Recent Progress in Application of Spectroscopic Methods for Assigning Absolute Configuration of Optically Active Sulfoxides

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Abstract: In the recent years, in addition to the more traditional methods based on X-ray diffraction and mechanistic considerations, the problem of the configurational assignment of optically active sulfoxides has been approached with spectroscopic methods. In this review the methods based on the use of NMR spectroscopy and electronic circular dichroism are described, as well as the emerging approaches based on the analysis of vibrational CD spectra, on the *ab initio* calculation of the optical rotation and on the cholesteric induction in nematic solvents. The advantage and limitations of each approach are discussed with a major attention to their reliability and practicality.

Keywords: Absolute configuration, sulfoxides, CD, optical rotatory power, NMR, VCD.

1. INTRODUCTION

The relevance of optically active sulfoxides in organic and medicinal chemistry is continuously increasing [1]. In fact, many bioactive compounds and drugs contain a chiral S=O moiety [2] and enantiopure sulfoxides are used as valuable synthetic intermediates [3] and ligands [4] for asymmetric synthesis. A number of approaches for their preparation has been therefore developed, the most important ones being the nucleophilic displacement of chiral sulfinates [5] and the enantioselective oxidation of sulfides [6]. The assignment of absolute configuration (AC) to chiral sulfoxides, either coming from natural sources or asymmetric synthesis is then an issue of primary importance in organic chemistry and, besides the classical chemical correlation, a number of spectroscopic approaches have been developed to this end [7]. The X-ray analysis has been of fundamental importance in early studies, allowing to establish the AC of some optically active sulfur compounds, suitable to be used as reference compounds for assignments of AC to related chiral sulfoxides. The sulfoxide whose AC was assigned for the first time by X-ray was (+)-methyl-L-cysteine sulfoxide [8], but the real breakthrough in this field was obtained with the AC determination of (-)-menthyl-*p*-iodophenylsulfinate [9], by internal comparison with the known stereochemistry of (-)-menthol, and of (*R*)-(+)-methyl-*p*-tolyl sulfoxide, by the Bijvoet method [10]. The knowledge of the AC of these compounds allowed to establish that the Anderson reaction of Grignard reagent with sulfinic esters occurs with inversion of configuration at sulfur [11], a discovery which was the basis for the AC assignment of a lot of sulfoxides obtainable by the Anderson procedure. Despite of its undisputed importance and reliability, X-ray analysis however presents the drawback that pure suitable single crystals are needed and therefore this technique cannot be employed in the case of compounds which are not solid or are difficult to crystallize. For this reason, a great effort has been devoted to the development of alternative approaches based on spectroscopic method, i.e. NMR and chiroptical spectroscopies, techniques that allow to establish the AC of sulfoxides by solution measurements. Aim of this review article is then to cover the field of the AC assignment of optically active sulfoxides (i.e. a topic which has been completely neglected so far) discussing the more recent advances obtained by NMR and chiroptical techniques, giving emphasis to the generality and reliability of the methods. Within the chiroptical approaches will be analysed not only the methods based on electronic circular dichroism, but also the very recent studies based on the *ab initio* calculation of vibrational circular dichroism spectra and optical rotation.

2. NMR SPECTROSCOPY

Despite the widespread use of NMR spectroscopy for AC assignments [12], its employment to chiral sulfoxides is still limited to a few cases. The most common approach for NMR-based AC assignment of sulfoxides requires the use of chiral solvating agents (CSA's). Such compounds can give rise to non-covalent interactions with the sulfoxide (mainly by hydrogen bonding) then inducing chemical shifts changes in the protons nearby the stereogenic sulfoxide moiety. An optically active sulfoxide gives rise to diastereomeric complexes when interacting with both enantiomers of the CSA and the sense of induced non-equivalence (i.e. the sign of the differences in chemical shifts between the same ^{1}HNMR signal in the two diastereomers) can be empirically related to the sulfoxide AC. Therefore, in order to determine the AC of a sulfoxide it is necessary to record the NMR spectrum of both its diastereomeric adducts with a CSA, either by adding both enantiomers of the CSA to an enantiopure sulfoxide or by adding one enantiomer of the CSA to an enantiomerically enriched sulfoxide, then to measure the chemical shift differences of the signals due to the protons on each side of the S=O stereogenic center in both the adducts. From the sign of such differences it is possible to determine which one of the diastereomeric complexes has been formed and then the AC of the starting sulfoxide. Such approach is rather simple and rapid, but present some important drawbacks. The main one is that the correlation between the induced chemical shift differences

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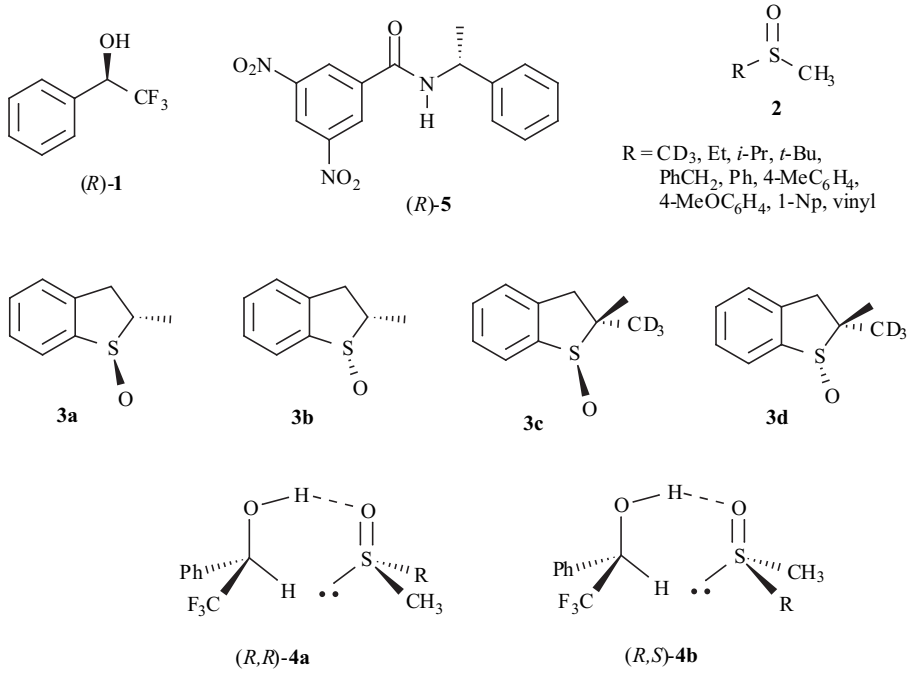
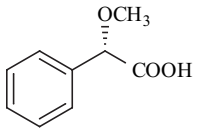


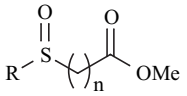
Fig. (1). Solvation model for interaction of (*R*)-**1** with both (*R*) and (*S*) configurated aryl methyl sulfoxides.

and the substrate AC is completely empirical. Moreover, in order to achieve a reliable correlation, the prevalent conformation of the complexes must be known, a very difficult task in this case, where non-covalently bonded species are present in solution. With such labile adducts a fast equilibrium between several species and conformations is certainly present in solution, therefore also the chemical shift non-equivalences displayed are often too small for a reliable detection of the AC.

In a pioneering work Pirkle and Beare [13] described the use of (-)-(*R*)-2,2,2-trifluoro-phenylethanol (**1**) for the analysis of the enantiomeric purity of alkyl methyl and aryl methyl sulfoxides **2** (Fig. (**1**)), also reporting an empirical correlation between the sense of induced non-equivalence of the proton chemical shifts and the sulfoxides AC. The same approach was further extended to the cyclic sulfoxides **3a-d** [14]. A solvation model, which attempts to rationalize the observed experimental behaviour was also proposed (Fig. (**1**)) [15]. In such a model the chiral alcohol and the sulfoxide can give rise to weak intermolecular interactions through the hydrogen bonding of the hydroxy and sulfoxide moieties. The inductive effects of the proximate electron withdrawing CF_3 group render in fact the alcoholic hydrogen more acidic and then prone to interact with the basic S=O group. In the solvate (*R,R*)-**4a**, coming from (*R*)-**1** and an (*R*)-configured alkyl methyl sulfoxide, the methyl group faces the CF_3 moiety, while the R group is *syn* to the phenyl ring. The opposite situation holds for the diastereomeric solvate (*R,S*)-**4b**. Because of shielding by the phenyl, one expect the methyl NMR signal to occur at higher field for (*R,S*)-**4b** than for (*R,R*)-**4a**. The converse is expected for the protons of the R alkyl moiety, which will display resonances at higher field for (*R,R*)-**4a** than for (*R,S*)-**4b**. This model is consistent with the experimental data reported [14,15] where, in every instance, the sense of non-equivalence of the two groups on either side of sulfur are opposite and correlated to the sulfoxide AC. In a similar approach the CSA (*R*)-(-)-(3,5-dinitrobenzoyl)-α-phenyl-ethylamine (**5**) (Fig. (**1**)) was later used by Kagan and co-workers [16] to determine the enantiomeric purities of chiral sulfoxides obtained by enantioselective oxidation of sulfides [6c,d]. These authors also tentatively proposed an empirical correlation between the observed NMR signal splitting and the sulfoxides AC [17]. In the case of complex spin systems like quasi-symmetrical chiral dialkyl sulfoxides; the poorly acidic CSA's **1** and **5** give rise to weak interactions which are not able to induce detectable non-equivalence of the sulfoxide protons. Buist and Marecak [18] showed therefore that with such substrates an acidic CSA like (*S*)-(+)-α-methoxy phenylacetic acid (**6**) (Fig. (**2**)) is able to discriminate both dialkyl and benzyl alkyl sulfoxides **7a-d** (Fig. (**2**)), allowing both ee determination and an empirical AC assignment. The proposed [18] complexation model between (*S*)-**6** and sulfoxides (Fig. (**2**)) resembles the one suggested by Pirkle and co workers [15,19] for (*S*)-**1** (Fig. (**1**)). Here, the two molecules are tightened together by an hydrogen bonding between the carboxy and sulfoxide groups, while the non-equivalence of the protons on each side of the S=O moiety is again due to the relative position of the phenyl ring in the two diastereomeric complexes. The same authors also showed that acid (*S*)-**6** can be conveniently used for AC assignment of aryl and benzyl sulfoxides like **7e-g**, and **8a-c** [20], as well as complex galacto-sulfoxides [21], whose AC assignment was also subsequently confirmed by X-ray analysis [22]. Acidic CSA's (*S*)-α-methoxy-2-naphthyl acetic acid (**9**), (*S*)-α-methoxy-1-naphthyl acetic acid (**10**), (*S*)-Ibuprofen (**11**), and (*S*)-Naproxen (**12**) were also used by Noiret, Nugier-Chauvin and co-workers [23] (Fig. (**3**)) for ee and AC determination of dialkyl sulfoxides. These authors found that (*S*)-**9**, (*S*)-**10**, and (*S*)-**12**, having a large naphthalene moiety which can ensure a strong anisotropic effect, cause a larger signal splitting than (*S*)-**6**, thus allowing to carry out reliable



