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Assignment of the absolute configuration of large molecules by ab initio calculation of the rotatory power within a small basis set scheme: the case of some biologically active natural products

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Abstract—Ab initio calculations of the optical rotatory power (ORP) of some natural products **1**–**12** showing interesting biological properties (they are antibiotics, antimalarials, aromas and fragrances) have been carried out by means of the Hartree–Fock (HF) and density functional theory methods and small basis sets, using available packages such as DALTON 1.2 and GAUSSIAN 03. The results obtained fully support our previous conclusion [*J. Org. Chem.* **2003**, *68*, 5186] that for aromatic and/or largely unsaturated molecules, if the $[\alpha]_D$ is determined in sign and order of magnitude by the lowest-energy Cotton effect(s), the result of such simplified ab initio calculations of the ORP is completely reliable. When possible (i.e., small size molecules) the prediction made using extended (with diffuse functions) basis sets affords practically similar values. Therefore, even large molecules (50–60 atoms) can be treated using common desktop computers: this result is very important from a practical point of view. Compounds **8** and **12** did not fulfil the above criterion and therefore require a more accurate treatment.
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1. Introduction

Recently, several papers have appeared[1–9] from which the real possibility of reliably calculating the optical rotatory power (ORP) of organic compounds by ab initio quantum-mechanical techniques clearly results, affording a simple and fast method for the assignment of the absolute configuration (AC). This approach appears very attractive, even if some technical limitations exist: in fact Stephens et al. have pointed out[3c] that the density functional theory (DFT) method gives more accurate results than the Hartree–Fock (HF) method and that, in any case, large basis sets containing diffuse functions are necessary. An approach of this kind certainly provides more accurate results, but increases the computational effort. In other words, the theoretical assignment of AC becomes impossible for medium-large molecules (like the largest part of real compounds and, in particular, the most important from the applicative point of view, such as the biologically active ones: pharmaceuticals, agrochemicals, aromas and fragrances etc.) using the

common desktop computers. We reasoned that a safe configurational assignment can be made if the ab initio calculation reliably provides sign and just the order of magnitude of the ORP: this in principle could be obtained with a small basis set calculation, guaranteeing a low computational effort, even if forced to pay the price of reduced numerical accuracy. Hence we demonstrated[8a] that if the ORP is determined (sign and order of magnitude) by the lowest energy Cotton effects, then a small basis set calculation (at the DFT or even at the HF level) is sufficient, otherwise (ORP due to high energy Cotton effects) the use of more accurate approaches (i.e., DFT/large basis set) is necessary. In other words, an analysis of the experimental circular dichroism (CD) spectrum affords useful information for reducing the complexity of such ab initio calculations. In particular our study showed that the above CD criterion to simplify the computations can be applied even to large (30–40 atoms) unsaturated and/or aromatic molecules, which have intense Cotton effects in the vis–UV region. Herein we intend to further demonstrate the validity of our previous approach based on small basis set calculations. To this end we shall also use the DFT/B3LYP method which, generally speaking, offers more accurate results[3c] and, we shall also compare the small

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basis set ORP predictions with larger basis set (i.e., aug-cc-pVDZ) results, when possible (this is clearly possible only with small molecules, such as **6–12**). In addition, to further emphasise the reliability and usefulness of these calculations to the experimental organic chemist, we shall only treat quite large, real, biologically active molecules, such as (+)-griseofulvine, **1**, (+)-camptothecine, **2**, (+)-bulbocapnine, **3**, (−)-ancistrocladine, **4**, (+)-hamatine, **5**, (−)-spirobrassinine, **6**, (+)-*cis*-pterocarpan, **7**, (+)-*trans*-pterocarpan **8**, (+)-α-vetivone, **9**, the vetivone analogue (+)-**10** and the diastereoisomeric wine lactones (+)-(*R,S,R*)-**11**, and (−)-(*S,S,R*)-**12**. These compounds have been chosen for the following reasons; (i) all of them are known compounds for which the relationship between ORP and AC has been established, so the validity of our approach can be verified; (ii) CD spectra are reported in the literature (or have been measured in this work) except for (+)-**10**; (iii) they are all biologically active: **1** and **2** show[10] antibiotic activity; compound **3** has some different biological properties such as antioxidant and anticonvulsant effects,[11] **4** and **5** belong to the family of isoquinoline alkaloids, that is, compounds, which can act as antimalarials, molluscicidals etc.[12]; compound **6** possesses antifungal activity,[13] **7** and **8** are natural isoflavonoids, provided with several biological properties;[14] **9** and **10** are components of the oil of vetiver and therefore are widely used in the perfume industry[15] and **11** and **12** are fundamental constituents of the aroma of some white wines.[16]

