JOC Article
pubs.acs.org/joc

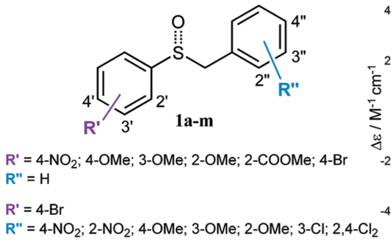
Systematic Investigation of CD Spectra of Aryl Benzyl Sulfoxides Interpreted by Means of TDDFT Calculations

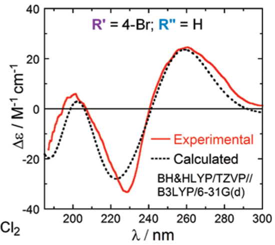
Gennaro Pescitelli,[†] Sebastiano Di Pietro,[†] Cosimo Cardellicchio,[‡]
Maria Annunziata M. Capozzi,[§] and Lorenzo Di Bari*[,†]

[†]*Dipartimento di Chimica e Chimica Industriale, Università di Pisa, via Risorgimento 35, 56126 Pisa, Italy,* [‡]*CNR-ICCOM, Dipartimento di Chimica, via Orabona 4, 70126 Bari, Italy, and* [§]*Dipartimento di Scienze Agroambientali, Chimica e Difesa Vegetale, Università di Foggia, Via Napoli 25, 71100 Foggia, Italy*

ldb@dcci.unipi.it

Received November 5, 2009





The CD spectra of 13 crystalline aryl benzyl sulfoxides **1a−m** with various substituents on the two aromatic rings were recorded in solution and in the solid state. Solution CD spectra were very homogeneous along the series, consisting in most cases of a couplet-like feature in the 200−300 nm region. The red-shifted component of the couplet, corresponding to the sulfoxide-centered n-π* transition, is always positive for (*R*) absolute configuration in accordance with Mislow's rule. The presence of a strong electron-withdrawing substituent on the phenyl ring (nitro or ester group) alters the shape of the CD spectrum. CD calculations using the TDDFT method were run for eight representative compounds using DFT-optimized geometries. In all cases, calculated spectra were in very good agreement with experimental ones and allowed for rationalization of the diverse spectral behaviors. It is demonstrated that TDDFT//DFT calculations represent a reliable option for assigning the absolute configuration of this class of compounds whenever crystals suitable for X-ray are not available. Solid-state CD spectra recorded with the KCl pellet technique were in some cases in agreement with those in solution. However, in other cases new and strong CD signals appeared which were interpreted as being due to intermolecular couplings in the crystals.

Introduction

A recent interest arose in the biological activity of chiral sulfoxides.[1] For example, omeprazole, a powerful proton pump inhibitor, is nowadays one of the best-selling drugs. Some alkyl sulfoxides inhibit alcohol dehydrogenases.[2] Many chiral sulfoxides play important roles in metabolic pathways as the first oxidation products of the corresponding sulfides, including methionine and biotin.[1] Furthermore, enantiopure sulfoxides have been widely used in asymmetric synthesis,[3−5] because they are easily prepared and induce a high level of enantioselection and the sulfinyl moiety can be easily removed at the end of the synthetic strategy.

Several methods have been proposed to establish the absolute configuration of sulfoxides. Crystals suitable for a satisfactory diffractometric X-ray analysis[6] were not obtained frequently, as result of the lack of the particular weak interactions[7] required to assembly the crystal building. On the other hand, several configurational assignments were

---

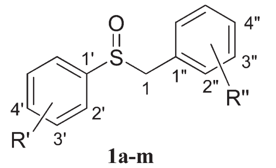
(1) Bentley, R. *Chem. Soc. Rev.* **2005**, *34*, 609–624.
(2) Cho, H.; Plapp, B. V. *Biochemistry* **1998**, *37*, 4482–4489.
(3) Fernandez, I.; Khiar, N. *Chem. Rev.* **2003**, *103*, 3651–3705.
(4) Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717–1760.
(5) Pellissier, H. *Tetrahedron* **2006**, *62*, 5559–5601.
(6) Mikolajczyk, M.; Drabowicz, J. *Top. Stereochem.* **1982**, *13*, 333–468.
(7) Naso, F.; Cardellicchio, C.; Capozzi, M. A. M.; Capitelli, F.; Bertolasi, V. *New J. Chem.* **2006**, *30*, 1782–1789.

DOI: 10.1021/jo902363c

based on chiro-optical spectroscopies since the earlier work of Mislow and co-workers,[8] who demonstrated that electronic circular dichroism (CD) and optical rotatory dispersion (ORD) are convenient tools to assign the absolute configuration of these molecules. The sulfinyl group is a moderately strong chromophore, showing an absorption band around 215 nm with $\varepsilon \approx 2500$ M^{-1} cm^{-1} in alcoholic solvents.[9] This so-called primary band[8b] is associated with a transition from oxygen lone pair n_O to π^*-type S=O orbital.[10] The two n_O and π^* orbitals are heavily mixed with bonding and nonbonding σ-type S−C orbitals, respectively. The tendency of sulfoxide-centered orbitals to mix with nearby orbitals of proper symmetry and energy is also evident in ethylene episulfoxide $(CH_2)_2SO$ described by Gottarelli et al.[11] For this compound, the virtual orbital involved in the first transition observed around 210 nm is rather of a σ^*_{S-O} type, and such a transition acquires a $\sigma-\sigma^*$ character. A large orbital mixing is also apparent for alkyl aryl sulfoxides. They show a single band around 250 nm in cyclohexane that decomposes in two bands in alcoholic solvents and acetonitrile, the first one (at 260−290 nm) being assignable to the phenyl ^1L_b transition and the second one (250−260 nm) to the sulfoxide-centered n-π^* transition,[8b,12] whose π^* orbital is however largely delocalized on the phenyl ring.

In correspondence with the apparent absorption bands, chiral nonracemic sulfoxides show intense CD bands or Cotton effects (CE) that are diagnostic of their absolute configuration, as first recognized by Mislow.[8] In particular, ORD spectra of alkyl aryl sulfoxides show a CE in the 235−255 nm region whose sign correlates with the configuration, a positive CE corresponding to the (*R*) enantiomer and a negative CE to the (*S*). This empirical correlation has been employed for configurational assignments of several alkyl aryl sulfoxides,[13] but it is not free from pitfalls and limitations.[14] Only recently, the first nonempirical interpretations of CD spectra of this class of compounds have appeared. In particular, Rosini and co-workers reported the CD spectra of several alkyl aryl sulfoxides where the aryl group is phenyl, *p*-substituted phenyl, 1- and 2-naphthyl, and 9-anthryl.[15,16] In the case of naphthyl and anthryl derivatives, CD spectra were well reproduced by coupled-oscillator calculations with DeVoe method taking into account the main aromatic transitions and the sulfoxide-centered transition, this latter described as $\sigma-\sigma^*$ according to Gottarelli.[11]

SCHEME 1. Sulfoxides 1a−m



1a-m

	R'	R"
1a [4NO$_2$/H]	4-NO$_2$	H
1b [4OMe/H]	4-OMe	H
1c [3OMe/H]	3-OMe	H
1d [2OMe/H]	2-OMe	H
1e [2COOMe/H]	2-COOMe	H
1f [4Br/H]	4-Br	H
1g [4Br/4NO$_2$]	4-Br	4-NO$_2$
1h [4Br/2NO$_2$]	4-Br	2-NO$_2$
1i [4Br/4OMe]	4-Br	4-OMe
1j [4Br/3OMe]	4-Br	3-OMe
1k [4Br/2OMe]	4-Br	2-OMe
1l [4Br/3Cl]	4-Br	3-Cl
1m [4Br/2,4Cl$_2$]	4-Br	2,4-Cl$_2$

These results were tentatively extended to phenyl derivatives as a qualitative means of interpretation, because the coupled-oscillator model requires that the two coupling chromophores undergo negligible conjugation or orbital overlap. This is not strictly the case for alkyl phenyl sulfoxides where a favorable overlap is expected between the sulfur lone pair and the adjacent π system, which is thought to dictate the most stable molecular conformation.[15]

Rather surprisingly, no other systematic discussion of CD spectra of sulfoxides has been reported since then in the literature. In particular, time-dependent density functional theory (TDDFT) calculations, which currently represent the most popular approach to quantitative predictions of chiroptical properties,[17] were applied only to a few specific cases and were found to correctly reproduce experimental CD spectra or optical rotations and to allow safe configurational assignments to be established.[18−21]

Now we report the CD spectra of 13 aryl benzyl sulfoxides (**1a−m**, Scheme 1) with various substituents on the two aromatic rings. Several sulfoxides with one benzyl- and one aryl-type substituent have been described to show biological activity.[22] The availability of a relatively large number of enantiopure sulfoxides originated from our previous investigation, which led to the important result that aryl benzyl sulfoxides could be easily prepared in a high enantiomeric purity (up to >98% ee) by a *tert*-butyl hydroperoxide (TBHP) enantioselective oxidation of the corresponding sulfides in the presence of a complex between titanium tetraisopropoxide and commercially available (*S*,*S*)- or (*R*,*R*)-hydrobenzoin (Scheme 2).[23]

This oxidation protocol is particularly efficient, because it is insensitive to the presence of water, works at room

---

[8] (a) Mislow, K.; Ternay, A. L., Jr.; Melillo, J. T. *J. Am. Chem. Soc.* **1963**, *85*, 2329–2330. (b) Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 1958–1976.

[9] Jaffe, H. H.; Orchin, M. *Theory and Applications of Ultraviolet Spectroscopy*; Wiley: New York, 1962.