(*S*)-**6**



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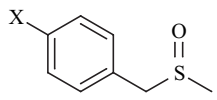
a R = C_8H_{17} n = 7
b R = C_7H_{15} n = 8
c R = $PhCH_2$ n = 7
d R = $PhCH_2$ n = 8
e R = $PhCH_2CH_2$ n = 7
f R = 2-$NpCH_2$ n = 7
g R = Ph n= 7



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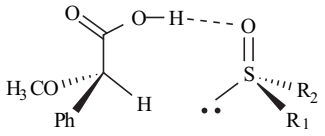
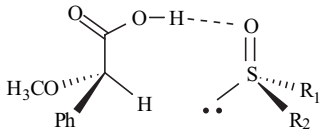
a X = CN
b X = F
c X = MeO

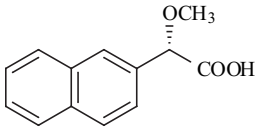


(*S,R*)-solvate

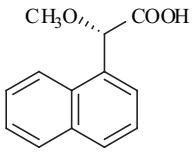


(*S,S*)-solvate

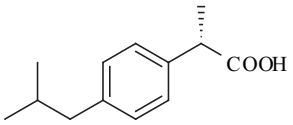
Fig. (2). Solvation model for interaction of (*S*)-**6** with both (*R*) and (*S*) configurated aryl methyl sulfoxides.



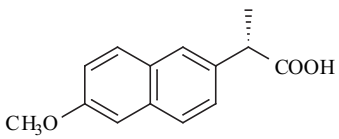
(*S*)-**9**



(*S*)-**10**



(*S*)-**11**



(*S*)-**12**

Fig. (3).

analysis also in the case of sulfoxides displaying complex NMR spectra and extended signal overlap. The acid (*S*)-**10** showed to be superior over the others, inducing larger signal non-equivalence and pointing out the importance of the aryl substitution (1-Np *vs.* 2-Np) on both the interaction with the substrate and the anisotropic effect exerted on the sulfoxide protons.

The host–guest complexation phenomenon is at the basis of the NMR stereochemical analysis of sulfoxides by means of axially chiral biaryl diols. Such compounds, in fact, are known to form host-guest complexes with a number of chiral compounds allowing, by crystallization, efficient optical resolution of the chiral guest compound [24]. Also in solution the formation of labile complexes with the guest can account for the non-equivalence of the substrate signals induced by such diols [25]. Toda *et al*. described the use of 2,2'-dihydroxy-1,1'-binaphthyl (**13**) [26] and 4,4',6,6'-tetrachloro-2,2'-bis(hydroxydiphenylmethyl)-biphenyl (**14**) [27] for the assignment of AC of aryl methyl and alkyl methyl sulfoxides by NMR spectroscopy (Fig. (**4**)). These authors observed that when sulfoxides were complexed with (*S*)-**13**, the methyl signal of (*S*) configured sulfoxides was at higher fields than the same signal of the (*R*) enantiomers. An interaction model explaining the observed behaviour was also suggested. In such a model it can be seen (Fig. (**4**)), that in the hydrogen bonded complex between (*S*)-**13** and (*S*)-sulfoxide, the methyl group is in front of the shielding anisotropic cone of the naphthalene moiety, while in the diastereomeric complex between (*S*)-**13** and the (*R*)-sulfoxide, the methyl is far away from the naphthyl group. This simplified analysis can justify the resonance differences of the methyl group in both the enantiomers.

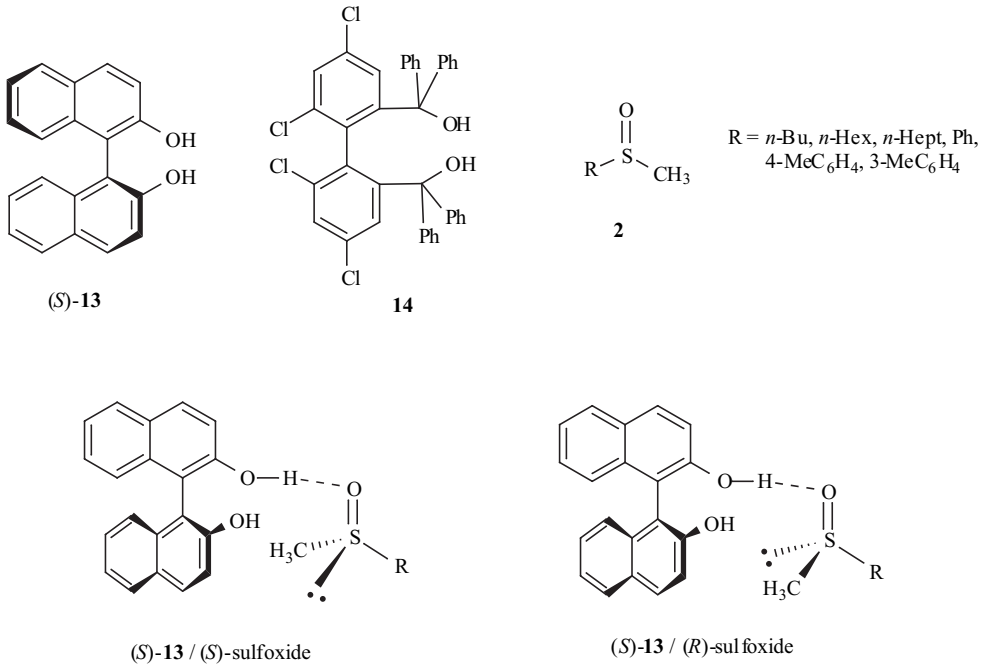
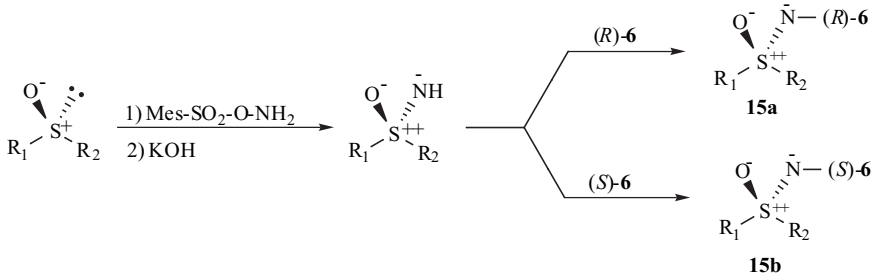


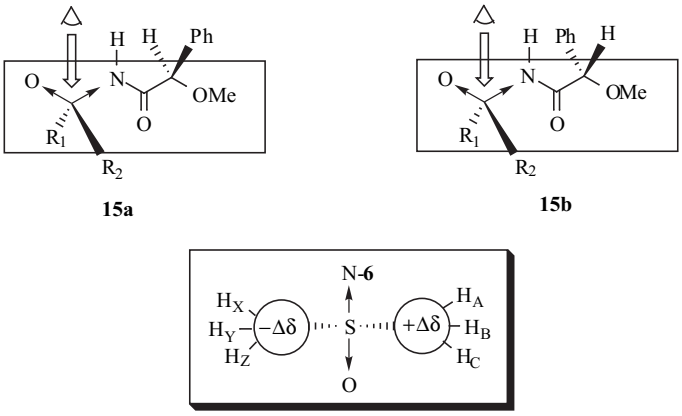
Fig. (4). Solvation model for interaction of (*S*)-**13** with both (*R*) and (*S*) configurated aryl methyl sulfoxides.



Scheme 1.

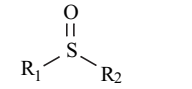
As outlined before, one of the major drawbacks of the use of CSA's to determine the AC is the intrinsic uncertainty allied to the conformational analysis of the labile complexes that are formed in solution. A higher reliability is therefore expected when chiral derivatizing agents (CDA's) bearing anisotropic aromatic groups are used. In this case the CDA is covalently bonded to the chiral substrate under examination (in this case the sulfoxide) and therefore the anisotropic effect due to the aromatic ring of the chiral auxiliary would be more significant than with the hydrogen bonded CSA's. A higher signal non-equivalence and then a higher reliability of the measurement is then expected. This approach was recently followed, for the first time on chiral sulfoxides, by Yabuuchi and Kosumi [28] who derivatized the sulfoxides with the CDA α-methoxy phenylacetic acid (**6**). In their approach the sulfoxide is first transformed in the corresponding sulfoximine by reaction with *O*-mesityl-sulfonylhydroxylamine [29], a reaction which proceeds with complete retention of configuration at the sulfur atom [30], and then the sulfonamide is reacted with the (*R*) and (*S*) enantiomer of **6**, obtaining the corresponding diastereomeric *N*-(methoxyphenylacetyl) sulfoximines **15a** and **15b**, respectively (Scheme (**1**)). According to the authors the more stable conformation of sulfoximines **15a** and **15b**, which minimize steric and dipole-dipole interactions, are the ones depicted in Fig. (**5**).

