STEREOCHEMICAL STUDIES, XX*

Studies on Cyclic 2-Hydroxycarboxylic Acids, III**

Molecular Structure and Dipole Moment Relationships of Ethyl *cis*- and *trans*-2-Hydroxycarboxylates

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The dipole moments of alicyclic ethyl *cis*- and *trans*-2-hydroxycarboxylates were studied. On the basis of the dipole moment values it proved possible to investigate the validity of the conformation rule in the case of these compounds. The fairly good agreement between measured and calculated dipole moments permitted to assume the presence of intramolecular hydrogen-bonds in the *cis*-isomers and of intermolecular hydrogen bonds in *trans*-isomers.

Introduction

Alicyclic ethyl *cis*- and *trans*-2-hydroxycarboxylates may serve as starting materials for the synthesis of stereochemically homogeneous bifunctional alicyclic derivatives. Several papers describe the synthesis and spectroscopic studies [5, 6] of *cis*- and *trans*-2-hydroxycyclopentanecarboxylic acid (**1**), *cis*- and *trans*-2-hydroxycyclohexanecarboxylic acid (**2**), *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acid, and of the respective esters [3, 4]. IR and NMR spectroscopy reveals primarily the intramolecular and intermolecular hydrogen bonds of the isomers as well as the preferential conformation of the individual substituents. IR spectroscopy and viscosity measurements led CASTELLS and PALAU [5] to the conclusion that in the molecules of ethyl *cis*- and *trans*-2-hydroxycyclopentanecarboxylate and ethyl *cis*- and *trans*-2-hydroxycycloheptanecarboxylate the *cis*-isomer is less prone to associate than the *trans*-isomer.

BAUMANN and MÖHRLE [7, 8] studied the conformation of isomers and determined their equilibrium constants [9]. Equatorial hydroxy groups promote a more pronounced association than axial ones. Based on NMR spectra of BAUMANN and

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MÖHRLE [8] as well as our own IR and NMR spectroscopic data, and measurement of dissociation constants and reaction rate of chromic acid oxidation, the preferential conformation of compounds **Ia** and **Ib** was established in agreement with literature data [10]. NMR spectra suggest that in *cis*-2-hydroxycyclohexanecarboxylic acid equatorial position may be assigned to the carboxy group and axial to the hydroxy group [6].

It seemed justified to investigate the interrelationship between physical constants of isomers and their configuration with regard to dipole moment studies, too. Determination of the dipole moments may enable us to examine the validity of the "conformation rule" in the specific case of these molecules.

Determination of the dipole moment

The dipole moments of ethyl *cis*- and *trans*-2-hydroxycyclopentanecarboxylate (**Ia,b**), ethyl *cis*- and *trans*-2-hydroxycyclohexanecarboxylate (**IIa,b**), and ethyl *cis*- and *trans*-2-hydroxycycloheptanecarboxylate (**IIIa,b**) (Fig. 1) were determined. The synthesis of the model compounds was published in former communications [4, 11]. The samples used for dipole moment measurements did not contain impurities [4, 11].
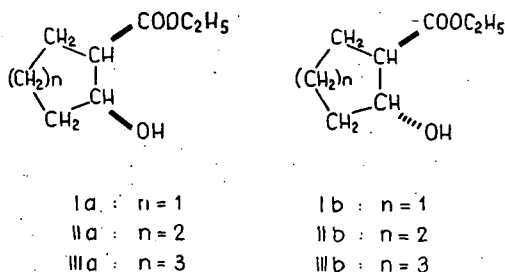
The determinations were made at $25\pm0.1°C$, the density d of the solutions was measured with a scaled dilatometer; n_D was assayed with Abbe's refractometer. The dielectric constant was recorded on a WTW Type DM 01 instrument at a frequency of 2 MHz, with a DFL 1 condenser. The cyclohexane used as solvent was dried on molecular sieve Klinosorb 4. The dipole moment was calculated according to HEDESTRAND [12] and GUGGENHEIM [13] from the following equation:

