

CIRCULAR DICHROISM OF SOME FIVE- AND SIX-MEMBERED LACTONES AND LACTAMS*

O. ČERVINKA^a †L. HUB^a, F. SNATZKE^{b**} and G. SNATZKE^c

^a Department of Organic Chemistry, Institute of Chemical Technology, Prague 6

^b Department of Organic Chemistry, Polish Academy of Sciences, Warsaw, Poland,

^c Department of Organic Chemistry, University of Bonn, G.F.R.

Received June 1st, 1972

Chiroptical properties of five- and six-membered monocyclic lactones and lactams I–VIII of known absolute configuration have been studied.

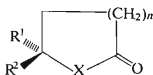
Up to now chiroptical properties of lactones and lactams have mostly been studied in the steroid, terpenoid or sugar series; there exist much more data on lactones than on lactams in the literature. Several empirical rules have been put forward connecting the absolute configuration with the sign of the corresponding Cotton effect of lactones within the $n \rightarrow \pi^*$ -transition. Klyne and coworkers¹ used a sector rule, Snatzke and coworkers² proposed another one with curved nodal surfaces. As we have discussed recently in more detail³ both rules are applicable, however, only for compounds which contain no chiral second sphere. The chirality of the latter is taken into consideration by the rules of Wolf⁴ and Legrand and Bucourt⁵; Beecham⁶ has shown that all earlier published ORD- and CD-curves of lactones could indeed be explained using these rules. Another one formulated by Okuda⁷ was demonstrated by Beecham⁶ to be in fact identical with that of Wolf⁴ or Legrand and Bucourt⁵. Recently, Korver⁸ has used the same approach to describe effects of temperature on chiroptical properties of some δ -lactones. According to this treatment^{4,5} a positive (negative) torsion angle along the C(=O)—C _{α} -bond gives rise to a negative (positive) Cotton effect around 215 nm. The same rule can be applied to the corresponding lactams⁴ at least in six-membered-ring compounds.

Almost all examples of five-membered lactones except those in the sugar series were such with a rigid lactone ring due to incorporation into a polycyclic system.

* This paper forms also part XLIV of the series On Asymmetric Reactions (by the Prague authors); Part XLIII: This Journal 38, 938 (1973). It is also Part LVIII of the series On Circular Dichroism (by the Bonn authors); Part LVII: Tetrahedron, in press.

** Formerly Werner—Zamojska.

It seemed, therefore, interesting to us to investigate the chiroptical properties also of such lactones and lactams which contain only one ring and consequently show conformational mobility (formulae *I–VIII*).



	n	X	R ¹	R ²		n	X	R ¹	R ²
<i>I</i>	1	O	H	CH ₃	<i>V</i>	2	O	H	CH ₃
<i>II</i>	1	O	COOH	H	<i>VI</i>	1	NH	CH ₃	H
<i>III</i>	1	O	COOCH ₃	H	<i>VII</i>	1	NH	COOH	H
<i>IV</i>	1	O	CH ₃	COOC ₂ H ₅	<i>VIII</i>	2	NH	H	CH ₃

The absolute configuration of (*S*)-(–)- γ -valerolactone⁹(*I*), (*S*)-(–)- γ -butyrolactone- γ -carboxylic acid (*II*) and its methyl ester¹⁰ (*III*), (*S*)-(–)- γ -caprolactone¹¹ (*V*), (*R*)-(+)- γ -valerolactam¹² (*VI*), (*S*)-(–)- γ -butyrolactam- γ -carboxylic acid¹³ (*VII*), and (*S*)-(+)- δ -caprolactam¹² (*VIII*) were established unambiguously. The absolute configuration of (*R*)-(+)- γ -valerolactone- γ -carboxylic acid (*IV*) was determined¹⁰ by the comparison of the plain ORD-curve of its reduction product with that of a similar compound and here might, therefore, exist a slight uncertainty (Table I).

