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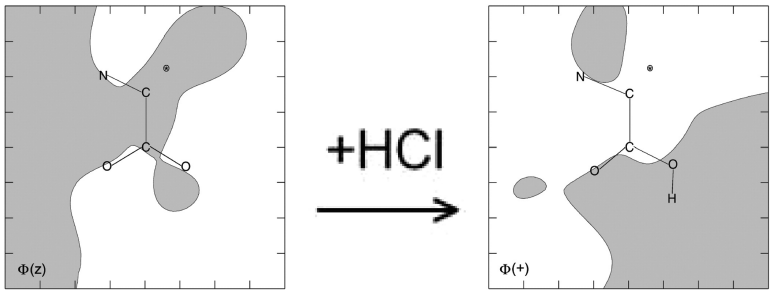

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Computational Modeling of the Optical Rotation of Amino Acids: A New Look at an Old Rule for pH Dependence of Optical Rotation

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Abstract: The molar rotation of a solution of a natural alpha amino acid is changed in the positive direction by addition of a strong acid. Three decades ago, an attempt to rationalize this old rule, named for Clough, Lutz, and Jirgensons (CLJ), was made by assigning circular dichroism octants for overlapping carbonyl n to pi* transitions. Modern quantum chemical methods allow us to take a new look at this phenomenon. Time-dependent density functional theory was used to model the electronic structure and transitions responsible for CLJ. We show that sector rules originally developed for circular dichroism (CD) can be applied to the optical rotation in this case, but with some restrictions, and with great caution, due to the change of the overall charge of the acids upon protonation and the distortion of the COO^- chromophore in the zwitterions. We have prepared sector maps based on first-principles computations to study the correspondence between CD and optical rotation for zwitterionic and protonated L-amino acid chromophores. The CLJ effect is correctly obtained from the computations for all 12 amino acids studied in this work.

Introduction

Already in the early days of chemistry it was known that solutions of certain compounds (now designated as chiral), many biological in origin, rotate a plane of polarized light by a specific number of degrees per the concentration of the compound and the path length of the light. Since the advent of polarimetry, other analytical techniques have evolved that are capable of linking molecular chiral structure with observable physical responses. Circular dichroism[1] (CD), both electronic and vibrational (infrared and Raman), has proven a useful technique for probing the configuration of optically active compounds. X-ray diffraction[2] has become an invaluable tool for determining the absolute configuration of compounds where crystals can be obtained. Recently, Raman optical activity[3] has emerged as a promising technique for assigning the absolute configuration of chiral molecules. However, for reasons of its ease of use and inexpensiveness, the simple polarimeter remains among the most widely applied probes of chirality.

Since the inception of polarimetry, scientists have strived to make a rational connection between the sign and magnitude of chiroptical response and molecular structure. It is important to note that *general* rules to predict the sign (or the magnitude) of the chiroptical response from the molecular structure without performing first-principles computations do not exist. Over the 20th century, several methods have been proposed to overcome this problem. Well-known examples are sector rules for the CD of specific chromophores, of which the carbonyl "octant rule"[4−6] is a subset, as well as the exciton chirality method[7] (also for CD), to name a few. These methods are invaluable tools for linking a molecule's CD to its absolute configuration. Unfortunately, the relation of the sign and magnitude of the optical rotation (OR) to molecular structure is less well understood except for simple cases where one can single out a chromophore that is almost exclusively responsible for the OR and for which sector rules may apply. One empirical rule for OR that caught our attention was developed in the early twentieth century,[8−10] and can be stated as follows: If upon acidification of an aqueous solution of an amino acid its specific rotation becomes more positive, the amino acid is of the "L" absolute configuration. If the opposite is true, then it is of the "D" configuration. This rule, named for Clough, Lutz, and Jirgensons[11] (CLJ), is not without exception, but it has been shown to be reliable in the assignment of the absolute configuration of a multitude of amino acids and has found occasional use in modern times.[12]

(1) Berova, N.; Nakanishi, K.; Woody, R. W. *Circular Dichroism: Principles and Applications*, 2nd ed.; John Wiley & Sons, Inc.: New York, 2000.
(2) Bijvoet, J. M. P., A. F.; van Bommel, A. J. *Nature* **1951**, *168*, 271.
(3) Haesler, J.; Schindelholz, I.; Riguet, E.; Bochet, C. G.; Hug, W. *Nature* **2007**, *446*, 526.
(4) Lightner, D. A.; Chang, T. C. *J. Am. Chem. Soc.* **1974**, *96*, 3015.
(5) Lightner, D. A.; Gawronski, J. K.; Bouman, T. D. *J. Am. Chem. Soc.* **1980**, *102*, 1983.
(6) Lightner, D. A.; Crist, B. V.; Kalyanam, N.; May, L. M.; Jackman, D. E. *J. Org. Chem.* **1985**, *50*, 3867.
(7) Harada, N. N., K. *Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, 1983.
(8) Clough, G. W. *J. Chem. Soc., Trans.* **1918**, *113*, 526.
(9) Lutz, I. O.; Jirgensons, B. *Ber. Dtsch. Chem. Ges. [Abt.] B: Abh.* **1930**, *63B*, 448.
(10) Lutz, O.; Jirgensons, B. *Ber. Dtsch. Chem. Ges. [Abt.] B: Abh.* **1931**, *64B*, 1221.
(11) Greenstein, J. P.; Winitz, M. *Chemistry of the Amino Acids*; John Wiley & Sons: New York, 1961.
(12) Vleggaar, R.; Ackerman, L. G. J.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3095.

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Since the turn of the 21st century, much of the effort to link the sign and magnitude of the chiroptical response measurements to local and global absolute configuration has centered on computational chemistry. This has been recently referred to as a "renaissance in chiroptical spectroscopic methods" which has sparked renewed interest in the field.[13] The current state of the art method for modeling specific rotation for most but the smallest molecules is time dependent density functional theory (TDDFT), and algorithms for performing such calculations are available in several popular program packages and other codes.[14−18] For recent reviews of computational techniques and applications, see the works of Polavarapu,[13,19] Crawford,[20] Pecul and Ruud,[21] and Autschbach.[22] Many of the papers published in this field of research center around benchmarking and improving upon these methods.[23−28] There have been many recent advances in the modeling of optical activity, a few examples of which will be mentioned here. Ruud and Zanasi,[29] Kongsted et al.,[30]and Mort and Autschbach[30,31] have studied the zero point vibrational contributions to chiroptical response properties. The temperature dependence of chiroptical responses has also been modeled.[31] Mennucci et al.,[32] Pecul et al.,[33] and Mukhopadhyay and co-workers[34] have reported methods to model the effects of solvents on optical rotation. Ruud and Helgaker,[35] as well as Crawford and co-workers,[36] have applied coupled-cluster methods to computing chiroptical properties, which should yield higher accuracy than the current standard functionals in TDDFT as more powerful computers and new algorithms make it more practical. Such progress means that theory continues to improve and makes the combination of molecular modeling with experimental measurement of specific rotation a more useful tool for the assignment of absolute configuration.

While focusing on improving the accuracy of molecular modeling is important in its own right, sometimes it is useful to take a look back at how the theories of today relate to the theories of the past. Obviously the CLJ rule cannot anymore be considered a major tool for the assignment of absolute configurations of amino acids. However, it is one of the rare examples where it appears to be possible to relate the sign of the optical rotation (here: a trend for closely related structures) to the absolute configuration. As such, the CLJ rule is of fundamental interest because, as already mentioned, the relationship(s) between the sign of the optical rotation and the molecular structure remains one of the great enigmas in stereochemistry. One of the goals of computational research in this field is to uncover these relationships which will ultimately lead to practical rules (perhaps similar to the sector rules of CD) for the easy prediction and rationalization of the sign of the OR based on a molecule's configuration. Such rules should have a firm foundation in first-principles theory. Another aspect of this study is the following: There are serious difficulties in modeling the OR of conformationally flexible molecules with small-magnitude ORs (for which amino acids are good examples).[37−40] Their computational modeling is further complicated by the need for treating solvent effects. However, we will show that the CLJ effect itself is reproduced quite well in the computations. The analysis of the origin of the CLJ effect will demonstrate that exceptions to the rule can be easily rationalized. Therefore, if an effect of similar type as CLJ can be exploited in studies of other chiral molecules we believe it would greatly improve the predictive power of computation-based assignments of absolute configurations in cases where conformational averaging of ORs causes unacceptable uncertainties in the computational results. Finally, for the carbonyl and the carboxyl chromophore in amino acid zwitterions and their protonated forms we show by mapping out "chiral sectors" that the problem of understanding OR−structure relationships can in some cases be reduced to an analysis of the CD.