2. Results and discussion

(+)-Griseofulvine **1**, is a highly unsaturated molecule that shows a large optical rotatory power (+352, chloroform). The CD spectrum (Fig. 1) showed a broad positive ($\Delta\varepsilon_{max}$ + 15 ca.) band in the range 350–270 nm, followed by a sequence of a positive ($\Delta\varepsilon$ + 32)/negative ($\Delta\varepsilon$ − 25) Cotton effects centred at about 230 nm.
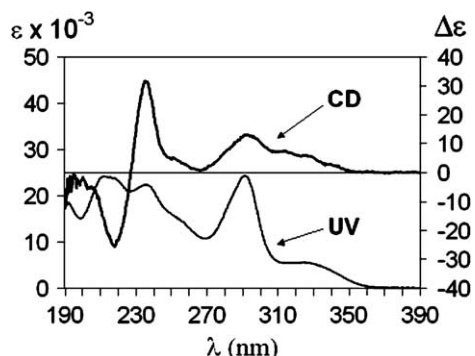

Figure 1. CD and UV spectra of (+)-**1** in methanol solution.

By applying the simplified Kroenig–Kramers transformations proposed by Moscowitz[17] the CD bands measured between 350 and 190 nm provide a contribution to the optical rotatory power at the sodium D line, $[\alpha]_D = +362$, that is, they determine the sign and numerical value of $[\alpha]_D$. Therefore, following the language used in Ref. 8a, we propose that this molecule belongs to class (a) and its $[\alpha]_D$ can be reproduced with a

small basis set treatment, even at the HF level. The first step in a calculation of the ORP is obtaining the input geometry. To this end, a conformational search has been carried out at DFT/B3LYP/6-31G* level, using a GAUSSIAN 98 package. Only conformers, which had energy within a 2 kcal/mol range over the most stable structure have been taken into account. (+)-**1** prevalently presents a conformer with the methyl group in axial position (Fig. 2). An HF/6-31G* calculation of ORP provides the correct sign and order of magnitude (50% ca. of the absolute value); in other words it gives us information, which is sufficient enough for a safe assignment of the AC.
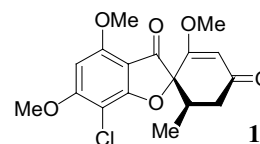
(+)-griseofulvine

$[\alpha]_D$
Exp. (CHCl$_3$)   : +352 [ref. 10]
Exp. (MeOH)   : +354
HF/6-31G*   : + 180
B3LYP/6-31G* : + 285

The DFT/B3LYP/6-31G* predicted value (+285) was in better agreement with the experiment, but did not add anything essential for a correct configurational assignment. Moreover, just in the case of **1**, which is a perfect class (a) molecule, we studied the effects of the input geometry and level of theory in calculating ORP, on the reliability of the results. So, we tested geometries obtained by molecular mechanics (MMFF94 force field) or semiempirical (AM1) methods. In addition even HF/STO-3G ORP calculations were attempted: the results are reported below.