The positive CD¹⁰ of the acid *II* has been explained³ by assuming that the Cotton effect of the lactone chromophore is stronger than that of the carboxylic acid chromophore and that the latter group adopts a quasiequatorial conformation. This makes the torsion angle along the C(=O)—C _{α} -bond negative and should thus lead to a positive CD. The same applies to the methyl ester *III* which indeed gives a positive Cotton effect, too. The CD of the methyl lactone *I* is also positive though the absolute configuration is opposite to that of *II* and *III* at C₍₄₎. All three compounds have an *S* configuration, however, because of different priorities according to the Cahn-Ingold-Prelog notation¹⁴. The absolute value of $\Delta\epsilon_{\max}$ of *I* is by more than one order of magnitude smaller than that of *II* and *III*. Obviously the small methyl group in this case does not anchor the five-membered ring in one single conformation, which leads to appreciable compensation of positive and negative contributions. The positive sign of the CD shows that the prevailing conformation is that which has a negative torsion angle, *i.e.* in which the methyl group adopts the quasiaxial conformation. The preponderance of this conformation cannot, however, be great as the CD is quite small. In the ethyl ester *IV* C₍₄₎ is doubly substituted by a methyl and an ethoxy-carbonyl group. The latter is even bigger than the COOH or COOCH₃ group and should, therefore, determine the conformation of the ring by adopting the quasiequatorial position. This seems to be indeed the case, as the CD is negative, however, in this case. The magnitude of $\Delta\epsilon_{\max}$ cannot be used for determination of the con-

formational equilibrium as the ethoxycarbonyl chromophore also contributes to the Cotton effect; the conformational freedom of the COOR-group is inhibited by the geminal methyl group and its CD is therefore not negligible.

The CD of two δ -substituted δ -lactones has recently been investigated in several solvents and at different temperatures by Korver⁸. He obtained bisignated* curves which can be explained on the basis of Wolf's⁴ assumption that an equilibrium between half-chair and boat conformation of the tetrahydropyran ring is present, the first giving rise to the band at longer, the latter to that at shorter wave-lengths. The acid V shows the same behaviour in giving a positive CD at about 241 nm and a negative one at about 213 nm. As in the case of Korver's⁸ lactones the ratio of half-chair to boat conformation decreases when going from hydrocarbon to ethanol solution. The sign of the two bands corresponds to negative (half-chair) and positive (boat) torsion angles around the C(=O)—C $_{\alpha}$ -bond^{4,5} which is in agreement with the general preference of equatorial methyl conformation in such a system. The same reasoning has been used recently to explain the CD of some other substituted chiral δ -lactones¹⁵⁻¹⁸.

The 2-pyrrolidin one ring of γ -lactams is also not planar as has been shown by X-ray analysis of two derivatives¹³. The lactam VI is heterochiral to lactone I and

TABLE I
Chiroptical Data of Some Lactones and Lactams

Compound	$[\alpha]_D^{20}$ ^a	Absolute configuration	λ_{\max} , ($\Delta\epsilon$) ^a
I	- 9.6 ^b	S	217 (+0.04) (O) 214 (+0.08) (E)
II	- 2.8 (W) + 10.6 (M)	S	216 (+1.79) (E) 217 (+1.51) (AN)
III	+ 6.8 (M)	S	215 (+0.59) (E) 214 (+0.20) (O)
IV	+ 7.0 (W)	R	217 (-1.30), 209 (-1.11) (E)
	- 1.2 (M)		217 (-1.13), 208 (-0.87) (O)
V	-38.8 (E)	S	241 (+0.05), 212 (-0.61) (E)
			242 (+0.22), 214 (-0.18),
			192 (-0.64) (O)
VI	+26.6 (W)	R	221 (-2.05) (AN) 215 (-2.89) (E)
VII	- 9.9 (W) + 5.7 (M)	S	218 (+4.55) (E) 221 (+3.16) (AN)
VIII	+27.5 (W)	S	222 (+1.43) (E) (227 (+1.90) (AN)

^a Abbreviations for solvents: AN acetonitril; E ethanol; M methanol; O isooctane; W water.

^b Liquid.

