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Assignment of the Molecular Absolute Configuration through the ab Initio Hartree−Fock Calculation of the Optical Rotation: Can the Circular Dichroism Data Help in Reducing Basis Set Requirements?[†]

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In this paper the calculation of the optical rotation (OR) of some rigid organic molecules, using the Hartree−Fock method with small (6-31G*, DZP) basis sets, has been studied thoroughly to carefully evaluate the scope and limitations of this method, previously introduced by other authors. Calculations on test molecules (compounds **1**−**13**) together with a careful analysis of their CD spectra allow a simple criterion for the reliability of this approach to be formulated: for unsaturated and/or aromatic (i.e., absorbing in the near-UV region) molecules, if the $[\alpha]_D$ is quantitatively determined by the lowest energy Cotton effect (at wavelengths >220 nm), then the HF/6-31G* result is reliable. The usefulness of this method for the experimental organic chemist has been further demonstrated because the OR (sign and order of magnitude) of compounds **14**−**19** (i.e., large molecules having considerable interest in organic chemistry), which fulfill the above criterion and for which an extended basis set treatment is not feasible owing to their size, is correctly predicted.

Introduction

The experimental specific optical rotatory power [α] measured, say, at the sodium D line can be, in principle, a priori calculated knowing the electric dipole−magnetic dipole polarizability tensor at the same wavelength.[1] However, the possibility of carrying out this calculation remained unexplored until a few years ago, and in the meantime, mainly simplified empirical[2a] and semiclassical[2b,c] models were elaborated. Only after the appearance of the seminal papers by Amos[3] and Helgaker et al.,[4] who implemented the ab initio (Hartree−Fock level of approximation) calculation of the electric−magnetic dipole polarizability tensor in the static limit (zero frequency) or at any wavelength, within the CADPAC[5] and DALTON[6] packages, respectively, the real possibility of ab initio calculating the optical rotation (OR) was pointed out by Polavarapu.[7a] As a consequence, the possibility of assigning the molecular absolute configuration (AC), simply by comparing the experimental optical rotation OR (say, at the sodium D line) with the Hartree−Fock (HF) predicted value, resulted. Subsequent papers by Polavarapu[7] himself and by the group of Beratan and Wipf[8] clearly demonstrated the real possibility of a computational assignment of the AC. On the other hand, other research groups[9−11] preferred the alternative approach based on the density functional theory (DFT). Two aspects of the DFT calculations appear attractive: first

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[†] This paper is dedicated to Professor S. F. Mason, FRS, on the occasion of his 80th birthday and in recognition of his pioneering contribution to the determination of the absolute configuration by chirooptical methods.

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of all, Stephens et al., in a systematic and rigorous investigation,[9c] have analyzed the accuracy of ORs calculated at the DFT/B3LYP and HF/SCF levels of approximation, providing a statistical analysis of the results obtained for 30 structurally different test molecules (28 being of known AC), assuming a variety of London basis sets ranging from small to very large ones. Their conclusions are rather pessimistic regarding the HF/SCF/small basis set predictions: they claim that the use of DFT methodologies in conjunction with large basis sets containing diffuse functions is necessary to obtain accurate results. In addition, Grimme[10a] has shown that the use of the TDDFT method, in conjunction with small, non-London basis sets of augmented valence double-ζ quality, provides, at least for molecules having low-lying excited states, quantitative predictions of experimentally measured OR values, even for large systems such as helicenes. Furthermore, Grimme et al.[10b] have extended the resolution of the identity (RI) approximation to the TDDFT frequency-dependent OR calculations, which seems to provide, for a limited set of molecules, reliable results at exceptionally low computation times.

All these facts seem to indicate that the DFT method is superior with respect to the HF approach. Nevertheless, going back to the Stephens paper,[9c] we note that, as far as the AC assignment is concerned, the HF/SCF/small basis set calculations reproduce correctly the experimental AC for 25−26 of 28 test molecules, while DFT/B3LYP calculations (same basis sets) provide the correct answer in 25−27 of 28 cases. The HF/SCF/large basis set assignments are correct in 26 cases, while DFT/B3LYP/large basis set calculations afford the correct answer in 27 cases. It appears that the two methods are almost equivalent for the assignment of the AC, the DFT/B3LYP method being only slightly better. This encouraging conclusion seems to be valid also for the small basis set calculations. Therefore, taking also into account that no DFT packages are at the moment available for OR calculations,[12] we started a research project aimed at fully analyzing the HF/OR calculations with the smallest possible basis set, to show under what circumstances they work satisfactorily. In particular, we were interested in verifying, following Grimme,[10a] if a large basis set is not needed for a reliable OR calculation at least in the case of molecules having low-energy (near-UV region) Cotton effects, i.e., a point which, to the best of our knowledge, has not been discussed in the literature yet and which would largely simplify these kinds of calculations, making them a reliable tool for the experimental organic chemist.

