Conformational Effects on the Optical Rotation of Alanine and Proline

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The natural optical activity of two chiral amino acids, alanine and proline, has been calculated using Hartree−Fock and density-functional theory with the Becke three-parameter Lee−Yang−Parr (B3LYP) functional employing analytical response theory. The dependence of the optical activity on the molecular conformation in the gas phase was investigated. In the case of proline, calculations were also carried out for the protonated and deprotonated molecules. The increase of the optical rotation of proline with increasing pH, found experimentally, is reproduced by our calculations. The optical rotation of both amino acids is found to be very sensitive to the molecular geometry, to the extent that it changes sign for the different conformers. For alanine, the sign of the optical rotation varies with the rotation of the amino or carbonyl groups.

I. Introduction

Because of the chiral nature of the building blocks of living matter, optical phenomena associated with chirality constitute an important topic in physical chemistry. The lowest-order phenomenon in the transparent region is natural optical activity, that is, the optical rotation of the polarization plane of linearly polarized light after transmission through a sample of chiral molecules. The specific optical rotation, a parameter characterizing natural optical activity, depends strongly on the conformation of the molecule[1−4] and is therefore in principle a sensitive tool for structural investigations. However, this sensitivity makes the correlation between the optical rotation and the electronic and geometrical structure a difficult task. Even for a rigid molecule, a seemingly small perturbation such as changing the solvent may have a significant effect on the optical rotation, even to the extent of reversing the sign of the rotation.[5,6] Theoretical simulations, where one can concentrate only on one particular factor influencing a given property, are therefore invaluable in developing an understanding of the different factors that influence an observed optical rotation.

Ab initio calculations of optical rotation have become possible only recently.[7−17] This slow emergence is due in part to the theoretical problems associated with the rigorous treatment of this phenomenon and in part to the low symmetry of chiral molecules and as a consequence the often large size of the systems of interest. The natural optical rotation of simple molecules has been computed by means of the Hartree−Fock (HF),[10,18,19] multiconfigurational self-consistent field (MCSCF),[19] coupled-cluster singles-and-doubles (CCSD),[13,20] and density-functional theory (DFT) methods.[11−13,21−24] Among these, HF and DFT are the only methods currently applicable to large molecules because of their favorable scaling with the size of the system. In the case of CCSD, and even more for MCSCF, the calculations of second-order properties for large molecules, in particular, those of biological interest, are still too expensive. Moreover, it has been shown[11−13] that DFT significantly improves on the HF results for optical rotation, especially when hybrid functionals are used.[11] In fact, in most cases DFT/B3LYP gives results of a quality comparable to that of CCSD.[13]

The main purpose of this study is to investigate the dependence of the optical rotation on the conformation of amino acids. Alanine, the simplest chiral amino acid, and proline, with its five-membered ring, were chosen as representative systems. The dependence of the optical rotation of amino acids on the molecular conformation came to our attention during a study of magnetochiral birefringence,[1] the higher-order analogue of natural optical activity. This is the axial birefringence generated by a static magnetic induction field with a component parallel to the direction of propagation of unpolarized light traversing a chiral sample, and it was shown in ref 1 to depend strongly on the molecular conformation of the proline molecule. We note that a study similar to the present investigation, but restricted to the HF level, has been carried out for the conformational dependence of the optical rotation of indoline and 2-methyl azetidine.[2] Moreover, the dependence of optical rotation on conformation in several small hydrocarbons and substituted hydrocarbons has been investigated at the DFT/B3LYP level in refs 23 and 24.

II. Theory and Computational Details

The optical-activity tensor is related to the (imaginary) electric-dipole−magnetic-dipole polarizability tensor $G'(-\omega; \omega)$, which for a frequency ω can be written in the length-gauge formulation as

$$G'_{\alpha,\beta}(-\omega; \omega) = -2\omega \text{Im} \sum_{n \neq 0} \frac{\langle 0| \hat{\mu}_\alpha |n\rangle\langle n|\hat{m}_\beta|0\rangle}{(\omega_{n0} - \omega)^2} = -\text{Im} \ll \hat{\mu}_\alpha; \hat{m} \gg \omega \quad (1)$$

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Here the sum runs over the excited-state manifold $|n\rangle$, $|0\rangle$ denotes the reference state, ω_{n0} indicates the excitation energy, and $\hat{\mu}_\alpha$ and $\hat{m}_\beta$ are the components of the electric and magnetic dipole operators, respectively.

The optical-activity tensor is related to the parameters determining electronic circular dichroism (ECD) spectra. The electric-dipole−magnetic-dipole polarizability can be associated with the optical rotatory strengths ^nR corresponding to transitions from $|0\rangle$ to $|n\rangle$ through the relation

$$G'_{\alpha,\beta}(-\omega;\omega) = 2\omega\mathrm{Im}\sum_{n\neq0}\frac{^nR}{(\omega_{n0}-\omega)^2} \qquad (2)$$

For a sample of randomly oriented molecules, the specific optical rotation $[\alpha]$ depends on the trace of the optical-activity tensor $\beta = -(1/3)\omega(G'_{xx} + G'_{yy} + G'_{zz})$ in the following manner:[25]

$$[\alpha] \approx 0.1343 \times 10^{-3}\cdot\beta\cdot\tilde{\nu}^2\cdot M^{-1} \qquad (3)$$

where β is given in atomic units, $\tilde{\nu}$ is the wavenumber of the incident radiation in cm^{-1}, and M is the molar mass in g mol^{-1}. The units of $[\alpha]$ are then given as deg cm^3 g^{-1} dm^{-1}. The natural optical activity of oriented samples includes a contribution from the electric-dipole−electric-quadrupole polarizability tensor that, however, is traceless and thus vanishes for freely rotating molecules.