Density functional geometry: B3LYP/6-31G*, ORP values

Method	Conf. A, 97%	Conf. B, 3%	Weighted average
HF/STO-3G	+169	−138	+160
HF/6-31G*	+180	−110	+171

Semi-empirical geometry: AM1, ORP values

Method	Conf. A, 93%	Conf. B, 7%	Weighted average
HF/STO-3G	+132	−121	+114
HF/6-31G*	+156	−99	+138

Molecular mechanics geometry: MMFF94, ORP values

Method	Conf. A, 78%	Conf. B, 22%	Weighted average
HF/STO-3G	+245	−34	+184
HF/6-31G*	+308	−25	+235

On the basis of the above results, it seems that, for molecules such as **1**, that is those which belong to class (a) molecules and have high ORP values (say, 100 units or more), determined in sign and order of magnitude by low-energy Cotton effects, a very simplified computational protocol can be carried out to attain a correct and rapid AC assignment. That is, a HF/STO-3G calculation of ORP on the molecular mechanics equilibrium structure, combined with a polarimetric measurement, is sufficient to provide the correct answer. Furthermore, on the conformation A of **1** optimised at DFT level, we have carried out a very expensive calculation of ORP at B3LYP/aug-cc-pVDZ level. We found an ORP value of +280, that is a value almost identical to the one found by a B3LYP/6-31G* calculation. Hence, we have demonstrated that for class (a) molecules such as **1**, to carry out a large basis set calculation may be unnecessary.

The antitumour compound (+)-camptothecine, **2**, ($[\alpha]_D = +54$, chloroform) shows the CD spectrum reported in Figure 3. Cotton effects are measured at 370 nm ($\Delta\varepsilon - 2$ ca.), 250 nm (sh, $\Delta\varepsilon + 22$ ca.) and 235 nm, $\Delta\varepsilon + 43$ ca.).

	Conformation A,	Population[a]
DFT/B3LYP/6-31G*		97%
AM1		93%
MMFF94		78%

	Conformation B,	Population[a]
DFT/B3LYP/6-31G*		3 %
AM1		7 %
MMFF94		22%
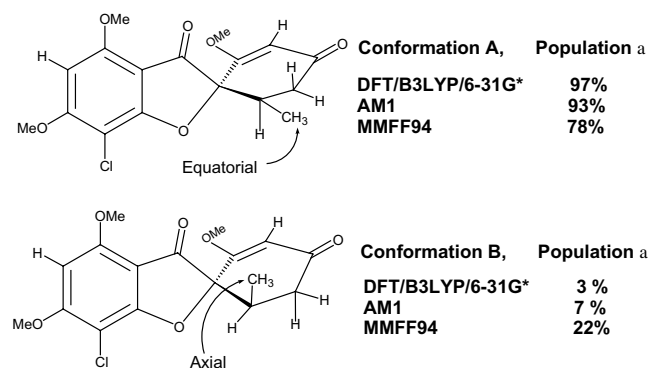
[a] Population found applying a Boltzmann statistics.

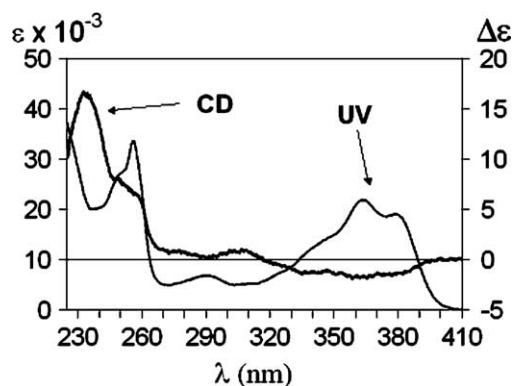**Figure 2.** The two most stable conformations for **2**.

Figure 3. CD and UV spectra of (+)-**2** in chloroform solution.

