

## CONFORMATION AND CHIROPTICAL PROPERTIES OF $\gamma$ -LACTONES OF ALDONIC ACIDS

S. BYSTRICKÝ, T. STICZAY, Š. KUČÁR and C. PEČIAR

*Institute of Chemistry,  
Slovak Academy of Sciences, 809 33 Bratislava*

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Chiroptical properties of  $\gamma$ -lactones of aldonic acids, 3-deoxy- $\gamma$ -lactones and 2-deoxy- $\gamma$ -lactones are discussed in terms of conformation of the five-membered lactone ring. In the evaluation of steric and electronic interactions between substituents on the ring atoms the non-bonding interaction between the carbonyl oxygen and vicinal substituents plays an important role. On the basis of this fact it is possible to derive correct conformations which are confirmed by values of the  $^1\text{H-NMR}$  coupling constants. The conformation of the ring is naturally reflected in the chiroptical properties of the molecule. From CD-measurements of  $\gamma$ -lactones of saccharides it is possible to decide whether the molecule exists in an  $^3E$  or  $E_3$  conformation.

Several empirical rules are available for the correlation of the steric structure of a molecule with the Cotton effect of the  $n \rightarrow \pi$  transition of the lactone group. Older rules are based on the orientation of the molecular skeleton relative to the chromophore<sup>1,2</sup>, the more recent ones take into account the chirality of the lactone ring<sup>3-5</sup>. For the calculation of the optical activity of carbonyl chromophores one-electron theory was suggested and developed<sup>6</sup>. According to this theory, the division of the space, occupied by the molecule, into sectors depends on the symmetry of the chromophore. The non-chromophoric moiety of the molecule acts as a perturbation field. This chiral effect of the environment is very sensitive to the relative geometry of the polarizable groups. As pointed out by Weigang<sup>7</sup>, the electronic structure of the lactone chromophore is considerably specific. According to Beecham<sup>5</sup>, the sense of the Cotton effect is determined by the orientation of the  $C_{(3)}$  atom, *i.e.* whether this atom is above or below the lactone plane. The author points out that this orientation is associated with the absolute configuration at the  $C_{(2)}$  atom. The effect of the orientation of a bulky group at  $C_{(4)}$  is not obvious. In some recent papers<sup>8,9</sup> the spectra of 5- and 6-membered lactones and lactams are interpreted as a sum of independent contributions of the chirality of the ring and of the configuration of the substituents at  $C_{(2)}$  which contain a free electron pair.

The aim of our work was to clarify and check the general validity of Beecham's conclusions by studying the relationship between the conformational arrangement and chiroptical properties.

## EXPERIMENTAL

The compounds were prepared using methods, described in the literature (Table I); their physical constants agree with the reported values.  $^1\text{H-NMR}$  spectra were obtained on a Tesla BS-487-B spectrometer at 80 MHz in  $\text{D}_2\text{O}$ . The CD-spectra were measured on an ORD/UV-5 JASCO spectropolarimeter equipped with a CD adaptor. The measurements were performed in aqueous solutions of concentration 1–2 mg/ml in 1–10 mm cells at room temperature.

## RESULTS AND DISCUSSION

Under the assumption that the four atoms of the lactone grouping,  $\text{C—O—C(O)—C}$ , are in one plane, two envelope conformations of the five-membered ring,  $^3E$  and  $E_3$ , are possible. In order to predict the conformation of a given compound, it is necessary to know the relative free energies of both these conformers. Determination of the free energies by quantum-chemical calculations is difficult but a qualitative analysis involving steric and electronic factors can also lead to the most probable conformers. The detailed data concerning non-bonding interactions in the pyranoid forms of saccharides are available<sup>10,11</sup>. They can be applied also to five-membered rings; they differ only in that in a five-membered ring the gauche non-bonding interactions are larger and the pseudodiaxial interactions are smaller, depending on the magnitude of the puckering of the five-membered ring. As a result of this puckering the *cis*-1,2-non-bonding interactions are not present whereas gauche 1,2-interactions (C/O, O/O) and an interaction between OH group on  $\text{C}_{(2)}$  and the carbonyl group still exist. There is also a 1,3-interaction between pseudoaxial substituents at  $\text{C}_{(2)}$  and  $\text{C}_{(4)}$  and, in  $\gamma$ -lactones of aldohexonic acids, an interaction between pseudoaxial substituents at  $\text{C}_{(3)}$  and  $\text{C}_{(5)}$ .