When the hypervirial theorem is fulfilled, which is the case for the exact wave function or for a variational wave function in the limit of a complete basis set, β does not depend on the choice of origin for the vector potential associated with the magnetic field, even though the individual components do. In the case of incomplete basis sets, the origin independence of β can be ensured by the use of gauge-including atomic orbitals (GIAOs).[19,26] β is also origin-independent in the alternative velocity−gauge formulation[22] with conventional atomic orbitals, although when this is adopted slower basis set convergence has been observed. The natural optical rotations reported in this paper have been calculated using GIAOs, unless otherwise noted. The implementation of GIAOs in the calculation of optical rotation has been described elsewhere.[11,13,19]

The structures of alanine and proline were optimized at the DFT level using the hybrid Becke three-parameter Lee−Yang−Parr (B3LYP) functional[27,28] as implemented in the Gaussian 98[29] program. The aug-cc-pVDZ basis set[30,31] was used for the geometry optimizations.

The calculations of the optical rotations were carried out using DFT/B3LYP[27,28] as implemented in a local version of the DALTON program.[32] A description of the DFT implementation of natural optical rotation in DALTON has been given in ref 13. We note that the Gaussian 98[29] and DALTON[32] forms of the B3LYP functional are not exactly equivalent because of small differences in the correlation part of the exchange−correlation functional.[13] For comparison, the optical rotation of proline and alanine was also calculated at the HF level. Some DFT calculations for proline were also repeated using the BHLYP (Becke half-and-half LYP) functional.[33]

The aug-cc-pVDZ basis set[30,31] was used for the calculations of the optical rotation. In a few selected cases, additional calculations were carried out in the larger aug-cc-pVTZ basis. A wavelength of 589.3 nm, corresponding to the sodium D line, was used in the optical rotation calculations because this frequency is most often used in experimental measurements.[34]
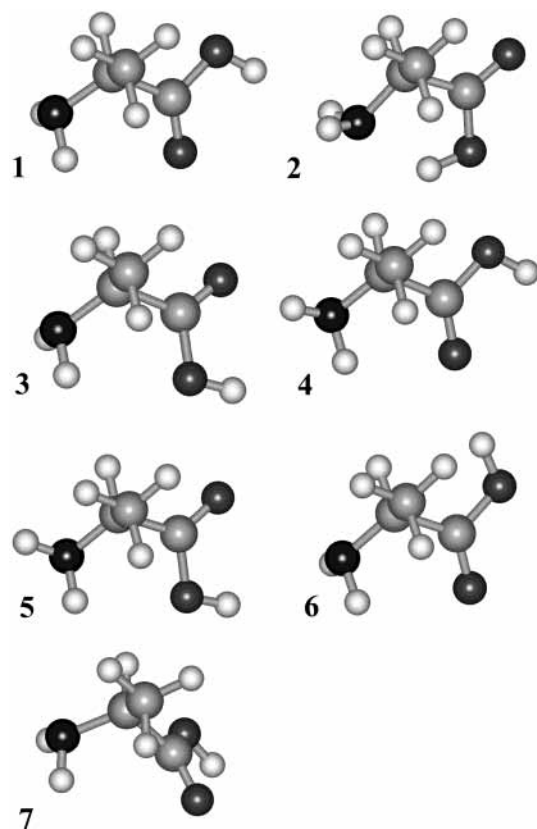

Figure 1. Optimized structures of (*S*)-alanine.

III. Results and Discussion

A. Conformational Dependence of the Optical Rotation in Alanine. *1. Stationary Points.* Several studies of the conformational space of alanine have been conducted, modeling both the gas-phase structure[35,36] and the structure in solution.[37,38] The structure of gaseous L-alanine has also been investigated experimentally.[39] In our DFT investigation of the conformational space of alanine, the structures obtained at the HF level in refs 35 and 36 were taken as starting points for the geometry optimizations.

Seven optimized structures corresponding to low-lying stationary points are shown in Figure 1. All of these are minima with the exception of structure **7**, which represents a saddle point between minima **1** and **3**. Even so, we present the results for structure **7** because its conformation differs significantly from the others, which has interesting consequences for the optical rotation (see below). The structures of the two lowest minima, **1** and **2**, one with a HNH···O=C hydrogen bond and the other with an H₂N···HO hydrogen bond are in good agreement with the structures of the two conformers found experimentally for gaseous alanine.[39] We note that our study of the conformations of alanine is likely to be incomplete because there may be other relatively low-lying minima on the potential energy surface and because there are undoubtedly many other transition states.

