Structure−Property Relationships of Prototypical Chiral Compounds: Case Studies[†,‡]

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Empirical rules based on chromophores, although beautifully simple, turn out to be too constrained to be of general use. This computational study of selected 3-methylhexane and camphor derivatives demonstrates the limitations of focusing on chromophores. We conclude that in a hybrid of experiment and theoretical computation lies the future of determining absolute configurations.

1. Introduction

Interpretation of strong cotton effects by empirical approaches such as the octant rule, on the basis of the optical-rotatory dispersion (ORD) or circular dichroism (CD) spectra, has traditionally been used, with reasonable success, to determine the absolute configurations of optically active compounds.[1] Just recently, a procedure based on an interpretation of CD-spectra by means of coupled-oscillator theory was devised to determine the absolute configuration of a set of sulfoxides.[2] These empirical rules mostly focus on chromophoric groups (which are responsible for strong cotton effects), assuming that they are required for a structure to display chiroptical properties. With that premise in mind, chromophores are used as reference points, around which the structures are orientated and classified. Traditionally, a functional group is considered to be a chromophore if there is a low-lying electronic excitation, usually in the UV−vis range, associated with the group. In the following, we will understand a chromophore in that sense and consider the "responsible" excitation, the *chromophoric* excitation.

However, there are compounds (the [n]triangulanes,[3] trishomocubane,[4,5] twistane,[6] and helicenes[8,17] are good examples) possessing intense ORDs and low-energy CD absorptions but lacking in chromophoric moieties (Figure 1). Hence, the limitations of chromophore-based rules are obvious. On the other hand, there are structures with high-energy CD absorptions and large ORDs but without clearly recognizable chromophoric groups to which the rules are not readily extended.[7,8] Then again, there are compounds with classical chromophores that defy characterization by normal means.[9] The following investigation of the interplay between structural and chiroptical properties of camphor and 3-methylhexane derivatives as prototypical models emphasizes the necessary complexity and sensitivity of the relationship between these properties. Our results call for using comparisons of measured and computed chiroptical properties for assigning optical rotations in place of empirical rules.

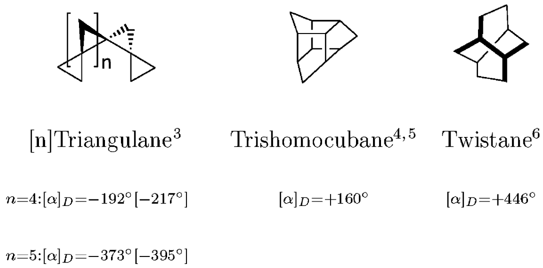

Figure 1. Molecules lacking chromophoric moieties but exhibiting high specific rotations. Hence, the limitations of chromophore-based rules are immediately apparent. Calculated $[\alpha]_D$ with DFT-SCI/TZVP in brackets.

2. Methods

All geometries were optimized to their respective minima at the B3LYP/6-31+G** level[10,11] of theory using the implementation of Gaussian 98.[12] The CD absorptions were obtained at the TZVP[13,14] level with DFT-SCI (density functional theory−configuration interaction)[15] using the B3LYP[10,11] functional as implemented for Turbomole 4.0,[16] except where noted. Although time-dependent DFT (TD-DFT)[17,18] could also be used, it is by far more time-consuming (about 1 month per compound vs several hours) and not necessarily more accurate for the compounds under investigation.[19]

When diffuse functions were added, the number of basis functions increased from 317 to 379 for **3c**. The computational cost increased from 43 days to 94 days on a Pentium-III/550 MHz. Compound **3a** was also computed using the aug-cc-pVTZ[20] basis set, which led to 565 basis functions, 113 days of computation on a Pentium-4/2 GHz, and no appreciable change of the ORD. Therefore, diffuse functions were not included.[21] All core orbitals were kept frozen for the CI computations. Since the CD spectra as well as the OR were needed for a thorough analysis, the ORDs were obtained by applying the sum-over-states method, which is equivalent to any other way of obtaining the ORD,[22] according to

$$\mathrm{ORD}(\nu) = \gamma \frac{8\pi^2 n h \nu^2}{3c} \sum_{i=1}^{N} \frac{R_{0i}}{\Delta E_{0i}{}^2 - h^2\nu^2} \qquad (1)$$

where n is molecules per volume, that is, concentration, N is the number of single excitations, R_{0i} is the rotatory power of

