiments with *p*-tolylmagnesium bromide are shown in Scheme 3. In the reaction with 1.2 molar excess of this reagent, the amidosulfite **5** enriched in the (*S*) diastereomer (dr = 67:33) was converted into the expected diastereomeric sulfinamides **6** almost quantitatively. The pure diastereomers were isolated from the crude reaction mixture by a standard silica gel column chromatography.

For both pure diastereomers of the sulfinamide **6** CD spectra were measured (J. Drabowicz, unpublished data) (Fig. 2). The recorded spectra show, like in the case of the starting amidosulfites **5**, an almost mirror-image shape in the region of 200–280 nm. It means that the sign of the observed Cotton effects, related obviously to aromatic transitions, can also be directly related with the absolute configuration at the stereogenic sulfur atom. Moreover, their comparison with the spectra of the particular diastereoisomer of the starting amidosulfite **5** clearly indicates that its reaction with *p*-tolylmagnesium bromide occurs with inversion of configuration at the stereogenic sulfur atom.

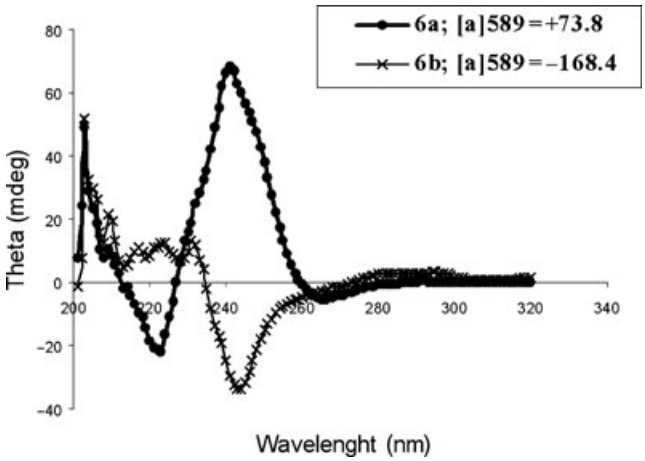
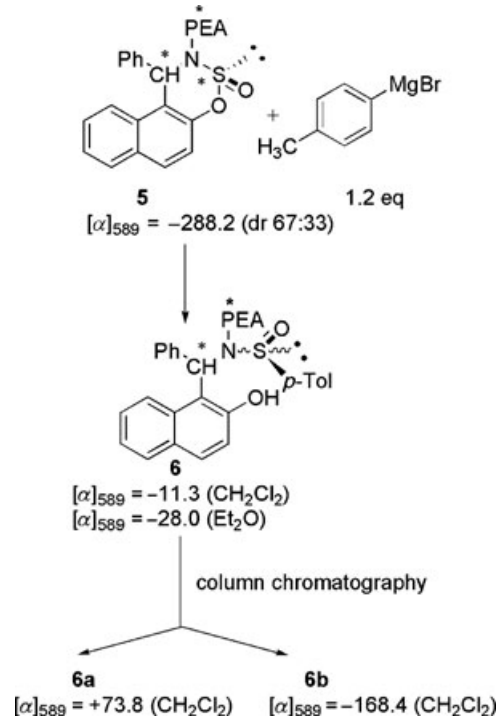


FIGURE 2 CD spectra of the diasteromeric sulfinamides **6a** and **6b**.

