Determination of Absolute Configuration of Acyclic 1,2-Diols with $Mo_2(OAc)_4$. 1. Snatzke's Method Revisited

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The method employing dimolydbenum tetraacetate for the assignment of the absolute configuration of optically active 1,2-diols is thoroughly revisited and applied to several compounds, some of which were synthesized by asymmetric cis-dihydroxylation. No exceptions were found to the empirical rule relating the sign of the induced CD spectrum and the configuration of the substrate, whatever its structure and sterical requirements. To broaden the scope of the method, its applicability to critical situations commonly encountered with synthetic products is tested. It is demonstrated that the method can be applied on samples with low chemical and optical purity, and that it may lend itself as a means to estimate the ee. The roles of the water content of the sample and of the diol-to-dimolybdenum ratio are investigated.

Introduction

The 1,2-diol moiety is ubiquitous in biomolecules. Carbohydrates and their compounds (glycolipids, glycoproteins, vitamins, nucleotides), steroids such as bile alcohols and brassinosteroids, sphingolipids, macrolides, and terpenoids such as hopanoids, they all contain one (or more) stereodefinite glycol moieties, which justifies the large effort, witnessed by the literature, in developing selective methods for its synthesis and characterization. Among the former, the most widely employed technique is the asymmetric dihydroxylation of olefins with catalytic osmium tetraoxide,[1,2] which also allows the prediction of the absolute configuration of the product with sufficient reliability.[3,4]

Apart from cases of substitution with chromophoric residues, 1,2-diols are intrinsically transparent in the UV−vis region commonly investigated by electronic spetroscopies. The weak n→σ* transitions localized on oxygen atoms (the first ones appearing at increasing energies) are in fact centered at about 175 nm, giving rise above 185 nm only to tails of absorptions very difficult to interpret. This fact prevents the use of chiroptical methods[5] for the direct analysis of 1,2-diols, unless a chemical derivatization is carried out on the substrate, with the aim of introducing suitable chromophoric groups, into a so-called Cottonogenic derivative.

The dibenzoate exciton approach of Harada and Nakanishi is by far the most widely employed method for assigning the absolute configuration of cyclic 1,2-diols on a nonempirical basis.[6] However, its application to acyclic substrates has proven to be not immediate, since in general several conformers with different spectroscopic properties coexist in solution.[6b] To circumvent the problem of conformational pliancy, two approaches have been followed. In the first, substrates containing one or two suitable chromophoric units, such as 1-aryl and 1,2-diarylethane diols, have been cyclized with proper reactants (endowed with further absorbing groups, if necessary), which makes possible a more or less straigthforward exciton analysis.[7] Alternatively, the traditional dibenzoate method, possibly extended to other chromophores, can be complemented by a detailed conformational analysis of the disubstituted product.[8] Despite the undoubted success in special cases, none of these methods has general scope; in particular the latter, which has been demonstrated indispensable for complex substrates (such

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as natural 1,2- and 1,3-polyols),[8] appears often inappropriate for simpler synthetic acyclic 1,2-diols.

For this reason, various alternative techniques have been set up in the years, mainly exploiting optical properties of transition metal complexes. Giving up the reliability of the nonempirical exciton model should be repaid by simplicity and immediacy of analysis. The common points to all the methods employing transition metals are the following: (1) a stock metal complex is used which is thermodynamically stable but kinetically labile in solution, so that ligand exchange or addition may occur; (2) the chiral substrate acts as a ligand of the metal center; (3) as a consequence to the ligation, the conformational freedom of the substrate must be restricted; this is expected, in particular, for polyfunctional molecules, with two or more ligating atoms which chelate the metal; (4) the stock metal complex has observable absorptions in the UV−vis region (metal d→d or f→f, or metal-to-ligand charge-transfer electronic transitions, or else $\pi\rightarrow\pi^*$ or others on the additional achiral ligands); (5) the Cottonogenic species, usually formed in situ by simple mixing of compounds (so, without requiring a true chemical derivatization prescribed by the exciton method), has observable Cotton effects, induced by the chiral ligand in correspondence of the transitions abovementioned; (6) the sign of one or more Cotton effects can be correlated with the structure, namely the absolute configuration, of the chiral ligand. Since the real structure of the Cottonogenic species is usually unknown, the correlation is, in all cases, exclusively empiric, which represents the major limitation to these approaches.