Results and Discussion

1. Test Molecules. To test this hypothesis, we decided to study the benchmark molecules **1**−**13** of Figure 1: for all of them experimental rotatory powers are known,[9c,13−22] and HF/OR calculations have not been reported for them so far (with the sole exception of **12**[9c]); hence, they constitute new tests to be added to those reported in refs 7−9.

This choice has been determined considering that they are all rigid structures;[23] therefore, difficulties coming from conformational flexibility should not arise. Furthermore, it is interesting to note that compounds **2**−**4**, **6**, **8**, and **9** are molecules where different chromophores are inserted in the same chiral backbone, derived from camphor. This fact is responsible for OR values which are different in order of magnitude and even in sign. Therefore, the correct reproduction of the experimental trend of OR versus structure constitutes a significant test of the reliability of our treatment. Our calculations do not take into account the role of the solvent; i.e., we did not use any solvent model. When possible (compounds **1**, **4**, **6**, **8**, **9**, and **12**), the calculated rotations are compared with experimental values in hydrocarbon solution, which should be the closest to the gas-phase values.[9c] In other words, we will not search for numerical accuracy[24] but, rather, for reliably reproducing the sign and order of magnitude of the OR at 589.3 nm. The OR

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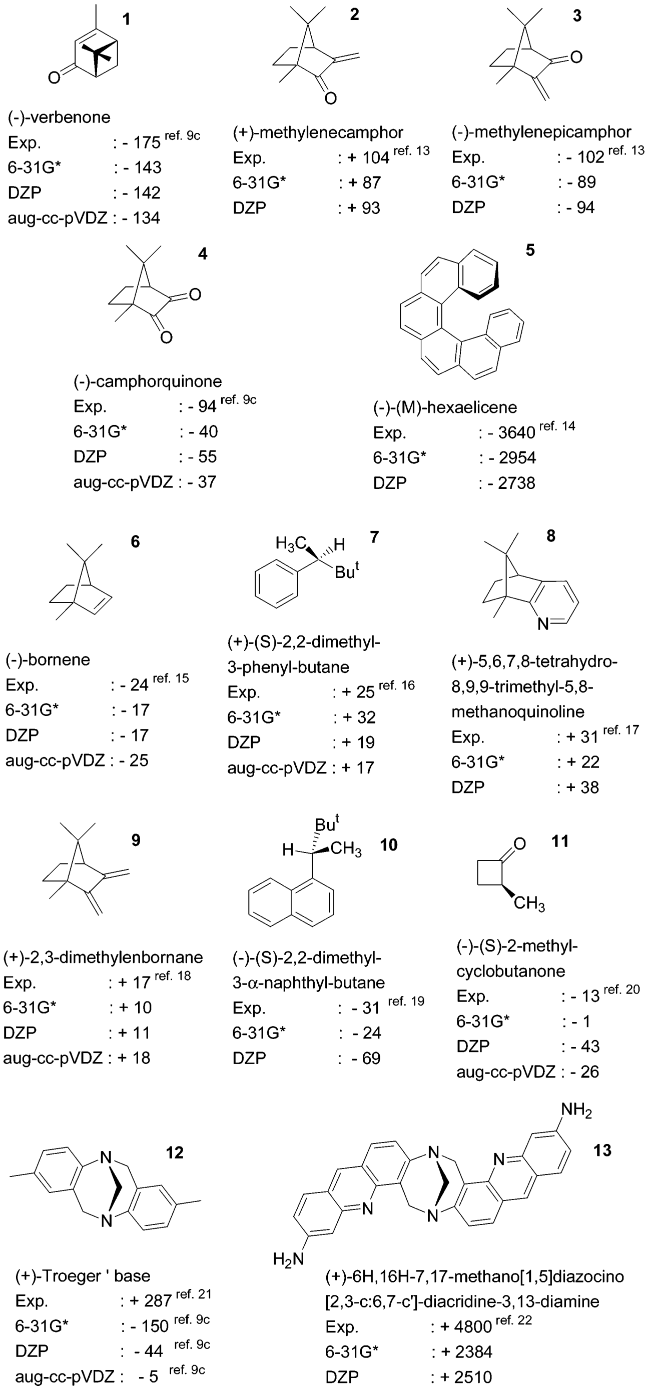