The relative energies and the corresponding specific optical rotations of the seven conformers are shown in Table 1. The optical rotation is positive for all stable structures, but the values vary significantly. The positive sign is consistent with experiment, which for a neutral L-alanine solution has been measured to be +2.7 cm³ g⁻¹ dm⁻¹,[34] which proves that the sign of optical rotation is not unambiguously related to the absolute configuration of a given amino acid. Only for saddle-point conformer **7** is the calculated optical rotation negative. The Boltzmann average over the structures under study results in +42.8 cm³

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TABLE 1: Relative Energy[a] ΔD_v and Natural Optical Rotation [α] of Neutral Alanine[b,c]

	ΔD_v (B3LYP) (kJ mol^{-1})	[α] (B3LYP) (deg cm^3 g^{-1} dm^{-1})	[α] (HF) (deg cm^3 g^{-1} dm^{-1})
1	0.00	58.2	44.0
2	1.58	36.9	11.8
3	4.85	123.6	24.4
4	4.88	44.2	57.5
5	9.18	20.1	22.3
6	20.44	55.2	41.2
7	4.22[d]	−85.3	−53.3

[a] Includes corrections for harmonic zero-point vibrations. [b] See Figure 1 for the labels. [c] All calculations were made with the aug-cc-pVDZ basis set. [d] Saddle point, one imaginary frequency.
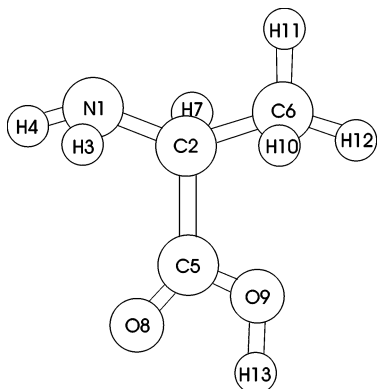

Figure 2. Numbering of atoms in alanine.

g^{-1} dm^{-1} at the DFT/B3LYP level and +26.1 cm^3 g^{-1} dm^{-1} at the HF level. Both values overshoot the experimental value, with the HF result being closer. We note that a comparison with experiment is of limited value because of the very large influence of the aqueous environment on the conformation, in particular, because alanine has a zwitterionic form in neutral aqueous solution.

The HF and DFT values for the optical rotation of alanine are very different, the difference depending strongly on the conformer. Previous calculations suggest that DFT using the B3LYP functional gives more reliable optical rotations than the HF method.[11−13]

An analysis of the optical rotation for the different conformers of alanine indicates that the most important factor determining the optical rotation is the orientation of the amino group with respect to the side chain, characterized by the τ(H4N1C2C5) dihedral angle, and the orientation of the carboxylic group, characterized by the τ(O8C5C2N1) dihedral angle. (See Figure 2 for the numbering of the atoms.) To study this effect in more detail, additional calculations were performed, allowing us to investigate separately the influence of the rotation of the amino group, the carboxylic group, and also the hydroxyl group in the carboxylic group on the optical rotation of alanine. To this end, a partial optimization of the alanine geometry was carried out with the relevant dihedral angles (τ(H4N1C2C5), τ(O8C5C2N1), and τ(H13O9C5C2)) frozen at a given value and the remaining geometric parameters relaxed. The starting structure was in all cases global minimum **1**. The optical rotations of the resulting structures are discussed below.

2. Rotation of the Amino Group. The dependence of the alanine optical rotation on the dihedral H4N1C2C5 angle, characterizing the orientation of the amino group, is shown in Figure 3. As already noted, this rotation has a strong influence on the optical rotation. For most dihedral angles, [α] is positive, with a maximum for τ(H4N1C2C5) close to 60° (structure **1**).
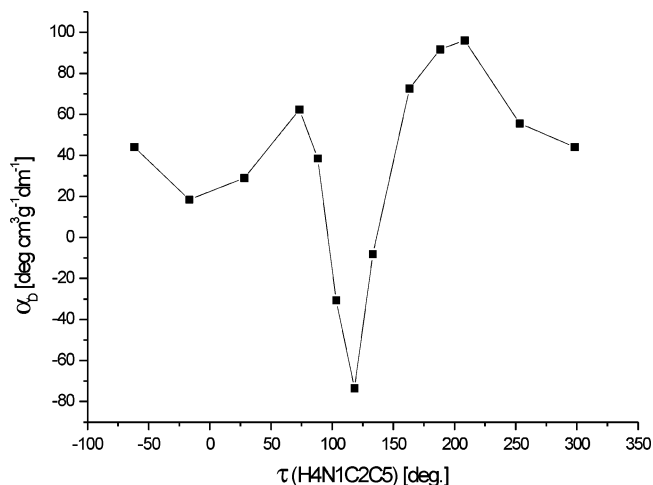
Figure 3. Dependence of the optical rotation of alanine on dihedral angle τ(H4N1C2C5) (rotation of the amino group).
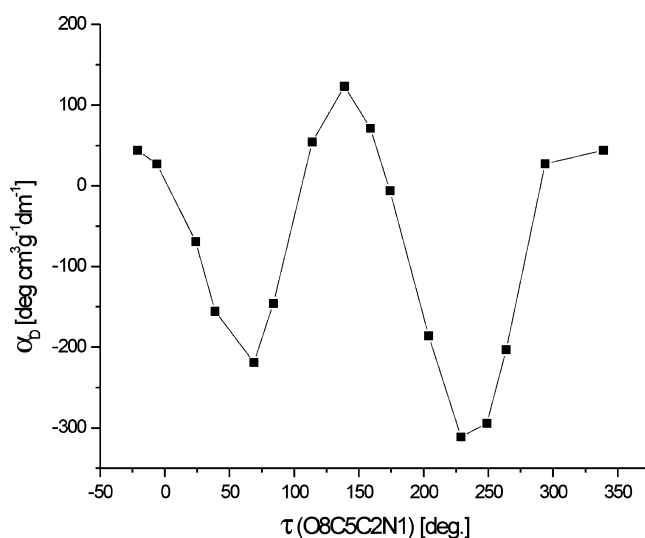
Figure 4. Dependence of the optical rotation of alanine on dihedral angle τ(O8C5C2N1) (rotation of the carboxylic group).