As far as the analysis of acyclic 1,2-diols is concerned, a number of transition metal complexes have been described in the literature fulfilling the above outlined requirements,[9−13] but all of them are either specific for certain classes of compounds, or, if of wide application, have proven to be not completely reliable. This is not the case for the method employing dimolybdenum tetraacetate [$Mo_2(AcO)_4$] developed by Snatzke and Frelek,[14] which may be regarded as the most convenient, versatile, and reliable one ever reported; the rigid structure imposed by the metal−metal quadruple bond, along with its peculiar electronic properties, are the reasons for this success. The ease of the procedure represents its major quality: the mixing of small amounts (about 10 μmol) of reagents, in commercial DMSO, at room temperature and open to air, leads in most cases immediately to a significant induced CD spectrum (ICD). The ICD spectra of about 30 acyclic 1,2-diols, mostly derived from carbohydrates or steroids, along with hypotheses on the structure of the active species, have been reported in the literature.[14]

Looking for methods for determining the stereochemistry of the products of asymmetric dihydroxylation, we exhaustively revisited Snatzke's procedure, broadening its scope to about 20 relevant chiral building blocks. In particular, we concentrated on substrates which could be critical from the point of view of sensitivity, or are endowed with potentially interfering functional and chromophoric groups. The method was tested for critical situations occurring with synthetic products, such as low optical and chemical purity, and once more it was found extremely reliable, to the point that it may lend itself to a first assessment of the enantiomeric excess. Furthermore, the effect of varying the diol-to-metal ratio on the spectra was investigated, to verify cases where the analyte is difficult to weigh or is of unknown purity. A full structural characterization of the Cottonogenic complex was also pursued, which will be described elsewhere.[15]

Results and Discussion

Experimental Procedure and Empirical Rule. According to the published procedure,[14] to a stock solution of about 0.6: 0.7 mg/mL of commercial $Mo_2(AcO)_4$ in commercial DMSO (analysis or spectroscopy grade), a quantity of the chiral sample is added so that the ligand-to-metal ratio is approximately 0.6/0.8, up to 1.0/1.2 for 1,2-diols of low optical purity. The first ICD spectrum is recorded immediately after the mixing, and its time evolution is controlled with a rate of about one spectrum every 10 minutes, until a stationary ICD is reached (usually, 30−40 min after the mixing). Compounds **1**−**19** (Chart 1) were examined; the ICD spectra are summarized in Table 1 and reported in Figures 1−4. Since the true concentration of the Cottonogenic species is unknown, the ICD is normalized to the diol concentration and referred to as $\Delta\epsilon'$.[14] In Figure 1 the spectrum of (*R*,*R*)-1,2-diphenylethane-1,2-diol (**1**) in $Mo_2(AcO)_4$ solution is reported. A series of four bands in the range 260−450 nm is apparent; following Snatzke's nomenclature, we refer to them as follows: band V (267 nm, positive Cotton effect); IV (305 nm, negative); III (approximately 350 nm, positive); II (375 nm, negative). In that region, up to three absorption bands can be observed for $Mo_2(AcO)_4$ in solution of DMSO, the most intense of which is centered at 305 nm and has been assigned to a metal-to-ligand charge-transfer transition.[14b,15] Band III is recognizable, if at all, only as an inflection (with the opposite sign) between the strongest two, while band I, detected at

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Chart 1

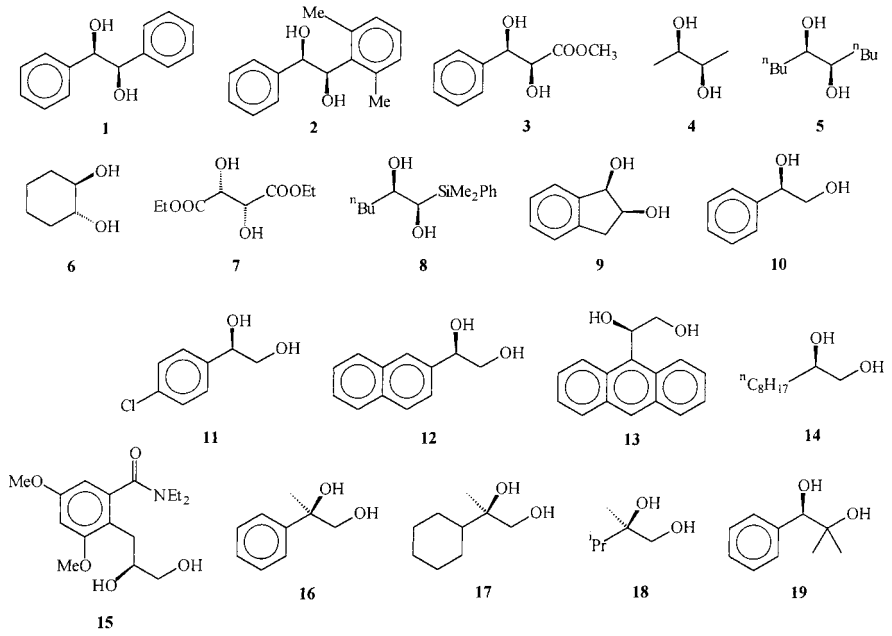


Table 1. Revelant Parameters of ICD Spectra at Stationary Conditions of Compounds 1−19 in Solution of Dimolybdenum Tetraacetate in Commercial DMSO (see text for experimental details, $\Delta\epsilon'_{ext}$ is normalized on the diol concentration)

