Journal of Chromatography, 236 (1982) 105–112
Elsevier Scientific Publishing Company, Amsterdam — Printed in The Netherlands

CHROM. 14,371

STUDY OF ALICYCLIC ETHYL *cis*- AND *trans*-2-HYDROXYCARBOXYLATES BY GAS CHROMATOGRAPHY

ÉVA TOMORI
Institute for Drug Research, P.O. Box 82, H-1325 Budapest (Hungary)
(First received June 4th, 1981; revised manuscript received September 15th, 1981)

SUMMARY

The structure and conformation of alicyclic *cis*- and *trans*-2-hydroxycarboxylates were studied by gas chromatography. As these substances serve as starting materials for the synthesis of stereospecific alicyclic compounds, it was of major importance to establish the stereochemical uniformity of each isomer. Further, the study of the structure and conformation of the iosmers was important *per se*, as these compounds, containing hydroxy and carbethoxy groups in vicinal positions, are prone to form intramolecular and intermolecular hydrogen bonds. Gas chromatography was the method of choice for the study of these hydrogen bonded structures.

INTRODUCTION

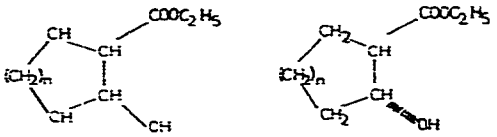
The synthesis of *cis*- and *trans*-2-hydroxycyclopentanecarboxylic acid[1], *cis*- and *trans*-2-hydroxycyclohexanecarboxylic acid[2], *cis*- and *trans*-2-hydroxycycloheptanecarboxylic acid[3,4] and *cis*- and *trans*-2-hydroxycyclooctanecarboxylic acid[4] has been reported. In the study of these compounds, infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy[5,6] were primarily used for the conformational analysis of intramolecular and intermolecular hydrogen bonds and the elucidation of the preferred conformation of the substituents. In addition to spectroscopic studies, Castells and Palau[5] also used viscosity measurements to confirm that the *cis*-isomer of 2-hydroxycyclohexanecarboxylic acid is less associated than the *trans*-isomer. In the course of conformational analyses, Baumann and Möhrle[7,8] determined the equilibrium constants of the isomers[9] and found that equatorial hydroxy groups promote a more pronounced association than axial groups. The preferred conformation of Ia and Ib (Fig. 1) was established, in agreement with literature data[10], by Baumann and Möhrle on the basis of NMR spectra[8] and by Bernáth *et al.*[4] on the basis of both IR and NMR spectra, and the measurement of the rate of chromic acid oxidation and dissociation constants[6]. According to NMR spectra, in *cis*-2-hydroxycyclohexanecarboxylic acid the equatorial position may be assigned to the carboxy group and the axial position to the hydroxy group[6].

By calculating the dipole moments of compounds I–III (Fig. 1), a means was

0021-9673/82/0000–0000/$02.75

established for establishing configuration–physical data relationships[11]. In earlier studies the retention index–molecular structure relationship for alicyclic *cis*- and *trans*-2-hydroxycarboxylates was studied by gas chromatography with the help of empirical equations[12] on the basis of the additivity of gas chromatographic interactions.

In this study the configuration of isomers of compounds I–IV (Fig. 1), the interactions of vicinal hydroxy and carbethoxy groups and the interactions of the stationary phase and individual groups were examined in detail.



Ia: n=1 Ib: n=1

IIa: n=2 IIb: n=2

IIIa: n=3 IIIb: n=3

IVa: n=4 IVb: n=4

Fig. 1. Model compounds

EXPERIMENTAL

Materials and reagents

The silylating agents hexamethyldisilazane (HMDS) and trimethylchlorosilane (TCMS) were obtained from Pierce (Rockford, IL, U.S.A.) and the stationary phases SE-30 and Reoplex 400 and the carrier Chromosorb W AW DMCS (80-100 mesh) from Applied Science Labs. (State College, PA, U.S.A.). The synthesis of model compounds was reported in refs. 4 and 11.

