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Absolute Configuration of Conformationally Flexible *cis*-Dihydrodiol Metabolites by the Method of Confrontation of Experimental and Calculated Electronic CD Spectra and Optical Rotations

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Abstract: We have determined the absolute configurations of conformationally flexible *cis*-dihydrodiol metabolites (*cis*-1,2-dihydroxy-3,5-cyclohexadienes), bearing different substituents (e.g., Br, F, CF_3, CN, Me) in 3- and 5-positions, by the method of confrontation of experimental and calculated electronic CD spectra and optical rotations. Convergent results were obtained by both methods in eight out of ten cases. For the difficult cases, where either conformer population and/or chiroptical properties (calculated rotational strengths of the long-wavelength Cotton effect or optical rotations) of contributing conformers remain inconclusive, the absolute configuration could still be correctly assigned based on one of the biased properties (either ECD or optical rotation). This approach appears well-suited for a broad spectrum of conformationally flexible chiral molecules.

Keywords: absolute configuration · circular dichroism · conformation analysis · density functional calculations · optical rotation

Introduction

Experimental determination of the absolute and relative configuration of organic as well as inorganic molecules currently relies on techniques such as X-ray crystallography, circular dichroism,[1] analysis of NMR spectra of diastereoisomeric derivatives[2] and chemical correlation.[3] In the case of complex natural products with multiple chiral centers, the latter two methods are of limited use since they are time-consuming and costly. On the other hand, NMR methods give only information about relative stereochemistry within a molecule. Applicability of these methods for flexible molecules with unusual structural features is also limited.[4] In principle, absolute configuration (AC) of a chiral molecule can be deduced from its optical rotation (OR) and/or its electronic circular dichroism (ECD) data. In practice, this requires the use of reliable methodologies for calculation of OR and/or ECD, followed by confrontation with the corresponding experimental data. In a way, this method is reminiscent of the use of Flack parameter[5] for the assignment of absolute configuration from the X-ray diffraction data.

Many successful assignments of both the absolute configuration as well as absolute conformation[6] of chiral molecules have been reported during the past decade by confrontation of experimental and theoretical ECD spectra.[7] Two frequently used methods of calculation of ECD spectra include the use of Gaussian program package,[8] with combines B3LYP hybrid functional with a large basis sets (for example (6-311++g(d,p) or aug-cc-pVDZ) or a combination of methods based on density functional theory (DFT) with those based on multireference configuration interaction (DFT/MRCI), with the use of smaller basis sets implemented in TURBOMOLE.[9,10] Fortunately both approaches provide good to excellent results, particularly in the case of rigid molecules, and allow not only the determination of the AC but also the preferred conformations of investigated molecules (absolute stereochemistry) in the same calculation process. Recently Diedrich and Grimme systematically investigated and critically reviewed the applications of modern quantum chemical methods for predicting ECD spectra.[11]

In recent years, advances in the field of theoretical chemistry have led to development of new computational approaches for calculating OR at various levels of accuracy.[12] The methods include Hartree–Fock (HF),[13] DFT[14]

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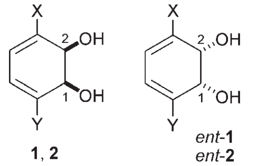
and coupled cluster [CC][15,16a] and allow direct assignment of AC. Although Hartree–Fock with small (6-31g* or DZP) basis sets can be effectively used,[17] DFT appears the best compromise between accuracy and computational costs.[16] Again, of all DFT functionals available, the B3LYP hybrid functional is the most widely used. For example, calculation of OR of (*P*)-(+)-[4]triangulane by very time-consuming CC methods gave only slightly better results that these obtained by DFT.[18] As it was shown by Cheeseman et al. the inclusion of diffuse function in the basis set is compulsory[19] and among the basis sets used for calculations of OR by these authors, aug-cc-pVDZ and 6-311++g(2d,2p) have been found the most effective. Additionally, the authors have claimed that the use of gauge-invariant atomic orbitals (GIAO) is mandatory for reliable predictions of OR.[19] Grimme has pointed out that origin-dependence of OR is not problematic if basis sets augmented by diffuse functions are used.[20] It should be noted that reliability of AC assignment of chiral molecules depends not only on the method used but also on the structure of the molecule. For rigid molecules which exhibit high values of OR, accuracy of OR calculations is higher than that for flexible molecules with small OR. Nevertheless, in many cases the accordance of experimental and theoretical data was found satisfactory.[21]

As it was pointed out above, the calculations of OR, as well as ECD, are very sensitive to inaccuracy in determining the equilibrium of participating conformers. Thus, carefully carried out conformational analysis of the molecule is the first and the most important step of the calculations. For rigid molecules, which were investigated in the pioneering years of the studies, this step could be neglected but for floppy molecules the relative energies of participating conformers should be calculated with the highest available accuracy.[14,22] It has been shown that even minor changes in molecule conformation can result in a change of sign and/or magnitude of calculated OR.[23] The issue of conformer equilibrium is further complicated by solvent effects.[24] The solvent effect has been traditionally approximated by inclusion of Lorentz factor, $(n^2+2)/3$, where n is the refractive index of the solvent. Surprisingly, the use of this correction implemented in B3LYP/aug-cc-pVDZ calculations of OR has led to less accurate results.[14] For this reason, there is a need to perform the calculations with the use of more advanced models of solvent–solute interactions.[25]

Recently, TDDFT calculations of both OR and ECD are being increasingly used for determining ACs.[26,27] The essence of such an approach has been summarized by Stephens et al. as providing higher reliability of the AC determination. If the use of OR and CD confrontation yields opposite ACs, the AC determination using either phenomenon is ambiguous.[27b] Such methodology has been used quite recently for the stereochemical characterization of cytotoxic natural products[28] and chiral rigid and flexible alkenes with satisfactory results.[29]

