Towards a Correlation of Absolute Configuration and Chiroptical Properties of Alkyl Aryl Sulfoxides: A Coupled-Oscillator Foundation of the Empirical Mislow Rule?

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This paper is dedicated to Professor Kurt Mislow

Abstract: The absorption and circular dichroism (CD) data for a series of alkyl aryl sulfoxides **1**–**16** of known *S* configuration have been analyzed. The strong bathochromic effect exerted by the nitro group in the *para* position of the phenyl sulfoxides indicates 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 **1**–**12**, as well as the 2-naphthyl sulfoxides **15** and **16**, must assume a conformation which permits such orbital overlap. The steric effect of the *peri* hydrogen in 1-naphthyl-substituted compounds **13** and **14** does not allow a conformation of this type, and in these compounds the above-mentioned 2p(C) and $3sp^3$(S) orbitals are positioned in almost orthogonal planes. This conformational difference is clearly shown by the absorption spectra: compounds **1**–**12**, **15**, and **16** show the lowest energy $\sigma \rightarrow \sigma^*$ transition of the sulfoxide chromophore at approximately 250 nm, indicating the existence of a conjugated S=O chromophore. In contrast, the corresponding absorption in **13** and **14** occurs at about 200 nm, indicating the presence of an isolated S=O chromophore. The CD spectra of **13** and **14** 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 $\sigma \rightarrow \sigma^*$ transition of the isolated S=O chromophore at 200 nm and the ^1B transition of the naphthalene chromophore. In fact, the Harada–Nakanishi rule predicts a negative CD couplet for an *S*-configured sulfoxide in the conformation found by UV analysis, as found experimentally. The CD spectrum of **13** is quantitatively reproduced by DeVoe coupled-oscillator calculations, strongly implying that a coupled-oscillator mechanism is operative in determining the optical activity of **13** and **14**. This approach has also tentatively been extended to the conjugated sulfoxides **1**–**12**, taking into account the coupling of the benzene chromophore ^1L_a transition with the $\sigma \rightarrow \sigma^*$ transition of the S=O chromophore. In this case the Harada–Nakanishi rule also predicts a negative CD couplet for the *S*-configured sulfoxides, as found experimentally.

Keywords: asymmetric synthesis · circular dichroism · configuration determination · conformation analysis · sulfoxides

Introduction

Despite the recognized importance of enantiopure sulfoxides as bioactive compounds,[1] valuable synthetic intermediates,[2] and ligands[3]for asymmetric synthesis, reliable and general methods for configurational assignment of these compounds are still lacking. In particular, no safe correlations between circular dichroism (CD) data and structure have been described, presumably because the origin of the chiroptical properties of the sulfoxide chromophore is not yet well understood. In a series of seminal papers, Mislow et al.[4] examined the chiroptical properties of several alkyl phenyl sulfoxides of known configuration and formulated an empirical rule to correlate CD data and absolute configuration, but only Gottarelli et al.[5] addressed the problem of a nonempirical understanding of the optical activity of the aliphatic episulfoxide chromophore. After these papers, a few reports[6, 7] have appeared in which the absolute configurations at the sulfur stereogenic centers of some alkyl aryl sulfoxides have been assigned simply by comparing CD spectra of structurally related compounds, without addressing the issue of the understanding of the mechanism that induces optical activity in these compounds. This deficiency has recently been pointed out by Gawronski, who noted[8] that until now the absolute configurations of aryl sulfoxides have not been derived from CD spectra. The intention of this paper is to

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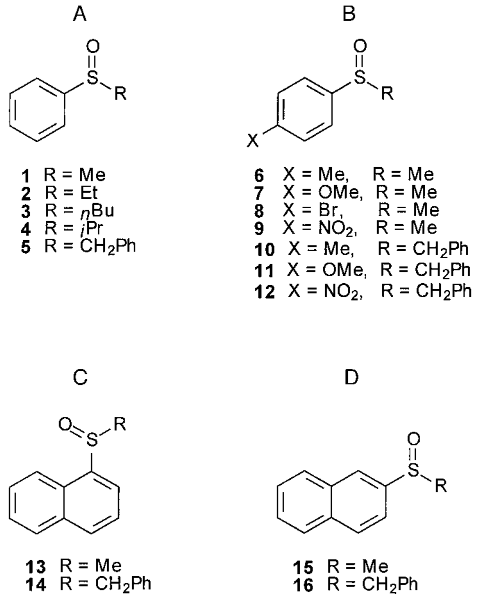
analyze the absorption and CD spectra of several alkyl aryl sulfoxides of different structures and known absolute configurations, with the aim of identifying the main mechanism responsible for the induction of optical activity in this chromophore and to formulate a simple and reliable, non-empirical relationship between spectrum and structure.

Results and Discussion

Synthesis: The subjects of this investigation are compounds **1**–**16** (Scheme 1). They were prepared in optically active form by following a previously described procedure:[7, 9] prochiral alkyl aryl sulfides were stereoselectively oxidized, by using *t*BuOOH in the presence of a chiral complex formed in situ from [Ti(*i*PrO)$_4$], H_2O, and (*R*,*R*)-1,2-diphenylethane-1,2-diol, to give the corresponding sulfoxides in 60–80% chemical yields and *ee*s up to 80% for alkyl aryl sulfoxides and up to 99% for aryl benzyl sulfoxides. The absolute configuration was assigned by comparison of $[\alpha]_D$ in the case of the known compounds **1**–**10**, **13**, and **15**,[10] while for the remaining derivatives **11**, **12**, **14**, and **16** it was assigned[7] by comparison of their CD curves with those of similar compounds of known configuration. All the compounds **1**–**16** are *S*-configured.

