Calculation of Electronic Circular Dichroism Spectra with Time-Dependent Double-Hybrid Density Functional Theory

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Time-dependent double-hybrid density functional theory is applied to the calculation of the electronic circular dichroism (CD) spectra of molecules. The TD-B2PLYP method is based on vertical excitation energies obtained from its hybrid-GGA part B2LYP in a conventional TD-DFT linear response treatment and a CIS(D) type perturbation correction for these excited states. A new benchmark set of six representative organic molecules with a wide variety of different electronic character is introduced for this investigation. The simulated TD-B2PLYP spectra are compared to experiment and those computed with the TD-B2LYP (i.e., no CIS(D) correction) and TD-B3LYP methods. Vertical excitation energies at the perturbatively corrected level are, in the majority of cases, more accurate than, e.g., with TD-B3LYP. Relative band positions are also reproduced better. In one example, the high-energy CD bands are not computed with sufficient accuracy, which is attributed to an instability of the perturbation correction. Due to the inclusion of a large portion of "exact" exchange (53%) in B2PLYP, the spectra feature less artificially created excited states and CD bands than with TD-B3LYP. In all six examined cases, TD-B2PLYP gives qualitatively correct spectra, whereas the hybrid functionals sometimes show a more erratic behavior. Therefore, we can recommend the use of the new double-hybrid approach for the computation of CD and the prediction of absolute configurations of chiral molecules.

Introduction

Chiral systems play an important role in chemistry, biology, pharmaceutics, and medicine. Therefore, developing methods for the analysis of chiral compounds is important for actual chemical research. One of the most widely applied spectroscopic techniques for investigating these systems is electronic circular dichroism (CD) spectroscopy. A combination of experimental measurements and theoretical computations of CD spectra allows one to determine absolute configurations of unknown compounds and enlighten their structure-chiroptic properties.

Electronic circular dichroism is based on the fact that left and right circular polarized light is absorbed differently by chiral molecules. Therefore, two different extinction coefficients can be observed whose difference $\Delta\epsilon = \epsilon_l - \epsilon_r$ is plotted in a CD spectrum.[1] Because this difference can become positive or negative, the absorption bands in a CD spectrum can also exhibit different signs. Compared to conventional UV/vis spectroscopy, this is an additional, useful spectral "dimension", since it makes the CD technique more sensitive to geometric and electronic properties of the analyzed molecule. This, however, on the other hand requires more sophisticated methods in concomitant theoretical treatments that simultaneously must yield accurate excitation energies, band intensities, and signs. Diedrich and Grimme carried out an evaluation of a variety of quantum chemical approaches and tested their reliability for the prediction of CD spectra.[2] Crawford and co-workers composed reviews about the current state of ab initio calculations of CD in the years 2006 and 2007.[3,4]

The most popular tool for the calculation of CD spectra (and properties of electronic excited states in general) is the time-dependent (linear response) density functional theory (TD-DFT) approach.[5−7] In the past, TD-DFT was applied to a variety of chiral systems to better understand their CD properties and to determine their absolute configurations.[2,8−28]

Overviews of the strongly related computation of (frequency-dependent) optical rotation by TD-DFT are given by Crawford et al.[3,4]

Although TD-DFT seems to be a method combining efficiency (low computation times) with reliable results, it exhibits certain deficiencies. These can affect the description of systems with ionic, charge-transfer, Rydberg, and multiple-excitation character.[29−34] The flaws of current TD-DFT implementations, including the popular B3LYP functional,[35,36] can be partially ascribed to the facts that, first, the exchange-correlation potentials show a wrong asymptotic behavior at large distances between electrons and nuclei[37] and, second, that current exchange-correlation functionals do not completely compensate for the self-interaction error.[31] In theoretical spectroscopy, systematic errors for the excitation energies lead to simulated spectra with absorption bands that are red- or blue-shifted compared to experiment. One common way to counterbalance these errors is to include a constant (state-independent) shift when simulating the spectra. In difficult cases sometimes observed in CD spectra, where a blue shift might lead to another result regarding the absolute configuration than a shift in the opposite direction, this procedure is dubious (for a recent example see the theoretical investigation of the plumericin and isoplumericin molecules by Stephens et al.).[14] A second problem is that actually higher lying states are often shifted toward the lower energetic region of a spectrum. These states do not have a real counterpart and are therefore called artificial or "ghost

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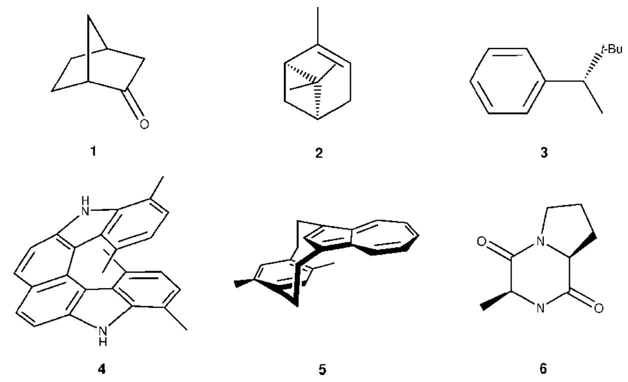

Figure 1. Structures of molecules **1**−**6**.

states".[29] One way of counterbalancing some of the shortcomings of TD-DFT is the admixture of a portion of "exact" (Hartree−Fock, HF) exchange (hybrid-GGA functionals). The optimum percentage of HF exchange may vary from molecule to molecule and state to state (e.g., valence compared to Rydberg states).[38−40] Moreover, the more "exact" exchange is included in the treatment the less electron correlation is considered, leading again to wrong excitation energies. Long-range correction schemes can compensate for the poor description of, e.g., Rydberg states, but so far they have not been applied to the simulation of CD spectra.

One way of making use of the benefits of HF exchange and still considering most of the electron correlation is the double-hybrid density functional (DHDF) approach[41] (for earlier related methods, see ref 42). It was originally developed for ground-state problems where it gave very promising results.[41,43] The idea of DHDFs is that an additive perturbative correlation energy based on Kohn−Sham orbitals can improve a hybrid-GGA functional energy. The first two developed DHDFs are the functionals B2PLYP[41] and mPW2PLYP.[44] A straightforward extension to excited states within the framework of TD-DFT has recently been proposed by Grimme and Neese.[45] The introduced TD-B2PLYP and Tamm-Dancoff approximation (TDA-B2PLYP) methods provide very promising results for a variety of molecular states. Compared to other density functionals, they feature a more balanced description of states of different character, leading on average to more accurate excitation energies with deviations from experiment of about 0.2 eV or less.