The methodology of confronting the calculated and experimental ECD and/or OR data has rarely been applied to study the structural properties of families of related organic molecules. Vicinal diols are among the most interesting chiral substrates for organic synthesis and for the use as supramolecular scaffolding units. Earlier and recent[29,30] studies have indicated that non-chromophoric hydroxy and other polar groups play decisive role in determining conformational equilibria and chiroptical properties of organic molecules. Recently we have shown that 1,2-dihydroxy-3,5-cyclohexadienes **2a**–**e** (Table 1) display conformational properties strongly influenced by the nature of substituent at C-3 and the pattern of hydrogen bonds involving the hydroxy groups. Consequently, the CD spectra—in particular the long-wavelength *cis*-diene Cotton effect—were shown to reflect both the absolute configuration and the conformation of dihydroxydiene molecules.[31]

Table 1. Configurations of cyclohexadienes **1a**–**j** and **2a**–**e**.



Compound	X	Y	Absolute configuration
1a	Br	F	(1*R*,2*S*)
1b	Br	CF_3	(1*S*,2*S*)
1c	Br	CN	(1*S*,2*S*)
1d	Br	Me	(1*S*,2*S*)
1e	F	CF_3	(1*S*,2*S*)
1f	F	CN	(1*S*,2*S*)
1g	F	Me	(1*S*,2*S*)
1h	CF_3	CN	(1*S*,2*R*)
1i	CF_3	Me	(1*S*,2*R*)
1j	CN	Me	(1*S*,2*R*)
2a	Br	H	(1*S*,2*S*)
2b	F	H	(1*S*,2*S*)
2c	CF_3	H	(1*S*,2*R*)
2d	CN	H	(1*S*,2*R*)
2e	Me	H	(1*S*,2*R*)

At the outset of this study we aimed at providing a generally applicable chiroptical method(s) for determination of absolute configuration of a family of dihydroxydienes. Here we present the results of our study on the determination of absolute configuration and conformation of ten dihydrodiols **1a**–**j** (Table 1), having all possible combinations of representative substituents X, Y (e.g., Br, F, CF_3, CN, Me), by confrontation of their calculated and experimental circular dichroism *and* optical rotation. It should be emphasised that, unlike the previous work, concerning monosubstituted 1,3-cyclohexadienes **2a**–**e** (Y=H),[31] this work deals with disubstituted 1,3-cyclohexadienes **1a**–**j** in which the differences in size and polarity of substituents X and Y may not be large enough to secure high bias for both enantioselectivity of the biocatalytic transformation (see ref. [32]) and conformational preferences of dihydroxy-1,3-cyclohexadienes, as well as for straightforward assignment of absolute configuration by chiroptical methods. Nevertheless, structural-chiroptical study (CD and OR) of 1,2-dihydroxy-3,5-cyclohexadiene molecules **1** should allow to semiquantitatively compare the propensities of substituents X and Y for controlling populations of pseudoenantiomeric *P* and *M* conformers of the dienes, by the balanced action of substituent steric effect, electronegativity and hydrogen bonding abilities and to uncover a reliable route to absolute configuration assignment.

Results and Discussion

Conformational analysis of dihydrodiols 1a–j: The CD spectra of dihydrodiols **1a–j** were calculated according to the methodology described in our previous publication.[31] First, low-energy conformers of **1a–j** were calculated and optimized with the use of B3LYP functional and enhanced basis set 6-311++g(d,p). This procedure yielded up to four conformers within 3 kcal mol^{-1} energy window for each dihydroxycyclohexadiene **1a–j**. In general, diastereoisomeric conformers having *P* or *M* helicity of the diene chromophore were further diversified by intramolecular hydrogen-bonding patterns and hydroxy group rotations. Thus, two *M*-helicity and two *P*-helicity stable conformers of the dihydroxycyclohexadiene molecule were in principle accessible (Scheme 1), all showing an intramolecular OH···O hydrogen bond.[33]

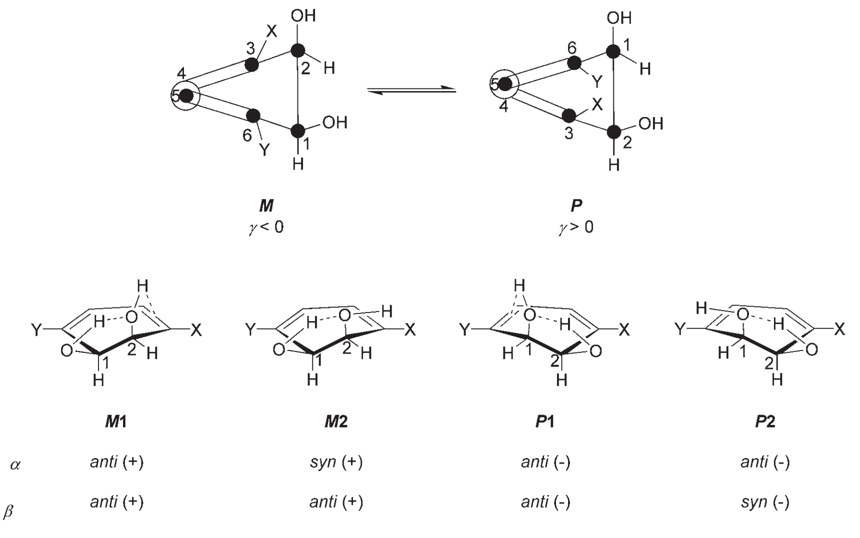
In ***M*1** and ***P*1** conformers both (H-C-O-H) torsion angles α and β, involving the hydroxy groups, are *anti* whereas ***M*2** and ***P*2** conformers are characterised by one *anti* and one *syn* H-C-O–H bond arrangements. The calculated values of α and β differ from the ideal ones, both being lower than either ±60 or 180° for *syn* and *anti* arrangements, respectively (Table A, Supporting Information). Torsion angle γ, characterizing helicity of the diene chromophore, is in the range ±10 to ±13° in accordance with previous calculations for **2a–e**.

