

DIRECT QUANTUM CHEMICAL CALCULATION OF ROTATORY STRENGTHS OF METHYLPYRROLIDONES

MODEL COMPOUNDS CONTAINING A PEPTIDE GROUP

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Abstract—CNDO/S method is used to compute the rotatory strengths of *L*-5-methylpyrrolid-2-one and *S*-3-methylpyrrolid-2-one, cyclic compounds containing a peptide group. The observed circular dichroism (CD) bands in the regions of 185 and 220 nm corresponded to $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions, respectively. The computed rotatory strengths indicate that nonplanarity of pyrrolidone ring makes a substantial contribution to the CD of compounds under consideration. The comparison of computed and experimental rotatory strengths suggests that both compounds have a nonplanar ring conformation.

Until very recently the calculation of rotatory strengths of optically active molecules was carried out on a model in which the molecule was partitioned into spatially separated groups. The electrons were considered as completely localized within such groups, and interactions between groups were treated by perturbation techniques. Semiempirical molecular orbital (MO) methods (EHT, CNDO/2, INDO, etc.) permit symmetry-adapted and maximally delocalized wave functions to be used for the calculation of rotatory strengths. Theoretically such direct calculations¹⁻⁷ seem to be more valid than the perturbation approach, especially if quantitative accuracy is the primary consideration.

In this work, direct calculations of rotatory strengths of methyl substituted pyrrolidones (rigid cyclic compounds containing a peptide group) are reported. Some perturbation approach results are given for comparison, and we also discuss results obtained for methylpyrrolidones⁷ by INDO method. Two methyl substituted pyrrolidones *L*-5-methylpyrrolid-2-one (Fig. 1a) and *S*-3-methylpyrrolid-2-one (Fig. 1b) will be considered. These compounds are characterized^{8,9} by intense CD bands near 185 and near 220 nm. It may be that these bands correspond to the $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ transitions of the peptide chromophore. It was originally supposed⁸ that 3-methylpyrrolid-2-one had the *R*-configuration and the anomaly of the observed CD sign was discussed. Later on, however, it was reported¹⁰ that the *S*-position is more probable for the methyl group. If the pyrrolidone ring is not planar and the only source of dissymmetry of *L*-5-methylpyrrolid-2-one and *S*-3-methylpyrrolid-2-one is the

presence of substituents, then by a quadrant rule¹¹ these compounds should be expected to have opposite signs for the CD of the $n \rightarrow \pi^*$ transition (negative for *L*-5 form and positive for *S*-3-form), which is in agreement with experiment.

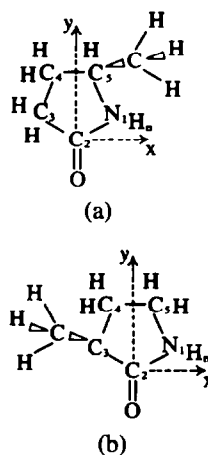


Fig. 1. Structure of calculated compounds (Z axis is directed upwards) (a) *L*-5-methylpyrrolid-2-one (b) *S*-3-methylpyrrolid-2-one.

However, there now exists experimental and theoretical evidence that the pyrrolidone ring is not necessarily planar.^{10,12,13} The structure of methylpyrrolidones discussed has not been studied experimentally,

but according to the X-ray data for *L*-pyrrolid-2-one-5-carboxamide,¹³ the pyrrolidone ring is nonplanar. If we assume that the peptide group atoms N,C,O of the pyrrolidone ring are in the $Z=0$ plane (Fig 1a) than according to X-ray findings¹³ atoms C_3 , C_4 and C_5 are out of the plane with $Z_{C_3} = +0.048 \text{ \AA}$, $Z_{C_4} = +0.301 \text{ \AA}$ and $Z_{C_5} = -0.127 \text{ \AA}$. Theoretical studies by Schellman and Lifson¹⁰ also revealed an essential deviation of pyrrolidone rings from planarity. They obtained for the Z -components of atoms C_3 , C_4 and C_5 (Fig 1a) of *L*-5-methylpyrrolid-2-one values $+0.03 \text{ \AA}$, $+0.029 \text{ \AA}$ and $+0.07 \text{ \AA}$ respectively. The nonplanar pyrrolidone ring may be an additional source of dissymmetry as compared to methyl substituent on the C_3 or C_5 atoms and they may significantly influence the optical activity.