					ICD bands λ_{ext} (nm), $\Delta\epsilon'_{ext}$[c]				
diol	steric confg.[a]	ee%	conc (mM)	molar ratio[b]	V	IV	III	II	I
(*R*,*R*)-**1**	"b*R*,b*R*"	99	1.14	0.78	269 (+0.08)	306 (−1.72)	354 (+ve in)	375 (−0.43)	nd
(*R*,*R*)-**2**	"b*R*,b*R*"	98	1.02	0.70	280 (+0.83)	306 (−1.92)	nd	360 (-ve sh)	nd
(2*S*,3*R*)-**3**	"b*R*,b*R*"	87	1.12	0.78	272 (+0.18)	307 (−0.81)	349 (+ve in)	384 (−0.29)	nd
(*R*,*R*)-**4**	"b*R*,b*R*"	98	1.23	0.85	276 (+1.50)	316 (−1.26)	nd	355 (-ve sh)	475 (−0.16)[d]
(*R*,*R*)-**5**	"b*R*,b*R*"	96	1.23	0.80	269 (-ve sh)	302 (−1.39)	nd	360 (-ve sh)	nd
(*R*,*R*)-**6**	"b*R*,b*R*"	99	1.12	0.78	273 (+0.47)	311 (−2.08)	nd	370 (−0.64)	nd
(*R*,*R*)-**7**	"b*S*,b*S*"	99	1.20	0.80	271 (−0.31)	304 (+1.13)	344 (−0.18)	389 (+0.40)	nd
(*R*,*R*)-**8**	"b*R*,b*R*"	99	1.06	0.73	nd	321 (−1.81)	nd	256 (−1.62)	474 (−0.12)
(1*R*,2*S*)-**9**	"1b*R*,2b*S*"	26	1.52	1.08	273 (+0.07)	311 (−0.32)	366 (+ve in)	399 (−0.07)	nd
(*R*)-**10**	"b*R*"	99	1.92	0.89	272 (+0.14)	308 (−0.65)	354 (+ve in)	374 (−0.18)	nd
(*R*)-**11**	"b*R*"	87	1.22	0.84	274 (+0.02)	308 (−0.61)	355 (+ve in)	368 (−0.17)	nd
(*R*)-**12**	"b*R*"	99	0.87	0.79	276 (+0.23)	309 (−2.29)	355 (+ve in)	375 (−0.33)	nd
(*R*)-**13**	"b*R*"	99	1.65	1.10	*f*	*f*	*f*	*f*	*f*
(*R*)-**14**	"b*R*"	75	1.31	0.93	271 (+0.07)	309 (−0.34)	nd	362 (−0.11)	nd
(*S*)-**15**[e]	"b*S*"	68	2.23	0.85	277 (−0.05)	308 (+0.18)	351 (−0.03)	nd	nd
(*R*)-**16**	"b*R*"	56	1.10	0.75	271 (+0.28)	313 (−0.15)	350 (+ve in)	370 (−0.08)	nd
(*R*)-**17**	"b*R*"	70	1.84	1.28	270 (−0.27)	308 (−0.25)	nd	361 (-ve sh)	nd
(*R*)-**18**	"b*R*"	30	2.92	2.08	270 (-ve sh)	305 (−0.16)	nd	nd	nd
(*R*)-**19**	"b*R*"	89	1.35	0.94	269 (+ve in)	308 (−1.07)	347 (+ve in)	358 (−0.57)	nd

[a] See text for definition. [b] Molar ratio between diol and $Mo_2(AcO)_4$. [c] Abbreviations: nd, not detected; in, inflection; sh, shoulder. [d] Additional band at 408 nm (+0.06). [e] Difference spectrum with respect to the CD of (*S*)-**15**, in anhydrous DMSO. [f] Anomalous spectrum; see text.

about 480 nm for some diols, is absent here. Below 265 nm a strong Cotton effect dominates the spectrum, whose significance is precluded by the solvent cutoff and by the first CD bands of the uncomplexed diol: the CD spectra of all compounds examined, with the exception of **13** and **15**, do not show appreciable Cotton effects in the range investigated, apart from occasional tails below 260−270 nm, which do not interfere significantly in the ICD spectrum. Since the intensity of the ICD spectrum is generally low, and the complexation of the chiral substrate far from quantitative, when the inherent CD spectrum is nonnegligible it may be profitably subtracted from the ICD. The sign and the relative intensities of the bands do not change with time (Figure 1), while the total intensity increases of about 50% from the first to the stationary spectrum. Starting from 2 to 3 h after the mixing, the intensity of the ICD spectrum is observed decreasing. After several hours, signals are so weak that a significant spectrum cannot be recorded any more. A similar trend has been observed for all samples reported in Table 1, indicating that the control of the time evolution is often unnecessary, and that the only precaution to be observed is to employ a freshly prepared stock solution.

