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Ab Initio Calculation of Optical Rotatory Dispersion (ORD) Curves: A Simple and Reliable Approach to the Assignment of the Molecular Absolute Configuration

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Abstract: In this paper, both Hartree−Fock (HF) and density functional theory (DFT) methods have been used to make ab initio calculations of the optical rotatory power of selected molecules at several wavelengths; that is, part of the optical rotatory dispersion (ORD) curve has been predicted. This approach constitutes a new, simple, and reliable method to assign the molecular absolute configuration, at least for rigid molecules such as those studied in the present work. In fact, in this way, it is possible to overcome the difficulties connected to some relevant cases, in particular that of (−)-β-pinene, for which even a very high-level (DFT/B3LYP/6-311++G(2d,2p)) calculation affords the wrong sign of the optical rotation at 633 nm. On the contrary, the predicted ORD curve, even using small basis sets, reproduces (below 400 nm) the experimental trend well, allowing for the correct configurational assignment. This result clearly shows that to have a reliable configurational assignment the comparison between experimental and predicted rotation values must be carried out at different wavelengths and not at a single frequency. The reason for this is that working at wavelengths approaching the absorption maximum the $[\alpha]_\lambda$ values become larger and their prediction becomes more reliable. Coupling the use of an inexpensive instrument (a polarimeter working at a few wavelengths) with the use of a DFT-calculation package can also allow the experimental organic chemist to arrive, quickly and reliably, at the assignment of the molecular absolute configuration.

Introduction

Thanks to recent progress in computational methods, the ab initio prediction of optical rotation (OR) is now possible,[1−7] and therefore, the theoretical assignment of the molecular absolute configuration (AC) could be carried out, taking into account that, for instance, the OR at the sodium D line, that is, the most common parameter to label optically active compounds, can be reliably calculated. According to the general theory,[8−10] the OR is obtained as the specific rotation $[\alpha]_\lambda$, for each angular frequency $\omega = 2\pi\nu = 2\pi c/\lambda = 2\pi c\bar{\nu}$ of the incident radiation, through the calculation of the optical parameter β, which is directly connected to the trace of the frequency-dependent electric dipole-magnetic dipole polarizability tensor $\mathbf{G}'$, that is

$$[\alpha]_\lambda = \frac{1.34229 \times 10^{-4}\beta\bar{\nu}^2(n^2+2)}{3M}$$

$$\beta = -\frac{1}{3\omega}\mathrm{Tr}[\mathbf{G}'(\omega)]$$

$$G'_{\alpha\beta}(\omega) = -\frac{4\pi}{h}\sum_{j\neq 0}\frac{\omega}{\omega_j^2 - \omega^2}\mathcal{R}\langle\langle 0|\hat{\mu}_\alpha|j\rangle\langle j|\hat{m}_\beta|0\rangle\rangle$$

where the specific rotation is in unit of deg[dm(g/cm^3)]$^{-1}$, β is in bohr^4, the radiation wavenumber is in cm^{-1}; n is the refractive index of the medium, M is the molar mass in g/mol; ω_j is the

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transition frequency from ground state $|0\rangle$ to excited state $|j\rangle$, $\hat{\boldsymbol{\mu}}$ and $\hat{\boldsymbol{m}}$ are the electric and magnetic dipole operators, respectively.

It is recognized by some authors[3a,7a,7d] that at the sodium D line β is, in general, a small quantity because two of the diagonal components of $\mathbf{G}'$ almost cancel the third one. As a consequence, even small changes in the electronic distribution may produce rather large contributions to the OR computed value. Such changes may be induced by several factors, for example, the choice of basis set, electron correlation, solvent effect, equilibrium geometry, vibrational contributions, and the effect of dispersion passing from a static to a dynamic approach. All of these effects have been deeply explored and found to be very significant and also sometimes cooperate to give fortuitous cancellation of errors.[1a,3a−c,4b,4c,7a,7b] Currently, there seems to be a general agreement on the computational requirements needed for reliable OR predictions,[1g,3c,4a,7b] that is, the use of a dynamic method together with a proper treatment of the electron correlation and the use of large basis sets containing diffuse functions. Within these respects, the recently introduced cavity ring-down polarimetry (CRDP)[6a,7b] for probing, with unprecedented sensitivity, the circular birefringence and circular dichroism in the gas phase marks the beginning of a new era of OR measurements and possibly of absolute configuration assignments, as almost homogeneous comparison between experimental and theoretical results can now be done, for example, the case of (*S*)-propylene oxide.[11] Furthermore, we have recently shown[12] that even HF/small basis set (for example, a HF/6-31G*) calculations can be employed for a reliable calculation of OR (at least in the cases of highly unsaturated and/or aromatic molecules possessing low-lying Cotton effects, determining the OR at the sodium D line in sign and order of magnitude). The numerical agreement between predicted and experimental values is poorer with respect to the above-quoted calculations,[1g,3c,4a,7b] but the sign and order of magnitude of OR are correctly reproduced. In addition, this simplified treatment can also be applied to the case of large molecules, which cannot be dealt with using extended basis sets, but these are the real target of interest for experimental chemists. All of these considerations clearly strengthen the expectation that such calculations, affording a correct value of the optical rotatory power, constitute a reliable method to assign the molecular absolute configuration. However, the HF/small basis set approach does not work properly[12] for a simple molecule that fulfils the criterion reported above, that is, (+)-camphor, because the wrong sign of OR is predicted by a HF/small basis set treatment. In addition, a recent paper[6c] by Vaccaro et al. pointed out that even a very accurate treatment can fail: this is the case of (−)-β-pinene, for which a DFT/B3LYP/6-311++G(2d,2p) calculation affords +21 (at 633 nm), but the experimental value, in the gas phase, is −17. These facts throw some doubts on the reliability of these calculations. Therefore, in this paper, we approached the problems related to the OR calculation of these and other molecules to understand when we can trust the ab initio prediction of the OR to solve one of the most important problems of organic stereochemistry, that is, the assignment of the absolute configuration.[13] In summary, the present paper is organized as follows. First, we show that a reliable calculation of the optical rotary power at the sodium D line (i.e., far from the absorption region of the most common organic molecules) is a difficult task, taking into account the smallness of the β value (the parameter that determines the sign and magnitude of $[\alpha]_\lambda$). One way to have larger (and more easily predictable) β values is to approach the absorption region of the molecule under investigation: this clearly suggests that the calculation of the optical rotation at several wavelengths (instead of at a single frequency) and the comparison with the corresponding experimental data certainly constitute a safer way to assign the absolute configuration. This conclusion is not new: Sjoberg and co-workers showed[14] experimentally, as early as 1955, that a comparison of chiroptical data made on several wavelengths affords a more reliable answer than a comparison at a single wavelength, as far as the configurational assignment is concerned. However, such criterion did not find a systematic application in the field of AC assignment by the ab initio calculation of OR: only the AC of (−)-2,8,9-trihydroxy-3,4-dihydro-2*H*-anthracen-1-one has been assigned just doing the calculation[2h] at three different wavelengths. So, in the second section of this paper, for the first time, a systematic use of the prediction of ORD curves and their comparison with experimental data for AC assignments will be made. To this end, we shall not only employ the DFT/B3LYP method, which, following Stephens and co-workers,[3c] has to be considered as the method of choice but also describe the results of the corresponding HF computations to try to understand the reasons of its failure. As it will be clear later, we shall calculate the ORD curves near to but not at the frequency of the resonance, following a protocol first introduced by Polavarapu,[1f] which assumes the infinite-lifetime approximation. The calculation of the ORD in the resonant frequency region has been presented by Ruud et al.[7f] only this year.