However, for a rather narrow range of dihedral angles between 95 and 140°, the optical rotation is negative. This can probably explain why the optical rotation is so small for conformer **2**, where τ(H4N1C2C5) is about 145°. The most negative value of the optical rotation occurs when τ(H4N1C2C5) is about 120°, that is, with the lone pair of the amino group cis to the C2−C5 bond. For larger τ(H4N1C2C5) angles, the optical rotation increases steeply to large positive values, but no stable conformation with this orientation of the amino group was found in our study.

3. Rotation of the Carboxylic Group. The dependence of the optical rotation of alanine on the orientation of the carboxylic group (as expressed by the value of dihedral angle τ(O8C5C2N1)) is even stronger than the dependence on the orientation of the amino group; see Figure 4. The value of [α] spans a wide range from −300 deg cm^3 g^{-1} dm^{-1} to +100 deg cm^3 g^{-1} dm^{-1}. There are two values of τ(O8C5C2N1) for which the optical rotation is the most negative: about 60 and 240°. In both configurations, the C2−C6 bond is coplanar with the carboxylic group. The orientation of the carboxylic group, with τ(O8C5C2N1) of about 280°, is responsible for the negative value of the optical rotation for conformer **7**.

The most positive values for the optical rotation are observed when the C2−N1 bond is roughly in the same plane as the carboxylic group, that is, for τ(O8C5C2N1) close to 0 and 150°.
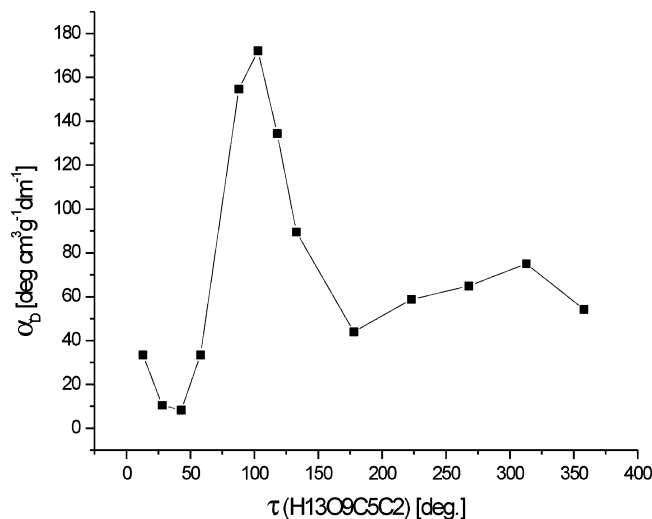
Figure 5. Dependence of the optical rotation of alanine on dihedral angle $\tau(H13O9C5C2)$ (rotation of the hydroxyl group).

This is probably the factor responsible for the large optical rotation observed for conformer **3**, where $\tau(O8C5C2N1)$ is close to 140°.

4. Rotation of the Hydroxyl Group. Another factor influencing the optical rotation of alanine may be the position of the proton in the carboxylic group with respect to the COO plane. However, considering the fact that the optical rotations of structures **1** and **4**, which differ primarily in the conformation of the OH group, are similar, this factor seems unlikely to be as important as the conformation of the amino and carboxylic groups with respect to the methyl group.

Indeed, for most values of $\tau(H13O9C5C2)$—the dihedral angle that determines the relative position of the proton in the carboxylic group—the optical rotation remains almost constant. The only exception is the range of $\tau(H13O9C5C2)$ values between 60 and 180°, where there is a steep peak for 120° and the optical rotation reaches high positive values (close to 180 deg cm^3 g^{-1} dm^{-1}). However, this is unlikely to influence the optical rotation of the stable conformers of alanine much because the carboxylic group tends to be planar ($\tau(H13O9C5C2)$ close to 0 or 180°). The optical rotation for the conformers of alanine obtained from **1** by rotating the OH group is always positive.

B. Conformational Dependence of Optical Rotation in Proline. The analysis of the conformational dependence of the optical rotation in proline is more difficult than in alanine because there are at least two important geometrical factors influencing this property: the relative orientation of the amino and acidic groups and the ring conformation. In the case of alanine, the simplest chiral amino acid, only the former contributes, and we used this to explore the optical rotation in a large part of the conformational space (though still not exhaustively). For proline, which is a much more complicated system, we shall investigate the optical rotation only for the stable conformers. However, for proline, we also consider the effects of protonation and deprotonation on the optical rotation, comparing these with experimentally observed changes in the optical rotation in solutions with different pH values.

