Short Communication

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Application of Axial-haloketone Rule to Lactones

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In ketone formation of a strong and inherently dissymmetric chromophore due to the interaction between lone pair electrons of the axial halogen substituents at C_α associated with a strong molecular rotation and red shift at the extremum has been known as the axial-haloketone rule.[1] Although optical rotatory dispersion (ORD) and circular dichroism (CD) of many lactone have been reported,[2~8] the application of the rule to lactone has not yet been fully studied. However the skeleton contribution of the lactone ring has been studied both in δ-[4] and γ[5]-lactones.

In this communication we present the CD of some lactones which suggests the possibility of applying of this rule to lactones. Two types of lactones, non-bridged γ-lactones I~IX which have a more 'axial'[9] C_α substituent and α,γ-bridged lactones XII~XVII which have a more 'equatorial' C_α substituent were studied.

The structures of the lactones are shown in Fig. 1. The non-bridged lactones were prepared from D(−)-pantolactone I (a) and L(+)-homoserine-γ-lactone hydrochloride VII (b), and α,γ-bridged lactones were from D(−)-quinide XIII by the reactions which are known to proceed with the retention or the conversion of the configuration, all having a heteroatom attached to C_α. For comparison the CD of dihydrocoronopilin X,[7] γ-tetrahydrosantonin XI[7] and gibberellin (A_9 methylester XII[8]) are adopted from literatures. They have a methyl group at C_α and the ring puckering increases from β,γ-*cis*-bridged X, β,γ-*trans*-bridged XI to α,γ-bridged lactones, associated with increasing $[\theta]$ and a redshift at the CD maximum.

The molecular ellipticities $[\theta]$, the wave length at the CD maximum and the red shift of the maximum from X in non bridged lactones and from XII in α,γ-bridged lactones are shown in Table I. The following should be noted in non-bridged lactones. (1) The sign of Cotton effect (C.E.) was determined according to the configuration at C_α. The R (or S) configuration gave positive (or negative) sign which agrees with the prediction from the axial-haloketone rule when the rule is applied

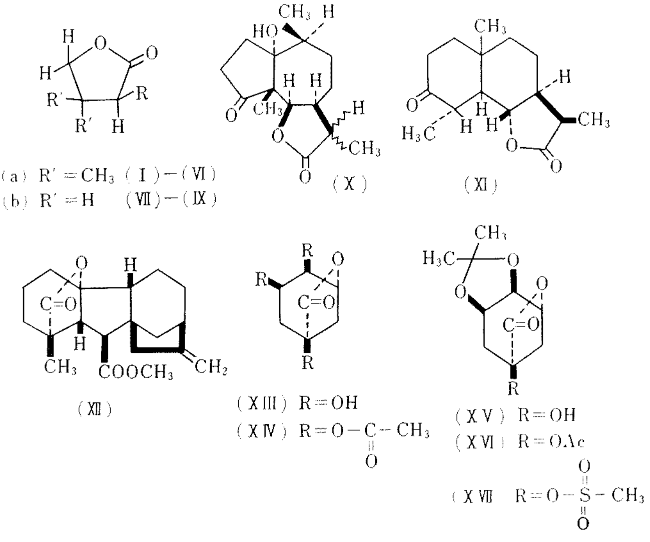

FIG. 1. The Structures of the Lactones Shown in Table I.

TABLE I. CD AND ORD, SIGN, MAGNITUDE AND RED SHIFT

CD and ORD measurements. On a JASCO ORD/UV-5, 1 cm cell, about 1 mg/ml in methanol except III in ether and IX in ethanol. $[\theta]$, corrected relatively using D-pantolactone ($[\theta]_{222}=-12.8\times10^3$ in 95% ethanol) at 25°C. VIII and IX were partially racemized and should have qualitative values. XIII and XV have also been reported[5] without the above-correction and qualitatively accorded with our's.