Results and Discussion

Smallness of β. In this section, we will start showing that the accurate $[\alpha]_\lambda$ calculation is really a difficult task when carried out at wavelengths far from the absorption region, whereas the OR values predicted at wavelengths that approach

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Table 1.

molecule	method	$\omega^{-1}G'_{xx}$	$\omega^{-1}G'_{yy}$	$\omega^{-1}G'_{zz}$	β	$[\alpha]_D$
H_2O_2 ($\varphi = 120°$)	HF	−1.138	0.198	0.891	0.016	18.4
	B3LYP	−1.201	0.387	0.960	−0.049	−55.3
(+)-propylene oxide	HF	−0.754	−0.736	1.447	0.014	9.5
	B3LYP	−0.820	−0.812	1.587	0.015	10.2
(−)-dimethylallene	HF	5.949	−3.259	−2.066	−0.208	−118.2
	B3LYP	5.850	−4.687	−0.438	−0.241	−137.0
(+)-camphor	HF	0.408	2.925	−3.450	0.039	9.8
	B3LYP	0.240	4.891	−5.847	0.239	60.6
(−)-Troeger's base	HF	−60.688	91.855	−31.037	−0.043	−6.7
	B3LYP	−72.442	116.468	−37.053	−2.324	−358.9

the absorption region are more likely to be reliable. Therefore, the calculation of OR at several wavelengths that approach the absorption region could afford a configurational assignment that is safer than that obtained through a prediction at a single frequency. Usually, in reporting OR calculations, little attention is devoted to the diagonal component of the $\mathbf{G}'$ (see refs 3a and 7d for a few exceptions), and almost exclusively $[\alpha]_D$ results are given. At the sodium D line, quite frequently, two of the $\mathbf{G}'$ diagonal components almost cancel the third one, and as a consequence, error propagation may produce a serious effect ending with a quite large relative error on β. To illustrate this point we compare in Table 1 the HF and DFT/B3LYP diagonal components and the average value of the ω^{-1} $\mathbf{G}'$ tensor, computed at 589.3 nm, adopting the fairly good Sadlej polarizability consistent basis set,[15] for some test molecules. Obviously, neither of the two methods provides exact solutions, but some indications about the effect of changing the electron distribution can be clearly seen.

As a rule, for all cases, two diagonal tensor components are positive (or negative), almost cancelling the third one, giving a relatively small β. Going from HF to DFT/B3LYP, the following can be observed: (i) a sign change of β, despite a substantial agreement between tensor components, as in the simple case of H_2O_2; (ii) a good coincidence of the results, as in propylene oxide; and (iii) a fortuitous agreement of the predicted optical rotations because a large discrepancy between some of the tensor components exists, as in the case of (−)-dimethylallene. For (+)-camphor, the ratio between HF and DFT/B3LYP tensor components is as large as 1.7, whereas the ratio between the OR predictions is much larger (>6). The case of (−)-Troeger's base is quite instructive: the agreement between HF and DFT/B3LYP tensor components is within 22% on average, whereas the DFT/B3LYP optical rotation is more than 50 times larger than the HF value.

Taking into account the previous theoretical works on OR determination,[3,4,7] there is nothing new about the comparison between HF and DFT/B3LYP results; here, we would remark that to obtain accurate OR predictions time-dependent correlated methods and high-quality (at least aug-cc-pVDZ) basis sets are required mainly because of the smallness of β, due to the near cancellation of the $\mathbf{G}'$ diagonal components. This fact is so general that it deserves to be justified in some way. From the definitions of β and $\mathbf{G}'$ one has

$$\beta(\omega) = \frac{4\pi}{3h}\sum_{j\neq 0}\frac{1}{\omega_j^2 - \omega^2}\mathcal{I}(\langle 0|\hat{\boldsymbol{\mu}}|j\rangle\cdot\langle j|\hat{\mathbf{m}}|0\rangle) \qquad (1)$$

and within the static limit ($\omega = 0$)

$$\beta(0) = \frac{4\pi}{3h}\sum_{j\neq 0}\frac{1}{\omega_j^2}\mathcal{I}(\langle 0|\hat{\boldsymbol{\mu}}|j\rangle\cdot\langle j|\hat{\mathbf{m}}|0\rangle)$$

