CHIROPTICAL PROPERTIES
OF 4-AZATRICYCLO[4,4,0,0³,⁸]DECAN-5-ONE — A LACTAM
WITH A NON-PLANAR *cis*-AMIDE GROUP

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CD spectra of the (−)-lactam given in the title were measured in six solvents. The parameters of dichroic bands (position, intensity and solvent shift) reflect the non-planar arrangement of the amide group. The negative $n - \pi^*$ band and the positive $\pi - \pi^*$ band are exhibited in the case of the (−)-enantiomer (with the non-planarity defined by $\Delta\omega = -14\cdot5°$ and $\Theta_N = 14°$). The essential features of the experimental results agree with the values calculated by the CNDO/S procedure. An additional band, probably of the Rydberg $n - 3s$ type, localized between the $n - \pi^*$ and the $\pi - \pi^*$ bands, was detected in cyclohexane and in acetonitrile.

The non-planar amide group represents an inherently chiral chromophore and therefore a significant specific response of the contingent non-planarity of this group can be expected in the spectra of circular dichroism. To facilitate a reliable identification of this phenomenon, which would be able to modify the present concept of the relationship between structure and chiroptical properties of peptides, it appears useful to study the CD spectra of rigid compounds exhibiting a forced non-planarity of the amide group[1]. In a preliminary communication[2] we reported some CD data of (−)-(2S, 5S)-4-azatricyclo[4,4,0,0³,⁸]decan-5-one (I), an optically active *cis*-lactam possessing the twistane skeleton (for the synthesis *cf.*[1]). The possibility to observe the well separated Cotton effects, corresponding to $n - \pi^*$ and $\pi - \pi^*$ transitions of the amide group in this compound, the rigidity of the twistane system, the known absolute configuration[1] and the known spatial arrangement in the crystalline state[3], enable to obtain a more detailed understanding of the chiroptical properties of the non-planar amide group by a thorough analysis of the CD curves. Such analysis represents the subject of this paper.

EXPERIMENTAL

CD spectra were recorded on Roussell-Jouan CD 185/II Dichrographe equipped with a cryostat enabling the measurement at low temperatures. The following spectral grade solvents were used: methanol, cyclohexane, acetonitrile, 1,1,1,3,3,3-hexafluoro-2-propanol and 2,2,2-trifluoroethanol. Unless otherwise stated the measurements were performed at 25°C and at the approximate con-

centration 0·25 mg per ml. The experimental curves thus obtained were simulated by Gaussian bands with the parameters estimated in order to describe most precisely the long-wavelength part of the spectrum. Hewlett-Packard 9830 calculator was utilized for this procedure. Separation of the single Gaussian bands was finished on CDC 3300 computer using the GENLSS program reported by De Tar[4]. The given experimental values of optical rotatory strength are related to Gaussian parameters obtained in this way. Direct quantum chemical calculation of optical rotatory strength was executed within the basis of the CNDO/S wavefunction using the parameterization according to Jaffé and coworkers[5]. Details of this calculation based on the method of Gould and Hoffmann[6] are described[7] separately in connection with the more precise quantum chemical study of the optical rotatory strength of the lactam *I*. Perkin-Elmer 356

CD Spectra of the Lactam (−)-*I* in Different Solvents

Solvent	Values obtained directly from the spectra[a]		Values obtained upon separation[a]			
	λ_{max}	$\Theta_{max} \cdot 10^{-3}$	λ_{max}	$\Theta_{max} \cdot 10^{-3}$	Δ_{max}	$R \cdot 10^{39}$
n — π* transition						
Cyclohexane	231·5	−30·1	232·00	−30·30	15·60	−2·51
Acetonitrile[b]	227·5	−37·0	228·10	−36·80	15·20	−3·02
Methanol	220·0	−38·5	219·50	−38·50	14·90	−3·22
Water	217·5	−45·3	216·60	−46·50	13·20	−3·49
2,2,2-Trifluoroethanol	214·0	−41·5	212·50	−45·00	14·00	−3·65
1,1,1,3,3,3-Hexafluoro- -2-propanol	211·5	−38·6	209·10	−50·00	12·90	−3·80
π — π* transition						
Cyclohexane	196·5	30·1	196·97	31·42	10·51	2·07
Acetonitrile[b]	196·0	32·3	196·15	33·30	9·49	1·98
Methanol	195·0	22·7	196·54	25·32	11·59	1·84
Water	194·0	25·3	196·89	29·76	11·46	2·13
2,2,2-Trifluoroethanol	193·5	22·8	195·95	31·41	11·73	2·32
1,1,1,3,3,3-Hexafluoro- -2-propanol	192·0	20·7	196·91	34·51	13·00	2·81
Rydberg *n*-3s transition						
Cyclohexane	215·0	c	209·87	−7·52	9·24	−0·41
Acetonitrile[b]	211·0	c	215·91	−4·40	7·08	−0·18

[a] Θ_{max} the maximum molar ellipticity deg cm² mol⁻¹, Δ_{max} band halfwidth in nm, *R* rotatory strength in cgs. [b] Measurement is influenced by a quantitative inaccuracy caused by the high vapour tension of acetonitrile at laboratory temperature. [c] Shoulder.

spectrophotometer was utilized for the measurements of the UV spectra in methanol, cyclohexane and 3-methylpentane. The compound used for the spectroscopic measurements was described in our previous study[1].

