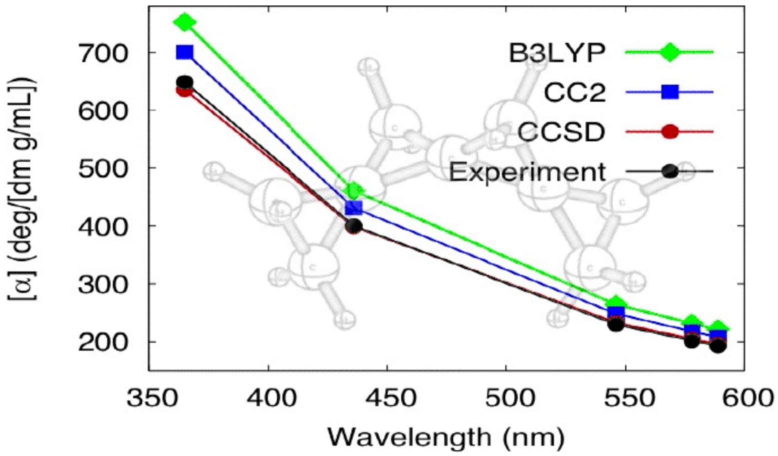
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

Communication

Ab Initio Calculation of Optical Rotation in (*P*)-(+)-[4]Triangulane

T. Daniel Crawford, Lesley S. Owens, Mary C. Tam, Peter R. Schreiner, and Henrik Koch

J. Am. Chem. Soc., **2005**, 127 (5), 1368-1369• DOI: 10.1021/ja042787p • Publication Date (Web): 13 January 2005



Journal of the American Chemical Society is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

J|A|C|S
COMMUNICATIONS

Ab Initio Calculation of Optical Rotation in (*P*)-(+)-[4]Triangulane

T. Daniel Crawford,*,[†] Lesley S. Owens,[†] Mary C. Tam,[†] Peter R. Schreiner,[‡] and Henrik Koch[§]

Department of Chemistry, Virginia Tech, Blacksburg, Virginia 24061, Institut für Organische Chemie,
Justus-Liebig Universität, Heinrich-Buff-Ring 58, 35392 Giessen, Germany, and Department of Physical Chemistry,
Norwegian University of Science and Technology, N-7491, Trondheim, Norway

Received November 30, 2004; E-mail: crawdad@vt.edu

Understanding, predicting, and manipulating the properties of chiral molecules is a primary objective of organic chemistry.[1] Much of today's organic synthetic methodology aims "simply" to control the absolute and relative configurations of stereogenic centers. This control is a matter of grave importance to the pharmaceutical industry, where the stereochemical purity of chiral drugs is ideally achieved by synthetic design rather than by stereoisomer separation of the final product. The drug thalidomide, prescribed to pregnant women in the 1960s for morning sickness, is a sad example where this factor was underestimated: although one enantiomer works as a sedative, the other is a potent teratogen and damages fetal tissue, and both are formed in vivo through rapid interconversion.[2]

Although the assessment of the enantiomeric purity of chiral species is routinely achieved by measuring optical rotation angles and integrating chiral GC/HPLC traces, determining the absolute configuration is more difficult. For noncrystalline compounds, asymmetric synthesis or less secure chiroptical and NMR methods are used. All of these approaches are time-consuming, and none are guaranteed to be successful.

An alternative approach is to compute directly the chiroptical properties of selected molecular structures and subsequently compare the results with the associated experimental data, typically optical rotation angles, of the original compound.[3] Unfortunately, this task is even more difficult because of limited experimental results. Although vibrational circular dichroism and Raman optical activity methods provide much more information than simple polarimetry,[4] the corresponding spectrometers are not available to most synthetic chemists. Thus, theory is faced with a tremendous task: to provide optical rotation data where both the sign and magnitude of the rotation are important, and the acceptable "error bars" are virtually zero because a sign change implies a configurational inversion. Only the most accurate and reliable theoretical models are up to such a task.

Coupled cluster theory is the most successful ab initio quantum chemical approach developed to date.[5] For many small molecules, coupled cluster theory, in conjunction with large one-electron basis sets, has been found to give exceptionally accurate results for commonly studied molecular properties such as equilibrium geometries, vibrational and UV/vis spectra, and thermochemical properties.[6] Its level of reliability is presently unmatched by any other quantum chemical model, including the density-functional theory (DFT) approaches,[7] and thus coupled cluster theory is often referred to as the "gold standard" of quantum chemistry.