Now, assuming an approximation introduced in the past to compute several kinds of second-order molecular properties,[16] which consists of choosing an average excitation energy $\Delta\omega$ for all states, the last expression can be rewritten as

$$\beta(0) \approx \frac{4\pi}{3h}\frac{1}{\Delta\omega^2}\sum_{j\neq 0}\mathcal{I}(\langle 0|\hat{\boldsymbol{\mu}}|j\rangle\cdot\langle j|\hat{\mathbf{m}}|0\rangle)$$

The sum on the rhs of the above equation is vanishing because of Kuhn's sum rule for the rotatory strengths.[8,9] Of course, β is not totally vanishing because the approximation of the average excitation energy is a quite crude one. However, this justifies the smallness of β, especially for the static limit, that is, far from resonance. Hence, one way to obtain more reliable β values, that is, smaller relative errors, would be to get far away from the static limit and, even better, making ω approach a transition frequency, for example the first one. Obviously, the smaller the denominator in the equation giving β is, the larger the absolute value of all three diagonal components of $\mathbf{G}'$ will be; simultaneously, the latter will not have the tendency to cancel out when summed together, and then the magnitude of β will increase as observed. This suggests computing the OR dispersion curves, or at least the OR at several wavelengths, to appreciate the trend of the results, which is opposite for two enantiomers. To this end, the adopted method of calculation should provide, at least, the correct sign of the rotational strength associated with the first Cotton effect. This is a less difficult task than the OR calculation at a single wavelength because even the HF method usually gives the correct answer. However, it should be mentioned that the HF transition frequencies are very often largely shifted toward high energy[11,17] and, as a consequence, the HF OR dispersion curves are blue shifted by an amount that can be as large as 100 nm even when adopting large basis sets. However, the approach discussed in the following is general and can be employed at any level of theory; in particular, small basis set DFT/B3LYP OR dispersion curves could be very useful in the case of large organic molecules. So, in the following discussion, we shall use this approach to carry out ab initio calculations of OR at single frequencies and of ORD curves for some selected molecules.

Synthesis, Measurements, and Calculations. The test molecules chosen (Table 2) are all rigid systems (to avoid

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Table 2.

1a

(-)-verbenone
(-)-4,6,6-Trimethyl-bicyclo[3.1.1]hept-3-en-2-one
$[\alpha]_D$ exp. (hexane) : - 180
HF/ 6-31G* : - 144
B3LYP/ 6-31G* : - 251

1b

(-)-4-methylverbenene
(-)-2,6,6-Trimethyl-4-methylene-bicyclo[3.1.1]hept-2-ene
$[\alpha]_D$ exp. (hexane) : - 40
HF/ 6-31G* : - 105
B3LYP/ 6-31G* : - 121

2a

(-)-fenchone
(-)-1,3,3-Trimethyl-bicyclo[2.2.1]heptan-2-one
$[\alpha]_D$ exp. (hexane) : - 44
HF/ 6-31G* : - 67
B3LYP/ 6-31G* : - 85

2b

(-)-methylenefenchone
(-)-1,3,3-Trimethyl-2-methylene-bicyclo[2.2.1]heptane
$[\alpha]_D$ exp. (hexane) : - 68
HF/ 6-31G* : - 85
B3LYP/ 6-31G* : - 99

3a

(+)- camphor
(+)-1,7,7-Trimethyl-bicyclo[2.2.1]heptan-2-one
$[\alpha]_D$ exp. (hexane) : + 59
HF/ 6-31G* : - 6
B3LYP/ 6-31G* : + 23

3b

(-)-methylenecamphor
(-)-1,7,7-Trimethyl-2-methylene-bicyclo[2.2.1]heptane
$[\alpha]_D$ exp. (hexane) : - 36
HF/ 6-31G* : - 57
B3LYP/ 6-31G* : - 50

4a

(+)-nopinone
(+)-6,6-Dimethyl-bicyclo[3.1.1]heptan-2-one
$[\alpha]_D$ exp. (hexane) : + 7
HF/ 6-31G* : + 1
B3LYP/ 6-31G* : + 13

4b

(-)-β-pinene
(-)-6,6-Dimethyl-2-methylene-bicyclo[3.1.1]heptane
$[\alpha]_D$ exp. (hexane) : - 15
HF/ 6-31G* : - 5
B3LYP/ 6-31G* : + 27
B3LYP/ Sadlej : + 25

5

(-)-Troeger's base
(-)-2,8-Dimethyl-6*H*,12*H*-5,11-methano-dibenzo[*b*,*f*][1,5]diazocine
$[\alpha]_D$ exp. (hexane) : - 267 (- 287 [3c])
HF/ 6-31G* : + 134
HF/ aug-cc-pVDZ : + 5 [3c]
B3LYP/ 6-31G* : - 165

difficulties coming from the conformational flexibility) having known absolute configuration. Furthermore, it is interesting to note that compounds **1a**−**4a** are ketones, and **1b**−**4b** are the corresponding olefins. So, we have pair of molecules (**a** and **b**) where different chromophores are inserted in the same chiral backbone. In addition, in the case of non-comercially available molecules (such as **1b**, **2b**, and **3b**), they have been obtained from the corresponding ketone (**1a**, **2a**, and **3a**). The

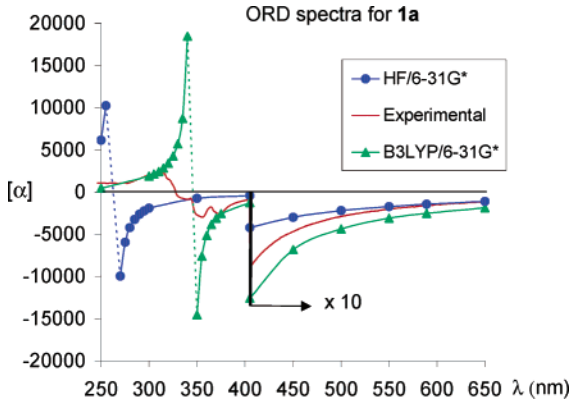

Figure 1. Experimental (−) and predicted (●, HF/6-31G*; ▲, B3LYP/6-31G*) ORD curves for **1a**. The experimental ORD curve has been measured in hexane.

synthesis of (−)-**3b** has been carried out by Wittig olefination starting from commercial (+)-**3a**.[18] For the synthesis of (−)-**1b** and (−)-**2b**, we used the same procedure starting, respectively, from commercial (−)-**1a** and (−)-**2a**. All the $[\alpha]_D$ values reported in Table 2 have been measured in hexane solution at $c \approx 1$ g/100 mL, which is the concentration mostly used by experimental organic chemists (in the case of (−)-**5** only the concentration is 0.6 g/100 mL): the solvent choice has been made taking into account that hexane is the best solvent[3c] to compare experimental values and the calculated results for the isolated molecule. For the same reason, all of the ORD spectra have also been measured in hexane solution. Our analysis starts considering verbenone **1a** and corresponding diene **1b**.

