

## FEATURE ARTICLE

The Current State of *Ab Initio* Calculations of Optical Rotation and Electronic Circular Dichroism Spectra

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The current ability of *ab initio* models to compute chiroptical properties such as optical rotatory dispersion and electronic circular dichroism spectra is reviewed. Comparison between coupled cluster linear response theory and experimental data (both gas and liquid phase) yields encouraging results for small to medium-sized chiral molecules including rigid species such as (*S*)-2-chloropropionitrile and (*P*)-[4]triangulane, as well as conformationally flexible molecules such as (*R*)-epichlorohydrin. More problematic comparisons are offered by (*S*)-methyloxirane, (*S*)-methylthiirane, and (1*S*,4*S*)-norbornenone, for which the comparison between theory and experiment is much poorer. The impact of basis-set incompleteness, electron correlation, zero-point vibration, and temperature are discussed. In addition, future prospects and obstacles for the development of efficient and reliable quantum chemical models of optical activity are discussed, including the problem of gauge invariance, scaling of the coupled cluster approach with system size, and solvation.

## I. Introduction

The three-dimensional dissymmetry that characterizes chiral molecules also leads to their distinguishable enantiomeric responses to chiral electromagnetic fields (*e.g.*, left- and right-hand circularly polarized light).<sup>1</sup> If the details of the corresponding circular birefringence, dichroism, or scattering intensity differences are known in advance and can be related to a particular structure motifs, such responses may also be used to identify the absolute configuration of an enantiomerically pure sample. X-ray analyses may provide such details only if a single crystal is available and if the molecule incorporates a sufficiently heavy atom to allow reliable anomalous dispersion measurements.<sup>2</sup> In the case of noncrystalline compounds, however, often the only viable route to assignment of the absolute configuration

is asymmetric total synthesis of a known stereoisomer followed by comparison of its chiroptical spectra to those of the original compound. Unfortunately, this is frequently a costly and time-consuming endeavor. If, on the other hand, accurate, reliable, and efficient theoretical predictions of molecular chiroptical responses were available, these would be invaluable for the determination of absolute configurations of such chiral isolates.

Many *ab initio* theoretical methods are now well established as essential tools for understanding and predicting chemical phenomena, such as reaction kinetics, thermochemistry, and spectroscopy. For many properties such as molecular structure, vibrational and UV/vis spectra, *etc.* of small organic molecules, such tools are capable of providing accuracy rivaling even the best available experimental methods.<sup>3–5</sup> In the past decade much effort has also been expended toward the development of such first-principles models of optical activity, including Hartree–

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Fock,<sup>6</sup> density-functional theory (DFT),<sup>7–9</sup> and coupled cluster (CC) approaches.<sup>10–15</sup> Although a great deal of progress has been made, the task is nevertheless formidable, due to both the complexity of the problem and the difficulty of direct comparison to appropriate experimental data by which the efficacy of such models must be judged. For example, although the vast majority of laboratory measurements of optical rotation angles are made in liquid-phase environments, almost all available *ab initio* models are capable of simulating the chiroptical response only of isolated molecules. Given that the influence of solvent can often be dramatic—even altering the sign of the observed rotation in some cases (*vide infra*)—comparison between theory and experiment is problematic at best. In addition, the development of even gas-phase models of optical activity is complicated by issues of unphysical coordinate-origin and/or gauge dependence, conformational flexibility, vibrational/temperature effects, *etc.*, and the best routes to overcome these problems have yet to be identified for the most advanced theoretical methods.

This article describes recent efforts in our laboratory to develop high-level *ab initio* models for determining optical rotation angles and electronic circular dichroism spectra. Our work has focused on CC theory, sometimes described as the “gold standard” of quantum chemistry because of its oft-cited accuracy in reproducing experimentally determined structural, thermochemical, and spectroscopic properties. However, as we explain below, it is not yet known precisely what level of theoretical rigor is required to obtain “the right answer for the right reason” for optical rotation and circular dichroism spectra. Although the CC approach is more mathematically complicated and computationally expensive than simpler models such as DFT, its key advantage is that it is systematically extensible toward the formally exact limit; *i.e.*, each level of approximation may be superseded by an even more complete wave function expansion. Assuming sufficient computational resources are available, this “convergent” nature of CC theory provides a natural diagnostic for the quality of a given calculation and is thus crucial to unraveling the Gordian complexity of optical activity.

The nature of this article does not provide sufficient space to describe in sufficient detail the many important efforts underway in the field of optical activity, including that by Stephens,



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Cheeseman, and co-workers in the development and application of time-dependent DFT methods of optical activity;<sup>7–9,16–18</sup> by Polavarapu and co-workers in Hartree–Fock and more recently DFT treatments of optical rotation and especially its relationship to circular dichroism spectra through Kronig–Kramers-type transformations;<sup>6,19–21</sup> by Rosini and co-workers in simplified approaches to assignment of absolute configuration;<sup>22,23</sup> by Ruud and co-workers<sup>10,24</sup> and by Pedersen, Koch, and co-workers<sup>25–28</sup> in CC-level models; by Beratan, Wipf, and co-workers in the applications of such models to natural products chemistry;<sup>29–32</sup> and by Autschbach and co-workers to studies of vibrational effects and of inorganic species.<sup>33–36</sup> Interested readers may find more complete discussions in a number of recent reviews by Stephens,<sup>9</sup> Polavarapu,<sup>37,38</sup> Ruud,<sup>39</sup> and Crawford.<sup>40</sup>

## II. Theoretical Background

The usual quantum mechanical starting point for describing the interaction of a plane polarized electromagnetic wave with an isolated chiral molecule is the semiclassical, perturbational approach of Rosenfeld,<sup>41</sup> who showed that the induced electric-dipole moment may be written as<sup>1,42</sup>

$$\langle \vec{\mu} \rangle = \alpha \vec{E} + \frac{1}{\omega} \mathbf{G}' \frac{\partial \vec{B}}{\partial t} \quad (1)$$

where  $\vec{E}$  and  $\vec{B}$  represent the applied, time-dependent electric, and magnetic field vectors. The  $\alpha$  tensor denotes the usual electric-dipole/electric-dipole polarizability, but the key quantity for natural optical activity is the analogous  $G'$  tensor,

$$\mathbf{G}'(\omega) = -\frac{1}{\hbar} \sum_{j \neq 0} \text{Im} \left[ \frac{\langle \psi_0 | \vec{\mu} | \psi_j \rangle \langle \psi_j | \vec{m} | \psi_0 \rangle}{\omega_{j0} - \omega - i\Gamma_{j0}} + \frac{\langle \psi_0 | \vec{m} | \psi_j \rangle \langle \psi_j | \vec{\mu} | \psi_0 \rangle}{\omega_{j0} + \omega + i\Gamma_{j0}} \right] = -\langle \langle \vec{\mu}; \vec{m} \rangle \rangle_{\omega} \quad (2)$$

where (in atomic units)  $\vec{\mu} = -\vec{r}$  and  $\vec{m} = -1/2 \vec{L} = -1/2 \vec{r} \times \vec{p}$  are the electric- and magnetic-dipole vector operators, respectively, and  $\omega$  denotes the frequency of the incident polarized radiation field. (The notation,  $\langle \langle \vec{\mu}; \vec{m} \rangle \rangle$ , is often used within response theory to denote a perturbed expectation value.<sup>43</sup>) The excitation energy between states  $\psi_0$  and  $\psi_j$  is given by  $\omega_{j0} = E_j - E_0$ , and the dephasing rate between the states,  $\Gamma_{j0}$ , is normally taken to be zero on the assumption that the field frequency,  $\omega$ , is far from resonance.<sup>44,45</sup> This allows one to combine the two terms within the brackets (recognizing that  $\langle \psi_0 | \vec{m} | \psi_j \rangle = -\langle \psi_j | \vec{m} | \psi_0 \rangle$ ) to obtain the more familiar expression,

$$\mathbf{G}'(\omega) = -\frac{2\omega}{\hbar} \sum_{j \neq 0} \frac{\text{Im}[\langle \psi_0 | \vec{\mu} | \psi_j \rangle \langle \psi_j | \vec{m} | \psi_0 \rangle]}{\omega_{j0}^2 - \omega^2} \quad (3)$$