Ia : n = 1	Ib : n = 1
IIa : n = 2	IIb : n = 2
IIIa : n = 3	IIIb : n = 3

Fig. 1

$$P_\infty = \frac{\varepsilon_1-1}{\varepsilon_1-1}\left[\frac{M_2}{d_1}+\frac{M_1}{d_1^2}\beta\right]+\frac{3M_1\cdot\alpha}{(\varepsilon_1+2)^2\cdot d_1}$$

with the following symbols:

B — slope of the density *vs.* mole fraction straight line

ε_1 — value of the dielectric constant *vs.* mole fraction straight line extrapolated to infinite dilution

α — slope of the dielectric constant *vs.* mole fraction straight line

d_1 — value of the density *vs.* molar fraction straight line extrapolated to infinite dilution

M_1 — molecular weight of the solvent

M_2 — molecular weight of the solute.

The dipole moment at known K_∞ value is

$$\mu = 0.221\,23\,\sqrt{P_\infty - R},$$

where R is the sum of atomic and electronic polarization. The approximate value of R may be calculated from the molecular refraction (by multiplying with $+1.05$):

$$R = MR_D \cdot 1.05.$$

The measured data are listed in Table I.

Table I

Dipole moments of alicyclic ethyl cis- and trans-2-hydroxycarboxylates (Ia,b—IIIa,b) measured and calculated with HEDESTRAND'S *method*

Compound	X_2	$\varepsilon_{1,2}^{25}$	$d_{1,2}^{25}$		$\mu_{1,2}$ (D)
Ia	0.005 0.010 0.015 0.020	2.0586 2.0967 2.1353 2.1741	0.7805 0.7824 0.7840 0.7863	$\alpha = 7.700$ $\beta = 0.358$ $\varepsilon_1 = 2.019$ $d_1 = 0.7788$	2.75
Ib	0.005 0.010 0.015 0.020	2.0461 2.0746 2.0984 2.1281	0.7784 0.7806 0.7824 0.7847	$\alpha = 5.223$ $\beta = 0.395$ $\varepsilon_1 = 2.018$ $d_1 = 0.7765$	2.221
IIa	0.005 0.010 0.015 0.020	2.0500 2.0968 2.1298 2.1745	0.7782 0.7812 0.7832 0.7859	$\alpha = 7.730$ $\beta = 0.401$ $\varepsilon_1 = 2.010$ $d_1 = 0.7770$	2.740
IIb	0.005 0.010 0.015 0.020	2.0560 2.0867 2.1140 2.1460	0.7776 0.7805 0.7816 0.7839	$\alpha = 5.866$ $\beta = 0.4266$ $\varepsilon_1 = 2.027$ $d_1 = 0.7752$	2.359
IIIa	0.005 0.010 0.010 0.020	2.0603 2.1035 2.1360 2.1742	0.7794 0.7815 0.7834 0.7854	$\alpha = 7.710$ $\beta = 0.435$ $\varepsilon_1 = 2.022$ $d_1 = 0.776$	2.703
IIIb	0.005 0.010 0.015 0.020	2.0546 2.0835 2.1115 2.1400	0.7785 0.7810 0.7826 0.7846	$\alpha = 5.750$ $\beta = 0.407$ $\varepsilon_1 = 2.025$ $d_1 = 0.7779$	2.324

The dipole moments of the molecules were calculated by GUGGENHEIM's method [13]:

$$\mu^2 = \frac{27kT}{4\pi N} \cdot \frac{1}{d_1(\varepsilon_1 + 2)^2} \cdot (a_\varepsilon - a_n) \cdot M_2,$$

too, where

k — $1.381 \cdot 10^{-16}$ (Boltzmann constant)

N — $6.023 \cdot 10^{-23}$ (Avogadro number)

d_1^{25} — density of cyclohexane (0.77389 g/ml)

n_D^{25} — refraction index of cyclohexane (1.4233)

ε_1 — dielectric constant of cyclohexane (2.0199)

M_2 — molecular weight of the solute

a_ε — $\varepsilon_{1,2} - \varepsilon_1 = f(w_2)$

a_n — $n_{D1,2}^2 - n_{D1}^2 = f(w_2)$,

Plotting the data measured in 5 or 6 dilute solutions (of 1—7 mole percent) the above calculations were performed and the results obtained are listed in Table II.