RESULTS

The essential features of the CD spectra of $(-)$-4-azatricyclo$[4,4,0,0^{3,8}]$decan-5-one (I) are clear from Fig. 1 and Table I. Consistently with the part of these data reported previously[2] it is possible to identify a negative Cotton effect corresponding to the $n - \pi^*$ transition and a positive one lying in the range of the amide $\pi - \pi^*$ transition. These bands are observed throughout the whole series of solvents used. The wavenumbers of the $n - \pi^*$ transition exhibit a linear correlation with the molar transition energies E_T characterizing the polarity of the particular solvents[8] (correlation coefficient 0·968, four experimental points; E_T values corresponding to the used fluorinated solvents are unknown and the correlation may be performed only for solutions in cyclohexane, acetonitrile, methanol and water). Similarly, the optical rotatory strength of the $n - \pi^*$ transition can be correlated to E_T values (correlation coefficient 0·992, four experimental points). On the other hand, neither position nor rotatory strength of the $\pi - \pi^*$ transition exhibit any regular relation to solvent polarity. The bathochromic shift of the $n - \pi^*$ transition observed in less polar solvents (22·9 nm for the pair 1,1,1,3,3,3-hexafluoro-2-propanol–cyclohexane) may be found analogously in
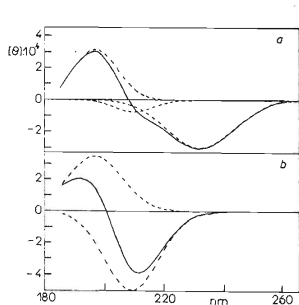

FIG. 1

CD Spectra of the Lactam $(-)$-I

a Cyclohexane; *b* 1,1,1,3,3,3-hexafluoro--2-propanol; ———— experimental curve; ----- separated Gaussian bands.
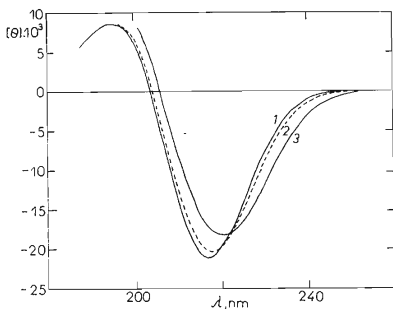
FIG. 2

Temperature Dependence of the CD Spectra of the Lactam $(-)$-I in Methanol

1 At $-90°C$; *2* at $-70°C$ (dashed line); *3* at $0°C$ (the curve measured at $40°C$ is practically identical).

the CD spectra of other amides[9,10]. In addition to the Cotton effects mentioned above further weak negative band at 210 and 216 nm respectively can be detected in the CD curves measured in cyclohexane and in acetonitrile. Up to this time we designated this band as $n - \sigma^*$ (cf.[2]). Throughout the present paper we term it Rydberg $n - 3s$ transition following Basch and coworkers[11,12]. The temperature dependence of the parameters of the Gaussian bands is given in Table II (for the measurement in acetonitrile). Upon lowering the temperature all the bands observed exhibit hypsochromic shift accompanied by an enlargement of the corresponding rotatory strength. Analogous effects can be observed in methanolic solution (Fig. 2). The measurements repeated in ten times diluted solutions have proved the Cotton effects of the lactam I to be independent on concentration.

Ultraviolet spectra of the lactam I (Fig. 3) exhibit the presence of the $n - \pi^*$ band in form of a shoulder at approximately 228 nm. The maximum corresponding to $\pi - \pi^*$ band lies at 202 nm. The simulation of these spectra with the aid of the sum of Gaussian bands affords the following estimates for the parameters of the both bands: In 3-methylpentane $n - \pi^*$ band at λ_{max} 226 nm $(\varepsilon = 310)$, $\pi - \pi^*$ band

TABLE II

Temperature Dependence of CD Parameters of the Lactam (−)-I

The measurement was carried out in acetonitrile. The given values (see note [a] under the Table I) were obtained upon separating the Gaussian bands.

