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CIRCULAR DICHROÍSM OF γ-LACTAMS AND THEIR SIGN DETERMINATING FACTORS

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It has been reported on six-[1,2] and seven-membered[3] lactams which have no heteroatom substituents at Cα that CD signs are determined by the ring chirality. However in γ-lactams especially in γ-lactams which have a heteroatom substituent such as hydroxyl or amino group at Cα, no satisfactory explanation have been presented. Recently in γ-lactones we suggested that CD sign and magnitude can be determined by addition of two effects:(1) configuration at Cα and (2) ring chirality.[4,5] In this communication we present some CD results which enable the above principles to γ-lactams and wish to draw attention to the CD data not only on signs but also their magnitude and red shift which might be useful in configurational and conformational analysis of γ-lactams. Five γ-lactams(I-V) with heteroatom substituent at Cα are studied together with corresponding γ-lactones(I'-V') in the similar solvents and two γ-lactams without heteroatom substituent at Cα(VI and VII) are quoted from literatures.[6,7]

The CD sign and molar ellipticity are shown in Table together with the configuration at Cα and ring chirality in Fig. The ring chirality of I,II,IV and V were posturated as A,A,B and B using Dreiding model framed up according to their PMR spectra(Jab,ab') and Karplus theory.[8] In VI and VII the ring chirality were assumed as A and B according to the possible preferable quasi-equatorial conformation of the bulky group at Cα. In III it was assumed as A because of the two of three bulky substituents hold equatorial.

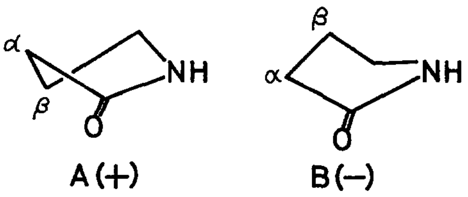


Fig Ring chirality and CD sign of γ-lactams

The results are briefely summerized as follows.

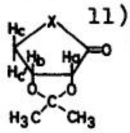
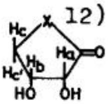
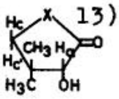
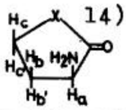
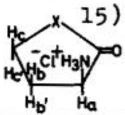
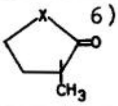
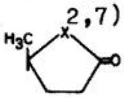
(1) In V -VII which have no lone pair electrons on Cα substituent, the CD signs are determined by the ring chirality, that is A gave positive sign and B gave negative sign. It should be noted that this ring chirality effect in γ-lactams gave opposite sign to γ-lactones reported by Beecham.[9)]

(2) In I - IV which have lone pair electrons on Cα substituent, the CD signs are determined by Cα configuration. S-Configuration gave positive sign and R-gave negative sign as well as ketone[10)](axial-haloketone rule) and lactone[4)] in which the signs are explained due to "the formation of inherently dissymmetric chromophore between π-electron of carbonyl and lone pair electrons on Cα substituent." It was known to cause a red shift of CD maximum about 5 - 10 nm from usual n-π* chromophore. The wavelength at CD maximum and the red shift against VII are shown in Table. It gave red shift of 5-10 nm in I-IV and no red shift or rather small blue shift in VII and VII suggesting the formation of such chromophore in I-IV.

(3) The CD magnitude can be well explained by an extention of the CD rules obtained in γ-lactone that addition of Cα effect and ring chirality effect determine the [θ] value. It should be noted that the ring chirality effect of γ-lactam V-VII gave molar ellipticities of 6000-10000 which is about three to five times higher than those of γ-lactones. Thus, in II and IV the addition of two factors of opposite signs gave relatively small molar ellipticities and in III the result gave positive sign in water and negative sign in methanol. On the other hand in V-VII the effect of Cα configuration is negligible and are determined only by the ring chirality.

(4) When Cα substituent is amino group, another possibility to determine the configuration is suggested using CD change accompanied with the salt formation. Thus lone pair electrons of nitrogen in free amine(IV) is masked by protonation in its hydrochloride(V) which prevents the formation of the chromophore between carbonyl and lone pair electrons. It was also shown that corresponding γ-lactone (IV' and V') gave just the same CD change due to hydrochloride formation.

Table CD sign, magnitude and red shift of γ-lactams and γ-lactones.

No. compd.	γ-lactams(X=NH) config.	ring (pred. of sign)	γ-lactams(X=NH) $[\theta]\times10^{-3}(\lambda_{max})$shift	γ-lactones(X=O)	γ-lactones(X=O) $[\theta]\times10^{-3}(\lambda_{max})$shift	solv.
I  11)	R(-)	A(+)	-7.87 (218) +8	I'	-9.16 (221)	W
			-8.12 (222.5) +7.5		-6.92 (222) +8	M
II  12)	R(-)	A(+)	-2.89 (211) +1	II'	-12.9 (218)	W
			-4.40 (219) +4		-10.9 (221.5)+7.5	M
III  13)	R(-)	A(+)	+0.79 (221) +11	III'	-17.3 (219)	W
			-1.04 (217) +2		-13.1 (221) +7	M
IV  14)	S(+)	B(-)	+1.80 (218) +8	IV'	+8.17 (219)	W
			+0.90 (223) +8		+7.72 (217) +3	M
V  15)	S(+)	B(-)	-10.3 (210) 0	V'	+1.89 (217)	W
			-8.20 (210s) (-5)		+1.60 (221) +7	M
VI  6)	R	A(+)	+6.06 (212.5) +2.5	VI'		W
			+5.60 (217.5) +2.5			M
VII  2,7)	R at C_γ	B(-)	-7.20 (210) 0	VII'2)	S-config.	W
			-9.54 (215) 0		+0.26 (214) 0	E

W:Water, M:Methanol, E:Ethanol. s:at the shortest wavelength measured.

CD measurement: On a Jasco J-20A, 1 mm cell, about 1 mg/ml except VI-VII at 25°C. [θ] corrected relatively using D-pantolactone ($[\theta]_{222} = -12.8 \times 10^3$ in 95% ethanol).

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11) Prepared by the method of S.Hanessian,J.Org.Chem.,34,675(1969),mp.147-8°C, $[\alpha]^{23}_{589}$=-59.6°(C=0.91,methanol),Mass:m/e 157(M^+),PMR data:Jab6.3,Jbc,bc' 0.5,4.0 cps(in D_2O).

12) Prepared by the method of Hanessian.11) mp.153-4°C(d), IR:1690cm^{-1}(amide), Mass:m/e 117(M^+), TLC:2-propanol:water(4:1) medium, PMR data: Jab5.2, Jbc,bc'0.5,3.5 cps(in D_2O).

13) III was prepared by sublimation of D-4-amino-3,3-dimethyl-2-hydroxy butanoic acid obtained by action of sodium azide in DMF and then catalitic hydrogenation on Pd-C from D-pantolactone. mp.151-3°C, IR: 1690 cm^{-1} $[\alpha]^{23}_{589}$=+25.6°(C=1,methanol), Mass: m/e 129(M^+).

14) Prepared by the method of S.Willkinson, J.Chem.Soc., 104(1951).PMR data: Jab,ab'=8.2,10.0 cps.(in D_2O).

15) mp186°C, $[\alpha]^{23}_{589}$=-23°(C=1,water), PMR data: Jab,ab'=8.5,10.2 cps.(in D_2O).