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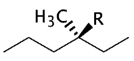
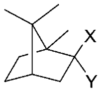
TABLE 1: Structures Studied



1



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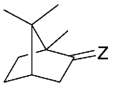

3

	1a	**1b**	**1c**	**1d**
R =	OH	SH	CHO	CO_2H
	1e	**1f**	**1g**	
R =	OCH_3	Br	Cl	
	2a	**2b**	**2c**	**2d**
X =	H	OH	H	Br
Y =	OH	H	Br	H
	2e	**2f**	**2g**	
X =	CH_3	H	CH_3	
Y =	H	CH_3	CH_3	
	3a	**3b**	**3c**	
Z =	O	S	CH_2	

the excitation from the ground state to the *i*th excited state, ν is the frequency of the incident light, ΔE_{0i} is the energy of the *i*th excitation, and γ is a solvent-dependent Lorentz correction,[23] which is 1 in the gas phase. The number of excitations was restricted to the number of valence shells in our calculations, as excitations beyond that limit would either be second excitations from the valence shell or excitations from the core.

Camphor derivatives are structurally rigid and some experimental data for comparison are available. In our experience, the computations tend to overestimate the ORDs[27,24] at the Na−D wavelength. However, the shift due to the optical density of the solvent generally shifts the ORD toward *higher* values; γ attempts to correct for differences in optical density. This is exemplified with neat borneol (**2a**): for $\gamma = 1$ the calculated ORD is lower than experiment, while corrections for the optical density ($\gamma > 1$) increase the calculated value above experiment confirming the above conclusion. As noted by others,[25] gas-phase ORD data are generally not available and we therefore restrict the following discussion to the computational results as they are solely based on well-defined, physical quantities. However, the agreement of computed ORD and ORD data measured in nonpolar solvents is typically quite good.[25] In particular, the *sign* for the optical rotations at a particular wavelength (e.g., the Na−D line) is reproduced in most cases (cf. Tables 2, 3). This allows absolute configurations to be assigned reliably by matching computed and measured CD or ORD curves.

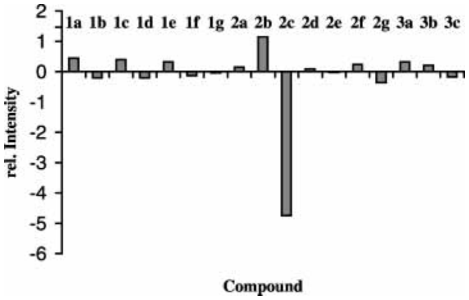

Figure 2. Contributions of the lowest-lying excitation of **1a**−**3c** relative to respective $[\alpha]_D$ ($\gamma 8\pi^2 nhcR(\tilde{A} \rightarrow \tilde{X})/3(589.3^2\Delta E^2_{\tilde{A}-\tilde{X}} - h^2c^2)$ $1/[\alpha]_D$).

3. Results and Discussion

In contrast to the camphor family, the experimental chiroptical properties of 3-methylhexane derivatives are not well understood. Because of their conformational flexibility, it is only possible to obtain Boltzmann-weighted, averaged ORDs, which tend to be very small (Table 2), but the minimum-energy geometry dominates the average. In the literature, the phrases crypto-chirality[26] and, more to the point, crypto-optically active[27] have been coined to describe these observations. Not surprisingly, very little experimental chiroptical data are available on flexible alkanes and their simple derivatives. We studied these types of structures to show that, even in such simple compounds, the chiroptical properties are not directly dependent on a particular chromophore. They depend rather on the complex nature of both the nuclear and electronic structures of ground as well as excited states.

One way of evaluating the importance of a particular chromophore is to compare its chromophoric rotatory contribution (in our cases the lowest-lying excitations) relative to the sum of *all* contributions (Figure 2). For most of the studied molecules, the contribution of an individual chromophore is less than 50%, but more alarmingly, for half of the molecules, this contribution has the “wrong” sign!