Temperature °C	λ_{max}	$\Theta_{max} \cdot 10^{-3}$	$\varDelta_{max}$	$R \cdot 10^{39}$
		$n - \pi^*$ transition		
−40	227·10	−34·10	15·20	−2·81
0	227·80	−33·10	15·20	−2·72
40	228·60	−32·60	15·20	−2·67
		$\pi - \pi^*$ transition		
−40	195·22	27·93	10·60	1·87
0	195·94	29·03	9·84	1·80
40	196·75	29·65	9·27	1·72
		Rydberg n-$3s$ transition		
−40	215·72	−3·35	7·24	−0·14
0	216·55	−3·09	7·12	−0·13
40	216·60	−3·06	6·45	−0·11

at λ_{max} 202 nm ($\varepsilon = 3400$); in cyclohexane $n - \pi^*$ band at λ_{max} 226 nm ($\varepsilon = 330$), $\pi - \pi^*$ band at λ_{max} 204·5 nm ($\varepsilon = 2600$).

DISCUSSION

The CD data of the lactam $(-)$-I listed in Tables I and II exhibit relatively high degree of accuracy due to: a) the favourable signal-to-noise ratio given by the high values of the measured molar ellipticities; b) the small mutual overlap of the main ($n - \pi^*$ and $\pi - \pi^*$) bands in less polar solvents; c) the possibility of comparing the data collected in various solvents at several concentrations and temperatures. The separation procedure consistent for this series of measurements affords information involving the minimum number of the necessary Gaussian bands, the integral area under the experimental CD curve and, finally, the reliable parameters for the $n - \pi^*$ and $\pi - \pi^*$ transitions. On the contrary the weak Cotton effect at approximately 210 nm is given with the calculated values of parameter standard deviations greater by one order of magnitude. The assignment of the both intensive Cotton effects to $n - \pi^*$ and $\pi - \pi^*$ transitions of the amide group is supported by an ample experimental material obtained on other simple amides, e.g.[13]. In the case of the third band, the assignment still remains uncertain, although similar "mystery bands" were several times observed in the CD and UV spectra of amides and small
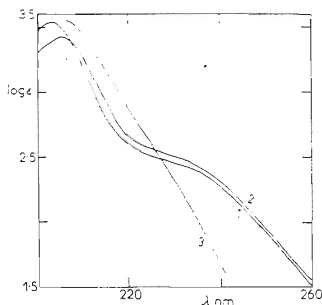
FIG. 3

UV Spectra of the Lactam I in 1 3-Methyl-pentane, 2 Cyclohexane, 3 Methanol
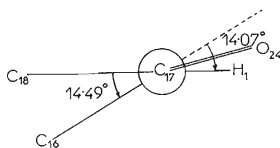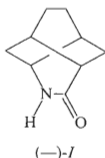
FIG. 4

Projection of the Non-planar Amide Group in the Lactam $(-)$-I According to the Three-dimensional X-Ray Analysis[3]

For better insight the angles were slightly enlarged in comparison to the actual values.

peptides[11,12,14,15]. Some of the factors which could give rise to the formation of this band (*e.g.* intermolecular association, electronic transition involving the σ-skeleton of the molecule, splitting of the $n - \pi^*$ band to vibronic components) can be eliminated upon considering the rigidity of the molecule of the lactam *I*, the concentration independence of the CD spectra and the presence of the band in both the cyclohexane and acetonitrile solutions. The band in question is most probably due to a transition involving the molecular orbitals of the σ-skeleton. This conclusion is supported by the calculations of the UV spectra of simple amides performed by Basch and co-workers[11,12] who used the SCF CI procedure within the expanded basis set containing the extra valence shell $3s$ and $3p$ orbitals. These calculations indicate the presence of the Rydberg $n - 3s$ transition in the area of consideration.

(—)-*I*

The most important result of our study is the possibility to assign the signs of the Cotton effects to the amide group of the defined chirality. We may state that the amide group according to Fig. 4 is characterized by a negative Cotton effect in the area of the $n - \pi^*$ transition and by a positive effect corresponding to the $\pi - \pi^*$ transition. The features of the CD curves are substantially affected by the inherent chirality of the non-planar amide group. This fact can be derived from the distinct bathochromic shift of the both bands as compared with the bands of amides possessing virtually planar amide groups, from the generally high values of molar ellipticities in the extrema and namely from the unusually intensive band of the $n - \pi^*$ transition compared to the $\pi - \pi^*$ one. While in the case of the usual amides and peptides the $n - \pi^*$ band is much weaker than the $\pi - \pi^*$ band, the intensities of the both bands of the lactam *I* are in a ratio of approximately 1 : 1.

The non-planarity of the amide group alters also the character of the UV spectra, especially that of the $n - \pi^*$ transition. Compared to the UV spectra of other amides, where it cannot be usually detected, this band lies in the case of the lactam *I* at longer wavelength and exhibits an unusually high extinction coefficient.