1. Neutral Proline. The conformational space of neutral proline has been frequently studied in the literature.[40–43] The extensive study of Ramek, Kelterer, and Nikolić,[42] in which 12 stable low-lying conformations were found, was carried out at the HF level using a small basis set. The structures obtained in ref 42 were used as starting points for our DFT calculations, in a similar manner as done for alanine.
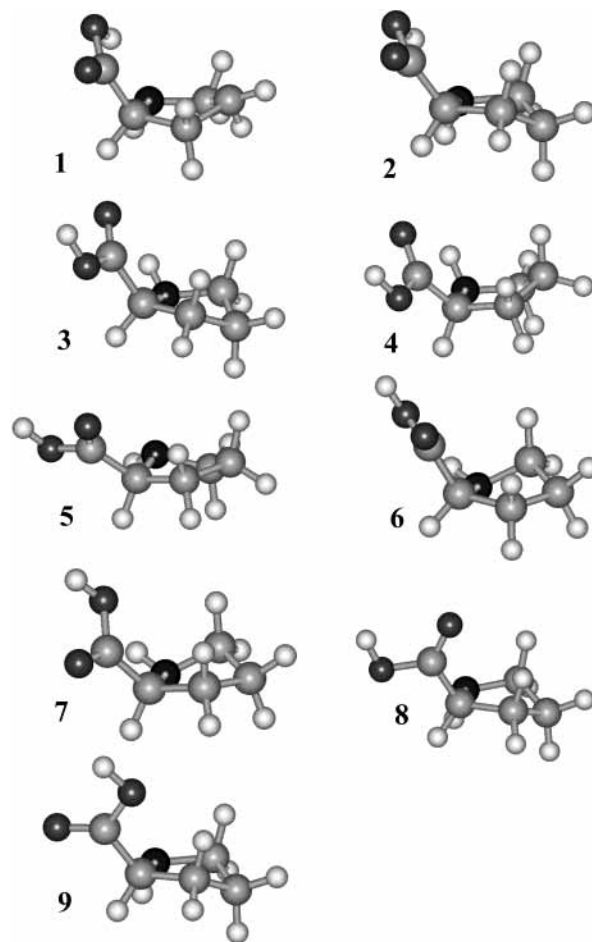

Figure 6. Optimized structures of neutral (*S*)-proline.

Nine optimized structures of neutral proline, numbered according to their relative energies, are shown in Figure 6. All of these are minima on the potential energy surface. Our results differ from those reported in ref 42, where a conformer corresponding to our structure **3** was found to be the global minimum. In addition, some of the structures reported in ref 42 were found to be unstable at the DFT level, and two of the conformers shown in Figure 6 (**4** and **8**) were not reported in ref 42. We note at this point that low-lying conformer **4** was not previously reported at the DFT level.[40]

We shall not discuss the structures of proline in any detail because a comprehensive study was recently presented in ref 43. Instead, we focus on the optical rotation. We note only that, as expected on the basis of previous studies,[40–43] the conformers with the lowest energy are stabilized by internal hydrogen bonds—O—H···N in the case of **1** and **2** and N—H···O in the case of **3** and **4**—and they have exo (**1** and **4**) or endo (**2** and **3**) forms of the ring.

The natural optical rotations of proline [α] calculated at the DFT and HF levels are listed in Table 2, together with the energies (relative to the global minimum and including corrections for zero-point vibrations) of the different conformers. In agreement with the experimentally established sign for the specific rotation of L-proline,[34] most conformers have a negative optical rotation.

As for alanine, the dependence of the optical rotation of proline on the molecular conformation is very strong. In some cases (conformers **5** and **8**), sign changes are observed. The most important factor determining the sign and magnitude of the optical rotation appears to be the orientation of the carboxylic

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TABLE 2: Relative Energy[a] ΔD_v and Natural Optical Rotation [α] of Different Conformers of Neutral Proline[b,c]

	ΔD_v (B3LYP) (kJ mol^{-1})	[α] (B3LYP) (deg cm^3 g^{-1} dm^{-1})	[α] (HF) (deg cm^3 g^{-1} dm^{-1})
1	0.00	−112.0	−70.1
2	1.63	−184.3	−103.5
3	4.64	−127.6	−67.0
4	6.06	−49.2	−38.8
5	11.74	11.0	5.5
6	12.04	−108.1	−47.2
7	12.13	−1.4	−50.8
8	14.17	48.1	54.0
9	15.57	−28.7	−15.3

[a] Including corrections for harmonic zero-point vibrations. [b] See Figure 6 for the labels. [c] All calculations were made with the aug-cc-pVDZ basis set.

group. When an internal hydrogen bond is formed between the carboxylic group and the amino nitrogen (and when the carboxylic group is coplanar with the C_α−N bond), the optical rotation is large and negative. See, for example, the four lowest-lying structures. The structures with the carboxylic group perpendicular to the C_α−N bond display small negative (or, as for conformer **5**, positive) optical rotations. For a given ring conformation, the specific rotation is more negative when the O−H···N internal hydrogen bond is formed than in the case of the N−H···O hydrogen bond (compare **1** and **3** with **2** and **4**). As for alanine, large differences are observed between the DFT and HF values.

The Boltzmann average performed on the specific rotation of the conformers shown in Figure 6 is −133.9 deg cm^3 g^{-1} dm^{-1} at the DFT level and −79.1 deg cm^3 g^{-1} dm^{-1} at the HF level. In an aqueous solution with pH 7.0, the experimental value is −85.0 deg cm^3 g^{-1} dm^{-1}.[34] The HF value is thus in better agreement with experiment than is the DFT result. However, the structures of proline in aqueous solution are bound to be different from those in the gas phase, and the relative stability of the different conformers may also differ. We note, in particular, that proline in an aqueous solution with neutral pH assumes a zwitterionic form that is unstable in the gas phase. Therefore, no conclusions on the relative performance of HF and DFT can be drawn from comparisons of ab initio calculations on the isolated neutral molecule with experimental observations in aqueous solutions.