Optical rotation (OR), also known as circular birefringence, refers to the rotation of plane-polarized light as it passes through a nonracemic sample of a chiral species. The trace of  $\mathbf{G}'$  is related to the *specific rotation* [i.e., the total optical rotation, normalized for path length (dm) and concentration (g/mL)] of nonoriented molecules, which is commonly denoted as  $[\alpha]_{\omega}$ . This implicit averaging over all molecular orientations<sup>42</sup> leads to the following expression for  $[\alpha]_{\omega}$ , in deg dm<sup>-1</sup> (g/mL)<sup>-1</sup>:

$$[\alpha]_{\omega} = \frac{(72.0 \times 10^6) \hbar^2 N_A \omega}{c^2 m_e^2 M} \times \left[ \frac{1}{3} \text{Tr}(\mathbf{G}') \right] \quad (4)$$

where  $\mathbf{G}'$  and  $\omega$  are given in atomic units,  $N_A$  is Avogadro's number,  $c$  is the speed of light (m/s),  $m_e$  is the electron rest mass (kg), and  $M$  is the molecular mass (amu). (It should be emphasized that the above expression holds only for freely tumbling molecules; oriented systems such as chiral crystals or surfaces require additional contributions from the electric quadrupole tensor.<sup>1</sup>) The magnitude of the rotation is characteristic of the detailed molecular structure of the compound and varies with the wavelength of the incident light, known as optical rotatory dispersion (ORD). This phenomenon was first observed by Arago in 1811 and by Biot in 1812 in quartz crystals, and Biot's later experiments established that the same rotation could be observed in solutions of camphor and turpentine. The indispensable text by Barron provides an excellent review of the historical development of optical activity as well as its fundamental quantum mechanical principles.<sup>1</sup>

Electronic circular dichroism (ECD) spectra are derived from the differential absorption of left- and right-circularly polarized light by a chiral sample. The ECD scalar rotational strength of a given electronic transition,  $R_{j0}$ , is the dot product of the transition electric- and magnetic-dipole vectors, *viz.*

$$R_{j0} = \text{Im}\{\langle \psi_0 | \vec{\mu} | \psi_j \rangle \cdot \langle \psi_j | \vec{m} | \psi_0 \rangle\} \quad (5)$$

i.e., just the numerator of each term in the summation of eq 3. In terms of the response function, the rotational strength is given by the residue,  $\lim_{\omega \rightarrow \omega_{j0}} (\omega - \omega_{j0}) \text{Im}\langle \langle \vec{\mu}; \vec{m} \rangle \rangle_{\omega}$ . Thus, the determination of the rotational strength requires first the calculation of the excited-state wave functions and transition energies, followed by construction of either the individual transition moments or the analogous transition strengths. Rotational strengths are commonly reported in units of 10<sup>-40</sup> esu<sup>2</sup> cm<sup>2</sup>, which may be obtained from rotational strengths in atomic units simply by multiplication by 471.44354.

**A. The Linear Response Approach.** The form of eqs 2 and 3 implies that one must potentially compute the complete set of excited-state wave functions to build the Rosenfeld tensor and subsequently determine the optical rotation. Although this approach is conceptually straightforward, it is also computationally very expensive, because in many cases literally thousands of excited states are necessary to achieve convergence<sup>46</sup> (though some applications have taken advantage of schemes to limit the number of terms in the summation<sup>47</sup>). A much more efficient approach is to use linear response theory.

In the usual time-dependent perturbation theory used to derive the Rosenfeld tensor, the perturbed wave functions are expressed as linear combinations of the eigenfunctions of the unperturbed (time-independent) Hamiltonian,  $H$ , thus leading to the simple energy denominators appearing in eqs 2 and 3. We are free, however, to choose any convenient set of functions that are complete on the space used to represent  $H$ . If we start with eq 2 (with all  $\Gamma_{j0} = 0$ ), we may step backward by inserting the resolution of the identity, *viz.*,  $1 = \sum_k |\psi_k\rangle \langle \psi_k|$ , to obtain

$$\begin{aligned} \mathbf{G}'(\omega) &= -\frac{1}{\hbar} \sum_{j \neq 0} \text{Im}[\langle \psi_0 | \vec{\mu} | \psi_j \rangle (\omega_{j0} - \omega)^{-1} \langle \psi_j | \vec{m} | \psi_0 \rangle - \\ &\quad \langle \psi_0 | \vec{\mu} | \psi_j \rangle (\omega_{j0} + \omega)^{-1} \langle \psi_j | \vec{m} | \psi_0 \rangle] \\ &= -\frac{1}{\hbar} \sum_{j,k \neq 0} \text{Im}[\langle \psi_0 | \vec{\mu} | \psi_j \rangle \langle \psi_j | (\omega_{j0} - \omega)^{-1} | \psi_k \rangle \times \\ &\quad \langle \psi_k | \vec{m} | \psi_0 \rangle - \langle \psi_0 | \vec{\mu} | \psi_j \rangle \langle \psi_j | (\omega_{j0} + \omega)^{-1} | \psi_k \rangle \langle \psi_k | \vec{m} | \psi_0 \rangle] \\ &= -\frac{1}{\hbar} \sum_{j \neq 0} \text{Im}[\langle \psi_0 | \vec{\mu} | \psi_j \rangle \langle \psi_j | X_m(+\omega) | \psi_0 \rangle - \\ &\quad \langle \psi_0 | \vec{\mu} | \psi_j \rangle \langle \psi_j | X_m(-\omega) | \psi_0 \rangle] \quad (6) \end{aligned}$$

where the magnetic-field-perturbed wave functions,  $X_m(\pm\omega)$ , are defined *via*

$$\langle \psi_j | X_m(\pm\omega) | \psi_0 \rangle \equiv \sum_{k \neq 0} \langle \psi_j | (\omega_{j0} \mp \omega)^{-1} | \psi_k \rangle \langle \psi_k | \vec{m} | \psi_0 \rangle \quad (7)$$

To solve eq 7, we invert the matrix on the right-hand side to obtain

$$\sum_{j \neq 0} \langle \psi_k | (\omega_{j0} \mp \omega) | \psi_j \rangle \langle \psi_j | X_m(\pm\omega) | \psi_0 \rangle = \langle \psi_k | \vec{m} | \psi_0 \rangle \quad (8)$$

Finally, if we have chosen a set of "excited" unperturbed wave functions,  $\{\psi_j\}$ , that are *not* eigenfunctions of  $H$ , then we obtain a system of linear equations that we must solve for  $X_m(\pm\omega)$ :

$$\sum_{j \neq 0} \langle \psi_k | (H - E_0 \mp \omega) | \psi_j \rangle \langle \psi_j | X_m(\pm\omega) | \psi_0 \rangle = \langle \psi_k | \vec{m} | \psi_0 \rangle \quad (9)$$

where we assume that  $E_0 = \langle \psi_0 | H | \psi_0 \rangle$ .

It may appear as though we have made the task of constructing  $\mathbf{G}'$  much more complicated. However, if we choose zeroth-order functions,  $\psi_j$ , that are simpler than the eigenfunctions of  $H$ , *e.g.*, the set of orthonormal Slater determinants upon which we might build a configuration-interaction-like ground-state wave function,  $\psi_0$ , then the task is, in fact, much easier. Instead of a full diagonalization of the matrix representation of  $H$ , which is required for the sum-over-states approach, we need only solve the systems of linear equations in eq 9 and use the results to evaluate eq 6, *an approach that is much more computationally efficient than and completely equivalent to the sum-over-states*. Thus, we see that linear response theory is merely a non-canonical form of the same time-dependent perturbation theory used to derive  $\mathbf{G}'$  in the first place.<sup>48</sup>

**B. Coupled Cluster Theory.** The question remains as to the specific choice of functional form of the wave function that we will use in eqs 6 and 9. Our work has focused on the so-called coupled cluster (CC) approximation, an *ab initio* model that is widely regarded as one of the most reliable for many molecular properties.<sup>3,5,49–51</sup> The CC electronic wave function is based upon an exponential expansion of Slater determinants of the form

$$|\psi_{\text{CC}}\rangle = e^{\hat{T}}|\phi_0\rangle \quad (10)$$

where  $\hat{T}$  is a second-quantized “cluster operator” that generates substituted determinants from the reference determinant,  $\phi_0$ , most often, but not necessarily, taken to be a Hartree–Fock wave function. Although  $\hat{T}$  is typically truncated at a practical level of substitution (*e.g.*, singles and doubles, which defines the CCSD approach) the power-series representation of the exponential implicitly incorporates higher substitutions into the total wave function. Electronic energies calculated using CC theory scale correctly with the size of the system/number of electrons; *i.e.*, they are size-extensive,<sup>51–53</sup> but they are non-variational because they are defined as the reference expectation value of a similarity-transformed Hamiltonian,  $\bar{H}$ :

$$E_{\text{CC}} = \langle\phi_0|e^{-\hat{T}}\hat{H}e^{\hat{T}}|\phi_0\rangle = \langle\phi_0|\bar{H}|\phi_0\rangle \quad (11)$$

The non-Hermitian character of  $\bar{H}$  implies that the “right” and “left” CC wave functions for a given state are not simple adjoints of one another, unlike in conventional CI theory, *viz.*,

$$\langle\tilde{\psi}_{\text{CC}}| = \langle\phi_0|(1 + \hat{\Lambda})e^{-\hat{T}} \quad (12)$$

where  $\hat{\Lambda}$  is a de-excitation/substitution cluster operator defined similarly to  $\hat{T}$ .