FIGURE 1. Test molecules.

calculations have been carried out by means of the DALTON[6] package, using London orbitals and starting from B3LYP/6-31G* fully optimized geometries[26] obtained with GAUSSIAN 98[27] on a Pentium IV (2200 MHz, 1.5 GB RAM) based PC ruled by the Linux operating system. The results obtained can be discussed as follows.

(i) Compounds **1**−**5** show large OR values (100 units or even much more, as in the case of hexahelicene, **5**, which shows an extremely large optical rotatory power), and our HF calculations using small basis sets give more than satisfactory results: in fact, the sign and a large fraction of the experimental OR are correctly reproduced. These results are not unexpected, taking into account the conclusions by Stephens.[9c]

(ii) In addition, for the above-mentioned camphor derivatives, the experimental trend of OR versus structure is correctly reproduced (**2** vs **3**, **2** vs **6**, **3** vs **8**). It is also noteworthy that, even in the cases of low ORs, satisfactory results can be obtained using our simplified approach: see **6**−**8**. These interesting results can be interpreted taking into account that **1**−**8** are all molecules possessing chromophoric systems with low-lying excited states, so the Grimme considerations[10a] apply: $[\alpha]_D$ values are dominated by the lowest energy Cotton effects, and to describe them sufficiently well, extended basis sets are not needed. In Table 1 we have collected quantitative CD data referring to the lowest energy Cotton effect (rotatory strength and wavelength position) of compounds **1**−**13** and to the contribution due to this Cotton effect to the optical rotation at the sodium D line. To this end we made use of the simple formula for Kronig−Kramers transforms reported by Moscowitz:[33]

$$[\alpha_i]_D = 9151.47/(\text{molecular mass})R_i[\lambda_i^2/(589^2 - \lambda_i^2)] \qquad (1)$$

where $[\alpha_i]_D$ is the contribution to the rotatory power at the sodium D line coming from the ith Cotton effect, R_i is the reduced rotational strength of the ith Cotton effect, and λ_i is its wavelength in nanometers.

The data reported in Table 1 clearly show that the OR at 589 nm of **1**−**8** is dominated by the lowest energy

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[24] As Stephens has clearly pointed out[9c] the OR magnitude is affected by several factors, in addition to solvent effects, such as experimental errors and vibrational effects. The importance of the vibrational effect has been recently pointed out.[25]

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[26] This choice is due to the fact that in this way we have a homogeneous comparison with analogous data reported in the literature.[9c] In addition it is interesting to note that the use of the B3LYP/6-31G* method requires in the case of **14**, for instance, 17 h of CPU time on our machine, while HF/SCF/6-31G* requires 12 h and HF/SCF/3-21G requires 2 h. In any case all these times are shorter than the CPU time required for the HF/SCF/6-31G* OR calculation (23 h); therefore, the preparation of geometries is not the rate-determining step of the overall process. Interestingly, the computed HF/SCF/6-31G* optical rotations are similar in the three cases: −275 (B3LYP/6-31G*), −224 (HF/SCF/6-31G*), and −234 (HF/SCF/3-21G).

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TABLE 1. Contribution of the Lowest Energy Cotton Effect to $[\alpha]_D$ for Molecules 1−13

molecule	R_1 (λ_1, nm)[a]	$[\alpha_1]_D$[b]	$[\alpha]_D$(exptl)	CD in ref
1	−9.5 (338)	−285	−175 (hexane)	28
2	+2.7 (344)	+77	+104 ($CHCl_3$)	13
3	−3.4 (346)	−100	−102 ($CHCl_3$)	13
4	−0.9 (490)	−111	−94 (hexane)	29
5	−343 (326)	−4219	−3640 ($CHCl_3$)	30
6	−6.4 (200)	−56	−24 (C_6H_6)	31
7	+2.3 (262)	+32	+25 (neat)	23a
8	+4.9 (280)	+70	+31 (cyclohexane)	17
9	−1.2 (251)	−15	+17 (hexane)	18
10	+2.0 (280)	+26	−31 (CCl_4)	23b
11	+0.5 (305)	+21	−13 ($CHCl_3$)	20
12	−18 (297)	−226	+287 (hexane)	32
13	+75 (425)	+1646	+4800 (ethanol)	22