Table III contains the comparative figures obtained by both methods. The dipole moment of the *cis*-isomers is always higher.

Based on the measured dipole moments displayed in Table III, it may be concluded that the dipole moment values are not substantially influenced by ring sizes.

Vectorial additive method for the calculation of dipole moments

The dipole moments of molecules are determined by their conformation. Knowing the approximate geometry of a given substance, its dipole moment may be calculated theoretically on the basis of its bond angles and bond moments, respectively. Using the unit vectors of the substituents of the cyclopentane and cyclohexane skeleton [14, 15], calculations based on the assumed conformation of the compounds could be performed. According to our vector analysis, and in agreement with BAUMANN's studies [8], the envelope form was chosen. BAUMANN's studies revealed that, though the substituents had no direct influence on the conformation of the ring itself, the interaction between functional groups may promote a preferential orientation. In the case of 1,2-disubstituted cyclopentanes the *trans*-isomer tends to adopt envelope conformation, consequently both substituents are in pseudoequatorial position. In the *cis*-isomer, having envelope conformation, only one of the substituents is pseudoequatorial, thus the energy content of the *cis*-isomer is higher than that of the *trans*-isomer.

In the case of *cis*- and *trans*-cyclohexane derivatives equatorial—axial and diequatorial orientation may be assigned to the substituents. The unit vectors of these conformers were used in the calculations.

The dipole moment of compounds containing freely rotating or rigidly fixed substituents, respectively, may be calculated on the basis of GILMAN's method [27] as follows:

$$\mu^2 = \mu_0^2 + \sum_{i=1}^{n} \mu_i^2 + 2 \sum_{i=1}^{n} \mu_i (\mu_0 a_{ix} + \mu_{0y} \cdot a_{iy} + \mu_{0z} \cdot a_{iz}) \times \cos Q_i +$$

$$+ 2 \sum_{i \neq j}^{n} u_i u_j (a_{ix} a_{jx} + a_{iy} a_{jy} + a_{iz} a_{jz}) \cos Q_1 Q_2,$$

wherefrom the simplified equation

$$\mu^2 = \mu_1^2 + \mu_2^2 + 2\mu_1 \mu_2 (a_{1x} a_{2x} + a_{1y} a_{2y} + a_{1z} a_{2z}) \cos Q_1 Q_2$$

Table II

Dipole moments of alicyclic ethyl cis- and trans-2-hydroxycarboxylates (Ia,b—IIIa,b) determined by GUGGENHEIM's *method* [13]

Compound	W_2	$n_{D1,2}^2 - n_{D1,2}^2$	$n_{1,2}^{25}$	$\varepsilon_{1,2} - \varepsilon_1$		μ (D)
Ia	0.011 0.020 0.030 0.040	0.0010 0.0021 0.0031 0.0041	1.42339 1.42372 1.42431 1.42445	0.0430 0.0850 0.1280 0.1710	$a_n = 0.101$ $a_\varepsilon = 4.22$	2.772
Ib	0.010 0.020 0.030 0.040	0.0009 0.0018 0.0027 0.0036	1.42335 1.42365 1.42400 1.42430	0.0320 0.0640 0.0960 0.1230	$a_n = 0.09$ $a_\varepsilon = 3.07$	2.375
IIa	0.010 0.020 0.030 0.040	0.0011 0.0021 0.0031 0.0041	1.42341 1.42372 1.42431 1.42445	0.0380 0.7700 0.1140 0.0540	$a_n = 0.101$ $a_\varepsilon = 3.80$	2.760
IIb	0.010 0.020 0.030 0.040	0.0010 0.0020 0.0030 0.0039	1.42339 1.42370 1.42405 1.42440	0.0300 0.0610 0.0930 0.1220	$a_n = 0.099$ $a_\varepsilon = 3.080$	2.479
IIIa	0.011 0.022 0.032 0.043	0.0014 0.0028 0.0041 0.0055	1.42350 1.42410 1.42450 1.42500	0.0404 0.0836 0.1175 0.1549	$a_n = 0.135$ $a_\varepsilon = 3.61$	2.784
IIIb	0.011 0.022 0.032 0.043	0.0013 0.0026 0.0040 0.0053	1.42320 1.42400 1.42449 1.42490	0.0341 0.0636 0.0916 0.1220	$a_n = 0.135$ $a_\varepsilon = 2.85$	2.462