In the diastereomeric adduct **15a** the phenyl group then faces the R_2 moiety, exerting an anisotropic shielding, and shifting upfield the protons NMR signals. The R_1 moiety is instead shielded in the diastereomer **15b**, where its ^{1}HNMR signals are shifted upfield. Therefore, for any proton on the R_2 moiety $\delta_S > \delta_R$, where δ_R and δ_S are the chemical shifts of such proton in **15a** and **15b**, respectively, and then the difference in chemical shift in the two adducts is $\Delta\delta = \delta_S - \delta_R > 0$. The opposite holds for the protons on the R_1 side. According to this approach, in order to determine the AC of a chiral sulfoxide, it is necessary to prepare its sulfoximines with both enantiomers of **6**, to measure their ^{1}HNMR spectra and to determine the $\Delta\delta$ values for each proton. By using the empirical model on Fig. (**5**) it is possible, from the sign of the $\Delta\delta$, to determine on which side of the N-S-O moiety is located the fragment bearing a given proton and, therefore, the AC of the sulfoxide. This approach was tested successfully on the dialkyl and benzyl alkyl sulfoxides reported in Fig. (**6**), of known AC. In this method, the reliability of data interpretation and then, the AC assignment, lies on the assumption that the major conformers of **15a** and **15b** are the ones reported in Fig. (**5**). The authors, however, did not provide any proof about the actual conformation and therefore this AC assignment is still made on pure empirical basis.

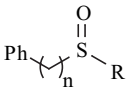


15a **15b**

Fig. (5). "Sulfoximine Model" for assignment of absolute configuration.



R_1 = *i*-Pr R_2 = Et
R_1 = *n*-Bu R_2 = Et
R_1 = Hexyl R_2 = Et
R_1 = Hept R_2 = Et
R_1 = *n*-Bu R_2 = Me
R_1 = *i*-Bu R_2 = Me



n = 1 R = *i*-Bu
n = 1 R = *n*-Bu
n = 2 R = Et
n = 3 R = Et
n = 4 R = Et

Fig. (6).

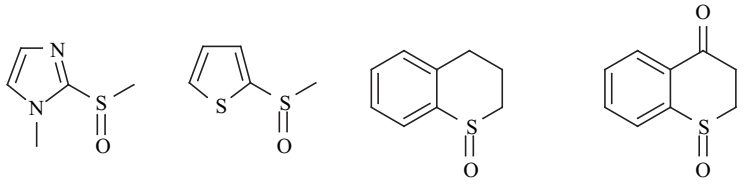
3. CHIROPTICAL METHODS

Electronic Circular Dichroism

The use of electronic circular dichroism spectroscopy (ECD) for assigning sulfoxides AC goes back to the seminal papers of Mislow and co-workers [31], who examined a series of alkyl aryl sulfoxides having known AC [32], thus establishing a first empirical correlation between their spectral features and AC. Studying the ORD spectra of such compounds they pointed out that "...the long wavelength Cotton effect corresponding to the primary band (i.e. the intense band at ca. 235-255 nm) has a high molecular amplitude of the order of 10^5 and *the positive sign characterizes the absolute (R)-configuration*". This empirical Mislow rule allowed the experimentalists to assign the AC of different alkyl aryl sulfoxides by simple comparison of their ECD spectrum with that of structurally similar sulfoxides having known configuration, then applying the so called "empirical path" of Snatzke [33]. This approach has been also more recently used to assign [34] the AC of the optically active heterocyclic sulfoxides 1-methyl-2-imidazolylmethyl sulfoxide (**16**) and 2-thienylmethyl sulfoxide (**17**) (Fig. (**7**)), prepared by the Anderson procedure, and the AC of several alkyl aryl sulfoxides produced by asymmetric oxidation of the corresponding sulfides by myoglobin mutants [35]. By comparison of the ECD spectra with those of the corresponding phenyl and 1-naphthyl alkyl sulfoxides has been also assigned the AC of some pyridyl and 2-isoquinolyl alkyl sulfoxides [36]. Further examples of AC assignment of optically active sulfoxides by the Mislow rule concern some interesting bioactive compounds such as the enantiomers of the non-steroidal anti-inflammatory agent sulindac [37] and the natural compound sparsomycin [38], showing biological activity against various tumours, bacteria, fungi and viruses.

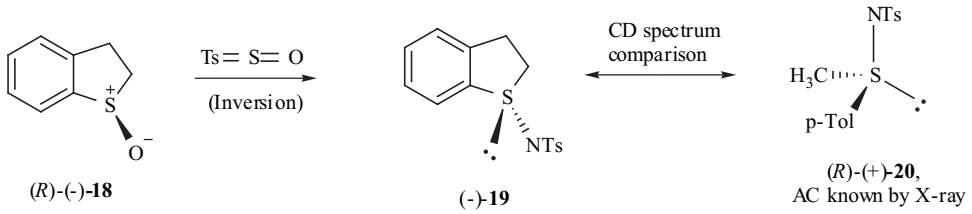
The empirical comparison of ECD spectra has been applied also in the case of cyclic alkyl aryl sulfoxides. The AC of (-)-2,3-dihydrobenzo [b]thiophene-1-oxide (**18**) was assigned by Cram and co-workers [39] (Scheme (**2**)) by converting (-)-**18** to the corresponding N-*p*-toluensulfonylimide (-)-**19** and comparing the UV/ORD spectra of (-)-**19** to the ones of the sulfonylimide **20** of known AC. The ORD spectra of (-)-**19** and (*R*)-(+)-**20** were in a mirror image relationship, leading to the assignment of (*S*) AC for (-)-**19**. Because the conversion of (-)-**18** to (-)-**19** occurs with inversion of configuration, therefore an (*R*) AC is assigned to (-)-**18**.

Knowing this configurational correlation, the AC of 1-thiochroman-*S*-oxide (**21**) [40] and that of 1-thiochromanone-*S*-oxide (**22**) (Fig. (**7**)) [41] has been also assigned, simply empirically comparing their ECD spectra with the one of **18**. It is interesting to note that both the AC assignment of **18** [39] and **22** [41] have been established choosing as reference compounds either the sulfonylimide **20** or the sulfoxide **18**; the use of (-)-(*S*)-phenyl ethyl sulfoxide, an equally reasonable choice as reference compound, would have



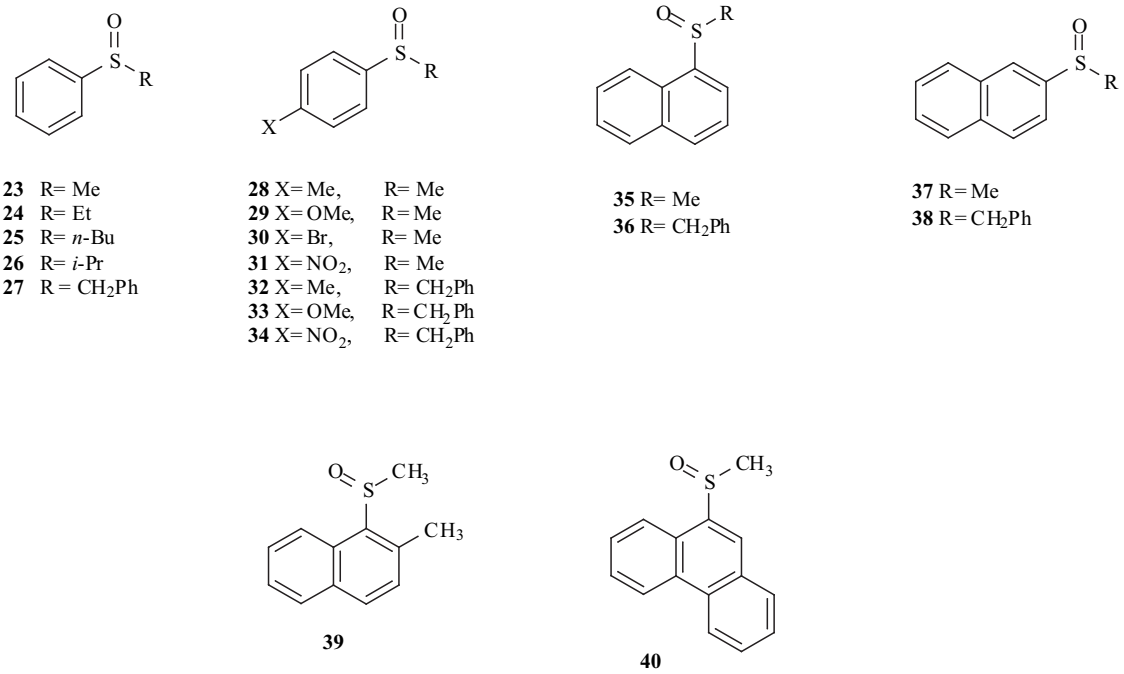
16 **17** **21** **22**

Fig. (7)



(*R*)-(-)-**18** (-)-**19** (*R*)-(+)-**20**, AC known by X-ray

Scheme 2.



23 R= Me
24 R= Et
25 R= *n*-Bu
26 R= *i*-Pr
27 R = CH_2Ph

28 X= Me, R= Me
29 X= OMe, R= Me
30 X= Br, R= Me
31 X= NO_2, R= Me
32 X= Me, R= CH_2Ph
33 X= OMe, R= CH_2Ph
34 X= NO_2, R= CH_2Ph

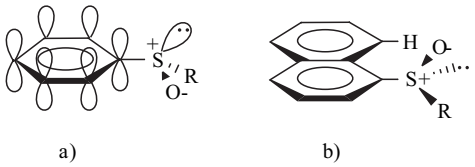
35 R= Me
36 R= CH_2Ph

37 R= Me
38 R= CH_2Ph

39 **40**

Fig. (8).

afforded the opposite assignment. The same empirical comparison of the CD spectra has been employed to determine the absolute configuration of several 1,3-benzodithiole 1-oxides and 2-alkyl-benzodithiole 1-oxides [42].



a) b)

Fig. (9). The 2p(C)-3sp^3(S) overlap in alkyl phenyl sulfoxides 23-34 (a), and the absence of overlap in 1-naphthyl compounds 35 and 36 (b).