In this work, a thorough evaluation of the performance of TD-B2PLYP for the prediction of CD spectra is carried out. So far the new approach has been applied successfully to the CD spectrum of the (*M*)-heptahelicene molecule.[45] For the present evaluation we propose a test set comprising six different molecules (see Figure 1). These molecules are (*R*)-norcamphor (**1**), (*S*,*S*)-(−)-α-pinene (**2**), (*S*)-2-phenyl-3,3-dimethylbutane (**3**), (*M*)-tetramethylpyrrolohelicene (**4**), (*S*)-14,17-dimethyl[2](1,3)-azuleno[2]paracyclophane (**5**), and cyclo-(*S*)-proline-(*S*)-alanine (**6**). Molecules **1** and **2** were part of several test sets in the past, whereas the other four systems represent new examples. We chose these systems also to encourage researchers to evaluate new methods on other than the commonly examined compounds. Indeed, the CD spectra of systems **3** and **6** are investigated for the first time here with a sophisticated quantum chemical method. The CD spectrum of **4** was investigated twice in the past, though the nature of its absorption bands has never been discussed.[46,47]

Besides testing whether TD-B2PLYP is a reliable method for determining absolute configurations of molecules, our aims are to evaluate, first, whether TD-B2PLYP can solve the above-mentioned shift problem as it tends to give more accurate excitation energies.[45] Second, we will investigate whether the inclusion of more "exact" exchange inhibits the emergence of ghost states in CD spectra. Third, we want to examine how the perturbation correction influences the CD spectra and particularly in what terms higher lying excited states are treated by this correction. This is often easier to examine in CD than in conventional UV/vis spectroscopy because the problem of overlapping bands is not that severe in the former technique. The TD-B2PLYP approach will be compared to results obtained with the hybrid-GGA part of the double-hybrid functional (TD-B2LYP) and the popular TD-B3LYP method as it basically contains the same density functional components as TD-B2LYP and TD-B2PLYP.

Theory

Double-hybrid density functionals are situated on the fifth rung in Perdew's scheme of "Jacob's ladder"[48] as they include virtual Kohn−Sham orbitals (KS orbitals). Compared to hybrid-GGA functionals (fourth rung), where some part of the exchange functional is substituted by "exact" (HF) exchange, DHDFs additionally substitute some part of the correlation functional by mixing in a nonlocal perturbative correlation. This correlation part basically is obtained by a second-order Møller−Plesset (MP2) type treatment based on KS orbitals and eigenvalues. In the following, a brief account of the double-hybrid density functional B2PLYP[41] is given. First, Kohn−Sham orbitals are generated from the hybrid-GGA portion of the DHDF, which is denoted by B2LYP,

$$E_{\mathrm{XC}}^{\mathrm{B2LYP}} = (1 - a_{\mathrm{X}})E_{\mathrm{X}}^{\mathrm{B88}} + a_{\mathrm{X}}E_{\mathrm{X}}^{\mathrm{HF}} + (1 - a_{\mathrm{C}})E_{\mathrm{C}}^{\mathrm{LYP}} \qquad (1)$$

The hybrid-GGA part B2LYP contains Becke 1988 (B88)[49] exchange $E_{\mathrm{X}}^{\mathrm{B88}}$ combined with "exact" exchange $E_{\mathrm{X}}^{\mathrm{HF}}$ and Lee−Yang−Parr (LYP)[50] correlation $E_{\mathrm{C}}^{\mathrm{LYP}}$. The a_{X} and a_{C} are mixing parameters for the "exact" exchange and perturbative correlation, respectively. A second-order perturbation treatment, based on the KS orbitals and eigenvalues resulting from the B2LYP calculation, is carried out yielding the correlation energy $E_{\mathrm{C}}^{\mathrm{PT2}}$ that is scaled by the mixing parameter a_{C}. Thus, the final form of the B2PLYP exchange correlation energy $E_{\mathrm{XC}}^{\mathrm{B2PLYP}}$ is given by

$$E_{\mathrm{XC}}^{\mathrm{B2PLYP}} = E_{\mathrm{XC}}^{\mathrm{B2LYP}} + a_{\mathrm{C}}E_{\mathrm{C}}^{\mathrm{PT2}} \qquad (2)$$

Note that B2PLYP depends only on two parameters. Optimization of these with respect to ground-state thermodynamic properties gave values of 0.53 for a_{X} and 0.27 for a_{C}.[41] For recent attempts to find improved values, see ref 51.

Electronically excited states can be calculated within the framework of TD-DFT.[5−7] For the interaction of matter with weak electromagnetic radiation, the TD-DFT formalism can be based on linear response theory by taking into account the adiabatic approximation of DFT.[7] The poles of the response function correspond to the excitation energies, and the resulting equations are described by a random-phase approximation (RPA)-type eigenvalue problem. What we call TD-B2PLYP is in fact a simplified ansatz: instead of a fully time-dependent treatment of all parts of the energy functional, first, the excitation energy $\omega_{\mathrm{TD\text{-}B2LYP}}$ is calculated for the hybrid-GGA portion B2LYP. This is done within the standard TD-DFT formalism. In a second step a perturbative correction is added to this part. This procedure is completely analogous with a B2PLYP treatment of the electronic ground state. In the present form of

TD-B2PLYP[45] theory, this correction $\Delta_{(D)}$ is based on the CIS(D) method (*configuration interaction with perturbative doubles correction*) developed by Head-Gordon and co-workers.[52] Basically CIS(D) is a second-order perturbation treatment based on a CIS reference wave function involving single and double excitations of the CIS determinant or in other words double and triple excitations with respect to the Hartree−Fock ground-state determinant. In spin orbital form this correction term is given by

$$\Delta_{(D)} = \sum_{ia} v_a^i t_a^i - \frac{1}{4}\sum_{ijab} \frac{(u_{ab}^{ij})^2}{\epsilon_a + \epsilon_b - \epsilon_i - \epsilon_j - \omega_{\mathrm{CIS}}} \qquad (3)$$

with

$$v_i^a = \frac{1}{2}\sum_{jkbc} \langle jk\|bc\rangle [t_b^i t_{ca}^{jk} + t_a^j t_{cb}^{ik} + 2t_b^j t_{ac}^{ik}]$$

$$u_{ab}^{ij} = \sum_c \langle ab\|cj\rangle t_c^i - \langle ab\|cj\rangle t_c^j - \sum_k \langle ka\|ij\rangle t_b^k - \langle kb\|ij\rangle t_a^k \qquad (4)$$

Here, *i*, *j*, and *k* refer to occupied spin orbitals in the reference determinant and *a*, *b*, and *c* to virtual orbitals, and *t* stands for single- and double-excitation amplitudes, respectively. The first term on the right-hand side of eq 3 is dubbed “direct term” and can be interpreted as an orbital relaxation energy. The second term is the so-called “indirect term” as it additionally involves double excitations of “CIS-inactive” electrons and therefore provides a MP2 type correlation energy for the electronic excited state.

In our TD-B2PLYP approach, the above procedure is applied to the B2LYP determinant and the RPA type excitation amplitudes from the TD treatment replace the corresponding CIS amplitudes. The calculated correction $\Delta_{(D)}$ is weighted by the factor a_C and added to the excitation energy of the hybrid portion $\omega_{\text{TD-B2LYP}}$, yielding the total excitation energy $\omega_{\text{TD-B2PLYP}}$

$$\omega_{\text{TD-B2PLYP}} = \omega_{\text{TD-B2LYP}} + a_C\Delta_{(D)} \qquad (5)$$

The factor a_C has the same value as that for the ground state in B2PLYP (0.27). Note that in this procedure only the energy is corrected while all computed properties (e.g., transition moments for CD) refer to the conventional TD-hybrid-GGA (i.e., TD-B2LYP) level. TD-B2PLYP calculations can thus be performed with any quantum chemical program that has TD-DFT as well as CIS(D) type algorithms included. Although it is in principle possible to fully derive also the CD intensities including the PT2 term, this would lead to computationally very demanding calculations (of TD-MP2 complexity). The same holds for the related computation of optical rotation in a B2PLYP linear response treatment. In the TD-B2PLYP ansatz presented here, the PT2 part formally scales as order N^5 with system size compared to the standard hybrid-GGA part with N^4 scaling. The prefactor for the PT2 part, though, is in typical applications rather small, and thus TD-B2LYP or TD-B3LYP are not much (less than a factor of 2) faster than TD-B2PLYP. Moreover, extensive previous experience shows that the crucial point in theoretical CD spectroscopy is the correct computation of vertical excitation energies and that the transition moments, which are already quite accurate with standard functionals, are of less importance. Furthermore, better excitation energies indirectly influence the band intensities when finite band widths are considered and bands strongly overlap (which is often the case).

