

QUANTUM CHEMICAL CALCULATIONS
ON 4-AZATRICYCLO[4,4,0,0^{3,8}]DECAN-5-ONE — A LACTAM
WITH A NON-PLANAR *cis*-AMIDE GROUP

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The position of the N—H bond in the lactam *I* given in the title was optimized by the CNDO/2 method. On the basis of the found non-planarity of the *cis*-amide group ($\Delta\omega = -14.5^\circ$, $\theta_N = 26.4^\circ$, regular pyramid on the nitrogen atom), the values of oscillator and rotatory strengths of the $n - \pi^*$ and $\pi - \pi^*$ transitions were computed using the CNDO/S procedure. With the exception of the band positions, very good agreement with experimental results was obtained.

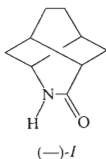
Recently the optical rotatory strengths of cyclic chiral amides have been investigated¹⁻⁶ by quantum chemistry. These studies were carried out in order to recognize the behaviour of the amide chromophore in simple chiral systems, as well as to establish a basis for precise interpretation of the relationship between conformation and chiroptical properties of peptides and proteins. Optical activity of the $n - \pi^*$ transition of the planar amide group in N-acetylamino sugars and in chiral γ -lactams was investigated within the framework of one-electron theory^{3,7} and a quadrant rule indicating C_{2v} effective symmetry of this transition² was suggested. According to semiempirical calculations of Ramachandran, Sasisekharan and coworkers^{8,9} compared with X-ray data^{9,10} the amide group can easily become non-planar due to torsion on the C—N bond associated with a partial change of nitrogen atom hybridization, giving rise to a pyramidal arrangement. We should, therefore, relate parameters $\Delta\omega$, θ_N , characterizing the extent of non-planarity (Fig. 1), to the optical rotatory strength of both the $n - \pi^*$ and $\pi - \pi^*$ transitions of the amide group. Semiempirical calculations of optical rotatory strengths of several γ -lactams possessing non-planar amide groups were carried out^{5,6} using INDO CI and CNDO/S wavefunctions. However, a systematic study has yet to be reported.

In a previous study¹¹ we reported a set of CD data on (–)-(2*S*, 5*S*)-4-azatricyclo-[4,4,0,0^{3,8}]decan-5-one (*I*), a rigid lactam with a non-planar amide group. Upon separating the single Gaussian bands from the experimental CD curves of this compound, two significant Cotton effects were found within the range of 210–230 nm and at 195 nm respectively, corresponding to $n - \pi^*$ and $\pi - \pi^*$ transitions of the

amide group. In addition to these Cotton effects, a weak band was observed at 210–215 nm and tentatively assigned to a Rydberg $n - 3s$ transition in accord with published reports^{12,13}. Experimental values of optical rotatory strength thus obtained are, particularly in the case of the $n - \pi^*$ transition, greater (an order of 10^{-39} cgs is reached) than the corresponding values related to chiral amides possessing planar amide groups. Considering the relatively high accuracy of these experimental data and the rigid structure of the lactam *I* of known geometry in the crystalline state¹⁴, this compound appears suitable for performing a quantum chemical study of the optical rotatory strength of the non-planar amide group.

CALCULATIONS

The preferred geometry of the amide group in the lactam (*-I*) was studied by the standard CNDO/2 method, using the original parameterization^{15,16}. Convergence of all orbital energies to 10^{-4} eV was required for the SCF procedure to be terminated. As a first approximation of the Fock matrix, that resulting from the previous calculation was used. This procedure reduces by approximately one third the number of iterations required.



Due to the inherent chirality of the non-planar amide group, the optical rotatory strength should be calculated in a direct procedure, starting from the wave function obtained in the all valence electron framework. We have chosen the CNDO/S method suggested for the calculation of electronic spectra¹⁷. Repulsion integrals were approximated according to Mataga and Nishimoto¹⁸ and the parameterization used was taken from the report of Jaffé and coworkers¹⁹. A constant width of configuration interaction involving 36 singly excited configurations among six highest occupied and six lowest virtual orbitals was maintained in the whole series of calculations.