We begin with a computational benchmarking on a test set of 12 common L-amino acids to see how well TDDFT can replicate the CLJ effect. Next we focus more closely on alanine, the smallest chiral amino acid, to show why, from a quantum mechanical prospective, the CLJ rule exists the way it does. The reasons the rule is obeyed for many amino acids and disobeyed for a few are discussed. Finally we take a look back to an explanation of the CLJ rule from 3 decades ago, to investigate to what extent this rationale fits with data obtained from first-principles theory.

Computational Methods

The computational methods used in this work are detailed in a previous publication,[38] where TDDFT based computations of optical rotations of amino acids were exhaustively benchmarked.[37] A brief summary follows: All data were computed with the Turbomole[16] quantum chemical software, version 5.7.1. The calculations were performed with the Becke three parameter B3-LYP and BHLYP[41] hybrid functionals as implemented in the Turbomole code. Molecular geometries were optimized with the default doubly polarized valence triple-ζ (TZVPP) basis set from the Turbomole library; all energies used for Boltzmann averaging were computed with this basis. Response

(13) Polavarapu, P. L. *Chem. Rec.* **2007**, *7*, 125.
(14) Baerends, E. J.; et al. *Amsterdam Density Functional*, version 01; Scientific Computing and Modeling: Amsterdam, The Netherlands, 2006.
(15) Frisch, M. J.; et al. *Gaussian03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.
(16) *Turbomole*, Ahlrichs, R.; Bar, M.; Haser, M.; Horn, H.; Kolmel, C. *Chem. Phys. Lett.* **1989**, *162*, 165.
(17) *DALTON, a molecular electronic structure program*, Release 2.0, 2005; see http://www.kjemi.uio.no/software/dalton/dalton.html.
(18) Bylaska, E. J.; et al. *NWChem, A Computational Chemistry Package for Parallel Computers*, version 5.0; Pacific Northwest National Laboratory: Richland, WA, 2006.
(19) Polavarapu, P. L. *Chirality* **2002**, *14*, 768.
(20) Crawford, T. D. *Theor. Chem. Acc.* **2006**, *115*, 227.
(21) Pecul, M.; Ruud, K. The ab initio calculation of optical rotation and electronic circular dichroism. In *Advances in Quantum Chemistry*; Elsevier Academic Press Inc: San Diego, 2005; Vol. 50, pp 185.
(22) Autschbach, J. *Computing Letters* **2007**, *3*, 131.
(23) Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Stephens, P. J. *J. Phys. Chem. A* **2000**, *104*, 1039.
(24) Stephens, P. J.; Devlin, F. J.; Cheeseman, J. R.; Frisch, M. J. *J. Phys. Chem. A* **2001**, *105*, 5356.
(25) Autschbach, J.; Patchkovskii, S.; Ziegler, T.; van Gisbergen, S. J. A.; Baerends, E. J. *J. Chem. Phys.* **2002**, *117*, 581.
(26) Grimme, S.; Furche, F.; Ahlrichs, R. *Chem. Phys. Letters* **2002**, *361*, 321.
(27) Giorgio, E.; Viglione, R. G.; Zanasi, R.; Rosini, C. *J. Am. Chem. Soc.* **2004**, *126*, 12968.
(28) Stephens, P. J.; McCann, D. M.; Cheeseman, J. R.; Frisch, M. J. *Chirality* **2005**, *17*, S52.
(29) Ruud, K.; Zanasi, R. *Angew. Chem., Int. Ed.* **2005**, *44*, 3594.
(30) Kongsted, J.; Pedersen, T. B.; Jensen, L.; Hansen, A. E.; Mikkelsen, K. V. *J. Am. Chem. Soc.* **2006**, *128*, 976.
(31) Mort, B. C.; Autschbach, J. *Chemphyschem* **2007**, *8*, 605.
(32) Mennucci, B.; Tomasi, J.; Cammi, R.; Cheeseman, J. R.; Frisch, M. J.; Devlin, F. J.; Gabriel, S.; Stephens, P. J. *J. Phys. Chem. A* **2002**, *106*, 6102.
(33) Pecul, M.; Marchesan, D.; Ruud, K.; Coriani, S. *J. Chem. Phys.* **2005**, *122*.
(34) Mukhopadhyay, P.; Zuber, G.; Goldsmith, M. R.; Wipf, P.; Beratan, D. N. *Chemphyschem* **2006**, *7*, 2483.
(35) Ruud, K.; Helgaker, T. *Chem. Phys. Lett.* **2002**, *352*, 533.
(36) Crawford, T. D.; Owens, L. S.; Tam, M. C.; Schreiner, P. R.; Koch, H. *J. Am. Chem. Soc.* **2005**, *127*, 1368.
(37) Kundrat, M. D.; Autschbach, J. *J. Phys. Chem. A* **2006**, *110*, 4115.
(38) Kundrat, M. D.; Autschbach, J. *J. Phys. Chem. A* **2006**, *110*, 12908.
(39) Pecul, M.; Ruud, K.; Rizzo, A.; Helgaker, T. *J. Phys. Chem. A* **2004**, *108*, 4269.
(40) Pecul, M. *Chem. Phys. Letters* **2006**, *418*, 1.
(41) Becke, A. D. *J. Chem. Phys.* **1993**, *98*, 5648.

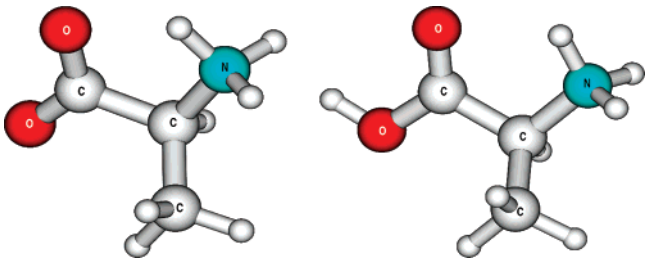


Figure 1. Optimized zwitterionic (left) and cationic (right) structures of alanine.

calculations were performed with the aug-cc-pVDZ basis.[42] All optimizations and response calculations included the COnductor-like Screening MOdel (COSMO)[43] of solvation applied to the ground state. For molecules for which multiple conformers exist, the energies used to compute relative conformer populations at 293 K included COSMO corrected electronic energies as well as zero point energies; additional terms needed to compute relative Gibbs free energies were not included since it is not clear how the computed (gas-phase) corrections for ΔG relate to *solvated* molecules. Except where otherwise noted, molar rotations were calculated at the wavelength of the sodium D-line (589.3 nm). All molar rotations are reported in units of deg·cm^2/(dmol). The center of mass has been used for the coordinate origin for all response calculations. While all results are formally origin dependent, this dependence is minimized in variational methods when large basis sets such as aug-cc-pVDZ are used; see our earlier work and the references cited therin.[37] As a practical test, moving the gauge origin 10 Å from the center of mass of an alanine cation produced a change in molar rotation of only 3 deg·cm^2/(dmol). (Using a different program with a formally gauge-origin independent method yielded changes an order of magnitude smaller. The residual gauge-origin dependence can be attributed due to finite convergence thresholds and numerical imprecision in solving the linear response equations).

Results and Discussion

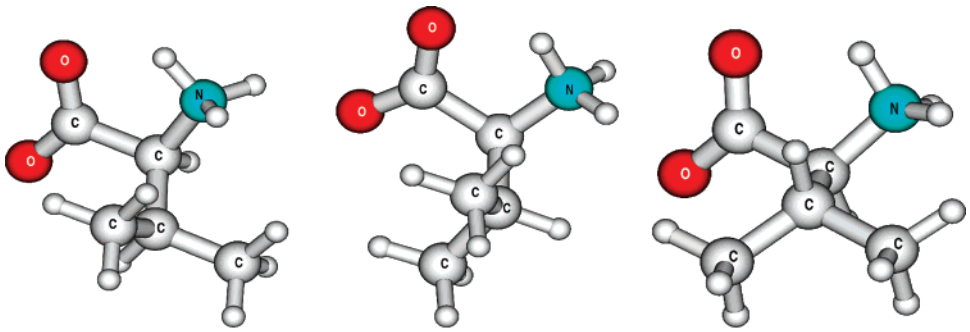
1. Modeling the Molar Rotation of the Zwitterionic and Cationic (Protonated) Amino Acids in Solution. Before further discussion of the CLJ rule, it must be established that the computational method employed here can reproduce the effect. For this benchmarking, 12 optically active L-amino acids were selected: alanine, cysteine, histidine, isoleucine, leucine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, and valine. They were chosen primarily because they do not have large conformational spaces, so to limit the number of structures for which computations were needed. The chiroptical response of each amino acid was computed for the protonation states they adopt in neutral and acidic solutions. All of the amino acids studied here take the zwitterionic form in pure water and become protonated on the carboxylate group at low pH. (Previous work by Pecul et al.[39] mentioned a related change of the optical rotation between protonated and non-zwitterionic proline and alanine in the gas phase, but the work did not directly address the aqueous forms responsible for CLJ.) This protonation is found to preferentially occur on the carboxylate oxygen trans to the amino group,[37] which is illustrated in Figure 1. This resulted in one protonated form of each amino acid being found for every zwitterionic rotamer. Histidine is unique among this set in that it becomes doubly protonated in strong acid. The second protonation occurs at the imidazole ring. As a consequence one deprotonated form was considered for each zwitterionic form.[38]