In our previous study[31] we have shown that the rotation of each of the hydroxy group around the C–O bond in diols **2a–e** had a profound effect on the potential energy surfaces (PES) of these molecules. Likewise, in the case of 1,4-disubstituted dihydrodiols **1a–j**, well defined low energy conformers are found in each case (see Table 2 and Figure A1, Supporting Information).[34]

Table 2. Calculated at B3LYP/6-311++g(d,p) level relative energies (ΔE: upper line, ΔG: lower line) in kcal mol^{-1} and percentage populations (in brackets) of conformers of dihydrodiols **1a–j**.

Dihydrodiol	***M*1**	***M*2**	***P*1**	***P*2**
1a	0.00 (32)	0.10 (27)	0.07 (28)	0.50 (13)
	0.23 (24)	0.00 (35)	0.31 (21)	0.34 (20)
1b	1.31 (7)	1.30 (7)	0.67 (21)	0.00 (65)
	1.51 (5)	1.18 (8)	0.56 (24)	0.00 (63)
1c	0.25 (19)	0.06 (27)	0.10 (25)	0.00 (29)
	0.46 (16)	0.00 (34)	0.37 (18)	0.03 (32)
1d	0.00 (54)	0.29 (33)	0.85 (13)	–
	0.03 (44)	0.00 (47)	0.95 (9)	
1e	1.54 (5)	–	0.83 (18)	0.00 (77)
	1.67 (4)		0.67 (23)	0.00 (73)
1f	0.48 (17)	0.41 (19)	0.25 (25)	0.00 (39)
	0.62 (14)	0.21 (29)	0.50 (17)	0.00 (40)
1g	0.00 (61)	0.55 (24)	0.79 (15)	–
	0.00 (53)	0.22 (36)	0.91 (11)	
1h	1.13 (11)	0.00 (77)	1.67 (4)	1.33 (8)
	0.95 (14)	0.00 (75)	1.91 (3)	1.32 (8)
1i	0.63 (25)	0.00 (73)	2.01 (2)	–
	0.50 (30)	0.00 (69)	2.34 (1)	
1j	0.03 (44)	0.00 (47)	0.97 (9)	–
	0.22 (37)	0.00 (55)	1.14 (8)	

***P*1** and ***P*2** conformers are found in the region corresponding to negative values α and β, whereas the opposite holds for ***M*1** and ***M*2** conformers. It can be noted that PES for **1a–c**, **e**, **f** and, to a lesser extent, for **1g** are qualitatively (visually) similar for *P*-helicity conformers only. Except **1g**, these dihydroxydienes bear two polar substituents (different from a Me group) in 1- and 4-positions. Similarities of PES contours are less obvious in the case of *M* conformers, save for **1b** and **e** as well as for **1d**, **g** and **i**.



Scheme 1. Diastereomeric *P* and *M* conformations of *cis*-dihydrodiols, torsion angles α (H-C2-O-H), β (H-C1-O-H), γ (C3-C4-C5-C6), and typical hydrogen bonding patterns between the hydroxy groups in conformers ***M*1**, ***M*2**, ***P*1**, ***P*2**.

A rather complex conformer equilibrium mixture (Table 2) reflects the competitive nature of substituents X and Y in determining the preferred hydrogen-bonding pattern involving the hydroxy groups and, consequently the preferred diene conformation. Calculations indicate that in each conformer of *cis*-dihydrodiols **1a–j** there is present an intramolecular

OH···O hydrogen bond with the length in the range 2.12–2.25 Å (see Supporting Information). While the equatorial hydroxy group is engaged in an intramolecular OH···O hydrogen bond, the axial hydroxy group provides additional stabilizing force by the formation of OH···π hydrogen bond in both ***M*1** and ***P*1** conformers. The calculated H···C3 and OH···C6 distances are in the range 2.44–2.50 Å for the axial OH group and 2.97–3.12 Å for the equatorial OH group. In ***M*2**- and ***P*2**-type conformers one of the H–O bonds (the one in a *syn* arrangement of H-O-C-H) is parallel to either C–X or C–Y bond, providing stabilization of such a conformer by a dipole–dipole interaction (X = Y = F, Br, CN). Consequently, the OH···O hydrogen bond is slightly shorter (0.01–0.04 Å) in ***M*2** and ***P*2** conformers compared with the corresponding ***M*1** or ***P*1** counterparts. In the case of **1e** and **i** the difference of hydrogen bond lengths is in opposite direction (0.01 and 0.07 Å, correspondingly). There is no evidence for short contacts (hydrogen bonds) between the axial hydroxy groups and the vicinal X or Y group, the distances OH···X(Y) being in general longer than 2.9 Å (for OH···F) and up to 3.7 Å (for OH···N in CN group). The exception is the CF_3 substituent, forming a short (2.4 Å) contact with the axial hydroxy group in all investigated dihydrodiols. This H···F hydrogen bond is apparently highly stabilizing the corresponding conformers, making them the lowest-energy species of dihydrodiols **1b** (***P*2**), **1e** (***P*2**), **1h** (***M*2**) and **1i** (***M*2**), with calculated populations in the range 63–77 % (Table 2). Moreover, as a result of competition between the CF_3 and F substituents in **1e** there is no low energy ***M*2** conformer found within the 3 kcal mol^{-1} window. This can be interpreted as a strong preference for CF_3···HO(ax) hydrogen bond formation against C-F/OH(ax) dipole–dipole interaction. Whereas organic fluorine generally accepts a hydrogen bond with difficulty,[35] favourable geometry (as in the case of a CF_3 group) apparently makes such interaction thermodynamically feasible. An X-ray diffraction study of *ent*-**1e**[32] shows an ***M***-type conformer, with no intramolecular hydrogen bonds.