[a] R_1 is the reduced rotational strength of the lowest energy Cotton effect, and λ_1 is the wavelength in nanometers of the lowest energy Cotton effect. [b] $[\alpha_1]_D$ is the contribution to the rotatory power at the sodium D line coming from the lowest energy Cotton effect; see eq 1 in the text.

Cotton effect present in the CD spectrum of these molecules: we have, for instance, an experimental OR of 3640 for **5** versus a contribution from the lowest energy Cotton effect of 4219! This happens for all the other compounds, the only exception being **2**, the contribution being now only 74% of the experimental optical rotatory power. In any case, these results indicate that the lowest energy Cotton effect is responsible for the experimental OR: as a consequence, if it occurs in the near-UV region, even a small basis set should be sufficient to afford a correct OR calculation, and then a reliable AC assignment could be made. It is really comforting that by improving the basis set the results do not change significantly. This is obviously true for the compounds with large rotations (e.g., **1**−**4**) but, most importantly, is also true for molecules having small rotatory powers (e.g., **6**−**8**): for instance in the case of **7** the calculated OR values are +32 (6-31G*) and +17 (aug-cc-pVDZ), while for **6** we have −17 (6-31G*) and −25 (aug-cc-pVDZ). In summary, reliable calculations can be carried out employing the HF approach with small basis sets even for molecules with small rotatory power (ca. 20 units), provided they possess Cotton effects in the near-UV region, i.e., if the OR at the sodium D line is determined (sign and magnitude) by the lowest energy Cotton effect.

(iii) The cases of **9**−**11** indirectly support the above interpretation. Interestingly, for all these compounds the optical rotatory power (589 nm) and the lowest energy Cotton effect have opposite signs (Table 1). The CD spectrum in hexane of **9**[18] shows a negative Cotton effect (λ 251 nm, $\Delta\epsilon$ −0.6) and a positive one at 205 nm ($\Delta\epsilon$ +2.3). The former Cotton effect affords a contribution to $[\alpha]_D$ of −15 and the latter of +29. In the CD spectrum of **10**[23b] (λ 315 nm, $\Delta\epsilon$ +0.05; λ 280 nm, $\Delta\epsilon$ +1.0; λ 210 nm, $\Delta\epsilon$ −15.0; in heptane) a strong negative Cotton effect at 210 nm (which gives a contribution to $[\alpha]_D$ of −175) must also be taken into account, to have the correct sign and order of magnitude of the experimental OR. Since both these additional transitions are reasonably low energy $\pi-\pi^*$ valence shell excitations, it is not unexpected that our HF/6-31G* calculations give the correct answer. Molecule **11** is a saturated ketone: here the lowest energy Cotton effect[20] (λ 305 nm, $\Delta\epsilon$ +0.2, in isooctane) provides a contribution (Table 1) at 589 nm which is even larger and opposite the experimental rotation. Considering the shape of the CD spectra of saturated ketones, this means that the rotatory power is determined by CD bands in the far-UV region, $\lambda \ll 200$ nm.[34] Therefore, for **11**, it is necessary to take into account transitions occurring at much higher energies. In fact, the 6-31G* calculation affords an ambiguous answer. Using a slightly larger basis set (DZP), one obtains the comforting value of −43; i.e., the sign and order of magnitude of OR are now correctly reproduced. The use of an extended basis set with diffuse functions leads to better numerical agreement with the experiment for **11**: −26 (aug-cc-pVDZ). The case of **12** is much more instructive: here even the theoretical HF/aug-cc-pVDZ prediction fails.[9c] The reason is that the CD spectrum (λ 297 nm, $\Delta\epsilon$ −17; λ 273 nm, $\Delta\epsilon$ +12; λ 243 nm, $\Delta\epsilon$ +26; in ethanol/isopentane/ether, 2:5:5) of the dextrorotatory enantiomer shows (Table 1) a very intense ($\Delta\epsilon$ −17) lowest energy (297 nm) Cotton effect, which provides a rotation of ∼−226 at 589 nm. Considering that the experimental OR is +287, a huge contribution (∼+500) has to come from the higher energy Cotton effects. This requires a really accurate description of them; therefore, this problem cannot be approached by our simplified method, and more accurate methods, such as the DFT ones, must be taken into account.[9c] These results have an important consequence since they indicate that the shape of the CD spectrum can help in selecting the basis set: if the OR and the lowest Cotton effect in the near UV have the same sign, even a 6-31G* or DZP basis set can be reliably employed. The case of compound **13** provides further support to the present hypothesis. This molecule has a structure which is very similar to that of the Troeger base, but in contrast to **12**, it shows between 450 and 220 nm (i.e., in the near-UV region) a series of three clearly separated Cotton effects (reasonably $\pi-\pi^*$ transitions of the acridine chromophore): 425 nm, $\Delta\epsilon$ +26; 290 nm, $\Delta\epsilon$ +218; 250 nm, $\Delta\epsilon$ −163; in ethanol. The 425 nm Cotton effect provides (Table 1) an OR of +1646 (i.e., about 35% of the experimental value, +4800). The following positive couplet gives +1519, so the three bands in the near-UV afford 66% of $[\alpha]_D$. Our 6-31G* calculation gives +2384, i.e., the correct sign and 50% of the experimental rotation, a more than satisfactory result for our simplified approach. In other words two molecules, such as **12** and **13**, having very similar structure behave very differently with respect to the present HF/6-31G* treatment, and this different behavior can be related to and predicted by looking at the CD spectrum: **12**, for which there is a strong contribution, coming from the lowest energy Cotton effect, opposite in sign to the large experimental OR, cannot be dealt with using an HF/6-31G* calculation; on the contrary, in the case of **13** (for which the lowest Cotton effect gives a strong contribution at 589 having the same sign as the experimental OR) the HF/6-31G* method works more than satisfactorily.