[10] Frolov, Y. L.; Sinegovskaya, L. M.; Gusarova, N. K.; Efremova, G. G.; Trofimov, B. A. *Russ. Chem. Bull.* **1978**, *27*, 901–904.

[11] (a) Bendazzoli, G. L.; Palmieri, P.; Gottarelli, G.; Moretti, I.; Torre, G. *J. Am. Chem. Soc.* **1976**, *98*, 2659–2660. (b) Moretti, I.; Torre, G.; Gottarelli, G. *Tetrahedron Lett.* **1976**, 711–714. (c) Bendazzoli, G. L.; Palmieri, P.; Gottarelli, G.; Moretti, I.; Torre, G. *Gazz. Chim. Ital.* **1979**, *109*, 19–25.

[12] Mangini, A.; Pallotti, M.; Tiecco, M.; Dondoni, A.; Vivarelli, P. *Int. J. Sulfur Chem. A* **1972**, *2*, 69–78.

[13] Donnoli, M. I.; Superchi, S.; Rosini, C. *Minirev. Org. Chem.* **2006**, *3*, 77–92.

[14] Laur, P. H. Steric aspects of sulfur chemistry. In *Sulfur in Organic and Inorganic Chemistry*; Senning A., Ed.; Marcel Dekker: New York, 1972; Vol. 3, pp 91−274.

[15] Rosini, C.; Donnoli, M. I.; Superchi, S. *Chem.—Eur. J.* **2001**, *7*, 72–79.

[16] Donnoli, M. I.; Giorgio, E.; Superchi, S.; Rosini, C. *Org. Biomol. Chem.* **2003**, *1*, 3444–3449.

[17] (a) Crawford, T. D. *Theor. Chem. Acc.* **2006**, *115*, 227–245. (b) Diedrich, C.; Grimme, S. *J. Phys. Chem. A* **2003**, *107*, 2524–2539. (c) Rappoport, D.; Furche, F. *Lect. Notes Phys.* **2006**, *706*, 337–354. (d) Autschbach, J. *Chirality* **2010**, in press; DOI: 10.1002/chir.20789.

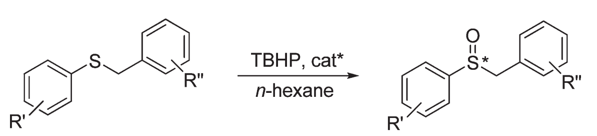
[18] Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, J.; Rosini, C. *Org. Lett.* **2002**, *4*, 4595–4598.

[19] Petrovic, A. G.; He, J.; Polavarapu, P. L.; Xiao, L. S.; Armstrong, D. W. *Org. Biomol. Chem.* **2005**, *3*, 1977–1981.

[20] Casarini, D.; Lunazzi, L.; Mancinelli, M.; Mazzanti, A.; Scafato, P. *Chirality* **2009**, *21*, 16–23.

[21] Wang, Y.; Raabe, G.; Repges, C.; Fleischhauer, J. *Int. J. Quantum Chem.* **2003**, *93*, 265–270.

SCHEME 2. Enantioselective Synthesis of Aryl Benzyl Sulfoxides



cat* = Ti(O-*i*-Pr)$_4$/ (*S*,*S*)- or (*R*,*R*)-hydrobenzoin

Molar ratio: Ti(O-*i*-Pr)$_4$:hydrobenzoin:sulfide:TBHP 1:2:20:22

temperature, is performed in *n*-hexane, and can be easily scaled up.[23] The (*R*)-sulfoxides were obtained by using the (*S*,*S*)-hydrobenzoin as a ligand of titanium, whereas the (*S*)-sulfoxides were obtained in the presence of the (*R*,*R*)-hydrobenzoin. This stereochemical outcome and the high enantioselectivity of the oxidation were also substantiated by a theoretical study.[23]

In the present investigation, we recorded the CD spectra of **1a**−**m** both in solution and in the solid state. Solid-state CD spectra[24] are useful tools for stereochemical investigations of organic molecules, in particular for absolute configurational assignments.[25] We also report the results of TDDFT calculations of CD spectra for representative aryl benzyl sulfoxides, using DFT-computed structures and available X-ray geometries. Aim of the present contribution is to demonstrate that TDDFT calculations are able to reproduce CD spectra of aryl benzyl sulfoxides and can be employed as a useful tool for the prediction and interpretation of CD of these and related substrates.

Results

1. Experimental CD Spectra in Solution. Aryl benzyl sulfoxides **1a**−**m** (Scheme 1) are indicated in the following text with the notation **1x** [R′/R″], where R′ and R″ are the substituents at the phenyl and the benzyl phenyl ring, respectively, e.g., **1h** [4Br/2NO$_2$] is 4′-bromophenyl (2-nitrophenyl)methyl sulfoxide. Figure 1 shows the CD spectra of compounds (*R*)-**1a**−**m** measured in acetonitrile solutions. The spectra for available (*S*) enantiomers of **1a** and **1b**, shown in Figure S1 (Supporting Information), are the perfect mirror images of the corresponding (*R*) antipodes.

Aryl benzyl sulfoxides **1b**,**c**,**f** (Figure 1b,c) show CD spectra similar to alkyl aryl sulfoxides,[15] with minimal differences due to the replacement of an alkyl with the benzyl group. They consist, for (*R*) absolute configuration, of a moderately intense positive band around 260 nm and a negative one around 230 nm. A smaller positive band may appear around 300 nm, sometimes as a shoulder on the long-wavelength side of the stronger close band. Based on the similarity with alkyl phenyl sulfoxides,[15] the CE at 260 may be assigned to the sulfoxide group primary transition, while those at 225 and 300 nm to benzene ^1L_a and ^1L_b transitions, respectively. The sulfoxide primary band has positive sign for the (*R*)-configuration for all compounds and follows Mislow's empirical rule for alkyl aryl sulfoxides.[8] With respect to 4- and 3-methoxyphenyl compounds **1b** and **1c**, the 2-methoxy isomer (*R*)-**1d** [2OMe/H] shows an additional positive CD band around 280 nm, which has a corresponding strong absorption band at 281 nm in CH$_3$CN ($\varepsilon \approx 5600$ M^{-1} cm^{-1}; see Figure S2, Supporting Information). Peculiar red-shifted spectra are shown by the nitrophenyl sulfoxide **1a** [4NO$_2$/H] and the ester **1e** [2COOMe/H] (Figure 1a), consisting of a series of bands of alternating sign in the 200−350 nm region, the first of which (from the right) is again positive for the (*R*) enantiomers.

The 4-bromophenyl derivatives (*R*)-**1g**−**m** with a substituted benzyl phenyl ring have CD spectra similar to that of the parent compound (*R*)-**1f** [4Br/H] (Figure 1c−e). They are consistent with that of (*S*)-benzyl phenyl sulfoxide described by Rosini et al. (extrema at 257 nm, $\Delta\varepsilon = -30.4$ M^{-1} cm^{-1}, and 226 nm, +48.1).[15] This demonstrates that both the *p*-bromo-substitution at the phenyl ring and the various substituents on the benzyl phenyl ring affect the general appearance of the CD spectrum only to a small extent. The only compound in the series showing some difference is the nitro derivative **1g** [4Br/4NO$_2$], whose positive CD band in the 240−300 nm region is detectably split (Figure 1e).

2. Calculations of CD Spectra. 2.1. Choice of Calculation Method: Model Compounds. Simulation of CD spectra of **1a**−**m** in solution started from the generation of input geometries and the choice of the most suitable functional and basis set for DFT and TDDFT calculations. A series of preliminary calculations were performed on methyl phenyl (**2**), ethyl phenyl (**3**), and benzyl phenyl (**4**) sulfoxides (Scheme 3). Due to the spectral homogeneity of alkyl aryl sulfoxides discussed above, the choice of such model compounds was considered appropriate. Conformational searches with molecular mechanics methods led for each compound to a single or a limited number of low-energy minima that were optimized with DFT. B3LYP/6-31G(d) optimized geometry for **2** was in very good agreement, in terms of bond lengths and angles, with the structure calculated by Agranat and co-workers with the larger 6-311G(d,p) basis set.[26] A torsional energy scan relative to C$_{2'}$−C$_{1'}$−S−O dihedral (phenyl/S=O dihedral, $d_{\mathrm{Ph/SO}}$) revealed the presence of a single minimum with $d_{\mathrm{Ph/SO}}$ between 0 and 10° and a maximum at $d_{\mathrm{Ph/SO}} \approx 100°$ destabilized by around 5 kcal mol^{-1}. B3LYP reoptimization of the minimum led to $d_{\mathrm{Ph/SO}} = +3.0°$ with 6-31G(d) and +7.1° with 6-311G(d,p) basis set, reproducing Agranat's results.[26] Compounds **3**

---

[22] (a) Montgomery, J. I.; Toogood, P. L.; Hutchings, K. M.; Liu, J.; Narasimhan, L.; Bradena, T.; Dermyer, M. R.; Kulynych, A. D.; Smith, Y. D.; Warmus, J. S.; Taylor, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 665–669. (b) Catto, M.; Nicolotti, O.; Leonetti, F.; Carotti, A.; Favia, A. D.; Soto-Otero, R.; Méndez-Álvarez, E.; Carotti, A. *J. Med. Chem.* **2006**, *49*, 4912–4925. (c) Venkatesan, A. M.; Davis, J. M.; Grosu, G. T.; Baker, J.; Zask, A.; Levin, J. I.; Ellingboe, J.; Skotnicki, J. S.; DiJoseph, J. F.; Sung, A.; Jin, G.; Xu, W.; McCarthy, D. J.; Barone, D. *J. Med. Chem.* **2004**, *47*, 6255–6269. (d) Ng, H. P.; May, K.; Bauman, J. G.; Ghannam, A.; Islam, I.; Liang, M.; Horuk, R.; Hesselgesser, J.; Snider, R. M.; Perez, H. D.; Morrissey, M. M. *J. Med. Chem.* **1999**, *42*, 4680–4694. (e) Dannhardt, G.; Kiefer, W.; Nowe, U. *Arch. Pharm.* **1995**, *328*, 681–686. (f) Honda, Y.; Masuda, Y.; Yoshida, T.; Sato, F.; Kurokawa, M.; Hosoki, K. *Arzneim.-Forsch.* **1995**, *45*, 1057–1060. (g) Nelson, M. L.; Park, B. H.; Levy, S. B. *J. Med. Chem.* **1994**, *37*, 1355–1361. (h) Hornsby, P. J.; Harris, S. E.; Aldern, K. A. *Chem.-Biol. Interact.* **1984**, *51*, 335–346. (i) Fulton, A.; Norman, T. R.; Cheng, H.; Burrows, G. D. *J. Affective Disord.* **1982**, *4*, 261–269.