FIG. 1

The Angles $\Delta\omega$, θ_N and θ_C Defined for the Case of the *cis*-Amide Group

The method of calculating the optical rotatory strength was derived from the direct procedure described by Gould and Hoffmann²⁰. The original computer program was modified in order to enable utilization of the configuration interaction technique. Describing the wave function of the excited state ψ_j by a linear combination of Slater determinants representing the wave functions ψ_r , ψ_s of the particular singly excited configurations, and expressing the matrix elements of electric and magnetic dipole operators in atomic units, the optical rotatory strength (in cgs units) amounts to:

$$R_{0j} = -6.412 \cdot 10^{-37} \sum_{r,s} C_{\psi_r} C_{\psi_s} \frac{\langle \Psi_0 | \nabla | \Psi_r \rangle}{E_r - E_0} \langle \Psi_s | \mathbf{r} \times \nabla | \Psi_0 \rangle, \quad (1)$$

where C_{ψ_r} , C_{ψ_s} are the corresponding LCI coefficients and $(E_r - E_0)$ represents the diagonal element of the LCI matrix given in eV. Thus, separately for each configuration, the electric transition moment calculated in gradient representation is transformed into a dipole length formalism. At least in the case of compound I, this procedure improves agreement of the computed values of rotatory strength with the experimental data. Although the transition moments were calculated with inclusion of all two-center integrals, the CNDO/S molecular orbitals used were not deorthogonalized²¹, since use of such a procedure does not influence the results qualitatively⁴. Numerical calculations were carried out by a CDC 3300 computer.

RESULTS

Calculating the optical rotatory strength of the lactam (-)-I with the aid of the CNDO/S method, and starting with the geometry derived from X-ray data¹⁴, the

TABLE I

CNDO/S Calculation of the Optical Rotatory Strength of Lactam (-)-I

The molecular geometry used was derived from the approximate geometry of the twistane skeleton²² on replacing the $C_{(4)}$ atom by a nitrogen, then by addition of coordinates of hydrogens and of the oxygen atom of the amide group. The absolute configuration had to be reversed. The following supplementary geometrical parameters were used: Bond lengths C—H 0.109 nm, C=O 0.124 nm, N—H 0.102 nm. A regular tetrahedral arrangement of the hydrogen atoms on skeletal carbons was assumed to occur. The torsion $\Delta\omega$ amounts to -29° , the value of Θ_N is 29° (the N—H bond eclipses the C=O one).

Quantity	$n - \pi^*$ transition	$\pi - \pi^*$ transition
$\lambda_{\text{exp.}}^a$, nm	232.0	197.0
$\lambda_{\text{calc.}}$, nm	280.4	178.9
$R_{\text{exp.}}^a \cdot 10^{39}$, cgs	-2.51	2.07
$R_{\text{calc.}} \cdot 10^{39}$, cgs	-1.15	1.00

^a Experimental values are related to a measurement performed in the cyclohexane solution¹¹.

computed positions of both the $n - \pi^*$ and $\pi - \pi^*$ transitions, as well as the numerical values of rotatory strength, are reproduced very inaccurately¹¹. On the other hand, the calculation based on the very approximate geometry deduced from the twistane skeleton²² (Table I) resulted in an improvement of the optical rotatory strength of the $\pi - \pi^*$ transition and of the positions of both bands in question. It appears clear from this finding that even with such a rigid compound the geometrical arrangement found in the crystalline state need not necessarily reproduce all the features of molecular geometry occurring in solution and that a geometry optimization can probably improve the results. The sole atom which may substantially alter its position in solution is the hydrogen atom bonded to the nitrogen atom of the amide group. Calculating its optimum position we start from: a) the Ramachandran relation

$$\Theta_N = -2\Delta\omega \quad (2)$$

which is not fulfilled in the case of crystallographic data on lactam⁻¹ ($\Delta\omega = -14.49^\circ$, $\Theta_N = 14.07^\circ$). The angle Θ_N determined by the position of the above hydrogen atom, and representing the extent of the pyramidal character of the bonds attached to nitrogen, is too small; b) the N—H bond length (0.0919 nm) is small in comparison with the recommended average value²³ (0.1 nm). The position of the hydrogen atom