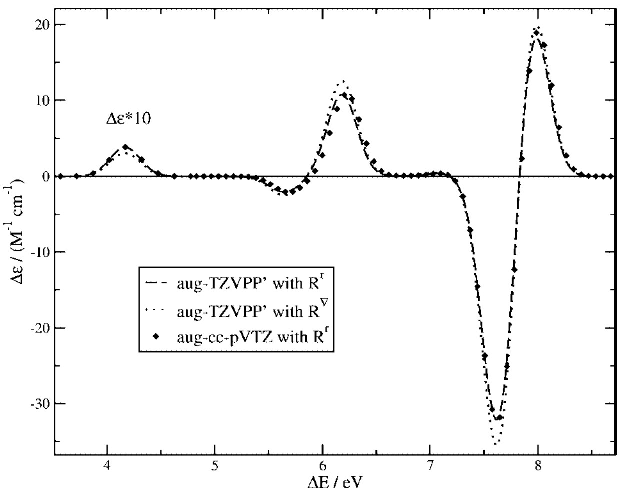

Figure 2. Comparison of the influence of technical parameters for the theoretical CD spectra of (*R*)-norcamphor (**1**). The spectra were obtained with the B2PLYP method and the basis sets aug-TZVPP′ and aug-cc-pVTZ. In the case of the aug-TZVPP′ basis, two spectra were simulated by using the rotational strengths obtained with the dipole length (R^r) and velocity (R^∇) formalism, respectively. The aug-cc-pVTZ spectrum was simulated by using R^r values. The intensity of the first band at ca. 4 eV was enhanced by a factor of 10 in each case.

Computational Details

All calculations were carried out with the TURBOMOLE V5.9 suite of programs.[7,53−64] The CIS(D) type perturbative correction in the TD-B2PLYP approach was calculated with the program RICC[65] developed in our group. The structures of molecules **1**−**4** were optimized with the RI-MP2 (RI = resolution of the identity)[66,67] method. For the geometry of the cyclophane (**5**) the density functional PBEsol,[68] which is adequate for the description of the complex stereoelectronic effects in this case,[69] was used. This optimization was also carried out within the RI approximation.[59] The structures of the two relevant conformers of **6** were computed with B3LYP.[35,36] These optimizations included the COSMO[70] model to simulate effects of the solvent acetonitrile (dielectric constant of ϵ = 37.5).[71] For all optimizations the Ahlrich’s triple-ζ type basis sets with one set of polarization functions (TZVP) were applied.[72] The (TD-)DFT calculations were carried out with the numerical quadrature grid m4.[64] The convergence criterion for the optimizations regarding the change of total energy between two subsequent optimization cycles was set to 10^{-7} E_h.

Vertical excitation energies and rotational strengths in dipole length form (R^r) were calculated according to the TD-B2PLYP, TD-B2LYP, and TD-B3LYP formalisms. The R^r values were compared with those obtained from the origin-independent velocity formalism (R^∇). For the computation of chiroptical properties with TD-DFT methods there is usually no major difference between these two values. In fact, the length form seems to be more robust in terms of, e.g., quicker convergence to the basis set limit and therefore is the better choice (as was shown in detail for the calculation of the related frequency-dependent optical rotation).[73] In the case of TD-B2PLYP, the R^r values of the B2LYP calculation were taken to simulate the spectra, as the perturbation correction only affects the vertical excitation energies (see above). To validate this choice, we compare the CD spectra of (*R*)-norcamphor simulated with R^r and R^∇ in Figure 2. One can clearly see that there are only tiny differences between the intensities of both spectra.

All TD-DFT calculations were carried out with Ahlrichs type basis sets.[72] The reason is that these are more efficient than the

TABLE 1: Comparison of Positions and Intensities of CD Bands in the Experimental and Theoretical Spectra of Molecules 1−6

	expt		B2PLYP		B2LYP		B3LYP	
	ΔE[a]	$\Delta\varepsilon$[b]	$\delta\Delta E$[c]	η[d]	$\delta\Delta E$	η	$\delta\Delta E$	η
(*R*)-Norcamphor (**1**)								
A	4.25	0.42	− 0.08	0.9	0.23	1.0	−0.06	0.8
B	6.29	−3.3	−0.64	0.6	0.41	0.8	−0.75	0.3
C	6.77	18.9	−0.59	0.6	0.46	0.7	−0.67	0.4
D	7.33	−9.4	0.27	3.4	0.96	2.9	0.03	2.0
(*S*,*S*)-(−)-α-Pinene (**2**)								
A	5.66	2.6	−0.27	0.9	0.03	1.0	−0.52	1.4
B	6.14	−7.4	−0.32	1.7	−0.03	1.7	−0.63	0.7
C	6.77	18.1	0.38	0.9	−0.03	0.9	−0.60	0.9
(*S*)-2-Phenyl-3.3-dimethylbutane (**3**)								
A	4.75	0.16	0.37	1.7	0.80	1.7	0.53	2.4
B	5.88	3.4	0.19	0.9	0.10	0.9	0.01	1.2
C	6.49	23.8	0.32	0.8	0.55	0.8	0.25	1.3
(*M*)-Tetramethylpyrrolohelicene (**4**)								
A	3.34	8.6	0.17	4.8	0.43	5.2	−0.02	3.9
C	3.93 [e]	−65.3	0.03	2.7	0.36	3.4	−0.15	2.0
F	5.71	150.1	−0.02	1.5	0.68 [e]	1.5	0.04	2.3
(*S*)-14,17-Dimethyl[2](1,3)azuleno[2]paracyclophane (**5**)								
A	1.91	− 1.4	0.10	0.8	0.37	0.9	0.27	1.0
B	3.36 [e]	− 1.4					−0.1	−1.0
C	3.96	9.4					−0.11	1.4
D	4.20	27.4	−0.04	0.1				
E/F [e]	4.76	− 66.7	−0.02	1.0	0.19	1.4	−0.01	0.9
G	5.69	168.2	−0.05	1.1	0.45	1.0	−0.05	0.9
H	6.25	− 46.0	−0.29	1.8	0.20	1.1	−0.21	1.6
Cyclo-(*S*)-proline-(*S*)-alanine (**6**)								
A	5.19	1.9	0.21	0.1	0.66	0.01		
B	5.55	− 3.7	0.20	0.3	0.68	0.2	0.11	0.7
C	5.89	4.7	0.53	3.5	1.24	4.4	0.31	0.5
D	6.42	−41.7	0.40	1.3	1.2	1.6	0.10	0.4