[23] (a) Naso, F.; Capozzi, M. A. M.; Bottoni, A.; Calvaresi, M.; Bertolasi, V.; Capitelli, F.; Cardellicchio, C. *Chem.—Eur. J.* **2009**, *15*, 13417–13426. (b) Capozzi, M. A. M.; Cardellicchio, C.; Naso, F.; Rosito, V. *J. Org. Chem.* **2002**, *67*, 7289–7294.

[24] (a) Kuroda, R.; Honma, T. *Chirality* **2000**, *12*, 269–277. (b) Kuroda, R. Solid-state CD: application to inorganic and organic chemistry. In *Circular Dichroism: Principles and Applications*, 2nd ed.; Berova, N., Nakanishi, K., Woody, R. W., Eds.; Wiley-VCH: New York, 2000; pp 159−184.

[25] Pescitelli, G.; Kurtán, T.; Flörke, U.; Krohn, K. *Chirality* **2009**, in press; DOI: 10.1002/chir.20795.

[26] Marom, H.; Biedermann, U.; Agranat, I. *Chirality* **2007**, *19*, 559–569.

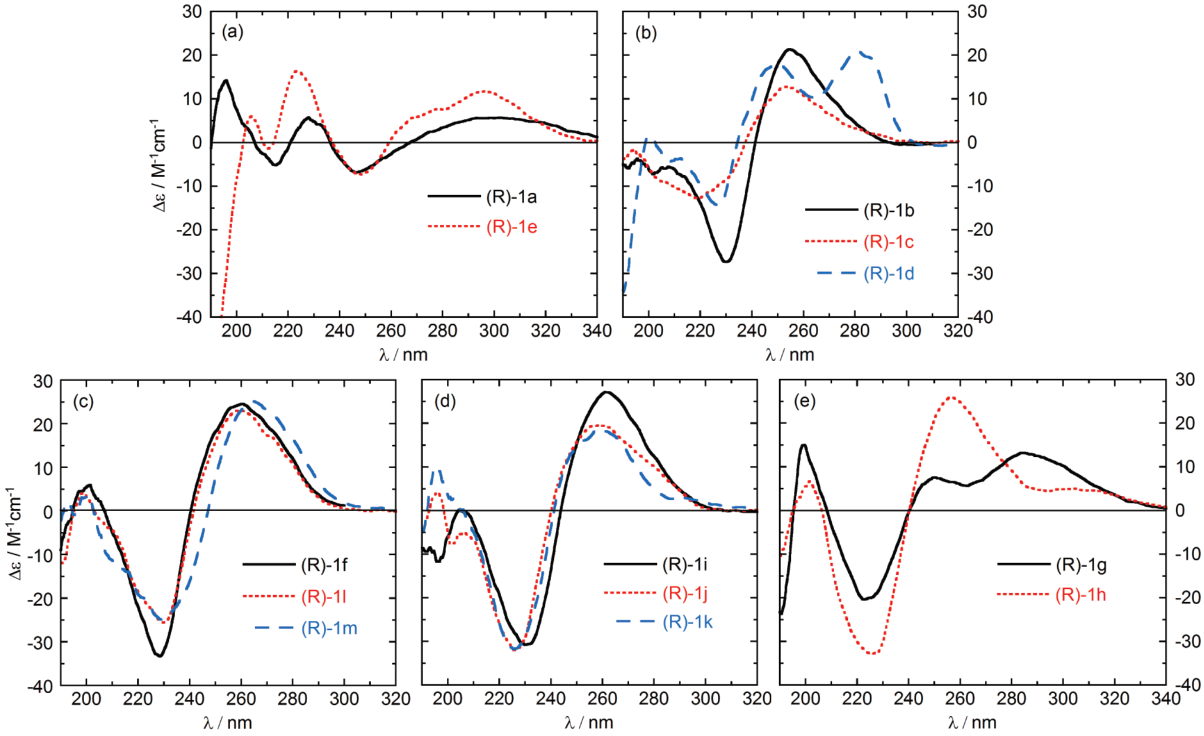
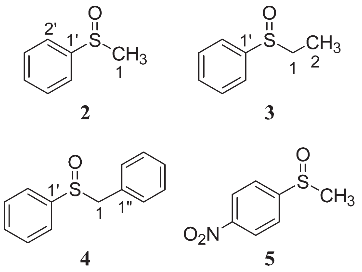


FIGURE 1. CD spectra of sulfoxides (*R*)-**1a**−**m** in acetonitrile.

SCHEME 3. **Model Sulfoxides 2−5**



and **4** have an additional degree of freedom relative to the rotamerism around the S−C$_1$ bond. In both cases, three rotamers were found by DFT calculations, which are labeled *a* (anti), *g*+ (gauche plus), and *g*− (gauche minus), corresponding to C$_{1'}$−S−C$_1$−C$_2$ (or C$_{1''}$) dihedrals $d_{\mathrm{PhS/C1}} \approx 180°$, +60°, and −60°, respectively (see Table S1, Supporting Information). For compound **3** with (*R*) configuration, *a* and *g*+ conformers had similar population quite larger than that of conformer *g*−. For compound (*R*)-**4**, conformer *a* was the most stable, while the two *g* conformers had similar energies. Populations evaluated at the B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) level were slightly different from those obtained with B3LYP/6-31G(d), while the difference between B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) and full B3LYP/6-311+G(d,p) results was minimal (Table S1, Supporting Information). Moreover, inclusion of PCM (polarizable continuum solvation model)[27] for acetonitrile in B3LYP/6-311+G(d,p) single point calculations affected the computed relative populations to a very small extent. In the minimum-energy structures of (*R*)-**3** and (R)-**4**, the phenyl/S=O dihedrals $d_{\mathrm{Ph/SO}}$ are again in the range between +3° and +6°.

TDDFT calculations were run on DFT-optimized geometries for compounds **2**−**4** with various functionals (BP86,[28] B3LYP,[29] PBE0,[30] and BH&HLYP,[31] in order of increasing HF exchange amount) and basis sets (SVP, TZVP, and aug-TZVP, in order of increasing size),[32] and the resulting CD spectra were compared with experimental literature data (see Figure S3, Supporting Information, for (*S*)-**3**).[15] For **3** and **4**, the Boltzmann-weighted average CD spectrum was evaluated at 300 K over three DFT (B3LYP/6-311+G(d,p)//B3LYP/6-31G(d)) energy minima (*a*, *g*+, and *g*−). Among the functionals used, the best match between experimental and calculated CD spectra, in terms of relative intensity and position of the two major bands, was obtained with BH&HLYP. This functional afforded a systematic frequency overestimation of ~3,000 cm^{-1} for all predicted transitions (corresponding to a blue shift of 12 and 20 nm at 200 and 260 nm, respectively, e.g., for (*S*)-**4**, average calculated CD, bandwidth σ = 2500 cm^{-1}: 226 nm ($\Delta\varepsilon$ = −20 M^{-1} cm^{-1}), 202 nm (+25); experimental in CH$_3$CN:[15] 247 nm (−14), 217 nm (+26)). Both B3LYP and PBE0 overestimated the energy separation between the two major bands, affording a less satisfying agreement (see Figure S3 in Supporting

---

(27) *Continuum Solvation Models in Chemical Physics: From Theory to Applications*; Tomasi, J., Mennucci, B., Cammi, R, Eds.; Wiley: Chichester, 2007.

(28) (a) Becke, A. D. *Phys. Rev. A* **1988**, *38*, 3098–3100. (b) Perdew, J. P. *Phys. Rev. B* **1986**, *33*, 8822–8824.

(29) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648–5652.

(30) Adamo, C.; Scuseria, G. E.; Barone, V. *J. Chem. Phys.* **1999**, *111*, 2889–2899.

(31) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 1372–1377. (Gaussian'03 and Gaussian'09 add a B88-type[28a] gradient exchange correction to the original BH&H scheme).

(32) Schafer, A.; Huber, C.; Ahlrichs, R. *J. Chem. Phys.* **1994**, *100*, 5829–5835.

Information for **3**). BP86 performed worst along the series. As for the basis set, using BH&HLYP as functional the agreement observed was similar for the three sets tested. The good performance of the smallest basis set SVP is especially noticeable. Use of small basis sets like 6-31G(d) has been suggested as an expedient to save computational time viable in some conditions.[33] For the present compounds, however, the overall computational time using TZVP is still reasonable, and therefore the BH&HLYP/TZVP combination was employed in the following calculations and a frequency correction[34] of $-3{,}000\ \mathrm{cm}^{-1}$ (+20 nm at 260 nm) was applied in all cases. The only exceptions concern methoxyphenyl derivatives **1b** [4OMe/H] and **1d** [2OMe/H], for which B3LYP led to better results than BH&HLYP (no frequency correction was needed in these cases).