Even if the lowest-energy CD band was opposite in sign to the specific rotation, the overall CD spectrum (using again the Moscowitz simplified Kroenig–Kramers transform) gave a contribution to the ORP at 589 nm of about +179. This means that **2** can also be considered as belonging to class (a)[8a], so the HF/6-31G* treatment is

expected to give the correct answer. This case presents an additional difficulty with respect to the previous one as for this molecule three different conformers must be taken into account. These conformers differ simply for the position of the terminal methyl group of the axial ethyl with respect to the aromatic moiety. At HF/6-31G* level they are all dextrorotatory with numerical values in the order of +40 units.
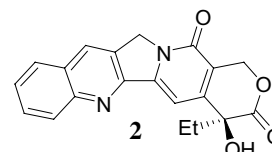

(+)-camptothecine

$[\alpha]_D$
Exp. (CHCl₃)   : +54
HF/6-31G*   : + 44
B3LYP/6-31G*   : + 97

The HF/6-31G* weighted average gave a predicted value of +44, which is in very good agreement with the experimental one. Interestingly, the DFT result seemed to be less accurate than the HF one (vide infra). The cases of the biaryl compounds (+)-bulbocapnine **3**, (−)-ancistrocladine **4** and (+)-hamatine **5**, are particularly interesting. We first considered alkaloid (+)-bulbocapnine, **3**.
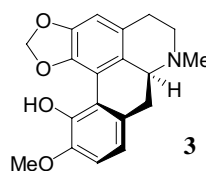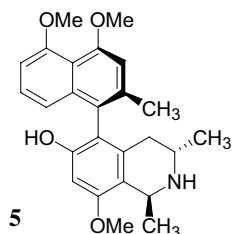

(+)-bulbocapnine

$[\alpha]_D$
Exp. (CHCl₃)   : +237 [ref. 18]
HF/6-31G*   : + 234
B3LYP/6-31G*   : + 274
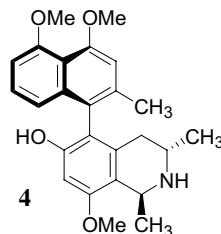
(-)-ancistrocladine

$[\alpha]_D$
Exp. (MeOH)   : - 23 [ref. 19a]
HF/6-31G*   : - 90
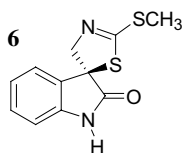B3LYP/6-31G*   : - 87

(+)-hamatine

$[\alpha]_D$
Exp. (CHCl₃)   : + 68 [ref. 19a]
HF/6-31G*   : + 115
B3LYP/6-31G*   : + 149

This compound is a biaryl system where the torsion defined by the two aromatic ring is blocked by a bridge, so from the conformational point of view no particular problems derive here. Compound **3** possesses a quite large specific rotation[18] and its CD spectrum has also been reported[18] so we can easily ascertain that this molecule belongs to class (a) as well. As a matter of fact, the result of the HF/6-31G* calculation is +234, in very

good agreement with experiment, furthermore, the DFT/B3LYP/6-31G* calculation also gave a good result. Compounds **4** and **5** possess two stereogenic carbon atoms having the same AC in the two compounds and the opposite sense of twist around the C_{ar}–C_{ar} axis. This constitutes the relevant feature from the $[\alpha]_D$ point of view; in fact whilst **4** is levorotatory **5** is dextrorotatory. The ORP values and CD data for both these compounds are already known:[19] both **4** and **5** belong to class (a). The input geometry for the calculations has been found assuming for the two carbon atoms the configuration reported in the literature and the ORP calculations have been carried out for a dihedral angle between the benzene rings ($\theta = -84°$ and $+81°$ for **4** and **5**, respectively), which guarantees the minimum energy of the systems. In this way the HF/6-31G* predictions are -90 for **4** and $+115$ for **5**. These figures are satisfactory in sign and order of magnitude, even if numerically speaking they are much higher than the experimental values. Interestingly, even the DFT numbers, which in general are more accurate predictions,[3c] were not much different from those provided by the HF calculations. A reason for this could be found in the geometries used: they refer to a minimum of energy but the real potential energy curve as a function of the dihedral angle between benzene rings is quite flat, that is, such a dihedral angle may assume different values around the minimum one. As a consequence, only doing the calculation for the minimum energy conformer is a crude treatment. A more rigorous approach requires averaging over several relative orientations of the aromatic rings but this treatment is beyond the aims of the present paper.[3d,7c]