The signs of bands II and IV are those most safely related to the absolute configuration of the diol.[14] After forming the Cottonogenic derivative, the diol is constrained into a chiral, gauche arrangement, with two diastereomorphous *g*+ and *g*− structures possible (Scheme 1). The preference for one of them is determined by the size of the substituents: the bulkier ones prefer a *pseudo*-equatorial position pointing away from the remaining portion of the complex. According to Snatzke, band IV has the same sign of the O−C−C−O dihedral angle in

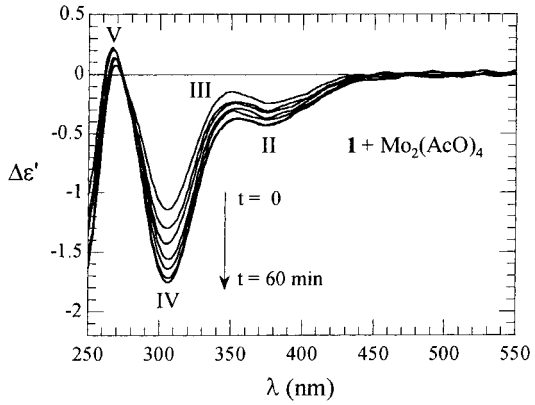


Figure 1. Time evolution of ICD spectra of (*R*,*R*)-1,2-diphenylethane-1,2-diol (**1**, ee 99%), 1.14 mM, in solution of dimolybdenum tetraacetate, 1.46 mM, in DMSO. Time $t = 0$ corresponds to about 5 min after the mixing. $\Delta\epsilon'$ is normalized on the diol concentration.

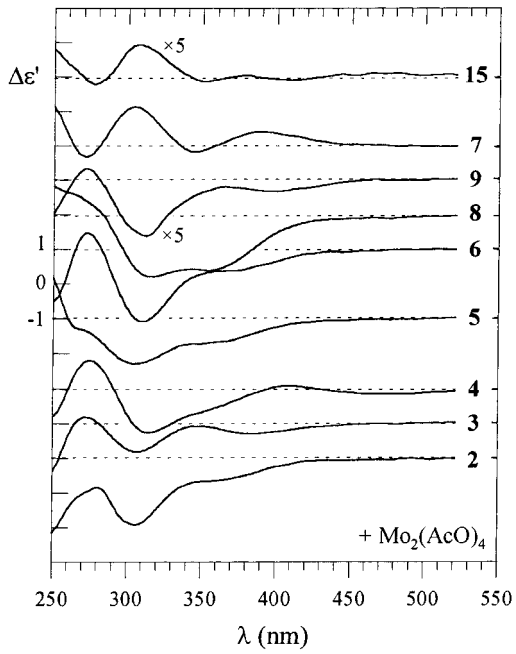


Figure 2. ICD spectra at stationary conditions of compounds **2**−**9** and **15** in solution of dimolybdenum tetraacetate in DMSO; conditions reported in Table 1. $\Delta\epsilon'$ is normalized on the diol concentration.

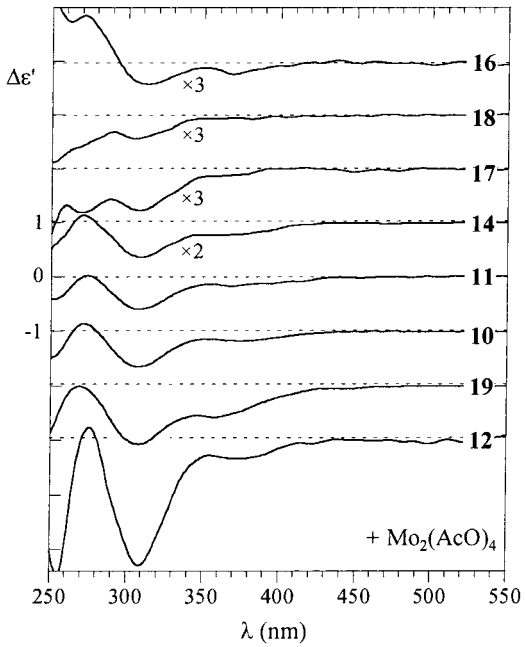


Figure 3. ICD spectra at stationary conditions of compounds **10**−**12**, **14**, and **16**−**19** in solution of dimolybdenum tetraacetate in DMSO; conditions reported in Table 1. $\Delta\epsilon'$ is normalized on the diol concentration.

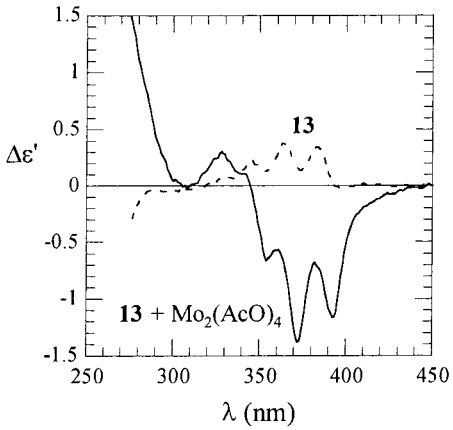


Figure 4. CD spectrum of (*R*)-9′-anthrylethane-1,2-diol (**13**, ee 99%), 1.80 mM, in DMSO (dashed line) and ICD spectrum at stationary conditions of **13**, 1.65 mM, in solution of dimolybdenum tetraacetate, 1.50 mM, in DMSO (solid line). $\Delta\epsilon'$ is normalized on the diol concentration.

the favored conformation; if such a more stable structure is recognizable from the inspection of the molecular structure of the diol (which is not always trivial), the assignment of the absolute configuration of the chiral ligand from the sign of the ICD spectrum is immediate.