The absorption and CD data of the series of alkyl aryl sulfoxides **23-38** (Fig. (**8**)), having known (*S*) configuration, were carefully analyzed [43], in order to understand the origin of the optical activity in this class of compounds and to formulate a non empirical correlation between spectra and structure. As a first result, it was possible to obtain important conformational information from the analysis of the absorption spectra. In fact, the strong bathochromic effect exerted by the nitro group in the *para* position of the phenyl sulfoxides **31** and **34** revealed that the sulfur atom acts as an electron donor moiety towards the phenyl ring. Such behavior requires a significant 2p(C)-3sp^3(S) overlap and therefore the phenyl (and *p*-substituted phenyl) sulfoxides **23**–**34** as well as the 2-naphthyl ones **37** and **38**, must assume a conformation which allows such orbital overlap (Fig. (**9a**)). The steric effect of the *peri* hydrogen in 1-naphthyl substituted compounds **35** and **36** does not permit a conformation of this type and in these compounds the above 2p(C) and 3sp^3(S) orbitals are placed in almost orthogonal planes (Fig. (**9b**)).

This conformational difference is clearly revealed by the absorption spectra: compounds **23**–**34** and **37**, **38** show the lowest energy $\sigma \rightarrow \sigma^*$ transition of the sulfoxide chromophore at 250 nm ca., indicating the existence of a conjugated S=O chromophore. On the contrary, in **35** and **36** the same absorption occurs at 200 nm ca., indicating the presence of an isolated S=O chromophore. The CD spectra of **35** and **36** (Fig. (**10**)) show a negative couplet-like feature between 250 and 200 nm. This spectral feature can be interpreted in terms of exciton coupling between the allowed $\sigma \rightarrow \sigma^*$ at 200 nm of the isolated S=O chromophore and the ^{1}B transition of the naphthalene chromophore. Molecular mechanics calculations provide the most stable conformation of **35** reported in Fig. (**11**).

Taking into account that the $\sigma \rightarrow \sigma^*$ transition of the sulfoxide chromophore is polarized (*vide infra*) as reported in Fig. (**11**), its coupling with the dipole relative to the ^{1}B transition of the naphthalene chromophore provides,

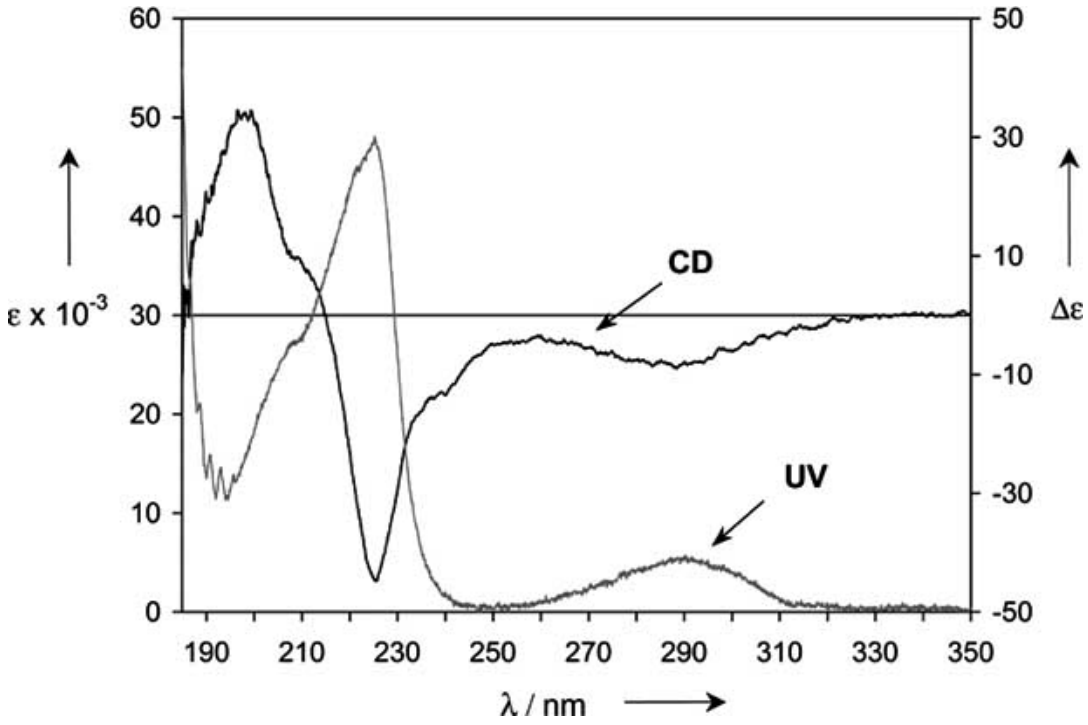


Fig. (10). UV (grey line) and CD (black line) spectra of (-)-**35** in acetonitrile.

following the exciton chirality approach for an (*S*)-configured sulfoxide, a negative chirality (Fig. (**11**)) and then a negative CD couplet, as experimentally found. DeVoe calculations on the 1-naphthyl substituted sulfoxides have been also carried out choosing **35** as a model compound and assuming arbitrarily (*S*) configuration at the sulfur stereogenic center. As input geometry the molecular geometry reported in Fig. (**11**) was employed. A single oscillator, polarized along the long axis of the naphthalene ring, carrying a dipole strength of 40 D^2 centered at 220 nm was employed to describe the naphthalene ^1B_b transition and a single oscillator, polarized along the C_{Me}-C_{Ar} direction and carrying a dipole strength of $10D^2$, was employed to describe the 210 nm $\sigma \rightarrow \sigma^*$ electrically allowed transition of the sulfoxide chromophore. In this way, the absorption spectrum was satisfactorily reproduced and the calculated CD spectrum showed extrema at 225 nm (Δε -88) and 206 nm (Δε +95) well comparing with the negative Cotton effect at 225 nm (Δε -45) and the positive one at 200 nm (Δε +35) in the experimental spectrum. In a subsequent paper [44] the DeVoe treatment was extended to (-)-1-(2-methylnaphthyl) methyl sulfoxide (**39**) and (-)-9-phenanthrylmethyl sulfoxide (**40**), i.e. alkyl aryl sulfoxides having the same conformational features of **35** (Fig. (**8**)). In all these compounds, in fact, the sulfur lone pair and the aromatic p orbitals, being on orthogonal planes, cannot exchange electrons, fulfilling the conditions for a correct application of the exciton model.

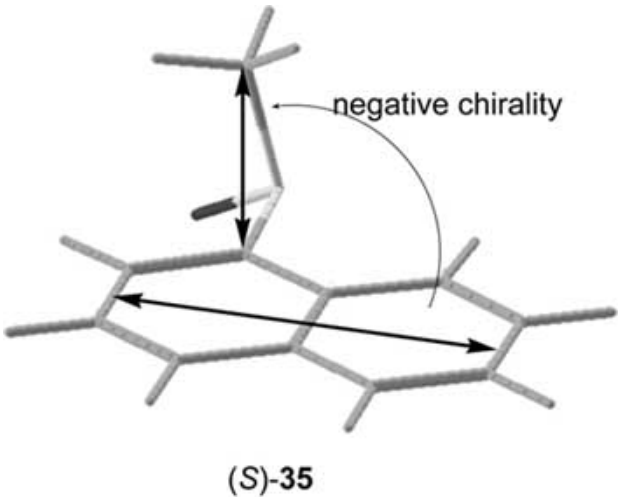


Fig. (11). Exciton chiralities defined by the allowed ^1B transitions of the naphthalene and S=O chromophores in *E*-(*S*)-**35**.

In the CD spectrum of **39** (Fig. (**12**)), in contrast to **35**, a positive couplet was present at about 220 nm. This interesting difference was interpreted in terms of the exciton chirality approach, taking into account that these two sulfoxides assume in solution different conformations. In fact, as demonstrated by NMR studies of Casarini *et al.* [45], the *E* form prevails for **35**, while for **39** the *Z* form is the prevailing one (Fig. (**13**)).

Such conformational difference can be explained considering that in **35**, in order to prevent steric hindrance, the smallest substituent on the sulphur atom (i.e. the lone pair) points toward the *peri*-hydrogen atom, while in **39** the lone pair is directed toward the more hindering methyl group on the 2 position of the naphthalene ring. Thus, for **39** the ^1B_a transition and the $\sigma \rightarrow \sigma^*$ sulfoxide transition dipole moment give rise to a positive chirality couplet for the same absolute configuration (Fig. (**14**)).