Comp.	C-2		C.E. sign	CD Max.			ORD 1st. Ext.	
	subst.	config.		$[\theta]\times10^{-3}$	(nm)	Red shift	$[M]\times10^{-3}$	(nm)
Non bridged						from (X)		
(a) (I)	$-OH$	R	−	−12.5	(223)	+ 8	−5.7	(236)
(II)	$-OCH_3$	R	−	− 6.9	(225)	+10	−2.2	(240)
(III)	$-OSi(CH_3)_3$	R	−	− 7.7	(226)	+11	−1.6	(240)
(IV)	$-O\underset{\overset{\|}{O}}{C}CH_3$	R	−	− 6.6	(220)	+ 5	−3.0	(235)
(V)	$-OSO_2CH_3$	R	−	− 6.8	(221)	+ 6	−2.4	(235)
(VI)	$-Cl$	S	+	+ 8.3	(220)	+ 5	+3.0	(237)
(b) (VII)	$-NH_2$	S	+	+ 5.3	(217)	+ 2	+1.9	(234)
	$-NH_3^+Cl^-$	S	+	+ 1.6	(221)	+ 5	−0.035	(238)
(VIII)	$-Cl$	R	−	− 5.4	(226)	+11	−1.5	(247)
(IX)	$-Br$	R	−	− 8.0	(232)	+16	−2.1	(258)
β,γ-Bridged								
(X)	$-CH_3$		+	+ 3.5	(215)			
(XI)	$-CH_3$	R	+	+ 4.5	(217)			
α,γ-Bridged						from(XII)		
(XII)	$-CH_3$	R	−	− 5.3	(222)	0		
(XIII)	$-OH$	S	−	− 8.9	(222)	0	−4.3	(236)
(XIV)	$-O\underset{\overset{\|}{O}}{C}CH_3$	S	−	−12.7	(217)	− 5	−6.0	(234)
(XV)	$-OH$	S	−	− 7.9	(222)	0	−4.5	(236)
(XVI)	$-O\underset{\overset{\|}{O}}{C}CH_3$	S	−	−14.5	(218)	− 4	−6.4	(233)
(XVII)	$-OSO_2CH_3$	S	−	−11.3	(220)	− 2	−5.2	(236)

to lactones.[1]

(2) The heteroatoms gave a red shift of about 5∼16 nm from the methyl group as in the case of axial halogens in ketones. The red shift was sensitive to the nature of substituents and also to a slight difference of conformation.

(3) They gave larger $[\theta]$ as compared with X and XI, suggesting that the contribution of the C_α 'axial' heteroatom might be large enough to cancell the skeleton contribution. In the two series of lactones (a) and (b) the order of the magnitude is as follows:

$$\text{(a)}\ -\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}H > -\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: > -\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}Si(CH_3)_3 > -\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}SO_2CH_3$$

$$> -\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}CH_3 > -\underset{\cdot\cdot}{\overset{\cdot\cdot}{O}}COCH_3 > 6600.$$

$$\text{(b)}\ -\underset{\cdot\cdot}{\overset{\cdot\cdot}{Br}}: > -\overset{\cdot\cdot}{N}H_2,\ -\underset{\cdot\cdot}{\overset{\cdot\cdot}{Cl}}: > 5700.$$

On the other hand, in α,γ-bridged lactones, the sign of C.E. was determined by the skeleton contribution according to Beecham's rule[5] and the introduction of heteroatoms such as hydroxyl, acetohydroxyl, and methanesulfonyl groups instead of methyl groups XII gave a negligibly small red shift or a rather small blue shift as in the case of equatorial halogens in ketones.

The red shift of CD maximum and contribution to the CD sign by 'axial' heteroatoms in non-bridged γ-lactones and the small blue shift and negligible contribution to the CD sign by 'equatorial' heteroatoms in α,γ-bridged lactones strongly suggest the possibility of applying of the axial-haloketone rule to lactones. Here the substituents are not limited to halogens but can be more widely extended to other heteroatoms such as oxygen and nitrogen so long as they have lone pair electrons.

The formation of a inherently dissymmetric chromophore between lactone carbonyl and heteroatoms was also shown in the solvent effect of VII in which the amino group at C_α gave a very weak CD peak when the lone pair electrons of nitrogen were masked in the form of hydrochloride. However, it increased to a strong band four times more than in a form of free amine in which the lone pair electrons of nitrogen were exposed after neutralization with KOH.

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9) Here the terms, more 'axial' and more 'equatorial,' are used tentatively to express the difference in the projection angle of the substituents from the lactone plane by inspection.