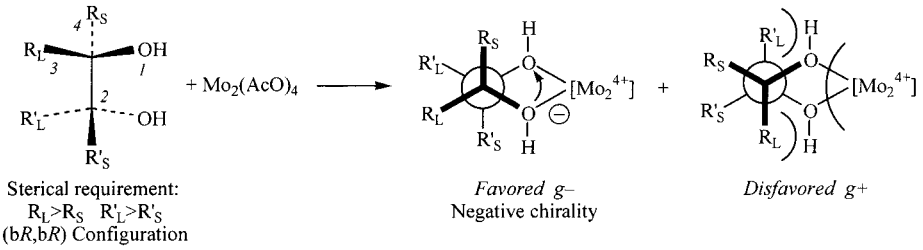
To make the empirical rule further explicit, we suggest the use of "b*S*" and "b*R*" descriptors, introduced by Snatzke and Gerards for monohydroxy alcohols.[16] As depicted in Scheme 1, for each alcoholic chiral carbon, the first priority is given to the hydroxyl, the second to the adjacent −C−OH, and the remaining two substituents are ordered according to their bulkiness. In most cases "b*S*" corresponds to *S* and "b*R*" to *R*. With this notation, the empirical rule may be reformulated as follows: a "b*R*" or "b*R*,b*R*" 1,2-diol, for which a ligating structure with a negative O−C−C−O dihedral is the most stable, gives rise to negative ICD bands II and IV. Among the numerous acyclic 1,2-diols investigated, in the present work (Table 1) or in ref 14, no exceptions are found.[17]

Systematic Investigation of 1,2-Diols. With reference to Figures 2−3 and to Table 1, the following conclusions may be drawn about the dependence of the ICD spectrum on the structure of the chiral substrate.

(16) Gerards, M.; Snatzke, G. *Tetrahedron: Asymmetry* **1990**, *1*, 221.

(17) The case of methyl (*S*)-glicerate (with "b*R*" configuration) reported in ref 14a,c does not represent a true exception. In fact, the ICD spectrum for this compound is considerably different from the usual ones: a strong, positive Cotton effect is apparent at 335 nm, whose position is hardly affected by the adjacent, smaller negative bands; it cannot then be attributed to the diagnostic band IV, usually appearing at 305 nm and occasionally shifted at longer wavelengths by coalescence with the close band II of the same sign. In such cases, the unusual ICD spectrum should warn not to apply the current method, so methyl glicerate is not to be considered a true exception.

Scheme 1. Relation between the Sterical Configuration of the Substrate and the Sign of the O−C−C−O Dihedral in the Cottonogenic Derivative[a]



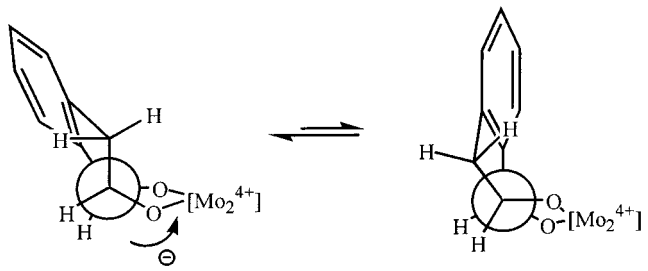
Sterical requirement:
$R_L>R_S$ $R'_L>R'_S$
(b*R*,b*R*) Configuration

[a] Italic numbers on the left refer to the priority of the substituents for the upper alcoholic chiral carbon within the "b*R*"/"b*S*" nomenclature.

They complement already reported results.[14a,e] (1) The method is entirely versatile since any compound, whatever the substitution at alcoholic carbons, may be treated. Various functional groups, such as esters, amides, and ethers (compounds **3**, **7**, and **15**) and others[14f] do not interfere. Carboxylic acids, which ligate dimolybdenum,[14b] must be converted into esters. The presence of several hydroxy and/or amino groups would prevent its employment; a library of reference CD curves is available for multichromophoric derivatives of many of these substrates, making the exciton approach feasible.[6b,8] (2) The method is quite sensitive with respect to the differences in the size of substituents, which is the factor determining the sign of the induced optical activity. This is especially appreciated for *prim/ter* diols **16**−**18**, with two alkyl substituents competing for the *pseudo*-equatorial position. The difference between the sterical requirement of a methyl and an isopropyl group (compound **18**) is sufficient for obtaining an effective stereoselection in the formation of the complex. (3) As already reported,[14] *sec/sec* and *sec/ter* diols, especially with aryl and bulky substituents and when the conformation is favorably locked, give the most plain and intense ICD spectra, while diols with a *prim* alcohol and less bulky substituents give weaker ICD spectra. We must stress that since the intensity of each spectrum is not entirely reproducible, depending in the first place on the aging of the stock solution of $Mo_2(AcO)_4$ in DMSO, the comparison between the intensities of different spectra has to be made with caution. (4) The low intensity of ICD spectra sets the low limit of the sample concentration to about 0.1 μmol/mL. This is enough low in the context of synthetic substrates, but may be not sufficient for natural compounds available in minute amount. On the other hand, the same problem prevents any conformational investigation, and also a microscale exciton approach[6b] would rely on the availability of reference CD spectra. (5) Up to this point, the method has proven to be completely reliable: no exceptions to the empirical rule "b*R*,b*R*" or "b*R*" configuration → negative band IV are known. Obviously, this observation does not justify an uncritical application of the method; special attention must be paid in ascertaining whether the diagnostic band is altered by unexpected contributions to the optical activity.