The same sequence described above of (a) conformational search, (b) DFT geometry optimizations at the B3LYP/6-31G(d) level, (c) single point calculations at the B3LYP/6-311G+(d,p) level to estimate relative energies, (d) TDDFT calculations with BH&HLYP/TZVP (or B3LYP/TZVP) on all populated minima (including PCM for a few representative cases), and (e) averaging of CD spectra was applied to several representative aryl benzyl sulfoxides among the series **1a**−**m**. Diagrams and relevant data of DFT-calculated energy minima are summed in Tables S2−3 (Supporting Information), and the results of TDDFT calculations are shown in Figures 2, 3, 4, and 5 and S7.

2.2. Compound 1f [4Br/H]. The most straightforward case is compound (*R*)-**1f** [4Br/H], which will be described first. DFT calculations resulted in three minima (labeled as *a*, *g*+, and *g*−, see Table S2 in Supporting Information) relative to the rotamerism around the S−CH$_2$ bond, with a slight preference for *g*+ (absolute minimum, 38% population at 300 K) and *a* (+0.05 kcal mol^{-1}, 33%) over the *g*− conformer (+0.20 kcal mol^{-1}, 27%). The second possible degree of conformational freedom, that is, the rotamerism around the phenyl−CH$_2$ bond, led to a single energy minimum with the CH$_2$−S bond nearly perpendicular to the benzyl phenyl ring. The low-energy structures for **1f** are shown in Figure S4 (Supporting Information). Calculated CD spectra are very similar for *a* and *g*+ conformers in the low-energy region and consist of a positive couplet-like feature between 210 and 300 nm (frequency corrected, Figure 2a). A monosignate and weaker negative CD band is instead computed for *g*− between 210 and 300 nm. As a consequence, the weighted average spectrum is dominated by *a* and *g*+ contributions. For (*R*)-**1f** it consists of a moderately intense positive couplet-like feature with extrema at 260 and 220 nm (frequency corrected), followed by two weaker CEs around 200 and 185 nm, respectively positive and negative. Overall, the average calculated CD for (*R*)-**1f** [4Br/H] is in almost perfect agreement with the experimental one (compare Figures 2a and 1c; a direct comparison is shown in Figure 7b below). Introduction of a solvent model (PCM)[27] for acetonitrile in both energy and CD calculations did not improve the overall result, actually, the agreement with the experimental spectrum was worse at high energies (see Supporting Information, Figure S7c).

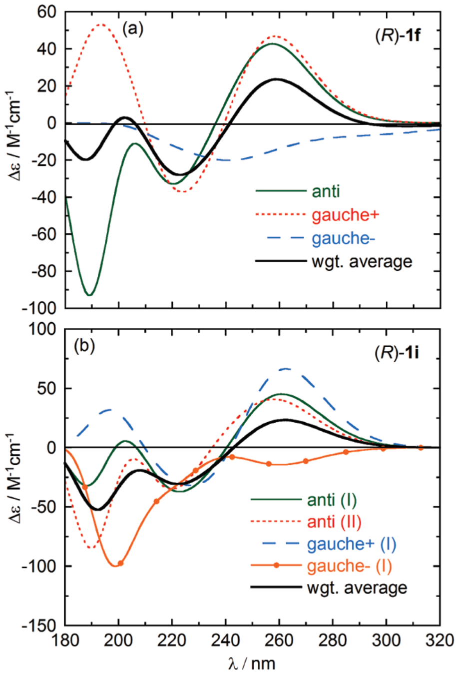


FIGURE 2. CD spectra calculated for sulfoxides (*R*)-**1f** [4Br/H] (a) and (*R*)-**1i** [4Br/4OMe] (b) with BH&HLYP/TZVP on B3LYP/6-311G+(d,p)//B3LYP/6-31G(d) structures. Average spectra are obtained by Boltzmann weighting at 300 K of the calculated spectra for various energy minima (three for **1f**, six for **1i**, of which the results for the lowest-energy four are shown; see Table S2 in Supporting Information). Band-width $\sigma = 2500\ \mathrm{cm}^{-1}$, frequency correction $-3{,}000\ \mathrm{cm}^{-1}$.

CD spectra recorded at variable temperatures from 262 to 348 K (−36 to +50 °C) are in accordance with the conformational picture found by calculations, because increasing the temperature led to a slight intensity decrease for the positive CD band, while the negative one was relatively less affected (Figure S5, Supporting Information).

The first positive CE (from the red) calculated for (*R*)-**1f** essentially arises from a HOMO → LUMO transition. Analysis of Kohn−Sham orbitals (MO) revealed that both HOMO and LUMO are delocalized over a large molecular portion (see Figure S6, Supporting Information). In particular, the HOMO (MO 74) may be thought to arise from the combination of oxygen lone pair n_{O}, a bonding $\sigma_{\mathrm{S-C1}}$ between sulfur and methylene carbon, and bonding π orbitals over the two aromatic rings, both of benzene e_{1g} (π_3) type.[9] Conversely, the LUMO (MO 75) consists of the two aromatic π^* orbitals (benzene e_{2u} type, or π_5) plus an antibonding $\sigma^*_{\mathrm{S-C1}}$ MO. Therefore, the first observed transition for **1f** [4Br/H] corresponds to the sulfoxide primary band described by Mislow. The situation for the negative CE at 230 nm is less clear-cut, as it results from the superposition of many different transitions, two of which are associated with moderately intense negative rotational strengths. The main contribution to the first of them, computed at 222 nm (frequency corrected), is the transition to the LUMO from the occupied MO 71, which may be described as a combination of oxygen lone pair n_{O}, a bonding $\sigma_{\mathrm{S-C1'}}$ between sulfur and phenyl carbon, and a phenyl π orbital of e_{1g} type (Figure S6 in Supporting Information). The second transition concurring to the negative CD band is calculated at

---

(33) Giorgio, E.; Tanaka, K.; Verotta, L.; Nakanishi, K.; Berova, N.; Rosini, C. *Chirality* **2007**, *19*, 434–445.

(34) Bringmann, G.; Gulder, T. A. M.; Reichert, M.; Gulder, T. *Chirality* **2008**, *20*, 628–642.

215 nm and it is instead the combination of several single-electron promotions from MO 71 and MO 74 to various virtual orbitals, with small CI (configuration interaction) coefficients. As for the ^1L_b-type aromatic transition, it appears as one of the components of two transitions predicted around 245 nm (frequency corrected), both with negligible oscillator and rotational strength, submerged by the sulfoxide primary band. The fact that the present TDDFT calculations seem to especially overestimate the energy of this kind of transition (benzene ^1L_b) has been observed before,[35] but it has no or very small effect on the overall shape of the computed CD curves of aryl benzyl sulfoxides, because of the inherent weakness of the associated CD bands.

2.3. Methoxy Substituent on the Benzyl Phenyl Ring: Compound 1i [4Br/4OMe]. The results of calculations on a second 4-bromophenyl derivative, namely, (*R*)-**1i** [4Br/4OMe], did not substantially deviate from those previously discussed. The only difference consists in the additional degree of freedom relative to the rotamerism of the methoxy group, and thus six energy minima needed to be considered (Table S2 in Supporting Information). In this case too, the agreement between the average calculated and experimental CD spectrum was very good (Figures 1d and 2b, direct comparison shown in Figure 7d below), which also allowed us to confirm (*R*)-(+) absolute configuration associated with positive CD at 260 nm. In fact, compound **1i** is the only one in the series whose absolute configuration had not been assigned by X-ray analysis[23] or known before. Similarly to what found for **1f**, inclusion of PCM for acetonitrile in CD calculations did not affect much the two major transitions, while some difference with respect to the calculations in vacuo was observed at higher energies (see Supporting Information, Figure S7f).

2.4. Nitro Substituent on the Benzyl Phenyl Ring: Compounds 1g [4Br/4NO$_2$] and 1h [4Br/2NO$_2$]. For the compounds containing a nitro-substituted benzyl phenyl ring such as **1g** [4Br/4NO$_2$] and **1h** [4Br/2NO$_2$], some differences arose in terms of calculated geometries and spectra with respect to the cases presented so far. The 4-nitro isomer (*R*)-**1g** allowed only three rotamers *a*, *g*+, and *g*− (Table S2 in Supporting Information); their relative energies (and populations at 300 K) were +0.09 kcal mol^{-1} (38%), 0 (absolute minimum, 45%) and +0.57 kcal mol^{-1} (17%), that is, the *g*− is quite less populated than for (*R*)-**1f** [4Br/H]. This is probably due to an unfavorable dipole−dipole alignment between the nitrobenzene and sulfinyl group. For the 2-nitro isomer (*R*)-**1h**, the *a* rotamer is by far the most populated (87%), whereas the *g*− is not at all (overall population < 2%), perhaps due to repulsive electrostatic interaction between nitro and sulfoxide groups in the *g* rotamers. Average TDDFT-calculated CD spectra were in both cases in good agreement with experimental ones (Figures 1e and 3, a direct comparison for **1g** is shown in Figure 7c below), but some details need to be added. For **1g** [4Br/4NO$_2$], the splitting of the first CD band between 240 and 350 nm was not reproduced by calculations in vacuo, unless admitting a larger contribution from the *g*− isomer than predicted by B3LYP/6-311+G(d,p)//B3LYP/6-31G(d) (Figure 3a). The result was practically unchanged using geometries optimized at B3LYP/6-311+G(d,p) level or introducing PCM for acetonitrile in energy calculations (see Supporting Information, Table S3). However, when PCM was employed in TDDFT calculations too, all conformers acquired a positive CD signals around 240 nm (frequency corrected, Figure S7d, Supporting Information). As a result, the weighted average spectrum showed two positive bands above 230 nm similar to the experimental one (Figure 3a), although the intensity of the short-wavelength component is overestimated.