Abstract in Italian: *Sono stati analizzati gli spettri di assorbimento e di dicroismo circolare (DC) degli alchil aril solfossidi* ***1**–**16**, di configurazione assoluta S. Un gruppo nitro in posizione para del fenil solfossido esercita un forte effetto batocromo, indicando che l'atomo di zolfo agisce come elettron donatore nei confronti dell'anello benzenico. Tale fenomeno richiede una significativa sovrapposizione degli orbitali 2p(C)–3sp^3(S), per cui sia i solfossidi fenilici p-sostituiti* ***1**–**12** che quelli 2-naftilici **15** e **16** devono avere una conformazione tale da permettere la sovrapposizione di questi orbitali. L'effetto sterico dell'idrogeno peri nei composti 1-naftil sostituiti **13** e **14** non permette una conformazione di questo tipo e quindi in questi derivati gli orbitali 2p(C) e 3sp^3(S) sono su piani ortogonali. Questa differenza conformazionale è chiaramente mostrata dagli spettri di assorbimento: i composti **1**–**12**,**15** e**16** presentano la transizione* $\sigma \rightarrow \sigma^*$ *di più bassa energia del cromoforo solfossidico a circa 250 nm, suggerendo la presenza di un cromoforo S=O coniugato. Al contrario, in* ***13** e **14** lo stesso assorbimento si trova a circa 200 nm, indicando la presenza di un cromoforo S=O isolato. Gli spettri di DC di **13** e **14** presentano una specie di couplet eccitonico negativo tra 250 e 200 nm. Tale andamento spettrale può essere attribuito all'accoppiamento eccitonico tra la transizione permessa* $\sigma \rightarrow \sigma^*$ *a 200 nm del cromoforo S=O isolato e la transizione* ^1B *del cromoforo naftalenico. Infatti, per un solfossido di configurazione assoluta S ed avente la conformazione che abbiamo ricavato dall'analisi UV, la regola di Harada–Nakanishi prevede un couplet negativo nello spettro di DC, come osservato sperimentalmente. Lo spettro DC di* ***13** è stato riprodotto quantitativamente adoperando il modello ad oscillatori accoppiati dovuto a DeVoe, confermando che, effettivamente, l'attività ottica di **13** e **14** è determinata da un fenomeno di accoppiamento eccitonico. Questo trattamento è stato tentativamente esteso anche ai solfossidi coniugati **1**–**12**, prendendo in considerazione l'accoppiamento della transizione* ^1L_a *del cromoforo benzenico con la transizione* $\sigma \rightarrow \sigma^*$ *del cromoforo S=O. Anche in questo caso la regola di Harada e Nakanishi prevede, per solfossidi di configurazione S, un couplet negativo, come trovato sperimentalmente.*

Absorption and CD spectra—the empirical Mislow rule: So that the absorption and CD data of alkyl aryl sulfoxides might be discussed in a concise and clear manner, compounds **1**–**16** were divided into four classes, according to the nature of their aromatic and alkyl moieties (Scheme 1). Class A comprises alkyl phenyl sulfoxides; the aromatic moiety is kept constant and the alkyl residue is varied. Class B encompasses sulfoxides with a *p*-substituted phenyl moiety, together with either a methyl or a benzyl group; the *para* substitution on the aromatic ring is varied, while the alkyl residues remain the same. 1-Naphthyl alkyl and 2-naphthyl alkyl sulfoxides were separated into classes C and D, respectively. The main features of the absorption and CD spectra of **1**–**16** are collected in Table 1, while the absorption and CD spectra of compounds **2**, **8**, **9**, **13**, and **15** (representative examples of each one of the classes above) are given in Figure 1, Figure 2, Figure 3, Figure 4, and Figure 5 (see below), respectively. We first analyzed the CD and UV spectra of phenyl and *p*-substituted phenyl alkyl sulfoxides belonging to classes A and B. The spectra of all these compounds presented similar features; in the range of 195–300 nm they showed two absorption maxima with—in the CD spectra—two corresponding Cotton effects of opposite sign. For example, the spectra of **2** (Figure 1) and **8** (Figure 2) featured absorption bands at about 200–220 nm ($\varepsilon \approx 12000$) and about 250 nm ($\varepsilon \approx 8000$), while Cotton effects were observable in their CD spectra at 210–220 nm ($\Delta\varepsilon \cong 25-30$) and 245 nm ($\Delta\varepsilon \cong -15$).



Scheme 1. Alkyl aryl sulfoxides **1**–**16**, divided into four classes.

Table 1. Main CD data[a] (in acetonitrile).

	Ar	R	λ [nm] ($\Delta\varepsilon$)
1	Ph	Me	244 (−13.9); 216 (+28.5)
2	Ph	Et	247 (−14.2); 217 (+25.8)
3	Ph	*n*Bu	247 (−15.7); 218 (+27.8)
4	Ph	*i*Pr	250 (−12.0); 216 (+25.2)
5	Ph	PhCH$_2$	257 (−30.4); 226 (+48.1)
6	p-MeC$_6$H$_4$	Me	245 (−15.4); 220 (+23.1)
7	p-MeOC$_6$H$_4$	Me	246(−23.6); 225 (+26.2)
8	p-BrC$_6$H$_4$	Me	249 (−14.8); 222 (+27.9); 196 (−20)
9	p-NO$_2$C$_6$H$_4$	Me	293 (−2.9); 234 (+5.1); 217 (−3.6); 208 (+1.1); 197 (−9.2)
10	p-MeC$_6$H$_4$	PhCH$_2$	254 (−20.8); 222 (+29.1)
11	p-MeOC$_6$H$_4$	PhCH$_2$	255 (−34.0); 230 (+36.6)
12	p-NO$_2$C$_6$H$_4$	PhCH$_2$	300 (−8.2); 247 (+8.3); 230 (−7.0); 216 (+7.3); 197 (−15.1)
13	1-naphthyl	Me	288 (−8.9); 225 (−44.5); 199 (+34.0)
14	1-naphthyl	PhCH$_2$	292 (−14.4); 237 (−39.6); 210 (+28.9)
15	2-naphthyl	Me	247 (−11.2); 223 (+34.0)
16	2-naphthyl	PhCH$_2$	256 (−23.5); 242 (−17.9); 225 (+51.3); 198 (+14.9)

[a] Data corrected to 100% *ee*.

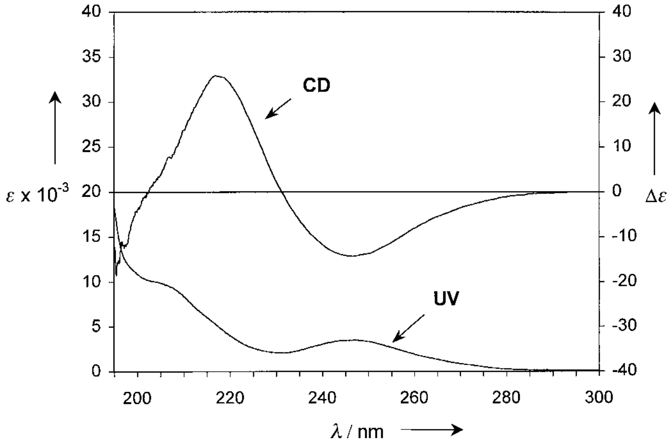


Figure 1. The electronic absorption (UV) and circular dichroism (CD) spectra of **2** in acetonitrile.

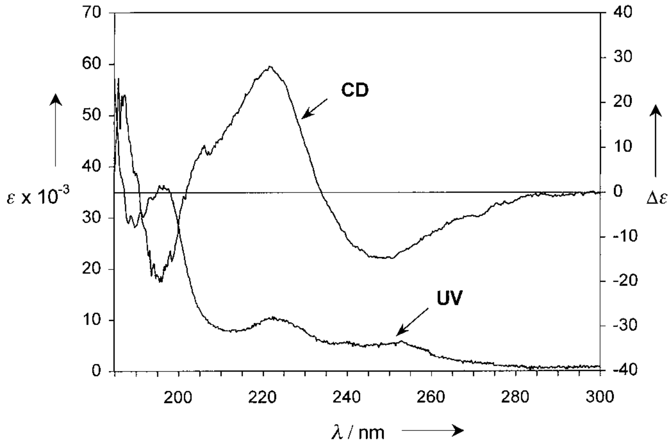


Figure 2. The electronic absorption (UV) and circular dichroism (CD) spectra of **8** in acetonitrile.