2. Protonated Proline. Six optimized conformational structures of protonated proline, numbered in order of increasing energy, are shown in Figure 7. The conformational space of protonated proline has been studied previously at the DFT level.[40] Surprisingly, structure **a**, which according to our results is a global minimum, was not found in ref 40. Instead, structure **b** was claimed to be the global minimum. According to ref 40, the oxygen-protonated conformers are much higher in energy than the nitrogen-protonated ones, so no oxygen-protonated conformers are considered in the present work.

All of the conformers in Figure 7 are minima on the potential energy surface of protonated proline. The lowest-lying structure (**a**) has an exo conformation of the ring and an internal N−H···O hydrogen bond between the amino group and the carbonyl oxygen of the carboxylic group. Structure **b**, only slightly higher in energy than **a**, differs from the latter only in the ring conformation, which now has an endo form.

The energies of the conformers of the protonated proline and the respective specific HF and DFT optical rotations are presented in Table 3. The optical rotation is negative for all conformers studied. A comparison of conformers **a** and **b** and of **c** and **e** indicates that, for the same arrangement of the
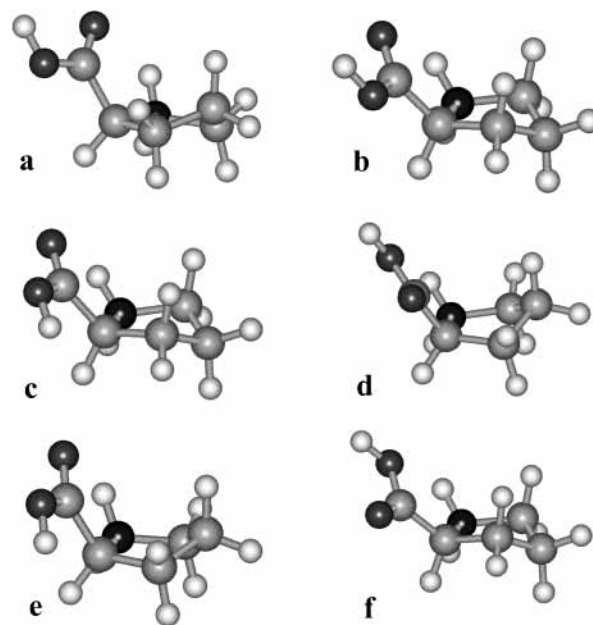
Figure 7. Optimized structures of cationic (*S*)-proline.

TABLE 3: Relative Energy[a] ΔD_v and Natural Optical Rotation [α] of Different Conformers of Protonated Proline[b,c]

	ΔD_v (B3LYP) (kJ mol^{-1})	[α] (B3LYP) (deg cm^3 g^{-1} dm^{-1})	[α] (HF) (deg cm^3 g^{-1} dm^{-1})
a	0.00	−64.3	−24.6
b	0.84	−133.0	−70.8
c	21.33	−167.6	−103.5
d	21.37	−73.2	−48.3
e	30.06	−89.1	−50.4
f	31.18	−86.3	−64.2

[a] Including corrections for harmonic zero-point vibrations. [b] See Figure 7 for the labels. [c] All calculations were made with the aug-cc-pVDZ basis set.

carboxyl group, the conformers with the endo form of the ring have more negative specific rotations than the exo ones, as also observed for neutral proline. Conformers **d** and **f** have similar optical rotations, despite the difference in the ring conformation. However, in this case, the orientation of the carboxyl group with respect to the N_α−C bond is slightly different for **d** and **f**, so the two effects—ring conformation and orientation of the carboxyl group—may cancel each other. Conformers **b** and **c** and conformers **a** and **e** differ in the value of τ(HOCH), the dihedral angle in the carboxylic group. The optical rotation tends to be more negative for the conformers with the dihedral angle close to 180° than for those with τ(HOCH) of about 0°.

The experimental specific rotation of proline in an acidic environment (pH 0.3) is −52.6 deg cm^3 g^{-1} dm^{-1}.[34] The Boltzmann average of the calculated specific rotation of protonated proline over all conformers is −92.8 deg cm^3 g^{-1} dm^{-1} at the DFT level and −43.8 deg cm^3 g^{-1} dm^{-1} at the HF level. Again, the HF value is closer to experiment than is the DFT value. At both the HF and the DFT levels, the specific rotation becomes less negative upon protonation.

3. Deprotonated Proline. The structures of deprotonated proline are displayed in Figure 8. All of them have previously been characterized at the DFT level,[41] although the relative energies of the conformers reported there differ from these obtained in the present work. This is probably due to the use of a smaller basis set in ref 41. The ring has an endo conformation for structures **A** and **C** and an exo conformation for structure
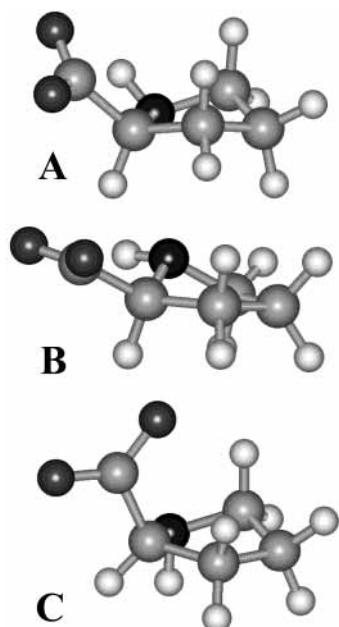
Figure 8. Optimized structures of anionic (S)-proline.