Comments to ICD Spectra. Some spectra deserve further comment. Diethyl (*R*,*R*)-tartrate (**7**) had been previously recognized as an exception to the empirical rule.[14c] As a matter of fact, our sample follows the expectation "b*S*,b*S*" configuration → positive band IV; the reasons for this odd disagreement are unclear. The fact that a 1,2-diol with two strongly polar α groups, potentially competitive for the ligation of Mo_2^{4+}, obeys anyway the empirical rule, is extremely comforting.

Scheme 2



The ICD spectrum for (*R*,*R*)-1-(dimethylphenylsilyl)-hexane-1,2-diol (**8**) has an unexpected time evolution, with the intensity ratio of bands II/IV increasing with time. This might be explained with two competing and slowly equilibrating complexes with different ICD spectra; this is the first report of application of the current method to a silanediol.

(1*R*,2*S*)-Indane-1,2-diol (**9**) is a rare example of an *erythro* diol; despite its cyclic nature, two enantiomorphous arrangements of the O−C−C−O moiety are still possible. From inspection of the molecular model (Scheme 2), it is clear, in the light of the negative ICD band IV, that the conformer with negative chirality and the phenyl group in a *pseudo*-equatorial position is preferred as expected.

Compound (*S*)-**15** is extremely interesting since its synthesis by osmium-catalyzed cis-dihydroxylation violates Sharpless' mnemonic device for the facial enantioselectivity.[4e] The red-shifted ^1L_b band of the polysubstituted aromatic ring gives rise to nonnegligible Cotton effects above 250 nm, so that the difference spectrum needed to be evaluated. Moreover, because of the very low intensity of the induced Cotton effects in solution of $Mo_2(AcO)_4$, it was necessary to employ dried DMSO to get an observable ICD (vide infra). In these conditions, a positive band IV is obtained in accordance to the "b*S*" configuration.

Among the various aromatic substrates tested with potentially interfering chromophores, only the anthryl group seems to prevent the application of the method. (*R*)-9′-anthrylethane-1,2-diol (**13**) shows a significant inherent CD spectrum in the region 300−400 nm, allied to the anthracene ^1L_a (short-axis polarized) transition. The ICD spectrum in solution of $Mo_2(AcO)_4$ (Figure 4), rather than being overwhelmed by the inherent CD, shows in the same region a moderately strong, negative, and vibronically structured band, which must be assigned to the Cottonogenic derivative. It can in principle arise from various mechanisms of coupling between the low-energy strong aromatic transition and the ones allied to the dimolybdenum core.[18]

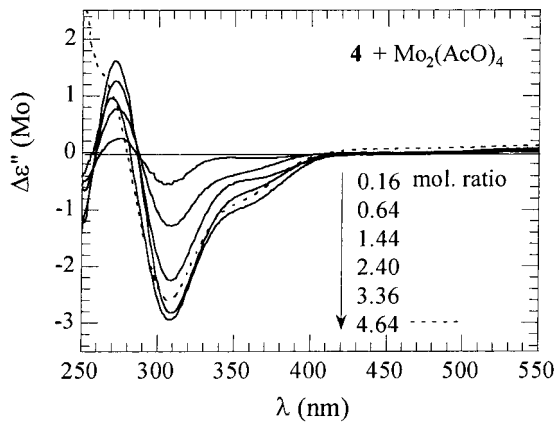


Figure 5. ICD spectra at stationary conditions of (*R*,*R*)-butane-2,3-diol **4** (ee 98%) in solution of dimolybdenum tetraacetate, 5.72 mM, in DMSO, at increasing diol-to-metal molar ratios. $\Delta\epsilon''$ is normalized on the dimolybdenum concentration.

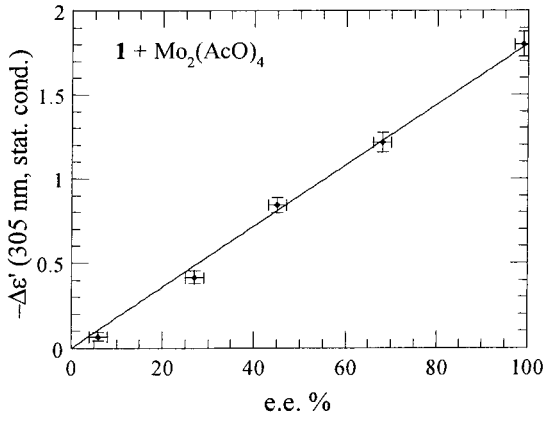


Figure 6. Relation between $-\Delta\epsilon'$ at 305 nm and ee of the sample for ICD spectra at stationary conditions of (*R*,*R*)-1,2-diphenylethane-1,2-diol (**1**), 1.14/1.18 mM, in solution of dimolybdenum tetraacetate, 1.46 mM, in DMSO. $\Delta\epsilon'$ is normalized on the diol concentration.