In this paper we study in detail the influence of molecular conformation on the computed rotatory strengths of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions of *L*-5-methylpyrrolid-2-one and *S*-3-methylpyrrolid-2-one using for this purpose wave functions obtained by CNDO/S method. We considered the following cases: (i) *L* and *S* forms with a planar ring; (ii) *L* form with a nonplanar ring as determined by X-ray analysis of *L*-pyrrolid-2-one-5-carboxamide;¹³ (iii) *L* and *S* forms with a nonplanar ring structure found theoretically by Schellman and Lifson.¹⁰

Method of calculation

The rotational strengths R_i of the transition from the ground state ψ_0 to the i th excited state ψ_i were calculated from

$$R_i = \frac{e\hbar}{m(E_i - E_0)} \langle \psi_0 | \hat{p} | \psi_i \rangle \cdot \langle \psi_i | \hat{m} | \psi_0 \rangle \quad (1)$$

where e , \hbar , m are, respectively, the electronic charge, Planck's constant divided by 2π and electronic mass, $E_0 - E_i$ is the energy of the electronic transition $0 \rightarrow i$, \hat{p} and \hat{m} are the linear momentum and magnetic dipole operators, respectively.

The use of (1) instead of more usual expression

$$R_i = Tm \langle \psi_0 | \hat{\mu} | \psi_i \rangle \cdot \langle \psi_i | \hat{m} | \psi_0 \rangle$$

where $\hat{\mu}$ is the electric dipole operator, insures origin independence of the results. Some other benefits gained by using formula (1) for the calculation of rotational strengths are discussed in detail.⁶

To obtain ψ_0 and ψ_i we used the CNDO/S variant of CNDO/2 method specially developed by Del Bene and Jaffé^{14,15} for the calculation of molecular excited states. The CNDO/S scheme implies the use of limited configuration interaction (CI) and throughout this paper the CI calculation was carried out for the 50 singly excited states corresponding to the transitions from 10 upper occupied orbitals to the 5 lowest virtual orbitals.

In MO methods the calculation of R_i is reduced to the evaluation of matrix elements of \hat{p} and \hat{m} over atomic orbitals (see e.g.¹). Matrix elements of both operators consist of one- and two-centre integrals and using the basic properties of Slater atomic orbitals the one-centre integrals are easily determined.¹ For calculation of

two-centre integrals we used the relation (2) derived by Linderberg in the framework of the semiempirical model.¹⁶

$$i\hbar \langle \chi_{\mu A} | \hat{p} | \chi_{\nu B} \rangle = (\mathbf{R}_A - \mathbf{R}_B) \beta_{\mu A \nu B} \quad (2)$$

Here $\chi_{\mu A}$ is the μ th atomic orbital an atom A and $\beta_{\mu A \nu B}$ is the resonance integral.

As a result we obtain:

$$\begin{aligned} p_{kl} = & \hbar \sum_A W_{sp}^A [(C_{3A} C_{xA} - C_{5A} C_{xA})x \\ & + (C_{3A} C_{yA} - C_{5A} C_{yA})y + (C_{3A} C_{zA} - C_{5A} C_{zA})z] \\ & + \frac{m}{\hbar} \sum_A \sum_B (\mathbf{R}_A - \mathbf{R}_B) \sum_{\mu} \sum_{\nu} C_{\mu A} C_{\nu B} \beta_{\mu A \nu B} \\ m_{kl} = & \frac{\hbar e}{2mc} \sum_A \{ W_{sp}^A \mathbf{R}_A \times [(C_{3A} C_{xA} - C_{5A} C_{xA})x \\ & + (C_{3A} C_{yA} - C_{5A} C_{yA})y + (C_{3A} C_{zA} - C_{5A} C_{zA})z] \\ & + (C_{yA} C_{zA} - C_{zA} C_{yA})x + (C_{zA} C_{xA} - C_{xA} C_{zA})y \\ & + (C_{xA} C_{yA} - C_{yA} C_{xA})z \} \\ & - \frac{e}{2c\hbar} \sum_A \sum_B \sum_{\mu} \sum_{\nu} C_{\mu A} C_{\nu B} (\mathbf{R}_B \times \mathbf{R}_A) \beta_{\mu A \nu B} \end{aligned}$$

where $C_{\mu A}$ is the expansion coefficient of $\chi_{\mu A}$ in the l th molecular orbital; \mathbf{R}_A is a position vector of atom A ; x , y , z are unit vectors in direction x , y , z respectively;

$$W_{sp} = \langle 2s | \nabla | 2p_z \rangle = \langle 2s | \nabla | 2p_y \rangle = \langle 2s | \nabla | 2p_x \rangle$$

The integrals W_{sp} were calculated by using such Slater orbital exponents which permit to obtain for one-centre Coulomb integrals values adopted in the CNDO/S method (Table 1).

Table 1. Slater orbital exponents adopted for the calculation of W_{sp} , and the resulting W_{sp}

	C	N	O
α	1.123	1.215	1.316
W_{sp}	0.613	0.663	0.718

The calculation of rotational strengths in the framework of the perturbation approach was carried out according to expressions (3) and (4) from the paper by Woody and Tinoco¹⁷ with the parameters used by these authors.