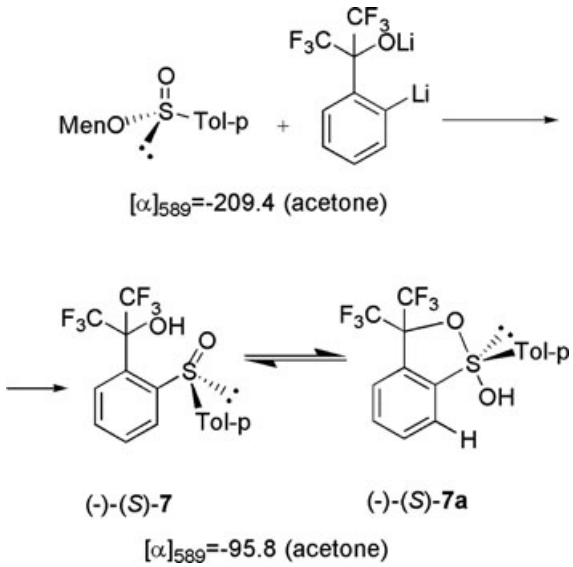


SCHEME 3

SYNTHESIS OF OPTICALLY ACTIVE p-*TOLYL* o-*[(2-HYDROXY-1,1,1,3,3,3-HEXAFLUORO)PROPYL]PHENYL SULFOXIDE (**7**) AND A POSSIBILITY OF ITS EXISTENCE IN AN EQUILIBRIUM WITH A SULFURANE STRUCTURE (**7a**)*

Optically active *p*-tolyl *o*-[(2-hydroxy-1,1,1,3,3,3-hexafluoro)propyl]phenyl sulfoxide (**7**) constitutes an interesting model of a tetravalent, tricoordinated sulfinyl derivative for which the existence of an equilibrium with a sulfurane structure (**7a**) could be considered. To test this idea, we prepared it by the reaction of diastereomerically pure *O*-menthyl *p*-toluenesulfinate with ortho-lithiated perfluorocumyl alcohol (Scheme 4) (J. Drabowicz and A. Zając, unpublished data).

The existence of an equilibrium between the sulfoxide **7** and the sulfurane **7a** was indicated by some ^{19}F NMR spectra recorded at room temperature for deuterochloroform solutions in which two sets of absorptions were observed for the magnetically nonequivalent trifluoromethyl groups (Fig. 3).



SCHEME 4

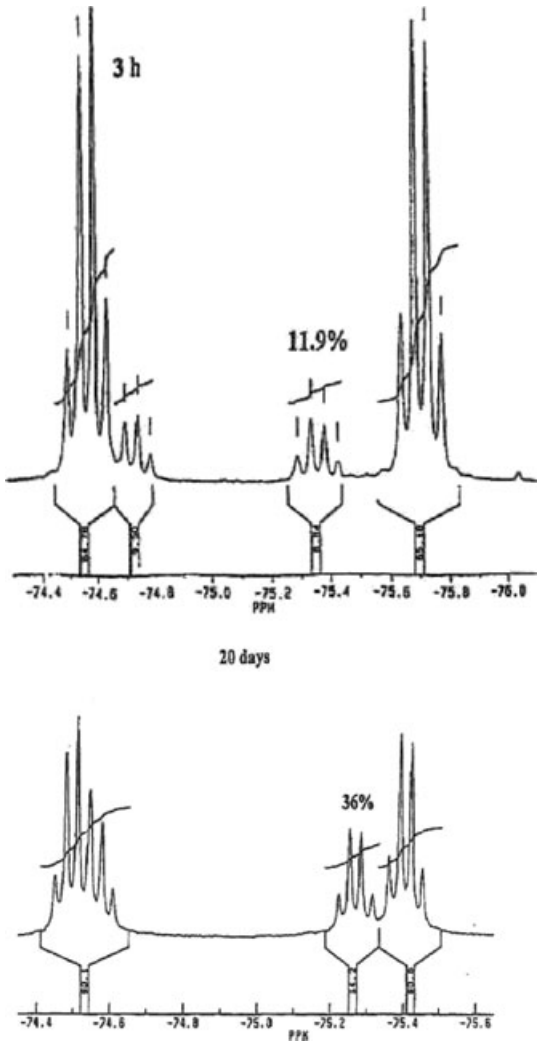


FIGURE 3 ^{19}F NMR spectra of the mixtures of **7** and **7a**.

Moreover, we were able to isolate during the standard silica gel column chromatography fractions showing very different melting points (the first fraction had mp 163–165°C whereas the second one had mp 80–85°C). It is interesting to note that an X-ray analysis of a single crystal having optical rotation $[\alpha]_{589} = -95.8$(acetone) and sharp melting point 172–173°C (Fig. 4) showed, however, a tetrahedral arrangement of substituents (two carbons, an oxygen, and a lone electron pair) around the stereogenic sulfur atom and the (*S*) absolute configuration. Taking into account this result, it is evident the fractions showing mp 80–85°C should contain a bigger amount (or mostly) of the sulfurane **7a**.