Regarding compounds of class A, we may observe that the nature of the alkyl R group does not affect the shape either of the absorption or of the CD spectra, at least in the wavelength range studied (see Table 1 and Figures 1 and 2). Also, *p*-substitution, which varies in compounds of class B, has only negligible effects on the position and intensity of the above bands, both in absorption and CD spectra, with the exception of the NO$_2$ group, which gives rise to a strong bathochromic shift of both bands (compare the data for **1**, **6**, **7**, and **8** with those of **9** in Table 1 and Figure 2 with Figure 3). It is important to note that all the compounds studied, possessing the same *S* absolute configuration, show the same negative/positive sequence in the sign of their Cotton effects, on moving from longer to shorter wavelengths. This correlation was first formulated[4] in 1965 by Mislow et al., who examined the CD spectra of some alkyl phenyl sulfoxides, differing only in the size of the R group (Me, Et, *i*Pr, etc.). The data presented here also extend the validity of this rule to *p*-phenyl-substituted compounds. In order to understand the origin of such spectral features, a more detailed analysis of the transitions involved is needed. The absorption and CD spectra of alkyl phenyl sulfoxides have been studied in the past by Mislow et al.,[4] who assigned the 255 nm transition to an excitation of an electron of the S=O lone pair into a higher energy σ* orbital. This absorption band is in fact shifted towards the blue on changing from a nonprotic (e.g., acetonitrile) to a protic (e.g., methanol) solvent, the absorption bands exhibiting behavior typical of lone-pair excitations.

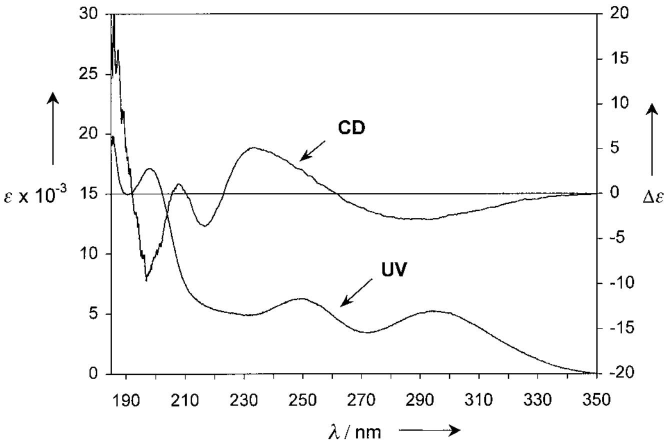


Figure 3. The electronic absorption (UV) and circular dichroism (CD) spectra of **9** in acetonitrile.

The experimental and theoretical work of Gottarelli et al.,[5] has also shown that, in dialkyl sulfoxides, the lowest energy $\sigma \rightarrow \sigma^*$ transition, situated at approximately 210 nm, is allowed both magnetically and electrically, clearly pointing out that this transition is very similar to the $n \rightarrow \pi^*$ one in ketones. For alkyl aryl sulfoxides, we can therefore relate the transition at 245 nm to a conjugated sulfoxide chromophore. The 220 nm band may instead be assigned to the ^1L_a transition of the benzene chromophore; in a strongly perturbed benzene chromophore (benzaldehyde, methyl benzoate, thioanisole, etc.[11]) this is allowed, with polarization along the C_{Ar}-perturber axis. The absorption spectrum of the α-naphthyl substituted compound **13** reveals features typical of the α-substituted naphthalene chromophore (Figure 4),[12] with a band at 290 nm and a second absorption at 225 nm. The first band corresponds to the allowed ^1L_a transition, which, being polarized along the short axis, is strongly affected by a substituent in the 1-position and red-shifted with respect to the analogous absorption in the parent naphthalene. The ^1L_b transition, which occurs at 310 nm in naphthalene, is not observable because, as generally happens in the α-substituted compounds, it is covered by the more intense ^1L_a band. The intense absorption at about 220 nm is associated with the allowed ^1B_b transition (polarized along the long axis of the naphthalene nucleus). As far as the CD spectrum of **13** is concerned, a negative Cotton effect ($\Delta\varepsilon \approx -9$) is found, corresponding to the ^1L_a transition (288 nm), followed by an intense negative Cotton effect that corresponds to the naphthalene ^1B transition, and by a positive band at 199 nm. The latter absorption was assigned by Baker et al.[6b] to the $\sigma \rightarrow \sigma^*$ transition of the S=O chromophore, although no experimental proof for this assignment was provided. However, we observed that the positive Cotton effect, at 199 nm in CH_3CN, is clearly blue-shifted to 191 nm in methanol, thus confirming the $\sigma \rightarrow \sigma^*$ character of the absorption in this spectral region. To summarize, in both the similar *S* sulfoxides **13** and **14** we have, in the range 250–200 nm, a sequence of negative/positive CD bands, with the negative one associated with the naphthalene chromophore ^1B transition and the positive one (200 nm) with the sulfoxide chromophore $\sigma \rightarrow \sigma^*$ transition. The absorption and CD data for the 2-naphthyl sulfoxide **15** (Figure 5) look very different from those of **13**. In fact, we are now dealing with a β-substituted naphthalene chromophore, and the absorption spectrum shows all the features of such.[12] The β-substitution mainly affects the ^1L_b and ^1B_b transitions (long-axis polarization) rather than the ^1L_a transition (short-axis polarization), so very weak absorptions are visible between 300 and 330 nm (^1L_b), while the allowed ^1L_a and ^1B transitions can be observed at about 280 nm and 225 nm, respectively. The most striking difference between the absorption spectra of **13** and **15** is that the latter displays an allowed absorption in the 230–270 nm range, whereas no such bands are present in the spectrum of **13**. The 250 nm band in the absorption spectrum of **15** is of the same nature ($\sigma \rightarrow \sigma^*$ of the conjugated sulfoxide chromophore) as the analogous band in compounds **1**–**12**; indeed, on changing from CH_3CN to methanol as solvent, this absorption is significantly blue-shifted. Clearly, the intense band at 223 nm is associated with the naphthalene ^1B transition. In the CD spectrum of **15** (Figure 5), Cotton effects associated with both the ^1L_b and the ^1L_a transition are observable between 320 and 270 nm, while two bands of opposite sign (negative/positive sequence for *S* absolute configuration at the sulfur atom) are present between 270 and 200 nm, and are associated with the sulfoxide $\sigma \rightarrow \sigma^*$ transition and the naphthalene ^1B transition, respectively. It is interesting to note that in **15** the sulfoxide $\sigma \rightarrow \sigma^*$ transition occurs at longer wavelengths than ^1B, while the opposite sequence is found in the spectrum of **13**. In this respect, the CD behavior of **15** and **16** strictly resembles that of compounds **1**–**12**. This simple phenomenological analysis of the absorption and CD spectra of the sulfoxides **1**–**16** strongly endorses the validity of the Mislow rule, and increases its scope considerably.