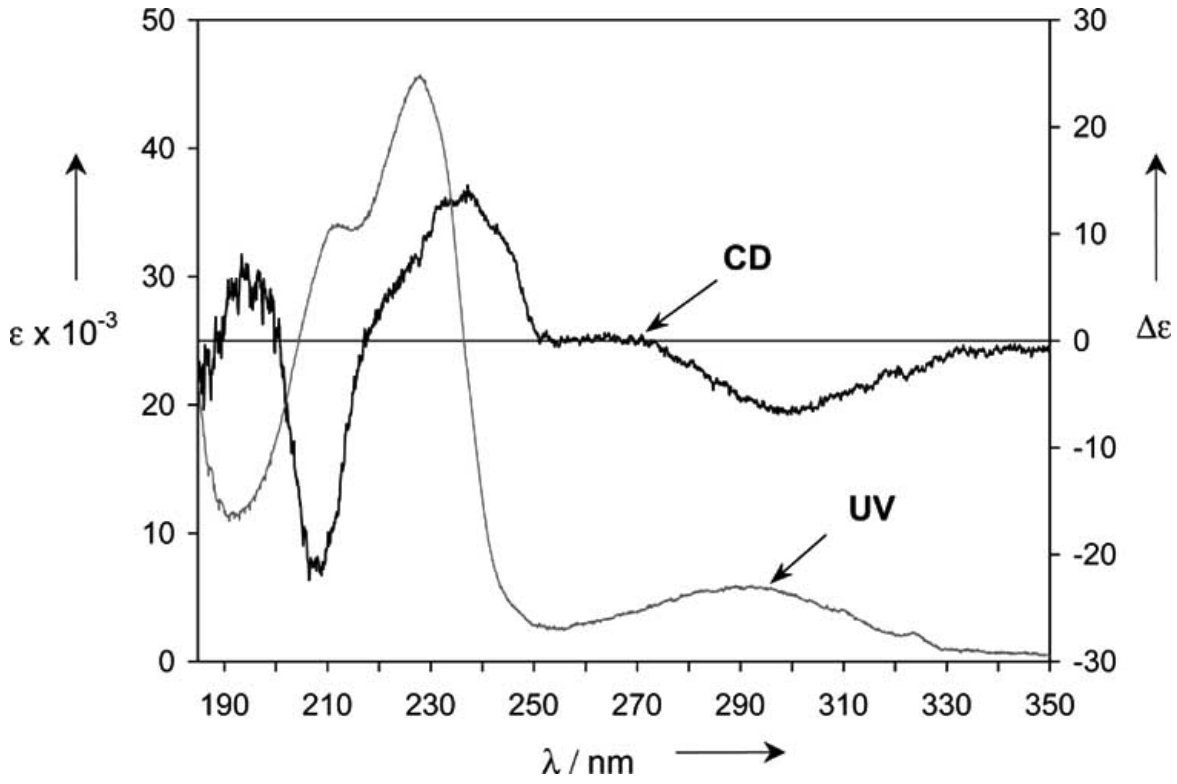
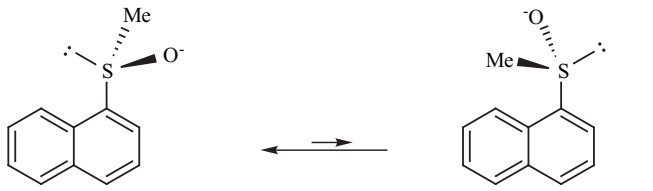
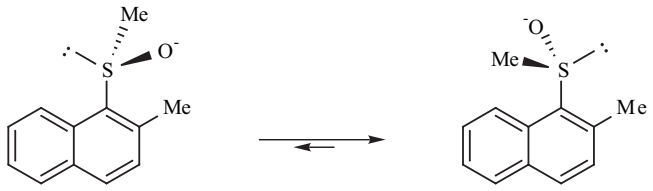


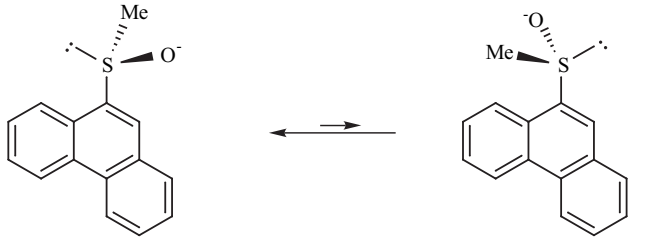
Fig. (12). UV (grey line) and CD (black line) spectra of (-)-**39** in acetonitrile.



(*S*)-**35**, *E* (*S*)-**35**, *Z*



(*S*)-**39**, *E* (*S*)-**39**, *Z*



(*S*)-**40**, *E* (*S*)-**40**, *Z*

Fig. (13).

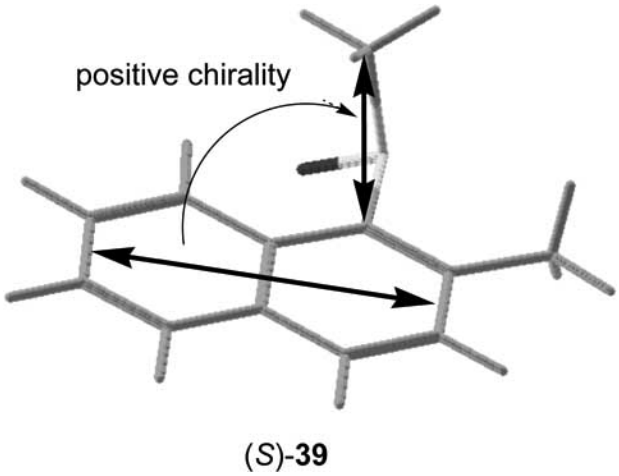


Fig. (14). Exciton chiralities defined by the allowed ^{1}B transitions of the naphthalene and S=O chromophores in and *Z*-(*S*)-**39**.

A quantitative reproduction of the experimental CD spectra carrying out DeVoe calculations for the 1-naphthyl sulfoxides **35** and **39** was also attempted. The input geometries were obtained by molecular mechanics calculations, assuming an (*S*) AC. The naphthalene allowed transition at about 225 was described by two long-axis polarized dipoles, at 220 nm carrying, a dipole strength of 30 D^2 and at 215 nm with a dipole strength of 10 D^2, respectively, while for the sulfoxide transition the same parameters previously used [43] were employed. The experimental and calculated CD spectra for **35** and **39**, obtained taking into account the Boltzmann conformer distribution determined by MM calculations, are collected in Fig. (**15**) and (**16**),. respectively. The agreement is quite satisfactory, demonstrating the correlation (-)/(*S*) in both cases.

In the case of **39** (Fig. (**16**)), a better quantitative agreement between experiment and theory was afforded using conformer population obtained by *ab initio* calculations [46], pointing out the importance of a correct knowledge of the actual *E/Z* conformers ratio for quantitative agreement between experimental and predicted spectra. The case of the phenanthryl sulfoxide **40** was more complex: the CD spectrum (Fig. (**17**)) shows a number of bands, no clear exciton couplets appear, and in correspondence to the strongly allowed band of the phenanthrene chromophore at about 250 nm, only a weak Cotton effect is measurable.

All these facts hamper a simple application of the exciton chirality approach and therefore DeVoe calculations were undertaken. The MM calculations afforded the structure of the conformers (Fig. (**13**)) and their distribution (*E/Z* 90/10). The drawings of Fig. (**13**) show clearly that the conformational situation of **35** and **40** is very similar, because the third aromatic ring does not exert any appreciable effect. As far as the description of the phenanthrene chromophore transitions is concerned, a series of dipoles was placed at 250 nm (28 D^2, long axis polarization), 240 nm (10 D^2, short-axis polarization) and 205 nm (10 D^2, short-axis polarization) as suggested by some CNDO/S-CI [47] calculations. Again, for the sulfoxide transition the same parameters used in the previous work [43] were used. A weighted average of the spectra of the two pure *E* and *Z* conformers affords the calculated spectra reported in Fig. (**18**): the main features of the experimental

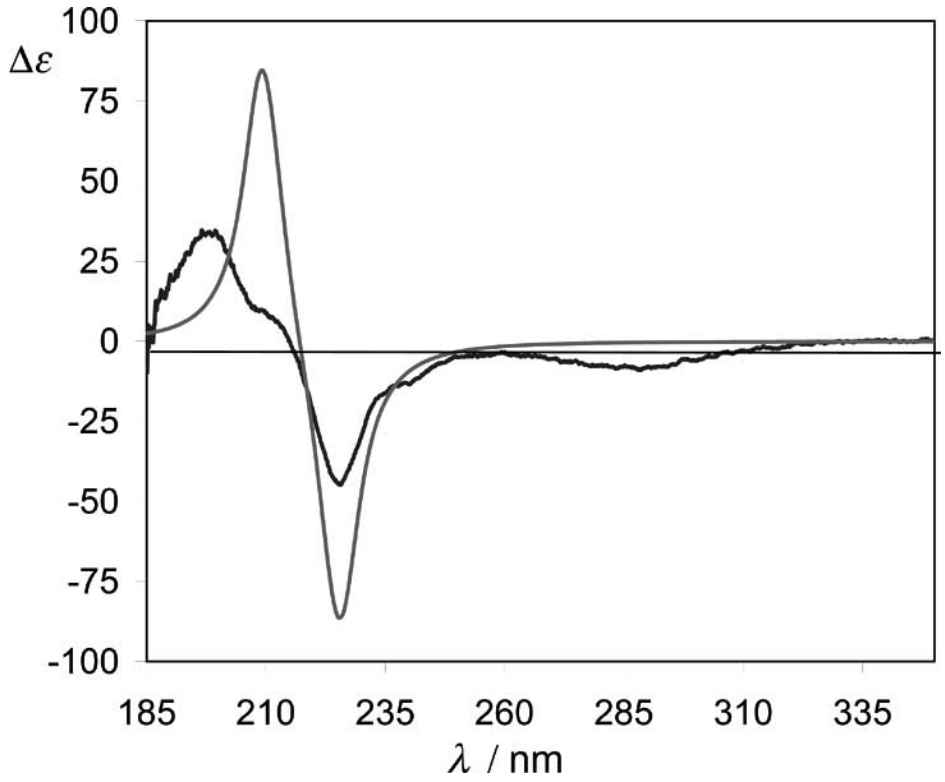


Fig. (15). Experimental (black line) and theoretical (grey line) CD spectra of (*S*)-**35**.