The methyl group appears the least competitive of all substituents in stabilizing the low energy conformer via the methyl–hydroxy group interaction. In fact, there is no calculated low-energy conformer in which axial *syn*-hydroxy group is next to the methyl group. In all four methyl substituted dihydrodiols **1d**, **g**, **i**, and **j** the axial hydroxy group in *syn* conformation is next to the polar substituent (Br, F, CF_3, CN), in the last two cases this conformer (***M*2**) is the most populated one. Interestingly, an X-ray diffraction study[32] indicates that in the case of **1j** a ***P***-type conformer with no intramolecular hydrogen bonds is present in the crystal. Due to intermolecular hydrogen bonding the preferred ***P*** conformer in the solid state may result from crystal packing forces.

In terms of relative populations of homohelical conformers ***M*** (=***M*1** + ***M*2**) versus ***P*** (=***P*1** + ***P*2**) the suit follows the same pattern. CF_3 substituent strongly favours the conformer with vicinal axial hydroxy group (i.e., ***P*** for **1b** and **1e**, ***M*** for **1h** and **1i**) to the extent 86–98 %. On the other hand, a methyl substituent enhances the population of the conformers having an axial hydroxy group in a vicinal position to the polar group (Br, F, CF_3, CN) in **1d**, **g**, **i**, and **j**, to the extent of 84–98 %. Thus, the combination of CF_3 and CH_3 groups appears to work strongly cooperatively, making dihydrodiol **1i** practically *M*-homohelical. Previous calculations for compound **2c** (X = CF_3, Y = H) have shown a very similar tendency, that is, only one conformer (***M*2**) was found to contribute to the equilibrium within the 3 kcal mol^{-1} window.[31]

Dihydrodiols **1a**, **c** and **f**, bearing a combination of Br, F or CN substituents (X, Y) represent more demanding cases, in terms of correct prediction of conformational equilibrium from calculation. In these three cases all four conformers are populated, with ΔE differences between individual conformers not exceeding 0.5 kcal mol^{-1} (Table 2). In terms of competitiveness between C-X···H-O and C-Y···H-O dipole interactions (conformers ***M*2** versus ***P*2**) we note only a slight preference for either Br or CN against F substituent. In addition, the total population of ***M*** versus ***P*** conformers for the three dihydrodiols **1a**, **1c** and **1f** is also in favour of the conformers with axial hydroxy group next to either Br or CN rather than F substituent. This is in contrast to the results of X-ray determination of the structure of *ent*-**1f**, in which axial hydroxyl group is found proximate to the fluorine.[32]

In summary, the calculation yields population of conformers of dihydroxycyclohexadienes **1** profoundly shifted toward either ***M*** or ***P*** when X or Y is CF_3 or Me. Difficult cases for analysis represent dihydroxydienes where both X and Y are Br, F or CN, since only small conformational preferences are indicated by calculations.

Absolute configuration of 1a–j by confrontation of calculated and experimental CD spectra: Following the finding of low-energy conformers of **1a–j**, their electronic absorption and circular dichroism spectra were computed using the TDDFT method at the mPW1PW91/6-311++g(2d,2p) level of theory.[36] The computed energies (λ_{max}) and oscillator strengths (*f*) of the lowest-energy π–π* transition show dependency on the nature of substituents X and Y in **1a–j** (Table 3).

These data for individual conformers of **1a–j** do not differ significantly. On the other hand, the presence of the cyano group results in significant increase of oscillator strength and lowering the energy of the transition. This substitution effect is also seen in the experimental UV maxima of dihydrodiols **1a–j** (Table 4).

Thus about 35 nm red shift and twofold increase of ε_{max} is brought about by substituting the F, CF_3 groups in **1e** with Br, CN in **1c**. In general, the substituent electronic effect increases in the order F < CF_3 < Me < Br < CN, as previously noted.[31]

The calculated rotational strengths (*R*) of individual conformers of dihydroxydienes **1a–j** (Table 3) are of opposite sign for *P*- and *M*-helicity molecules. Apparent exception are the conformers of bromine substituted dihydroxydienes (**1a**, **b**) for which there is observed a tendency for uniform

Table 3. Calculated (mPW1PW91/6-311++g(2d,2p) level) oscillator strengths (f) and rotational strengths (R) of individual conformers of dihydroxydienes **1a**–**j**.

Compound	Conformer	f (λ_{max}) [nm]	R [$\times 10^{-40}$ erg esu cm Gauss^{-1}]
1a	***M*1**	0.155 (294)	0.7
	***M*2**	0.157 (292)	−6.2
	***P*1**	0.162 (294)	21.
	***P*2**	0.164 (293)	24.5
1b	***M*1**	0.182 (296)	29.8
	***M*2**	0.200 (291)	15.9
	***P*1**	0.222 (297)	4.9
	***P*2**	0.239 (298)	8.3
1c	***M*1**	0.282 (318)	42.0
	***M*2**	0.302 (314)	28.7
	***P*1**	0.323 (319)	−20.4
	***P*2**	0.332 (320)	−17.8
1d	***M*1**	0.205 (296)	−5.1
	***M*2**	0.210 (293)	−11.1
	***P*1**	0.212 (294)	14.4
1e	***M*1**	0.111 (276)	−3.7
	***P*1**	0.127 (279)	12.7
	***P*2**	0.139 (280)	16.4
1f	***M*1**	0.198 (298)	11.4
	***M*2**	0.212 (296)	3.3
	***P*1**	0.213 (300)	−17.2
	***P*2**	0.220 (301)	−14.3
1g	***M*1**	0.119 (282)	−39.6
	***M*2**	0.118 (283)	−41.3
	***P*1**	0.118 (281)	21.4
1h	***M*1**	0.163 (303)	39.9
	***M*2**	0.224 (301)	22.5
	***P*1**	0.165 (303)	−55.3
	***P*2**	0.214 (301)	−40.0
1i	***M*1**	0.176 (282)	−16.1
	***M*2**	0.193 (283)	−18.8
	***P*1**	0.148 (280)	−6.6
1j	***M*1**	0.275 (304)	13.8
	***M*2**	0.285 (305)	12.6
	***P*1**	0.248 (302)	−21.0

Table 4. Experimental UV data for *cis*-dihydrodiols **1a**–**j** in cyclohexane, acetonitrile and water solutions.