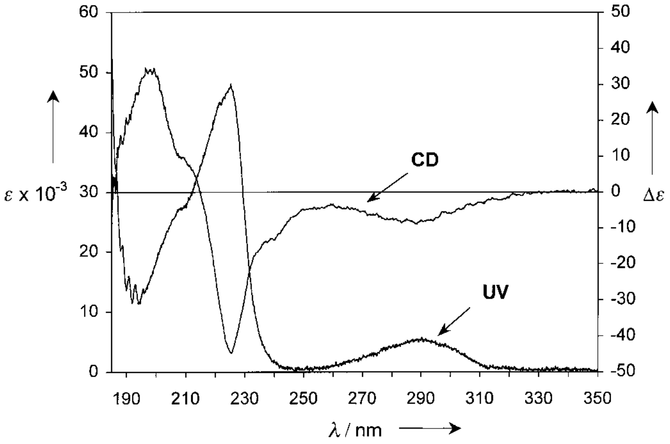


Figure 4. The electronic absorption (UV) and circular dichroism (CD) spectra of **13** in acetonitrile.

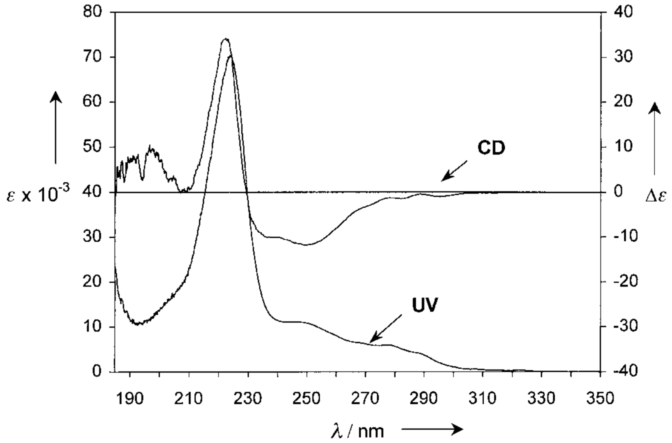
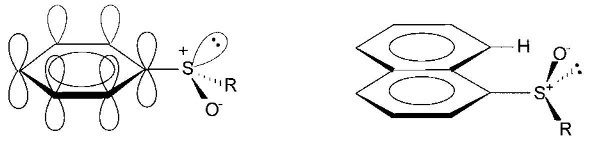


Figure 5. The electronic absorption (UV) and circular dichroism (CD) spectra of **15** in acetonitrile.

Conformational considerations: Since the aim of this investigation is to formulate a nonempirical correlation between CD spectrum and absolute configuration, knowledge of the most populated conformations of compounds **1**–**16** is required. From this point of view, the examination of the UV spectra carried out in the previous paragraph provides very useful results. As a matter of fact, within the series **1**–**12**, only *p*-NO_2 substitution dictates a strong bathochromic shift of the absorption bands, in comparison with the unsubstituted compound (see Table 1 and Figure 1 vs Figure 3). In contrast, *p*-Me, *p*-Br, and *p*-OMe substituents have negligible effect (see Table 1 and Figure 1 vs Figure 2). Behavior of this kind has previously been observed in the case of alkyl phenyl sulfides and was interpreted[13] as a strong indication that the sulfur atom acts as an electron donor, by using its lone pair electrons, but not as an electron acceptor, which would involve the vacant d orbitals. In the case at hand, the significant red shift, caused solely by substitution with a strongly electron-withdrawing group, must mean that only these groups can extend the conjugation, that is, a negative charge is placed on the *para* C atom.[14] Clearly, this effect will operate only if there is an efficient $2p(C)-3sp^3(S)$ overlap. In order to have such an overlap, the structure[15] of the alkyl phenyl sulfoxides **1**–**12** must be that described in Scheme 2 (left) for a sulfoxide of *S* absolute configuration. The second observation concerns compounds **13**–**16**. It has been observed that the absorption spectra of α-naphthyl derivatives **13** and **14** are significantly different from those of their β-naphthyl counterparts **15** and **16**, which show an allowed transition in between the naphthalene ^1L_a ($\lambda = 290$ nm) and ^1B_b ($\lambda = 220$ nm) bands at about 255 nm. Clearly, according to its frequency position, intensity, and solvent effects, this band is associated with the $\sigma \rightarrow \sigma^*$ transition of a conjugated S=O chromophore, as discussed above. In contrast, this band is absent between 230 and 280 nm in the absorption spectrum of **13** and **14**, while an allowed transition is present on the high-energy side of ^1B_b. This last band, taking into account its energy position, intensity, and behavior on changing the solvent, has been assigned to the $\sigma \rightarrow \sigma^*$ transition of an isolated S=O chromophore (vide supra). Therefore, while we have a conjugated sulfoxide chromophore for compounds **1**–**12**, **15**, and **16**, in the case of **13**–**14** we have an isolated S=O chromophore. As far as compounds **13** and **14** are concerned, owing to the steric hindrance exerted by the *peri* hydrogen, the sulfoxide is forced into a conformation in which the smallest group on sulfur points towards the hydrogen in the 8-position, and the most stable conformation for an *S* sulfoxide is that represented in Scheme 2 (right). In this situation, the lone pair cannot give rise to overlap with the 2p orbitals of the aromatic nucleus, which lie in an orthogonal plane. This conformational choice can be supported as follows: first of all, it has been shown by NMR spectroscopy that the above-described conformer is the most stable in 1-naphthyl-*tert*-butyl sulfoxide.[16] This compound[6b] and **13**, which have the same configuration, have spectra completely similar in number, sign, position, and intensity of their Cotton effects, clearly establishing the similar conformational situation of these two compounds. It is also well known that, in aromatic amides derived from 1-(1-naphthyl)ethylamine, the hydrogen linked to the chiral center is directed[17] towards the *peri* hydrogen. Furthermore, the solid state structure of 1-(2-bromonaphthyl)*tert*-butyl sulfoxide shows that the lone pair, which is the smallest substituent, points towards the bromine, which is the largest atom.[18, 19] The conformational analysis developed so far deserves some additional comment. The chosen conformations of compounds **1**–**16** are determined by a compromise between electronic (orbital overlap and, therefore, stabilization by resonance) and repulsive steric factors. The above analysis, although completely qualitative, is supported by clear experimental evidence. It is interesting to point out that, in the case of **13**, such conformational findings agree with the result of ab initio calculations reported by Benassi et al.,[15] while in the case of alkyl phenyl sulfoxides there are some slight differences. In fact, in the ab initio structures, the $2p(C)-3sp^3(S)$ overlap seems not to play a large role. However, it has to be noticed that very recent density functional theory (DFT) calculations on vinyl sulfoxides have clearly indicated that some interactions between the sulfur lone pair and the double bond contribute significantly to stabilization of a specific conformation, overwhelming even repulsive steric interactions.[20] This particular aspect deserves further theoretical investigation.