In the CC linear-response (CCLR) model, first discussed by Dalgaard and Monkhorst in the early 1980s (ref 54) and further developed by the Scandinavian and Florida groups,<sup>55–60</sup> the response of the ground-state wave function to the external (time-dependent) electromagnetic wave is calculated directly, parameterized in the same convenient basis of zeroth-order Slater determinants used to construct the unperturbed wave function. This leads to the following frequency-dependent, second-quantized expression for the linear response function:

$$\mathbf{G}'(\omega) = -\text{Im}\left\{\hat{C}^{\pm\omega}\hat{P}(\bar{\mu}(-\omega),\bar{m}(\omega))\left[\langle\phi_0|\hat{\Lambda}[\hat{\mu},\hat{X}_m^\omega]|\phi_0\rangle + \frac{1}{2}\langle\phi_0|\hat{\Lambda}[[\bar{H},\hat{X}_\mu^\omega],\hat{X}_m^{-\omega}]|\phi_0\rangle\right]\right\} \quad (13)$$

where the overbar denotes similarity transformation of the given operator analogous to that used for the Hamiltonian in eq 11.

The permutation operator  $\hat{C}^{\pm\omega}$  simultaneously changes the signs on the chosen field frequency and takes the complex conjugate of the expression, and  $\hat{P}$  symmetrizes the expression with respect to the perturbations  $\bar{\mu}$  and  $\bar{m}$ . The perturbed cluster operators are computed by solving systems of linear equations analogous to eq 9, *e.g.*,

$$\sum_j \langle\phi_i|(\bar{H} - \omega)|\phi_j\rangle\langle\phi_j|\hat{X}_m^\omega|\phi_0\rangle = -\langle\phi_i|\bar{m}|\phi_0\rangle \quad (14)$$

Note that eq 13 is nonsymmetric in that it depends quadratically on the right-hand perturbed wave functions,  $\hat{X}$ .

CC theory also offers a route to modeling ECD spectra through its equation-of-motion (EOM-CC)<sup>57</sup> and linear response<sup>56</sup> variants in which excited states are approximated as eigenfunctions of the similarity-transformed Hamiltonian appearing in eq 11:

$$e^{-\hat{T}}\hat{H}e^{\hat{T}}\hat{R}_n|\phi_0\rangle = \bar{H}\hat{R}_n|\phi_0\rangle = E_n\hat{R}_n|\phi_0\rangle \quad (15)$$

where  $\hat{R}_n$  is a cluster operator for the  $n$ th excited state. Just as for the ground-state wave function, the non-Hermitian nature of the similarity-transformed Hamiltonian leads to a left-hand eigenvalue problem that is distinct from its right-hand counterpart, but with the same eigenvalues,

$$\langle\phi_0|\hat{L}_n\bar{H} = \langle\phi_0|\hat{L}_nE_n \quad (16)$$

where  $\hat{L}_n$  is a de-excitation cluster operator and the excited-state counterpart of  $\hat{R}_n$ . These excited-state wave functions lead to expressions for the transition strengths of eq 2 that may be directly related to experimentally measured rotational strengths.

**C. Origin Independence and Gauge Invariance.** Approximate calculations of electromagnetic-field-dependent properties such as OR angles and ECD rotational strengths often suffer from an unphysical lack of invariance with respect to the choice of coordinate origin and/or the choice of representation of operators such as the electric-dipole operator (with the latter commonly referred to as “gauge invariance”). For properties such as NMR chemical shieldings, which depend on energy derivatives with respect to an external magnetic field, it is well-known that the origin dependence can be corrected using, for example, gauge-including atomic orbitals (GIAOs).<sup>61–65</sup> For OR angles and ECD rotational strengths, however, GIAOs only resolve the problem for models built upon variationally optimized molecular orbitals, such as Hartree–Fock or DFT.<sup>7,8</sup> For approximate wave functions such as CC (or, for that matter, truncated configuration interaction), where the component MOs remain fixed (usually at the Hartree–Fock level), GIAOs do not produce origin-independent rotations.<sup>58,66</sup>

An origin-independent form of the optical rotation can be obtained, however, by choosing the dipole-velocity representation of the electric-dipole operator in eq 2, which makes use of the linear momentum operator,  $\bar{p}$ , instead of the position operator,  $\bar{r}$ .<sup>67,68</sup> However, the dipole-velocity representation tends to give unreasonably large results because its  $\omega = 0$  (static) limit does not decay to zero as it should. Pedersen and co-workers suggested a work-around to this problem for OR by subtracting the static limit values of  $\mathbf{G}'$  from the value at a particular choice of  $\omega$  (the so-called “modified velocity-gauge” (MVG) approach).<sup>68</sup>

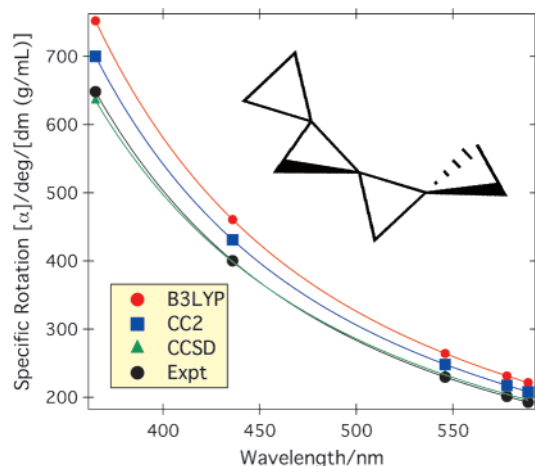
### III. Applications

We have implemented the coupled cluster linear response formulation of the Rosenfeld tensor in the open-source *ab initio*

**TABLE 1: Specific Rotation ( $\text{deg dm}^{-1} (\text{g/mL})^{-1}$ ) of (*P*)-[4]Triangulane<sup>a</sup>**

wavelength/ nm	B3LYP <sup>b</sup>	CCSD(LG) <sup>c</sup>	CCSD(MVG) <sup>b</sup>	expt <sup>d</sup>
589	221.5	186.3	196.0	192.7
578	231.4	194.5	204.5	201.3
546	264.3	221.6	232.9	229.7
436	460.7	380.7	398.7	400.2
365	752.2	609.2	635.4	648.2

<sup>a</sup> Computed at the B3LYP/6-31G\* optimized geometry using the aug-cc-pVDZ basis set. <sup>b</sup> Reference 12. <sup>c</sup> The center of mass was used for the coordinate origin. <sup>d</sup> Reference 72.



**Figure 1.** Optical rotatory dispersion spectra of (*P*)-(+)-[4]triangulane using the aug-cc-pVDZ basis set. The modified velocity-gauge was used for CC-level results.

program package, PSI3.<sup>69</sup> This program is currently capable of computing specific rotations and CD rotational strengths for small to medium-sized chiral molecules with up to several hundred basis functions. The PSI3 program is freely available under the GNU general public license. The B3LYP rotations reported below were computed with the Gaussian 03 package<sup>70</sup> using the time-dependent DFT formalism with GIAOs to ensure origin independence.