Gas chromatography

An HP 5830 gas chromatograph equipped with a flame-ionization detector was used. The glass columns (2 m × 4 mm I.D.) were packed with the stationary phases SE-30 (5%) and Reoplex 400 (20%) (columns A and B, respectively). The injection temperature was 240°C, the column temperatures were (A) 120°C and (B) 160°C and the detector temperature was 240°C. The carrier gas (nitrogen) flow-rate was 45 ml/min.

Derivatization

Amounts of 1 mg of compounds I–IV were made to react with the silylating reagent pyridine–HMDS–TMCS (2:2:1) at room temperature for 1 h. A 1-μl volume of each sample was injected into the apparatus.

RESULTS AND DISCUSSION

The physical data for ethyl *cis*- and *trans*-2-hydroxycyclopentanecarboxylate

(Ia and b), ethyl *cis*- and *trans*-2-hydroxycyclohexanecarboxylate (IIa and b), ethyl *cis*- and *trans*-2-hydroxycycloheptanecarboxylate (IIIa and b) and ethyl *cis*- and *trans*-2-hydroxycyclooctanecarboxylate (IVa and b) are compiled in Table I. The physical data for the *cis*-isomers are generally higher than those for the *trans*-isomers, except for their boiling points and viscosities. These types of compounds follow Van Alkel's rule[11], and the higher boiling points of the *trans*-isomers may be due to associated molecules. This property of the molecules is retained under gas-chromatographic conditions, also as is apparent from the relative retention data in Table II, the *trans*-isomers being eluted from both columns with higher retention times than the *cis*-isomers. Compared with the more hindered *cis*-isomers, in the *trans*-isomers the equatorial hydroxy group can interact freely with the stationary phase, resulting in higher retention times. Möhrle and Baumann[9], in assessing the equilibrium constants of the compounds, concluded that association is much better promoted by equatorial than by axial hydroxy groups. Under gas chromatographic conditions no significant association occurs, but it remains an inherent property of the *trans*-isomers to interact more intensely than *cis*-isomers with the stationary phase. Evaluating the separation

TABLE I

PHYSICAL DATA FOR ALICYCLIC ETHYL *cis*- AND *trans*-2-HYDROXYCARBOXYLATES

Compound	*Isomer*	*B.p. (°C)*		n_D^{25}		η^{25} *(lit.)*
		Measured	*Literature*	*Measured*	*Literature*	
Ethyl 2-hydroxy-cyclopentane-carboxylate	*cis*	129–130 (42 mmHg)	54–56 (0.1–0.2 mmHg) (ref. 10)	1.4551	1.4551 (ref. 10)	0.075 (ref. 10)
	trans	139–140 (42 mmHg)	57.5–60 (0.1–0.2 mmHg) (ref. 10)	1.4536	1.4534 (ref. 10)	0.084 (ref. 10)
Ethyl 2-hydroxy-cyclohexane-carboxylate	*cis*	134–135 (39–40 mmHg)		1.4600	1.4600 (ref. 17)	0.109 (ref. 17)
	trans	143–144 (39–40 mmHg)	120–121 (30 mmHg) (ref. 17)	1.4596	1.4596 (ref. 17)	0.191 (ref. 17)
Ethyl 2-hydroxy-cycloheptane-carboxylate	*cis*	142–143 (40 mmHg)		1.4684	1.4683 (ref. 11)	
	trans	148–149 (40 mmHg)		1.4670	1.4675 (ref. 17)	
Ethyl 2-hydroxy-cyclooctane-carboxylate	*cis*	147–148 (40 mmHg)		1.4750		
	trans	151–152 (40 mmHg)		1.4749		

TABLE II

RELATIVE RETENTIONS AND SEPARATION FACTORS OF ALICYCLIC ETHYL *cis*- AND *trans*-2-HYDROXYCARBOXYLATES

Compound	*Relative retention**		*Separation factor (α)***	
	5% SE-30, 120°C	*20% PEGA, 160°C*	*5% SE-30, 120°C*	*20% PEGA, 160°C*
Ia	4.50	4.74	1.18	1.62
Ib	5.30	7.70		
IIa	7.10	6.70	1.12	1.33
IIb	7.90	8.90		
IIIa	13.70	9.82	1.09	1.33
IIIb	15.00	13.10		
IVa	26.77	17.83	1.00	1.28
IVb	26.77	22.86		
Cyclohexanol	1.00 (2 min)	1.00 (2.2 min)		

* t' relative to cyclohexanol = 1.00.