Scheme 2. The $2p(C)-3sp^3(S)$ overlap in alkyl phenyl sulfoxides **1**–**12** (left), and the absence of overlap in 1-naphthyl compounds **13** and **14** (right).

CD analysis and formulation of a nonempirical configuration correlation: Once the nature of the electronic transitions present in the absorption spectra of compounds **1**–**16** has been understood, and a reasonable conformational assignment made for compounds **1**–**12**, **15**, and **16** on the one hand and compounds **13**–**14** on the other, a nonempirical analysis of the CD spectra can be attempted. Let us start our analysis by considering first the case of compounds **13**–**14** in the 200–250 nm range. In their UV spectra (between 200 and 250 nm), these compounds have a couple of electronically allowed transitions to which, in the CD spectra, correspond to two Cotton effects of almost equal intensity and opposite sign. As we have previously shown, the S=O and the naphthyl chromophores do not overlap, and so we are entitled to treat this system using the coupled-oscillator model for nondegenerate transitions.[21] We shall employ such a model at a qualitative level, using the aromatic chirality rule[22] of Harada and Nakanishi. The conformational situation is that reported in Scheme 2 (right) and two chromophores are present: the sulfoxide and the α-naphthalene. The isolated sulfoxide chromophore, following the analysis of Gottarelli et al.,[5] has a $\sigma \rightarrow \sigma^*$ transition located at about 210 nm and polarized along the C_1-C_2 direction of the $C_1-(S{=}O)-C_2$ moiety. In this range, the α-naphthalene chromophore shows the ^1B_b transition, polarized along the long axis. As show in Figure 6, in which an *S*-configured compound is depicted, these dipole moments define a negative chirality, and so a negative couplet is to be expected in the corresponding spectral range, as observed experimentally. The qualitative analysis discussed above can be put on a quantitative basis by using coupled-oscillator calculations of optical activity, by means of DeVoe's

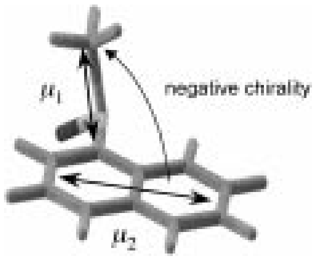


Figure 6. In 1-naphthyl methyl sulfoxide of *S* absolute configuration, the transition dipole moment of the 210 nm $\sigma \rightarrow \sigma^*$ excitation of the S=O chromophore, polarized along the $C_{Ar}-C_R$ direction, and the ^1B_b transition dipole moment of the naphthalene chromophore, polarized along the long axis, define a negative chirality. A negative couplet is therefore to be expected between 200 and 250 nm.

all-order polarizabity model.[23, 24] This model has been successful in formulating spectra/structure relationships for organic molecules,[25] high-molecular-weight compounds,[26] and coordination compounds.[27] DeVoe calculations were carried out on the 1-naphthyl substituted sulfoxides, choosing 1-naphthyl methyl sulfoxide as a model compound and arbitrarily assuming *S* configuration at the stereogenic sulfur center. The molecular geometry represented in Scheme 2 (right) and Figure 6 was employed as input geometry. A single oscillator, polarized along the long axis of the naphthalene ring and with a polarizability of 40 D^2 centered at 220 nm was employed to describe the naphthalene ^1B_b transition. At the same time, a single oscillator polarized along the $C_{Me}-C_{Ar}$ direction, with a polarizability of 10 D^2, was employed to describe the 210 nm transition of the sulfoxide chromophore. The relative orientation of the two dipoles in the sulfoxide molecule is reported in Figure 6. In this manner, the absorption spectrum is satisfactorily reproduced, $\lambda = 225$ ($\varepsilon_{max} \approx 41000$), 210 nm ($\varepsilon_{max} \approx 20000$), while the experimental values are $\lambda = 225$ ($\varepsilon_{max} \approx 50000$), 210 nm ($\varepsilon_{max} \approx 30000$). The calculated CD spectrum shows extremes at 225 nm ($\Delta\varepsilon$ -88) and 206 nm ($\Delta\varepsilon$ $+95$), which compare satisfactorily with the experimental ones (λ 225 nm ($\Delta\varepsilon$ -45), λ 200 nm ($\Delta\varepsilon$ $+35$)). These results clearly indicate that the coupled-oscillator mechanism is the main source of optical activity in this range, and that other mechanisms such as electric magnetic coupling[28] can be disregarded. Considering that the UV/CD features of **1**–**12**, **15**, and **16** are very similar to those of **13**–**14** analyzed above (i.e., two electronically allowed transitions are present in the electronic spectrum, with two corresponding Cotton effects of opposing sign and similar intensity in the CD spectrum), it is tempting to use the coupled-oscillator model for the former compounds as well. Even if this model can correctly be applied only to systems with negligible orbital overlap and electron exchange between the interacting chromophores,[21] it has also been used in cases in which such orbital overlap cannot be disregarded, such as distorted dienes,[29] in 1,1′-binaphthyls with small dihedral angles,[30] and in twisted 2,2′-bipyridines,[25p] always providing *qualitatively correct* answers. We feel justified then in tentatively subjecting the conjugated sulfoxide chromophores **1**–**12**, **15**, and **16** to the same treatment, by means of the exciton model, at least at a qualitative level.[31] For *S*-configured sulfoxides **1**–**12**, the conformation in Scheme 2 (left) is allowed. In such a structure, the ^1L_a transition dipole and the sulfoxide transition moment define a negative chirality (Figure 7) and, thus, a negative CD couplet should be observed, as found experimentally. Compounds **15** and **16** have two possible extremes for "conjugated" conformations, as represented below in Figure 8, differing in the relative orientation of the oxygen and the H atom on C_1: *transoid* (top) and *cisoid* (bottom). In these structural situations, the electric dipole of the ^1B transition of the naphthalene chromophore and that of the allowed transition of the sulfoxide moiety define a positive and negative chirality, respectively. As a negative couplet is present in the CD spectrum, our coupled-oscillator analysis indicates that the *transoid* conformation is the prevailing one, even if we cannot at present provide any explanation of this fact.

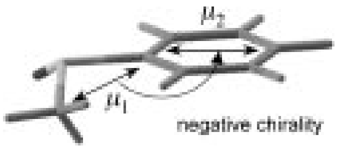


Figure 7. In an alkyl *p*-substituted phenyl sulfoxide of *S* absolute configuration, the transition dipole moment of the $\sigma \rightarrow \sigma^*$ excitation of the S=O chromophore, polarized along the $C_{Ar}-C_R$ direction, and the ^1L_a transition dipole moment of the substituted benzene chromophore, define a negative chirality. A negative couplet is therefore to be expected between 200 and 280 nm.