*SYNTHESIS OF 3-SULFINYLTHIOPHENES **8** AND ATTEMPTS TO POLYMERIZE THEM*

Among conjugated polyaromatics, thiophene-containing oligomers and their functionalized analogues are among the most attractive organic materials for the construction of optoelectronic devices, organic semiconductors, biosensors, and artificial enzymes. Their applications for these purposes result from the fact that they form supramolecular self-assembled aggregates [9–11], which in a solid state display a rich diversity of conformations and packing [12]. It is obvious that the nature of such supramolecular self-assembled aggregates should be strongly influenced by the presence of the chiral substituents. Therefore, the synthesis of chiral monomers and their polymerization constitute an interesting synthetic challenge. With this in mind, we prepared as model structures optically active *p*-tolyl (3-thienyl)-ethyl sulfoxide (**8**) and *O*-(3-thienyl)-ethyl *t*-butanesulfinate (**9**) and polymerized them to the structures **8a** and **9a** according to the literature [13]. Unfortunately, in both cases racemic compounds were obtained (Schemes 5 and 6).

THE FIRST NONEMPIRICAL CIRCULAR DICHROISM DETERMINATION OF THE ABSOLUTE CONFIGURATION OF N*-PHTHALIMIDOSULOXIMINES BASED ON EXCITON COUPLING MECHANISM AND CORRELATION WITH THE ABSOLUTE CONFIGURATION OF CHIRAL SULFOXIDES*

The last two decades have witnessed increasing use of optically active sulfoxides in asymmetric synthesis [4] and extensive search for their application as bioactive products and/or synthetic drugs [14]. Despite these facts, one can find only a very few methods used to determine their absolute configuration

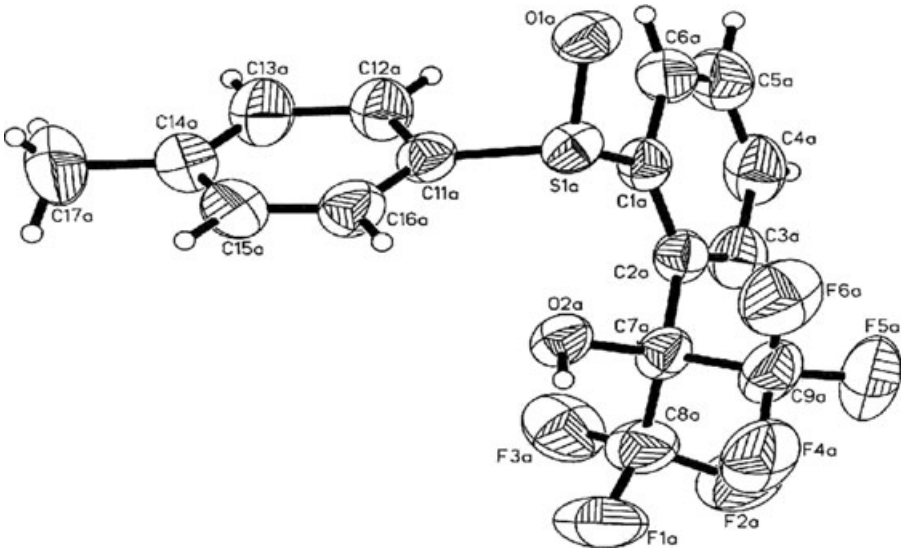
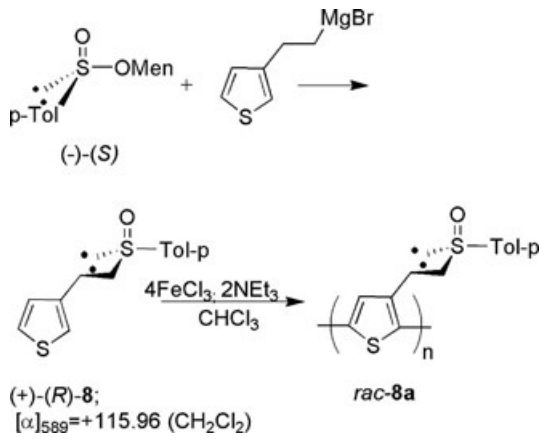
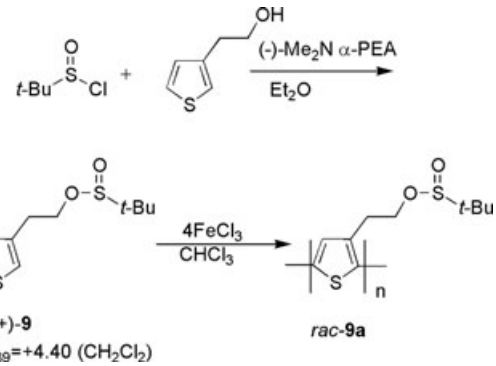