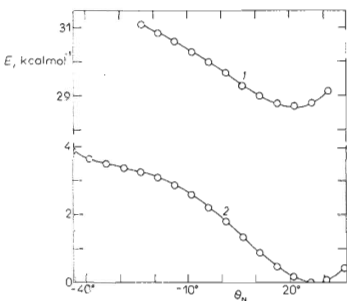


FIG. 2

The Total CNDO/2 Energy of the Lactam (—) Related to the Angle Θ_N

Computed for the N—H bond length: 1 0.0919 nm, 2 0.1065 nm. A value of $E = 0$ kcal mol⁻¹ was arbitrarily assigned to the structure exhibiting minimum energy.

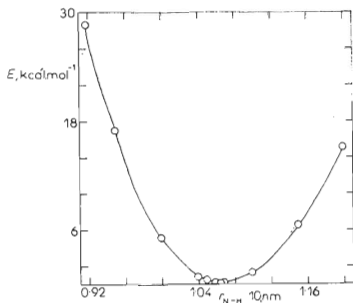


FIG. 3

The CNDO/2 Energy of the Lactam (—) Related to the N—H Bond Length

The calculation was performed for $\Theta_N = 21.4^\circ$. The energy scale is related to the zero point given in Fig. 2.

was optimized by the CNDO/2 method in three steps. First, the value of θ_N corresponding to a minimum total energy at the original value of the bond length was found (21.4°; Fig. 2). Using this value of θ_N , the N—H bond length was optimized (0.1065 nm; Fig. 3). Then a second energy minimization with respect to the angle θ_N was performed (Fig. 2). The overall energy minimum was found at $\theta_N = 26.4^\circ$; this value satisfies Eq. (2). Optimizing the position of the hydrogen atom, a total energy decrease of approximately 29 kcal mol⁻¹ was reached. Most of this change results from lengthening of the N—H bond (approximately 28.5 kcal mol⁻¹) while variations of θ_N are much less critical. (The energy increase in the range of θ_N 15–35° is less than 0.5 kcal mol⁻¹). Then, the preferred geometry of the amide group obtained in this way was utilized in the CNDO/S calculation of the UV and CD spectra (Table II).

Owing to the possibility of small variations of θ_N , and since an analogous motion of the hydrogen atoms was demonstrated in the formamide molecule on the basis of an analysis of microwave spectra²⁴, it appears useful to study a relation connecting the spectral parameters of both the $n - \pi^*$ and $\pi - \pi^*$ transitions of the lactam (-)I with the value of this angle. The optical rotatory strengths of the both transitions (Fig. 5) cross a nodal plane in the range close to the planar arrangement of the bonds attached to the nitrogen atom ($\theta_N \sim 0^\circ$). The shortest wavelength of the $n - \pi^*$ transition is also computed in close proximity to this plane (Fig. 6). On the other hand, the computed position of the $\pi - \pi^*$ transition exhibits only a monotonous hypo-

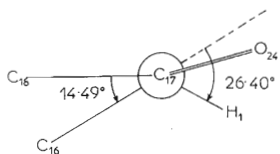


FIG. 4

Optimized Geometry of the Amide Group of Lactam (-)I

For clarity the dihedral angles were slightly enlarged.