For alanine since only one zwitterionic structure could be found and only one of its protonated structures has a significant population at room temperature, modeling its molar rotation is a straightforward process from the perspective of conformational averaging. Modeling of the larger amino acids is more complicated, since they can be found in multiple conformations at ambient temperature. Of the other 18 common naturally occurring chiral amino acids, proline is unique in that its ring structure restricts the side chain to two energetically favored conformations. For the rest of the amino acids, the number of possible rotamers that must be considered for a particular molecule depends mainly on the number of carbon−carbon bonds around which rotation may occur. For valine and phenylalanine, rotation about the $C_\alpha-C_\beta$ bond results in three structures that must be modeled. For the aromatic compounds histidine, tryptophan, and tyrosine, six low energy conformers were found, generated by combining the threefold rotation about the $C_\beta-C_\alpha$ axis with the twofold rotation about the $C_\gamma-C_\beta$ bond. Cysteine, isoleucine, leucine, serine, and threonine all contain two threefold axes of rotation which means that nine possible rotamers of each had to be considered in this conformational search, though steric issues dictated that fewer than nine optimized structures were found for some of these. The rest of the amino acids commonly found in mammalian proteins have even greater conformational flexibility than the aforementioned molecules, so for them an *ab initio* conformational averaging of the optical rotation of all possible rotamers was deemed impractical, at present. Therefore for the purpose of studying the CLJ rule this study is limited to the 12 amino acids already listed.

Identification of every energetically accessible conformer of a molecule is critical to the correct modeling of its molar rotation. Ascertaining the relative populations of these conformers is also extremely important, since the molar rotation of a compound that can be measured experimentally represents a weighted average of this chiroptical response of the molecule in all of its possible conformations. Unlike many other linear response properties, optical rotations of different conformers can differ in magnitude *and* sign. Obtaining reliable Boltzmann averages of amino acid rotamers has been identified as a source of error in the past; especially in cases where the average can be biased by intramolecular hydrogen bonding, which is difficult to model correctly.[37,38]

The importance of Boltzmann averaging can be illustrated by using the valine zwitterion as an example. This molecule can adopt three possible conformations in solution, which are illustrated in Figure 2. The naming designations of the rotamers, t, g, and h, refer to whether a group (one of the two methyl groups in the case of valine) is *trans* or *gauche* to the carboxylate group, or it is sterically *hindered* between the carboxylate and amino group. The three rotamers differ from each other only in the angle about the $C_\beta-C_\alpha$, bond, but this distinguishing factor is enough to cause the conformers to yield molar rotations of differing sign. As such, the molar rotation that is modeled for a valine zwitterion depends strongly on the Boltzmann factor that is calculated for each of these rotamers. Errors in these mole fractions will likely result in an erroneous computed molar rotation Boltzmann average.

(42) Woon, D. E.; Dunning, T. H. *J. Chem. Phys.* **1994**, *100*, 2975.
(43) Schafer, A.; Klamt, A.; Sattel, D.; Lohrenz, J. C. W.; Eckert, F. *Phys. Chem. Chem. Phys.* **2000**, *2*, 2187.



h,t	g,h	g,t
0.0kJ/mol	+4.3kJ/mol	+5.3kJ/mol
-52.6	57.8	-60.6

Figure 2. Rotamers of zwitterionic valine, along with their computed relative energies at the B3LYP/TZVPP level and molar rotations at BHLYP/aug-cc-pVDZ.

Table 1. Computed and Measured Molar Rotations [ϕ] at 589.3 nm for Selected L-amino Acid Solutions[a]

molecule	computed molar rotation B3LYP	BHLYP	experimental[b]	# of conformers CLJ obeyed for
alanine zwitterion	5.4	−1.5	1.6	
alanine cation	27.2	27.8	13.0	1/1
Δ[ϕ]	21.7	29.3	11.4	
cysteine zwitterion	−51.9	−46.2		
cysteine cation	9.8	11.3	7.9[c]	7/8
Δ[ϕ]	61.7	57.5		
histidine zwitterion	−62.4	−45.7	−59.8	
histidine dication	105.4	88.3	18.3	4/6
Δ[ϕ]	167.7	134.0	78.1	
isoleucine zwitterion	−3.9	−7.4	16.3	
isoleucine cation	84.7	74.9	51.8	9/9
Δ[ϕ]	88.7	82.3	35.5	
leucine zwitterion	−48.8	−52.1	−14.4	
leucine cation	84.5	74.6	21.0	9/9
Δ[ϕ]	133.3	126.7	35.4	
phenylalanine zwitterion	−36.8	−41.4	−57.0	
phenylalanine cation	97.5	81.8	−7.4	3/3
Δ[ϕ]	134.3	123.2	49.6	
proline zwitterion	−127.3	−101.5	−99.2	
proline cation	−93.1	−65.3	−69.5	2/2
Δ[ϕ]	34.2	36.2	29.7	
serine zwitterion	−6.3	−5.6	−7.9	
serine cation	6.7	12.1	15.9	7/7
Δ[ϕ]	13.0	17.7	23.8	
threonine zwitterion	−4.6	−12.6	−33.9	
threonine cation	52.9	48.8	−17.9	7/7
Δ[ϕ]	57.5	61.4	16.0	
tryptophan zwitterion	−46.0	−54.1	−68.8	
tryptophan cation	−46.8	−23.4	13.0	4/6
Δ[ϕ]	−0.8	30.7	81.8	
tyrosine zwitterion	−29.9	−34.8		
tyrosine cation	74.3	57.8	−19.2[c]	5/6
Δ[ϕ]	104.2	92.6		
valine zwitterion	−39.5	−39.2	6.6	
valine cation	90.9	79.4	33.1	3/3
Δ[ϕ]	130.4	118.6	26.5	
TOTAL				61/67

[a] Δ[ϕ] is the CLJ effect. $\Delta[\phi] = [\phi]_{cation} - [\phi]_{zwitterion}$ in deg·cm^2/dmol. [b] Experimental values from Greenstein and Winitz[11] except where otherwise noted. [c] Merck Index, 12th ed.[45]

The average molar rotations of this as well as the other 11 amino acids modeled are summarized in Table 1. Details about the geometries used, as well as their individual computed molar rotations and Boltzmann populations are available in the Supporting Information. The response properties were originally modeled using the popular B3LYP hybrid DFT functional. In light of concerns about the frequent underestimation of excitation energies by this functional and the consequential overestimation of molar rotation, calculations with another common functional, BHLYP, were carried out for comparison.[44] Results with both functionals are presented. For both sets of response calculations the aug-cc-pDVZ basis set was employed, which is well established for calculating these chiroptical properties.[26,28]

The first comparison to be made in Table 1 is between the computed and measured signs of the molar rotation values for the zwitterionic and cationic forms of the L-amino acids being studied. For the zwitterionic forms, the computed and measured molar rotations agree in sign for ten of the molecules when the B3LYP hybrid functional is used, and for 9 out of 12 molecules with the BHLYP functional. For the cationic (protonated) forms, theory and experiment agree for 8 out of 11 molecules for both functionals, with tryptophan being deemed inconclusive due to disagreement among experimental values in the literature. The fact that theory and experiment disagree in the sign of the molar rotation for several of these molecules is not unexpected. Many of these values are relatively small in magnitude,[28] and often the result of the partial cancellation of larger optical rotations of conformers as illustrated in Figure 2.