6

(-)-spirobrassinin

$[\alpha]_D$

Exp. (CH$_2$Cl$_2$)	: -150 [ref.13]
HF/6-31G*	: - 245
B3LYP/6-31G*	: - 327
B3LYP/aug-cc-pVDZ	: - 365

(−)-Spirobrassinine, **6**, is another interesting biologically active molecule. Its $[\alpha]_D$ and CD data have recently been reported by Harada and co-workers,[13] who assigned the AC of **6** as described, just from the analysis of the CD spectrum. This compound is a class (a) molecule and in fact the HF/6-31G* prediction gives a satisfactory result (−245 vs experimental −150), even if the theoretical evaluation is certainly too large. Surprisingly, the ORP values obtained both at 6-31G* and aug-cc-pVDZ level using the DFT/B3LYP functional differed from the experimental number more than the HF/6-31G* ones (vide infra). The case of the diastereoisomeric pterocarpans **7** and **8** was quite instructive. These differ in structure as **7** possesses a *trans* ring junction, whilst in **8** the same junction is *cis*; however both of them are dextro- and highly-rotating compounds, and their CD spectra have been recently reported.[14]
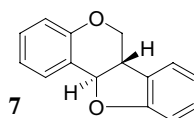
(+)-(S,R)-trans-pterocarpan

$[\alpha]_D$

Exp. (CHCl$_3$)	: + 70 [ref. 14]
HF/6-31G*	: + 103
B3LYP/6-31G*	: + 129
B3LYP/aug-cc-pVDZ	: + 77

7
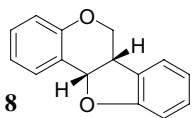
(+)-(S,S)-cis-pterocarpan

$[\alpha]_D$

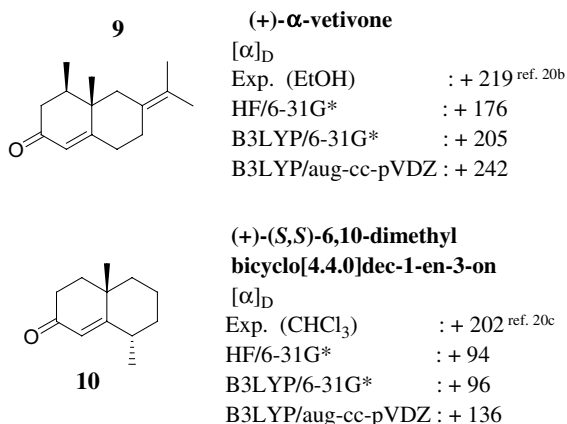|	
Exp. (CHCl$_3$)	: + 196 [ref. 14]
HF/6-31G*	: + 337
B3LYP/6-31G*	: + 361
B3LYP/aug-cc-pVDZ	: + 251

8

Compound **7** is perfect class (a) compound (the contribution to $[\alpha]_D$ coming from the low energy Cotton effect is +66, versus an experimental value of +70). In fact, the small basis set predictions (both HF and DFT) are quite satisfactory: +103 and +129, respectively. Passing to the larger aug-cc-pVDZ basis set improved the calculated DFT value, but did not add anything essential for a correct configurational assignment.