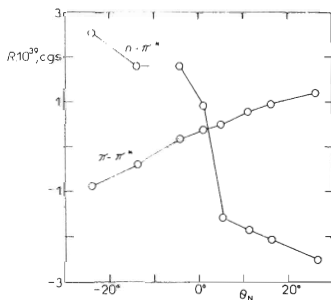


FIG. 5

Optical Rotatory Strengths of the $n - \pi^*$ and $\pi - \pi^*$ Transitions of Lactam (-)I Computed as Functions of the Pyramidal Arrangement of the Amide Nitrogen (the value θ_N)

chromic shift with an increase in Θ_N . If we compare changes in the static charge distribution on the atoms constituting the amide group in the ground state, and in the first electronically excited singlet state relative to the value of Θ_N (Fig. 7), we observe remarkably anomalous values of charge on nitrogen, oxygen and carbon atoms in the range of the nodal plane mentioned above.

TABLE II
CNDO/S Calculation of the Optical Rotatory Strength of Lactam (—)-I. Optimized Molecular Geometry was Used

Quantity	$n - \pi^*$ transition	$\pi - \pi^*$ transition
$\lambda_{\text{exp.}}^a$, nm	232.0	197.0
$\lambda_{\text{calc.}}$, nm	289.0	163.8
$f_{\text{exp.}}^b$	0.0056	0.0345
$f_{\text{calc.}}$	0.0082	0.1316
$R_{\text{exp.}}^a \cdot 10^{39}$, cgs	-2.51	2.07
$R_{\text{calc.}} \cdot 10^{39}$, cgs	-2.51	1.21

^a See note under the Table I; ^b oscillator strength measured in 3-methylpentane.

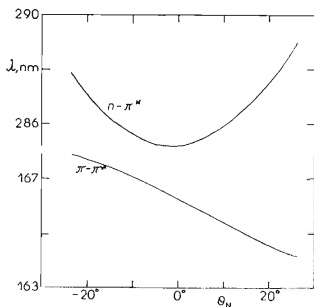


FIG. 6
The Shifts of the $n - \pi^*$ and $\pi - \pi^*$ Transitions in the Molecule of (—)-I Computed Relative to Θ_N (CNDO/S)

DISCUSSION

The polycyclic structure of lactam *I* gives this molecule a high degree of rigidity. Considering this property, as well as the high precision of X-ray analysis¹⁴, the possibility that some skeletal atoms deviate significantly on change of state of the molecule from crystals to solution would appear improbable. The same precision is reached in determining the position of the oxygen atom of the amide group. In addition, the pyramidal character exhibited at the carbonyl carbon atom is usually negligible according to Ramachandran and coworkers⁸⁻¹⁰. Therefore, optimization of the molecular geometry with respect only to the less accurately known positions of the hydrogen atoms is justified. Chiroptical properties of the lactam in question can be significantly influenced only by the hydrogen bonded to the nitrogen of the amide group. For these reasons, optimization was limited to a search for the most advantageous position of this atom.

On the contrary to the situation in the crystalline state, the value of angle θ_N found by optimization conforms well to relation (2). Hence, from the geometrical point of view, a regular pyramidal arrangement on the nitrogen atom (*i.e.* both substituents on N deviate from the O—C—N plane by approximately the same angle)

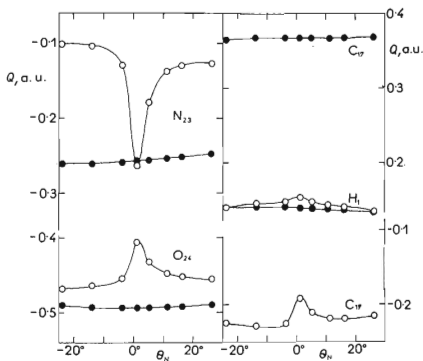


FIG. 7

Alterations of the Charge Distribution in the Amide Group of Lactam (—) *I* Related to the Developing Pyramidal Arrangement of Bond Attached to the Nitrogen Atom (●—●—●) Ground State Charge Distribution; (○—○—○) First Excited Singlet State Charge Distribution

The values given are in atomic units.

is found. An analogous situation was detected²⁵ by computation also in the case of 2-acetamido-1,3-propanediol, studied in connexion with the chiroptical properties of acetylated 3-amino-3-deoxyhexoses. However, the structure of 2-acetamido-1,3-propanediol is flexible and has a *trans*-amide arrangement. Therefore this compound represents a case similar to earlier investigated molecules⁸⁻¹⁰.