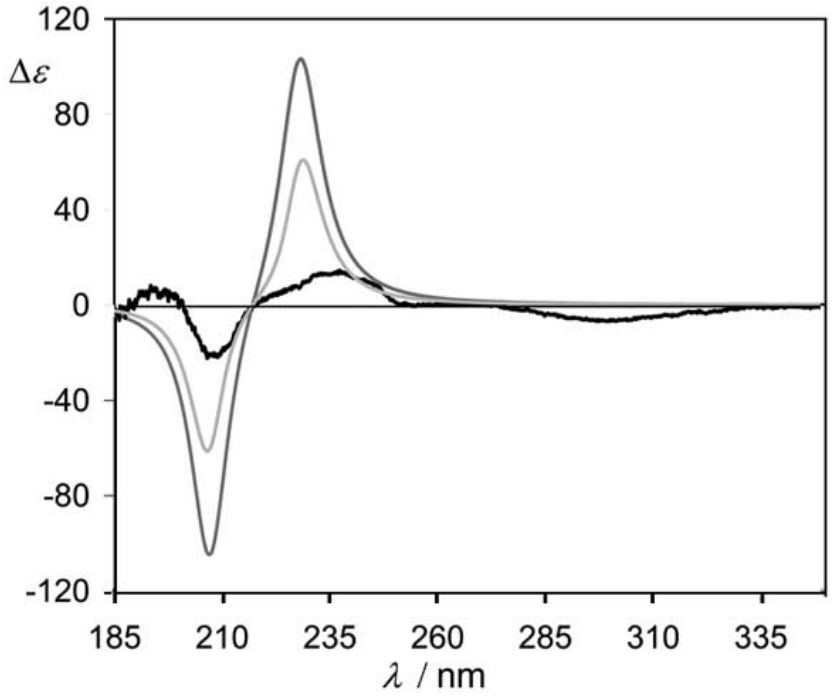


Fig. (16). Experimental (black line) and theoretical CD spectra of (*S*)-**39**. Grey line obtained using Z/*E* ratio provided by MMX calculations, light grey line obtained using *Z*/*E* ratio provided by *ab initio* calculations.

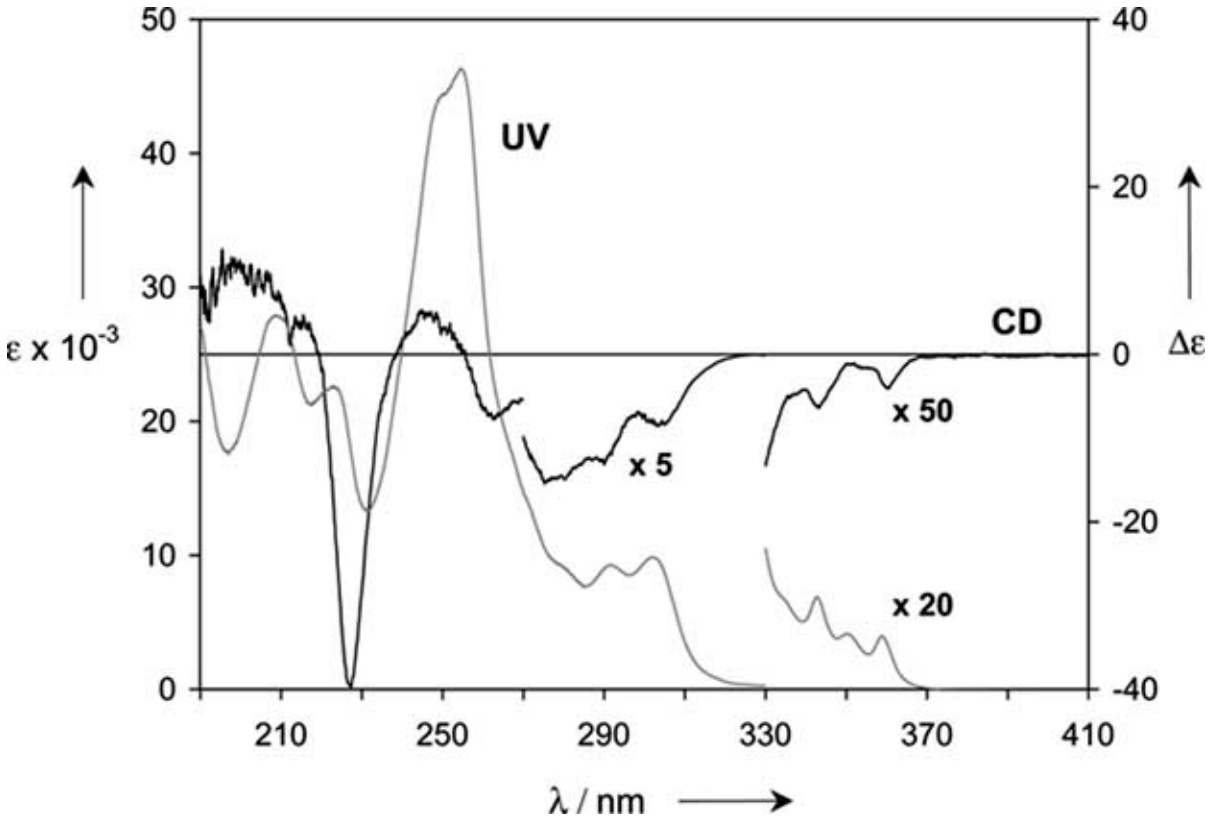


Fig. (17). UV (grey line) and CD (black line) spectra of (-)-**40** in acetonitrile.

CD spectrum (i.e. correct sequence of positive, negative, positive Cotton effects and also the right order of magnitude of the intensity) were quite well reproduced, affording the configurational correlation (-)-(*S*).

Drabowicz and co-workers [48] have recently set up a new method for determining the AC of alkyl aryl sulfoxides: they in fact assigned the AC of *N*-phthalimidosulfoximines from the analysis of their ECD spectra by means of the exciton model. These *N*-phthalimidosulfoximines are S-

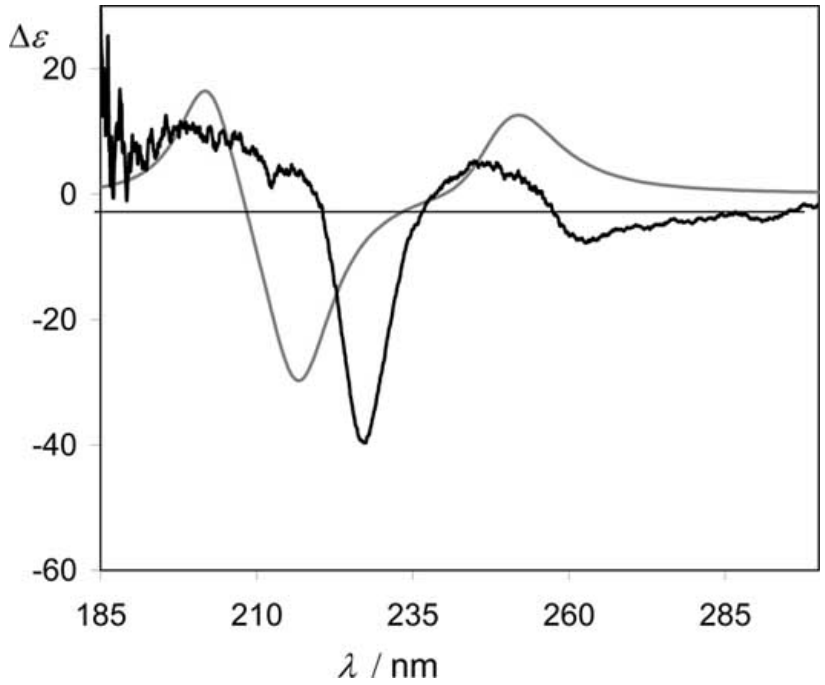
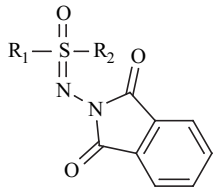


Fig. (18). Experimental (black line) and theoretical (grey line) CD spectra of (*S*)-**40**.

chiral compounds, which can be derived from sulfoxides *via* a process believed to proceed with retention of configuration [49]. These authors analysed the alkyl aryl *N*-phthalimidosulfoximines **41a-f** (Fig. (**19**)). For a given (*R*) configuration at the S atom the bischromophoric system shown in Fig. (**20**) is obtained, where three rotamers have to be considered, with regard to the rotation about the S-N bond.



41 a R_1=4-MeC_6H_5 R_2 =Me
b R_1= 4-MeC_6H_5 R_2 =Et
c R_1 = 4-MeC_6H_5 R_2 =*n*-Pr
d R_1= 4-MeC_6H_5 R_2 =*i*-Pr
e R_1 = 4-MeC_6H_5 R_2 =*t*-Bu
f R_1 = Ph R_2 =Me

Fig. (19).

A careful conformational analysis (MM+ search), followed by PM3 optimisation, showed that conformer A is the most abundant one. In rotamer A the ^1L_a transition dipole moment of the 4-tolyl chromophore and the 220 nm transition dipole of the phthalimido group (both polarized along the chromophore long-axis) define a negative chirality and therefore a negative CD couplet should appear in the ECD spectrum of a (*R*) configured *N*-phthalimido-sulfoximines, as experimentally found for compound **41a-f**. Therefore, once established the AC of the *N*-phthalimidosulfoximines by this approach, a new method of assigning the AC of alkyl aryl sulfoxides results, taking into account the stereochemical linkage between these compounds and the *N*-phthalimidosulfoximines. A completely different approach has been used to assign [50a] the AC of (-)-rubroflavin (**42**), an interesting natural compound containing an alkyl aryl sulfoxide moiety and responsible of the spectacular color reactions on bruising showed by some species of mushrooms. Controlled stereochemical fragmentation of (-)-**42** (Scheme (**3**)) affords (-)-3-methanesulfinyl-5-(methylthio)phenol (**43**) the ECD spectrum of which was interpreted by quantum-mechanical semiempirical CNDO/2S calculations. The necessary geometrical input data were obtained, assuming (*R*) configuration at the S atom, by the AM1 method, by a systematic variation of the dihedral angles θ_i, defined as shown in Scheme (**3**). For each conformer the ECD spectrum