We have recently developed a new implementation of a coupled cluster linear response approach[8] that is applicable to optical rotation. This approach is based on the quantum mechanical foundations established by Rosenfeld in 1928,[9] who showed that the angle of rotation, $[\alpha]_\omega$, of plane-polarized light of frequency ω in a chiral medium is related to the trace of the electric-dipole magnetic-dipole polarizability tensor

$$\beta(\omega) = \frac{2}{\hbar}\mathrm{Im}\sum_{n\neq 0}\frac{\langle 0|\mu|n\rangle\langle n|m|0\rangle}{\omega_{n0}^{2}-\omega^{2}} \qquad (1)$$

Here μ and m denote the electric and magnetic dipole operators, respectively, and the summation runs over excited electronic (unperturbed) wave functions, n.

Using the coupled cluster singles and doubles linear response model (CCSD-LR), we have computed the specific rotation of the chiral molecule trispro[2.0.0.2.1.1]nonane (also known as [4]triangulane; see Figure 1) at several wavelengths. This molecule is the first of a new series of σ-[*n*]helicenes with remarkably large specific rotations, ranging from 197.2 deg/[dm (g/mL)] at 589 nm to more than 600 deg/[dm (g/mL)] at 365 nm, despite its lack of either an asymmetrically substituted carbon atom or a long-wavelength chromophore.

We have compared our results to the experimental ORD curve recently obtained by de Meijere et al., who, in a veritable tour de force of organic synthetic methodology, synthesized (*P*)-[4]triangulane.[10] This unique molecule provides an opportunity for comparison between experiment and state-of-the-art theoretical models of optical rotation because of its rigid structure. For further comparison, we have also used the more approximate second-order coupled cluster response method (CC2) developed by Christiansen, Koch, and Jørgensen[11] and the time-dependent density-functional theory (TD-DFT) approach of Cheeseman, Stephens, Devlin, and Frisch with the B3LYP functional.[12] All three models were used in conjunction with the diffuse-augmented correlation-consistent polarized-valence double-ζ (aug-cc-pVDZ) basis set of Dunning and co-workers.[13] The CCSD-LR calculations were carried out with the PSI3 program package,[14] the CC2 calculations with the DALTON package,[15] and the TD-DFT calculations with the Gaussian03 package.[16] To obtain origin-independent results, the CCSD and CC2 calculations make use of the velocity-gauge approach described by Pedersen and co-workers,[17] while the TD-DFT results were obtained using gauge-including atomic orbitals.[12]

Figure 2 summarizes the theoretical and experimental optical rotation data available at five different wavelengths: 589, 578, 546, 436, and 365 nm, using the B3LYP/6-31G*-optimized geometry. While the TD-DFT and coupled cluster approaches are qualitatively correct (i.e., all three models give the correct sign of $[\alpha]_\omega$), the TD-DFT method consistently overestimates the value of the rotation by up to 104 deg/[dm (g/mL)] (15−16%). CC2 improves upon the TD-DFT results and reduces the error to about 8% (at most 52 deg/[dm (g/mL)]). Finally, the CCSD results are in superb agreement with experiment, with errors of only 1.5−12.8 deg/[dm (g/mL)]. This level of agreement is necessary for a robust quantum

---

[†] Virginia Tech.
[‡] Justus-Liebig Universität.
[§] Norwegian University of Science and Technology.

10.1021/ja042787p CCC: $30.25 © 2005 American Chemical Society

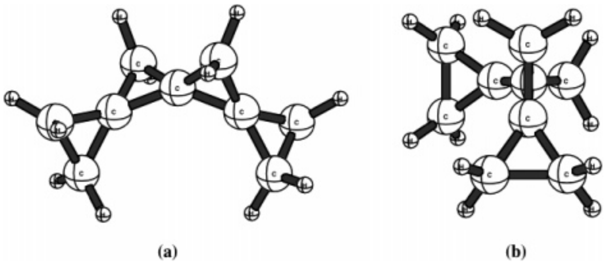


Figure 1. Structure of (*P*)-[4]triangulane: (a) side view of the four, fused cyclopropane rings; (b) view down the molecular helical axis, illustrating the *P* configuration used in this study.