TABLE 4: Relative Energy[a] ΔD_v and Natural Optical Rotation [α] of Different Conformers of Deprotonated Proline[b,c]

	ΔD_v (B3LYP) (kJ mol^{-1})	[α] (B3LYP) (deg cm^3 g^{-1} dm^{-1})	[α] (HF) (deg cm^3 g^{-1} dm^{-1})
A	0.00	−622.9	−86.1
B	17.88	150.7	26.3
C	31.50	139.8	−34.8

[a] Including corrections for harmonic zero-point vibrations. [b] See Figure 8 for the labels. [c] All calculations were made with the aug-cc-pVDZ basis set.

B. The relative energies and the corresponding specific rotation of the three conformers of deprotonated proline are shown in Table 4.

There are much larger differences between the HF and DFT results for the optical rotation of deprotonated proline than for neutral and protonated forms, as may be understood by considering the calculated electronic excitation energies ω_{n0} and optical rotatory strengths ^nR (cf. eq 2). The calculated excitation energies of the selected conformers of proline and the corresponding optical rotatory strengths (calculated using the same methods and basis set as for the optical rotation) are listed in Table 5. Large contributions from these low-lying states to the calculated optical rotation of the anion means that the discrepancies in the excitation energies are propagated to the calculated optical rotation. Large differences between the DFT/B3LYP and HF results for deprotonated proline also occur in the case of the optical rotatory strengths. Predictably, the difference between the DFT and HF results for the optical rotation is reduced when the BHLYP functional, which has a larger contribution of exact exchange than B3LYP, is used. The results, not shown to avoid excessive numerical data, usually fall between the HF and B3LYP results. For the anionic proline, this leads to more realistic DFT values, although the HF numbers still yield a result much closer to experiment (vide infra).

The DFT/B3LYP excitation energies listed in Table 5 suggest that anionic proline should be a colored species, although no experimental observation of this has been reported, indicating that the DFT method is not well suited for handling anionic proline. The poor performance of DFT for anionic species and

TABLE 5: First Excitation Energy ω_{10} and Corresponding Optical Rotatory Strength ^1R of Various Conformers of Proline Calculated Using the aug-cc-pVDZ Basis Set

	ω_{10} (B3LYP) [eV]	ω_{10} (HF) [eV]	^1R (B3LYP) [10^{-40} esu^2 cm^2]	^1R (HF) [10^{-40} esu^2 cm^2]
		neutral structures		
1	5.21	6.44	−7.8	−2.4
2	5.30	6.49	−10.3	−1.9
3	4.92	6.67	−1.9	0.3
4	5.02	6.70	9.3	4.0
5	4.92	6.50	−2.3	−1.9
6	4.73	6.42	−5.9	−6.1
7	4.91	6.51	16.1	3.6
8	4.93	6.49	−10.3	−6.0
9	5.09	6.48	6.0	−3.5
		cationic structures		
a	5.94	6.85	7.7	5.4
b	5.97	6.86	5.6	4.6
c	5.89	6.72	5.2	3.2
d	6.43	5.62	−3.3	−8.7
e	5.87	6.72	7.4	4.3
f	5.67	6.45	−1.5	−1.3
		anionic structures		
A	3.08	5.76	−3.8	−3.7
B	3.07	5.72	4.1	30.0
C	2.84	5.50	0.3	−4.9

TABLE 6: Comparison of Optical Rotation Calculated with and without GIAO Atomic Orbitals[a]

	aug-cc-pVDZ		aug-cc-pVTZ	
	no GIAOs	GIAOs	no GIAOs	GIAOs
1	−112.0	−114.4	−111.9	−113.2
a	−64.3	−66.3	−63.9	−64.2
A	−673.8	−622.9	−633.4	−633.6
B	220.5	150.7		
C	76.3	139.8		

[a] DFT/B3LYP calculations.

diffuse states in general is well known and is related to the self-interaction problem and the incorrect asymptotic behavior of the exchange−correlation functional.[44,45] When a small basis set, without diffuse functions, is used, the electronic density is contracted, and the calculated energy of a diffuse state is increased, leading to a partial cancellation of the errors arising from the incorrect asymptotic behavior of the DFT functional in the calculation of excitation energies. However, when sufficiently diffuse basis sets (such as aug-cc-pVDZ) are used, this error cancellation is missing.

Another conclusion that can be drawn from the results in Table 5 is that the extreme sensitivity of the optical rotation to conformational changes is connected to large changes in the optical rotatory strength with molecular conformation rather than to changes in the excitation energy. This is as expected because the orientation of the chromophores with respect to the remaining part of a chiral molecule is known to have a major influence on the rotatory strengths, as shown, for example, in peptides. See refs 46 and 47 for recent reviews. However, no simple correlations of the optical rotatory strengths of the lowest excitations with the optical rotation could be established.

It is interesting that in the DFT calculations (where the lowest excitation is fairly close to the sodium D-line excitation) there is a large difference between the optical rotations obtained with and without GIAOs in the aug-cc-pVDZ basis. See Table 6. Whereas the difference between the GIAO and non-GIAO results is less than 5 deg cm^3 g^{-1} dm^{-1} in the transparent region (as for neutral and cationic proline), it can be as large as 80 deg cm^3 g^{-1} dm^{-1} for the anionic form, suggesting that

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the optical rotation calculated with DFT for deprotonated proline is less reliable than the results for neutral and protonated forms. By contrast, in the larger aug-cc-pVTZ basis, the differences between GIAO and non-GIAO results for the anionic form are similar to those for neutral and anionic forms. The results in Table 6 also suggest that, when used in conjunction with GIAOs, the relatively small aug-cc-pVDZ basis is sufficiently large for our purposes, giving results similar to those of the aug-cc-pVTZ basis.