**A. Rigid Systems.** To consider separately electronic and large-amplitude vibrational effects on the chiroptical properties in question, we first report our results for two conformationally rigid molecules: (*P*)-[4]triangulane and (*S*)-2-chloropropionitrile. Issues related to Boltzmann averaging over low-lying conformers will be addressed in the next subsection.

**1. (*P*)-[4]Triangulane.** One of the first chiral molecules to which we applied the coupled cluster linear response model was the  $\sigma$ -helicene (*P*)-(+)-[4]triangulane, a rigid helical structure consisting of four fused cyclopropane rings, also known as trispiro[2.0.0.2.1.1]nonane.<sup>12</sup> (See Table 1 and Figure 1.) This molecule was first synthesized in enantiomerically pure form in 1999 by de Meijere and co-workers,<sup>71,72</sup> who measured large (liquid-phase) specific rotations—ranging from 192.6  $\text{deg dm}^{-1} (\text{g/mL})^{-1}$  at 589 nm to nearly 650  $\text{deg dm}^{-1} (\text{g/mL})^{-1}$  at 365 nm—even though the molecule contains no long-wavelength chromophore to dominate the summation in eq 2. Coupled cluster singles and doubles (CCSD) linear response calculations using the modified velocity gauge (MVG) reproduce the experimental results to better than 2% across the entire range of wavelengths, whereas the length-gauge approach (LG), with the center-of-mass taken as the coordinate origin, underestimates experiment by 3–6%. The B3LYP approach<sup>73,74</sup> (using the time-dependent DFT formalism<sup>75</sup>), on the other hand, overestimates the experimental rotations by ca. 15%, a discrepancy we have

**TABLE 2: Specific Rotation ( $\text{deg dm}^{-1} (\text{g/mL})^{-1}$ ) of (*S*)-2-Chloropropionitrile<sup>a</sup>**

wavelength/ nm	B3LYP <sup>b</sup>	CCSD(LG) <sup>b,c</sup>	CCSD(MVG) <sup>b</sup>	expt <sup>d</sup>
633	-15.7	-9.9	-8.0	-6.8 $\pm$ 2.3
589	-18.5	-11.7	-9.4	-8.3 <sup>e</sup>
436	-39.3	-23.6	-19.5	
355	-71.6	-40.6	-34.0	-37.9 $\pm$ 2.9

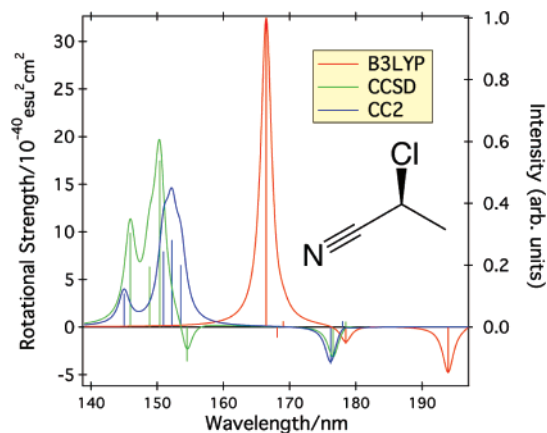
<sup>a</sup> Computed at the B3LYP/6-311++G\*\* optimized geometry using the aug-cc-pVTZ basis set. <sup>b</sup> Reference 14. <sup>c</sup> The center of mass was used for the coordinate origin. <sup>d</sup> Reference 78. <sup>e</sup> Interpolated gas-phase value.

attributed in part to the functional's underestimation of the electronic excitation energies.

Although the comparison between theory and experiment is encouraging, several questions remain as to the reliability of the results in this case. First, the completeness of the CCSD/aug-cc-pVDZ model, in terms of both electron correlation and one-electron basis set, has not yet been studied. Second, the experimental data were measured in the neat state, and, as will be discussed below, gas- and liquid-phase rotations can sometimes differ significantly. In addition, temperature effects have not been accounted for in the theoretical models, and more recent studies have indicated that vibrational corrections cannot always be ignored.

**2. (*S*)-2-Chloropropionitrile.** The impact of solvation on chiroptical properties has come under renewed scrutiny recently with the first quantitative measurements of specific rotation under ambient conditions for gas-phase samples by Vaccaro, Wiberg, and co-workers using their newly developed technique of cavity ring-down polarimetry (CRDP).<sup>76–79</sup> They have applied this experimental approach to a number of small molecules, thus providing vital benchmark data for the development of high-accuracy theoretical models. In 2005, Wiberg *et al.* reported the gas-phase specific rotation of (*S*)-2-chloropropionitrile at two wavelengths, 633 and 355 nm, as well as the neat-state rotation at the sodium D-line, 589 nm. Comparison of their measurements to B3LYP results revealed significant basis-set effects with correlation-consistent basis sets yielding specific rotations more than a factor of 2 larger than their experimental counterparts. However, Wiberg *et al.* also observed that the inclusion of electric-field-dependent (EFD) functions<sup>80</sup> in the basis set reduced the B3LYP rotations to within the experimental error bars.

(*S*)-2-Chloropropionitrile is a valuable test case for coupled cluster models because of its small size, thus allowing for tests of basis-set completeness.<sup>14</sup> As shown in Table 2, the CCSD linear response model in conjunction with triple- $\zeta$  basis sets yields specific rotations that compare closely to the gas-phase results—to within the experimental error bars for the longer wavelength and bracketing experiment at 355 nm. The LG and MVG approaches differ by a few degrees in this case, and both agree well with experiment. The B3LYP approach, on the other hand, again overestimates the experimental rotations by more than a factor of 2 at 633 nm. This finding agrees with our earlier study of (*P*)-[4]triangulane, in that the DFT model underestimates the electronic excitation energies of (*S*)-2-chloropropionitrile as well. Further testing of basis-set completeness (*e.g.*, using doubly augmented sets and higher zeta levels) yields only small shifts from the results reported in Table 2, suggesting that the EFD functions do not necessarily improve the comparison to experiment as previously hoped. In addition, we must again note that these studies do not consider the effects of molecular vibrations or temperature, and further analysis is



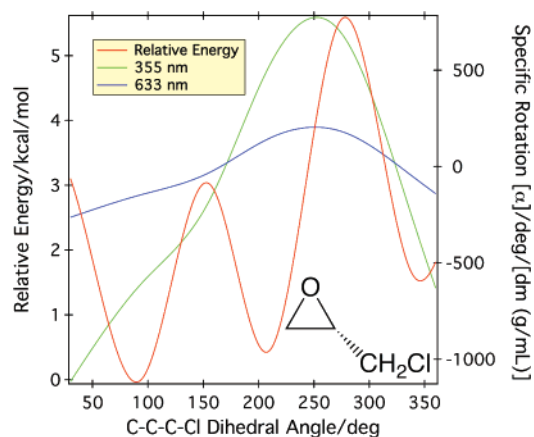
**Figure 2.** Theoretical electronic circular dichroism spectra of (*S*)-2-chloropropionitrile using the aug-cc-pVDZ basis set. The velocity-gauge representation was used for both CC and DFT rotational strengths. Rotational strengths (left-hand axis) are displayed as stick spectra. Band profiles (right-hand axis) were produced using Lorentzian line shapes with a full-width at half-maximum of 2 nm.

required for a completely robust comparison between theory and experiment.

Simulations of the electronic CD spectrum of (*S*)-2-chloropropionitrile are given in Figure 2 using both B3LYP and CC methods.<sup>14</sup> The DFT and CC spectra differ qualitatively in this case, with the former yielding both longer wavelength excitations and larger rotational strengths, both of which contribute to the behavior of the specific rotations shown in Table 2. Unfortunately, no direct comparison to experimental results is possible in this case due to the lack of gas-phase CD spectra. Though it is clear that the largest contributor to the observed negative specific rotation is the lowest-lying  $n \rightarrow \pi^*$  excitation, the total rotation includes significant contributions from a vast number of electronic states. Indeed, a sum-over-states calculations using B3LYP and eq 2 fails to reproduce the total rotations of Table 2 even when 100 excited states are included in the summation.

**B. Conformationally Flexible Molecules.** Both [4]triangulane and 2-chloropropionitrile are conformationally rigid, meaning that only a single minimum on the potential energy hypersurface contributes to the total specific rotation or CD spectrum. However, many chiral molecules of interest to organic chemists exhibit significant conformational flexibility, and thus rotations for all of the low-lying minima must be taken into account for comparison between theory and experiment.