Compound	Cyclohexane		Acetonitrile		Water	
	ε	λ [nm]	ε	λ [nm]	ε	λ [nm]
1a	5700	276	6100	274	6000	274
1b	7400	282	7400	280	7700	280
1c	9600	300	9100	299	9800	300
1d	7400	282	7500	280	7500	281
1e	4200	266	4300	265	4300	264
1f	6700	284	7100	283	7300	284
1g	4500	266	4500	265	4500	265
1h	5900	282	7300	281	7600	281
1i	5700	274	5700	274	5900	273
1j	9000	294	9200	293	9500	295

(positive) sign of rotational strength (however, ***M*2** conformer of **1a** is an exception). Whereas the sign of rotational strength of the lowest energy π–π* transition of conformers of dihydroxydienes **1d**, **e** and **g** is in agreement with the sense of helicity of the diene chromophore, it is of opposite sign in the case of cyano-substituted dihydroxydienes **1c**, **f**, **h**, and **j**, as it was previously documented for monosubstituted cyanodiene **2d**.[31] One additional observation is that the calculated rotational strengths of ***M*1**/***M*2** or ***P*1**/***P*2** conformers of each dihydroxydiene do not differ strongly, again ***M*1**/***M*2** conformers of **1a** being an exception to the rule.

The sign (but not necessarily the magnitude) of the calculated rotational strength of the long-wavelength transition results mainly from additive contributions of substituents X and Y, that is, CN, F, Me > Br, CF_3. Note, however, that the contributions of CN and Br substituents are of opposite sign to those of F, Me and CF_3 (Tables B and C, Supporting Information). This additivity is more consistent for parent 1,4-disubstituted cyclohexadienes, than for their dihydroxy derivatives **1a**–**j**.

From the calculated rotational strengths of individual conformers, CD spectra of **1a**–**j** were obtained by adding the conformer contributions weighted to conformer population. The resulting CD curves were confronted with the experimental ones (Figure 1).

Experimental CD spectra were measured in three solvents of different polarity: cyclohexane, acetonitrile and water. It was anticipated that the CD spectra in the least polar solvent would most closely correspond to the calculated ones, since the conformer population would be governed by intramolecular hydrogen-bonding patterns, similar to those found by calculations. Thus we find that the CD spectra measured in cyclohexane correspond to calculated ones in the case of **1a**, **d**, **h**, **i**, and **j**, at least as far as the long wavelength Cotton effect is concerned. Additionally, good agreement would also be seen if the calculations were performed for *ent*-**1b**, *ent*-**1c**, *ent*-**1e** and *ent*-**1g**. This confirms the absolute configurations of all these dihydroxydienes, except **1f**, established by empirical stereochemical correlation determinations and (for *ent*-**1e** and **1j**) by X-ray diffraction studies.[32]

The case of *ent*-**1f** is more complex. In acetonitrile and water solutions its long-wavelength Cotton effect is negative, changing to near zero in cyclohexane solution. A positive long-wavelength Cotton effect is expected for the absolute configuration *ent*-**1f**, established by chemical correlation method, since the Cotton effect at 284 nm calculated for **1f** is negative. Despite the observed tendency for a positive Cotton effect of *ent*-**1f** in non-polar media, overall fit of the calculated and experimental CD curves is not satisfactory.

Seeking possible reasons for the difficulty of unequivocal determination of absolute configuration of **1f** by the CD confrontation method we note that the CD spectra of many other dihydroxydienes do not show strong dependence on solvent polarity (Figure 1). However there are exceptions, in the case of **1d** and **f**. Molecules of these compounds contain substituents X, Y (Br/Me or F/CN) of similar properties, hence their conformer population in solution may be more strongly influenced by interactions with polar solvent molecules, leading to sign reversal of the long wavelength Cotton effect between the cyclohexane and water solutions.

In order to overcome the difficulties associated with the determination of conformer contributions to the CD spectrum we measured the CD spectrum of **1f** in the solid state (KBr pellet) and calculated the CD spectrum using conformer coordinates obtained from X-ray structure determina-