Finally, we note that Snatzke and co-workers report, for acyclic aliphatic *prim*/*sec* diols, ICD spectra slightly different from ours,[14a,e] namely with a prominent band I, whose sign does not correlate with the absolute configuration, and band II often not appearing. However, for some compounds we found a certain dependence of minor spectral features on the nature of the sample. For instance, a sample of **4** with low chemical purity showed a spectrum different from that reported in Figure 2, with the region above 400 nm not structured. This fact may lead to the conclusion that the band I can be due to a different way of ligation that seems to be effective only in certain conditions for small and unhindered substrates.

Relation between Ligand-to-Metal Ratio and ICD Spectrum. Figure 5 reports the ICD spectra of mixtures of $Mo_2(AcO)_4$ and (*R*,*R*)-butane-2,3-diol (**4**) for several ligand-to-metal (namely, diol-to-dimolybdenum) molar ratios. As can be seen, the appearance of the spectrum, in terms of both the position and the relative intensities of bands II and IV, remains substantially unchanged with varying the quantity of the chiral ligand; a similar trend is observed for most substrates. We conclude that even a rough weighing of the sample is sufficient for recording a significant spectrum, unlike what was recommended in the original recipe.[14c,d,g] In particular, compounds difficult to handle and weigh, available in minute amounts, or with unknown chemical purity, may be treated with the current method without loss of significance. At the same time, given the good linearity, at least up to 2−3 equiv, between ICD intensity and ligand concentration, a slight excess of the diol may be preferred for compounds giving rise to weak ICD spectra; this may be extremely useful, for example, for unhindered substrates or for samples with low optical purity. The complete independence of the sign of the ICD on the ligand-to-metal ratio is one of the advantages of dimolybdenum with respect to other transition metals, e.g., Ni.[11b,c]

The relation between the intensity of ICD spectrum and the ligand-to-metal ratio will be analyzed quantitatively in a following paper,[15] in order to draw structural conclusions on the active species. We may anticipate that two active complexes are apparent in solution in the common conditions of measurement, one of which dominates the ICD spectrum in the diagnostic region and has a 1:1 stoichiometry with a relatively low formation constant.

Relation between Enantiomeric Excess of the 1,2-Diol and ICD Spectrum. Figure S1 (Supporting Information) reports the stationary ICD spectra obtained for samples of (*R*,*R*)-1,2-diphenylethane-1,2-diol (**1**) with various enantiomeric compositions, in solution of $Mo_2(AcO)_4$, with a ligand-to-metal molar ratio approximately equal to 0.8. The appearance of the ICD spectra, and their time evolution, is identical in the five cases; moreover, most remarkably, the quantitative relation between the $\Delta\epsilon'_{ext}$ at 305 nm (band IV) at stationary conditions and the ee is exactly linear (Figure 6). The simplest, but not the only, model which can justify the observed regularity implies a 1:1 ligation between the diol and the Mo_2^{4+} unit. More importantly, this result sheds new light on the potentiality of the current empirical approach. Provided that (a) the same stock solution is used, (b) spectra are recorded after each other, and (c) the stationary conditions are reached, the ICD spectra are entirely reproducible also from a quantitative point of view. In principle, if one sample of known enantiomeric composition is available, one can estimate with sufficient precision (say 5%, for a substrate leading to an intense ICD) the ee of a second sample. Again, the current method is demonstrated extremely sensitive: for the sample of **1** with ee = 6%, for which the molar ratio between the metal and the excess of (*R*,*R*) molecules of ligand is about 20:1, a signal-to-noise ratio of 4:1 is obtained in the diagnostic region; in conclusion, a minute amount of chiral substrate, even with low enantiomeric purity, is required for a reliable configurational analysis.

Relation between Water Content of DMSO and ICD Spectrum. Given its high hygroscopicity, commercial dimethyl sulfoxide contains a considerable amount of water. In the original recipe for the experimental procedure,[14c,d,g] it is reported the use of commercial (spectroscopy grade) DMSO, and the necessity of drying is not stressed. As a matter of fact, in most cases even DMSO for analysis can be used; the solvent employed for all spectra showed in Figures 1−5 was found to

(18) A referee suggested that the most likely mechanism should involve magnetic dipole allowed transitions on the dimolybdenum, which couple favorably with the aromatic transitions thanks to the diminished conformational flexibility in the Cottonogenic complex.

contain 3200 ppm of water (Karl Fischer method). Since we observed, however, a marked effect of the water content on the ^{1}H NMR spectra of the CD-active solutions,[15] we envisaged the possibility of a similar effect on the ICD spectra.