While the correlation of the signs of theoretical and experimental molar rotations yields somewhat mixed results, the comparison of the *change* in molar rotation when a particular amino acid is protonated/deprotonated is far more promising. According to Greenstein and Winitz, the molar rotations for all of the amino acids studied become more positive when they are protonated with strong acid than when they are in their zwitterionic forms in aqueous solution. They named this phenomenon after Clough, Lutz, and Jirgensons.[11] When the computed differences in molar rotations are tabulated, we find that with the B3LYP functional this rule is obeyed for 11 out of 12 of these molecules. (We will comment on the outlier later.) With the BHLYP functional the CLJ effect is successfully modeled for all of the molecules in this test set.

The reason that the difference in molar rotations may be modeled with greater reliability than the absolute values of these rotations themselves is obviously due to a balanced cancellation

(44) Mori, T.; Inoue, Y.; Grimme, S. *J. Org. Chem.* **2006**, *71*, 9797.

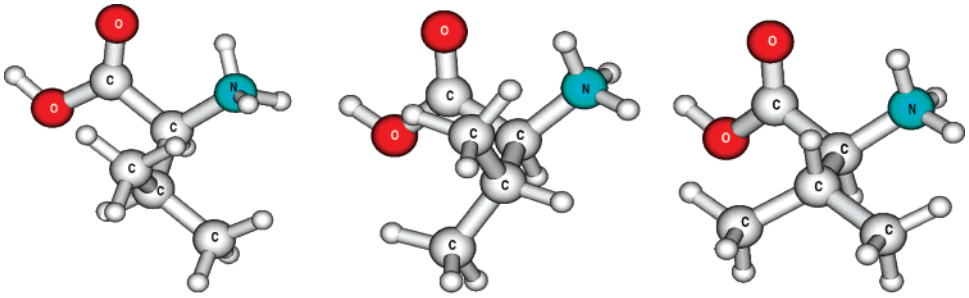


Figure 3. Rotamers of protonated valine, along with their computed relative energies and molar rotations (BHLYP/aug-cc-pVDZ//B3LYP/TZVPP).

of errors. Potential sources of error in TDDFT calculations may include: imprecision in calculated molecular geometries, insufficient treatment of solvent effects, neglect of vibrational/thermal effects, possible nonlinear concentration effects, residual gauge origin dependence, approximations in the exchange-correlation potential and kernel, basis set truncation, and inaccurate Boltzmann weighting of conformers. For a discussion of some of these sources of error, see the work of Stephens et al.,[24] as well as other works.[21,22,44,46−48] When attempting to model a molar rotation that is relatively small in magnitude, the combination of these errors may cause the sign of molar rotation that is modeled and the one that is measured to disagree. But when modeling two very similar molecules using an identical model chemistry and taking the difference of the results, many of these sources of error can subtract out, leaving behind a computed difference that is meaningful. Since the correct CLJ behavior is obtained for all of the amino acids modeled here it is reasonable to conclude that the *change* in optical rotation is obtained for the correct reasons. This finding suggests that modeling the change in optical rotation, for instance upon protonation (if possible), for a molecule other than an amino acid may be useful for assigning its absolute configuration even in cases where the optical rotation's magnitude in itself is too small to be a reliable measure. However, further studies would certainly be required to confirm this hypothesis.

More insight regarding the utility of the CLJ rule may be gained by looking at the rightmost column of Table 1. This column lists the number of rotamers that each amino acid may be found in, and how many of the corresponding zwitterion/cation pairs the CLJ rule is obeyed for in the computations. In this case no difference was seen regardless of which hybrid functional was employed, so separate columns for each are not listed.

Consider valine again as an illustrated example. The three rotamers of the valine cation are depicted in Figure 3. Note that each rotamer structure has a corresponding zwitterionic structure already shown above in Figure 2. We find that protonation causes a positive change in molar rotation for all of the rotamers: for the h,t rotamer $\Delta[\phi] = +50.4$, for the g,h rotamer $\Delta[\phi] = +75.6$, and for the g,t rotamer $\Delta[\phi] = +94.1$. (To the extent that the relative rotamer populations remain the same upon protonation, these $\Delta[\phi]$ values are of the same order of magnitude as the overall measured $\Delta[\phi]$.) Since all rotamers of valine, as well as isoleucine, leucine, phenylalanine, proline, serine, and threonine obey the CLJ rule, one wishing to use it to assign absolute configuration could chose *any* rotameric form to model and still make the correct assignment. This stands in contrast to assigning absolute configuration based on molar rotation alone, where all low-energy rotamers must be modeled, and their resulting molar rotations need to be averaged in the correct proportions to achieve the correct result. As already pointed out, the Boltzmann averaging might introduce additional uncertainties about the quality of the computed results.

There are however amino acids for which the CLJ rule is not universally obeyed for all of the conformers. These include cysteine, histidine, tyrosine, and tryptophan. One feature that these all have in common is that all possess unsaturated functional groups (π orbitals), or, in the case of cysteine, lone pair orbitals on its sulfur atom. These orbitals can take part in electronic transitions in the near UV, and as we have shown previously for the aromatic amino acids, these low-energy excitations may have a great effect on the observed specific rotation.[38] The effect of such chromophores is discussed in more detail in the following section.

2. The Relationship between Circular Dichroism Excitations and Molar Rotation. The direct linear response method for computing optical rotation that was used in the first section does well to model transparent-region chiroptical properties, but without further analysis it reveals little about the electronic effects responsible for these effects. To further explore why Clough−Lutz−Jirgensons' rule is obeyed in most cases and why in a few others it breaks down, we decided to investigate the electronic transitions that give rise to molar rotation at 589.3 nm. According to the Kramers−Kroning relationship,[49] or the sum over states (SOS) equation for molar rotation (eq 1 below, where typically $\omega < \omega_{01}$), one may expect the lowest energy CD transitions to be the most responsible for optical rotation in the transparent region because of the relatively small denominators.

$$[\phi]_\omega = 91.43028 \cdot \omega^2 \sum_{n \neq 0} \frac{R_{0n}}{\omega_{0n}{}^2 - \omega^2} \qquad (1)$$

(45) *The Merck Index*, 12th ed.; Merck & Co., Inc.: Whitehouse Station, NJ, 1996.
(46) Coriani, S.; Baranowska, A.; Ferrighi, L.; Forzato, C.; Marchesan, D.; Nitti, P.; Pitacco, G.; Rizzo, A.; Ruud, K. *Chirality* **2006**, *18*, 357.
(47) Kowalczyk, T. D.; Abrams, M. L.; Crawford, T. D. *J. Phys. Chem. A* **2006**, *110*, 7649.
(48) Polavarapu, P. L. *Chirality* **2006**, *18*, 348.
(49) Polavarapu, P. L. *J. Phys. Chem. A* **2005**, *109*, 7013.

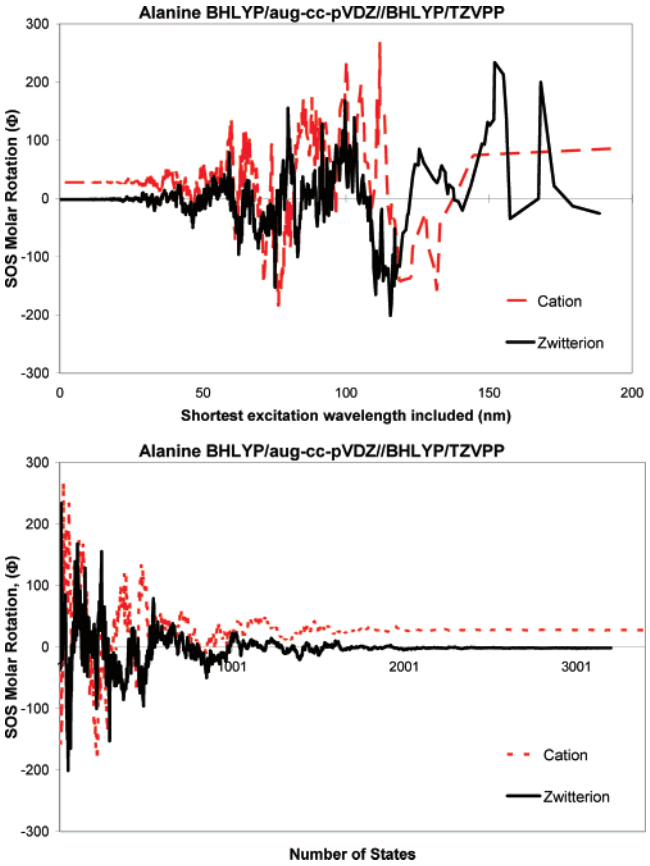


Figure 4. Molar rotation of alanine computed from the truncated sum over states, $[\phi]^k_\omega$ of eq 2, versus the absorption wavelength for state number k (top, read from right to left).