It is noteworthy that to the best of our knowledge **1b** is reported for the first time in an optically active form. We have chosen these two molecules on the basis of the reasoning that they are both rigid, have the same chiral skeleton, and differ only in the nature of chromophoric system (α,*β*-unsaturated ketone in **1a** and a conjugated diene in **1b**). In addition, for both of these compounds, the optical rotatory power at 589.3 nm is determined in sign and order of magnitude by low-lying Cotton effects (i.e., they belong to case a)),[12] so for them, an HF/small basis set treatment should afford the correct value of OR. Table 2 clearly shows that the optical rotatory power is correctly calculated in sign and order of magnitude also in the case of **1b**, which possesses a low OR value. The calculated ORD curves (HF and DFT/B3LYP, small basis set, together with the experimental ones in hexane) of **1a** and **1b** are reported in Figures 1 and 2, respectively. The experimental ORD curve of **1a** presents a clearly negative Cotton effect centered at ∼350 nm, whereas for **1b**, only a negative plain curve is measured down to 250 nm. It is quite easy to note that the experimental trend is correctly reproduced by the calculations. However, an important aspect must be pointed out: the HF result gives an ORD curve that is substantially blue shifted with respect to the experimental one, whereas the DFT/B3LYP result is much better. This it is quite evident for **1a**. The behavior of the HF curve is in agreement with the intrinsic features of this uncorrelated method, which usually provides electronic excitation energies at shorter wavelengths.[17] Moreover, it should be pointed out that both time-dependent HF and DFT methods adopted here are not suitable for making predictions in cor-

(18) Money, T.; Palme, M. H. *Tetrahedron: Asymmetry* **1993**, *4*, 2363.

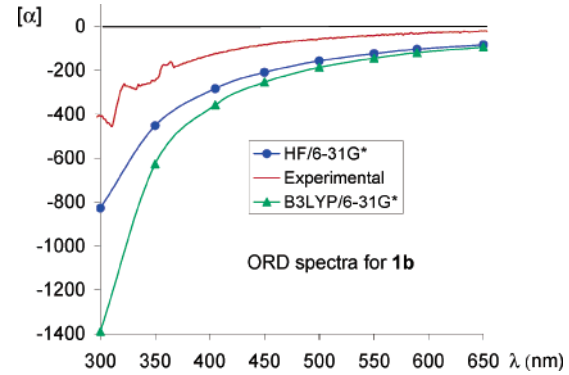

Figure 2. Experimental (—) and predicted (●, HF/6-31G*; ▲, B3LYP/6-31G*) ORD curves for **1b**. The experimental ORD curve has been measured in hexane.

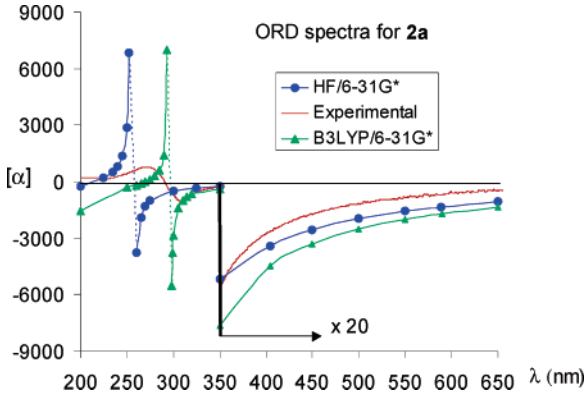

Figure 3. Experimental (—) and predicted (●, HF/6-31G*; ▲, B3LYP/6-31G*) ORD curves for **2a**. The experimental ORD curve has been measured in hexane.

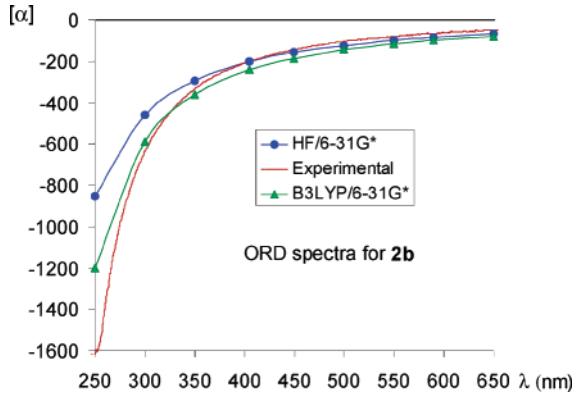

Figure 4. Experimental (—) and predicted (●, HF/6-31G*; ▲, B3LYP/6-31G*) ORD curves for **2b**. The experimental ORD curve has been measured in hexane.

respondence to an electronic resonance; in fact, the calculation of the ORD in the resonant frequency region has been made possible by Ruud et al.[7f] only this year. Therefore, we limit our discussion to only the portion of ORD curve that approaches the resonance.