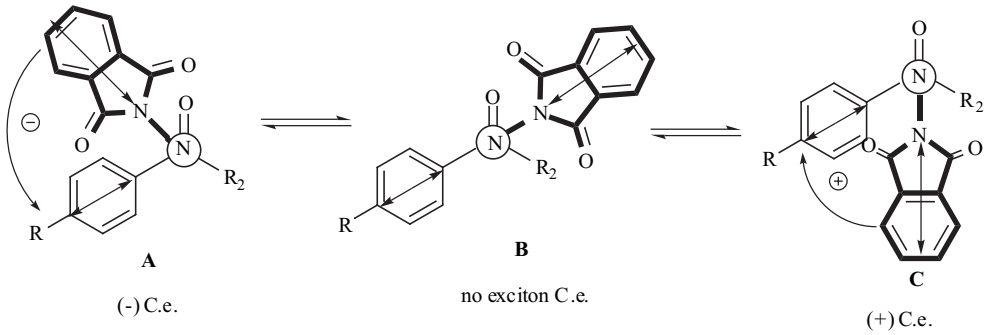
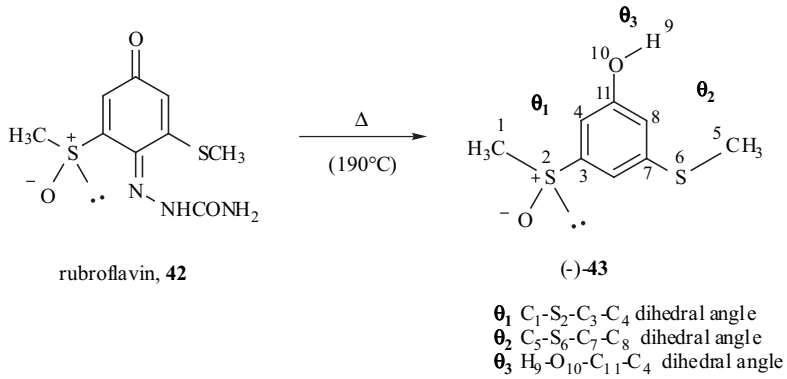


Fig. (20). Signs of Cotton effects for rotamers of N-phtaloimidosulfoximines of (*R*)-configuration.



Scheme 3.

was calculated by the CNDO/2S method, including 169 configurations. The rotational strengths were calculated using the origin independent dipole-velocity formalism. The CD spectrum was obtained as a sum of Gaussians, centred at the wavelength of the corresponding transition. The final spectrum obtained as a weighted average over the conformer populations, shows an (*S*) AC for (-)-**43** and therefore, considering that the sulfinyl group is configurationally stable during the thermolysis, also for the natural **42**. In a subsequent paper [50b], Raabe and co-workers confirmed these results by repeating the same treatment, but performing the geometry optimisation and the CD calculations by means of *ab initio* methods. Comparing the signs of the observed and calculated longest wavelength Cotton effects they again assigned (*S*) AC to **43**. Additional calculations revealed that the tricoordinate S atom in **42** and in **43** is configurationally stable under the conditions of thermolysis, and therefore they again concluded that the AC at the sulfur atom of both the products is (*S*). In a third paper [50c] of this series, Fleischhauer and co-workers analysed directly the ECD spectrum of (-)-**42**, avoiding its thermal degradation to a simpler sulfoxide. By means of high level DFT calculations on arbitrarily configured (*S*)-**42**, they found one quinoid isomer as the most stable one and from this structure obtained, by TDDFT calculations, a theoretical CD spectrum both in the presence and absence of a solvent. The satisfactory agreement between experimental and predicted (the agreement is better taking into account the solvent influence) CD data permits to conclude that natural (-)-**42** has indeed (*S*) AC, confirming the results of all the previous work. Other CNDO/S-CI calculations were employed to assign [51] the AC to enantiomers of 1,11-dimethyl-5,7-dihydrobenzo[c,e]thiepin S-oxide, resolved by LC upon swollen microcrystalline triacetyl cellulose [52]. The (*S*) configuration was then safely attributed to the first eluted (-) enantiomer.

Vibrational Circular Dichroism (VCD)

Although the first measurements of VCD data were reported [53] in the 1970s, this technique remained unused for many years. VCD spectra were in fact very difficult to measure because the ratio of the intensities of VCD bands relative to their parent unpolarized infrared (IR) absorption bands is generally an order of magnitude smaller than the same ratio between ECD and UV bands. Two major advancements made recently this technique potentially very powerful for structural determinations. First of all, commercial Fourier transform instrumentation for the measurement of VCD spectra has become available, greatly enhancing the accessibility of the technique [54]. Secondly, *ab initio* theoretical methods based on Density Functional Theory (DFT) have been developed and implemented [55] in quantum chemistry packages [56], permitting the routine, reliable prediction of VCD spectra. Therefore VCD spectroscopy can be now straightforwardly employed [57] to the determination of the AC of chiral molecules, by comparing experimental IR and VCD spectra with the calculated ones for a given AC of the molecule under study. After measuring the IR and VCD spectra, the theoretical spectra are determined as follows. First, the more stable conformation(s) (at room temperature) are predicted (at B3LYP/6-31G* level or higher) then, using these structure as input data, IR and VCD for any conformation are calculated, and finally, theoretical spectra are produced by the Boltzmann weighted average of such spectra. Comparison between experiment and prediction allows to determine the correct AC. The vibrational techniques possess a couple of advantages over ECD: (a) a vibrational CD spectrum presents many more Cotton effects than an ECD spectrum, so a configurational assignment based on VCD spectroscopy is certainly more reliable than the same assignment based on ECD, simply because sign and intensity of more bands have to be compared; (b) all the portions of a chiral molecule are VCD-active, so specific chromophores are not required. On the other hand, it may need (owing to a generally low signal-to-noise ratio) more time to obtain a good spectrum, with respect to ECD, and the instrumentation is still rather expensive, constituting another important obstacle to the diffusion of this technique. Very recently, this emerging approach has been successfully employed for the AC determination of alkyl aryl sulfoxides [58]. The AC of the naphthyl sulfoxide **39**, also studied [44] by ECD, was determined by the VCD approach [46]. The IR and VCD spectra of **39** were measured between 1600 and 400 cm^{-1}: the VCD spectrum was dominated by two main features at 950 cm^{-1} and 1070 cm^{-1}, respectively, the latter being attributable to the S-O stretching vibration. Other VCD intensities over much of the spectrum were really weak and for many vibrational transitions VCD was not detectable. *Ab initio* calculations (DFT/B3PW91/TZ2P) predicted for **39** the two stable conformations *E* and *Z* (see Fig. (**13**)), *Z* being lower in energy than *E* by 0.48 Kcal/mole (corresponding to a *Z/E* ratio of 70/30). In both

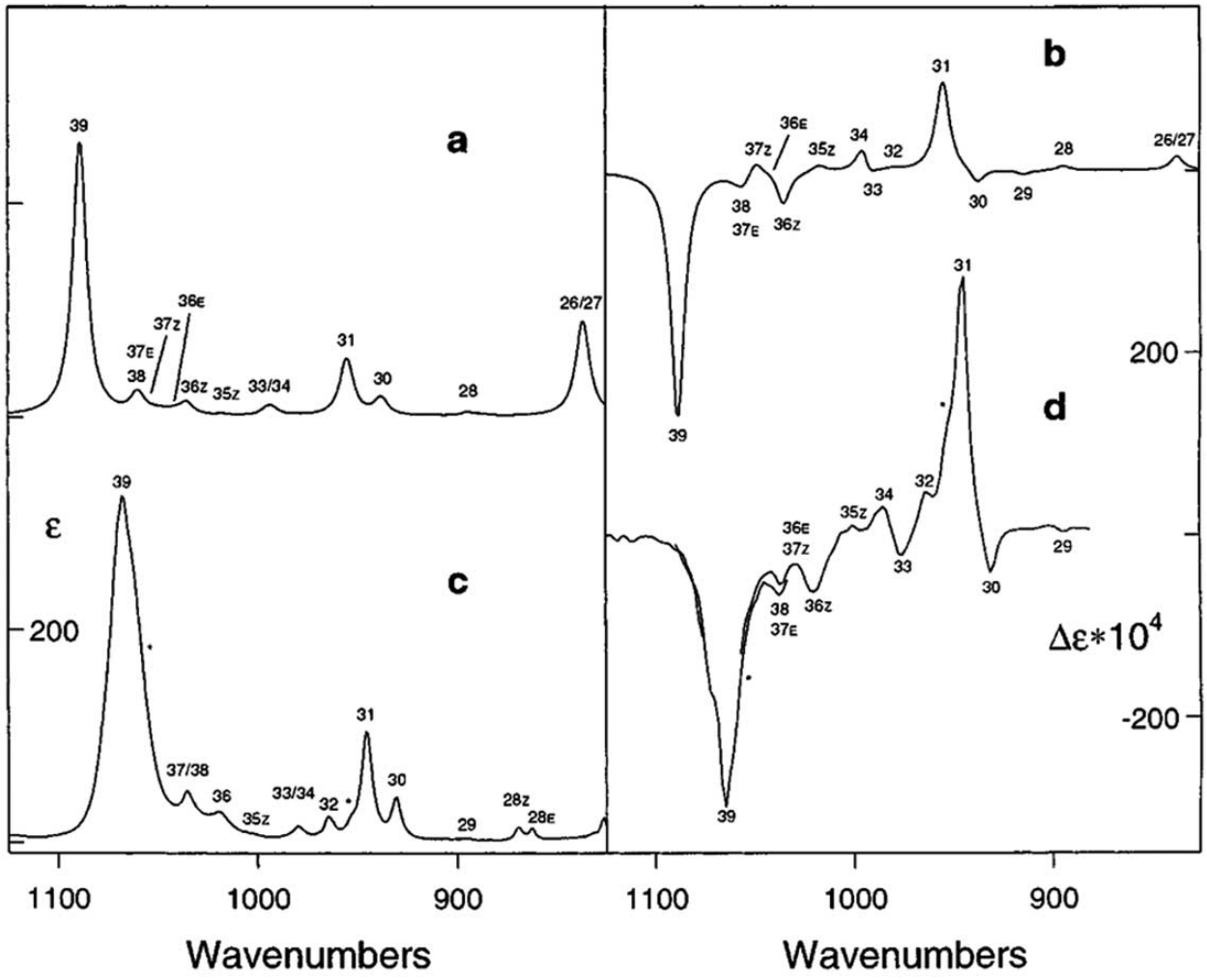


Fig. (21). IR and VCD spectra originating in modes 28-39 in **40**. **a, b** : B3PW91/TZ2P *E/Z* spectra; **c, d**: experimental spectra.

conformations the S-O bond was rotated from coplanarity with the naphthyl moiety by 30-40º. The VCD spectrum predicted for (*S*)-**39** at DFT/B3PW91/TZ2P level, as weighted average of *E* and *Z* VCD spectra, is in excellent agreement (Fig. (**21**)) with the experimental one of (-)-**39**, unambiguously defining, for the first time, the AC of **39** as (*R*)-(+)/(*S*)-(-).