We have chosen the geometries of methylpyrrolidones under consideration in the following manner. In all cases the bond lengths of pyrrolidone ring were equal to those obtained by X-ray for *L*-pyrrolid-2-one-5-carboxamide¹³ and methyl group was considered in staggered conformation. For *L*-5 form two nonplanar ring conformations were taken: experimental¹³ and theoretical,¹⁰ and for the former conformation we considered with three Z -components of H-atom from group NH (Fig 1a) equal to 0,

+0.079 and -0.079 Å. Because of the lack in the paper¹⁰ of a precise information about the details of ring structure for S-3 form we used in our calculations of rotational strengths of nonplanar S-3 form the geometry obtained in¹⁰ for L-5 form since according to diagrams of that paper L-5 and S-3 forms have the similar ring structure.

RESULTS AND DISCUSSION

As we mentioned earlier both L-5-methylpyrrolid-2-one and S-3-methylpyrrolid-2-one exhibit the CD bands in the region of 220 and 185 nm. Results of our CNDO/S calculation confirms the suggestion expressed previously in^{8,9} that these transitions are, respectively, $n \rightarrow \pi^*$ transition ($\lambda_{\text{calc}} \approx 300$ nm, oscillator strength, $f_{\text{calc.}} \sim 10^{-4}$) and $\pi \rightarrow \pi^*$ transition ($\lambda_{\text{calc}} \approx 175$ nm, $f_{\text{calc.}} \approx 0.3$). A notable (as compared to experiment) shift towards the longwave region of the calculated $n \rightarrow \pi^*$ transition may be caused by some limitations of the approximate CNDO/S method and, moreover, the calculation corresponds to the case of a molecule in vacuum and it is well known that a solvent induces a blue shift of the $n \rightarrow \pi^*$ transition and red shift of the $\pi \rightarrow \pi^*$ transition as compared to the gas phase.

The calculated rotatory strength of $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions are presented in Tables 2 and 3. Let us first consider the results obtained for a planar ring conformation. In this case both L-5-methylpyrrolid-2-one and S-3-methylpyrrolid-2-one have rotatory strengths of opposite signs, and this result is in agreement with most general features of the theory of optical activity and with the quadrant rule for $n \rightarrow \pi^*$ transitions, in particular. For both compounds the calculated rotatory strengths agree in sign with experimental data. The agreement with the experiment in the magnitude is observed only in the case of $n \rightarrow \pi^*$ transitions. As follows from Tables 2 and 3, a

Table 2. Calculated rotatory strengths of different conformations of L-5-methylpyrrolid-2-one (in 10^{-40} CGSE)

Ring conformation	$n \rightarrow \pi^*$	$\pi \rightarrow \pi^*$
Planar	-3.8	+2.8
Found experimentally in L-pyrrolid-2-one-5-carboxamide ¹³ $z_{C_3}^{\delta} = 0.048$, $z_{C_4} = 0.301$, $z_{C_5} = -0.127$ $z_{H_N} = 0$	-1.5	+15.4
Previous structure with a hydrogen atom H_N out of the plane of peptide group $z_{H_N} = 0.079$ $z_{H_N} = -0.079$	-0.1 -2.1	+12.0 +16.9
Found theoretically by Schellman and Lifson ¹⁰ $z_{C_3} = -0.03$, $z_{C_4} = 0.29$, $z_{C_5} = 0.07$ $z_{H_N} = 0.02$	-3.6	-2.4
Experiment ^a	-6.8	+12.5

^aThe coordinate z (in Å) characterizes the extent of the deviation of given atom from the plane $z = 0$ defined by atoms of the peptide group N_1C_2O (Fig 1).

Table 3. Calculated rotatory strengths of different conformations of S-3-methylpyrrolid-2-one (in 10^{-40} CGSE)

Ring conformation	$n \rightarrow \pi^*$	$\pi \rightarrow \pi^*$
Planar	+5.5	-0.8
Found theoretically by Schellman and Lifson ¹⁰ $z_{C_3} = -0.03$, $z_{C_4} = 0.29$, $z_{C_5} = 0.07$ $z_{H_N} = 0.02$	+4.1	-9.2
Experiment ^a (in different solvents)	from +2.2 to +6.1	from -3.6 to -8.0

better agreement between experimental and calculated values for the $\pi \rightarrow \pi^*$ transition is reached when the nonplanarity of the pyrrolidone ring is taken into account. The only exception is the result for L-5 form with a ring conformation deduced theoretically, for which the calculated rotational strength of the $\pi \rightarrow \pi^*$ transition has a sign opposite to that determined experimentally (Table 2). At the same time the results for $n \rightarrow \pi^*$ transition of nonplanar L-5 form with the pyrrolidone ring determined by X-ray analysis deviate more from experimental values than in the case of a planar conformation.