The same comments, about rotatory power and ORD calculations, can be made in the case of **2a** and **2b**, that is, a saturated ketone and a simple olefin, which again, belong to case a but have much simpler chromophores and lower OR values than **1a**. The values of OR are collected in Table 2, and the ORD curves are reported in Figures 3 and 4, respectively. The data in Table 2 clearly show that the $[\alpha]_D$ values of **2a** and **2b** are correctly reproduced (sign and order of magnitude) at a small

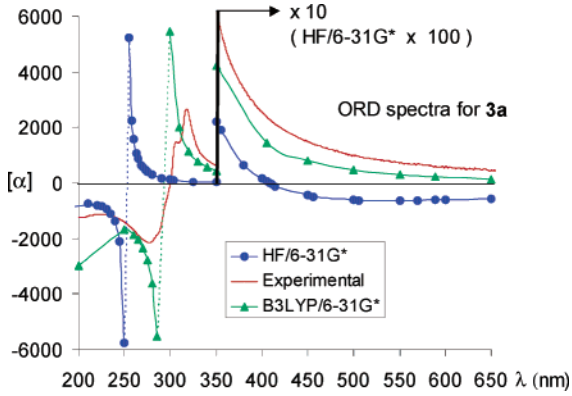

Figure 5. Experimental (—) and predicted (●, HF/6-31G*; ▲, B3LYP/6-31G*) ORD curves for **3a**. The experimental ORD curve has been measured in hexane.

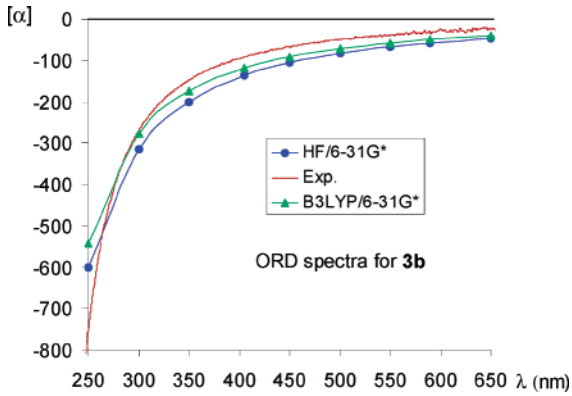

Figure 6. Experimental (—) and predicted (●, HF/6-31G*; ▲, B3LYP/6-31G*) ORD curves for **3b**. The experimental ORD curve has been measured in hexane.

basis set level, both using the HF and DFT/B3LYP methods. Again, the Cotton effect of **2a** at 300 nm is very well reproduced by DFT/B3LYP calculation, whereas the HF method, even if it gives the correct negative Cotton effect, provides a considerable blue shift (Figure 3). It is also noteworthy that the experimental ORD curve of **2b** is very well reproduced both at the DFT/B3LYP and HF level (Figure 4).

Also in the case of **3b**, everything is working very well: OR at 589 nm (Table 2), HF/ORD and DFT/ORD as reported in Figure 6. This result is not surprising, taking into account that **3b** is a case a) molecule as well. The case of **3a** is really interesting; in fact, as we discussed in the Introduction, only a DFT approach (even with a small basis set) provides[3c] the correct OR value at 589 nm: these results are collected in the Table 2. Of course, the ORD curve calculated within a DFT scheme (Figure 5) reproduces very well the experimental data. However, even the HF/small basis set ORD curve gives a trend very similar to the experimental one, the only difference being that at wavelengths longer than 409 nm the predicted and the experimental curve are opposite in sign, in agreement with the discussion about the smallness of β far from the resonance, previously given. This means that the calculation of the optical rotation in a range of wavelengths, that is, a part of an ORD curve, when compared to the experimental one, constitutes a safer tool for configurational assignment. At this stage some comments are needed: first of all, a calculation using a small basis set guarantees a fast answer, so it is certainly more convenient to repeat such a calculation several times to obtain

at least a short ORD curve rather than to do a prediction at a single frequency but using an extended basis set. In fact, considering that the computational complexity of the available methods is proportional at least to the 4th power of the basis set size, it is easy to see that sixteen 6-31G* basis set calculations take the same amount of time as a single aug-cc-pVDZ basis set calculation, with the former basis set being roughly half the size of the latter. In addition, the computer time is not the only parameter to take into account; that is, the memory requirement could be so high, even for a medium-size organic molecule adopting a large basis set, to make the calculation not feasible at all, at least on a desktop PC. Second, the ORD HF/small basis set calculation on (+)-camphor affords the right answer because we penetrate in the n−π* Cotton effect, and clearly in this range, the OR values are determined by this CD band only; in other words even (+)-camphor becomes a true case a) molecule. This could suggest the real trick to do reliable OR calculations: using wavelengths that are sufficiently near to a Cotton effect so that the sum in the Rosenfeld eq 1 is dominated by a single term and the problem of the smallness of β is overcome, see the discussion about the smallness of the β parameter given previously. This is particularly true in this case, where we are dealing with a valence-shell Cotton effect (because of an n−π* transition), and thus, even the use of a 6-31G* basis set is sufficient (the calculated rotational strength for the n−π* transition of **3a** at HF/6-31G* level is +1.8 × 10^{-40} (erg esu cm/Gauss) versus an experimental value of +2.4 × 10^{-40}). Third, now we can understand why the OR calculation at 589.3 nm is wrong with the HF/6-31G* approach: the use of this basis set, although it is sufficient to give the right sign of the 290 nm CD band, places this Cotton effect at about 250 nm; that is, it is blue shifted, with respect to the experimental CD band, about 40 nm. This means that its positive contribution to the $[\alpha]_D$ value can be overcome by a negative contribution coming from shorter wavelength CD bands. By contrast, the DFT method places this Cotton effect in the right position on the wavelength scale, and therefore now its contribution to $[\alpha]_D$ cannot be overcome by negative contributions coming from higher energy CD bands. In addition, this basis set may introduce tremendous errors in reproducing the higher-energy Cotton effects, so the sum in the Rosenfeld eq 1 provides a wrong result. In other words, at 589.3 nm, β is a very small number, its magnitude is smaller than the computation uncertainty, and its sign could be wrong, which actually happens. On the contrary, near 290 nm, the **G′** tensor is determined predominantly by a strong contribution from the n−π* transition, and because the β value is a large number, its magnitude is larger than its computation uncertainty, and the sign is safely predicted. The cases of **4a**, (+)-nopinone, a saturated ketone, and corresponding alkene **4b**, (−)-β-pinene, are even more illustrative. In the case of **4a**, the experimental rotation is a small number (for this reason this molecule constitutes a difficult problem), and the numbers produced by HF/6-31G* calculations are even smaller (Table 2), so a clear answer cannot be given. The DFT calculations are certainly better. However, the prediction (both at the HF and DFT level) of the ORD curves eliminates any doubt (Figure 7). For **4b**, (Table 2) we have that the predicted B3LYP values both at the small (6-31G*) and large (Sadlej) basis set level afforded the wrong sign. The correct (in sign) result obtained at the HF/6-31G* level is certainly fortuitous,