[a] In electronvolts. [b] In liters per mole per centimeter. [c] $\delta\Delta E = \Delta E_{\mathrm{theor.}} - \Delta E_{\mathrm{expt}}$; in electronvolts. [d] $\eta = (\Delta\epsilon_{\mathrm{theor.}})/(\Delta\epsilon_{\mathrm{expt}})$. [e] Averaged over several bands.

corresponding ones proposed by Dunning,[74−77] as the latter contain more primitive Gaussian functions. In our case a TZVPP[72] basis with discarded f-functions was applied to all atoms except for hydrogen, for which a TZVP basis was used. In the following, this mixed basis set is denoted by TZVPP′. In the case of molecules **1** and **2**, diffuse spd-functions, which have been taken from the Dunning basis set aug-cc-pVTZ,[74−77] were added to all atoms. The resulting basis set is dubbed aug-TZVPP′. Because the RI approximation is also used for the perturbative corrections, auxiliary basis functions are needed, which were taken from the TURBOMOLE library.[63] To give an example for the efficiency of the here-proposed basis set, we carried out an additional TD-B2PLYP calculation with the aug-cc-pVTZ basis set in the case of molecule **1**. The simulated CD spectrum (here the R^{r} values were used) is also shown in Figure 2. One can clearly see that both basis sets give almost identical results.The total computation time increases by a factor of 5 for aug-cc-pVTZ compared to aug-TZVPP′.

All theoretical CD spectra were simulated by overlapping Gaussian functions for each transition. A value of $\sigma = 0.2$ eV for the width of the absorption band at a height of $1/e$ was chosen.

Results and Discussion

In this section, the CD spectra obtained with the three methods B2PLYP, B2LYP, and B3LYP are compared to each other and the performance is evaluated by comparison to experimental data. In the following we will skip the prefix “TD” because all discussed spectra are based on a TD-DFT treatment. Each of the six molecules is discussed separately. For each molecule, the three theoretical spectra are shown in one figure and compared with the experimental spectrum. Additionally, the positions and rotational strengths of individual transitions obtained with B2PLYP are shown as vertical bars. For representative CD bands the error $\delta\Delta E$, which is the difference between the theoretical and experimental excitation energies, is computed. A positive value for this difference means therefore that theoretical bands are blue-shifted (too high in energy) and vice versa. Note that $\delta\Delta E$ in the general case refers to the positions of entire CD bands, which can contain several transitions, instead of the typically reported errors that are based on a state by state comparison.

To evaluate the intensities and signs of the absorption bands, the quotient $\eta = \Delta\epsilon_{\mathrm{theor}}/\Delta\epsilon_{\mathrm{expt}}$ is calculated. An absolute value greater than unity means that the intensity of the theoretical band is overestimated and vice versa, while a negative value indicates a wrong sign, which may lead to problems in the assignment of absolute configuration. The values for $\delta\Delta E$ and η together with experimental excitation energies and intensities $\Delta\epsilon$ are shown in Table 1. Note that in two cases (**1** and **2**) experimental gas-phase spectra are examined, which allow a direct comparison with our calculations. In the remaining four cases the experimental spectra were recorded in solution, which

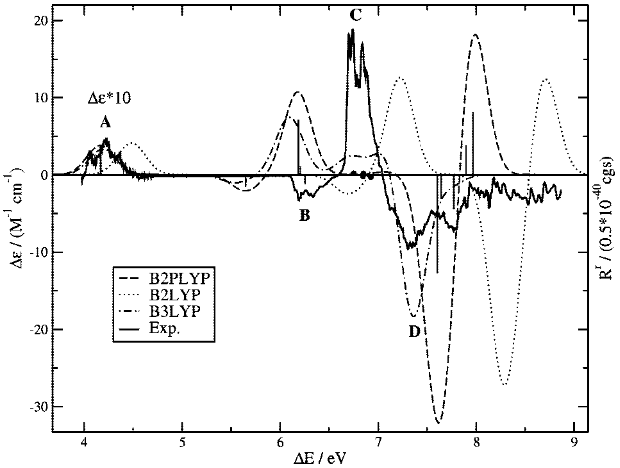

Figure 3. Comparison of theoretical and experimental CD spectra of (***R***)-norcamphor (**1**). The theoretical spectra were obtained with B2PLYP, B2LYP, and B3LYP by using the aug-TZVPP′ basis set. In each case the first 15 electronic transitions were computed. Bars indicate the positions and rotational strengths of electronic transitions calculated with B2PLYP. Dots mark transitions with small rotational strengths. The intensity of band **A** was enhanced by a factor of 10 in all cases. The experimental spectrum was recorded in the gas phase.[79]

typically leads to a red shift of about 0.1−0.2 eV compared to the gas phase.

(*R*)-Norcamphor. The basic chromophore in the bicyclic ketone **1** is the carbonyl group. It is a so-called inherent achiral chromophore as it exhibits local C_{2v} symmetry that is perturbed by the chiral sphere of the rigid bicyclic backbone. The first electronic transition in carbonyl compounds is the electric dipole-forbidden but magnetically dipole-allowed n→π* transition at about 4 eV. Its intensity and sign in a CD spectrum depend strongly on its surrounding chiral sphere, which is the basis of the famous empirical octant rule for ketones.[78] Although it yields qualitatively correct results for simpler ketones, it is not valid for the description of bicyclic ketones such as, e.g., **1**.

Pulm et al. recorded gas-phase spectra of camphor derivatives (including **1**) and compared them with thorough theoretical investigations based on the DFT/SCI method.[79] Their theoretical results were later confirmed by Diedrich and Grimme.[2] The experimental gas-phase spectrum is shown in Figure 3. It exhibits four distinct absorption bands. The positions and intensities of these four bands are given in Table 1. The n→π* transition (**A**) at 4.25 eV shows a positive sign. Because of the low intensity, all bands **A** were enhanced by a factor of 10 in Figure 3. The next three bands **B**−**D** belong to the n→3(spd) Rydberg series. Pulm et al. pointed out that the sign of band **B** is rather sensitive to the chiral sphere and that high-lying σ→π* valence transitions mix with the n→3d transitions.

The spectra obtained with B2PLYP, B2LYP, and B3LYP are also shown in Figure 3. The B2PLYP and B3LYP spectra show good agreement with experiment and with each other in terms of excitation energies and band intensities. The position of band **A** is underestimated by 0.08 eV (B2PLYP) and 0.06 eV (B3LYP), respectively. The intensities are slightly lower than in the experiment. In the B2LYP spectrum, band **A** is blue-shifted by roughly 1.0 eV. The signs of the next two bands are correct, but the their excitation energies are underestimated by B2PLYP and B3LYP and overestimated by B2LYP. The B2PLYP errors are −0.64 eV for the n→3s and −0.59 eV for the n→3p bands. The B3LYP errors are slightly larger with −0.75 and −0.67 eV, respectively. The errors for B2LYP are opposite (i.e., 0.41 and 0.46 eV). The positions of both bands relative to each other are reproduced quite well: the spacing between the maxima of bands **B** and **C** is 0.48 eV experimentally, 0.53 eV for B2PLYP and B2LYP, and 0.56 eV for B3LYP. The intensities of both bands are underestimated by all methods though the error is largest for B3LYP with a quotient $\eta = 0.3$ and 0.4, respectively. The position of the fourth band is blue-shifted compared to experiment for all methods though the error for B3LYP is smallest with a deviation of only 0.03 eV. B2PLYP shows an error of 0.27 eV, and B2LYP is off by almost 1 eV. The intensity of this band is overestimated by more than a factor of 2 (B3LYP). It has to be noted that B3LYP additionally yields an artificial band with positive sign between bands **C** and **D**, whereas the other two methods do not exhibit this flaw.