FIGURE 4 Thermal ellipsoidal plot of the levorotatory enantiomer of the sulfoxide **7**.

[15,16]. The first one is based on an empirical rule formulated by the Mislow group after examining the chiroptical properties of several alkyl aryl sulfoxides of known absolute configuration [17]. Very recently strong support was found by a nonempirical analysis of a series of CD spectra of optically active alkyl aryl sulfoxides, using the coupled-oscillator model for nondegenerate transitions [18]. Simultaneously, we have reported [19] on the first nonempirical correlation of the absolute configuration and chiroptical properties of alkyl aryl *N*-phthalimidosulfoximines based on the analysis of their exciton-split bichromophoric Cotton effect. This allows simultaneous determination of the absolute configuration of the parent alkyl aryl sulfoxides owing to the fact that *N*-phthalimidosulfoximines **10** are derived from sulfoxides **11** in a reaction that proceeds with retention of the configuration (Scheme 7) [20].

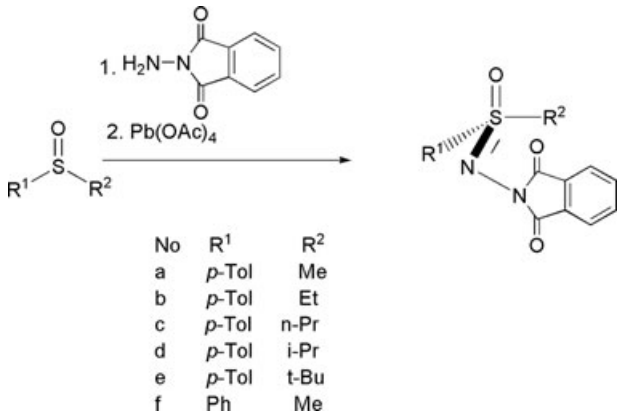


SCHEME 5

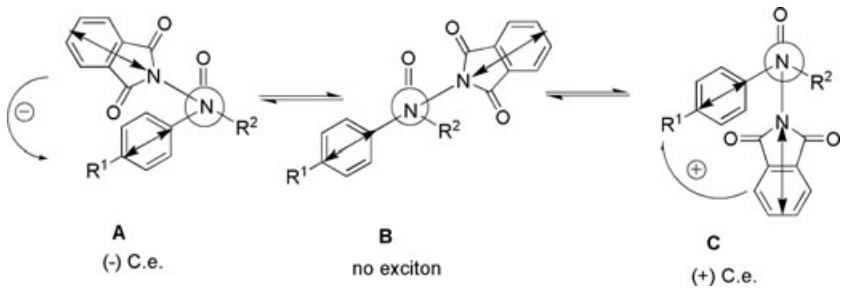


SCHEME 6

For the sulfoximines **10**, where R^1 = aryl, this method for the assignment of absolute configuration is based on the analysis of the exiton-split bichromophoric Cotton effect, which for a given *R* configuration at the sulfur atom is shown in Scheme 8.