The known experimental values of the optical rotatory strength of $n - \pi^*$ and $\pi - \pi^*$ transitions of the lactam *I* can be compared with those computed quantum chemically. Direct calculation of optical rotatory strength, based on the semiempirical CNDO/S wavefunction, relates this chiroptical parameter to the

geometrical arrangement of the molecule. The geometry was in this case derived from the X-ray data[3]; the bond lengths and angles are given in Fig. 5 and the cartesian coordinates of atoms are listed in Table III. Using the notation of Ramachandran[16], the non-planarity of the amide group in the compound *I* may be described by the angles $\Delta\omega = -14.49°$ (torsion of the C—N bond), $\Theta_N = 14.07°$ (pyramidicity of the nitrogen atom) and $\Theta_C = 5.02°$ (pyramidicity of the carbonyl carbon atom). Results of the calculation are given in Table IV. The signs of the both intensive Cotton effects agree with the experiment. The calculated numerical values reproduce well the higher rotatory strength of the $n - \pi^*$ transition, however, the ratio of the rotatory strengths of the both transitions is considerably different from the experimental result. The rotatory strength of the $\pi - \pi^*$ transition is unrealistically small in comparison with that of the $n - \pi^*$ transition. Finally, the positions of the both bands are computed very inaccurately, of course this inaccuracy still occurs very often when performing MO calculations of this type, *e.g.*[13]. Owing to the fact that the basis set used was limited to valence electron shell, it was not possible to calculate Rydberg transitions. Despite the shortcomings mentioned here, the comparison of the CNDO/S computation with the experimental data establishes a suitable starting point for a more thorough theoretical study of the optical rotatory strength of the lactam *I*, *cf.*[7].
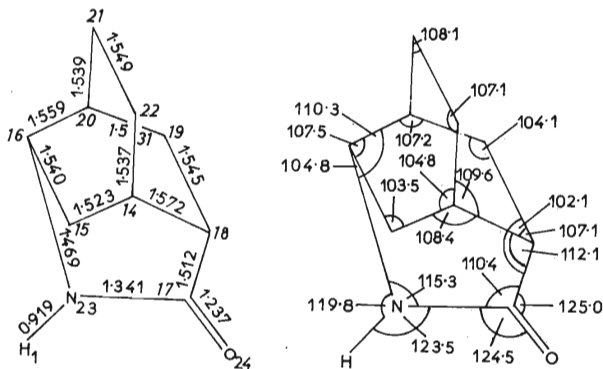

FIG. 5

Molecular Geometry of the Lactam (−)-*I* Estimated by the Three-dimensional X-Ray Analysis

The atoms 2—13 represent the hydrogens localized in CH and CH$_2$ groups. These are not shown here. Bond lengths in nm and bond angles are given.

TABLE III

Cartesian Coordinates of the Atoms Constituting the Molecule of the Lactam (−)-I Derived from the X-Ray Data

Atom	X nm . 10^1	Y nm . 10^1	Z nm . 10^1
H_1	−0·76636	1·84865	−0·00790
H_2	0·88865	1·24552	2·31119
H_3	2·43410	1·79028	2·15947
H_4	1·17917	2·91598	0·40323
H_5	1·39779	−1·48792	−0·08568
H_6	2·82477	−0·33192	−1·52583
H_7	1·35521	0·17214	−1·97742
H_8	2·37441	2·24346	−1·41788
H_9	4·42961	1·30952	−0·78344
H_{10}	3·95268	2·33332	0·45291
H_{11}	4·20023	0·42385	1·68310
H_{12}	3·98824	−0·44663	0·27085
H_{13}	2·14690	−0·73683	1·99041
C_{14}	2·22600	−0·04385	1·25792
C_{15}	1·70354	1·32668	1·66928
C_{16}	1·28612	1·96775	0·33249
C_{17}	0·00000	0·00000	0·00000
C_{18}	1·41695	−0·52639	0·00000
C_{19}	2·02646	0·18062	−1·23156
C_{20}	2·36425	1·58626	−0·72645
C_{21}	3·73760	1·44142	−0·04727
C_{22}	3·69236	0·19718	0·86734
N_{23}	0·00000	1·34119	0·00000
O_{24}	−1·01565	−0·69970	−0·08916

TABLE IV

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

Quantity	$n - \pi^*$ transition	$\pi - \pi^*$ transition
$\lambda_{exp.}{}^a$, nm	232·00	196·97
$\lambda_{calc.}$, nm	286·77	164·95
$R_{exp.}{}^a$. 10^{39}, cgs	−2·51	2·07
$R_{calc.}$. 10^{39}, cgs	−1·05	0·03

^{a} Experimental values correspond to the measurement performed in cyclohexane.

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