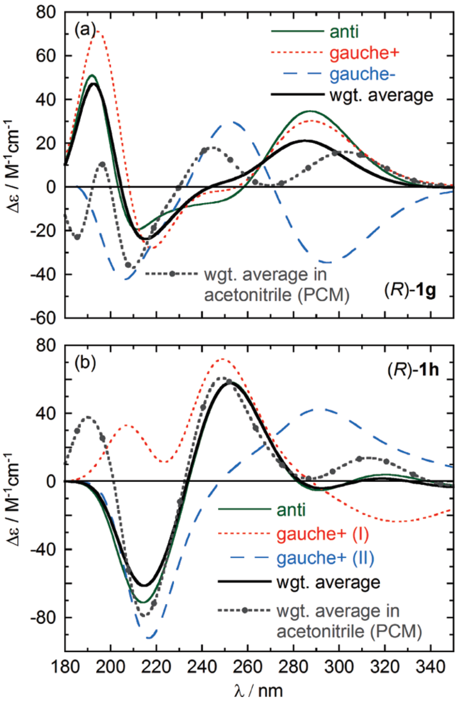


FIGURE 3. CD spectra calculated for sulfoxides **1g** [4Br/4NO$_2$] (a) and **1h** [4Br/2NO$_2$] (b) with BH&HLYP/TZVP on B3LYP/6-311G+(d,p)//B3LYP/6-31G(d) structures. Average spectra are obtained by Boltzmann weighting at 300 K of the calculated spectra for three energy minima (see Table S2 in Supporting Information). The spectra labeled with (PCM) are the average obtained by employing PCM solvation model for acetonitrile both in single point (DFT) and TDDFT calculations (Table S3 and Figure S7d,e in Supporting Information). Band-width σ = 2500 cm^{-1}, frequency correction −3,000 cm^{-1}.

In the CD spectrum of (*R*)-**1h** [4Br/2NO$_2$] three transitions of alternating sign −/+/− were predicted in the long-wavelength region (> 280 nm, frequency corrected, Figure 3b). The middle one is associated with the largest absolute rotational strength and is conceivably responsible for the positive CE at 305 nm seen in the experimental spectrum (Figure 1e). The assignment is supported by the fact that, after running DFT (single point) and TDDFT calculations with PCM, the average spectrum did display a more intense positive band at 312 nm (frequency corrected, Figures 3b and S7e, Supporting Information). The difference with respect to the calculations in vacuo is mainly due to a switch in population between the two *g*+ conformers (related to the nitrophenyl ring flip and labeled as I and II, Table S2, Supporting Information). Therefore, for both compounds (*R*)-**1g** [4Br/4NO$_2$] and **1h** [4Br/2NO$_2$] the inclusion of a solvation model partially improved the agreement between

---

(35) (a) Pescitelli, G.; Di Bari, L.; Caporusso, A. M.; Salvadori, P. *Chirality* **2008**, *20*, 393–399. (b) Mazzini, F.; Pescitelli, G.; Di Bari, L.; Netscher, T.; Salvadori, P. *Chirality* **2009**, *21*, 35–43.

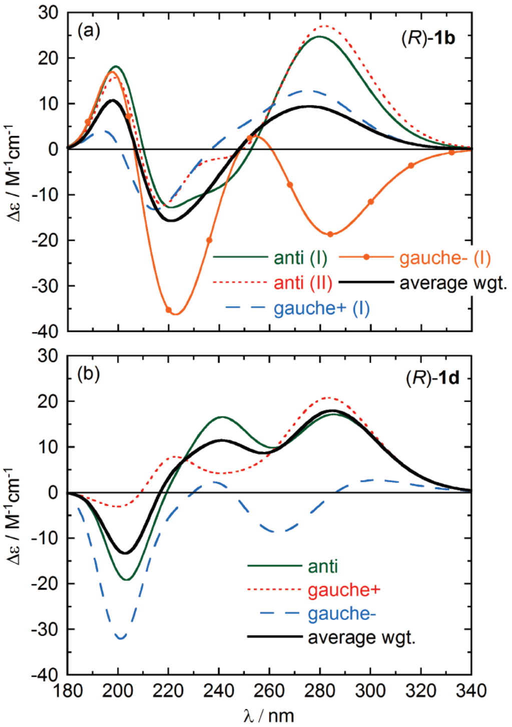


FIGURE 4. CD spectra calculated for sulfoxides (*R*)-**1b** [4OMe/H] (a) and (*R*)-**1d** [2OMe/H] (b) with B3LYP/TZVP on B3LYP/6-311G+(d,p)//B3LYP/6-31G(d) structures. Average spectra are obtained by Boltzmann weighting at 300 K of the calculated spectra for various energy minima (three for **1d**, six for **1b**, of which the results for the lowest-energy four are shown; see Table S2 in Supporting Information). Band-width σ = 2500 cm^{-1}, no frequency correction.

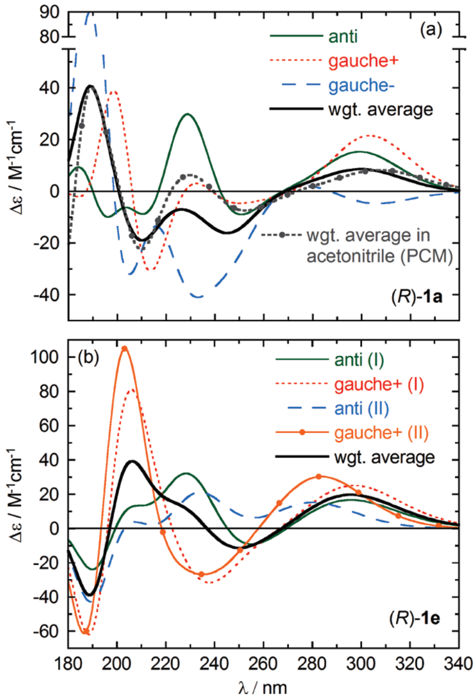


FIGURE 5. CD spectra calculated for sulfoxides **1a** [4NO$_2$/H] (a) and **1e** [2COOMe/H] (b) with BH&HLYP/TZVP on B3LYP/6-311G+(d,p)//B3LYP/6-31G(d) structures. Average spectra are obtained by Boltzmann weighting at 300 K of the calculated spectra for three (**1a**) or four (**1e**) energy minima (see Table S2, Supporting Information). The spectrum labeled with PCM is the average obtained by employing PCM solvation model for acetonitrile in single point (DFT) and TDDFT calculations (Table S3 and Figure S7a in Supporting Information). Band-width σ = 2500 cm^{-1}, frequency correction −3,000 cm^{-1}.

calculated and experimental CD spectra. However, it must be stressed that the calculations in vacuo were already enough accurate for, e.g., the hypothetical purpose of assigning absolute configurations.

The three calculated transitions above 280 nm for **1h** all involve the LUMO, which is an almost pure π^* orbital localized on the nitrobenzene ring. On the contrary, the stronger positive CD calculated at 253 nm (frequency corrected) mainly arises from the HOMO → LUMO+1 transition. These latter MOs are both delocalized on the whole molecule including the sulfinyl group and may be thought to correspond, respectively, to the HOMO and LUMO described above for **1f** [4Br/H] and the associated transition to the sulfoxide primary band. Therefore the discrepancies between the CD spectrum of **1f** and its *o*-nitrobenzyl analogue **1h** [4Br/2NO$_2$] are mainly due to an energy redistribution of MOs, while the sign and character of the major CD band (sulfoxide primary band) remain unchanged.

2.5. Methoxy Substituent on the Phenyl Ring: Compounds 1b [4OMe/H] and 1d [2OMe/H]. As far as sulfoxides with substituents different from bromine on the phenyl ring are concerned, compound **1b** [4OMe/H] has a CD spectrum similar to that of **1f** [4Br/H], and both DFT and TDDFT calculations are in agreement with the already described trend. Six low-energy conformations were obtained through B3LYP/6-31G(d) geometry optimizations (Table S2, Supporting Information), which arise from a combination of the rotamerism around S−CH$_2$ (*a*, *g*+ and *g*− rotamers) and C−OMe bonds (two rotamers indicated as I and II). In this case too, the observed positive couplet-like feature between 200 and 300 nm for the (*R*) configuration (Figure 1b) was correctly reproduced by the average B3LYP/TZVP-calculated CD (Figure 4a). Use of the PCM solvation model in both energy and CD calculations did not affect substantially the result (see Table S3 and Figure S7b, Supporting Information). For the *o*-isomer (*R*)-**1d** [2OMe/H], only one conformation is possible for the methoxy group to avoid a steric contact with the sulfoxide one; moreover, the *g*− rotamer is very disfavored with respect to *a* and *g*+ due to the electrostatic repulsion between the two S═O and OMe groups (Table S2, Supporting Information). The peculiar shape of the CD spectrum of (*R*)-**1d**, showing two distinct positive bands in the long wavelength region, is well reproduced by B3LYP/TZVP calculations (Figures 1b and 4b). For both isomers **1b** [4OMe/H] and **1d** [2OMe/H], the first (from the red) CE is due to the HOMO → LUMO transition corresponding to the sulfoxide primary transition, with MO characters similar to those analyzed above for **1f**. The differences observed in the remaining calculated CD bands seem to be related to the fact that the perturbation exerted by the methoxy substituent on the phenylsulfinyl ring is larger for the *p*- than the *o*-isomer. In fact, in both cases the electron-donating group destabilizes all the virtual orbitals localized on the attached phenyl ring; however, this effect is weaker for the *o*-isomer, and hence a less pronounced impact on the CD is manifest.