SCHEME 7



SCHEME 8

The relative population of the three rotamers **A–C** (with regard to the rotation about the S—N bond) considered in the model were selected according to the results of computations (MM+ method using HyperChem. and PM3) carried out for the model molecule **10f**. Rotamer **A** with a negative N–N–S–Ph angle was found to contribute most abundantly to the population of the rotamers. The next conformer with the energy 1.6 kcal mol^{-1} higher corresponded to the rotamer **C** with a rather small positive N–N–S–Ph torsion angle. The considered exciton coupling in rotamers **A–C** results from the coupling of the 4-tolyl ^1L_a electric dipole transition moment (belonging to the absorption band at ca. 215 nm) with the electric dipole transition moment of the 220-nm transition of the phthalimide moiety [21]. Since both transitions are polarized along the chromophore long axis, their position is independent of the rotation around the (*S*)-(4-tolyl) and N—N bonds, respectively. Thus, rotamer **A** generates a negative exciton split Cotton effect for the above-mentioned transitions and the *R* configuration, whereas rotamer **B** essentially does not contribute to the Cotton effects in the 210–230-nm range. The CD spectrum recorded for (*R*)-**10a** shows a negative Cotton effect at 232 nm and a positive Cotton effect at 215 nm (corresponding to a UV_{max} at 228 nm), and (*S*)-**10c** shows opposite effects, a positive Cotton effect at 235 nm and a negative Cotton effect at 216 nm (Fig. 5), which is in full agreement with the considered stereochemical model.

The pattern of signs of the Cotton effects appears consistent with the configuration throughout the remaining members of a series of investigated compounds: (*R*)-**10b**, −14.5 (235) and +6.8 (216); (*S*)-**10d**, +14.2 (233) and −6.7 (217); (*R*)-**10e**, −16.7 (232) and +12.6 (215); (*R*)-**10f**, −12.6 (233) and +9.1 (214).

DETERMINATION OF ABSOLUTE CONFIGURATION, PREDOMINANT CONFORMATION, AND TAUTOMERIC EQUILIBRIUM OF ENANTIOMERIC SULFOXIDES AND t-*BUTYLPHENYLPHOSPHINOTHIOIC ACID BASED ON VCD SPECTRA*

Recently, the combination of experimental and ab initio absorption and VCD spectra has extensively been used for determining the absolute

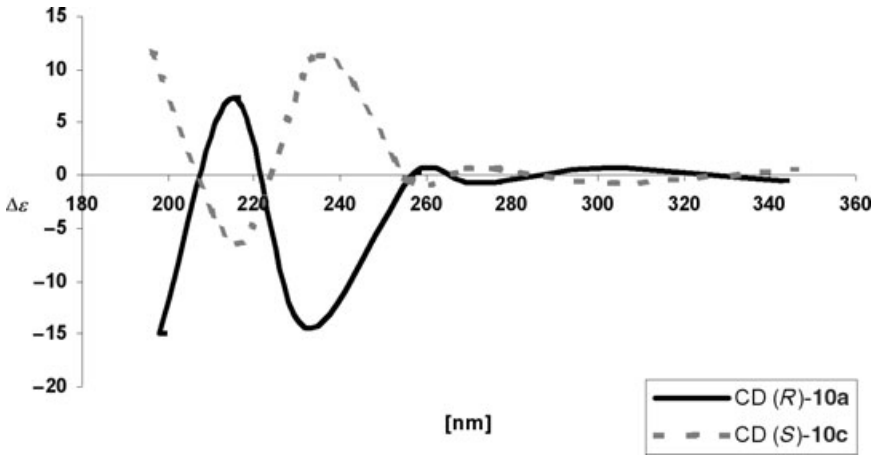


FIGURE 5 CD and UV spectra of (*R*)-**10a** and (*S*)-**10c** in acetonitrile solution.

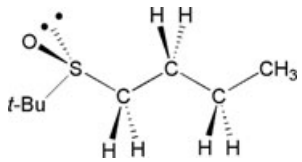


FIGURE 6 The most populated conformation of *n*-butyl *tert*-butyl sulfoxide.