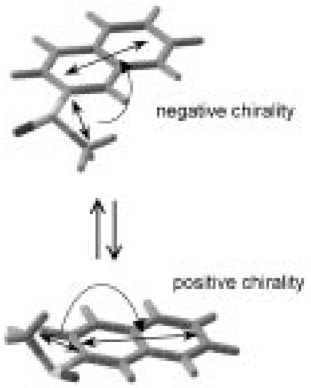


Figure 8. The two conjugated conformations allowed for **15**. In the *transoid* conformation (top), the ^1B transition dipole of the allowed $\sigma \rightarrow \sigma^*$ transition of the sulfoxide chromophore defines a negative chirality, while in *cisoid* conformation (bottom) the same dipoles define the opposite chirality.

Conclusion

Even if this analysis does not constitute an exhaustive interpretation of the chiroptical properties of alkyl aryl sulfoxides, a few important conclusions can be drawn. First of all, a number of different alkyl aryl sulfoxides have become available in optically active form by means of our efficient and versatile enantioselective oxidation methodology, allowing comparative study of the UV/CD spectra of differently substituted compounds. Secondly, such comparative and systematic analysis has enabled us to define the conformations of these species, distinguishing between conjugated sulfoxides, which possess a typical allowed transition at 250 nm, and nonconjugated compounds in which the above band is missing. In the former case, there is a significant 2p(C)–3sp^3(S) overlap that is completely absent in the latter. In other words, we have pointed out the possible importance of electronic effects in defining the conformational behavior of these compounds, and then the dilemma, raised by Mislow in his seminal 1965 paper,[4b] about the role played by a 2p(C)–3sp^3(S) versus 2p(C)–3d(S) overlap has been resolved in favor of the former. It is interesting to note that this significant result has been achieved mainly by the use of ultraviolet absorption spectroscopy. This technique is the method of choice here, where we have conjugated and nonconjugated sulfoxide chromophores, depending on steric effects, that is, a typical case of steric hindrance to resonance. This shows how UV spectroscopy, a method underused in structural analysis, gives, at least on some occasions, a quick and sure answer. From a stereochemical point of view, we have demonstrated that, at least in the case of the nonconjugated sulfoxides, the coupled-oscillator mechanism is the source of optical activity (at least in the 250–200 nm range); this allows safe and reliable correlation between CD spectrum and absolute configuration at the sulfur stereogenic center. We have also proposed the extension of the same treatment to the conjugated sulfoxides—at least at a qualitative level—taking into account the fact that some conjugated molecules have been treated previously[25p, 29, 30] in terms of such a model and the correct answer obtained (vide supra). As we stated at the beginning of this paragraph, this paper does not pretend to be a conclusive treatment of the relationships between chiroptical properties and stereochemistry in the alkyl aryl sulfoxides, because some questions are still open: i) the role played by electronic effects in determining the structure would merit subjection to theoretical studies by means of quantum mechanical techniques, in order to understand the electronic nature of the C–S bond in depth; ii) the question of the extension of the exciton model to the conjugated systems represents another important challenge. Even here, the assistance of more sophisticated calculations will certainly be important in defining the mechanisms responsible for the optical activity. This would certainly solve the problem of the optical activity of the conformationally nonhomogeneous sulfoxides **15** and **16**. Work is in progress along these lines.

Experimental Section

General: HPLC analyses were performed at room temperature on Daicel Chiralcel OB (cellulose tribenzoate) or Chiralcel OJ (cellulose tris(*p*-methylbenzoate)) columns.[7] Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. ^{1}H NMR (300 MHz) and ^{13}C NMR spectra were recorded in CDCl$_3$. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. Absorption and CD spectra were recorded on a JASCO J 600 spectropolarimeter at RT in acetonitrile ($c \approx 6 \times 10^{-3}$ M) in 0.1 and 1.0 mm cells. During measurement, the instrument was thoroughly purged with N$_2$. CCl$_4$ was distilled from CaH$_2$ and stored over activated 4 Å molecular sieves. [Ti(*i*PrO)$_4$] was distilled prior to use under N$_2$ atmosphere. Commercially available *tert*-butyl hydroperoxide (TBHP, 70 % in water) was purchased (Aldrich) and used without further purification. Analytical and preparative TLC were performed on Merck 60 F-254 0.2 mm and 2.0 mm silica gel plates, respectively, and column chromatography was carried out with Merck 60 silica gel (80–230 mesh). Enantiomerically pure (*R*,*R*)-1,2-diphenylethane-1,2-diol was prepared by asymmetric dihydroxylation of (*E*)-stilbene.[32] Racemic sulfoxides were prepared by oxidation of the corresponding sulfides with 30 % hydrogen peroxide, according to literature procedures.[33]

General procedure for catalytic oxidation of sulfides. [Ti(*i*PrO)$_4$] (23.6 µL, 0.08 mmol) and H$_2$O (28.8 µL, 1.6 mmol) were added dropwise and sequentially to a suspension of (*R*,*R*)-diphenylethane-1,2-diol (34.3 mg, 0.16 mmol) in CCl$_4$ (5 mL). The sulfide (1.61 mmol) was added to the resulting homogeneous solution and was with stirred at room temperature for 15 min. The solution was then cooled to 0 °C, and TBHP (70 % in water, 440 µL, 3.22 mmol) was added. The mixture was left stirring at 0 °C for 2 h, then diluted with CH$_2$Cl$_2$, and dried over Na$_2$SO$_4$ for a few minutes. After filtration and evaporation of solvent, the residue was immediately purified by preparative TLC (Et$_2$O as eluent) or column chromatography (EtOAc), isolating the pure sulfoxide.

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[1] a) P. Pitchen, *Chem. Ind.* **1994**, 636; b) M. Tanaka, H. Yamazaki, H. Hakasui, N. Nakamichi, H. Sekino, *Chirality* **1997**, *9*, 17; c) S. von Unge, V. Langer, L. Sjölin, *Tetrahedron: Asymmetry* **1997**, *8*, 1967; d) H. L. Holland, F. M. Brown, B. G. Larsen, *Tetrahedron: Asymmetry* **1994**, *5*, 1129; e) C. A. Hutton, J. M. White, *Tetrahedron Lett.* **1997**, *38*, 1643; f) S. Morita, J. Matsubara, K. Otsubo, K. Kitano, T. Ohtani, Y. Kawano, M. Uchida, *Tetrahedron: Asymmetry* **1997**, *8*, 3707; g) H. L. Holland, F. M. Brown, *Tetrahedron: Asymmetry* **1998**, *9*, 535; h) T. Nishi, K. Nakajima, Y. Iio, K. Ishibashi, T. Fukurawa, *Tetrahedron: Asymmetry* **1998**, *9*, 2567.

[2] a) M. C. Carreño, *Chem. Rev.* **1995**, *95*, 1717; b) G. Solladié, *Synthesis* **1981**, 185; c) K. K. Andersen in *The Chemistry of Sulfones and Sulfoxides* (Eds.: S. Patai, Z. Rappoport, C. J. M. Stirling), Wiley, Chichester, **1988**, Chapter 3, pp. 53–94; d) G. H. Posner in *The Chemistry of Sulfones and Sulfoxides* (Eds.: S. Patai, Z. Rappoport, C. J. M. Stirling), Wiley, Chichester, **1988**, Chapter 16, pp. 823–849; e) F. Colobert, A. Tito, N. Khiar, D. Denni, M. A. Medina, M. Martin-Lomas, J. L. G. Ruano, G. Solladiè, *J. Org. Chem.* **1998**, *63*, 8918; f) P. Bravo, M. Crucianelli, A. Farina, S. V. Meille, A. Volonterio, M. Zanda, *Eur. J. Org. Chem.* **1998**, 435.