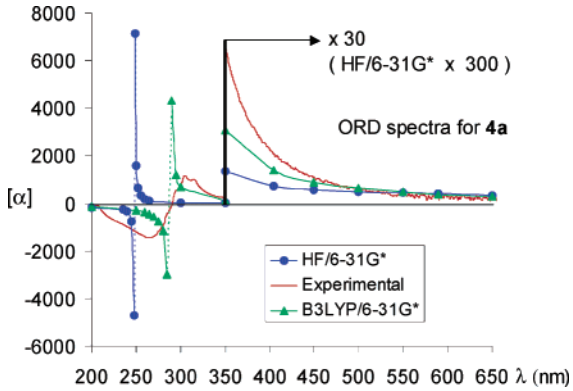

Figure 7. Experimental (—) and predicted (●, HF/6-31G*; ▲, B3LYP/6-31G*) ORD curves for **4a**. The experimental ORD curve has been measured in hexane.

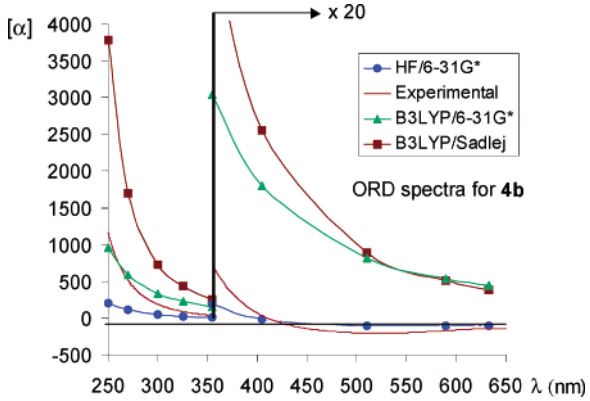

Figure 8. Experimental (—) and predicted (●, HF/6-31G*; ▲, B3LYP/6-31G*; ♦, B3LYP/Sadlej) ORD curves for **4b**. The experimental ORD curve has been measured in hexane.

considering that London and non-London calculations afford predictions that are opposite in sign. Most importantly, even the DFT/B3LYP/6-311++G(2d,2p) calculation affords the wrong answer (at λ = 633 nm, the calculated value is +21 and the experimental value is −17); note that here, we are comparing the theoretical prediction with an experimental value measured in gas phase, hence no solvent effects are present. We have calculated the ORD curve of **4b** at DFT/B3LYP/Sadlej level obtaining a curve which reproduces very well the experimental ORD trend (Figure 8). We used the DFT/B3LYP method and the Sadlej basis set because we reported[11] that this approach works very well for the OR calculation. It is interesting to note that at 589.3 nm this method also gives the wrong result, and only at wavelengths shorter than 400 nm, the sign of OR is correctly reproduced, pointing out again that the calculation of an ORD spectrum affords the right configurational answer. It is even more interesting and important to note that even an HF or DFT/B3LYP calculation using a small basis set (6-31G*) reproduces (Figure 8) the experimental shape (at least below 350 nm), confirming the power and reliability of ORD calculation for configurational assignments. It is important, at this stage, to note that **4b** (and **5**, vide infra) in contrast to the previous **1a**−**4a** does not belong to the above-defined case a) molecules.[12] In fact, the CD spectrum of (−)-β-pinene **4b** in the gas phase shows,[19] between 220 and 170 nm, a sequence of positive/negative bands, whereas in the hexane solution, only the positive Cotton effect is measurable. As a consequence, the contribution of this Cotton effect to the OR at 589 nm is +170 versus an

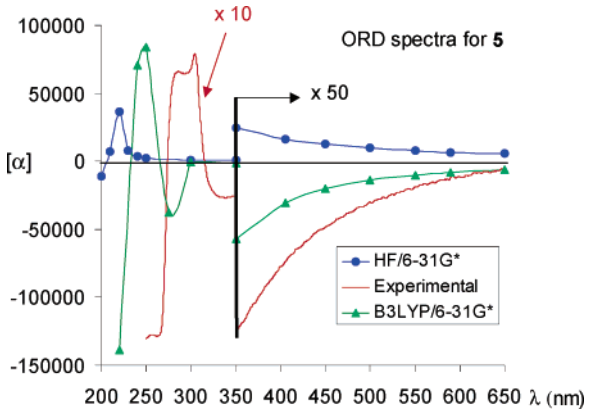

Figure 9. Experimental (−) and predicted ●, HF/6-31G*; ▲, B3LYP/6-31G*) ORD curves for **5**. The experimental ORD curve has been measured in hexane.

experimental value of −15, indicating clearly that higher Cotton effects determine the sign of $[\alpha]_D$. Thus, the case of this molecule is deeply different from that of **2b** and **3b**, for which a very good agreement between the experimental and calculated values is found. In other words, although **2b** and **3b** belong to class a) (see above) and for them even a simplified treatment gives the correct answer, it could be possible to predict a lot of difficulties for the OR calculation at 589 nm in the case of (−)-β-pinene (**4b**) because $[\alpha]_D$ is determined (sign and magnitude) by shorter-wavelength CD bands.