2.6. Nitro or Carboxy Substituent on the Phenyl Ring: Compounds 1a [4NO$_2$/H] and 1e [2COOMe/H]. The singular CD spectra of the nitro and methoxycarbonyl derivatives **1a** [4NO$_2$/H] and **1e** [2COOMe/H] were also well reproduced by CD calculations (Figures 1a and 5, a direct comparison for **1a** is shown in Figure 7a below). The calculations correctly predicted both the distinctive red shift with respect to the other derivatives, and the series of CD bands with alternating sign appearing in the 180−350 nm range (frequency corrected). For **1a**, DFT geometry optimizations resulted in the usual three rotamers *a*, *g*+, and *g*−, the latter being the most stable (Table S2, Supporting Information), for which TDDFT computed quite different CD spectra (Figure 5a). In the resulting average spectrum, the third CD band (experimentally a positive maximum at 228 nm for (*R*)-**1a**) is partially submerged by flanking negative bands and appears as a negative maximum around 225 nm (frequency corrected). The agreement with the experimental spectrum improved after introducing PCM for acetonitrile in DFT (single point) and TDDFT calculations (see Supporting Information, Table S3 and Figure S7a). With respect to the calculations in vacuo, the relative population of the *a* isomer increased substantially (from 29% to 42%). As a consequence, the weighted average CD spectrum displayed a positive band at 215 nm (frequency corrected) and acquired the same appearance of the experimental spectrum with a series of five bands with alternating sign (Figure 5a). The first band around 300 nm is due to the HOMO → LUMO transition, but these two MOs have quite different character with respect to **1f** [4Br/H] and analogous cases. In fact, the HOMO (MO 68) is a combination of n_O, σ_{S-C1}, and π (e_{1g}-type) orbitals, the latter localized over the benzyl phenyl but not the nitrophenyl ring, whereas the LUMO (MO 69) is a π^* orbital localized on the nitrophenyl ring (Figure S8, Supporting Information). The second calculated CD band is largely due to a $\pi-\pi^*$ transition of the nitrophenyl ring. The third transition is mainly a promotion from the HOMO to MO 71, which consists of two aromatic π^* orbitals plus an antibonding σ^*_{S-C1}, thus resembling the LUMO of **1f**. Overall, the apparent red shift observed for **1a** with respect, e.g., to the bromine analogue **1f** [4Br/H] is justified by the stabilizing effect exerted by the electron-withdrawing nitro substituent on the orbitals of the attached phenyl ring. This effect is stronger on the virtual orbitals, first of all the LUMO, than on the HOMO and following occupied orbitals.

Similar arguments may be applied to the discussion of the CD spectrum of **1e** [2COOMe/H] with an electron-withdrawing carboxy group on the phenylsulfinyl ring. The first calculated transition at 293 nm (frequency corrected) was again mainly the HOMO → LUMO. The two MOs have character similar to that of the corresponding MOs of **1a**, the HOMO being a combination of n_O, σ_{S-C1}, and benzyl phenyl π orbitals and the LUMO being mainly a π^* orbital localized over the carboxyphenyl ring. As in the case of **1d** [2OMe/H] discussed above, the *g*− rotamer of (*R*)-**1e** had much higher DFT-computed energy than *a* and *g*+ (Table S2, Supporting Information) because of the electrostatic repulsion between the ester and the sulfinyl moiety. The ester group may assume two different conformations, with either the C=O or the C−OMe facing the sulfinyl group, the former (labeled as I) being much more stable than the latter (II, Table S2, Supporting Information). As a result, only two conformations, *a*(I) and *g*+(I), contributed significantly to the average calculated CD of (*R*)-**1e** [2COOMe/H] (Figure 5b), which is in good agreement with the experimental one (Figure 1a).

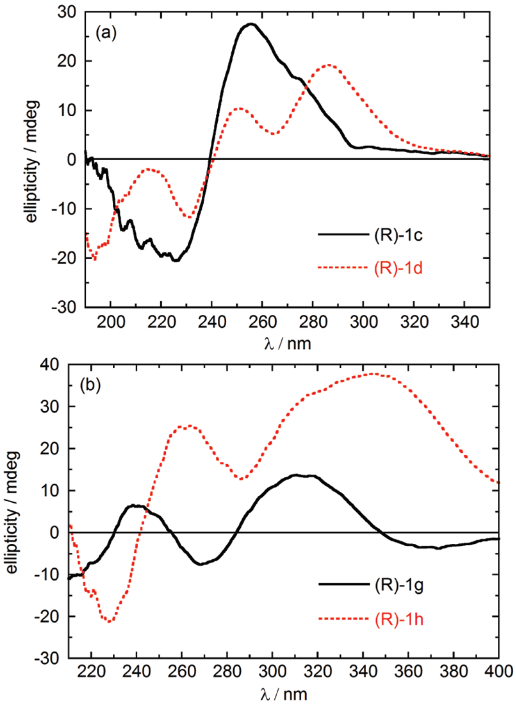


FIGURE 6. Solid-state CD spectra measured as KCl pellets for sulfoxides (*R*)-**1c**, **1d**, **1g**, and **1h**.

3. CD Spectra in the Solid State. The absolute configuration and the crystal structure of sulfoxides **1a**, **1c**−**e**, **1g,h** and **1j**−**l** had been investigated by X-ray analysis.[23] In the present work, we decided to measure CD spectra on microcrystalline samples of these compounds with the technique of KCl pellet[24,25] (see Figures 6 and S9 in Supporting Information). The observed solid-state CD spectra of compounds **1c** [3OMe/H] and **1d** [2OMe/H] (Figure 6a), and of **1k** [4Br/2OMe], **1l** [4Br/3Cl] and to some extent **1e** [2COOMe/H] (Figure S9a) were comparable with the spectra in solution. On the other hand, the spectra of **1g** [4Br/4NO$_2$] and **1h** [4Br/2NO$_2$] (Figure 6b) and of **1a** [4NO$_2$/H] and **1j** [4Br/3MeO] (Figure S9b) showed substantial differences with respect to the corresponding solution spectra.

As an example of the first class, the X-ray structure of compound (*R*)-**1d** [2OMe/H] shows a conformation of *g*+ type with respect to the S−C$_1$ torsion, with a value of $d_{PhS/C1}$ = +65.6°. DFT calculations afforded a very similar geometry for the *g*+ rotamer. The CD spectrum calculated by TDDFT on this geometry (Figure 4b) is in agreement with the solid-state CD spectrum of (*R*)-**1d** (Figure 6a). In many situations when the solid-state CD is determined by the absolute conformation of a single, "isolated" molecule, a very good agreement has been observed between experimental solid-state CD spectra and those calculated with TDDFT using the X-ray geometries as input structures.[25]

On the other hand, solution and solid-state CD spectra of sulfoxides **1g** [4Br/4NO$_2$] and **1h** [4Br/2NO$_2$] are very different (Figures 1e and 6b), because new bands appear in the latter. The DFT-optimized geometry of **1g** for the *g*+

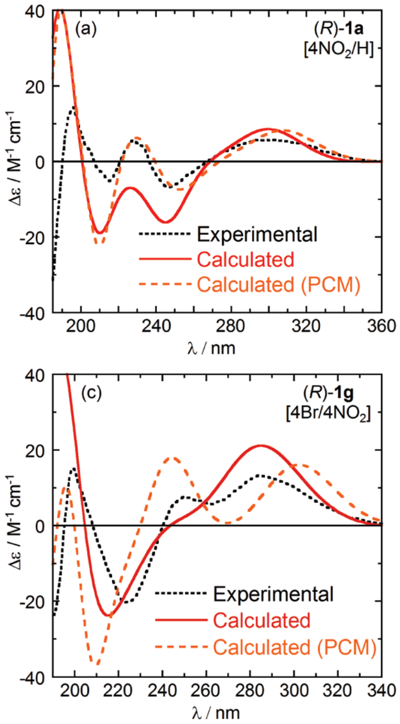


FIGURE 7. Comparison between experimental and calculated CD spectra for sulfoxides (*R*)-**1a,f,g,i**. See captions of Figures 2, 3, and 5 for details on calculated spectra.

rotamer is in very good agreement with the X-ray geometry, showing a *g*+ conformation with $d_{\mathrm{PhS/C1}} = +51.8°$. However, the TDDFT-calculated CD for this geometry (Figure 3a) is not in agreement with the solid-state CD of (*R*)-**1g** (Figure 6b), because the negative bands at 270 and 370 nm are not reproduced. Conversely, the X-ray geometry of **1h** shows an *a* conformation with $d_{\mathrm{PhS/C1}} = -166.9°$, similar to the DFT-optimized geometry for the *a* rotamer, with the exception of an increased torsion angle of the nitro group with respect to the phenyl ring (observed dihedral, −34°; calculated, −25°). TDDFT-calculated CD for the DFT-optimized and the X-ray geometry were very similar to each other, but neither could reproduce the intense positive CD band seen at 345 nm in the solid-state CD spectrum of (*R*)-**1h** (Figure 6b). Probably, in the solid-state CD spectra of compounds **1g**, **1h**, and others behaving similarly, effects inherent to the crystalline state are present, such as intermolecular interactions of the exciton type between aryl chromophores belonging to distinct molecules packed together in the crystal.[24,25]

Discussion

Ground-State Properties. Geometry optimizations with the DFT method on model compounds **2**−**4** as well as on several aryl benzyl sulfoxides belonging to the series **1** have resulted in a small set of low-energy structures. An almost coplanar arrangement between the S═O bond and the attached phenyl ring is always present, as shown also by experimental[7,23,36] and other computational investigations.[19,26] In particular, in X-ray structures of sulfoxides **1a**, **1c**−**e**, **1g,h**, and **1j**−**l** the $d_{\mathrm{Ph/SO}}$ dihedrals are below 12° (absolute values), with the only exception of compound **1c** [3OMe/H], in which it is 24°. In our B3LYP/6-31G(d)-optimized geometries, the values of the phenyl/S═O dihedrals $d_{\mathrm{Ph/SO}}$ are in the 0−10° range, with values up to 15° observed only for a few hindered *gauche* conformers (relative to the rotamerism around S−C$_1$ bond).