Similarly as in the case of hexopyranosides, the C/O pseudodiaxial interaction is evidently very unfavourable also in  $\gamma$ -lactones of aldonic acids. As a result of this destabilising effect compounds with *lyxo*, *mano*, *arabino* and *altro* configuration

TABLE I  
Values of Coupling Constants of the  $\gamma$ -Lactones in  $\text{D}_2\text{O}$

Compound	$J_{2,3}$	$J_{3,4}$	$J_{4,5}$	$J_{4,5}$	$J_{5',5'}$
D-Ribono <sup>a</sup>	5.7	0.6	4	4	12.5
D-Allono-	5.7	>0.5	4.8	—	—

<sup>a</sup> Similar values have been found in acetone<sup>12</sup>.

will exist in conformation  ${}^3E$  whereas *gulo* and *galacto* compounds in the conformation  $E_3$ . Compounds with configuration *ribo*, *allo*, *talo*, *xylo*, *gluco*, and *ido* contain disputable pseudodiaxial interactions C/H or O/H. The C/H interaction in pyranoses is twice as great as the O/H interaction. This energy difference is used to be regarded as decisive in the conformational assignments and should lead in the case of configurations *ribo*, *allo*, *xylo* and *gluco* to  ${}^3E$  conformation and in the case of *talo* and

TABLE II  
CD Data for Aldono- $\gamma$ -lactones

No	Compound	CD		Ref.
		$\Delta\epsilon(\lambda, \text{nm})$		
Aldohexono- $\gamma$ -lactones				
<i>I</i>	D-Allono-	-2.96	(220)	15
<i>II</i>	D-Glucono-	-2.35	(219)	16
<i>III</i>	3-Deoxy-D-glucono-	-2.92	(220)	17
<i>IV</i>	2-Deoxy-D-glucono-	+1.73	(213)	18
<i>V</i>	D-Mannono <sup>a</sup>	+2.87	(220)	16
<i>VI</i>	3-Deoxy-D-Mannono-	+1.68	(219)	17
<i>VII</i>	D-Gulono-	-3.22 <sup>b</sup>	(221)	16
<i>VIII</i>	D-Galactono-	-4.33 <sup>b</sup>	(221)	16
<i>IX</i>	3-Deoxy-D-galactono-	-2.07	(218)	17
<i>X</i>	2-Deoxy-D-galactono-	+0.85	(208)	19
<i>XI</i>	D-Talono-	+3.49	(222)	20
<i>XII</i>	3-Deoxy-D-talono-	+2.24	(219)	17
Aldopentono- $\gamma$ -lactones				
<i>XIII</i>	D-Ribono-	-3.57 <sup>b</sup>	(220)	21
<i>XIV</i>	D-Xylono-	-3.58	(221)	22
<i>XV</i>	3-Deoxy-D-ribo-	-1.14	(215)	17
<i>XVI</i>	D-Lyxono-	+3.07	(220)	23
<i>XVII</i>	D-Arabono-	+4.57 <sup>b</sup>	(222)	24
<i>XVIII</i>	3-Deoxy-D-arabono	+0.82	(221)	17

<sup>a</sup> The enantiomeric compound was measured; <sup>b</sup> the values are in a good agreement with Beecham<sup>5</sup>.