An additional interesting comment can be made concerning (−)-Troeger's base **5**. For this compound, the OR computation by the DFT/B3LYP method gives satisfactory results (see Table 2), whereas the HF calculation (even when using quite large basis sets, such as aug-cc-pVDZ) always produces the wrong sign. For this reason, Stephens et al. pointed out[3c] that we can trust only in OR calculations carried out by the DFT/B3LYP method. In a previous paper, we suggested[12] that because (−)-Troeger base presents a very intense, positive, low-lying CD band that provides a strong (+200), positive contribution to the optical rotation at 589.3 nm, it is absolutely required to have a correct description of the higher-energy Cotton effects, so a method that is more accurate than HF is needed. In Figure 9, we report the experimental ORD curve (hexane) together with those calculated by the DFT/B3LYP/6-31G* method: clearly a satisfactory reproduction of the experimental data is provided, at least down to 350 nm. At shorter wavelengths, the sequence (−, +, −) of the Cotton effects is correctly reproduced, even if a blue shift of about 50 nm (of the predicted curve with respect to the experimental one) is observed. It is noteworthy that a simple HF/6-31G* computation reproduces the experimental ORD trend only below 300 nm. Here, the blue shift (of the calculated vs experimental curve) is more than 80 nm. The above results clearly show the limitations of ORD protocol at Hartree−Fock level, and it seems that a DFT/B3LYP calculation at several wavelengths could be the method of choice to reach a reliable AC assignment, also within a small basis set scheme, which is necessary to deal with medium−large size molecules, as the biological active ones, that is, the largest part of molecules having practical interest. We are now able to propose a simple and reliable protocol to assign the molecular absolute configuration of an organic unsaturated and/or aromatic (i.e., absorbing in the near-UV region) compound, by means of ab initio calculation of the optical rotatory power. The first step is measuring the experimental ORD curve in a suitable range of wavelengths and the second step is calculating the ORD curve in the same range of frequencies by means of the DFT/B3LYP/6-31G* method. This approach will couple the better accuracy of the DFT method (with respect to the HF one) in terms of wavelength position of the individual Cotton effects, allowing a simple comparison with the experimental data, with the speed of the calculation, even if it is repeated several times.

Conclusions

The main result of this investigation is that the calculation of the OR repeated at different wavelengths (prediction of the ORD curve) constitutes a reliable method for the assignment of the molecular absolute configuration. One could argue that this approach strongly depends on the measurement of the ORD curve, which nowadays is not so easy to obtain because modern chiroptical spectroscopy is mainly based on circular dichroism. However, it must be noticed that modern polarimeters[20] allow us to make OR measurements at several wavelengths and thus, the availability of OR values at some different wavelengths could be a simple alternative to the measurement of a continuous ORD spectrum. Moving at shorter wavelengths, we go nearer to absorption regions, which may guarantee that we are approaching a single Cotton effect with the consequent reduction of the contributions due to the other Cotton effects in the Rosenfeld sum; this leads to a larger β, and, hence, a most reliable predicted OR value. Another criticism could be that one could attempt the AC assignment directly predicting the CD spectrum itself. A CD calculation requires the introduction of a shape factor to compare the overall shape of the experimental spectrum with the predicted one; often, this comparison in not so easy because a large number of near-in-frequency and opposite-in-sign transitions may derive. Therefore, such an approach can be safely used only 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 present approach, we have simply to compare a few numbers (experimental and predicted OR, at different wavelengths), which, in addition, at least in the cases similar to those described in this paper, are obtained in a reasonable time of calculation. One could also argue that in this paper we have treated only rigid molecules. However, in principle, the same treatment can be extended also to flexible molecules. Clearly, an accurate conformational analysis is an absolute prerequisite and this step can cost some more computational effort, even if no fundamental reasons prevent its application to these systems. To conclude, by coupling the use of an inexpensive instrument (a polarimeter working at a few wavelengths) with the use of an ab initio DFT calculation package, the experimental organic chemist will arrive, quickly and reliably, at the assignment of the molecular absolute configuration.

(19) Drake, A. F.; Mason, S. F. *Tetrahedron* **1977**, *33*, 937.

(20) It is to be noticed that nowadays polarimeters working at a few discrete wavelengths (880, 633, 577, 546, 435, 405, 365, 334, 325, 313, 302, 296, 280, and 253 nm) are commercially available at a contained (15 000 euro ca.) price. Clearly, with such instrumentation, the problem posed by the (−)-β-pinene molecule can be easily solved.

Computational Methods

All calculations have been carried out on a simple PC endowed with a single PentiumIV 2.2-GHz processor. All geometries have been fully optimized at DFT/B3LYP/6-31G* level using the Gaussian 98 package. All of the geometries are real minima; no imaginary frequencies were found.

All the OR calculations have been carried out by means of time-dependent HF and DFT methods as available within Gaussian,[21] Dalton,[22] and Turbomole[23] packages. In particular, (i) all the OR calculations at HF/6-31G* level have been carried out using London orbitals (which ensure the origin independency of the results) as implemented in the Dalton 1.2.1 package; (ii) all the OR calculations at DFT/B3LYP/6-31G* level have been carried out using London orbitals as implemented in the Gaussian 03 package; (iii) the OR calculation at the DFT/B3LYP/Sadlej level has been carried out with Turbomole 5.6 package. A reviewer noticed that the B3LYP functional implemented in Turbomole is different from that of Gaussian03. However, the differences between the functionals for properties in general are small, although there are large differences in absolute energies. We remark that Turbomole has been used in this work only in the case of the DFT/B3LYP/Sadlej calculation of **4b**, because Gaussian03 gave convergence problems.