Replacing oxygen by sulfur seems to imply, falsely, that the excitation associated with the chromophoric group retains its sign, even if the overall ORD has changed sign (Figure 3). This entails that the chromophoric group has perturbed the remainder of the molecule enough to reverse the sign of the sum of the contributions of all but the lowest-lying excitation. Hence, a structural rule for the lowest-lying excitation seems valid, but not for the rest of the molecule. The same is true for a substitution of $=CH_2$ by $(CH_3)_2$, which is not a classical chromophore. A replacement of sulfur by $=CH_2$, both chro-

TABLE 2: Selected Properties of 1a−g and 2a−g Calculated with B3LYP/TZVP and DFT-SCI(B3LYP)/TZVP[a]

molecule	**1a**	**1b**	**1c**	**1d**	**1e**	**1f**	**1g**
ΔE_{01}/nm	169.930	217.865	301.153	219.918	167.512	214.437	177.383
R_{01}/°	17.312	−4.190	−2.136	−4.916	0.990	−1.434	−0.592
calcd $[\alpha]_D$/ °	−126.9	109.4	−91.8	−112.7	−178.8	−71.5	63.2
expt $[\alpha]_D$/°	−1.8[28]	N/A	N/A	−19.7[29]	N/A	N/A	N/A
μ/debye	1.643	1.609	2.908	1.708	1.286	2.397	2.269
molecule	**2a**	**2b**	**2c**	**2d**	**2e**	**2f**	**2g**
ΔE_{01}/nm	174.640	169.065	209.791	207.008	151.268	152.953	152.120
R_{01}/°	−14.211	−1.288	2.280	1.191	7.630	0.709	20.598
calcd $[\alpha]_D$/ °	−34.6	23.0[b]	−74.6	−123.8	−77.3	4.7	108.4
expt $[\alpha]_D$/°	−37.3[30]	34.6[31]	−30.8	−62.3	N/A	N/A	N/A
μ/debye	1.456	1.922	2.474	2.518	0.016	0.113	0.075

[a] For compounds **1a**−**g** experimental values are conformationally averaged and therefore not expected to compare quantitatively with the computations. Remarkably, however, the signs are reproduced in all but one of the experimentally available cases. [b] DFT-SCI rendered −23.0° and therefore called for confirmation. This value was computed using TD-DFT as implemented for Turbomole 5.3.[16] The CD-spectrum differed merely by the sign of the first excitation, which had a very low rotatory strength, highlighting the sensitivity of this compound to small changes in excitation energies.

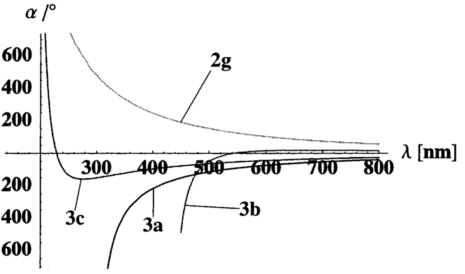

Figure 3. Wavelength-dependent ORD of **3a**, **3b**, **3c**, and **2g**. Notice that **3a** and **2g** as well as **3b** and **3c** are qualitatively comparable.

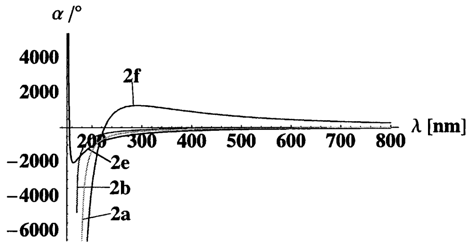

Figure 4. Wavelength-dependent ORDs of **2a**, **2b**, **2e**, **2f** (scaled by a factor of 100 to facilitate comparison). Notice that **2e** and **2f** are qualitatively comparable.

TABLE 3: Selected Properties of 3a−c Calculated with B3LYP/TZVP and DFT-SCI(B3LYP)/TZVP[a]

molecule	3a	3b	3c
ΔE_{01}/nm	294.716	430.755	187.268
R_{01}/°	−3.488	−2.191	16.946
calcd $[\alpha]_D$/°	−76.0	15.4[19]	−45.4
expt $[\alpha]_D$/°	−47.55[32]	30.4[33]	−52.88[34]
μ/debye	3.337	3.414	0.680

[a] All signs are reliably reproduced.