A comparison between B3LYP and B2LYP, whose GGA components are basically the same, shows that the inclusion of more "exact" exchange leads to a blue shift of the band and increasing errors for the excitation energies. This effect is compensated for by the perturbative correlation contribution as demonstrated by the red shift of the B2PLYP spectrum compared to B2LYP. The reason why the errors for the Rydberg states remain relatively large is that even B2PLYP suffers from the wrong asymptotic behavior of the B88 exchange-correlation potential. Moreover, the CIS(D) correction itself (even when based on KS-DFT input) describes Rydberg excitations not very well (see ref 45 and references therein), which is an additional error source in the case of B2PLYP.

(*S*,*S*)-(−)-α-Pinene. The chiral olefin **2** contains a triply substituted, endocyclic carbon−carbon double bond. The chirality of **2** is primarily not induced by a torsion of this double bond but by the methyl groups in the so-called third chiral sphere. Similar to the n→π* transition in chiral ketones, an octant rule was developed for the n→π* transition in chiral olefins.[80] Due to the mixing of this valence with several Rydberg transitions, the octant rule is not valid for a series of compounds including **2**. Diedrich and Grimme confirmed the strong mixing between these states and could show that the nature and interpretation of each absorption band observed in the CD spectrum strongly depends on the method.[2] The most recent calculations of CD spectra of chiral alkenes with TD-DFT were carried out by McCann and Stephens in 2006.[12] Among others they also simulated the spectrum of the enantiomer of **2**.

The experimental spectrum was recorded in the gas phase by Mason et al. (Figure 4).[81] It shows five bands in the range between 5.7 and 7.7 eV. The theoretical spectra obtained with the three investigated methods are also shown in Figure 4. A comparison with experiment is done for the first three bands also in Table 1. These values and a visual inspection of the spectra in Figure 4 show that the B2LYP approach yields the best results. The absolute errors for excitation energies are in every case only about 0.03 eV, and except for band **B**, whose intensity is overestimated by a factor of about 2, the intensities are in very good agreement with experiment. The B3LYP approach, which contains less "exact" exchange than B2LYP/B2PLYP, provides the largest errors. The positions of the first three bands are red-shifted by 0.52, 0.63, and 0.60 eV. The B2PLYP bands are also red-shifted and lie between those of the other two methods. The errors are between −0.27 and −0.38 eV. The intensities of the three bands are almost the same as for B2LYP. The spacings between the bands are qualitatively correct for B2LYP and B3LYP. In the case of the double-hybrid functional, the gap between bands **B** and **C** is overestimated by a factor of about 2 (0.6 eV in the experiment and 1.3 eV for

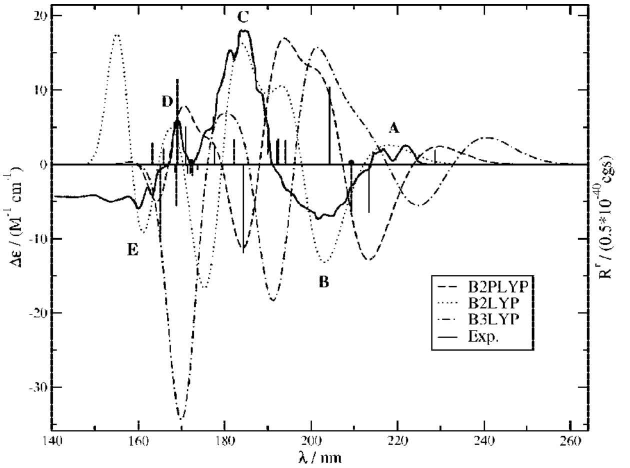

Figure 4. Comparison of theoretical and experimental CD spectra of (*S*,*S*)-(−)-α-pinene (**2**). The theoretical spectra were obtained with B2PLYP, B2LYP, and B3LYP by using the aug-TZVPP′ basis set. In each case the first 25 electronic transitions were computed. Bars indicate the positions and rotational strengths of electronic transitions calculated with B2PLYP. Dots mark transitions with small rotational strengths. The experimental spectrum was recorded in the gas phase.[81]

B2PLYP). An analysis of the last two higher lying bands seems to be difficult, as each theoretical method provides a rather different picture.

(*S*)-2-Phenyl-3,3-dimethylbutane. Compound **3** is an example for a planar, achiral benzene chromophore that is perturbed by an attached asymmetric carbon atom. Because the chirality-inducing substituent is rather bulky, conformational stability is to be expected, making this molecule ideal for an analysis of this fundamental chromophore. Compound **3** was the first compound of this type whose CD spectrum was investigated experimentally in the 1970s.[82] Zandomeneghi carried out the first theoretical investigation of **3** on the basis of the classical model of coupled oscillators.[83] Giorgio et al. added this molecule to a test set for computations of optical rotation.[84] The present work is the first quantum chemical investigation of its CD properties.

The experimental spectrum was recorded in a mixture of methylcyclohexane and isopentane. It clearly exhibits three absorption bands with positive signs that can be assigned to the typical electronic transitions of a substituted benzene. According to the Platt nomenclature[85] these are the transitions into the L_b (band **A**), L_a (band **B**), and the B_b and B_a states (band **C**). Because the substituent is saturated, additional states are not expected and, thus, any theoretical method should exactly predict these four lowest-lying excited states as mentioned above. Only B2PLYP and B2LYP feature these four transitions. Because of its smaller amount of "exact" HF exchange, B3LYP yields an additional artificial transition between the L and B states with an excitation energy of 6.65 eV and a nonnegligible rotational strength of 16.7×10^{-40} cgs units.

All theoretical spectra exhibit three bands with correct positive signs. The intensities are overestimated in the case of the first band, while the accuracy is acceptable for the last two bands with quotients $\eta = 0.9$ and 0.8 for the B2PLYP and B2LYP methods. B3LYP overestimates these last two bands slightly. The relative intensities when comparing the bands with each other are qualitatively correct: the intensities increase when going from band **A** to **C**. The best agreement with experiment for band **A** is found for B2PLYP, although its position is blue-shifted by 0.37 eV. The errors are larger for the other two functionals (i.e., 0.80 eV for B2LYP and 0.53 eV for B3LYP).