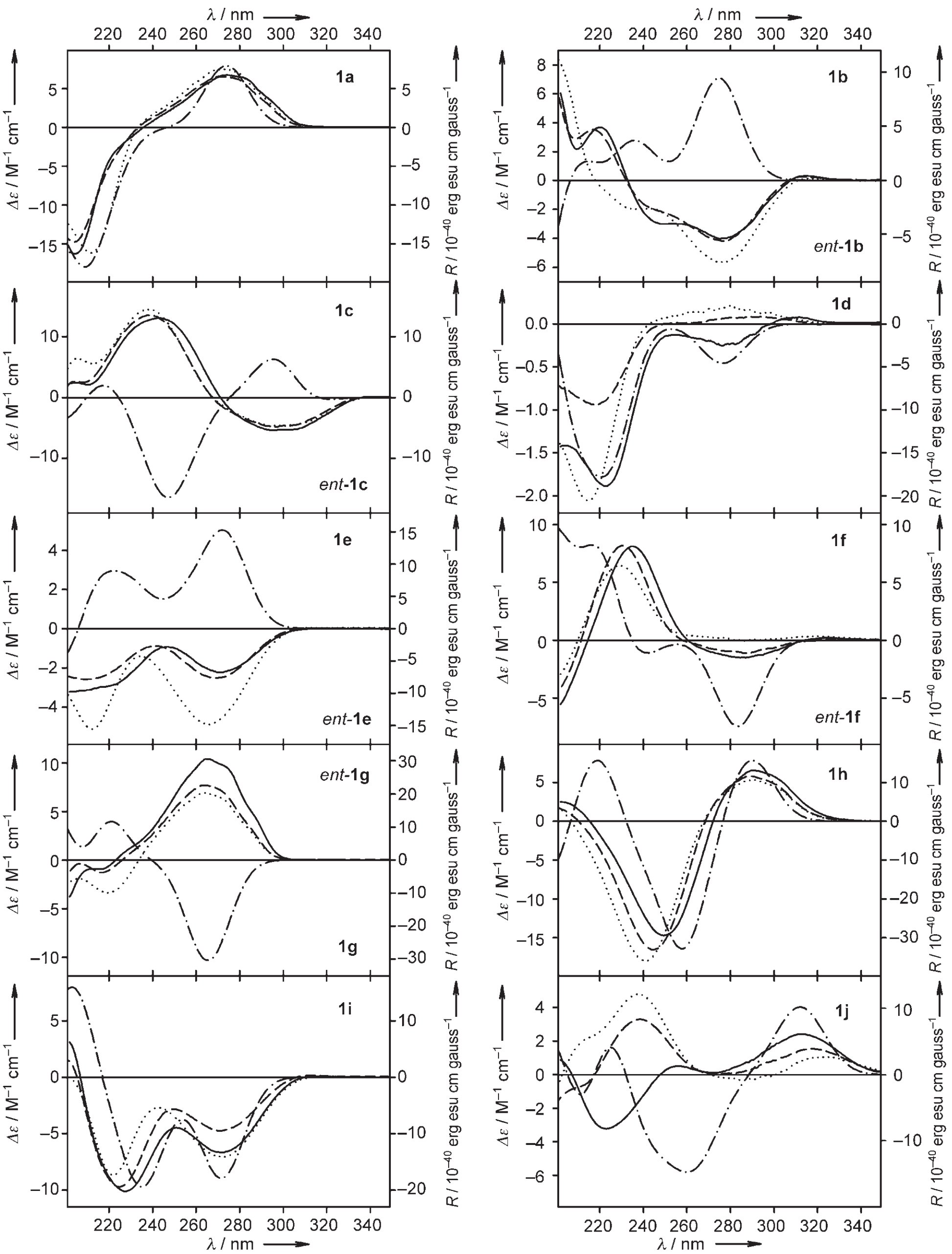


Figure 1. CD spectra of *cis*-dihydrodiols **1a–j** in cyclohexane (——), in acetonitrile (-----), in water (•••••), and Boltzmann averaged calculated at TD-DFT/mPW1PW91/6-311++g(2d,2p) level of theory CD spectra of *cis*-dihydrodiols **1a–j** (–•–•). Rotational strengths *R* were calculated in dipole-length representation. All calculated spectra were wavelength corrected to match experimental long-wavelength λ_{max} values. Note that the CD spectra of enantiomers of *cis*-dihydrodiols **1b**, **c**, **e**, **f** and **g** were measured.

tion.[32] This method allows us to avoid problems intrinsic to calculation of the structure and population of conformers with high accuracy. In the event we obtained a solid-state CD spectrum featuring a weak positive maximum above 300 nm and a negative Cotton effect at about 255 nm. These features correspond to the calculated CD spectrum of either ***P*1** or ***P*2** conformer of *ent*-**1f** (*P* conformer of the diene was found in the crystal structure). Thus, the absolute configuration of *ent*-**1f** has been confirmed by the solid-state CD confrontation method.

While the method appears to be generally applicable, its limitation is a possible contribution of the CD signals intrinsic to the solid state,[37] mainly due to exciton-type interactions between chromophores in the molecules fixed in the crystal space. In the present case this contribution does not appear essential since the intermolecular distances between the diene chromophores in the crystal are relatively long (over 8 Å).

Absolute configuration of 1a–j by confrontation of calculated and experimental optical rotations: In order to strengthen absolute configuration determination results by the CD confrontational method we carried out calculations of optical rotation ([α]$_D$), using B3LYP/6-311++g(2d,2p) level of theory. Such calculations are now becoming of increasing importance for absolute configuration assignments.[12–30] The reports show that safe configurational assignments can be arrived at by confronting experimental and calculated optical rotations for compounds having rigid structures (limited number of low energy conformers) and high [α]$_D$ values (usually considered at the level ±100). The "zone of indeterminacy" has been reported by McCann and Stephens for calculated optical rotations of alkenes.[29] The cases presented here (**1a–j**) are more demanding, since there are several conformers contributing to optical rotation and their rotations (see infra) differ in sign and magnitude.

The calculations of optical rotation were performed for conformers ***M*1**, ***M*2**, ***P*1**, and ***P*2**, using B3LYP/6-311++g-(2d,2p) level of theory. The results of these calculations, as well as the experimental [α]$_D$ data are shown in Table 5.

In general, the signs of optical rotations and long-wavelength Cotton effects (Table 3) of the corresponding conformers of **1a–j** are the same (exceptions are ***M*2** conformers of **1b**, **1c** and **1h**, ***M*1** and ***M*2** conformers of **1f** and ***P*1**

Table 5. Calculated at B3LYP/6-311++g(2d,2p) level and measured optical rotations for *cis*-dihydrodiols **1a**–**j**.