In a basic environment (pH 13.8), the specific rotation of proline is -93.0 deg cm^3 g^{-1} dm^{-1}.[34] The calculated Boltzmann averages of the specific rotation of the deprotonated proline over the conformers under consideration are -622.4 deg cm^3 g^{-1} dm^{-1} at the DFT level and -86.1 deg cm^3 g^{-1} dm^{-1} at the HF level. Both values are close to the optical rotation obtained for the lowest-lying conformer of deprotonanted proline, the other two conformers being much higher in energy. The DFT/B3LYP Boltzmann average is far from experiment. The observed experimental trend of an increasingly negative optical rotation with increasing pH is thus well reproduced by HF theory but not by the B3LYP functional. The absolute value of the optical rotation for the anionic form is apparently significantly overestimated by DFT, and the DFT/B3LYP results for the anionic form are clearly not reliable.

IV. Summary and Conclusions

The natural optical rotation has been calculated using HF and DFT methods for seven low-lying stationary points of alanine and nine stationary points of proline, in their neutral form as occurring in the gas phase. In addition, calculations were carried out for protonated proline (six conformers) and deprotonated proline (three conformers). For alanine, the dependence of the optical rotation on the orientation of the amino and carboxyl groups (with respect to the side chain) and on the internal conformation of the carboxyl group was systematically investigated.

As far as the molecular structure is concerned, the two lowest conformers of alanine—one with an HNH···O=C hydrogen bond and the other with an H_2N···HO hydrogen bond—are consistent with experimental findings for gaseous alanine.[39] The lowest conformers of neutral proline, stabilized by internal hydrogen bonds, O−H···N or N−H···O, and with exo or endo forms of the ring, are in agreement with previous theoretical studies. The lowest conformers of the cationic and anionic forms also have internal hydrogen bonds (N−H···O) and exo or endo ring conformations.

The most important factors that determine the optical rotation in alanine are the orientations of the amino and carboxylic groups relative to the side chain. As the amino group rotates, [α] remains positive for most dihedral angles—it takes on a maximum with the lone pair of the amino group trans to the side chain; a second maximum occurs in the cis position, but no stable conformation of this orientation was found. When the lone pair is cis to the carboxylic carbon atom, [α] is large but negative. As the carboxylic group rotates, [α] spans an even wider range than with the amino rotation, being most negative when the carboxylic group is coplanar with the side chain and most positive when it is coplanar with the C−N bond. The internal rotation of the OH group has a smaller influence on [α], which always remains positive.

In proline, the conformation of the ring as well as the orientations of the amino and carboxylic groups influence the optical rotation, the endo conformers tending to have a more negative specific rotation than the exo ones. As for alanine, there are sign inversions for certain conformations of neutral and deprotonated prolines. In neutral proline, the optical rotation is large and negative when the carboxyl group is coplanar with the C_α−N bond and an internal hydrogen bond is formed; when the carboxyl group is perpendicular to the C_α−N bond, small negative or even positive optical rotations are observed. For a given ring conformation, the specific rotation is more negative with an O−H···N internal hydrogen bond than with an N−H···O hydrogen bond.

The extreme sensitivity of optical rotation to conformational changes is connected to large changes in optical rotatory strength (which can be associated with numerator of the sum-over-states expression for the $G'(-\omega; \omega)$ tensor) with molecular conformation and not to changes in excitation energy (denominators of the sum-over-states expression for the $G'(-\omega; \omega)$ tensor). This is as expected because the orientation of the chromophores with respect to the remaining part of a chiral molecule is known to have a major influence on the rotatory strength. However, no simple correlations of the optical rotatory strengths of the lowest excitations with the optical rotation could be established.

Boltzman averages of neutral, protonated, and deprotonated prolines were calculated and compared with experimental values in neutral, acidic, and basic aqueous solutions, respectively. The decrease in the absolute value of [α] when the pH is lowered is correctly mirrored at both levels of theory, the HF results being much closer to experiment than the DFT results. However, the almost perfect agreement of the HF results with experiment is probably coincidental because we have ignored the effects of solvation, which may be very large for an aqueous solution of an amino acid as a result of the formation of hydrogen bonds. Furthermore, the zwitterionic form that amino acids adopt in an aqueous solution is unstable in the gas phase and cannot be reproduced in our calculations. Rovibrational effects, which may change the optical rotation by as much as 30%,[17] have also been neglected. Although the inclusion of rovibrational contributions is very difficult for flexible molecules with many low-lying local minima, the solvent effects can be estimated more easily, for example, by means of the polarizable continuum model.[15]

As stated above, the HF results for proline are in much better agreement with experiment than are the DFT results, but our study is inconclusive because many factors influence the experimental values. Indeed, for semirigid molecules, DFT has been found to be the method of choice for the calculation of optical rotation.[11,20] Nevertheless, for the anionic form of proline, the DFT values are clearly unreliable because the excitation energies are strongly underestimated, probably because of the DFT self-interaction problem.

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