Here $[\phi]$ is in units of deg·cm^2/(dmol), ω is the angular frequency of light ($2\pi\cdot\nu$), ω_{0n}, is the n'th excitation frequency out of the ground state with R_{0n} the rotatory strength of the transition in units of 10^{-40} esu^2·cm^2. The sum runs over all states. We define the incomplete summation up to excited-state no. k as

$$[\phi]^k_\omega = 91.43028\cdot\omega^2 \sum_{n=1}^{k} \frac{R_{0n}}{\omega_{0n}{}^2 - \omega^2} \qquad (2)$$

In Figure 4 we have plotted $[\phi]^k_\omega$ for the prototypical chiral L-amino acid, alanine. The first excitations in the respective zwitterionic and cationic forms are largely responsible for the CLJ effect. The top part of this figure displays the truncated SOS molar rotation, eq 2, of alanine in the two forms of interest as a function of the wavelength of the highest-energy electronic excitation, k, which is included in a calculation of the truncated SOS molar rotation according to eq 2. The bottom of Figure 4 depicts the same data, except here as a function of k, the number of states included in $[\phi]^k_\omega$.[50]

If all excited states possible for a given basis set (whether physically meaningful or not) are included in the summation it ultimately yields the same results as the linear response computation.[50] The sum converges on the right side of the second graph (the left side of the first graph) as the number of states approaches the limit of the basis set. The advantage of using the SOS equation is that it allows us to investigate not just what the molar rotation of a compound is, but also which excitations are responsible for that response, according to the SOS analysis. Here it is shown that the lowest electronic excitation, at the far right side of the first graph, causes a pronounced CLJ effect in the molar rotation. That is, at this first step of the SOS summation, the molar rotation of the cationic form of the L-amino acid is seen to be more positive than that of the zwitterion. Higher lying excitations dampen this effect. The sum rule,[51] $\Sigma_n R_{0n} = 0$, indicates that such damping is more likely than not, since the sum of the rotatory strengths beyond the first must equal the opposite of that of the first excitations so that their sum can be zero. Experience shows that the R_{0n} values strongly oscillate as n increases.[52] However, this R_{0n} damping only diminishes the magnitude of the CLJ effect observed to result from the first CD excitations, and the sign of the $\Delta[\phi]$ for the zwitterion → cation reaction remains the same in the end: it is positive for L forms of the amino acids. The analysis of the alanine CD spectrum therefore strongly suggests that the structural origin of the CLJ rule for α-amino acids can be rationalized by examining the trend for the lowest CD transition upon protonation. This OR/CD relationship will be investigated in more detail below. As a general disadvantage of the SOS analysis we note the abundance of large contributions in the sum which makes it difficult to single out a few important terms without applying a "bias" of physical reasoning that assigns the low lying excitations a particular significance. However, exclusion of this excitation in the SOS would mean that the CLJ effect is *not* obtained.

Computing the entire sum of electronic excitations is an arduous task, which becomes impractical with our chosen basis set for the larger molecules in our test set. However calculating the molar rotation resulting from just the lowest CD transition is straightforward, and as Figure 4 has shown it is this transition that appears to be very influential regarding the CLJ effect under investigation. Therefore, the portion of molar rotations resulting from these lowest energy CD transitions was modeled for the rest of our test set of molecules. The results are summarized in Table 2. We note here that all CD transitions are computed with the length gauge dipole representation, however computations of partial molar rotations with the velocity gauge dipole always agreed in sign and agreed in magnitude with those with the length gauge, therefore origin dependence does not effect our conclusions.

When the rightmost column of Table 2 is compared with the corresponding column in Table 1, the pattern becomes obvious. For all the molecules in the set for which the CLJ rule is not obeyed for all rotamers, there exists a chromophore that gives rise to a lower energy electronic transition than that of the carboxylate/carboxylic acid present in all zwitterionic/cationic amino acids. For most of the molecules for which CLJ is obeyed for all rotamers, one of the carboxylate/carboxylic acid chromophore excitations is the lowest in energy. The only molecule with an aromatic chromophore for which the CLJ rule is obeyed for all conformers is phenylalanine, which has been shown to have a very weak π to π^* transition in its phenyl group, as the

(50) Wiberg, K. B.; Wang, Y. G.; Wilson, S. M.; Vaccaro, P. H.; Cheeseman, J. R. *J. Phys. Chem. A* **2006**, *110*, 13995.

(51) Condon, E. U. *Rev. Mod. Phys.* **1937**, *9*, 432.

(52) Krykunov, M.; Kundrat, M. D.; Autschbach, J. *J. Chem. Phys.* **2006**, *125*, 13.

Table 2. Computed Longest Excitation Wavelengths, λ, and Partial Molar Rotations $[\phi]_{589.3nm}$ From This Excitation for Selected L-Amino Acid Solutions[a]

molecule	excitation wavelength, λ (nm)		molar rotation caused by first excitation [ϕ]		lowest energy chromophore
	B3LYP	BHLYP	B3LYP	BHLYP	
alanine zwitterion	211.4	188.6	−147.8	−25.7	carboxylate
alanine cation	203.9	192.6	106.7	85.5	carboxylic acid
Δ	−7.4	4.0	254.5	111.2	
cysteine zwitterion	218.0	204.6	6.2	31.1	thiol
cysteine cation	230.8	204.5	31.9	16.0	thiol
Δ	12.8	−0.1	25.7	−15.1	
histidine zwitterion	229.7	209.1	−93.5	−38.6	imidizole
histidine dication	211.1	196.5	683.3	302.6	imidizole
Δ	−18.6	−12.6	776.8	341.2	
isoleucine zwitterion	210.0	188.6	−162.6	−36.4	carboxylate
isoleucine cation	206.6	194.6	180.1	123.8	carboxylic acid
Δ	−3.4	6.0	342.7	160.2	
leucine zwitterion	208.3	188.1	−103.0	−19.0	carboxylate
leucine cation	207.5	196.1	208.5	150.4	carboxylic acid
Δ	−0.8	8.0	311.5	169.4	
phenylalanine zwitterion	234.7	223.1	−5.9	−3.7	phenyl
phenylalanine cation	235.1	222.9	17.1	−0.7	phenyl
Δ	0.4	−0.2	23.0	3.0	
proline zwitterion	211.3	188.6	−60.5	−24.0	carboxylate
proline cation	204.9	193.2	102.9	73.6	carboxylic acid
Δ	−6.4	4.6	163.4	97.6	
serine zwitterion	209.9	188.3	−128.2	−36.5	carboxylate
serine cation	207.2	195.2	132.4	79.6	carboxylic acid
Δ	−2.7	6.9	260.6	116.1	
threonine zwitterion	207.3	186.7	−89.2	−24.0	carboxylate
threonine cation	208.6	196.7	190.0	108.2	carboxylic acid
Δ	1.3	10.0	279.2	132.2	
tryptophan zwitterion	277.4	254.3	−55.0	−37.6	indole
tryptophan cation	280.1	247.4	−8.2	−44.1	indole
Δ	2.7	−6.9	46.8	−6.5	
tyrosine zwitterion	253.2	236.3	24.0	15.7	phenol
tyrosine cation	258.0	235.4	207.6	32.6	phenol
Δ	4.8	−0.9	183.6	16.9	
valine zwitterion	215.4	189.4	−162.8	−41.8	carboxylate
valine cation	212.0	197.2	149.1	113.2	carboxylic acid
Δ	−3.4	7.8	311.9	155.0	

[a] Δ = cation value − zwitterion value. Molar rotation [ϕ] is in deg·cm^2/(dmol).

nearly D_{6h} symmetry of the group makes this transition strongly forbidden.

The data set for the 12 L-amino acids further supports the conclusion that Clough−Lutz−Jirgensons' rule can be rationalized by the study of low lying electronic transitions in the carboxylate and carboxylic acid chromophores. Furthermore, they indicate that any chromophore that has electronic transitions that are low in energy can potentially interfere with this effect, eventually causing the rule to break down. For cysteine, histidine and tyrosine, our calculations hint at the beginning of a breakdown since the rule is disobeyed for one or more pairs of conformers, though for the ensemble average of conformers the rule is still obeyed. Experimental data indicate that CLJ is valid for cysteine and histidine, but no published information is available for tyrosine. For tryptophan, for which we earlier showed[38] that the indole group, not the carboxylate chromophore dominates optical rotation at the sodium D-line, our computations yield somewhat ambiguous results. Response calculations with both the BHLYP and B3LYP functionals indicate that the CLJ rule is obeyed for only four out of six rotamer pairs, but disagree on whether or not the rule is obeyed when these results are averaged to give the result that should be physically observable, see Table 1. Experimental data are equally ambiguous on the last question, with some values indicating that tryptophan should obey the CLJ rule and some indicating that it should violate it. For discussion of this issue, see our previous work.[38]

In summary, it is apparent from the data that the n to π^* transition of the carboxylate/carbonyl chromophore can be regarded as responsible for the CLJ rule. Without this excitation the CLJ effect would not be obtained. For all the zwitterionic alpha L-amino acids studied, the circular dichroism of this transition is negative in sign, resulting in a negative contribution to their specific rotations at 589.3 nm. For all the cationic (protonated) L-amino acids studied the CD of this transition is positive, causing a positive perturbation in their specific rotations. Ultimately, for all of the L-amino acids where the lowest energy electronic transition is centered on this chromophore, the specific rotation will tend to be more positive in the protonated form than in the zwitterionic state, which is exactly what is observed experimentally.