Such a preferential conformation around the C$_{1'}$−S bond in alkyl or benzyl aryl sulfoxides means that the sulfur lone pair is not perfectly perpendicular to the aromatic plane, an arrangement that would imply $d_{\mathrm{Ph/SO}} \approx 35°$. A perfect parallelism between the sulfur lone pair (in a sp^3(S) atomic orbital)[15] and the aromatic π system (made up of 2p(C) AOs) would clearly maximize their overlap. However, since the extent of π-overlap between two equal p-type AOs follows the cosine of the relative dihedral angle,[9] in the present case the amount of overlap loss may be roughly estimated around 15% at most. The subsequent destabilization is therefore quite small and may be easily overcome by other factors such as steric ones. In fact, in the arrangement with the sulfur lone pair perpendicular to the aromatic plane, the C$_1$ methylene hydrogens would come too close to the *ortho* phenyl hydrogens (attached to C$_{2'}$ or C$_{6'}$). For example, on the torsional energy surface for methyl phenyl sulfoxide (**2**), for the point corresponding to $d_{\mathrm{Ph/SO}} = 35°$ the shortest C$_1$−H to C$_{2'}$−H (or C$_{6'}$−H) distance reached 2−2.2 Å values, that is, below the sum of two van der Waals hydrogen radii.

The case of nitro-substituted compound **1a** [4NO$_2$/H] deserves a further discussion. On the basis of the analysis of UV spectra of aryl methyl sulfoxides, it has been suggested that a nitro group in a position *para* to the sulfinyl may enhance the electron-donating attitude of this latter.[15] However, this effect is not manifest in our calculations. In fact, analysis of Kohn−Sham orbitals, charge densities, and calculated geometries for **1a** does not suggest any augmented

---

(36) Benassi, R.; Folli, U.; Iarossi, D.; Mucci, A.; Schenetti, L.; Taddei, F. *J. Chem. Soc., Perkin Trans. 2* **1989**, 517–521.

charge donation from the sulfinyl or increased conjugation with the phenyl ring with respect, e.g., to benzyl 4-bromophenyl sulfoxide (**1f**). To deal with a smaller system we decided to investigate methyl 4-nitrophenyl sulfoxide (**5**, Scheme 3), to be compared with methyl phenyl sulfoxide (**2**). The absolute minimum found by B3LYP/6-311G(d,p) calculations on **5** had $d_{\mathrm{Ph/SO}} = 5.2°$ and the distance between sulfur and phenyl carbon $r_{\mathrm{S-C1'}} = 1.832$ Å; for **2**, the two values were 7.1° and 1.830 Å, respectively. The charge density on the sulfur atom predicted with the Mulliken scheme was 0.68 for **5** and 0.69 for **2**; with the Natural Bond Orbitals scheme, the two values were 1.18 for both molecules. These results confirmed that the *p*-nitro group does not amplify the electron-donating tendency of the sulfinyl group or the aromatic/sulfinyl conjugation. On the other hand, it is evident that the nitro group stabilizes both the HOMO and the LUMO (the latter more than the former) by comparing the MO energies of **2** and **5**. Moreover, it greatly influences the character of both HOMO and LUMO in terms of localization on the aromatic rings. This effect is the same observed for nitro-containing aryl benzyl sulfoxides **1a** [4NO_2/H], **1g** [4Br/4NO_2], and **1h** [4Br/2NO_2] and has consequences on their CD spectra (*vide infra*).

Excited-State Properties. CD spectra in acetonitrile solution have been recorded for 13 aryl benzyl sulfoxides (*R*)-**1a**−**m**, most of which had not been previously reported in the literature, with the exception of numerical CD data for (*S*)-**1a** and **1b**.[15] As already underlined in the Results section, the aspect of the CD spectrum is quite well preserved along the whole series and consists of a couplet-like feature between 200 and 300 nm with the first (long wavelength) branch being positive for (*R*) absolute configuration. CD spectra deviating from the general trend were recorded for compounds **1d** [2OMe/H] and **1g** [4Br/4NO_2] (the first positive band is split) and for **1a** [4NO_2/H] and **1e** [2COOMe/H] (the whole spectra are sizably shifted to the red). In all cases considered, the CD associated with the so-called sulfoxide primary transition is positive for the (*R*) configuration, that is, it is in keeping with Mislow's empirical rule for alkyl aryl sulfoxides.[8] Such a consistency was not surprising because the effect of replacing an alkyl group with the benzyl one was found to be minimal, even when the aromatic ring carried auxochromic substituents. On the other hand, molecular orbital analysis (actually, Kohn−Sham orbitals were considered here)[37] revealed that the MOs involved in the relevant transitions are delocalized on the benzyl phenyl ring too; therefore the fact that a benzyl group does not appreciably affect spectral outcomes of sulfoxides is less obvious than anticipated.

CD spectra have been calculated with the TDDFT method for the eight benzyl phenyl sulfoxides **1a**−**b** and **1d**−**i**, using DFT-optimized geometries as input structures. In the very large majority of cases, a very good agreement has been observed between calculated and experimental spectra. A direct comparison between experimental and calculated spectra is shown in Figure 7 for four relevant compounds. Minor discrepancies, consisting in the appearance (intensity) of one band at intermediate energy, have been detected only for compounds **1a** [4NO_2/H], **1g** [4Br/4NO_2], and **1h** [4Br/2NO_2], but they would not preclude a correct absolute configurational assignment based on the comparison between calculated and experimental CD spectra. Moreover, as discussed above, these discrepancies were alleviated by introducing a PCM solvation model for acetonitrile in energy and excited states calculations. The good performance of the TDDFT//DFT calculation scheme employed is noteworthy considering that the "calculated" spectrum is in fact the weighted sum over three to six low-energy structures, most of which with sizable population at the working temperature. It can be concluded that relative populations of various conformers and their component CD spectra were both well predicted by the calculations, even in the absence of a solvent model.

For the majority of (*R*)-sulfoxides considered, the CD calculated for the *anti* and *gauche*+ conformer (relative to the rotamerism around S−C_1 bond) were quite similar at low energies. However, one would expect the CD spectra of aryl benzyl sulfoxides to be at least partially affected by the exciton coupling between the two aromatic rings, when in a proper reciprocal arrangement.[38] Considering for example the benzene ^1L_a transition, which is long-axis polarized in *p*-disubstituted benzenes,[9] the exciton coupling between two such transitions in aryl benzyl sulfoxides is expected to be much more effective for the *gauche* than for the *anti* conformer. Clearly, the exciton coupling is not the dominant mechanism of optical activity in the long wavelength region, although it may contribute to the CD in the high energy region for some substrates. For example, for **1f** [4Br/H] the calculated CD band around 190 nm (frequency corrected) is oppositely signed for *a* and *g*+ rotamers (Figure 2a).

Our results suggest that the most reasonable mechanism of optical activity to be considered for aryl benzyl sulfoxides (as well as for their alkyl phenyl analogues)[8b] is the intrinsic chirality of the chromophoric system. This latter must necessarily include the whole molecule, because MO analysis demonstrated that the two major CD bands are due to transitions involving Kohn−Sham orbitals delocalized over the whole molecule, including both aromatic rings. As reported in the Introduction, CD spectra of alkyl aryl sulfoxides have been interpreted through the coupled-oscillator model, in terms of the exciton coupling between the sulfoxide primary transition and the phenyl ^1L_a transition.[15] Such a treatment is only allowed upon the assumption that the sulfoxide and the benzene chromophores are isolated from each other, a situation that occurs if there is severe steric hindrance to S═O/aryl conjugation, as when the aromatic moiety is a 1-naphthyl or a 9-phenanthryl group.[16] The above findings demonstrate that this is not generally true for all aryl sulfoxides; as a consequence, a fundamental condition of the coupled-oscillator model, namely, that the two (or more) interacting chromophores are nonconjugated, is not valid for alkyl phenyl sulfoxides, though the model may appear to provide a correct answer.[15]

Our results demonstrate that a full and fairly accurate prediction of CD spectra of aryl benzyl sulfoxides and of related compounds may be achieved by means of the TDDFT//DFT calculation approach. Since the number of populated conformers to be taken into account for these substrates is rather small, the problems related with extensive

---

[37] (a) Stowasser, R.; Hoffmann, R. *J. Am. Chem. Soc.* **1999**, *121*, 3414–3420. (b) Kar, T.; Ángyán, J. G.; Sannigrahi, A. B. *J. Phys. Chem. A* **2000**, *104*, 9953–9963.