**1. (*R*)-Epichlorohydrin.** Our recent work on (*R*)-epichlorohydrin (also known as chloromethyloxirane) was the first application of CC linear response methods to a conformationally flexible molecule.<sup>13</sup> (*R*)-Epichlorohydrin has three energy minima along the C–C–C–Cl dihedral angle [labeled *cis* (339.4°), *gauche-I* or *g-I* (208.9°), and *gauche-II* or *g-II* (94°)], each with strong, antagonistic specific rotations ranging from *ca.* –450 to +500 deg dm<sup>-1</sup> (g/mL)<sup>-1</sup> at 355 nm (see Figure 3), whereas the total, averaged rotation remains monosignate across the measured dispersion curve. Wilson *et al.* reported CRDP gas-phase specific rotations of the (*S*) enantiomer of epichlorohydrin of –238.7 ± 2.3 deg dm<sup>-1</sup> (g/mL)<sup>-1</sup> at 355 nm and –55.0 ± 1.7 deg dm<sup>-1</sup> (g/mL)<sup>-1</sup> at 633 for a sample with 97% enantiomeric excess.<sup>79</sup> Solvent effects are particularly pronounced for epichlorohydrin in part because different solvents induce changes in the relative energies of the three conformations. In the neat state, for example, the *gauche-I* conformer accounts for 56% of the conformer populations, but in CCl<sub>4</sub>, its contribution falls to 35%.<sup>37</sup>



**Figure 3.** Relative energy (left-hand axis, in kcal/mol) and specific rotations (right-hand axis, in deg dm<sup>-1</sup> (g/mL)<sup>-1</sup>) of (*R*)-epichlorohydrin. All values computed at the B3LYP/aug-cc-pVDZ level of theory.

**TABLE 3: Conformationally Averaged Specific Rotation (deg dm<sup>-1</sup> (g/mL)<sup>-1</sup>) of (*R*)-Epichlorohydrin**

wavelength/ nm	B3LYP <sup>b</sup>	CCSD(LG) <sup>b,c</sup>	CCSD(MVG) <sup>b</sup>	expt <sup>d</sup>
633	66.6	56.3	52.1	55.0 ± 1.7
589	78.9	66.3	61.5	
355	302.5	240.0	224.8	238.7 ± 2.3

<sup>a</sup> Computed at the B3LYP/cc-pVTZ optimized geometry using the aug-cc-pVTZ basis set on carbon and oxygen and the aug-cc-pVDZ basis set on hydrogen. <sup>b</sup> Reference 13. <sup>c</sup> The center of mass was used for the coordinate origin. <sup>d</sup> Reference 79.

To compare between theory and experiment, a Boltzmann average of the specific rotations for each conformer must be computed. We have found that free energies determined using G3 theory<sup>81,82</sup> and complete-basis-set (CBS) extrapolations<sup>83,84</sup> of CCSD(T) energies<sup>85,86</sup> work well for this purpose, with the latter converged to better than a few tenths of a kcal/mol. As can be seen from Table 3, average specific rotations at the CCSD level based on these populations compare well to experiment using both length- and modified-velocity-gauge approaches, with the former (with the center-of-mass chosen as the origin) performing somewhat better. As before, B3LYP-based rotations overestimate the experimental rotations, by 15–25%. However, in this case, the differences between DFT and CCSD are strongly dependent on conformation, with the *cis* conformation exhibiting differences of up to 69%, and the *g-I* conformation only 11%. On the other hand, estimates of the liquid-phase rotations at 589 nm based on conformer populations reported by Polavarapu *et al.*<sup>37</sup> yield excellent comparison with experimental data for both CC and B3LYP, including the all-important changes in sign with the choice of solvent.

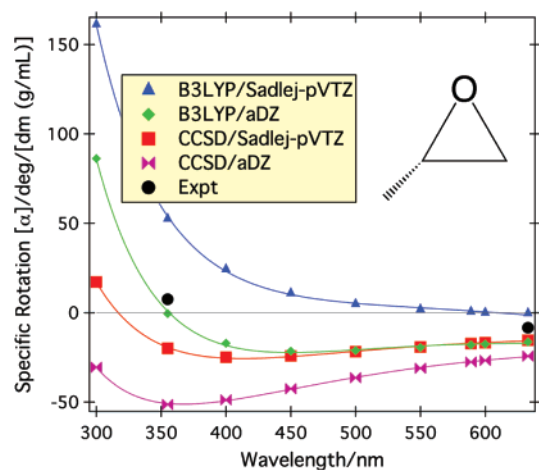
**2. (*R*)-3-Chloro-1-butene and (*R*)-2-Chlorobutane.** These two conformationally flexible molecules initially sparked the interest of Wiberg *et al.* in part because of questions regarding the role of the double bond in the specific rotation of the substituted butene.<sup>87,88</sup> Gas-phase CRDP rotations measured by Wilson *et al.* for these two molecules revealed approximately a factor of 2 difference in their total rotations, with (*R*)-3-chloro-1-butene giving larger values ( $[\alpha]_{633} = -53.3 \pm 1.0$  and  $[\alpha]_{355} = -259.4 \pm 1.0$  deg dm<sup>-1</sup> (g/mL)<sup>-1</sup>) than (*R*)-2-chlorobutane ( $[\alpha]_{633} = -32.3 \pm 1.0$  and  $[\alpha]_{355} = -121.4 \pm 1.2$  deg dm<sup>-1</sup> (g/mL)<sup>-1</sup>).<sup>79</sup> Wiberg and co-workers reported that B3LYP estimates of the specific rotation of 2-chlorobutane agree well with the gas-phase data<sup>88</sup> but overestimate the corresponding values for 3-chloro-1-butene by nearly a factor of 2.<sup>87</sup> These results motivated our own CC-level study of these systems.<sup>15</sup>

Each of these molecules exhibits three low-lying conformations, each of which may be characterized by its C–C–C dihedral angle,  $\tau$ . For 3-chloro-1-butene, the global minimum lies at  $\tau \approx 120^\circ$ , with local minima at  $\tau \approx 0^\circ$  and  $240^\circ$ , approximately 0.9 and 1.4 kcal/mol higher in energy, respectively. For 2-chlorobutane, the global minimum appears at  $\tau \approx 180^\circ$ , with additional minima at  $\tau \approx 60^\circ$  and  $300^\circ$ , only 0.6 and 0.9 kcal/mol higher, respectively. Although the final, Boltzmann-averaged specific rotations are negative for both molecules (*e.g.*,  $-60.6 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$  for (*R*)-3-chloro-1-butene and  $-27.6 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$  for (*R*)-2-chlorobutane at 589 nm at the CCSD(MVG)/TZ level of theory), the sign pattern for their individual conformers differs. For (*R*)-3-chloro-1-butene, two conformers exhibit negative rotations (including the global minimum), whereas for (*R*)-2-chlorobutane, two conformers exhibit positive rotations (*not* including the global minimum).

We found that the CCSD(MVG) approach coupled with a TZ-level basis set and CBS-CCSD(T) estimates of the Gibbs free energies of each conformer yields excellent agreement with the measured gas-phase specific rotations for both of these molecules. However, the rotations of the individual conformers differed substantially between B3LYP and CCSD, even though the former gives good agreement with experiment for 2-chlorobutane. In addition, CCSD simulations of the vacuum UV absorption and ECD spectra revealed large differences between the B3LYP excitation energies and rotational strengths, which we thus link to the different values of  $[\alpha]_\lambda$  given by each method. We therefore concluded that, in spite of the apparent errors of the B3LYP approach for individual conformers (relative to CCSD), it is still able to produce a reasonable *averaged* specific rotation for 2-chlorobutane.