Experimental Section

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian-Inova 500 (^{1}H 500-MHz and ^{13}C 125-MHz) or Bruker Aspect 300 (^{1}H 300-MHz) spectrometers. UV and CD spectra were recorded in hexane solution on a JASCO J-600 spectropolarimeter. Optical rotations were measured with a JASCO DIP-370 digital polarimeter. ORD curves were recorded in hexane solution on a JASCO J-810 spectropolarimeter equipped for ORD measurements. Column chromatography was carried out with silica gel Merck 60 (80−230 mesh). Gas chromatographic analyses were carried out on a GC/MS Hewlett-Packard 5080 series II, MS detector HP 5971, with a Supelco 57300-U (poly(dimethylsiloxane) (PDMS) phase) column. THF was freshly distilled prior its use on sodium benzophenone ketyl and was stored under nitrogen atmosphere. *n*-Butyllithium 2.5 M in hexane, (−)-fenchone (**2a**), (+)-camphor (**3a**), (+)-nopinone (**4a**), (−)-*β*-pinene (**4b**) (Aldrich products) and (−)-verbenone (**1a**) and (−)-Troeger's base (**5**) (Fluka products) were used as purchased. Methyltriphenylphosphonium bromide (Aldrich) was dried under vacuum for 3 h before its use.

(−)-4-Methylverbenene (1b). To a stirred solution of methyltriphenylphosphonium bromide (11.43 g, 32.02 mmol) in 80 mL of anhydrous THF was added 14 mL of *n*-butyllithium (2.5 M in hexane) dropwise under a nitrogen atmosphere. The solution was warmed at 50 °C and stirred for 2h, obtaining a red coloration. At this point, to the solution was added (−)-verbenone (**1a**) (3.02 g, 20.1 mmol) dropwise in 20 mL of anhydrous THF. The obtained solution was stirred under reflux for 24 h, cooled at room temperature, and then about half of the volume of the solvent was removed under reduced pressure, and 50 mL of petroleum ether was added. The organic layer was washed successively by 2 × 30 mL of water and 2 × 30 mL of brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and evaporated at reduced pressure. Chromatography on silica gel (eluent: petroleum ether) of the crude residue gave, after evaporation of solvent at reduced pressure, the crude product. After fractional distillation, we recovered 1.85 g (62% yield) of pure (−)-**1b** as a colorless liquid. $[\alpha]^{20}_D = -40$ ($c = 1$; hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (s, 3H); 1.37 (s, 3H); 1.47(d, 1H, $J = 9.0$ Hz); 1.81 (s, 3H); 2.13 (t, 1H, $J = 6.0$ Hz); 2.53 (m, 1H); 2.61(t, 1H, $J = 5.5$ Hz); 4.59 (s, 2H); 5.80 (s,1H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 23.1, 26.4, 35.8, 43.8, 48.4, 51.5, 104.6, 120.8, 148.7, 150.4 MS (EI): *m*/*z* 148 (M^+, 24), 133 (42), 106 (36), 105 (100), 103 (7), 79 (13), 77 (15). Anal. Calcd for $C_{11}H_{16}$: C, 89.12; H, 10.88. Found: C, 89.70; H, 10.30.

(−)-Methylenefenchone (2b). To a stirred solution of methyltriphenylphosphonium bromide (15.98 g, 44.73 mmol) in 80 mL of anhydrous THF was added 19 mL of *n*-butyllithium (2.5 M in hexane) dropwise under nitrogen atmosphere. The solution was warmed at 50 °C and stirred for 2 h, obtaining a red coloration. At this point, to the solution was added (−)-fenchone (**2a**) (4.27 g, 28.07 mmol) dropwise in 20 mL of anhydrous THF. The obtained solution was stirred under reflux for 30 h, cooled at room temperature, and then about half of the volume of the solvent was removed under reduced pressure, and 50 mL of petroleum ether was added. The organic layer was washed successively by 2 × 30 mL of water and 2 × 30 mL of brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and evaporated under reduced pressure. Chromatography on silica gel (eluent: petroleum ether) of the residue gave, after evaporation of solvent at reduced pressure, the crude product. After fractional distillation we recovered 2.78 g (66% yield) of pure (−)-**2b** as a colorless liquid. $[\alpha]^{20}_D = -68$ ($c = 1.08$; hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 3H); 1.08 (s, 3H); 1.20 (s, 3H); 1.22 (d, 2H); 1.45 (m, 3H); 1.68 (t, 1H); 1.84 (s, 1H); 4.57 (s, 1H); 4.61 (s,1H). MS (EI): *m*/*z* 150 (M_+, 28), 135 (10), 121 (14), 107 (100), 91 (20), 79 (20), 67 (9), 41 (12). Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 87.51; H, 12.49.

(−)-Methylenecamphor (3b). To a stirred solution of methyltriphenylphosphonium bromide, (15.95 g, 44.65 mmol) in 80 mL of anhydrous THF was added 19 mL of *n*-butyllithium (2.5 M in hexane) dropwise under nitrogen atmosphere. The solution was warmed at 50 °C and stirred for 2h, obtaining a red coloration. At this point, to the solution was added (+)-camphor (**3a**) (4.25 g, 27.8 mmol) dropwise in 20 mL of anhydrous THF. The obtained solution was stirred under reflux for 24 h, cooled at room temperature, and then about half of the volume of the solvent was removed under reduced pressure, and 50 mL of petroleum ether was added. The organic layer was washed successively by 2 × 30 mL of water and 2 × 30 mL of brine. The organic layer was then dried over anhydrous Na_2SO_4, filtered, and evaporated at atmospheric pressure (warning, the product **3b** sublimes easily). Finally, chromatography on silica gel (eluent: pentane) of the

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residue yielded, after evaporation of pentane at atmospheric pressure, 2.90 g (68% yield) of **3b** as a colorless solid. $[\alpha]^{20}_{D} = -36$ ($c = 0.96$; hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78 (s, 3H); 0.91 (s, 3H); 0.94 (s, 3H); 1.25 (m, 2H); 1.65 (t, 1H); 1.78 (m, 2H); 1.87 (d, 1H); 4.63 (s, 1H); 4.67 (s,1H). MS (EI): *m*/*z* 150 (M^+, 28), 135 (59), 121 (30), 107 (100), 93 (61), 79 (68), 41 (21). Anal. Calcd for $C_{11}H_{18}$: C, 87.93; H, 12.07. Found: C, 88.10; H, 11.90.

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