[3] a) K. Hiroi, Y. Suzuki, *Tetrahedron Lett.*, **1998**, *39*, 6499; b) R. Tokuyo, M. Sodeska, L. Aol, *Tetrahedron Lett.* **1995**, *36*, 8035; c) N. Khior, I. Fernandez, F. Alcudia, *Tetrahedron Lett.* **1993**, 34, 123.

[4] a) K. Mislow, A. L. Ternay, Jr., J. T. Melillo, *J. Am. Chem. Soc.* **1963**, *85*, 2329; b) K. Mislow, M. M. Green, P. Laur, J. T. Melillo, T. Simmons, A. L. Ternay, Jr., *J. Am. Chem. Soc.* **1965**, *87*, 1958; c) J. Jacobus, K. Mislow, *J. Am. Chem. Soc.* **1967**, *89*, 5228; d) F. D. Saeva, D. R. Rayner, K. Mislow, *J. Am. Chem. Soc.* **1968**, *90*, 4176.

[5] a) G. L. Bendazzoli, P. Palmieri, G. Gottarelli, I. Moretti, G. Torre, *J. Am. Chem. Soc.* **1976**, *98*, 2659; b) I. Moretti, G. Torre, G. Gottarelli, *Tetrahedron Lett.* **1976**, 711; c) G. L. Bendazzoli, P. Palmieri, G. Gottarelli, I. Moretti, G. Torre, G. *Gazz. Chim. Ital.* **1979**, *109*, 19.

[6] a) T. Sagae, S. Ogawa, N. Furukawa, *Bull. Chem. Soc. Jpn.* **1991**, *64*, 3179; b) R. W. Baker, G. K. Thomas, D. S. Ren, M. V. Sargent, *Aust. J. Chem.* **1997**, *50*, 1151.

[7] M. I. Donnoli, S. Superchi, C. Rosini, *Enantiomer*, **2000**, *5*, 181.

[8] J. Gawronski in *Methoden Org. Chem. (Houben–Weyl) 4th ed.*, **1995**, Vol. 1, Chapter 4.4, p. 499.

[9] a) S. Superchi, C. Rosini, *Tetrahedron: Asymmetry* **1997**, *8*, 349; b) S. Superchi, M. I. Donnoli, C. Rosini, *Tetrahedron Lett.* **1998**, *39*, 8541; c) M. I. Donnoli, S. Superchi, C. Rosini, *J. Org. Chem.* **1998**, *63*, 9392.

[10] a) J.-M. Brunel, P. Diter, M. Duetsch, H. B. Kagan, *J. Org. Chem.* **1995**, *60*, 8086; b) P. Pitchen, E. Duñach, M. N. Deshmukh, H. B. Kagan, *J. Am. Chem. Soc.* **1984**, *106*, 8188; c) H. Sakuraba, K. Natori, Y. Tanaka, *J. Org. Chem.* **1991**, *56*, 4124; d) T. Sugimoto, T. Kokubo, J. Miyazaki, S. Tanimoto, M. Okano, *J. Chem. Soc. Chem. Commun.* **1979**, 402.

[11] J. Murrel in *The Theory of Electronic Spectra of Organic Molecules*, Methuen, London, **1963**, Chapter 10.

[12] a) H. H. Jaffe, M. Orchin in *The Theory and Application of UV Spectroscopy*, Wiley, New York (USA), **1962**; b) S. Suzuki, T. Fujii, H. Baba, *J. Mol. Spectrosc.* **1979**, *47*, 243.

[13] See ref. [12a] pp. 480–481.

[14] It is interesting that, on the basis of IR studies, it was shown that the MeSO group acts as a net resonance donor (N. C. Coutress, T. B. Grindley, A. R. Katritsky, R. D. Topsom, *J. Chem. Soc. Perkin II* **1974**, 263); however, the above interpretation was found inconsistent with the NMR findings of Buchanan et al. (G. W. Buchanan, C. Rayes-Zamora, D. E. Clarke, *Can. J. Chem.* **1974**, *52*, 3895).

[15] It should be noted that the structure of Scheme 2 (left) is slightly different from the most stable conformation of phenyl methyl sulfoxide found by Benassi (R. Benassi, U. Folli, D. Iarossi, A. Mucci, L. Schenetti, F. Taddei, *J. Chem. Soc. Perkin Trans 2* **1989**, 517; R. Benassi, A. Mucci, L. Schenetti, F. Taddei, *J. Mol. Struct.* **1989**, *184*, 281), in which the S=O bond is almost coplanar with the phenyl ring.

[16] D. Casarini, E. Foresti, F. Gasparrini, L. Lunazzi, D. Macciantelli, D. Misiti, C. Villani, *J. Org. Chem.* **1993**, *58*, 5674.

[17] W. H. Pirkle, C. J. Welch, M. M. Hyun, *J. Org. Chem.* **1983**, *48*, 5022.

[18] R. W. Baker, D. C. R. Hockless, G. R. Pocok, M. V. Sargent, B. W. Skelton, A. N. Sobolev, E. Twiss (née Stanojevic), A. M. White, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2615.

[19] It is noteworthy that the conformation of Sceme 2 (right) is very similar to the most stable structure of *o*-substituted phenyl methyl sulfoxides (see ref. [15]).

[20] L. F. Tietze, A. Schuffenhauer, P. R. Schreiner, *J. Am. Chem. Soc.* **1998**, *120*, 7952.

[21] Treatments of the coupled-oscillator model and its application to organic stereochemistry: a) S. F. Mason, *Quart. Rev.* **1962**, *17*, 20; b) "Theory II", S. F. Mason, in *Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry* (Ed.: G. Snatzke), Wiley, London, **1967**, Chapter 4, p. 71; c) G. Gottarelli, S. F. Mason, G. Torre, *J. Chem. Soc. B* **1971**, 1349; d) E. Charney in *The Molecular Basis of Optical Activity—Optical Rotatory Dispersion and Circular Dichroism*, Wiley, New York, **1979**; e) S. F. Mason, *Molecular Optical Activity and Chiral Discrimination*, Cambridge University Press, Cambridge, **1982**.

[22] a) N. Harada, K. Nakanishi, *Acc. Chem. Res.* **1972**, *5*, 257; b) N. Harada, K. Nakanishi in *Circular Dichroic Spectroscopy: Exciton Coupling in Organic Stereochemistry*, University Science Books, Mill Valley, CA, **1983**; c) K. Nakanishi, N. Berova, in *Circular Dichroism: Principles and Applications* (Eds. K. Nakanishi, N. Berova, R. W. Woody), VCH, New York, **1994**, Chapter 13, p. 361.