** $\alpha = \frac{t'_{trans}}{t'_{cis}}$.

factors in Table II, it is apparent that the highest value was obtained in the gas chromatography of compounds Ia and b. This is in good agreement with spectroscopic data[10], confirming that there is a strong intermolecular interaction in the Ib isomer. At the same time we failed to achieve the separation of isomers IVa and b on SE-30. Compounds with a cyclooctane skeleton are the first representatives of medium-sized rings. The cyclooctane ring is flexible and the apolar stationary phase fails to promote the preferential positioning of the isomers which would permit separation. There exists a complex equilibrium as regards isomer conformation. The bulky carbethoxy group assumes preferentially an equatorial position, while the smaller hydroxy group may be either equatorial or axial. However, there is no question of an exclusively equatorial or axial orientation, only of a major proportion of one of the conformers. In Fig. 2 a representative example of the conformational equilibrium of compounds Ia and b is demonstrated.

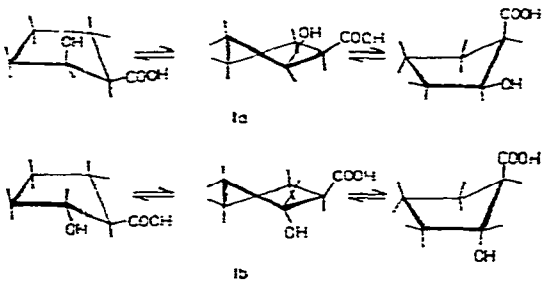


Fig. 2. Conformational equilibrium of ethyl *cis*- and *trans*-2-hydroxycyclopentanecarboxylate.

TABLE III

RELATIVE RETENTIONS AND SEPARATION FACTORS OF TRIMETHYLSILYLATED ALICYCLIC ETHYL *cis*- AND *trans*-2-HYDROXYCARBOXYLATES

Compound	*Relative retention**					*Separation factor (α)***				
	5% SE-30			*20% PEGA*		*5% SE-30*			*20% PEGA*	
	120°C	*140°C*	*160°C*	*120°C*	*160°C*	*120°C*	*140°C*	*160°C*	*120°C*	*160°C*
Ia	9.83			2.56		0.81			0.66	
Ib	8.00			1.71						
Cyclohexanol	1.00 (2.4 min)			1.00 (6.4 min)						
IIa		10.00		4.27			1.00		0.84	
IIb		10.00		3.55						
Cyclohexanol		1.00 (1.4 min)		1.00 (6.4 min)						
IIIa			11.00	6.25				1.00	1.00	
IIIb			11.00	6.25						
Cyclohexanol			1.00 (0.65 min)	1.00 (6.4 min)						
IVa			15.00		7.51			1.00		1.00
IVb			15.00		7.51					
Cyclohexanol			1.00 (0.52 min)		1.00 (4.6 min)					

* t' relative to cyclohexanol = 1.00.

** $\alpha = \frac{t_{trans}}{t_{cis}}$.

If the compounds are trimethylsilylated and subsequently submitted to gas chromatography (Table III), the elution order of compounds Ia and b and IIa and b is reversed, and compounds IIIa and b and IVa and b could not be separated on either of the stationary phases. The existence of an intramolecular hydrogen bond between the carbethoxy and hydroxy groups, reducing the polarity of the parent molecule, which is consequently eluted at a lower retention time, is confirmed by the reversal of the elution order following derivatization. In the presence of the protective group no intramolecular hydrogen bond is formed, and the components are eluted according to their physical properties. The rate of interaction between the trimethylsilyl *cis*- and *trans*-isomers and the stationary phase is reduced, in the case of compounds IIIa and b and IVa and b, to such an extent that the isomers cannot even be separated (see the separation factors in Table III). The α values in Table II decrease with increasing ring size; as the strength of intramolecular hydrogen bonds is lowered even the *cis*-isomers may show stronger interactions with the stationary phase.