3. How the SOS-Based Explanation of the CLJ Rule Relates to Semi-empirical Reasoning based on Overlapping CD Sectors. One semiempirical approach to rationalize circular dichroism that was developed decades ago is the octant rule. For a summary of the history and development of the octant rule, see Lightner's chapter in ref 1. This rule was first developed for ketones[53] then adapted for use in lactones.[54] It is this octant rule for lactones which Jorgensen (not to be confused with Jirgensons from CLJ) first used to rationalize the CLJ rule,[55] by using an argument similar to ours relating the lowest-energy CD transition to the change in molar rotation.

The way in which Jorgensen applied the sector rule in his CLJ explanation is illustrated in Figure 5. The principal idea was to represent the COO^- group of a zwitterion as an overlapping system of two C═O chromophores and to superimpose the respective sectors. Focusing on just the left part of the illustration will reveal how the area about a C═O group is separated into octants by planes. Two of the planes are dictated by the C_{2v} site symmetry of a carbonyl group. The other surface, which need not even be planar, varies throughout differing formulations of the octant rule. Moffit et al. originally assigned it as a plane bisecting the C═O bond;[53] here Jorgensen assigned it as a plane bisecting the carbon atom normal to its bond with the oxygen.

The interference pattern on the right side of Figure 5 represents Jorgensen's vision of the sectors that rationalize the optical activity of an amino acid in its zwitterionic form. This pattern is a simple supposition of the octants for two overlapping carbonyl chromophores, to form a carboxylate chromophore. For an L-amino acid, the perturbing group that makes the compound chiral is always centered above the plane of the paper in the upper right corner of the circular sector pattern, as is shown in Figure 6. (Note that the acidic proton that differentiates between the two structures is in the plane of this page, which is a nodal plane in the sector rule, and as such it has no direct effect on the optical rotation in the chromophore.) For the protonated

(53) Moffitt, W. W., R. B.; Moscowitz, A.; Klyne, W.; Djerassi, Carl. *J. Am. Chem. Soc.* **1961**, *83*, 4013.
(54) Klyne, W. *Proc. R. Soc. London, Ser. A* **1967**, *297*, 66.
(55) Jorgensen, E. C. *Tetrahedron Lett.* **1971**, *13*, 863.

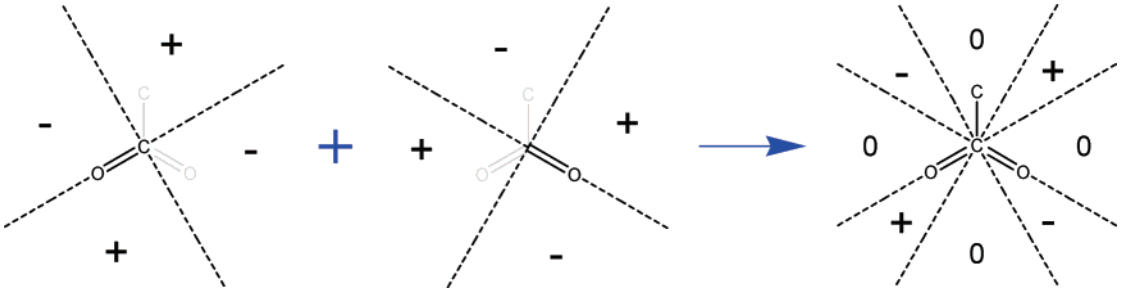


Figure 5. Formation of Jorgensen's sector rule for the carboxylate chromophore.[55] Plus and minus signs shown refer to the sign of the sector above the plane of the paper, signs of corresponding sectors below the page are the reverse.

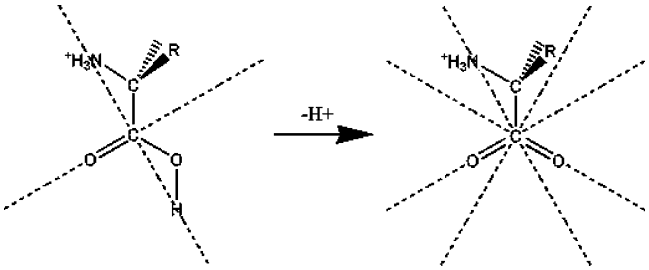


Figure 6. How protonated (left) and zwitterionic (right) L-amino acids fit into Jorgensen's sectors.

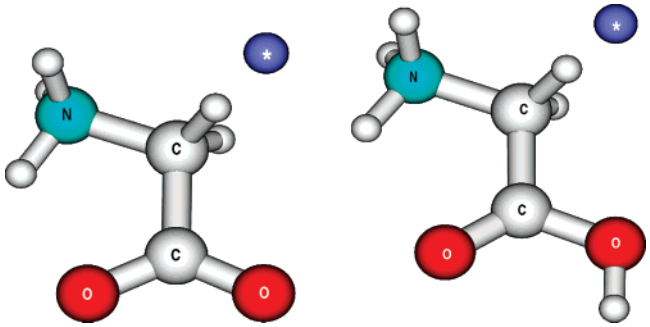


Figure 7. Glycine molecule with a chiral perturber above the plane positioned to mimic the chiroptical response seen in the L-amino acids. For our example, we have placed noble gas atoms and point charges in the position marked with an asterisk (*) to observe the resulting chiroptical response.

form, only one carbonyl group is present and so this perturbing group is oriented in a positive octant, and gives a positive contribution to specific rotation. For the zwitterionic form, depicting the chromophore as two C═O groups yields a more complicated set of sectors, and in this case the perturbing group falls into a zone that is far less positive than it was in for the protonated form.

Given the fact that the optical rotation can be written as a sum over all the CD transitions, eq 1, and the fact that the denominator in the equation is the smallest for low-energy transitions and ORs in the transparent region it appears natural to reduce the OR-structure problem to the CD-structure problem and try to apply CD sector rules. However, there are several important caveats: For one, *all* CD transitions contribute to the OR, and CD intensities can grow very large for high lying excitations, thereby overpowering the diminishing effect from the denominator in eq 1.[52] Without establishing by reliable theoretical methods that the OR−CD connection can indeed be made for the lowest-energy transition Jorgensen's argument is not sufficiently strong.

Empirical rules based on chromophores are not absolute, and have been known to fail to accurately model chiroptical response properties on occasions where more generally applicable first-principles methods such as TDDFT have succeeded.[56] Jorgensen's overlapping sector rational seems appealing, though the shape of those sectors need not be as strictly symmetrical as implied in Figure 5 unless the third plane dividing the sectors is precisely where Jorgensen assigned it. We decided to look at this assignment more closely to see if those sectors could in fact be "mapped out" using TDDFT by choosing a perturbing moiety to move about the carbonyl and carboxylate chromophore to investigate the variation of chiroptical as a function of the perturber's position.

Another assumption which is central to the rationalization of the CLJ rule that would need to be firmly established is Jorgensen's treatment of the carboxylate chromophore as a simple set of overlapping C═O chromophores, and that this model yields the correct behavior upon amino acid side chain perturbation. As we will show below one needs to consider the overall change in charge of the molecule upon protonation which complicates the model.

All the amino acids that exhibit the CLJ effect can be conceptually regarded as derivatives of glycine. Although the side chain that induces such an amino acid's chiroptical response varies considerably among the amino acids, what remains constant is the position of this perturbing group relative to the carbonyl/carboxylate chromophore: for all L-amino acids, this group is on the same side of the carbonyl/carboxylate mirror plane. We have investigated whether the CLJ effect could be induced in the glycine molecule by placing a perturbing moiety in this appropriate position. A glycine zwitterion and cation with a generic perturber in the appropriate position are illustrated in Figure 7.