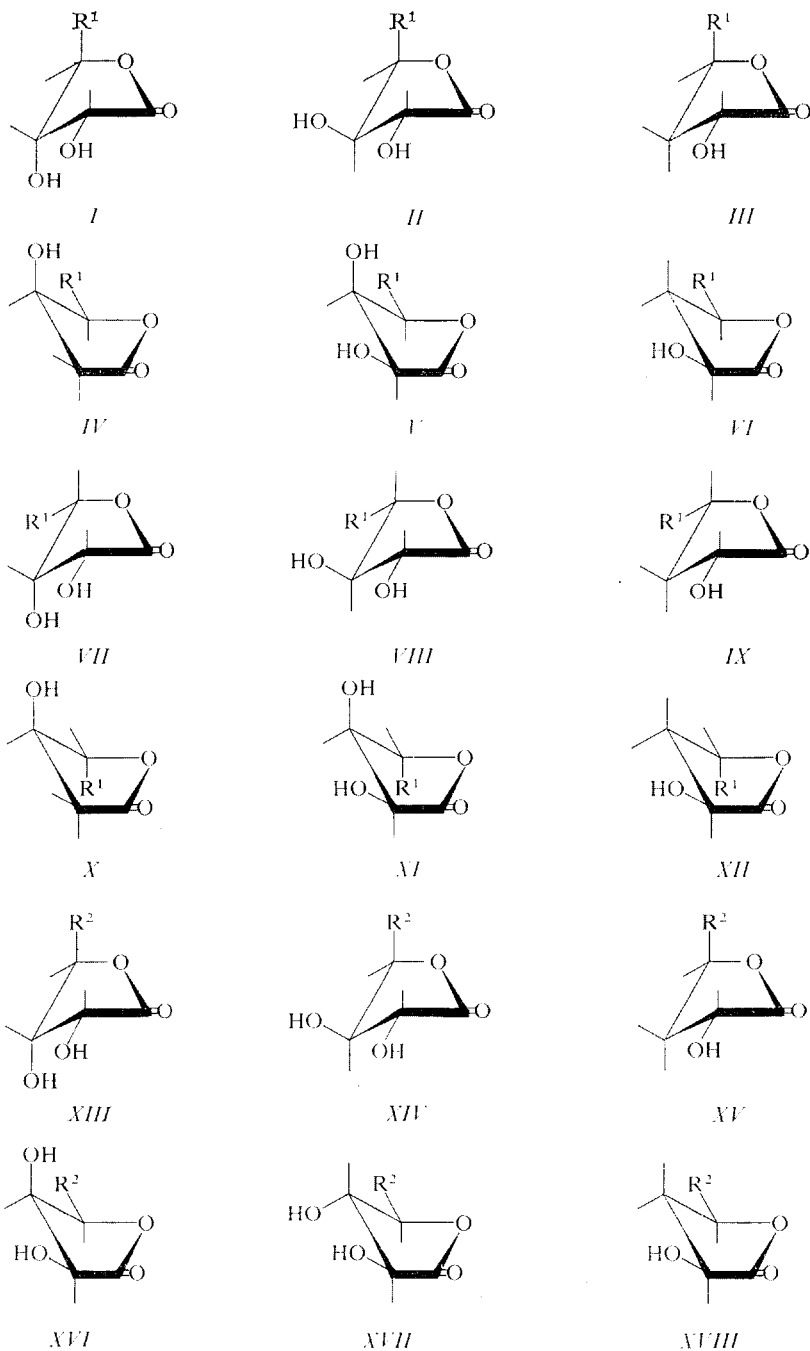
*ido* compounds to an  $E_3$  conformation. However, there is a hitherto not considered interaction between the OH group at  $C_{(2)}$  and the carbonyl group.

We measured the  $^1\text{H-NMR}$  spectra of D-ribo- $\gamma$ -lactone and D-allono- $\gamma$ -lactone (Table I). Contrary to the above predictions, the values of the coupling constants show that D-ribo- $\gamma$ -lactone and D-allono- $\gamma$ -lactone exist in the  $E_3$  conformation.

A quantum chemical calculation<sup>13</sup> on glyceraldehyde as a model compound has shown an energetic minimum in the region of  $30^\circ$  torsion angle between the C—OH and C=O bonds (syn-clinal arrangement) corresponding to a pseudoequatorial position of the hydroxyl. On the contrary, a pseudodiaxial position would correspond to an energy near the top of the energetic barrier with a maximum at  $90^\circ$  torsion angle. Here the main conformation determining factor is the strong vicinal interaction of the carbonyl group with the hydroxyl at the  $C_{(2)}$  atom and consequently the tendency of a 2-OH group to occupy the pseudoequatorial position in the lactone ring forces the unexpected conformation in the lactones mentioned. Accordingly, we can assume that for compounds with *ribo*, *allo*, *xylo* and *gluco* configuration the preferred conformation will be the  $E_3$  form whereas *talo* and *ido* stereoisomers will exist in the  $^3E$  form.

The CD-data of the  $\gamma$ -lactones of aldopentonic and aldohexonic acids, their 3-deoxy derivatives and 2-deoxyaldonolactones are given in Table II. The expected most stable conformations of the studied  $\gamma$ -lactones, as derived according to the above-discussed steric considerations, are given in Scheme 1. These forms are in accord with the chiroptical properties of the compounds. Compounds *I–III*, *VII–IX*, *XIII–XV* which have the *R*-configuration at the  $C_{(2)}$  atom display a positive Cotton effect and can be assigned a  $^3E$  conformation. The 2-deoxy derivatives exhibit only small rotational strength. The position of the  $n-\pi^*$  transition shows a hypsochromic shift caused by the absence of an interaction between non-bonding orbitals of the carbonyl and hydroxyl group. Since there is no hydroxyl at  $C_{(2)}$  it is possible to determine the preferred conformation only from the sign of the CD curve. The 3-deoxy derivatives exhibit the same sign of the Cotton effect as the corresponding aldono- $\gamma$ -lactones.

Our results proved the dependence of the orientation of the  $C_{(3)}$  atom on the configuration of the  $C_{(2)}$  atom, as expressed by the Beecham rule. The variously formulated lactone rules<sup>4,5,8,14</sup> can be put on a common basis, namely that the chiroptical behaviour of  $\gamma$ -lactones is unequivocally determined by conformational orientation of the ring skeleton — bearer of polarisable groups.



$R^1 = \text{CHOHCH}_2\text{OH}$   
 $R^2 = \text{CH}_2\text{OH}$

SCHEME 1

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