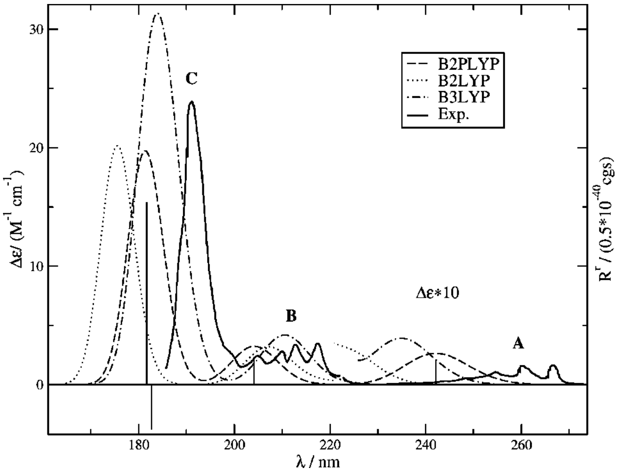

Figure 5. Comparison of theoretical and experimental CD spectra of (*S*)-2-phenyl-3,3-dimethylbutane (**3**). The theoretical spectra were obtained with B2PLYP, B2LYP, and B3LYP by using the TZVPP′ basis set. In the case of B2PLYP and B2LYP the first four electronic transitions were computed; in the case of B3LYP, the first five transitions. Bars indicate the positions and rotational strengths of electronic transitions calculated with B2PLYP. Dots mark transitions with small rotational strengths. The intensity of band **A** was enhanced by a factor of 10 in all cases. The experimental spectrum was recorded in a mixture of methylcyclohexane and isopentane (1:3).[82]

The B3LYP method seems to yield the best results for the other two bands with errors of only 0.01 and 0.25 eV. B2PLYP gives errors of 0.19 and 0.32 eV and B2LYP of 0.10 and 0.55 eV. Although B3LYP partially seems to give better results at first glance, the B2PLYP method has to be favored. First, band **C** contains the artificial transition with a rather large rotational strength in the case of B3LYP. Second, an evaluation of the relative band positions shows that B2PLYP is clearly superior. The experimental spacing between the maxima of the L_b and L_a bands is 1.13 eV. B2PLYP gives 0.95 eV and B3LYP only 0.67 eV, meaning that the L_b and L_a transitions lie too close to each other. B2LYP yields an even smaller gap of 0.43 eV. Parac and Grimme already reported in 2003 problems in the description of the L states of aromatic compounds with hybrid functionals.[33,34] Our results show that the perturbative correlation counterbalances the flaw of conventional hybrid functionals, which cannot describe the spacing between these two transitions accurately. The gap between the last two bands is experimentally 0.61 eV. Also here B2PLYP gives the best agreement with 0.74 eV compared to 0.85 (B3LYP) and 1.06 eV (B2LYP).

(*M*)-Tetramethylpyrrolohelicene. Helical structures play an important role, particularly in biochemistry (e.g., DNA, polypeptides). To better understand chiroptical properties of screw-shaped molecules, the helicenes have become important model compounds consisting of a strongly conjugated, inherent chiral chromophore. A thorough investigation of the CD spectra of helicenes with TD-DFT was carried out by Furche et al. in 2000.[25] Helicenes and other molecules with helical structures have recently been investigated with semiempirical methods.[86] Helicenes were also recently used as model compounds in a theoretical investigation of the two-photon circular dichroism phenomenon.[87]

The B2PLYP approach has already been successfully tested for the CD spectrum of (*M*)-heptahelicene.[45] Unpublished results obtained in our group show that it yields also very good results for the shorter homologues. In this work the CD spectrum of the more complicated (*M*)-tetramethylpyrrolohelicene (**4**) is discussed. The interesting aspect of **4** is that two benzene units

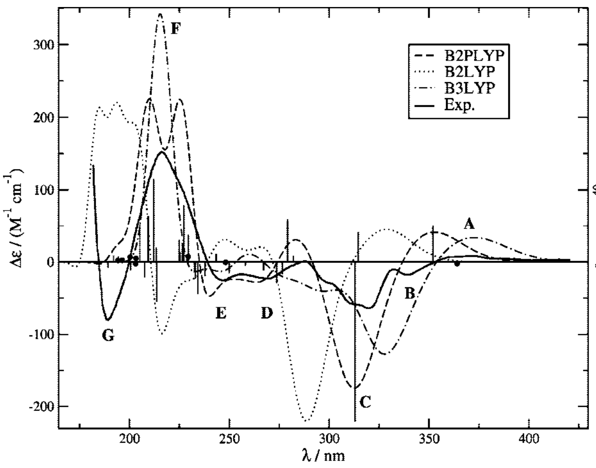

Figure 6. Comparison of theoretical and experimental CD spectra of (*M*)-tetramethylpyrrolohelicene (**4**). The theoretical spectra were obtained with B2PLYP, B2LYP, and B3LYP by using the TZVPP′ basis set. In the case of B2PLYP and B2LYP the first 40 (20 in *A* and 20 in *B* symmetry) electronic transitions were computed; in the case of B3LYP the first 30 transitions were considered. Bars indicate the positions and rotational strengths of electronic transitions calculated with B2PLYP. Dots mark transitions with small rotational strengths. The experimental spectrum was recorded in *n*-hexane.[46]

of a (*M*)-hexahelicene molecule are formally substituted by pyrrolo units. This hinders conjugation between the terminal and middle rings and is expected to strongly influence the shape of the CD spectrum. Theoretical investigations of **4** were carried out twice: in 1996 the system was examined with the semiempirical NDDOS/SCI method and in 1998 with TD-B3LYP.[46,47] The results allowed the determination of its absolute configuration, but the origin of the different absorption bands was not reported. The experimental spectrum was recorded in *n*-hexane and shows seven absorption bands in a range from 3.3 to 6.5 eV (Figure 6).[46] The system has C_2 symmetry so that electronic excited states in *A* and *B* symmetry are expected. For the calculation of the B3LYP spectrum 30 transitions (15 for each symmetry) were necessary. In the case of the B2PLYP method a total of 40 transitions had to be calculated in order to comprise the last two bands. This indicates problems of the perturbation correction for high-lying excited states. The B2LYP spectrum was simulated for all 40 transitions that were necessary for the B2PLYP calculation.

The first band in the spectrum of B3LYP is caused by the lowest electronic transition into the 1^1A state at 3.32 eV. The excitation energy and therefore the position of band **A** is in very good agreement with experiment (3.34 eV). The first band in the B2PLYP spectrum is also due to this 1^1A state though the lowest excited state has *B* symmetry (3.41 eV). Because of its small rotational strength (-2.4×10^{-40} cgs), it does not influence the spectrum. Band **A** is blue-shifted by approximately 0.17 eV compared to experiment. B2LYP also yields an A state as the lowest one. The error for the excitation energy is largest (0.43 eV). The signs of band **A** are correct, but their intensities are all overestimated. B3LYP gives the smallest error with an η value of about 4.

The second experimental band is not reproduced by any of the three methods. This is in agreement with the previous findings. The nature of band **B** has not been elucidated yet, but the theoretical results might indicate that it is of vibronic origin. Vibronic effects are not included in our study, and therefore certain characteristics of the spectra cannot be reproduced (for a method of calculating the vibronic fine structure in CD spectra, see ref 88).

In contrast to the first band, which was better described by B3LYP, band **C** in the B2PLYP spectrum fits the experiment better. A blue shift of only 0.03 eV is observed in contrast to B3LYP, which provides a red shift of 0.15 eV and to B2LYP with a blue shift of 0.36 eV. All three methods assign this band to a transition into the 2^1B state. The intensities are overestimated by a factor of 2 (B3LYP) and more.

A quantitative discussion of the next two bands is difficult. B2PLYP is the only method that correctly predicts positions, intensities, and signs as can be seen in Figure 6. An assignment of these two bands for the other two methods is not clearly possible.