Figure S2 (Supporting Information) shows the stationary ICD spectra of (*R*)-phenylethane-1,2-diol (**10**) in solution of $Mo_2(AcO)_4$, as a function of the addition of amounts of water up to 120 equiv; the first solution, obtained with thoroughly dried DMSO, contained approximately 70 ppm H_2O (Karl Fischer method). The appearance of the ICD spectra is unchanged: thus the efficiency of the method is not affected by the water content, unlike what reported for other techniques employing metal complexes (such as those of Pr and Eu) that require dry solvents.[11e,12] It must be observed that, apart from the solvent, water is also a common impurity of small, polar 1,2-diols obtained by asymmetric dihydroxylation; moreover, it represents a good model for all those contaminants which could potentially be competitive for the ligation of Mo_2^{4+}.

The intensity of the ICD spectrum is, however, strongly dependent on water. The addition of 1.0 μL of H_2O to 2 mL of CD-active solution, 2.7 mM in **10**, reduces the intensity of the band IV to about one-half; in that condition the global water content is about 800 ppm. This observation is of primary importance and demostrates that the sensitivity of the method may be greatly enhanced by the use of dried DMSO, especially when dealing with *prim* unhindered diols (such as **15**) giving rise to extremely weak ICD spectra.

Incidentally, also the time evolution of the spectra is greatly affected by the water content, with the most anhydrous samples reaching the stationary point considerably more slowly.[15] Such conditions may be employed in order to minimize the water content with respect to the Cottonogenic complex: a 10-fold more concentrated sample of **10** (28.2 mM with a 0.01 cm cell path length), using a thoroughly dried flask and cell, requires on the average about 100 min to reach the stationary point, against 40 min of the previous spectra.

Conclusions

In this paper we applied the method based on $Mo_2(AcO)_4$ to the determination of the absolute configuration of nineteen 1,2-diols, mostly synthesized by osmium tetraoxide catalyzed cis-dihydroxylation of the corresponding alkenes, and revisited the empirical rule developed by Snatzke relating the sign of the induced CD spectra and the absolute configuration of the 1,2-diol. To gain a better insight into the limits of applicability of the method, the dependence of the ICD spectra on various factors was investigated, such as the ligand-to-metal molar ratio, the enantiomeric excess of the substrate, and the water content in the solvent. It was demonstrated that a rough weighing of a small amount of the sample, with even low enantiomeric purity, is sufficient, in most cases, to obtain immediately a significant ICD spectrum; moreover, only the intensities, and neither the sign nor position, of the signals, depend on the water content of the solvent. The method shows itself to be a very reliable, versatile, and elastic empirical procedure for the assignment of the absolute configuration of that fundamental class of molecules, no exceptions being known to the empirical rule.

Experimental Section

CD spectra were recorded using a Jasco J600 spectropolarimeter, with a 0.1 cm cell (if not otherwise specified) in DMSO and at room temperature, with the following conditions: speed, 50 nm/min; time constant, 1 s; bandwidth, 2.0 nm; noise reduction was carried out with a low-pass filter. Enantiomeric excess were determined by the following: HPLC (diols **1**, **2**, **3**, **9**, **11**, **12**, **13**, **15**, **16**, **19**), using a Jasco PU-980 chromatograph equipped with a Jasco UV-975 detector (conditions are reported for each compound in the Supporting Information); ^{1}H NMR with tris[3-(heptafluoropropylhydroxymethylene-*d*-camphorato] europium^{III} [Eu(hfc)$_3$] as shift reagent[19] (diols **8**, **17**); NMR of the corresponding esters of α-methoxy-α-trifluoromethylphenylacetic acid (Mosher's reagent)[20] (diols **5**, **14**, **18**).

Dimolybdenum tetraacetate was purchased form Fluka and not purified. DMSO, spectroscopy or analysis grade, was purchased from Fluka, and dried according to the common procedure.[21]

Non racemic diols **4**, **6**, **7**, and **10** were commercially available (Aldrich and Fluka). Diols **1**, **3**, **5**, **9**, **11**, **12**, **13**, **14**, **16**, **18**, and **19** were synthesized from the corresponding commercial alkenes (Aldrich and Fluka) by asymmetric catalytic homogeneous dihydroxylation (AD) according to the Sharpless procedure.[1] Diol **2** was obtained by AD of *trans*-1,3-dimethyl-2-(2′-phenylethenyl)benzene, prepared following a published procedure.[22] Diol **8** was obtained by AD of 1-(dimethylphenylsilyl)-1-hexene prepared by hydrosilylation of 1-hexyne.[23] Diol **15** was obtained by AD of *N*,*N*-diethyl-2-allyl-3,5-dimethoxybenzamide as described elsewhere.[3e] Diol **17** was obtained by AD of 2-cyclohexylpropene obtained from cyclohexylmethyl ketone by Wittig reaction.

The structural characterization of synthetic compounds is reported in the Supporting Information.

Absolute configuration of synthetic diols was assigned according to Sharpless mnemonic device,[3] except for **15**, whose configuration was assigned in ref 4e.

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Supporting Information Available: ICD spectra (Figure S1) of (*R*,*R*)-1,2-diphenylethane-1,2-diol (**1**) with various ee, ICD spectra (Figure S2) of (*R*)-phenylethane-1,2-diol (**10**) as a function of water addiction, in solution of dimolybdenum tetraacetate in DMSO, and product characterization of synthetic compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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