In order to make the model computationally feasible, the perturbing group which is responsible for the dissymetry of the amino acid should be as simple as possible. The first perturber we used was a neon atom, placed 2.2 Å from the α-carbon, with a C−H−Ne angle of 180° to simulate a neutral group causing steric interaction. The results of the CD spectrum for such perturbed glycine systems, along with the CD spectra of natural chiral L-amino acids are depicted in Figure 8.

For both the zwitterionic and cationic amino acids, the chiroptical response manifested in the lowest energy circular dichroism transition that is responsible for the CLJ effect can be successfully reproduced by modeling the appropriate form of a glycine molecule perturbed by a neon atom. For each CD spectrum the sign of the first Cotton effect of the perturbed

(56) Rinderspacher, B. C.; Schreiner, P. R. *J. Phys. Chem. A* **2004**, *108*, 2867.

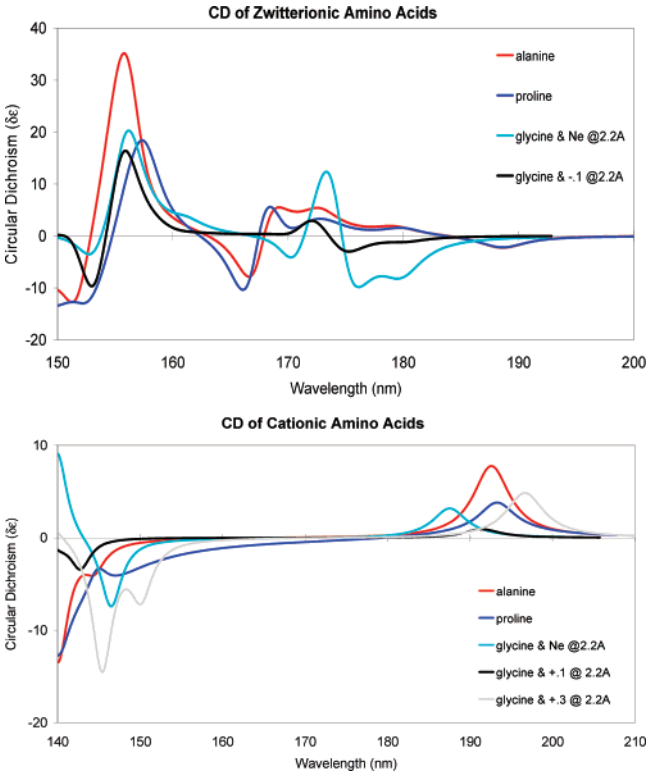


Figure 8. Computed near-ultraviolet circular dichroism spectra of glycine perturbed by point charges and by neon atoms as well as that of alanine and proline. See text for details. Spectra for zwitterionic (top) and protonated structures (bottom), respectively. An empirical Gaussian broadening of 0.09 eV was used for the plots.

glycine matches that of the corresponding chiral amino acids, of which alanine and proline are the examples displayed here. We found similar results were obtained with a helium atom used as the perturber (not shown). As the data from the test set of 12 L-amino acids suggest, the identity of the perturbing group causing the overall sign of the OR and of the CLJ effect is not important, so long as it does not give rise to electronic excitations that are lower in energy than those of the carbonyl/carboxylate chromophores. From a computational perspective this suggests that this perturbed glycine model can be simplified even further, by using a simple point charge. Point charges can also model inductive (electron withdrawing or electron donating) effects from the side chains on the carbonyl and carboxylate chromophores. For zwitterionic glycine a point charge of −0.1, when placed in the region where functional groups are attached to glycine's prochiral carbon in the L-amino acids, can induce virtually the same chiroptical response in the lowest energy CD transition of that molecule as is seen in the natural chiral amino acids. The first CD transition of the glycine cation can also be perturbed to appear similar to those of the chiral amino acids, but for this protonated form a *positive* point charge is needed to simulate the positive chiroptical response seen in the protonated forms of the chiral amino acids. For the cationic forms of the amino acids a glycine perturbed by a positive charge of +0.1 produced the correct sign of the first CD transition, although this transition was somewhat weak compared to the corresponding transitions seen in the chiral amino acids, alanine and proline. However adjusting the magnitude of the charge allowed for a better match of the intensity, and as can be seen in Figure 8 a perturbing charge of +0.3, when placed in the appropriate position relative to glycine, affords a lowest energy CD response of a magnitude more comparable to those of the alanine and proline cations.

One important feature present in the CD spectra as well as in the partial sum of optical rotations of Figure 4 is that for the protonated species the first CD transition is well separated from the higher lying excitations. For the zwitterions, this is not the case. That is, when comparing the zwitterionic to the protonated forms not only the signs of the lowest-energy CD transitions change but also the energies of the next several CD bands decrease considerably leading to several positive and negative CD bands in the range down to about 150 nm. In Figure 4 it is shown for alanine that the partial rotations from these excitations largely cancel. But their influence and that of higher lying excitations may be seen in sector patterns for the optical rotation that may lead to different qualitative appearances as those for the CD.

After identifying a simple perturber that can reproduce a CD transition pattern in glycine similar to those of chiral aliphatic amino acids (a CD pattern that reproduces the CLJ effect in a SOS equation) we have mapped out the chiroptical response to obtain sectors for optical rotation and CD derived from first-principles computations. To plot the CD and optical rotation sectors, we moved the perturbing charge by a step size of 0.1 angstrom over a glycine molecule and calculated the resulting lowest energy CD transition as well as the molar rotation at 589.3 nm each time. The perturbing charge was held at a fixed distance above the glycine molecule's plane at 1.3 Å, which is approximately the distance that the perturbing side chain is located above the chromophore plane in the chiral amino acids that exhibit the CLJ effect. The results of these calculations are depicted in Figure 9. The regions where the perturbing charge induces a positive first CD transition and a positive molar rotation are depicted in white; the negative regions are colored gray.

One immediately notes the correlation in the −COOH and $-COO^-$ regions between the circular dichroism sectors and molar rotation sectors for the glycine zwitterion and cation. This correlation forms a critical part in the overlapping-sectors explanation of the CLJ rule, since the CLJ rule relates the *molar rotations* of the protonated and deprotonated forms of an amino acid, while the sector rule for lactones which Jorgensen invoked is a rationale for the sign of the first *circular dichroism* excitation. Jorgensen's model simply assumes this correlation exists, even though it is not necessarily the case for both the forms of the amino acids. For the protonated form of glycine, a strong relationship between the molar rotation and first CD excitation is in fact readily apparent in the illustrations on the right side of Figure 9. Also, as already pointed out, for the electron deficient, cationic forms of the amino acids there is a large separation between the first and second electronic circular dichroism transitions, with the first occurring over 190 nm and the second not until under 150 nm; see Figure 8.

The sectors for the zwitterionic forms of amino acids differ from those of the corresponding cations. There is some connection between the signs of the CD and molar rotation for the zwitterions (Figure 9, left), but this correlation is not as good as that of the cations which we attribute to the aforementioned lowering of the energies of the higher excited states. As such, Jorgensen's assumption that molar rotation *sectors* are necessarily equal to CD sectors is undermined notwithstanding