Dihydrodiol	Conformer	Calcd $[\alpha]_D$	Calcd $[\alpha]_D$[a]	Exptl $[\alpha]_D$[b]
1a	***M*1**	+14	+45	+69
	***M*2**	−100		
	***P*1**	+138		
	***P*2**	+199		
1b	***M*1**	+52	+86	−67 (for *ent*-**1b**)
	***M*2**	−48		
	***P*1**	+68		
	***P*2**	+109		
1c	***M*1**	+117	−9	−12 (for *ent*-**1c**)
	***M*2**	−5		
	***P*1**	−91		
	***P*2**	−27		
1d	***M*1**	−33	−51	−17
	***M*2**	−134		
	***P*1**	+88		
1e	***M*1**	−55	+93	−41 (for *ent*-**1e**)
	***P*1**	+58		
	***P*2**	+112		
1f	***M*1**	−25	−80	+68 (for *ent*-**1f**)
	***M*2**	−115		
	***P*1**	−133		
	***P*2**	−53		
1g	***M*1**	−207	−195	+154 (for *ent*-**1g**)
	***M*2**	−275		
	***P*1**	+66		
1h	***M*1**	ca. 0	−52	−32
	***M*2**	−54		
	***P*1**	−142		
	***P*2**	−61		
1i	***M*1**	−107	−132	−118
	***M*2**	−146		
	***P*1**	+16		
1j	***M*1**	+82	+39	+92
	***M*2**	+13		
	***P*1**	−33		

[a] ΔE Boltzmann averaged. [b] In MeOH, corrected to 100% *ee*.

conformer of **1i**). A comparison of experimental and calculated $[\alpha]_D$ data (Boltzmann averaged for ΔE weighted population of conformers) indicates good agreement of the signs, except for diene **1c**. Therefore the absolute configurations of **1a**, **1b** and **1d**–**j** are confirmed by confrontation of experimental and calculated optical rotation data. The case of **1c** needs additional analysis. Misfit of signs of experimental and calculated optical rotations may not be surprising since the values of $[\alpha]_D$ are low, both calculated and experimental. Secondly, **1c** belongs to the group of dihydroxydienes (**1a**, **c**, **f**) having *M* and *P* conformers populated to a similar extent. In addition, the sum of calculated optical rotations for *M* and *P* conformers does not differ in magnitude (+112 vs −118). This is the underlying reason for difficulty in reliable assignment of absolute configuration of **1c** by a confrontation of signs of optical rotation. On the other hand, the sum of calculated rotational strengths for ***M*** and ***P*** conformers is quite different (+71 vs −38), hence the confrontation of signs of long-wavelength Cotton effects leads to correct assignment of the absolute configuration of **1c**. Exactly the opposite relationship holds for **1f**. Whereas the assignment of absolute configuration based on the CD spectra is met with difficulties (see above), the confrontation of optical rotations leads necessarily to a correct configurational assignment, since the calculated $[\alpha]_D$ values for all ***M*** and ***P*** conformers are of the same (negative) sign. The last example, **1a**, does not represent difficulties in the assignment of absolute configuration by either method, despite the fact that all four *P*- and *M*-helicity conformers are calculated within 0.5 kcal mol^{-1} energy window, as the sums of rotational strengths and optical rotations for ***M*** and ***P*** conformers are of very different magnitudes (−5 vs +46 and −86 vs +337). This leads to a conclusion that safe absolute configuration assignments can be obtained for compounds having several low energy conformers if conformer population is shifted significantly towards one family, contributing either positive or negative sign rotational strength or optical rotation (cases **1b**, **e**, **g**–**j**). If the population of conformers is indiscriminate by calculation, the assignment of absolute configuration can still be done if one considers the differences in sign and magnitudes of contributions of individual conformers to either rotational strength (CD) or optical rotation ($[\alpha]_D$), as shown for cases **1a**, **c**, and **f**. The underlying reason is the dependence of optical rotation on contributions due to *all* excitations in the molecule, whereas analysis of the CD spectra is usually limited to a selected Cotton effect. A corollary is that *both* the CD and optical rotation confrontational analyses should be used for the most reliable assignment of absolute configuration by chiroptical techniques, if several species contribute to the structure of investigated molecule. When *both* the computed CD and OR data are in agreement with the experimental results, the assignment of absolute configuration is correct. When the computed and experimental data for *both* CD and OR are of opposite sign, the assumed absolute configuration should be reversed. Finally, if *either* CD *or* OR data are of wrong sign compared with experiment, the source of disagreement should be investigated in order to obtain conclusive results.

The assignment of absolute configuration by confrontation of the ECD and optical rotation data can be extended to halogenated dihydrodiols, bearing substituents other than those shown in Table 1. The substituents X or Y include the ethyl (**1k**–**m**), the *n*-propyl (**1n**–**p**) groups, the chlorine (**1l**, **o**, **r**, **s**, **u**, **v**, **y**), and the iodine atoms (**1t**, **w**–**z**, see Table 6).

Due to structural similarity, the ethyl and *n*-propyl substituted dihydrodiols can be correlated with the corresponding methyl substituted analogues. Indeed, both the ECD and optical rotation data for **1k**–**p** have positive values and correlate with the data for enantiomers of **1d** or **g**. Consequently, the absolute configurations for **1k**–**p** are 1*R*,2*R*, as assigned in the original publication.[38] Likewise, the chlorine substituent mimics the bromine, for which the confrontation of calculated and experimental CD and UV data has been carried out. Thus, **1r** correlates with *ent*-**1c** and has the absolute configuration 1*R*,2*R*, as does **1s**, correlated to *ent*-**1c**.

Table 6. CD data, optical rotations and absolute configurations for other halogenated dihydrodiols **1k**–**z**.