At this point we can try to formulate a criterion to be used in deciding when the present simplified approach can be reliably employed. Using the simple formula in eq 1, as reported by Moscowitz,[33] the contribution of the lowest energy Cotton effect to experimental $[\alpha]_D$ can be

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roughly evaluated. If this contribution has the same sign as the experimental $[\alpha]_D$ and gives at least (Table 1) 70−80% of its value (or even more, as in **1**−**8** and **13**), our simplified approach can be safely used (case a). This approach will work well also when the lowest energy Cotton effect provides a contribution which is opposite in sign but represents only a small percentage of the experimental OR (case b).[35] When this contribution is opposite and as large as the experimental rotation but the absolute value of $[\alpha]_D$ is not particularly large (i.e., 10−30) (**9**−**11**), a larger basis set (DZP or even better aug-cc-pVDZ) is required (case c). Finally, if a large contribution (e.g., 100 or more) is opposite in sign to a large experimental $[\alpha]_D$ (100 or more) (**12**), DFT methods must be used (case d). At this point, it seems that with the present criteria we can approach the problem of reliably calculating the OR of unsaturated and/or aromatic compounds with low-lying Cotton effects simply by doing HF/small basis set computations. However, a problem arises: that of (+)-camphor. At a first glance, this molecule belongs to case a of our criterion; in fact, the lowest energy n−π^* Cotton effect (λ 300 nm, $\Delta\epsilon$ +1.6) gives a contribution to $[\alpha]_D$ of +51, almost the value of the experimental optical rotatory power at 589 nm (+57). On the contrary, Stephens et al. demonstrated[9c] that an HF/small basis set calculation gives an OR which is wrong both in sign and in order of magnitude. We are not able to provide a satisfying interpretation of this fact; however, we can make the following observations: (i) It must be noticed that we correctly reproduce by HF/6-31G* calculations the $[\alpha]_D$ of the camphor derivatives **2**−**4**, **6**, **8**, and **9**. Our approach works well, for instance, for **2** and **4**, which can be considered to derive formally from (+)-camphor by introducing a double C=C or C=O bond in position 3, respectively. In this way the nature of the chromophore is completely changed with respect to (+)-camphor: we now have two chromophores which possess several valence shell transitions in the near UV. (ii) We also studied the case of (−)-2-methylenebornane,[18] a compound that we prepared from (+)-(*R*)-camphor by Wittig olefination, i.e., by a substitution of the oxygen atom with a CH_2. The experimental OR value for this camphor−olefin is −34 (hexane), with $\Delta\epsilon$ −6.2 at 204 nm (hexane), and this Cotton effect provides an OR of −70. The HF/6-31G* result is −57, in satisfactory agreement with the experimental value, as should be expected according to our criterion. Moreover, the DALTON HF/6-31G* CD calculation for (+)-(*R*)-camphor shows that the rotational strength for the n−π^* transition is correctly reproduced, in sign and order of magnitude. This means that the difficulties in the HF/small basis set OR calculations found with camphor are due just to the saturated ketone chromophore. Therefore, we can state that the criterion formulated above works well for unsaturated and/or aromatic systems, with the exception of simple ketones.[36] It should be remarked that the above criterion does not constitute a limitation to the application of this theoretical method to the assignment of the absolute configuration; on the contrary, it will help when large molecules are treated. We shall demonstrate this point in the following section.