The separation may be affected, in addition to hydrogen bond interactions, by the existence of different conformers. Under the conditions of gas chromatography the bulky trimethylsilyl group is in an equatorial position whereas the carbethoxy

group of compounds Ia and b and IIa and b may be either in an axial or an equatorial position. In compounds IIIa and b and IVa and b the bulky trimethylsilyl group is always equatorial and the carbethoxy group connected to the carbon atom may easily take on a conformation where there is practically no difference between the angle of the two groups in the *cis*- and *trans*-isomers.

In Fig. 3 the conformational equilibrium of compounds IIa and b and IIa and b-TMS is demonstrated.

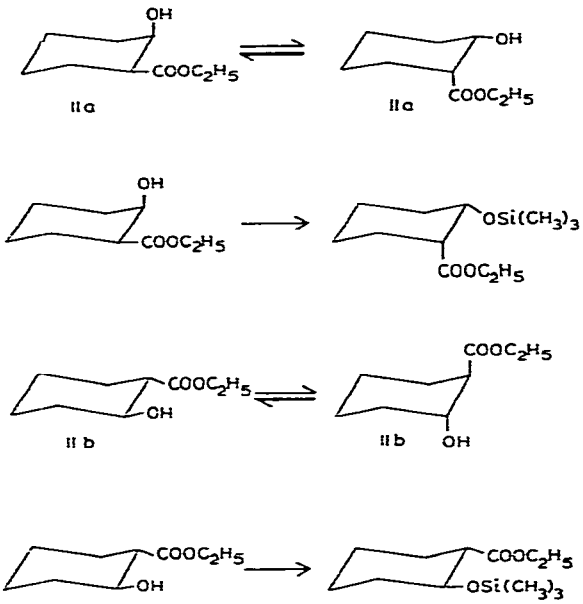


Fig. 3. Conformational equilibrium of compounds IIa and b and IIa- and b-TMS.

In the studies of intermolecular hydrogen bonds the retention indices of the compounds were measured as a function of column temperature. With increasing temperature the retention index increments of the *cis*-isomers were scarcely surpassed by those of the trans-isomers (Table IV). The interaction between the hydroxy and carbethoxy groups was reduced in the *cis*- and *trans*-isomer, respectively, with increasing column temperature and increasing ring size.

The interaction between the stationary phase and the axial and equatorial hydroxyl groups was enhanced.

The increase in retention indices with increasing column temperature indicates that both isomers are prone to enhanced association and interaction with the stationary phase. The importance of solubility differences in the separation of the isomers is well demonstrated by the standard molar free energy differences (Table V). With isomers of compounds I–III it can be concluded that the higher are the negative values the higher are the solubility differences between the pairs of isomers. As the conformation and the standard molar free energy differences are strongly correlated, it is assumed that the stronger the stabilizing effect exerted by the stationary phase on the isomers the better is the separation.

TABLE IV

RETENTION INDICES OF ALICYCLIC ETHYL *cis*- AND *trans*-2-HYDROXYCARBOXYLATES AS A FUNCTION OF COLUMN TEMPERATURE

Stationary phase: PEGA.