This study of lactam *I* shows that the trend of forming a regular pyramid on the nitrogen atom has a more general validity if the presented quantum chemical calculations are accepted as reliable. The cause of this preference for the regular pyramid may follow from the tendency to maximize the overlap between the orbitals of the carbonyl π system and the lone electron pair on nitrogen, even in the case of the non-planar amide group.

The values of optical rotatory strengths related to $n - \pi^*$ and $\pi - \pi^*$ transitions, which were computed for the optimized molecular geometry (Table II), agree well with the experimental results. (The computed values were compared with data measured in cyclohexane solution¹¹, since the approximation of the isolated molecule is best fulfilled in a non-polar solvent). The sole quantities which remain inaccurate are the positions of both transitions. This inaccuracy involves unknown positions of the 0-0 components of both bands and perhaps the parameterization used. Similar disagreements of experimental and theoretical positions of electronic transitions within the amide group have been reported elsewhere⁴⁻⁶.

The computed oscillator strength of the $n - \pi^*$ transition is close to the experimental value (Table II). The less reliable result concerning the $\pi - \pi^*$ transition (the computed value was approximately four times the experimental) can be explained in that only part of this absorption band lies in the accessible spectral region.

If we suppose that at low temperature the hydrogen atom is fixed in its equilibrium position, then according to a calculated relation between rotatory strength and Θ_N the Cotton effects connected with both bands under study should exhibit a hyperchromic effect on lowering the temperature. Such an effect was actually found¹¹. The observed hypsochromic shift of the both bands can be explained by a simultaneous action of solvent and the stabilization of the hydrogen atom position. Crossing the nodal plane, the optical rotatory strength of the $n - \pi^*$ transition undergoes a remarkable change and rapidly reaches a relatively high absolute value (Fig. 5). With the exception of the narrow range of Θ_N close to the nodal plane, these values are always greater than those corresponding to the $\pi - \pi^*$ transition. This conclusion agrees with the previous observation^{25,26} that non-planarity of the amide group is manifest by an increase in the intensity of the Cotton effect corresponding to the $n - \pi^*$ transition. The remarkable change of the $n - \pi^*$ rotatory strength in the proximity of the nodal plane is probably connected with a qualitative alteration of the character of this transition, which takes place when the arrangement of bonds on nitrogen becomes pyramidal. This suggestion follows the analysis of the static

charge distribution in the ground state and in the first electronically excited singlet state (Fig. 7). If hybridization of the amide nitrogen is sp^2 ($\theta_N = 0^\circ$) then the charge on this atom is practically equal in both the ground and first excited states and consequently the corresponding lone electron pair does not participate in the excitation process. On the other hand, a decrease of the negative charge on the oxygen atom in the course of this excitation indicates that with a planar arrangement of bonds on the amide nitrogen, the $n - \pi^*$ transition can be described as a transition of an electron from the oxygen n orbital. However, the pyramidal arrangement on nitrogen substantially alters this situation. In the latter case, the excitation process is accompanied by an appreciable decrease of the negative charge on nitrogen and the originally large charge alteration on the oxygen atom is diminished. Hence, it may be argued that at non-zero values of θ_N , characterizing a pyramidal arrangement on the nitrogen atom the $n - \pi^*$ transition arises to a great extent from the nitrogen n orbital.

Thus, the inherent chirality of the amide group in the lactam (-)I seems to have its primary source in the pyramidal arrangement on the nitrogen atom. As a consequence of this arrangement the $n - \pi^*$ transition is qualitatively altered and an experimentally detectable increase of the corresponding rotatory strength occurs. It is probable that the signs of both Cotton effects are then determined by a respective orientation of the lone electron pair on nitrogen and of the C=O bond of the amide group.

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