* This term was introduced by W. Klyne and should replace the older one "double humped".

in agreement with its absolute configuration shows a negative CD. $\Delta\epsilon_{\max}$ is, however, relatively large and this difference of rotational strengths of *I* and *VI* must at least in part be due to the presence of a hydrogen atom at the heteroatom. As in the case of the corresponding acid-lactone *II* the acid-lactam *VIII*, though being homochiral to *VI*, gives a strong positive CD. A similar difference has been found¹³ for the ω -iodo derivative of *VI* and the amide of *VII*. As in the crystalline state both compounds have the same helicity of the ring it was concluded¹³ that the determining factor for the CD is not the chirality of the second sphere, but a quadrant type rule for the COOR and CONR₂ groups. Calculations seem to support this view¹⁹. There is, however, no evidence that for these compounds the conformation of the ring and the side chain is the same on the crystal as in solution. Furthermore, in the iodo derivative the Cotton effect of the iodine chromophore²⁰ may interfere. We would like to favour, therefore, the same explanation for the signs of the CD as in case of the lactones, *i.e.*, that the ring helicity rule^{4,5} can be applicable also for the five-membered lactams. However, it cannot be excluded completely that substituents in the β -position (CH₃ or CH₂J and COOR or CONR₂) give contributions of opposite signs, as has been found for β -axially substituted cyclohexanones^{21,22}, though the special theoretical approach used by Mayers and Urry¹⁹ does not indicate such a change of signs. (*S*)- δ -Caprolactam (*VIII*) is homochiral to the corresponding lactone *V* and gives (in ethanol as well as in acetonitril) only one positive CD-band. Its position (222 and 225 nm, resp.) is just in between the values for the two lactone bands and it must correspond to the half-chair conformation as deduced from the rule⁷. It is interesting to note that only one band appears for *VIII*, whereas we have observed mostly two bands even for rigid δ -lactams.

Recently²³ it has been mentioned that third-sphere contributions to the CD of lactams follow a rule which is the reverse to that for lactones. Our examples show that second-sphere contributions are obviously the same in both homochiral series with five- and six-membered rings.

G. S. thanks the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support, F. W.-Z. the German Academic Exchange Service for a grant.

REFERENCES

1. Jennings J. P., Klyne W., Scopes P. M.: *J. Chem. Soc.* 1965, 7211.
2. Snatzke G., Ripperger H., Hartmann C., Schreiber K.: *Tetrahedron* 22, 3103 (1966).
3. Hrbek J. jr, Hruban L., Klásek A., Kochetkov N. K., Likhoshershtov A. M., Šantavý F., Snatzke G.: *This Journal* 37, 3918 (1972).
4. Wolf H.: *Tetrahedron Letters* 1965, 1075; 1966, 5151.
5. Legrand M., Bucourt R.: *Bull. Soc. Chim. France* 1967, 2241.
6. Beecham A. F.: *Tetrahedron Letters* 1968, 2355, 3591.
7. Okuda T., Harigaya S., Kiyomoto A.: *Chem. Pharm. Bull. (Tokyo)* 12, 504 (1964).
8. Korver O.: *Tetrahedron* 26, 2391 (1970).
9. Levene P. A., Haller H. L.: *Biol. Chem.* 69, 165 (1926).

10. Červinka O., Hub L.: *This Journal* 33, 2927 (1968).
11. Lukeš R., Jary J., Němec J.: *This Journal* 27, 735, (1962).
12. Červinka O., Fábryová A., Novák V.: *This Journal* 30, 1742 (1965).
13. Molin-Case J., Fleischer E., Urry D. W.: *J. Am. Chem. Soc.* 92, 4728 (1970).
14. Cahn R. S., Ingold Ch., Prelog V.: *Angew. Chem., Internatl. Ed.* 5, 385 (1966).
15. Lavie D., Kirson I., Glotter E., Snatzke G.: *Tetrahedron* 26, 2221 (1970).
16. Tschesche R., Hoppe H. J., Snatzke G., Wulff G., Fehlhäber H. W.: *Chem. Ber.* 104, 1420 (1971).
17. Caroll F. I., Blackwell J. T.: *Tetrahedron Letters* 1970, 4173.
18. Caroll F. I., Asha Sobti, Meck R.: *Tetrahedron Letters* 1971, 405.
19. Mayers D. F., Urry D. W.: *Tetrahedron Letters* 1971, 9.
20. Chaudri A. H., Goodwin D. G., Hudson H. R., Bartlett L., Scopes P. M.: *J. Chem. Soc. (C)* 1970, 1329.
21. Snatzke G., Eckhardt G.: *Tetrahedron* 24, 4543 (1968).
22. Snatzke G., Ehring B., Klein H.: *Tetrahedron* 25, 5601 (1969).
23. Klyne W.: Plenary Lecture at the Summer School on ORD and CD at Tirrenia, 1971.

Translated by the authors.