Band **F** is observed at 5.71 eV in the experimental spectrum. B3LYP predicts its position almost correctly with an error of 0.04 eV. In this energy range additional B2PLYP states are computed that were necessary to cover the whole range of the spectrum. Band **F** is split into two halves of similar intensity in the case of B2PLYP. The average excitation energy is 5.69 eV, which indicates an error of only 0.02 eV. The position of this band also had to be averaged in the case of B2LYP and is found to be blue-shifted by 0.68 eV. Due to the differences between the three methods a meaningful assignment of the nature of band **F** cannot be given. This also holds for the last band **G** that is not described by any of the three methods.

Summing up one can say that B2PLYP shows some deficiencies that are probably due to problems with the perturbation correction for the higher lying states. For the determination of the absolute configuration, however, it gives more reliable results than B3LYP as the first five bands are correctly calculated in position and sign, whereas B3LYP yields only three correct bands.

(*S*)-14,17-Dimethyl[2](1,3)azuleno[2]paracyclophane. In the past, the chiroptical properties of cyclophanes was a major research topic and several theoretical investigations have been carried out.[24,26,28,89−91] A very interesting cyclophane is molecule **5** because it is made out of two very different aromatic units. Grimme et al. already carried out a detailed experimental and theoretical analysis of this molecule.[24,26] Compound **5** consists of a benzene unit bridged with an azulene moiety. Chirality is induced by the two methyl groups in positions 14 and 17 and by the bridging unit together with the azulene chromophore.

We chose to include this system in our study as the spectrum covers a wide energy range between 2 and 6.5 eV (Figure 7) with a variety of different $\pi\rightarrow\pi^*$ states, including charge-transfer or exciton coupling. The spectrum consists of two parts, of which the first between 2 and 4 eV shows a lower intensity than the second one.

In general all three methods applied in this work are able to calculate the main aspects of the experimental spectrum. The functionals reproduce the first absorption band with the correct sign and intensity although the theoretical bands are consistently blue-shifted. The error is smallest in the case of B2PLYP (0.10 eV).

The next two bands **B** and **C** are only observed in the B3LYP spectrum. Band **B** is reproduced with the wrong sign. This weak band is likely to be caused by vibronic effects, which may be a reason for the wrong sign. Although B2PLYP does not yield band **B**, two electronic transitions with small rotational strengths (marked with dots in Figure 7) are computed in this region.

Band **D** is only reproduced by B2PLYP with a good agreement regarding the position (red shift of 0.04 eV) but a severe underestimation ($\eta = 0.1$) of its intensity. Regarding the next two bands, it is not clear whether they can be treated as two individual bands or just as one band with a vibronic fine

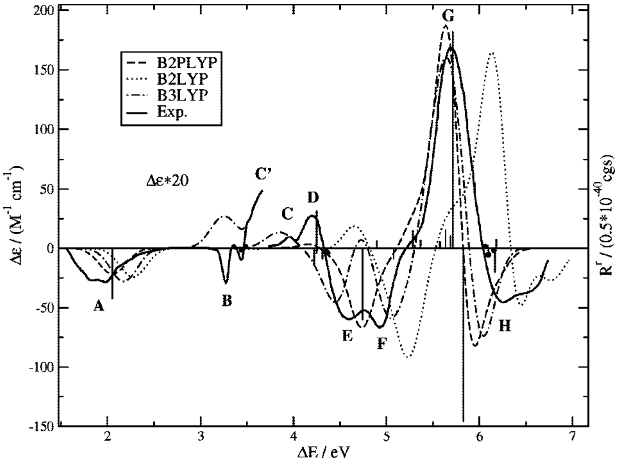

Figure 7. Comparison of theoretical and experimental CD spectra of (*S*)-14,17-dimethyl[2](1,3)azuleno[2]paracyclophane (**5**). The theoretical spectra were obtained with B2PLYP, B2LYP, and B3LYP by using the TZVPP′ basis set. In each case the first 25 electronic transitions were computed. Bars indicate the positions and rotational strengths of electronic transitions calculated with B2PLYP. Dots mark transitions with small rotational strengths. The intensities of bands **A**, **B**, and **C′** were enhanced by a factor of 20 in all cases. The experimental spectrum was recorded in *n*-hexane.[24]

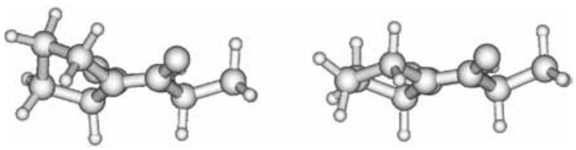

Figure 8. B3LYP+COSMO/TZVP optimized structures of conformers A (left) and B (right) of cyclo-(*S*)-proline-(*S*)-alanine (**6**).

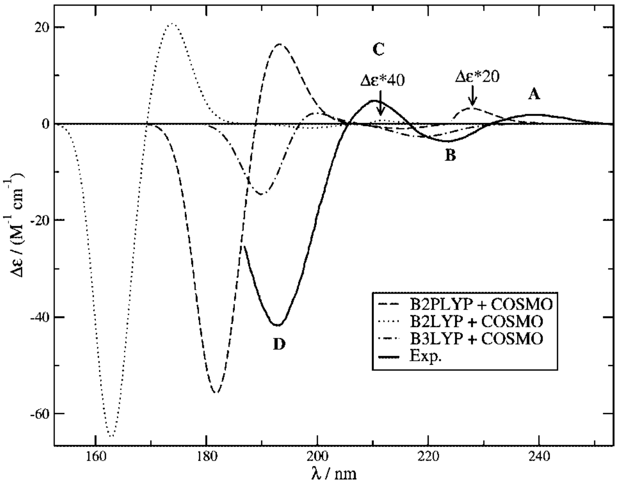

Figure 9. Comparison of theoretical and experimental CD spectra of cyclo-(*S*)-proline-(*S*)-alanine (**6**). The theoretical spectra were obtained for the two relevant conformers with B2PLYP, B2LYP, and B3LYP by using the TZVPP′ basis set and by applying a COSMO treatment for the electronic ground state in order to simulate solvent effects (ϵ = 37.5). For each conformer the first five electronic transitions were computed. The two spectra were weighted according to a Boltzmann population at 298 K in order to obtain the total spectrum, which is shown in this figure. The intensities of bands **A** are enhanced by factors of 20 and 40 for B2PLYP and B2LYP, respectively. The experimental spectrum was recorded in acetonitrile.[92]

structure. The hybrid functionals give two bands in the same region; the double-hybrid, only one. To make a comparison between the methods, an averaged excitation energy was calculated from the experimental spectrum and for the hybrid functionals. Qualitatively B2PLYP and B3LYP show comparable good results in terms of position, sign, and intensity.

Band **G** is reproduced almost identically by B2PLYP and B3LYP with small energy errors (−0.05 eV) and correct intensities. The last band **H** shows similarities between all three methods with errors of −0.20 eV and more.