The case of 3-chloro-1-butene also demonstrates the dangers of using origin-dependent approaches such as the LG approximation to the Rosenfeld tensor. We found that the CCSD-level specific rotation of (*R*)-3-chloro-1-butene at 355 nm varies dramatically between the MVG and LG approaches (with the center of mass chosen as the coordinate origin for the latter). Further analysis revealed that the origin-dependence vector of the LG approach,<sup>68</sup> which is straightforward to compute when both gauges are evaluated simultaneously, has a large norm ( $32.5 \text{ deg dm}^{-1} (\text{g/mL})^{-1}/a_0$  for the  $\tau \approx 0^\circ$  conformer at the CCSD/aug-cc-pVDZ level), indeed larger than even the highly sensitive norbornenone case ( $6.8 \text{ deg dm}^{-1} (\text{g/mL})^{-1}/a_0$ , *vide infra*), and much larger than the corresponding vector for 2-chlorobutane ( $3.9 \text{ deg dm}^{-1} (\text{g/mL})^{-1}/a_0$ ). This strong origin dependence for 3-chloro-1-butene invalidates the use of the LG approach in this case.

In addition, the 3-chloro-1-butene/2-chlorobutane example highlights another potential problem with conformationally flexible species, namely the use of simple Boltzmann averaging to evaluate the total rotation for comparison to experiment. We note that the energy difference between the 3-chloro-1-butene global minimum at  $\tau \approx 120^\circ$  lies 0.9 kcal/mol below the first local minimum at  $\tau \approx 0^\circ$ . Given that the lowest-energy torsional vibration of this molecule is only about  $100 \text{ cm}^{-1}$ , several vibrational levels of the global minimum will be populated at room temperature before the zero-point vibrational level of the first local minimum. Thus, the use of the conventional Boltzmann approach would tend to overestimate the contribution from the higher minima to the total rotation. An alternative approach would be to compute the corresponding average over the torsional vibrational wave functions explicitly.



**Figure 4.** Optical rotatory dispersion spectra of (*S*)-methyloxirane. The center of mass was chosen as the coordinate origin. Experimental data were taken from ref 79.

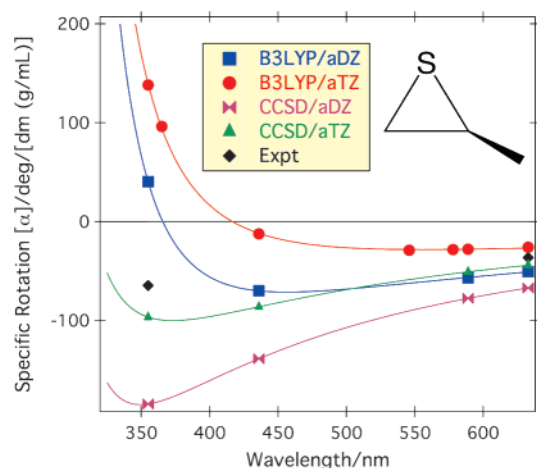
#### IV. Problematic Cases

The above results for (*P*)-[4]triangulane, (*S*)-2-chloropropionitrile, (*R*)-epichlorohydrin, (*R*)-3-chloro-1-butene, and (*R*)-2-chlorobutane notwithstanding, a number of problem cases remain that suggest that the simple approach described above involving only the electronic contributions to specific rotation and CD rotational strengths may not provide a sufficiently complete physical model of optical activity.

**A. (*S*)-Methyloxirane and (*S*)-Methylthiirane.** In 2004, we published the first systematic comparison of CC and DFT specific rotation data to gas-phase experimental measurements for the small molecule (*S*)-methyloxirane.<sup>11</sup> Although structurally similar to epichlorohydrin, methyloxirane exhibits much smaller specific rotations that are also bisignate between 350 and 400 nm. According to CRDP data published by the Vaccaro and Wiberg groups in 2000 (ref 76) and later refined in 2005 (ref 79), the 633 and 355 nm rotations of (*S*)-methyloxirane are  $-8.39 \pm 0.20$  and  $+7.39 \pm 0.30 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ , respectively.

We observed that, although both B3LYP and CCSD models (with aug-cc-pVDZ and Sadlej-pVTZ<sup>89,90</sup> basis sets) yield the correct sign of the long-wavelength rotations, only B3LYP reproduced the change in sign of the rotation at 355 nm. (See Figure 4.) However, we further showed that this apparent success of DFT is, in fact, related to its concomitant underestimation of the lowest Rydberg excitation energy (ca. 0.5 eV relative to the decidedly more accurate EOM-CCSD model). Thus, the B3LYP dispersion curve is correctly bisignate in the (*S*)-methyloxirane case only because it artifactually turns upward earlier than if its lowest excitation wavelength were correct. On the other hand, though the position of the lowest-energy Cotton pole is likely well described by CCSD, the model still fails to reproduce the correct dispersion behavior.

(*S*)-Methylthiirane provides another problematic case.<sup>91</sup> Gas-phase specific rotations measured by Wilson *et al.*<sup>79</sup> are monosignate between 633 and 355 nm and much larger than those of (*S*)-methyloxirane:  $[\alpha]_{633} = -36.5 \pm 1.7$  and  $[\alpha]_{355} = -64.7 \pm 2.3 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$ . However, unlike (*S*)-methyloxirane, CCSD produces the correct monosignate dispersion behavior—albeit with too large rotations by a factor of 2—and B3LYP incorrectly predicts a sign change between 355 and 450 nm, depending on the choice of basis set. (See Figure 5.) Again, the behavior of the methods is similar to the methyloxirane case in that the DFT model's dispersion curve turns



**Figure 5.** Optical rotatory dispersion spectra of (*S*)-methylthiirane. The center of mass was chosen as the coordinate origin. Experimental data were taken from ref 79.

upward much earlier than CCSD because of the large differences in the lowest excitation energies predicted by the two models. It is also worth noting that the CC-level ECD spectra of both (*S*)-methyloxirane and (*S*)-methylthiirane compare exceptionally well to gas-phase spectra measured by Breest *et al.* in 1994.<sup>92</sup>

In 2005, Ruud and Zanasi re-examined (*S*)-methyloxirane and considered the impact of molecular vibrations on the DFT specific rotations. They found that the magnitude of zero-point vibrational corrections (computed on the basis of a Taylor expansion of the property around a vibrationally averaged structure) increased with decreasing wavelength and, in the case of (*S*)-methyloxirane, the corrections pushed B3LYP rotations to more positive values, *i.e.*, further away from experiment. Mort and Autschbach considered the impact of molecular vibrations on the sodium D-line specific rotations of 22 conformationally rigid molecules at the B3LYP level of theory.<sup>33</sup> They found that such corrections (not including temperature dependence) can account for as much as 20% of the equilibrium value of the specific rotation and thus cannot always be ignored. Kongsted *et al.* extended this earlier work in 2006 to include coupled cluster methods and temperature dependence in the vibrational corrections for (*S*)-methyloxirane.<sup>28</sup> They found that, although vibrationally corrected B3LYP and SAOP methods overestimate the experimental rotations by approximately an order of magnitude, CC theory including approximate triples corrections yields final rotations close to the experimental results. They also reported that, although the methyl rotation produces the largest correction, all of the vibrational modes make non-negligible contributions.

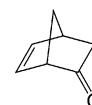
Unfortunately, the improved comparison between theory and experiment upon inclusion of vibrational effects observed by Ruud and Zanasi<sup>24</sup> and by Kongsted *et al.*<sup>28</sup> for (*S*)-methyloxirane does not appear to hold for (*S*)-methylthiirane. Table 4 compares temperature-dependent harmonic vibrational corrections for (*S*)-methyloxirane and (*S*)-methylthiirane using both B3LYP and CCSD.<sup>91</sup> For both molecules, we find that the magnitude of the correction increases with decreasing wavelength, in agreement with the observations of Ruud and Zanasi.<sup>24</sup> Furthermore, the B3LYP corrections tend to be much larger than the corresponding CCSD corrections by as much as a factor of 2, again in agreement with previous results. However, unlike for (*S*)-methyloxirane, vibrational effects overcorrect the CC-level specific rotation at short wavelengths, yielding the incorrect sign of  $[\alpha]_{355}$ . Though it is likely that these results will improve

**TABLE 4: Equilibrium and Vibrationally Corrected Specific Rotations ( $\text{deg dm}^{-1} (\text{g/mL})^{-1}$ ) of (*S*)-Methyloxirane and (*S*)-Methylthiirane**

wavelength/ nm	B3LYP			CCSD			expt <sup>b</sup>
	$[\alpha]_{\lambda}^{\text{eq}}$	$\Delta[\alpha]_{\lambda}$	$\langle[\alpha]_{\lambda}\rangle$	$[\alpha]_{\lambda}^{\text{eq}}$	$\Delta[\alpha]_{\lambda}$	$\langle[\alpha]_{\lambda}\rangle$	
( <i>S</i> )-Methyloxirane							
633	-9.6	12.9	3.3	-18.0	6.4	-11.6	-8.39 ± 0.20
589	-10.3	15.4	5.1	-20.4	15.9	-4.5	
355	18.8	68.3	87.1	-33.1	34.5	1.4	7.49 ± 0.30
( <i>S</i> )-Methylthiirane							
633	-27.6	11.8	-15.8	-44.3	6.3	-38.0	-36.5 ± 1.7
589	-30.0	15.1	-14.9	-50.8	5.2	-45.6	
355	131.2	226.9	358.1	-96.7	110.9	13.3	-64.7 ± 2.3

<sup>a</sup> Aug-cc-pVTZ equilibrium values with vibrational corrections from B3LYP/aug-cc-pVDZ and CCSD/aug-cc-pVDZ(C,O,S)+cc-pVDZ(H). All theoretical data were taken from ref 91. <sup>b</sup> Reference 79.