For **8** we have that the first CD band, which gives a contribution to the $[\alpha]_D$ of −88, that is, a number, which represents a significant fraction of the experimental rotation but is opposite in sign to it. However, the entire CD spectrum (between 300 and 200 nm) provided +97, that is only 50% of the experimental rotation. In other words, this molecule does not belong to case (a), so a calculation on this molecule using the small basis set approach cannot be considered reliable, and therefore we are unable to trust the result. The number obtained by the HF/6-31G* approach was +337, that is, we have the correct sign even if the prediction gives two times the experimental value. As expected[3c] the DFT/extended basis set treatment afforded a prediction, which was nearer to the measured number.
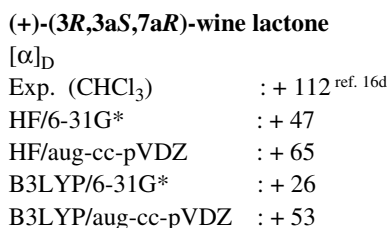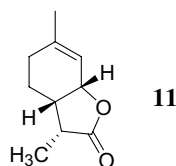
In the last part of this work we studied the calculation of the optical rotatory power of some compounds, which have a high interest as fragrances and aromas. Compound **9** is (+)-α-vetivone, one of the components of the oil of vetiver, an important ingredient in the perfume industry, owing to the unique heavy-sweet, woody and earthy notes of its smell.[15] Only a small part of its CD spectrum has been reported:[20a] a weak, negative Cotton effect ($\Delta\varepsilon - 0.8$ ca.) can be observed between 350 and 300 nm, followed by the onset of a positive Cotton effect. So, rigorously, **9** cannot be considered as a class (a) compound (the lowest-energy CD band is opposite in sign to the optical rotation). However, taking into account the weakness of this Cotton effect, it certainly would provide a small contribution to the $[\alpha]_D$. As a consequence, the case of **9** is similar to that of (+)-**2** discussed above and that **9** can be treated using a small basis set approach.

As can be seen from the data reported below, the experimental value is very satisfactorily reproduced using any small basis set approach. In addition, the

DFT/B3LYP/aug-cc-pVDZ result (which should be by far the best) is not really much better than the DFT/6-31G* result.

9   **(+)-α-vetivone**

[α]$_D$

Exp. (EtOH)	: + 219 [ref. 20b]
HF/6-31G*	: + 176
B3LYP/6-31G*	: + 205
B3LYP/aug-cc-pVDZ	: + 242

(+)-(S,S)-6,10-dimethyl bicyclo[4.4.0]dec-1-en-3-on

[α]$_D$

Exp. (CHCl$_3$)	: + 202 [ref. 20c]
HF/6-31G*	: + 94
B3LYP/6-31G*	: + 96
B3LYP/aug-cc-pVDZ	: + 136

10

Ketone **10** is another α,β-unsaturated compound contained in the vetiver oil although no CD data are known for it. However considering that our simplified treatment is quite successful with the conjugate ketones[8a] we decided to undertake some calculations on this compound as well. The HF/6-31G* approach gave the correct sign and order of magnitude of the optical rotatory power, but only 50% of the numerical value. The DFT results, both at the small and large basis set levels, were not much better than the HF/6-31G* prediction. Wine lactone **11** is a class (a) compound ([α]$_D$ = 112, Δε + 1.6 at 211 nm,[14]) so, following the previous discussion, the small basis set treatment should afford the right answer. In fact, the HF/6-31G* prediction gives +47 (i.e., again correct sign and 50% ca. of the experimental value) and the use of the larger aug-cc-pVDZ basis set slightly improves the result. Here, as it has been already noticed, the DFT results seem more different from the observed value than the corresponding HF predictions.

11

(+)-(3R,3aS,7aR)-wine lactone

[α]$_D$

Exp. (CHCl$_3$)	: + 112 [ref. 16d]
HF/6-31G*	: + 47
HF/aug-cc-pVDZ	: + 65
B3LYP/6-31G*	: + 26
B3LYP/aug-cc-pVDZ	: + 53

In effect, it should be noticed that the ORP is a property very difficult to calculate, because even small changes in the charge distribution induced by several factors (e.g., electron correlation, choice of basis set, molecular vibrations, influence of the solvent) may have significant

effects on the numerical result.[3a,7a,e,21] All these effects can cooperate to give fortuitous cancellation of errors, leading in some cases to HF values better than DFT/B3LYP calculated ORPs. However it is noteworthy that, in all the cases of class (a) molecules, the predicted signs of ORP were correct, in agreement with those found previously.[8a]