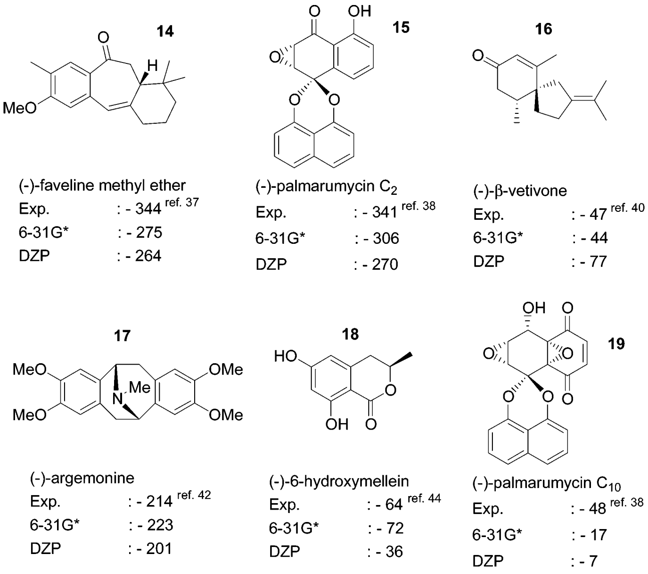

FIGURE 2. Natural products.

2. Applications to the Natural Product AC. In this section we discuss the cases of the natural compounds **14**−**19** (Figure 2).

They are all large, complex molecules for which the OR and CD data are reported in the literature; in any case we have always chosen unsaturated and/or aromatic compounds with strong absorption in the near-UV region. Favelin methyl ether, **14**, is a natural compound[37] showing cytotoxic activity. This compound is levorotatory ($[\alpha]_D$ −344, $CHCl_3$) and possesses a negative lowest energy Cotton effect at 340 nm which provides, at 589 nm, a contribution of about −429: we are in case a described above, so we may use the simplified approach, previously introduced. The calculated value for the *R* absolute configuration is −275 using HF/6-31G* (−264 employing HF/DZP), i.e., the sign and order of magnitude of the experimental value are nicely reproduced. This result allows us to confirm the absolute configuration of (−)-faveline methyl ether as *R*, as already established by an empirical analysis of the CD spectrum.[37] We study next the case of palmarumycin C_2, **15**. It is a secondary metabolite from various species of the fungal genus *Coniothyrium*. It exhibits a high biocidal activity against different bacteria, fungi, and algae.[38] The absolute configuration of (−)-**15** has been assigned[39] by Bringmann

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[35] Even though the use of a smaller nonpolarized basis set should not be recommended for this kind of calculation, according to a suggestion of a reviewer, we also carried out some HF/STO-3G and HF/3-21G OR calculations for selected compounds such as **1**, **5**, **7**, and **11**. The results obtained are as follows: (for **1**) STO-3G, −123; 3-21G, −124; (for **5**) STO-3G, −1745; 3-21G, −2934; (for **7**) STO-3G, +0.1; 3-21G +28; (for **11**) STO-3G, +33; 3-21G, +7. We can state that for compounds which fulfill our criterion a and showing very high rotatory power (say 200 units or more) a HF/3-21G or even STO-3G calculation will give the correct sign and order of magnitude of the OR, in a very short time (4 h for a large molecule such as **5**). On the contrary, the same computation fails miserably when the experimental rotatory power is small (20 units or less) and/or optical rotation and the lowest energy Cotton effect have opposite signs (see **7** and **11**).