The rotational strengths of nonplanar L-5 form with atom H_N out of plane defined by atoms O, C, N of peptide group are presented in Table 2. In this instance only numerical data but not the sign were changed. It is of interest that when H_N deviates from the peptide group plane its contribution to the rotatory strengths of the $n \rightarrow \pi^*$ transition is opposite to that expected according to the quadrant rule. This is probably explained by the fact that the quadrant rule was deduced for chromophore groups separated from the sources of dissymmetry in the sense of electronic overlap¹⁶ but the hydrogen atom attached to N cannot be regarded as nonoverlapping with the electrons of peptide chromophore.

Our results show that the conformation of the pyrrolidone ring affects significantly the CD of methyl-substituted pyrrolid-2-ones. The contribution to the optical activity of these compounds made by the nonplanar conformation of the pyrrolidone ring proved to be of the same order of magnitude as that caused by the presence of an dissymmetric methyl substituent and sometimes even more significant (as in the case of a rotatory strength of the $\pi \rightarrow \pi^*$ transition of S-3 form).

Taking into account the data presented in Tables 2 and 3 and the results of experimental and theoretical studies demonstrating a tendency of the pyrrolidone rings to assume a nonplanar structure, one may suggest that in the case of L-5 form a nonplanar conformation of the pyrrolidone ring found experimentally in pyrrolidonecarboxamide is more probable. In the case of S-3 form the nonplanar structure seems to be close to that predicted theoretically by Schellman and Lifson.¹⁰

In conclusion, it would be interesting to compare our results for the rotatory strengths of $n \rightarrow \pi^*$ transition of S-3 form with a planar ring and L-5 form with a planar and nonplanar ring with those obtained⁷ by the INDO

Table 4. Rotatory strengths of $n \rightarrow \pi^*$ transition of L-5 and S-3 forms of methylpyrrolid-2-one obtained by different methods (in 10^{-40} CGSE)

	INDO	CNDO/S	Experiment
L-5 with a plane ring	-10.5	-3.8	-6.8
L-5 with a nonplanar ring	+0.41	-1.5	
S-3 with a plane ring	+77.5	+5.5	from +2.2 to +6.1 (in different solvents)

Table 5. Rotatory strengths of L-5-methylpyrrolid-2-one and S-3-methylpyrrolid-2-one with a plane ring conformation calculated in the bounds of the perturbation approach (in 10^{-40} CGSE)

	$n \rightarrow \pi^*$	$\pi \rightarrow \pi^*$
L-5	<0.01	+3.9
S-3	+0.3	-3.0

method. The degree of deviation from planarity of nonplanar L-5 form⁷ corresponds to X-ray data for L-5-iodomethylpyrrolid-2-one and is close to that of L-pyrrolid-2-one-5-carboxamide used in our calculations. As seen from Table 4 in both methods the change of the ring conformation from planar to nonplanar leads to a decrease in the negative value of rotatory strength. In the INDO case the effect is more pronounced and the rotatory strength of $n \rightarrow \pi^*$ transition for nonplanar ring becomes positive contrary to the experimental CD sign. The calculation method used in⁷ gives a greater value of the rotatory strength for S-3 form than our method. Such a difference may be caused by two factors; a difference in the semiempirical MO method applied (INDO and CNDO/S) and difference in the evaluation of matrix elements of transition moments. Similar dependence of the results upon the methods used occur frequently in quantum chemical calculations even when not so sensitive values as rotatory strengths are estimated (for instance, calculation of conformation energies¹⁹). We suggest, nevertheless, that despite these shortcomings, the application of MO methods for calculating rotatory strengths is

promising enough and that research in this direction would prove fruitful.

As follows from the above, the direct calculation of rotatory strength made it possible to find a correlation between the structures of the pyrrolidone ring and the CD of methylpyrrolidones. What would the perturbation approach give in this case? Since this theory is based upon the assumption of non-overlapping of wave functions of chromophore and dissymmetric centres, so in our case this approach can be applied only to a planar ring conformation because atoms C₃ and C₅ deviation of which from the Z=0 plane affects the rotatory strengths are adjacent to the chromophore N₁C₂O. However, the rotatory strengths of the planar ring calculated by perturbation and MO methods vary considerably (cf the results presented in Table 5 with the corresponding data in Tables 2 and 3). In particular this concerns the rotatory strengths of the $n \rightarrow \pi^*$ transition which are invariably small when calculated on the basis of the perturbation theory. These failures of perturbation approach should be taken into account when this approach is applied to the analysis of the CD in complex systems.

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