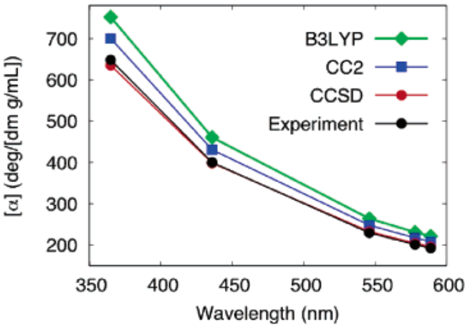


Figure 2. Experimental and theoretical ORD curves of (*P*)-[4]triangulane.

chemical model to be useful in determining the absolute configurations of unknown compounds, and these benchmark results are promising for future applications. However, we also note the differing computational expense of these methods: although each TD-DFT calculation required less than 1 day of computational time, each CCSD data point required approximately 1 week.

The substantial increase in the absolute value of the specific rotation with decreasing wavelength evident in Figure 2 indicates the onset of a positive Cotton effect. As can be seen from eq 1, as the energy of the incident light, ω, approaches that of one of the molecule's absorption bands, ω_{n0}, the Rosenfeld β tensor must exhibit a first-order pole and diverge to either positive or negative infinity. According to CCSD excitation energy calculations[18] with the PSI3 package, the lowest-lying absorption band of (*P*)-[4]-triangulane is of Rydberg type and lies at ca. 7.21 eV (172 nm). This point also explains TD-DFT's overestimation of the optical rotation: according to B3LYP calculations with the Gaussian03 package, the lowest excitation energy lies at 6.24 eV (199 nm), much lower than that computed by the CCSD method. (This type of error is common for modern TD-DFT in the prediction of diffuse, Rydberg states.) Thus, TD-DFT exhibits a much earlier onset of the Cotton pole, and its associated computed rotation is therefore larger across the entire ORD curve.[19]

There is room for improvement in the coupled cluster models to be certain that they provide "the right answer for the right reason", including recovery of residual electron correlation effects beyond the singles and doubles approximation and expansion of the basis set, as well as solvent effects, which can be an important factor for some systems.[20] Nevertheless, the coupled cluster calculations presented here are encouraging. In order for quantum chemical models to play a role in the determination of the absolute configurations of chiral molecules they must be able to provide an unprecedented level of accuracy and reliability in their predictions of optical rotation. The most robust ab initio models appear to be capable of achieving these high standards.

Acknowledgment. The authors dedicate this paper to Prof. A. de Meijere on the occasion of his 65th birthday for his seminal contributions to small-ring chemistry. T.D.C. was supported by a National Science Foundation CAREER Award (CHE-0133174), a Cottrell Scholar Award from the Research Corporation, and a New Faculty Award from the Dreyfus Foundation. P.R.S. was supported by the Deutsche Forschungsgemeinschaft and H.K. by the Norwegian Research Council through the Strategic University Program in Quantum Chemistry (Grant No. 154011/420).