[36] This problem deserves special interest: we are now carrying out an investigation about ketone OR calculations.

[37] Endo, Y.; Ohta, T.; Nozoe, S. *Tetrahedron Lett.* **1991**, *32*, 3083. The assignment of absolute configuration is reported by Ohta et al.: Ohta, T.; Endo, Y.; Kikuchi, R.; Kabuto, C.; Harada, N.; Nozoe, S. *Tetrahedron* **1994**, *50*, 5659.

[38] Krohn, K.; Florke, U.; Aust, H. J.; Draeger, S.; Sehula, B. *Liebigs Ann. Chem.* **1994**, 1093, 1099.

[39] Bringmann, G.; Busemann, S.; Krohn, K.; Beckmann, K. *Tetrahedron* **1973**, *53*, 1655.

et al. by the analysis of the CD spectrum, using semiempirical CNDO/S-CI calculations. The case of **15** is slightly more complex for two reasons. First of all, as already shown by Bringmann et al.[39] by semiempirical quantum mechanical methods and confirmed by our DFT conformational analysis, two different conformations having very different populations exist: 90% for one conformer and 10% for the other conformer. In addition the CD spectrum[39] shows the presence of a series of positive and negative bands, also having different intensities. However, it is noteworthy that our analysis of the CD contributions clearly demonstrates that the three low-energy CD bands (at 335, 250, and 225 nm[39]) give a contribution of −181 (versus the experimental value of −341). Therefore, we may expect that our approach will work well. In fact, the HF/6-31G* computations (also taking into account the existence of both the conformers, through a Boltzmann weighted average) gives the excellent value of −306 (i.e., the correct sign and 90% of the magnitude). The use of the DZP basis set leads only to a slight reduction of the magnitude. Compound **16**, (−)-β-vetivone, is one of the components of the oil of vetiver, an ingredient which is largely used in the perfume industry. The case of (−)-β-vetivone is similar to that of (−)-**15** since the existence of two conformers has to be taken into account: B3LYP/6-31G* calculations show that the structure with the methyl group of the cyclohexenone ring in an axial position prevails (85%), as suggested by NMR spectroscopy,[40] but an appreciable fraction of the conformer with the same methyl in an equatorial position (15%) is also present. Furthermore, $[\alpha]_D$ is small when compared to that of (−)-**14** and (−)-**15**, so one could think[9c] of a more difficult case. The CD spectrum of (−)-**16**[40] presents two main negative Cotton effects at 348 and 249 nm, reasonably due to valence shell transition of the α,β-unsaturated enone chromophore. Using the above approximate Kronig–Kramers transform formula, the contributions of the above Cotton effects to $[\alpha]_D$ are −16 and −24, which give a total of −40 to be compared to the experimental value of −47. These data suggest that (−)-**16** can be treated with the simplified approach, even if the OR is not large (from this point of view the situation is similar to that of (+)-**7**). Our HF/6-31G* calculation gives −102 for the major (axial) and +268 for the minor (equatorial) conformers. Taking into account the Boltzmann populations of the two conformers, the conformationally averaged $[\alpha]_D$ value is −44, in excellent agreement with the experimental one. The AC of (−)-argemonine, **17** ($[\alpha]_D$ −188, $CHCl_3$;[41] −214, EtOH[42]), has been assigned[41] by Mason and co-workers by means of the analysis of the CD spectrum using the exciton model. The CD spectrum of this antipode[41,42] shows Cotton effects at 275, 237, and 210 nm, which give (at 589 nm) contributions of +39, −156, and −519. Here, the first CD band gives a contribution at 589 nm which is opposite in sign to the experimental OR, but this value is only a minor part (20%) of the OR, and two intense negative CD bands follow: we are in case b discussed previously; therefore, a successful simplified calculation can be reasonably predicted. As a matter of fact, the theoretical (6-31G*) result is −223, which compares very well with the experimental value. The case of (−)-6-hydroxymellein, **18**, a natural dihydroisocoumarine from fungi,[43] is very similar to that of (−)-argemonine. The CD spectrum of **18**[43] shows bands at 293, 267, 248, and 230 nm, which provide contributions to the OR at 589 nm of +23, −66, +2, and −28, so the optical rotatory power calculated from these CD bands in the near-UV region is −69, a value which is very similar to the experimental[44] one (−64). The lowest energy Cotton effect is opposite in sign to the experimental OR, but it gives only 36% of the OR magnitude: we are in case b discussed above. In fact, the HF/6-31G* calculation now gives a very satisfactory value of −72 (experimental value −64). The case of palmarumycin C_{10}, **19**, another metabolite of the fungus *Coniothyrium palmarum* isolated by Krohn et al.,[38] to which the absolute configuration has been assigned[45] by quantum mechanical calculation of the CD spectrum, looks more difficult. Here, in fact, besides the difficulty due to the presence of two main conformers, as in the case of palmarumycin C_2 (a problem, however, that we can deal with reliably, as discussed above), there is a more important difficulty due to the fact that the CD spectrum reported[45] shows three bands in the near-UV region: 260, 231, and 211 nm, which give contributions of +23, −99, and +44, i.e., −32 in total (experimental value −48[38]). In other words, the experimental OR (a relatively small number) is coming from the combination of (at least) three Cotton effects, having different signs. This may give rise to problems related to the fact that the result (a small number) may derive from the arithmetic sum of three (different) components. However, the calculated HF/6-31G* OR (−17) is correct in sign and order of magnitude, even if it represents only 35% of the experimental value. These results indicate that even complex molecules, containing a large number of electrons, can be reliably treated with an HF/small basis set approach to obtain the sign and order of magnitude of the OR and then to make the assignment of the AC, if these compounds contain unsaturated chromophores which give rise to valence shell transitions in the vis–UV region. The examination of the CD data provides a tool to a priori predict if the result will be reliable or not, following the criterion previously formulated. Clearly, for new compounds of the same kind (synthetic or natural) these data have to be obtained, but recording an ECD spectrum down to 200 nm or even to 185 nm is certainly not a problem, nowadays. A CD calculation, even using semiempirical methods, requires the introduction of a shape factor, to compare the overall shape of the experimental spectrum with that of the predicted one, and often this comparison in not so easy because a large number of near-in-frequency and opposite-in-sign transitions may derive. This fact is even more important in the case of ab initio CD calculations. In the case of OR prediction we have simply to compare (sign and order of magnitude)