[38] Harada, N.; Nakanishi, K *Circular Dichroic Spectroscopy-Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.

conformational analyses are not encountered,[25] and the overall computational cost is quite limited. Therefore, when empirical predictions based on Mislow's rules are judged insufficient, a full quantum-mechanics CD calculation should be considered as a valid practical option. In that respect, a comparably efficient alternative to electronic CD is represented by vibrational CD (VCD) calculations.[13,39]

The apparently singular CD spectra of nitro and carboxy derivatives **1a** [$4NO_2$/H], **1e** [2COOMe/H], and to a minor extent, **1h** [4Br/$2NO_2$] could be explained through the analysis of the configurations (CI terms) contributing to the two major transitions and of the relative MOs. The electron-withdrawing group exerts a stabilization effect on the orbitals of the attached ring and provokes a large redistribution of the MOs energy scale and of the corresponding transitions, thus altering the CD shape. Furthermore, it affects the virtual orbitals (especially the LUMO) more than the occupied ones, leading to the red shift observed, e.g., for **1a** and **1e**.

One of the aspects that our calculations did not reproduce was the substantial hyper/batochromic effect apparent in the absorption spectrum of *o*-methoxyphenyl isomer **1d**, relative to the sulfoxide primary band, with respect to the *p*-isomer **1b**. However, the CD spectra of the two compounds were both well predicted. The observed phenomenon is reminiscent of the *ortho*-effect seen in the absorption spectra of 2- versus 4-methoxy benzaldehyde and acetophenone,[40] which must be related to the different mobility of the methoxy group in the two isomers and cannot be reproduced by calculations performed on single structures where the methoxy group is always coplanar with the aryl ring.

Solid-state CD spectra have been recorded for compounds **1a**, **1c**−**e**, **1g,h**, and **1j**−**l** that were available as crystalline samples characterized by X-ray analysis. Quite surprisingly, although almost half of the compounds showed solid-state CD spectra in accordance with solution ones, the second half gave solid-state CD spectra apparently dominated by intermolecular interactions in the crystals. These effects are difficult to be quantified,[25] as they would require calculating the CD on a more or less large ensemble of molecules as found in a crystal cluster,[41] which is beyond the scope of the present paper. We tried to highlight a possible relation between the spectral behavior and the crystal shape. The above compounds crystallize either in the monoclinic $P2_1$ or in orthorhombic $P2_12_12_1$ space groups, both types permitting in principle symmetry-allowed intracrystalline exciton interactions to be established. Unfortunately, no clear correlation was found between samples showing solid-state intrinsic CD effects and their crystal class.

Conclusions

We have reported CD spectra of a series of aryl benzyl sulfoxides with various substituents on the two rings, both in acetonitrile solution and in the solid state as KCl pellets. Solution CD spectra appear very homogeneous along the series and show in turn close similarity to the general trend observed for alkyl phenyl sulfoxides. A typical CD spectrum consists in a couplet-like feature between 210 and 300 nm with moderate intensity and positive sign of the long wavelength branch for (*R*) configuration. Clear differences with respect to typical spectra were only observed for compounds with auxochromic substituents at the 2- and sometimes 4-position of the phenylsulfinyl ring, such as nitro, methoxycarbonyl, and to a minor extent, methoxy. However, in all cases, analysis of transitions and relative MOs computed with DFT demonstrated that the CD corresponding to the so-called primary sulfoxide band is always positive for (*R*) absolute configuration.

Microcrystalline solid-state CD spectra were similar to solution ones for some sulfoxides, while for others they showed very different shapes with new bands and/or bands with altered intensity. These latter cases were interpreted as due to intermolecular couplings between molecules closely packed in the crystals. It must be concluded that for aryl benzyl sulfoxides solid-state CD does not always reflect the chirality of the isolated molecule and should be considered with caution as a source of stereochemical information.

The most important result from our investigation is that TDDFT calculations, run with hybrid functionals such as BH&HLYP and B3LYP and a moderately large basis set (TZVP) on DFT-computed geometries, are able to fully reproduce CD spectra of aryl benzyl sulfoxides. Therefore, as noted by other authors,[20] TDDFT//DFT calculations lend themselves as a reliable tool for interpreting the CD spectra of these and other related compounds and for determining their absolute stereochemistry.

Experimental Section

Enantiopure aryl benzyl sulfoxides **1a**−**m** were prepared by *tert*-butyl hydroperoxide enantioselective oxidation of the corresponding sulfides in the presence of catalytic amounts of the complex between titanium tetraisopropoxide and (*S,S*)- or (*R,R*)-hydrobenzoin according to previous work.[23] The enantiomeric purity of aryl benzyl sulfoxides **1a**−**m** was measured by HPLC after recrystallization and was in all cases ≥97%.[23] Employment of the (*S,S*)-ligand yielded (*R*)-sulfoxides, as established mainly by X-ray diffraction analysis (compounds **1a**, **1c**, **1d**, **1e**, **1f**, **1g**, **1h**, **1j**, **1k**, **1l**, **1m**) and as supported by the theoretical model derived for this type of oxidation.[23] The absolute configuration of compound (*R*)-(+)-**1b** is known,[15] and that of (*R*)-(+)-**1i** is confirmed by the present results.

CD spectra were recorded with a Jasco J-710 spectropolarimeter with the following measurement parameters: scan speed, 50 nm/min; bandwidth, 1 nm; response, 1 s; 4−8 accumulations. Solution samples were prepared by dissolving the proper amount of substrates in acetonitrile to afford ~1 mM concentration, which assures the prevalence of monomeric species.[8b] Cells with 0.01−0.05 cm path lengths were employed to keep absorbance below 1 au. Solid-state samples were prepared with the KCl pellet technique as follows.[25] Less than 1 mg of the crystalline compound was mixed with ~100 mg of oven-dried KCl, finely ground and pressed at ~10 ton under vacuum for 15 min to produce a glassy translucent disk. Several samples were prepared for each compound to ensure reproducibility. The pellet was mounted on a rotatable support placed as close as possible to the detector. On each sample, several CD spectra were measured upon rotation of the disk around the incident axis direction and 180° flip around the vertical. These spectra

---

(39) Drabowicz, J.; Zajac, A.; Lyzwa, P.; Stephens, P. J.; Pan, J.-J.; Devlin, F. J. *Tetrahedron: Asymmetry* **2008**, *19*, 288–294. and references therein.

(40) (a) Dearden, J. C.; Forbes, W. F. *Can. J. Chem.* **1958**, *36*, 1362–1370. (b) Dearden, J. C.; Forbes, W. F. *Can. J. Chem.* **1959**, *37*, 1305–1314.

(41) (a) Kerti, G.; Kurtán, T.; Borbás, A.; Szabó, Z. B.; Lipták, A.; Szilágyi, L.; Illyés-Tünde, Z.; Bényei, A.; Antus, S.; Watanabe, M.; Castiglioni, E.; Pescitelli, G.; Salvadori, P. *Tetrahedron* **2008**, *64*, 1676–1688. (b) Bringmann, G.; Maksimenka, K.; Bruhn, T.; Reichert, M.; Harada, T.; Kuroda, R. *Tetrahedron* **2009**, *65*, 5720–5728.

were almost superimposable to each other, demonstrating the absence of detectable spectral artifacts.[25]

Computational Section

Conformational searches with MMFF, geometry optimizations, torsional energy scans, and single-point calculations with DFT (B3LYP/6-31G(d), 6-311G(d,p), and 6-311G+(d,p)) were run with Spartan'06 and Spartan'09 (WaveFunction, Inc., Irvine, CA) using default parameters and convergence criteria. DFT calculations including solvation model (IEF-PCM, with parameters for acetonitrile) and TDDFT calculations were run with Gaussian'03 and Gaussian'09 (Gaussian, Inc., Wallingford, CT)[42] using various functionals and basis sets as described in the text. The number of transitions included in TDDFT calculations was 16 for SVP basis set, 16−24 for TZVP, and 24 for aug-TZVP. This latter was constructed by augmenting the TZVP basis set with a (1s1p1d/1s1p) set of primitive functions taken from the most diffuse functions of aug-cc-pVDZ set.[43] Dipole-velocity rotational strengths were employed to calculate CD spectra; however, the difference with dipole-length values was negligible (< 15%) for most transitions using TZVP basis. CD spectra were generated by applying a Gaussian band shape with 2000−2500 cm^{-1} half-height width. For BH&HLYP/TZVP calculations, a frequency correction of −3,000 cm^{-1} was applied as described in the text, corresponding to +12 nm and +20 nm at 200 and 260 nm, respectively. For each compound, all CD bands calculated above 190 nm had energies below the estimated ionization potential threshold and were mostly due to transitions involving virtual orbitals with negative eigenvalues.[44]

Acknowledgment. Professor Francesco Naso and Professor Carlo Rosini are gratefully thanked for useful discussions. This work was financially supported by the MIUR, Rome (PRIN Project: Stereoselezione in sintesi organica. Metodologie e applicazioni; FIRB project: RBPR05NWWC) and by the University of Bari.

Supporting Information Available: Experimental and computational data, complete ref 42, and Cartesian coordinates for all DFT-optimized structures. This material is available free of charge via the Internet at http://pubs.acs.org.

---

(42) (a) Frisch, M. J. et al. *Gaussian 03, Revision D.01*; Gaussian, Inc.: Wallingford, CT, **2004**. (b) Frisch, M. J. et al. *Gaussian 09, Revision A.02*; Gaussian, Inc.: Wallingford, CT, **2009**. (Complete references given in Supporting Information.)

(43) Kendall, R. A.; Dunning, T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796–806.

(44) Casida, M. E.; Jamorski, C.; Casida, K. C.; Salahub, D. R. *J. Chem. Phys.* **1998**, *108*, 4439–4449.