References

(1) (a) Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley and Sons: New York, 1994. (b) Charney, E. *The Molecular Basis of Optical Activity: Optical Rotatory Dispersion and Circular Dichroism*; John Wiley and Sons: New York, 1979.
(2) Wnendt, S.; Zwingenberger, K. *Nature* **1997**, *385*, 303.
(3) (a) Kondru, R. K.; Wipf, P.; Beratan, D. N. *Science* **1998**, *282*, 2247. (b) Grimme, S. *Chem. Phys. Lett.* **2001**, *339*, 380. (c) Ruud, K.; Stephens, P. J.; Devlin, F. J.; Taylor, P. R.; Cheeseman, J. R.; Frisch, M. J. *Chem. Phys. Lett.* **2003**, *373*, 606. (d) Polavarapu, P. L.; Petrovic, A.; Wang, F. *Chirality* **2004**, *15*, S143. (e) Giorgio, E.; Viglione, R. G.; Zanasi, R.; Rosini, C. *J. Am. Chem. Soc.* **2004**, *126*, 12968.
(4) (a) Stephens, P. J. *J. Phys. Chem.* **1985**, *89*, 748. (b) Barron, L. D.; Hecht, L.; McColl, I. H.; Blanch, E. W. *Mol. Phys.* **2004**, *102*, 731.
(5) (a) Crawford, T. D.; Schaefer, H. F. *Rev. Comput. Chem.* **2000**, *14*, 33. (b) Bartlett, R. J. In *Modern Electronic Structure Theory*; Yarkony, D. R., Ed.; World Scientific: Singapore, 1995; Chapter 16, pp 1047−1131. (c) Gauss, J. In *Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., Schreiner, P. R., Eds.; John Wiley and Sons: Chichester, 1998; p 615.
(6) (a) Lee, T. J.; Scuseria, G. E. In *Quantum Mechanical Electronic Structure Calculations with Chemical Accuracy*; Langhoff, S. R., Ed.; Kluwer Academic: Dordrecht, 1995; pp 47−108. (b) Helgaker, T.; Ruden, T. A.; Jørgensen, P.; Olsen, J.; Klopper, W. *J. Phys. Org. Chem.* **2004**, *17*, 913.
(7) Parr, R. G.; Yang, W. *Density-Functional Theory of Atoms and Molecules*; Oxford University Press: New York, 1989.
(8) Koch, H.; Jørgensen, P. *J. Chem. Phys.* **1990**, *93*, 3333.
(9) Rosenfeld, L. *Z. Physik* **1928**, *52*, 161.
(10) (a) de Meijere, A.; Khlebnikov, A. F.; Kostikov, R. R.; Kozhushkov, S. I.; Schreiner, P. R.; Wittkopp, A.; Yufit, D. S. *Angew. Chem., Int. Ed. Engl.* **1999**, *38*, 3474. (b) de Meijere, A.; Khlebnikov, A. F.; Kostikov, R. R.; Kozhushkov, S. I.; Schreiner, P. R.; Wittkopp, A.; Rinderspacher, C.; Menzel, H.; Yufit, D. S.; Howard, J. A. K. *Chem. Eur. J.* **2002**, *8*, 828.
(11) Christiansen, O.; Koch, H.; Jørgensen, P. *Chem. Phys. Lett.* **1995**, *243*, 409.
(12) (a) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. *J. Phys. Chem. A* **2000**, *104*, 1039. (b) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem. A* **2001**, *105*, 5356.
(13) (a) Dunning, T. H. *J. Chem. Phys.* **1989**, *90*, 1007. (b) Kendall, R. A.; Dunning, T. H.; Harrison, R. J. *J. Chem. Phys.* **1992**, *96*, 6796.
(14) Crawford, T. D.; Sherrill, C. D.; Valeev, E. F.; Fermann, J. T.; King, R. A.; Leininger, M. L.; Brown, S. W.; Janssen, C. L.; Seidl, E. T.; Kenny, J. P.; Allen, W. D. *PSI3.2* **2003**.
(15) Helgaker, T.; Jensen, H. J. Aa; Jørgensen, P.; Olsen, P.; Ruud, K.; Ågren, H.; Auer, A. A.; Bak, K. L.; Bakken, V.; Christiansen, O.; Coriani, S.; Dahle, P.; Dalskov, E. K.; Enevoldsen, T.; Fernandez, B.; Hättig, C.; Hald, K.; Halkier, A.; Heiberg, H.; Hettema, H.; Jonsson, D.; Kirpekar, S.; Kobayashi, S.; Koch, H.; Mikkelsen, K. V.; Norman, P.; Packer, M. J.; Pedersen, T. B.; Ruden, T. A.; Sanchez, A.; Saue, T.; Sauer, S. P. A.; Schimmelpfennig, B.; Sylvester-Hvid, K. O.; Taylor, P. R.; Vahtras, O. *DALTON 1.2* **2001**.
(16) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*; Gaussian, Inc.: Pittsburgh, PA, 2003.
(17) Pedersen, T. B.; Koch, H.; Boman, L.; de Meras, A. M. J. S. *Chem. Phys. Lett.* **2004**, *393*, 319.
(18) Stanton, J. F.; Bartlett, R. J. *J. Chem. Phys.* **1993**, *98*, 7029.
(19) Tam, M. C.; Russ, N. J.; Crawford, T. D. *J. Chem. Phys.* **2004**, *121*, 3550.
(20) Kumata, Y.; Furukawa, J.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3920.

JA042787P