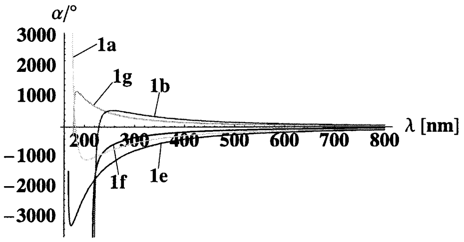

Figure 5. Wavelength-dependent ORD of **1a**, **1b**, **1f**, **1g**, and **1e**.

mophores, however, results in an inverted and shifted ORD. In this case, the excitation of the chromophore as well as the sum of all other contributions have changed. Therefore, a rule that merely relies on the position of the chromophore in a structure does not suffice to deduce the ORD.

Furthermore, exchanging X and Y in **2** has unpredictable outcomes (Figure 4). In the case of X = methyl and Y = H (**2e**), there is a change in sign, albeit **2e** has a rotatory power 10 times that of **2f**. For X = OH and Y = H (**2f**), there is no change in sign, even though the factor of 10 is again witnessed (Table 2).

A comparison of the substituted 3-methylhexanes (Figure 5) **1b** (R═SH) and **1a** (R═OH) reveals that their ORD spectra are basically "inverted". A simple explanation would be an inverted dipole moment vector because sulfur is less electronegative than carbon and a reversed dipole might result in an inverted transition dipole moment, which would account for the change in sign for the rotatory power of the chromophoric excitation. However, this is not the case because the contribution to the dipole moment along the origin vectors of oxygen and sulfur are −1.451 and −1.058, respectively (Table 3). While the contribution to the dipole moment in the direction of the thiol group is less than that of oxygen, it remains substantial and does not result in a sign change. Comparison of the results for the thiocarbonyl group in thiocamphor (**3b**) and the carbonyl function in camphor (**3a**) with those of the thiol and hydroxy groups in 3-methylhexane render a simple structural rule impossible. Exchange of OH by CH_3 leads to a change of sign of the ORD for **2a** to **2f**, while the sign is retained from **2b** to **2e**. Hence, no simple, structure-based rule is possible for predicting ORD spectra or the rotatory strengths of chromophoric excitations in asymmetric molecules.

4. Conclusions

This study shows that chiroptical spectroscopy is more sensitive to the overall molecular electronic structure than to the contribution of a particular chromophore. This is particularly evident for compounds *without* a chromophore, which can nevertheless exhibit large optical rotations at a set wavelength. The use of a single ORD value, even in a theoretical calculation, is not recommended as demonstrated by the computation on isoborneol and thiocamphor. Hence, a suitable recourse for assigning correct absolute configurations to optically active molecules is to combine experiment with theoretical computations, which are becoming more feasible as computer speed is increasing and programs are becoming more efficient. Matching of ORD spectra, or even better, continuous CD spectra, should therefore be the method of choice for assigning absolute configurations.[35]

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(19) TD-DFT calculations at the TZVP or higher level were conducted at considerable, computational cost (more than thrice the time) on **2a**−**c** ($[\alpha]_D = -25.5$, 23.0, -91.71, respectively), **2e** ($[\alpha]_D = -77.0$), **3a** ($[\alpha]_D = -106.3$), and **3b** ($[\alpha]_D = 15.4$). **2b** and **3b** were computed for comparison of the DFT-CI with an alternative method to discern the nature of the respective inconsistencies. It is our experience that $|[\alpha]_D|$ values are usually overestimated, yet both calculations on **3b** give lower absolute values than experiment, and although the sign is correct for **2b** in TD-DFT it still *underestimates* $[\alpha]_D$. Therefore, the low ORD is not an artifact of DFT-CI for **3b** and the reason for the bad performance of DFT-CI on **2b** goes deeper than a mere choice of method. DFT-CI ORDs for all other compounds were consistently closer to experiment and the CD spectra were qualitatively very similar, some even virtually identical.

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