Dihydrodiol	X	Y	Δε [nm][a]	$[\alpha]_D$[b]	Configuration	Reference dihydrodiol
1k[c]	Et	F	+3.43(264)	+147	(1*R*,2*R*)	*ent*-**1g**
1l[c]	Et	Cl	+0.39(282)	+92	(1*R*,2*R*)	*ent*-**1d**/**1m**
1m[c]	Et	Br	+0.25(283)	+27	(1*R*,2*R*)	*ent*-**1d**
1n[c]	*n*-Pr	F	+2.84(272)	+120	(1*R*,2*R*)	*ent*-**1g**
1o[c]	*n*-Pr	Cl	+0.57(276)	+45	(1*R*,2*R*)	*ent*-**1d**/**1p**
1p[c]	*n*-Pr	Br	+0.94(277)	+68	(1*R*,2*R*)	*ent*-**1d**
1r	CN	Cl	−2.60(294)	−3	(1*R*,2*R*)	*ent*-**1c**
1s	CF_3	Cl	−2.39(271)	−68	(1*R*,2*R*)	*ent*-**1b**
1t	CF_3	I	−1.46(286)	−56	(1*R*,2*R*)	*ent*-**1b**
1u	Cl	Me	−2.33(274)	−117	(1*S*,2*S*)	**1d**
1v	Cl	F	+2.40(267)	+90	(1*R*,2*S*)	**1a**
1w[d]	I	Me	+1.40(280)	+5	(1*S*,2*S*)	(**1d**)
1x[d]	I	F	+2.06(266)	+62	(1*R*,2*S*)	**1a**
1y[d]	I	Cl	+0.82(293)	+27	(1*R*,2*S*)	–
1z[d]	I	Br	+2.20(291)	+33	(1*R*,2*S*)	–

[a] In acetonitrile, corrected to 100% *ee*. [b] In methanol, corrected to 100% *ee*. [c] Data from ref. [38]. [d] Data from ref. [39].

Similar arguments apply to the dihydrodiols **1u** (configuration 1*S*,2*S*, reference dihydrodiol **1d**) and **1v** (configuration 1*R*,2*S*, reference dihydrodiol **1a**). Dihydrodiols **1l** and **o** bear substituents X, Y, both of which require correlation with the substituents being the subject of the present study. This can be done readily by cross-referring to *ent*-**1d** and **1m** or **p**.

The placement of the iodine substituent in the dihydrodiol moiety is challenging for the purpose of absolute configuration assignment. It is expected that both the size and the electronic properties of the iodine atom will have dominating effect on conformational and spectroscopic properties of the dihydroxycyclohexadiene molecule. Polarizability of the carbon–iodine bond and the electronic transitions within the iodine substituent may significantly limit the direct correlation of the ECD and optical rotation data with these of the bromine-substituted analogue. Indeed, the ECD and optical rotation data for the iodo-substituted dihydroxydiene **1w** (Table 6), whose absolute configuration 1*S*,2*S* has been previously independently assigned,[39] are of opposite sign to those for the bromine analogue **1d** of the same absolute configuration. Note the low $[\alpha]_D$ value recorded for **1w**. On the other hand, configurational assignment presents no conflict when confronting the ECD and optical rotation data for **1t** and *ent*-**1b** or for **1x**[39] and **1a**. Despite the fact that no reference dihydrodiol can be proposed for bishalogenated dihydrodiols **1y** and **1z**[39] we can still devise a general empirical correlation of iodine-substituted dihydrodiols ECD and optical rotation data with their absolute configuration by assuming a dominant effect of the iodine over that of the other substituent. Thus, when X in **1** is I, the ECD and optical rotation data are positive and the absolute configuration is invariably 2*S*, whereas 2*R* configuration correlates with a negative ECD and optical rotation data for the same compound.

Conclusion

1,4-Disubstituted *cis*-2,3-dihydroxy-3,5-cyclohexadienes **1a**–**j** are important synthetic intermediates obtained by enzymatic oxidation of simple 1,4-disubstituted benzene derivatives. Knowledge of their absolute configuration is of paramount importance for an understanding of enantioselectivity of the enzymatic transformation and for application of these compounds in diastereoselective syntheses. Whereas "classical" approaches for the determination of absolute configuration by X-ray diffraction analysis and chemical correlation can be successfully applied to many of the dihydrodiols reported here (see ref. [32] and a summary in Table 7), the present approach based on the confrontation of experimental and calculated ECD spectra as well as optical rotations can be consistently used for a large number of structurally related flexible molecules, having several contributing low-energy conformers.

Table 7. Summary of absolute configuration determinations of *cis*-dihydrodiols **1a**–**j** by different methods (+, conclusive result; −, inconclusive result).

Compound	CD (exptl vs calcd)	$[\alpha]_D$ (exptl vs calcd)	Stereochemical correlation	X-ray	NMR
1a	+	+	+		
1b	+	+	+[a]		
1c	+	−	+[a]		
1d	+	+	+		
1e	+	+		+[a]	
1f	−	+	+[a]		
1g	+	+			+[a]
1h	+	+	+		
1i	+	+			+
1j	+	+	+	+	

[a] These determinations were carried out for the enantiomeric *cis*-dihydrodiol.

In the majority of cases, both confrontational approaches converged to identical absolute configuration assignment. For these cases the sum of rotational strengths and optical rotations for contributing conformers is significantly biased towards either a positive or a negative value. Even more importantly, in this way difficult cases for which either confrontation of the ECD spectra (such as the case of **1f**) or optical rotations (such as the case of **1c**) are inconclusive, can still be treated with success if the assignment is based on the biased parameter. A comparison of conformer population and conformer contribution to the rotational strength of the long-wavelength Cotton effect points to a decisive role of the trifluoromethyl group. It shifts the conformational equilibrium towards the conformer (***M*2** or ***P*2**) with a strong intramolecular OH···F_3C bond and it also has a dominant effect on the chiroptical properties of dihydrodiols in this study. We also note, on the basis of the experimental ECD and optical rotation data alone, that the effect of an iodine substituent overrides the effect of any other substituent of the present study, in determining the sign of the long-wavelength Cotton effect and optical rotation of the dihydrodiol molecules **1**. This will be the subject of future computational studies when computational parameters for the iodine substituent are available at suitable level of accuracy.

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