Using the same VCD approach also the AC of the cyclic sulfoxides **21** [58b,d] and **22** [58c,d], was established with certainty to be (*R*)-(-)/(*S*)-(+). The AC of both compounds had been previously assigned only empirically by comparison (*vide supra*) of their ECD spectra with those of either sulfonylimide **20** or sulfoxide **18**, respectively. However some doubts remained on those structural determinations due to the questionable choice of the reference compounds. Other interesting applications of VCD spectroscopy to the assignment of the AC of sulphoxides concern the determination of (*R*) AC for both (-)-*tert*-butyl methyl sulphoxide (**44**) [58a] and (+)-*n*-butyl *tert*-butyl sufoxide (**45**) [59]. In the latter case IR and CD spectra of (+)-**45** were measured in $CDCl_3$ in the 2000-900 cm^{-1} region and compared with the *ab initio* (DFT/B3LYP/6-31G*) predictions of absorption and VCD spectra of several conformations of (*R*)-**45**. The good agreement between experimental and calculated VCD spectra indicated the configurational correlation (+)/(*R*) for this sulfoxide. Such AC determination forced to reconsider a previous conclusion [60] of the authors regarding the stereochemical outcome (retention) of the reaction of (*S*)-(-)-O-*n*-propyl *n*-butanesulfinate with *tert*-butyl magnesium chloride, which was based on an opposite configuration of (+)-**45**.

Ab Initio Calculation of the Optical Rotatory Power

The *ab initio* calculation [61,62] of the optical rotatory power, for instance at the sodium D line, i.e. $[\alpha]_D$, has become possible only very recently, mainly thanks to the extraordinary progresses of computational techniques. In this way it is now possible, at least in principle, to assign the molecular AC by a comparison between the experimental rotation and the value calculated *ab initio* by means of some commercially available packages [56,63,64]. According to the general theory [65], the OR is obtained as specific rotation $[\alpha]_\lambda$, for each angular frequency $\omega = 2\pi\nu = 2\pi c / \pi = 2\pi c\bar{\nu}$ of the incident radiation, through the calculation of the optical parameter β, which is directly connected to the trace of the frequency-dependent electric dipole-magnetic dipole polarizability tensor $\boldsymbol{G'}$, i.e.

$$[\alpha]_\lambda = 1.34229 \times 10^{-4}\ \beta\bar{\nu}^2\ (n^2 + 2)\ /\ 3M,$$

$$\beta = -\frac{1}{3\omega}\ \mathrm{Tr}\ [\boldsymbol{G}'(\omega)],$$

$$G'_{\alpha\beta}(\omega) = -\frac{4\pi}{h} \sum_{j \neq 0} \frac{\omega}{\omega^2_j - \omega^2}\ \Im(\langle 0|\hat{\mu}_\alpha|j\rangle\langle j|\hat{m}_\beta|0\rangle),$$

where the specific rotation is in unit of degrees [dm $(g/cm^3)]^{-1}$, β in units of $(bohr)^4$, the radiation wave number in cm^{-1}; n is the refractive index of the medium, M the molar mass in g/mol; ω_j is the transition frequency from ground state $|0\rangle$ to excited state $|j\rangle$, $\hat{\mu}$ and $\hat{m}$ the electric and magnetic dipole operators respectively. The assignment can be made if the theoretical result is fully reliable: from this point of view Stephens *et al.* established [61c] that a reliable *ab initio* calculation of the optical rotation requires the Time Dependent Density Functional Theory (TDDFT) method, Time Dependent Hartree-Fock (TDHF) being less accurate, the hybrid B3LYP functional, and large basis sets, containing diffuse functions, like aug-cc-pVDZ or larger. Such calculations require also the use, as input geometry, of a structure optimised at DFT/B3LYP/6-31G* level or higher. Just using this approach Stephens and co-workers assigned [66] the AC of the rigid sulfoxide 2*H*-naphtho[1,8-*bc*]thiophene 1-oxide (**46**) (Fig. (**22**)) and of the flexible sulfoxide **40** (Fig. (**8**)) for which no configurational assignments were known in the literature. The former shows $[\alpha]_D$ +91 (methanol) while **40** has $[\alpha]_D$ +269 (chloroform). A DFT/B3LYP/6-31G* conformational search, carried out on (*S*)-**46**, afforded only one minimum energy structure where the five-membered ring is almost planar. Optical rotation calculation at 589 nm at the DFT/B3LYP/aug-cc-pVDZ using the above input geometry gave +113, establishing for **46** the configurational correlation (*R*)-(-)/(*S*)-(+). By contrast, in the case of the flexible compound **40**, assuming (*S*) AC, two different conformers *E* and *Z* were found (Fig. (**13**)). For (*S*)-*Z* the predicted $[\alpha]_D$ value was -366, whilst for (*S*)-*Z* $[\alpha]_D$ was -47, the Boltzmann weighted average being -336. Comparison with the experimental +269 value, allowed to establish for **40** the configurational correlation (*R*)-(+)/(*S*)-(-).

Induction of Cholesteric Mesophases in Nematic Liquid Crystals (LC Technique)

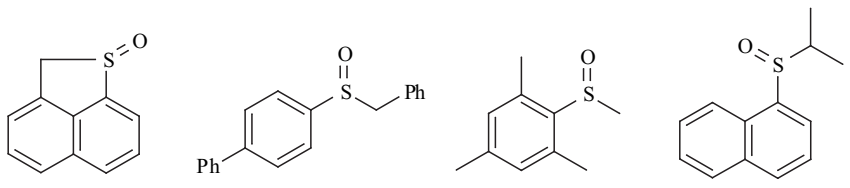
It is well known [67,68] that when a small amount of an optically active molecule is added to a nematic liquid crystal, a cholesteric phase is formed, having the helical pitch p as:

$$p = (c \cdot \beta \cdot ee)^{-1}$$

where c (gr/100 mL) is the concentration, ee is the enantiomeric excess of the solute and β is the helical twisting power of the solute. The helical twisting power β is a molecular property of the solute and describes the ability of a given chiral, non-racemic compound to twist the nematic phase. The sign of β is positive for a right-handed cholesteric and negative for a left-handed one. From a stereochemical point of view, β characterizes, at a given temperature, a chiral solute in a way similar to the optical rotatory power. However it is noteworthy that the origin of these two experimental values is completely different: optical rotation is a consequence of the interaction between light and matter, while β comes from a solute-solvent interaction. Therefore, one can expect to obtain different and independent information from LC techniques and chiroptical techniques: the former being more sensitive to the molecular shape. From a cholesteric induction experiment, one can obtain chiral information on the induced cholesteric (i.e. pitch and handedness) and therefore the helical twisting power of the dopant in that solvent (at a certain temperature). If a model or molecular theory relating molecular chirality to mesophase chirality is available, it is then possible to deduce stereochemical information about the dopant (such as absolute configuration) from such measurement. This approach has been very recently employed by Ferrarini, Gottarelli, Spada and co-workers [69] to relate the helical twisting power to the AC of a series of acyclic and cyclic alkyl aryl sulfoxides. The twisting power β of the sulfoxides **18**, **21**, **26, 28-39** and biphenyl benzyl sulfoxide **47**, mesityl methyl sulfoxide **48** and 1-naphthyl *i*-propyl sulfoxide **49** (Fig. (**22**)) has been determined in several nematic solvents. The sign of β which reflects the chirality of the induced helical arrangement of the solvent molecules, correlates with the AC of the stereogenic sulfur in nematics E7, Phase 1083, and ZLI2359: (*S*)-configured solutes induce (*M*)-chiral nematics. (*S*)-configured cyclic sulfoxides, which are forced to adopt a different conformation with respect to the parent acyclic compounds, induce, by contrast, (*P*)-chiral nematics. These experimental data can be interpreted by the "surface chirality model" [70], which allows the calculation of β in terms of the molecular properties of the dopant, i.e. the anisotropy and helicity of its molecular surface. The calculations reliably reproduce the behavior experimentally observed.

CONCLUSIONS

The analysis of the research papers carried out in the present work clearly shows the fundamental progresses done in the field of the AC assignment of optically active sulfoxides. Now many techniques are available to the experimental organic chemist to solve this problem, in addition to the established methods based on X-ray diffraction analysis and on reaction mechanisms. The spectroscopic methods fully developed in the recent years in



46 **47** **48** **49**

Fig. (22).

fact allow to carry out the structural determination in solution (avoiding the need of suitable single crystals, required by the X-ray method), and working on small amounts of the compound. It must be observed that, amongst the spectroscopic methods discussed herein, only those based on the analysis of the chiroptical properties guarantee (at least in our opinion) the required reliability. In fact the NMR-based approaches still rely on some structural assumptions (stoichiometry and structure of the solute/solvent aggregate) which cannot have secure foundations, while the chiroptical methods take into account only the solute conformation, and predict the chiroptical properties of the single conformers. The impressive progresses in the computational methods and in the instrumental techniques occurred in the last few years make the above two steps possible with a limited effort, allowing the experimental organic chemist to arrive quickly and reliably to the required AC assignment.

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