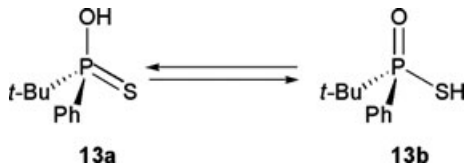


FIGURE 7 Tautomeric structures of *t*-butylphenylphosphinothioic acid **13**.

configuration and predominant conformations of chiral molecules in the solution phase [22–24]. This has been possible because of the recent improvements in VCD instrumentation and in ab initio applications using density functional theory (DFT) that provides vibrational frequencies and intensities that are comparable to the post-SCF calculations employing electron correlation. Recently we have measured [15a] the VCD of the dextrorotatory enantiomer of *n*-butyl *t*-butyl sulfoxide, (+)-**12**, and undertaken the state-of-the-art ab initio theoretical VCD investigations using the B3LYP/6-31G* basis set, and the results of these works were used for suggesting the absolute configuration and predominant conformations of (+)-**12**. It was concluded that among 27 considered conformations for *n*-butyl *t*-butyl sulfoxide **12**, the (T,t,t′) conformation (Fig. 6) is most populated.

Comparison of the experimental VCD spectra of (+) *n*-butyl *tert*-butyl sulfoxide **12** for which the significant VCD absorptions are as follows: a positive band at 1067 cm^{-1} and a positive–negative couplet with positive maximum at 1028 cm^{-1} and negative maximum at 1014 cm^{-1} with a predicated one—positive band at 1055 cm^{-1} and a positive–negative couplet, with the positive portion resolved into two positive bands (at 1014 and 1028 cm^{-1}) and the negative maximum at 1001 cm^{-1}—clearly indicate that the major VCD features observed for (+)-*n*-butyl *tert*-butyl sulfoxide **12** are reproduced in the predicted VCD spectrum for (*R*)-*n*-butyl *tert*-butyl sulfoxide **12**. Taking into account that the predicted spectrum for (*S*)-*n*-butyl *tert*-butyl sulfoxide **12** has opposite signs from those observed for (+)-*n*-butyl *tert*-butyl sulfoxide **12**, the (*R*)-configuration should be assigned to the (+)-enantiomer.

Vibrational absorption and circular dichroism spectra of dextrorotary, levorotary, and racemic mixture of *t*-butylphenylphosphinothioic acid **13** [25] have been measured in CCl_4 solution in the range 2000–900 cm^{-1}. The conformations for both tautomeric structures of (*S*)-*t*-butylphenylphosphinothioic acid **13a** and **13b** were investigated using the B3LYP functional with the 6-31G* basis. For the most stable conformation, the absorption and VCD spectra are predicted ab initio using the B3LYP functional, and B3PH91 was also used, with the 6-31G* basic set. The predicted spectra were compared to the experimental spectra. The comparison indicates that (–)-acid **13** is of the (*S*)-configuration and exists in only one tautomeric structure **13a** in CCl_4 solution (Fig. 7).

THE USE OF ENANTIOMERIC t-BUTYLPHENYLPHOSPHINOIC ACID FOR EE DETERMINATION

Very often the simplest approach to determination of the enantiomeric excesses of chiral compounds is based on the use of NMR measurements in the presence of chiral solvating agents (CSAs). Chiral compounds are able to form dynamic diastereomeric solvation complexes with the analyzed enantiomers, which can show nonequivalent spectra. Among the CSAs reported in the literature, the enantiomers of *t*-butylphenylphosphinothioic acid (−)-(*S*) or (+)-(*R*)-**13** have recently been applied for NMR analysis of many classes of chiral organic compounds. The first application of optically active (+)-(*R*)-**1** for the determination of the enantiomeric ratio of diverse structures of racemic phosphinate esters [e.g. RPhP(O)OR′; R = Me, Et, *i*-Pr, *t*-Bu, Ph; R′ = Me, Ph] and phosphinothioates [RPhP(O)SR but not RPhP(S)OR′] was reported by Harger [26]. In all ^1H NMR spectra (CCl_4) of esters investigated, chemical shift nonequivalence ($\Delta\delta$) induced by the addition of 1 mol equiv. of (+)-(*R*)-**13** was observed. The magnetic nonequivalence observed in NMR spectra of a large group of organic compounds in the presence of enantiomers of **13** is due to at least two factors. The first one results from the presence of aromatic rings and their diamagnetic effect. The second one is connected with a specific structural feature of the thioacids, which are proton donors and simultaneously hydrogen bond acceptors and may act as bidentate ligands. Therefore they can form solvates with other compounds utilizing their own acidic and basic centers. The formation of homo- and heterodimeric structures by the thioacid **13** illustrates its acidic and basic properties, which