*Note.* $\varepsilon_{1,2}^{25}$ data are to be found in Table I.

Table III

Dipole moments of alicyclic ethyl cis- and trans-2-hydroxycarboxylates calculated with GUGGENHEIM's *and* HEDESTRAND's *methods*

Compound	μ_G	μ_H	$\mu_\Delta = \mu_{cis} - \mu_{trans}$	
			G	H
Ia Ib	2.772 2.375	2.750 2.220	0.397	0.530
IIa IIb	2.760 2.479	2.740 2.359	0.281	0.381
IIIa IIIb	2.784 2.462	2.703 2.324	0.322	0.379

can be obtained, where

μ_0 — dipole moment of the rigidly fixed polar groups

$\mu_{0x}\mu_{0y}\mu_{0z}$ — projection in the direction of the coordinate axes of the dipole moment μ_0 of the groups

$\mu_i\mu_j$ — moments of the n rotating groups

Q_iQ_j — angles formed by group-moment-vectors with rotation axes a_ia_j

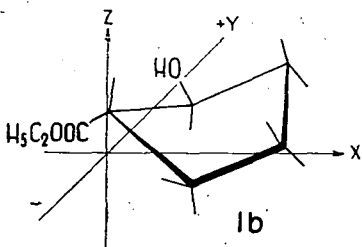$a_{ix}a_{ij}a_{iz}$ — unit vectors of the rotation axis i in the chosen coordinate system.

Bond moments and bond angles according to literature, used for the calculation of the dipole moment of ethyl *cis*- and *trans*-2-hydroxycyclopentane-carboxylate (**Ia,b**), are presented in Fig. 2.
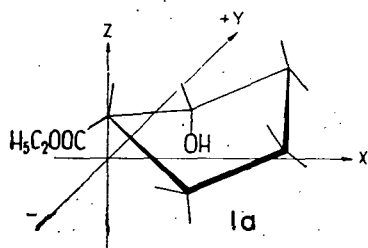
$$\vec{m}_{C_5H_{10}} = 0\ D \qquad [16]$$
$$\vec{m}_{OH} = 1.6\ D \qquad [18]$$
$$\vec{m}_{COOC_2H_5} = 1.8\ D \qquad [17]$$

$R \xrightarrow{\quad Q_2 \quad} X$ = 89° rotation angle of the carbethoxy group around axis a_1 [17]

$R \xrightarrow{\quad Q_1 \quad} X$ = 63° rotation angle of the hydroxy group around axis a_2 [18]
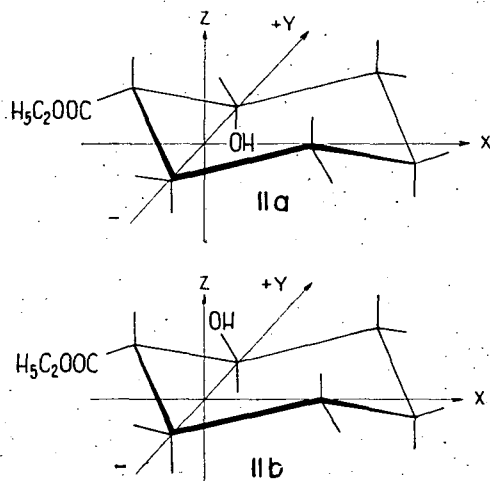
Fig. 2

Table IV lists the unit vectors of cyclopentane substituents [14] in the chosen coordinate system.