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[40] Speitzer, H.; Piringer, I.; Holzer, W.; Widhalm, M. *Helv. Chim. Acta* **1998**, *81*, 2292.

[41] Mason, S. F.; Vane, G. W.; Whitehurst, J. S. *Tetrahedron* **1967**, *23*, 4087.

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[45] Krohn, K.; Steingrover, K.; Zsila, F. *Tetrahedron: Asymmetry* **2001**, *12*, 1961.

a single number, which, in addition, at least in the cases similar to those described in this paper, is obtained in a reasonable time of calculation, even for large molecules.

Concluding Remarks

The most important result of the present investigation is that the combined use of OR and CD data permits a criterion to be set up to establish a priori whether an HF/small basis set approach to the theoretical prediction of OR can be reliably employed. When the criterion (the lowest energy Cotton effect in the near-UV region due to a valence shell transition determines the sign and magnitude of the optical rotation at the sodium D line) is fulfilled, the above approach provides the right answer, even in the case of molecules possessing low (ca. 20 units) optical rotatory power. On the contrary, when the above criterion is not satisfied, the calculation must be carried out by means of more accurate methods. However, it is important to stress that the fulfillment of the criterion does not hamper the applicability of the method: on the contrary, there are many large unsaturated and/or aromatic (i.e., absorbing in the near-UV region) molecules also having considerable practical interest for which an extended basis set treatment is not feasible (molecules **14**−**19**, for instance), so the possibility of carrying out a more simple (but reliable) treatment is absolutely required. It is also interesting to note that we have used only the HF approach to calculate OR because analogous DFT packages are not yet available.[12] However, it is important to point out that the results obtained (possibility of using a small basis set) can also be useful within the DFT approach. In summary, the availability of a reliable and simple method to calculate OR will certainly be of great help to the experimentalists involved in asymmetric organic synthesis, natural product chemistry, and chirooptical methods.

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Supporting Information Available: Details about optimized input geometries. This material is available free of charge via the Internet at http://pubs.acs.org.

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