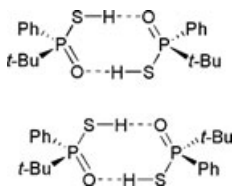


FIGURE 8 Homo- and heterodimeric structures of the thioacid **13**.

are evident in the phenomenon of the chiral self-discrimination of enantiomers (Fig. 8).

The acids (*R*)-**13** induce chemical shift nonequivalence of enantiomers in the ^{1}H NMR spectra of chiral phosphinic amides such as MePhP(O)NHPh and *t*-BuPhP(O)NH_2 [26]. The thioacid (+)-**13** was also found to be a useful chiral solvating agent for direct enantiomeric ratio determination (ee) of alcohols, diols, thiols, mercaptoalcohols, amines, aminoalcohols, hydroxyacids, and related compounds [27]. A very high sensitivity of the present method of enantiomeric analysis of chiral alcohols was best demonstrated by observation of magnetic nonequivalence in ^{1}H NMR spectra of the diastereomeric solvates formed by (*R*)-**13** with benzyl alcohol-d_1 and isopropyl alcohol-d_3 in which the stereogenicity at carbon is due to isotopic H $\rightarrow$ D substitution [27]. Similarly, it has been found that both enantiomeric forms of **13** are also suitable for the determination of the enantiomeric ratio of chiral amines. As the interactions between the components of acid **13**—amine in diastereomeric salts—are stronger than those in diastereoisomeric solvates with alcohols, the chiral shift differences, $\Delta\delta$, of the appropriate diastereotopic signals are as a rule greater. During the course of the study devoted to the determination of enantiomeric purity of a series of chiral 1,2-aminoalcohols [28], it was found that only **13** produces a high degree of magnetic nonequivalence ($\Delta\delta$ values of up to 400 Hz). Simultaneously, the resulting spectrum allows the assignment of *erythro* or *threo* configuration for a particular stereoisomer through measurement of vicinal *J* values. In addition, chiral *t*-butylphenylphosphinothioic acid **13** was applied for the NMR analysis of heteroatom compounds containing the stereogenic sulfur and phosphorus atom such as sulfoxides **16** [29] and phosphoryl compounds **17** [30]. Both (−)-(*S*)-**13** and (+)-(*R*)-**13** were applied for the NMR determination of enantiomeric excess (ee) value of chiral tertiary amine oxides [31]. It was demonstrated that **13** is able to induce simultaneously magnetic nonequivalence of the diastereotopic methyl and methylene protons of an alkyl chain or benzyl group

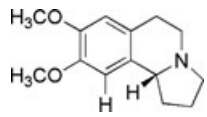


FIGURE 9 Cryspine A.

and an extremely large nonequivalence of the geminal *N*-methylene protons. Very recently, (+)-(*R*)-**1** was used as a CSA for the determination of enantiomeric excess of the antitumor alkaloid crispine A [32] (Fig. 9).

^{1}H NMR spectra of the obtained samples of the crispine show that the magnetic nonequivalence was visible for all groups of proton especially for the aromatic and OMe protons. The best diagnostic value has the absorption of the aromatic protons at C(10), which appears in the ^{1}H NMR spectrum of racemic crispine as a singlet and in the presence of (+)-(*R*)-**13** as two well-separated singlets.

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