Compound	*Isomer*	*Column temperature (°C)*							
		150		*160*		*170*		*180*	
		*I**	*b***	*I**	*b***	*I**	*b***	*I**	*b***
Ethyl 2-hydroxy-cyclopentane-carboxylate	*cis*	1934	0.159	1944	0.165	1964	0.151	1974	0.141
	trans	2074	0.157	2082	0.154	2101	0.146	2110	0.141
Ethyl 2-hydroxy-cyclohexane-carboxylate	*cis*	2003	0.157	2017	0.154	2038	0.146	2048	0.141
	trans	2106	0.157	2116	0.154	2134	0.146	2144	0.143
Ethyl 2-hydroxy-cycloheptane-carboxylate	*cis*	2168	0.157	2180	0.154	2202	0.155	2218	0.148
	trans	2273	0.157	2283	0.160	2306	0.146	2318	0.148
Ethyl 2-hydroxy-cyclooctane-carboxylate	*cis*	2310	0.159	2328	0.161	2353	0.146	2361	0.148
	trans	2377	0.159	2391	0.161	2416	0.160	2422	0.140

* I = retention index (index units).
** b = slope of n-alkane curve.

TABLE V

SEPARATION FACTORS (α) MEASURED AT 120°C AND CALCULATED STANDARD MOLAR FREE ENERGY DIFFERENCES OF ALICYCLIC ETHYL *cis*- AND *trans*-2-HYDROXY-CARBOXYLATES $\Delta(\Delta G)^0$

Compound	*Stationary phase*			
	5% SE-30		*20% PEGA*	
	$\Delta(\Delta G)^0$ *(cal/mole)*	α*	$\Delta(\Delta G)^0$ *(cal/mole)*	α*
Ethyl 2-hydroxy-cyclopentane-carboxylate	−129.0	1.18	−548.1	2.02
Ethyl 2-hydroxy-cyclohexane-carboxylate	−59.9	1.08	−440.7	1.76
Ethyl 2-hydroxy-cycloheptane-carboxylate	−67.2	1.09	−356.6	1.58

* $\alpha = \frac{t_{trans}}{t_{cis}}$.

The $\Delta(\Delta G^0)$ values were calculated from the equation

$$\Delta(\Delta G^0) = -RT\ln\alpha$$

The α values are given in Table V.

Vapour pressure differences also play an important role in the separation of the isomers. Isomers of compounds I–III could be separated by fractional distillation on a high-resolution column. The separation of isomers IVa and b required multiple fractionation and a stereochemically uniform product could be obtained only by preparative gas chromatography[4].

On the basis of relative retentions, the temperature dependence of the retention index and standard molar free energy data, it can be concluded that the preferred conformation of the substituents promotes mainly intramolecular and partly intermolecular interactions in the *cis*-isomers, whereas in the *trans*-isomers the intermolecular interactions are uniformly predominant, *i.e.*, hydrogen bonded structures exist even under the conditions of gas chromatography.

REFERENCES

1 J. Pascual, J. Sistoré and J. Regas, *J. Chem. Soc.*, (1943) 1949.
2 J. Pascual and J. Castells, *J. Amer. Chem. Soc.*, 74 (1952) 2899.
3 J. Pacual and J. Castells, *An. R. Soc. Esp. Fis. Quim., Ser. B*, 63 (1967) 455.
4 G. Bernáth, Gy. Göndös, P. Márai and L. Gera, *Acta Chim. Acad. Sci. Hung.*, 74 (1972) 471.
5 J. Castells and J. Palau, *J. Chem. Soc.*, (1964) 4938.
6 G. Bernáth, P. Sohár, K. L. Láng, J. Tornyai and Ö. K. I. Kovács, *Acta Chim. Acad. Sci. Hung.*, 64 (1970) 81.
7 H. Baumann and H. Möhrle, *Tetrahedron*, 25 (1969) 135.
8 H. Baumann and H. Möhrle, *Tetrahedron*, 23 (1967) 4331.
9 H. Möhrle and H. Baumann, *Justus Liebigs Ann. Chem.*, 716 (1968) 61.
10 H. R. Buys, *Conformational Investigations on Five-Membered Ring Compounds*, *Thesis*, State University, Leiden; Bronder-Offset, Rotterdam, 1968, and references cited therein.
11 É. Tomori, S. Ferenczi-Gresz and G. Bernáth, *Acta Phys. Chim. Szeged*, 20 (1974) 129.
12 É. Tomori, *Magy. Kém. Foly.*, 79 (1973) 488.