The case of the wine lactone **12** was definitely much more complicated, but we can learn a lot from it. First of all this compound has a low ORP (−13[16c]), in addition it does not belong to class (a), because it shows Δε + 1 ca. at 209 nm,[16a] so, following our previous discussion, it is expected that our simplified HF approach will not work in this case. A third difficulty is due to the fact that a conformational search shows that two different conformers, (a) and (b), are possible for **12**, with populations of 71% and 29%, respectively (Fig. 4).
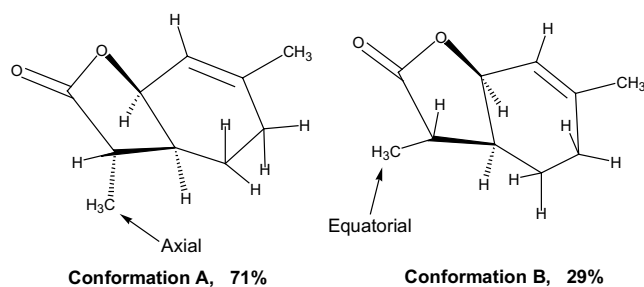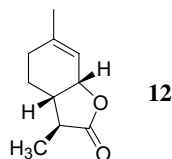

Conformation A, 71%   **Conformation B, 29%**

Figure 4. The most stable two conformations of **12**.

The HF prediction (both at 6-31G* and aug-cc-pVDZ level) gives positive (+14 and +31, respectively) numbers for the major conformer and negative and rather large (−27 and −75, respectively) values for the minor conformer, so the final answer, after a Boltzmann averaging, is +2 or 0, that is, numbers, which cannot be used for a confident configurational assignment. This result confirms our previous conclusion[8a] about the Troeger base: when the lowest energy Cotton effects afford a contribution opposite in sign to [α]$_D$ value, the HF calculation is useless.

Matters were better by means of the DFT/B3LYP method, because the averaged values were −61, both at 6-31G* and aug-cc-pVDZ level; in other words the correct sign is reproduced although the numerical value is certainly overestimated. The reason for such results, which is certainly not appealing from the numerical point of view, can be found by taking into account that the case of **12** is similar to that of (S)-propylene oxide.[8b] In fact, both compounds do not belong to the class (a), the lowest energy Cotton effect is in the far UV (vacuum UV for propylene oxide) that is in a region where the valence shell transitions begin to be accompanied even by Rydberg states.[22] In addition, the absolute value of ORP is low (for the epoxide [α]$_{355}$ = +10). It is noteworthy that the [α]$_{355}$ value of the epoxide has successfully been reproduced only by a very sophisticated and expensive DFT/B3LYP/aug-cc-pVTZ calculation.

12

(-)-(3S,3aS,7aR)-wine lactone
$[\alpha]_D$　Exp. (CHCl$_3$) : **-13** [ref. 16d]

$[\alpha]_D$ for conformation A (71%)
HF/6-31G*	: + 14
HF/aug-cc-pVDZ	: + 31
B3LYP/6-31G*	: **- 49**
B3LYP/aug-cc-pVDZ	: **- 32**

$[\alpha]_D$ for conformation B (29%)
HF/6-31G*	: - 27
HF/aug-cc-pVDZ	: - 75
B3LYP/6-31G*	: - 91
B3LYP/aug-cc-pVDZ	: - 133

$[\alpha]_D$ (Boltzmann average)
HF/6-31G*	: + 2
HF/aug-cc-pVDZ	: 0
B3LYP/6-31G*	: - 61
B3LYP/aug-cc-pVDZ	: - 61