Table IV

Unit vectors of cyclopentane substituents [14] in the chosen coordinate system

Position	Orientation	Unit vectors of substituents		
		x	y	z
1	equatorial	0.169	0.000	0.986
2	axial	−0.280	0.900	0.332
3	equatorial	−0.114	−0.039	−0.992

Bond moments and bond angles according to literature, used for the calculation of the dipole moment of ethyl *cis*- and *trans*-2-hydroxycyclohexanecarboxylate, are presented in Fig. 3.

mC_6H_1 $= 0$ D [16]
m_{OH} $= 1.6$ D [18]
$\overline{m}COOC_2H$ $= 1.8$ D [17]

$X = 63°$ rotation angle of hydroxy group around axis a_2 [16]

$X = 89°$ rotation angle of carbethoxy group around axis a_1 [17]
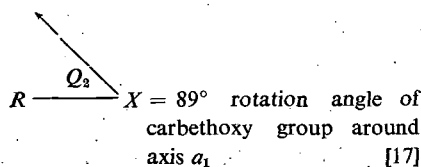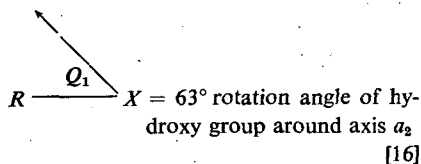

Fig. 3

Table V lists the unit vectors of cyclohexane substituents [15] in the chosen coordinate system.

Table V

Unit vectors of cyclohexane substituents [15] in the chosen coordinate system

Position	Orientation	Unit vectors of substituents		
		x	y	z
1	equatorial	−0.997	0.000	0.077
2	axial	−0.333	−0.067	0.940
2	equatorial	−0.333	−0.804	−0.492

Pertinent literature data of ethyl *cis*- and *trans*-2-hydroxycycloheptanecarboxylate were not available, consequently no vectorial calculations could be performed.

Using the above values of the substituent unit vectors, bond moments and bond angles, the dipole moments summarized in Table VI were obtained. ·

Table VI demonstrates the good agreement between the dipole moments calculated according to the supposed conformation and the measured values. This agreement is especially striking in the case of the *trans*-isomers. The discrepancies experienced in the *cis*-isomers will be dealt with later.

Table VI

Calculated and measured dipole moments of alicyclic ethyl cis- and trans-2-hydroxycarboxylates (Ia,b, IIa,b)

Compound	μ_{calc}	$\mu_{measured}$		$\mu_\Delta = \mu_{measured} - \mu_{calc}$	
		G	H	G	H
Ia	2.390	2.772	2.750	+0.372	+0.350
Ib	2.390	2.375	2.220	−0.015	+0.170
IIa	2.40	2.760	2.740	+0.360	+0.340
IIb	2.40	2.479	2.359	+0.079	−0.041

Discussion

Comparing the measured dipole moments of alicyclic ethyl *cis*- and *trans*-2-hydroxycarboxylates, it is apparent that the dipole moments of the *cis*-isomers are higher. Spectroscopic [5, 6] as well as other studies [9] revealed the presence of an intramolecular hydrogen bond in the *cis*-isomers.