**TABLE 5: Sodium D-Line Specific Rotations ( $\text{deg dm}^{-1} (\text{g/mL})^{-1}$ ) of (1*S*,4*S*)-Norbornenone**



method	$[\alpha]_{\text{D}}$
Hartree-Fock <sup>b</sup>	-607
B3LYP	-1214
CC2 (LG) <sup>bc</sup>	-998
CC2 (MVG)	-813
CCSD (LG) <sup>bc</sup>	-740
CCSD (MVG)	-558
expt <sup>d</sup>	-1146

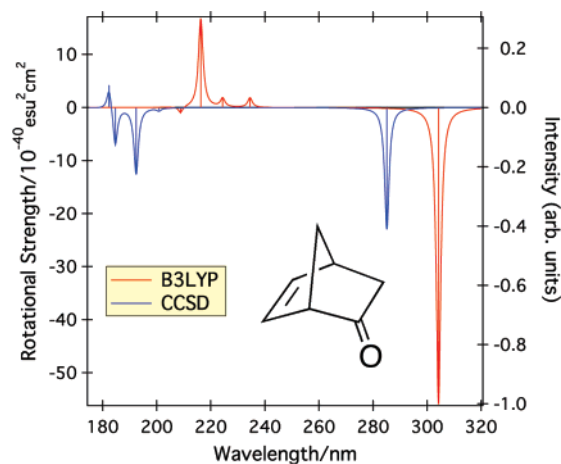
<sup>a</sup> Computed at the B3LYP/6-31G\* optimized geometry using the aug-cc-pVDZ basis set. <sup>b</sup> Reference 10. <sup>c</sup> The center of mass was used as the coordinate origin. <sup>d</sup> References 95 and 9.

by extension of the CC model to include higher excitations (*e.g.*, CC3 or CCSDT), and by consideration of anharmonicity effects, it is possible that the incorrect behavior of the CCSD ORD curve arises because the external-field wavelength is simply too “close” to the first electronic resonance of methylthiirane such that eq 3 is thus invalid. The additional dephasing terms in eq 2 ( $\Gamma_{j0}$ ) could be incorporated as empirical factors, as has been done by Norman *et al.*<sup>44</sup> and by Autschbach *et al.*,<sup>45</sup> but these terms have not yet been included using first-principles techniques.

**B. (1*S*,4*S*)-Norbornenone.** The optical activity of norbornenone (also known as bicyclo[2.2.1]hept-5-en-2-one or dehydronorcamphor) has been widely studied in liquid-phase environments and shown to yield an exceptionally large sodium D-line specific rotation in a variety of solvents: for the (1*S*,4*S*) enantiomer,  $[\alpha]_{589} = -1142 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$  (isooctane),<sup>93</sup>  $-1236 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$  ( $\text{CHCl}_3$ ),<sup>94</sup> and  $-1146 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$  (hexane).<sup>95</sup> On the other hand, quantum chemical calculations of the specific rotation vary wildly in magnitude, depending on the level of theory, as can be seen in Table 5. Although Hartree-Fock theory underestimates the experimental value in hexane by nearly a factor of 2, CC methods offer little improvement, with CC2<sup>96</sup> correcting the Hartree-Fock values toward experiment, and CCSD shifting away. Furthermore, the use of the origin-independent MVG approach for the CC models yields significantly smaller rotations than the origin-dependent dipole-length gauge approximation. On the other hand, the simpler (and less expensive) B3LYP approach provides a superb comparison with the experimental data, differing by only a few percent.

The source of the large difference between B3LYP and CCSD can be discerned from Figure 6, which depicts simulations of





**Figure 6.** Simulated electronic CD spectra for the lowest five electronic states of (1*S*,4*S*)-norbornenone using EOM-CCSD/aug-cc-pVDZ-(C,O)+cc-pVDZ(H) and B3LYP/aug-cc-pVDZ methods. The velocity-gauge representation was used for both CC and DFT rotational strengths. Rotational strengths (left-hand axis) are displayed as stick spectra. Band profiles (right-hand axis) were produced using Lorentzian line shapes with a full-width at half-maximum of 2 nm.

the electronic CD spectrum of (1*S*,4*S*)-norbornenone between 180 and 320 nm. The methods agree qualitatively but not quantitatively on the position and magnitude of the lowest-energy CD band, which corresponds to an  $n \rightarrow \pi^*$  transition involving the carbonyl moiety. B3LYP characteristically predicts a longer-wavelength transition than CCSD and also produces a larger rotational strength, similar to our CD simulations for (*S*)-2-chloropropionitrile<sup>14</sup> and (*R*)-3-chloro-1-butene.<sup>15</sup> Given that this feature is the largest contributor to the total optical rotation of norbornenone (though by no means the only contributor, as was recently demonstrated by Wiberg *et al.*<sup>46</sup>), the two discrepancies—long wavelength and larger rotational strength—produce the dramatic difference between B3LYP and CCSD values of  $[\alpha]_D$  shown in Table 5. In addition, as discussed first by Ruud *et al.*,<sup>10</sup> the B3LYP rotational strength and  $n \rightarrow \pi^*$  transition wavelength compares well to the liquid-phase experimental CD spectrum.<sup>97</sup>

What is the source of the apparent failure of coupled cluster theory in this case? Basis set incompleteness is unlikely; adding additional diffuse or higher angular momentum functions to the carbonyl and/or double bond changes the above rotations by a few  $\text{deg dm}^{-1} (\text{g/mL})^{-1}$  at most. Vibrational effects, such as those described above for methyloxirane and methylthiirane, seem equally unlikely because of the rigid nature of the norbornenone structure. Indeed, recent B3LYP calculations by Mort and Autschbach produced only a  $-53 \text{ deg dm}^{-1} (\text{g/mL})^{-1}$  zero-point vibrational correction<sup>33</sup>—much too small to explain the large discrepancy between CC and experiment.

At least two untested possibilities remain: First, additional correlation effects (*e.g.*, triple excitations and higher) may be important. These have been considered only for the methyloxirane system by Kongsted *et al.*,<sup>27</sup> and given the difference between Hartree–Fock and CCSD shown in Table 5, it would be surprising to find that triples could shift the CCSD (MVG) rotations by the factor of 2 required for better agreement with experiment. Second, norbornenone may exhibit large shifts between its gas- and liquid-phase specific rotations. Although no gas-phase polarimetry measurements have yet been carried out on norbornenone, the fact that the value of  $[\alpha]_D$  does not change dramatically between  $\text{CHCl}_3$ , isooctane, and hexane might suggest that one should expect the gas-phase rotations to be at least similar to their solvent-phase counterparts. However,

such shifts are not without precedent.<sup>98</sup> Both of these possibilities are under investigation, the results of which should be very enlightening to the efforts to develop accurate models of optical activity in chiral species.