[23] a) H. DeVoe, *J. Chem. Phys.* **1964**, *41*, 393; b) H. DeVoe, *J. Chem. Phys.* **1965**, *43*, 3199.

[24] In the DeVoe model, a molecule is considered to be composed of a set of subsystems: the chromophores. These are polarized by the external electromagnetic radiation and are coupled with each other by their own dipolar oscillating fields. The optical properties (absorption, refraction, optical rotatory dispersion, and circular dichroism) of the molecule under study can be calculated by taking into account the interaction of the subsystems. Therefore, this treatment requires a division of the molecule into a set of subsystems that have to be suitably characterized. Each group is represented in terms of one (or more) classical oscillator(s); each oscillator represents an electric-dipole-allowed transition, defined by the polarization direction $\mathbf{e}_i$ and the complex polarizability $\alpha_i(\nu) = R_i(\nu) + I_i(\nu)$. $I_i(\nu)$ is obtainable from the experiment, that is, from the absorption spectra of the compounds that can be considered good models of the subsystems, and $R_i(\nu)$ can be calculated from $I_i(\nu)$ by means of a Kronig–Kramers transform. From the general formulation of the DeVoe model, retaining only the terms to first order in G_{12} (physically, this means considering the electric dipole on the *i* chromophore to be caused only by the external electro magnetic field plus the dipolar fields of the other dipole polarized by the external field), the following expression can be deduced in the case of two different chromophores, each possessing only one electrically allowed transition which provides CD as a frequency function: $\Delta\varepsilon(\nu) = 0.014\pi^2 N\mathbf{e}_1 X\mathbf{e}_2 \boldsymbol{R}_{12} G_{12}\nu^2[I_1(\nu)R_2(\nu) + I_2(\nu)R_1(\nu)]$; $G_{12} = (1/r_{12})^3[\mathbf{e}_1.\mathbf{e}_2 - 3(\mathbf{e}_1\mathbf{e}_{12})(\mathbf{e}_2\mathbf{e}_{12})]$. Here, $\mathbf{e}_1$ and $\mathbf{e}_2$ are the unit direction vectors of the transition dipole moments of the first and second chromophore, respectively, R_{12} is the distance between them, G_{12} is the point-dipole–point-dipole interaction term, and ν is the frequency expressed in cm^{-1}. This expression gives rise to a couplet-like feature if the absorption maxima of chromophores 1 and 2 are close in frequency ("quasi-degenerate" coupled-oscillator system).

[25] a) M. Zandomeneghi, *J. Chem. Phys.* **1979**, *83*, 2926; b) M. Zandomeneghi, C. Rosini, A. F. Drake, *J. Chem. Soc. Faraday Trans. 2* **1981**, *77*, 567; c) C. Rosini, M. Zandomeneghi, *Gazz. Chim. Ital.* **1981**, 111, 493; d) P. Salvadori, C. Bertucci, C. Rosini, M. Zandomeneghi, G. Gallo, E. Martinelli, P. Ferrari, *J. Am. Chem Soc.* **1981**, *103*, 5553; e) C. Rosini, G. Giacomelli, P. Salvadori, *J. Org. Chem.* **1984**, *49*, 3394; f) C. Rosini, C. Bertucci, P. Salvadori, M. Zandomeneghi, *J. Am. Chem. Soc.* **1985**, *107*, 17; g) A. M. Caporusso, C. Rosini, L. Lardicci, C. Polizzi, P. Salvadori, *Gazz. Chim. Ital.* **1986**, *116*, 467; h) W. H. Pirkle, T. J. Sowin, P. Salvadori, C. Rosini, *J. Org. Chem.* **1988**, *53*, 826; i) M. Clericuzio, C. Rosini, M. Persico, P. Salvadori, *J. Org. Chem.* **1991**, *56*, 4343; j) C. Rosini, L. Franzini, P. Salvadori, G. P. Spada, *J. Org. Chem.* **1992**, *57*, 6820; k) C. Rosini, P. Salvadori, M. Zandomeneghi, *Tetrahedron: Asymmetry* **1993**, *4*, 545; l) G. Gottarelli, G. Proni, G. P. Spada, D. Fabbri, S. Gladiali, C. Rosini, *J. Org. Chem.* **1996**, *61*, 2013; m) C. Rosini, R. Tanturli, P. Pertici, P. Salvadori, *Tetrahedron: Asymmetry* **1996**, 7, 2971; n) C. Rosini, G. P. Spada, G. Proni, S. Masiero, S. Scamuzzi, *J. Am. Chem. Soc.* **1997**, *119*, 506; o) C. Rosini, R. Ruzziconi, S. Superchi, F. Fringuelli, O. Piermatti, *Tetrahedron: Asymmetry* **1998**, *9*, 55; p) C. Rosini, C. Bertucci, C. Botteghi, R. Magarotto, *Enantiomer*, **1998**, *3*, 365.; q) C. Rosini, S. Superchi, H. W. I. Peerlings, E. W. Meijer, *Eur. J. Org. Chem.* **2000**, 61.

[26] a) W. Hug, F. Ciardelli, I. Tinoco, *J. Am. Chem. Soc.* **1974**, *96*, 3407; b) F. Ciardelli, C. Righini, M. Zandomeneghi, W. Hug, *J. Phys. Chem.* **1977**, *81*, 1948; c) C. Bertucci, C. Carlini, F. Ciardelli, C. Rosini, P. Salvadori, *Polym. Bull.* **1981**, *5*, 535; d) J. Applequist, K. R. Sundberg, M. L. Olson, L. C. Weiss, *J. Chem. Phys.* **1979**, *70*, 1240; e) K. A. Bode, J. Applequist, *J. Phys. Chem.* **1996**, *100*, 17825; f) J. Applequist, K. A. Bode, *J. Phys. Chem. B* **1999**, *103*, 9767.

[27] a) M. Zandomeneghi, C. Rosini, P. Salvadori, *Chem. Phys. Lett.* **1976**, *44*, 533; b) C. Rosini, M. Zandomeneghi, P. Salvadori, *J. Chem. Soc. Dalton Trans.* **1978**, 822.

[28] J. A. Schellman, *Acc. Chem. Res.* **1968**, *1*, 194.

[29] A. Rauk, H. A. Peoples, *J. Comput. Chem.* **1980**, *1*, 240.

[30] See ref. [22b] pp. 194–195.

[31] One could argue that **1**–**12**, **15**, and **16** should be considered as intrinsically dissymmetric chromophores, requiring an MO treatment. We intend to begin such a type of analysis.

[32] H. C. Kolb, M. S. Van Nieuwenhze, K. B. Sharpless, *Chem. Rev.* **1994**, *94*, 2483.

[33] P. Lupattelli, R. Ruzziconi, P. Scafato, A. Degl'Innocenti, A. Belli Paolobelli, *Synth. Commun.* **1997**, *27*, 441.

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