The dipole moment of the *cis*-isomers should be lower due to the polarity-lowering effect of the intramolecular hydrogen bond. Other investigations [19], however, draw the attention to the circumstance that an intramolecular hydrogen bond enhances the rigidity of the skeleton, and thus increases the dipole moment. The increase in dipole moment of the *cis*-isomers may be attributed to the fact, that, due to the relative position of the functional groups in the *cis*-isomers, the skeleton of the molecule is less coplanar than in the *trans*-isomers with diequatorial substituents. Regarding the comparatively good agreement between measured and calculated dipole moments, it may be assumed that, under the applied conditions of measurement, the intermolecular hydrogen bond of the *cis*-isomers may be omitted, consequently, in the case of the *cis*-isomers of cyclopentane, cyclohexane, and cycloheptane derivatives, the presence of the intramolecular hydrogen bond may be considered the determining factor.

Knowing the dipole moments, the respective molecules may be studied according to the conformation rule. On the basis of AUWERS's equation [20, 21], in the case of *cis*—*trans*-isomers, it is the *cis*-isomer which has higher density, refraction index and lower molar refraction. This rule, or its modified form [26] can be used for comparing stereoisomers, though only interpretations on the basis of the conformation rule may lead to correct results [22]. ELIEL assumes that the less stable conformation may be assigned to the isomer of higher boiling point, refraction index, and density; *i.e.* it is the isomer of smaller molecular volume which has higher enthalpy. Isomers with conformations in which all substituents are equatorial, have lower boiling points, density and refraction index than those containing axial substituents as well.

Originally, the conformation rule was set up for cyclohexane derivatives; nevertheless it could be successfully applied to some cyclopropane, cyclopentane, cycloheptane and cyclooctane derivatives, too [23]. Its interpretation is the most clearcut in the case of hydrocarbons. Strong dipole—dipole interactions promote stronger association of the respective molecules through the increased dipole

moment; *i.e.* as a rule, in the case of dipole moments showing marked difference, the isomer having a higher dipole moment has a higher boiling point as well. The conformation rule, however, is not valid for isomers having highly different dipole moments. In this case ARKEL's dipole rule [24] should be applied, which is valid for broader ranges of dipole moment values (0.2 D).

ELIEL [25] demonstrated that in the case of polar substituents (OH, NH₂) boiling points do not follow the conformation rule, and the diequatorial *trans*-isomer has the higher boiling point. On the basis of his results obtained with 2-, 3-, and 4-methylcyclohexanols, he interpreted this fact with the circumstance that the intermolacular hydrogen bonds with the equatorial hydroxyl are more pronounced than in the case of axial conformers.

As a conclusion, van ALKEL's rule can be applied in the case of our model compounds. Components having higher physical constants (except boiling point and viscosity) have higher dipole moments as well. The higher boiling points of the *trans*-isomers may be due to intermolecular hydrogen bonds, which promote association. The intermolecular association of *trans*-isomers is confirmed both by spectroscopic studies and gas chromatographic data [4]. Dipole moment measurements were in agreement with LUTSKII's former observations [19] that in this type of molecules, beyond dipole—dipole interactions, intramolecular hydrogen bonds, enhancing the rigidity of the skeleton, may play a decisive role.

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СТЕРЕОХИМИЧЕСКИЕ ИССЛЕДОВАНИЯ, XX
ИЗУЧЕНИЕ ЦИКЛИЧЕСКИХ 2-ОКСИКАРБОНОВЫХ КИСЛОТ, III
СВЯЗЬ МЕЖДУ МОЛЕКУЛЯРНОЙ СТРУКТУРОЙ И ДИПОЛЬНЫМИ МОМЕНТАМИ ЭТИЛОВЫХ ЭФИРОВ *ЦИС-* И *ТРАНС-*2-ОКСИКАРБОНОВОЙ КИСЛОТЫ

Е. Томори, Ш. Ференци-Грес, Г. Бернат

Изучены дипольные моменты этиловых эфиров *цис-* и *транс-*2-оксикарбоновой кислоты. При известных величинах дипольных моментов представляется возможность проверки применимости конформационного правила. Хорошее совпадение между измеренными и рассчитанными величинами дипольных моментов указывает на вероятность наличия внутримолекулярных водородных связей у *цис-*изомеров и межмолекулярных — у *транс-*изомеров.