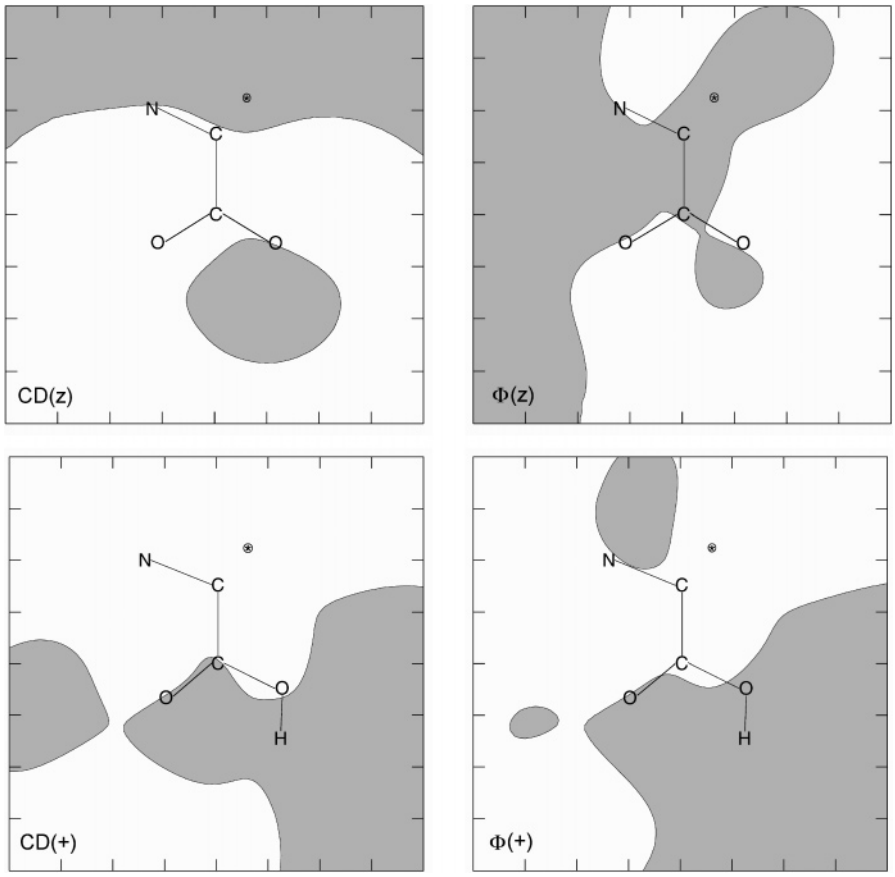


Figure 9. TDDFT computed "sectors" of the neutral zwitterionic (z, top) and protonated (cationic, +, bottom) glycine molecule. The left two pictures illustrate the sign of circular dichroism of the corresponding lowest energy CD transitions; the right two illustrate sectors for the molar rotation. Positive and negative areas are represented by light and dark shading, respectively. Note the greater correlation between the molar rotation and first CD sectors for the cationic form of the amino acid than for the zwitterionic form. The chromophore is in the plane of the page while the sectors are 1.3 Å above. The perturbing group was a point charge of +0.3 for the acid and −0.1 for the carboxylate. The approximate point of attachment of the side chain groups for L-amino acids is designated by an asterisk.

the fact that we indeed found from the SOS analysis that the CLJ effect can be attributed mainly to the lowest excitations from the C═O and COO^- chromophores. From Figures 4 and 8 it is clear that CD excitations beyond the lowest energy one are apt to have more of an effect on the molar rotation of the amino acid zwitterions than on the cations and therefore have an impact on the computed molar rotation sector patterns. In the region where the perturbing side chain is located (* in Figure 9), we note that the signs of the CD and the OR are the same for the zwitterionic and the protonated species, respectively. Therefore, for the perturbed glycine model the correct sign for the CLJ effect would be obtained from using the computed sector maps for the optical rotation as well as for the partial rotation from the lowest-energy CD transition. However, we remind the reader that the sectors for the zwitterions and the protonated form, respectively, have been obtained with opposite signs of the perturbing charges in order to yield the same behavior as found for chiral amino acids whereas Jorgensen's model does *not* require opposite sector patterns. We will discuss this issue in more detail below.

Whether the computed sectors for the glycine zwitterion closely resemble those of Jorgensen's overlapping sector model, shown in Figures 5 and 6, depends on the choice of the nodal plane for the C═O group. The computed sectors for the glycine zwitterion do bare some similarity to those of overlapping carbonyl octants, but only if the third nodal plane bisects the C═O bond, as Moffit et al. originally assigned it.[53] Because we have shown that the correlation between the shape of CD and molar rotation sectors for the amino acid zwitterions is not particularly good, the similarity between Jorgensen's overlapping *circular dichroism* sectors and our computed *molar rotation* sectors may be a coincidence. TDDFT calculations that we performed on a perturbed formate anion (not shown) for which the overlapping sector model should apply as well yielded little correlation between the sign of the first CD transition of a perturbed carboxylate anion and the sign of that system's molar rotation. Also, the C_{2v} symmetry implicit in Jorgensen's carboxylate model has obviously been quite strongly perturbed in the glycine chromophore, i.e., the two CO bonds are visibly different in the calculated sectors which further renders a direct application of an overlapping sector model difficult. The CD sectors seem to exhibit a more strongly pronounced octant effect about the carbon-oxygen bond that is farther from the amino group. This makes sense since this C═O bond should have more double bond character than the bond closer to the amino group, since the latter may be participating in intramolecular hydrogen bonding to some extent. The distortion of the overlapping octant behavior is significant and extends into the region on the sector map where the side chain perturbation is located.

Despite the computational results showing that the simple overlapping-sector model is not straightforwardly applicable to the optical rotation we have nonetheless argued that the CD of

the lowest transition can be made responsible for the CLJ effect. This may appear like a contradiction but it is not. Jorgensen's assumption of modeling CLJ with the circular dichroism was correct in the sense that the SOS equation indeed yields a (very strong) CLJ effect for just the first excitation. However, the sectors as computed from first principles only loosely resemble those of Jorgensen, and only near the C═O and COO^- chromophores, not in the region where the side chain actually appears as the perturber (indicated by an asterisk in Figure 9). In particular, if we consider the sign of the optical rotation obtained from the TDDFT sector maps in the region indicated by the asterisk then the correct sign of the CLJ effect (upon subtraction) is only obtained if the sectors about the C═O bond in the protonated form appear not as octants but as *anitoctants*. This finding agrees with the choice of the sign of the perturbing charge necessary to induce a CD pattern in glycine that has the same sign as those for chiral amino acids (as previously discussed, see Figure 8). In the past an "antioctant rule" has been applied to perturbing groups that are strongly electron withdrawing, like fluorine.[57] In this case of amino acids the perturber is an aliphatic or aromatic R group, which in the zwitterionic form exhibits the normal octant effect. But in the protonated form, where the molecule has an overall positive charge, we see that this perturbing group may induce an overall effect more akin to an electron withdrawing perturber because it is competing for negative charge with other groups in the electron deficient species. Seeing an organic perturbing group switch from causing an octant to antioctant effect, or in other words switching from having a *consignate* to a *dissignate* contribution to chirality is not unheard of. In fact the methyl group, the perturbing group in the simplest amino acid to obey the CLJ rule, has been known to switch from dissignate to consignate based on the polarity of the solvent used.[6] Here the perturbing groups, be they methyl (alanine), isopropyl (valine), isobutyl (leucine), et cetera all appear to change from consignate to dissignate upon protonation of their respective zwitterions. This change in behavior of the perturbing group based on the charge of the molecule to which it is attached was not considered in the empirical overlapping C═O sector model. Therefore, this simple model does not agree with the results of the TDDFT-based analysis despite the fact that in both cases the lowest CD transition is made mainly responsible for the overall occurrence of CLJ. The computations performed in this work along with the sector maps derived from these computations strongly suggest that a consignate-dissignate change along with the change of the overall charge is an important factor in the reasoning behind the CLJ rule.

(57) Barron, L. D. *Molecular Light Scattering and Optical Activity*, 2nd ed.; Cambridge University Press: Cambridge, UK, 2004.

Summary and Conclusions

The Clough−Lutz−Jirgensons (CLJ) effect has been successfully modeled by TDDFT for a set of 12 L-amino acids. A sum-over-states analysis of the molar rotation shows that the carboxylate/carboxylic acid chromophore is largely responsible for the effect. This explains why alpha amino acids with no other chromophores always obey the CLJ rule, while those with additional chromophores with excitations that interfere with those of the carboxyl/carboxylate group sometimes do not. In addition, TDDFT has been used to map out CD and molar rotation sectors for the amino acids and to show the effect of side chain position on these chiroptical response properties. Within the framework of the sector rules, the change in optical rotation upon protonation of an amino acid zwitterion results not only from a change in the geometry of the sectors upon protonation but also from a change in the action of the perturbing group: in the zwitterion this group appears to act quite similar to an electrostatic or steric repulsion, whereas in the cation the perturbing group is best modeled via a slight electrostatic attraction, resulting in a consignate contribution to chirality in the deprotonated form of amino acids and a dissignate contribution in the protonated forms. This fact that a perturbing group can have two differing effects on optical activity depending on the overall charge of the molecule was not indicated in the earlier rationale of the CLJ rule, but becomes apparent from the results of the computations. We hope that this knowledge will aid future investigations into better linking chiroptical response and molecular structure. For instance, similar effects as CLJ may be used for the assignment of absolute configurations of molecules other than amino acids using optical rotation measurements along with TDDFT computations. Such a procedure of comparing the *change* of optical rotation for closely related species to assign their unknown absolute configurations with the help of computations may be particularly useful for situations where the optical rotation itself is too small to yield a reliable configurational assignment or where conformational averaging adds significant uncertainties to the computed results.

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Supporting Information Available: Complete citations for refs 14, 15, and 18 as well as optimized structures and energies of the 12 amino acids studied in this work. This material is available free of charge via the Internet at http://pubs.acs.org.

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