Cyclo-(*S*)-proline-(*S*)-alanine. The CD spectra of a series of cyclic dipeptides containing (*S*)-proline were recorded and interpreted by Pančoška et al. in 1979.[92] Three of these dipeptides were theoretically reinvestigated by Carlson et al. in 2005.[93] In their studies the influence of ground-state geometries on the CD spectra simulated with the classical dipole-interaction model was tested. Their work also included dipeptide **6**, whose CD spectrum is calculated here for the first time fully quantum mechanically. The main part of the dipeptide is a piperazine-2,5-dione ring containing the two amide chromophores, which give rise to n→π* and π→π* transitions.

In this work structure optimizations at the B3LYP/TZVP level of theory were carried out. In contrast to previous investigations where only one conformer for **6** was found, these optimizations revealed the presence of actually two conformers within a relevant energy window of about 1 kcal·mol^{-1}. These two conformers are almost identical regarding the boat type conformation of the piperazine-2,5-dione ring but differ in the conformation of the five-membered pyrrolidine unit (see Figure 8, where the conformers are denoted by the capital letters A and B). Because of the polarity of the molecule and the small energy differences involved, we here include a COSMO[70] treatment in the optimizations to simulate the effects of the solvent acetonitrile. These B3LYP+COSMO/TZVP optimizations give an energy difference of 0.99 kcal mol^{-1} in favor of conformer B.

A fully consistent COSMO/TD-DFT treatment of electronically excited states is technically not possible at the moment. To estimate solvent effects on the CD spectra, we applied the COSMO model to the calculation of the ground state and solely used the COSMO modified orbitals and eigenvalues but otherwise carried out the standard gas-phase TD-DFT treatment. For each conformer, the first five excitation energies were calculated and a CD spectrum was simulated. The two resulting CD spectra were weighted according to a Boltzmann population at 298 K and then combined to give the final spectra shown in Figure 9. The weighting factors are 0.16 for conformer A and 0.84 for B.

The experimental spectrum was taken from Pančoška et al.[92] and shows four bands. The first two were assigned to the n→π* and the last two to the π→π* transitions.

The shape of the experimental spectrum is computed to be qualitatively correct with the B2PLYP and B2LYP approaches. The first two bands have the correct signs, although one has to admit that their intensities are severely underestimated. Both methods give rise to blue-shifted bands. In the case of B2PLYP the errors compared to experiment are smallest with about 0.2 eV (about 0.7 eV for B2LYP). The experimental spacing between both bands of 0.36 eV is reproduced quite well by both methods (i.e., 0.35 eV for B2PLYP and 0.38 eV for B2LYP).

The errors increase for the last two bands. They are blue-shifted by 0.53 and 0.40 eV for B2PLYP and by 1.24 and 1.2 eV for B2LYP. The experimental gap between bands **B** and **C** is overestimated by factors of 2 (B2PLYP) and 3 (B2LYP). The experimental spacing of 0.53 eV between the last two bands is slightly underestimated with 0.4 eV for B2PLYP and 0.49 eV for B2LYP. The intensity of band **C** is overestimated by a factor of roughly 4. The intensity of the last band fits the experiment relatively well. The relative intensities of the four bands are qualitatively correct for both methods.

The B3LYP spectrum is worse as it gives rise to three bands only. The reason is that the first two electronic states lie too close to each other and consequently the first band is covered by the second one. The errors regarding the positions of the three bands are 0.11, 0.31, and 0.10 eV. The spacing between bands **B** and **C** is overestimated with a value of 0.54 eV (experiment gives 0.34 eV), while it is underestimated with 0.32 eV for the last two bands. The intensities are also underestimated. Particularly bands **C** and **D** are too small by a factor of 2 and more, which leads to qualitatively incorrect relative intensities.

Additionally, we also carried out calculations in the gas phase in which the difference between the ground-state energies diminishes to 0.47 $\text{kcal}\cdot\text{mol}^{-1}$ (Boltzmann weighting factors of 0.31 (A) and 0.69 (B)). The final spectra, which also refer to the gas phase, are not shown here, but we would like to summarize some results. The B2PLYP and B2LYP spectra are red-shifted by 0.1 eV compared to the spectra in Figure 9. This finding is to be expected for $n \rightarrow \pi^*$ transitions in carbonyl compounds. Moreover the first two transitions lie too close to each other, meaning that instead of two bands with opposite signs only one band with negative sign is observed. This indicates that solvent effects play an important role for the shape of the spectra. Bands **C** and **D** are reproduced quite well, and particularly their intensities do not depend on the solvent effects considered. The B3LYP spectrum based on the gas-phase calculation does not show any resemblance with the experiment. The possible reason is the lack of sufficient "exact" exchange as the results become qualitatively reliable for the B2LYP approach.

Conclusions

The phenomenon of electronic circular dichroism (CD) enables the routine investigation of chiral systems and allows the elucidation of their structure-chiroptic properties and absolute configurations by computation. In this work time-dependent double-hybrid density functional theory in its B2PLYP form was evaluated regarding its performance for the prediction of electronic CD spectra. According to standard time-dependent density functional theory (TD-DFT), vertical excitation energies are calculated for the hybrid-GGA part and then corrected perturbatively yielding TD-B2PLYP excitation energies. The hybrid-GGA part contains a large portion of "exact" exchange (53%) that diminishes self-interaction error related problems but leads to an insufficient treatment of electron correlation. The latter effect is counterbalanced by the inclusion of the nonlocal perturbative CIS(D) type correlation in B2PLYP.

In this work TD-B2PLYP was compared to the hybrid-GGA methods TD-B2LYP and TD-B3LYP. These three approaches were applied to a new test set containing six molecules, of which two were investigated for the first time with quantum chemical methods. In our opinion this benchmark set seems to be very efficient as it contains just a few molecules that still show a wide variety of important characteristics. These are pure valence, pure Rydberg, and mixed Rydberg−valence transitions, charge-transfer excitations, and exciton coupling. We have included fundamental chromophores and biochemically relevant systems featuring extended π-conjugation, a helical structure, bridged aromatic chromophores, and peptide bonds. We encourage authors to make use of this set for future evaluations of new methods.

Our results show that TD-B2PLYP outperforms the standard hybrid-GGA methods. The majority of calculated excitation energies have smaller or at least the same errors as those computed with, e.g., TD-B3LYP. The inclusion of more "exact" exchange (i.e., from B3LYP to B2LYP) leads to a blue shift of CD bands. This error is counterbalanced in the TD-B2PLYP approach. The only problem seems to arise when the perturbative correction is applied to higher lying excited states as, e.g., found for the (*M*)-tetramethylpyrrolohelicene. Nevertheless, all of the six CD spectra computed with TD-B2PLYP are qualitatively correct. The TD-B3LYP method reproduced the spectrum of the pyrrolohelicene molecule rather badly and is inadequate for the description of the cyclic dipeptide cyclo-(*S*)-proline-(*S*)-alanine.

The diminished self-interaction error in TD-B2PLYP inhibits, moreover, the computation of artificial excited states ("ghost states"). This was shown for the (*R*)-norcamphor and (*S*)-2-phenyl-3,3-dimethylbutane molecules. Finally TD-B2PLYP reproduces relative band positions better than the hybrid-GGA approaches, except for (*S*,*S*)-(−)-α-pinene. In summary, we propose the TD-B2PLYP approach as a new routine method for the prediction of CD spectra, as it yields overall good results and in particular provides a more balanced description of states of different character than standard hybrid-GGA functionals.

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Supporting Information Available: Cartesian coordinates of all optimized structures used in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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