3. Conclusions

The main result of the present investigation is that the criterion formulated in our previous paper[8a] certainly to decide when a small basis set calculation (at the HF or, better, at the DFT level) can be confidently used to assign the AC by means of the OR prediction is fully confirmed, that is, if the low energy Cotton effects dominate the $[\alpha]_D$ in sign and magnitude, we shall have a safe answer even from such a simplified calculation. At this stage somebody could argue that, knowing the CD spectrum, one could attempt the AC assignment, directly predicting the CD spectrum itself. A CD calculation, even using semiempirical methods, requires the introduction of a shape factor, in order to compare the overall shape of the experimental spectrum with the predicted one. This comparison is often not so easy because a large number of near-in-frequency and opposite-in-sign transitions may derive. Therefore, such an approach can only be practical when the CD spectrum presents a well defined, isolated Cotton effect, so the problem of the shape of the spectrum can be avoided: a representative case is that of the saturated ketones, which have a low-energy 290 nm band, well separated from other Cotton effects.[3i] In the case of OR prediction we simply have to compare (sign and order of magnitude) a single number, which, in addition, at least in the cases similar to those described in this paper, is obtained in a reasonably time of calculation, even for large molecules. Furthermore, the availability of GAUSSIAN 03 makes DFT calculations easily accessible, so DFT/GIAO calculations can be carried out: this guarantees origin independence of the OR results even using small basis sets,[3a,c] therefore for case (a) molecules, such simplified treatments are reliable. As a consequence a strong reduction of the computational effort occurs, allowing also the treatment of large molecules. We have shown the utility, for the experimental organic chemist, of this kind of method to carry out configurational assignments because in this way we can deal with even large compounds (i.e., bulbocapnine, 60 atoms ca.). In addition, see our discussion about (+)-griseofulvin; if the experimental value of the rotatory power is large enough (say, 100 units or more) it may be possible to use even lower levels of theory in establishing input geometries and/or ORP values. These results are certainly very important for the experimental organic chemist without much expertise in computational techniques: such predictions can be done on a common desktop computer in a few hours. On the contrary, when the experimental $[\alpha]_D$ values are small numbers, the problem is more difficult because small optical rotations can derive (the case of **12** is particularly illustrative) from high-energy Cotton effects (which require the intervention of extended basis sets with diffuse functions) or from the existence of different conformers having opposite (even large) OR, so the small experimental number is the result of a sum of different contributions. Here the conformer distribution becomes a critical parameter while the role of the solvent in deciding it may be very important. Clearly, such cases require the use of high-level methods. In conclusion, the results of this investigation clearly show that the ab initio calculation of ORP constitutes a new and reliable method for the AC assignment, which is already available even to the experimental organic chemists without any expertise in computational chemistry.

4. Computational details

The molecular structure optimisation and the conformational search have been performed at DFT/B3LYP/6-31G* level, using the GAUSSIAN 98 code.[23] For the two conformers of **1**, the equilibrium geometries have been calculated also by AM1 semi-empirical method and MMFF94 molecular mechanics force field. Time-dependent HF/SCF calculations of ORP have been carried out adopting STO-3G (only for **1**) and 6-31G* basis sets, by means DALTON 1.2 package,[24] while time-dependent DFT/B3LYP/6-31G* by means of GAUSSIAN 03 package.[23] Origin independence of optical rotations is ensured by the using a gauge-invariant (including) atomic orbitals (or GIAOs), also know as London orbitals. For **1**, **6**, **7**, **8**, **9**, **10**, **11** and **12**, the time-dependent DFT/aug-cc-pVDZ ORP value has been reported as well. In these cases, the B3LYP functional has been used, as implemented in the TURBOMOLE 5.6 package,[25] with the origin dependence the results expected to be negligible for the (large) aug-cc-pVDZ basis set. It should be noted that Turbomole works only in the length formalism (providing origin-dependent results) when hybrid functionals (e.g., B3LYP) are used. The velocity formalism is allowed only with pure (e.g., BLYP) functionals, that, generally, as reported in Ref. 7b and found in some test calculations, provide less accurate predictions of the optical rotation. It is inter-

esting to note that the computational complexity of the method herein employed is proportional to the 4th power of the basis set size. It is easy to see that a 6-31G* basis set calculation is 16 times faster than an aug-cc-pVDZ basis set calculation, the former basis set being roughly half the size of the latter. In addition, the computer time should not be the only parameter taken into account, that is, the memory requirement could be so high, even for a medium sized organic molecule adopting a large basis set, to make the calculation not feasible at all, at least on a desktop PC.

5. Experimental section

UV and CD spectra for **1** and **2** were recorded in methanol and chloroform solution, respectively, on a JASCO J-600 spectropolarimeter. Optical rotations at sodium D line were measured in the same solvents with a JASCO DIP-370 digital polarimeter.

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