## V. Summary and Future Directions

Much progress has been made in the last 10 years in the development of high-level *ab initio* models of chiroptical response properties. For small- to medium-sized molecules such as 2-chloropropionitrile, epichlorohydrin, and [4]triangulane, coupled cluster linear response calculations of the Rosenfeld electric-dipole/magnetic-dipole polarizability tensor yield impressive comparisons to state-of-the-art experimental data, particularly for optical rotation. However, it is not yet clear to what lengths theoretical models must go to provide such accuracy and reliability for every system of interest, and difficult cases such as methyloxirane, methylthiirane, and norbornenone provide pertinent examples of the need for inclusion of higher-order corrections, such as zero-point vibration, temperature effects, and electron correlation. In addition, to reach the overarching goal of practical yet reliable computational tools that will assist in the assignment of absolute stereochemical configuration, we identify three important research directions that must also be pursued in the coming years: a properly gauge-invariant form of coupled cluster linear response theory for physically unambiguous chiroptical properties, a significant reduction in the scaling of coupled cluster theory with molecular size for calculations of larger chiral molecules, and the simulation of solvent–solute interactions for more realistic comparisons between theory and experiment.

**A. Gauge Invariance.** As noted earlier, the conventional CC linear response function is not invariant with respect to an arbitrary choice of gauge, *e.g.*, the length ( $\vec{r}$ ) and velocity ( $\vec{p}$ ) representations of the electric-dipole operator,

$$\mathbf{G}'(\omega) \propto -\text{Im}\langle\langle\vec{r};\vec{L}\rangle\rangle_{\omega} \neq -\omega^{-1}\text{Re}\langle\langle\vec{p};\vec{L}\rangle\rangle_{\omega} \quad (17)$$

A key result of this deficiency is that the length-gauge representation of  $\mathbf{G}'(\omega)$  unphysically depends on the choice of coordinate origin—an error that remains even in the limit of a complete basis set and cannot be resolved through the use of GIAOs. Although the modified velocity gauge approach suggested by Pedersen and co-workers yields correctly origin-independent results, it does not resolve the gauge problem entirely because of its unphysical static limit. This issue is relevant to the problematic cases of methylthiirane and norbornone, for example, because it is unclear how large of a difference in predicted optical rotation values would be observed between the current gauge-dependent approach and a well-founded invariant formulation.

This ambiguity may be overcome by reformulating the CC linear-response function based on variational optimization of the component MOs—referred to as the orbital optimized CC (OCC) method. This approach has been investigated in the past for a variety of reasons, including the treatment of artifactual symmetry-breaking problems and the development of active-space models.<sup>99–102</sup> In 1999, Pedersen, Koch, and co-workers first recognized the potential importance of OCC for achieving gauge invariance,<sup>66</sup> and in 2001 they reported an implementation for calculating oscillator strengths.<sup>103</sup> However, it remains to be seen whether the approach will be feasible calculations of chiroptical properties, and some criticism of the OCC approach has appeared in the literature.<sup>104</sup>

**B. Reduced-Scaling CC Response Theory.** The Achilles' heel of conventional CC theory is its high-order scaling with molecular size [ $\mathcal{O}(N^6)$  or worse]. This "polynomial scaling wall" prevents its routine application to larger, more chemically relevant molecules. Although the CCLR programs within the PSI3 package are very efficient, they still require considerable computational resources—in terms of both computing time and memory/disk storage—and thus are limited to computations of ORD or ECD spectra for at most 10–12 non-hydrogen atoms in the absence of molecular symmetry.

One route to overcoming this deficiency lies in the development of reduced-scaling coupled cluster models based on the local correlation *ansatz* first suggested by Pulay and Saebø in the 1980s.<sup>105–108</sup> The central assumption of this idea is that, by adopting well-localized forms of the MOs used to construct the determinantal expansion of the wave function, the parameters associated with interactions of electrons in spatially distant MOs should be negligible and may therefore be ignored. This approach has been utilized extensively by Werner, Schütz, and co-workers, who have demonstrated that it is possible to obtain CC ground-state energies (including perturbative triple excitations) for chains of up to 16 glycine molecules in a matter of hours using desktop workstations.<sup>108</sup>

We have focused on the extension of local-CC methods to the complicated problem of response properties, including specific rotation and circular dichroism spectra. However, using pilot programs based on our canonical-MO linear response programs, we have found that an electric-field perturbation shifts the distribution of the double-excitation ( $\hat{T}_2$ ) amplitudes upward by about 1 order of magnitude; *i.e.*, the perturbation significantly reduces the wave function sparsity. Thus, the conventional ground-state orbital domains that seem to work well for energy calculations are insufficient for accurate representations of the perturbed wave functions (eq 14) appearing in the response function. These domains may be expanded, however, by considering how the MOs themselves are perturbed by external electromagnetic fields—that is, by examination of the so-called coupled perturbed Hartree–Fock (CPHF) equations. For example, a single component of the Hartree–Fock dipole-polarizability tensor,  $\alpha$ , may be written as

$$\alpha_{xy} = \sum_i \sum_a^{\text{occ vir}} U_{ai}^x \mu_{ai}^y \quad (18)$$

where  $i$  and  $a$  index occupied and virtual MOs, respectively, the  $U_{ai}^x$  are the solutions to the CPHF equations, and  $\mu_{ai}^y$  are electric-dipole integrals. The summation over the virtual orbitals may be "back-transformed" into the AO basis and then partitioned into its individual atomic components (assuming the one-electron basis set is centered at the nuclei, as is typical) to give the total contribution of each atom per occupied orbital to the polarizability, *viz.*,

$$\alpha_{xy}^{iA} = \sum_{\rho \in A}^{\text{AO}} U_{\rho i}^x \mu_{\rho i}^y \quad (19)$$

where the summation includes only the basis functions on atom  $A$ . This provides a recipe for extending the domain of a given occupied orbital  $i$  to account for the field response. An advantage of this approach is that it applies equally well to "mixed" field-dependent properties, such as ORD and ECD, for which both electric- and magnetic-field perturbations must be applied. Although a "production-level" implementation is not yet complete, preliminary studies have shown that it is possible to

reproduce canonical CC dynamic polarizabilities for chain-like organic molecules using less than half the correlated wave functions but with less than 1% loss of accuracy.<sup>109</sup> Efforts to extend this work to chiroptical properties are underway.

**C. Solvation.** Most of the work described above focuses on systematic comparison between coupled-cluster response theory and gas-phase experimental data in an effort to elucidate the fundamental physical requirements of a reliable model of optical activity. However, given that the vast majority of experimental measurements of chiroptical properties are made in liquid environments, it is clear that any practical computational tool for assisting in the determination absolute configuration must incorporate an efficient yet accurate assessment of solvent effects on chiroptical response. Unfortunately, as noted earlier solvent–solute interactions can lead to significant perturbations in chiroptical spectra relative to their gas-phase counterparts. Indeed, the influence of the solvent on optical rotation in particular is often large and contrary to conventional wisdom, such as the observation by Vaccaro and co-workers that optical rotation measured in highly polar solvents such as acetone often provides a better comparison to gas-phase rotations than nonpolar solvents such as cyclohexane.<sup>79</sup> Continuum-based models<sup>110,111</sup> may offer an attractive solution to this problem due to their relative simplicity and affordability. A recent study by Mennucci *et al.* considered the applicability of the polarizable continuum model (PCM) in conjunction with DFT to optical rotation in a series of seven conformationally rigid chiral molecules, including fenchone,  $\alpha$ - and  $\beta$ -pinene, and others, and found that they could reproduce the experimental specific rotations in a number of polar (*e.g.*, acetone and methanol) and nonpolar solvents (*e.g.*, cyclohexane). However, the agreement for other solvents such as benzene and carbon tetrachloride was much poorer.<sup>16</sup> Kongsted *et al.* carried out CC-level calculations with a dielectric continuum approach for (*S*)-methyloxirane but found that such a model was unable to reproduce the experimental trends with respect to the choice of solvent (such as the change in sign of the rotation between benzene and water).<sup>27</sup>

It seems likely that a combination of continuum-based models coupled with explicit inclusion of solvent molecules at least within the cybotactic regime may be necessary to obtain reliable comparison with experiment. This will naturally require molecular dynamics simulations of solvent–solute interactions, an approach that is not viable at present given the computational cost of high-level quantum chemical methods, the above efforts toward reduced-scaling techniques notwithstanding. We remain optimistic, however, that the development of CC models of OR and CD spectra will provide a means for the future design and parametrization of computationally simpler approaches, such as semiempirical, DFT, and/or QM/MM models that will incorporate all the essential physical ingredients of an accurate theory of chiroptical response.

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