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Conformational Composition of Stereoisomers of 2,4,5-Trisubstituted 1,3,2-Dioxaborinanes

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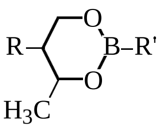
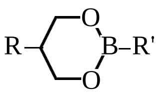
Abstract—^{1}H NMR spectroscopy and MM+ and AM1 calculations were used for configurational assessment of stereoisomers of 4-methyl-2,5-disubstituted 1,3,2-dioxaborinanes (differing in the configuration of the ring C^4 atom). The molecules are conformationally inhomogeneous; this is due to the internal rotation of the substituent at the C^5 atom, while in the *cis* isomers, in addition, by the equilibrium between the *S*-4*e*5*a* and *S*-4*a*5*e* *sofa* conformations, shifted to the latter form.

Most six-membered boric esters characteristically adopt a *sofa* conformation which allows the most effective interaction between the *n*-electron pairs of the oxygen atoms and the unoccupied orbital of the boron atom [1–7]. However, unsymmerically substituted 4-alkyl or 4,5-dimethyl derivatives are very flexible conformationally and thus feature conformational inhomogeneity [8–10]. The present work is a continuation of our stereochemical studies on cyclic boric esters with several chiral centers in the hydrocarbon part of the ring and is aimed at conformational assessment of stereoisomers of 2,4,5-trisubstituted 1,3,2-dioxaborinanes **I**–**IV** in comparison with the corresponding 2,5-disubstituted analogs **V**–**VII**, by means of ^{1}H NMR spectroscopy in combination with empirical (MM+ [11]) and semiempirical (AM1 [12, 13]) calculations by the HyperChem software [14].



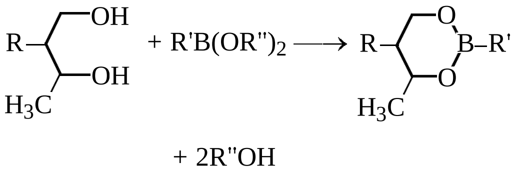
I–**IV**



V–**VII**

I, R = C_2H_5, R' = CH_3 (**a**), *i*-C_3H_7 (**b**); **II**, R = C_3H_7, R' = CH_3 (**a**), *i*-C_3H_7 (**b**); **III**, R = C_4H_9, R' = CH_3 (**a**), C_4H_9 (**b**); **IV**, R = CH_2=$CHCH_2$, R' = CH_3 (**a**), *i*-C_4H_9 (**b**); **V**, R = C_2H_5, R' = CH_3; **VI**, R = C_4H_9, R' = *i*-C_4H_9; **VII**, R = CH_2=$CHCH_2$, R' = *i*-C_3H_7.

Compounds **I**–**VII** were obtained from the corresponding 1,3-diols and acyclic esters of substituted boric acids [1].



Parameters of the ^{1}H NMR spectra of compounds **I**–**VII** (reported in [2, 5, 15] and obtained in the present work) are listed in Table 1. The coupling constants $^3J_{AX}$ in the spectra of stereoisomers of compounds **Ib**–**IVb** suggest equatorial or pseudoequatorial orientation of the substituent on the C^5 atom, while the differences in the chemical shifts of protons of the C^4–CH_3 point to the fact that the stereoisomers differ in the configuration of the C^4 atom. The magnitudes of vicinal coupling constants and the integral intensities of all proton groups suggest *cis* configuration of the major isomers and preferentially axial or pseudoaxial location of the methyl group at C^4. Further evidence for this suggestion comes from the observation of long-range coupling of equatorial H_B and $H_{A'}$ nuclei (*W* system; ^4J 0.8–0.9 Hz), which is uncharacteristic of the *trans* isomers. A distinctive feature of the *cis* derivatives is a less considerable, compared with the *trans* isomers, nonequivalence the H_A and H_B protons. The *trans* isomers of compounds **Ib**–**IVb** in certain spectral parameters ($\Delta\delta_{AB}$, coupling constants) are close to the corresponding 2,5-disubstituted 1,3,2-dioxaborinanes **V**–**VII**. The isopropyl group at the boron atom appears as an abnormal singlet [16, 17]. It should also be noted that the stereoisomeric composition of the parent 1,3-diols [18,19] is almost coincident with the ratio of the *cis* and *trans* isomers of compounds **Ib**–**IVb** (^{1}H NMR and GLC data), and, therefore, in

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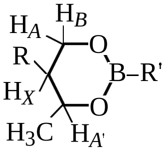
Table 1. Parameters of the ^{1}H NMR spectra of cyclic boronic esters **I–VII**



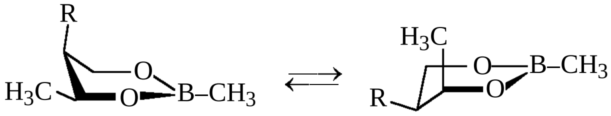
Comp. no.	Chemical shift, δ, ppm						*J*, Hz				*cis* : *trans* Ratio	
	H_A	H_B	$\Delta\delta_{AB}$	$H_{A'}$	H_X	C^4–CH_3	$^3J_{AX}$	$^3J_{BX}$	$^3J_{A'X}$	$^4J_{A'B}$	^{1}H NMR[a]	GLC
cis-**Ib**	3.74	3.86	0.12	4.14	1.86	1.13	9.4	4.6	4.5	<0.8	52:48	55:45
trans-**Ib**	3.59	4.00	0.41	3.81	1.44	1.25	8.8	4.0	8.0	–		
V	3.60	4.00	0.40	–	1.89	–	10.3	4.2	–	–	–	–
cis-**IIb**	3.74	3.86	0.12	4.15	1.98	1.14	9.5	4.7	4.2	0.8	60:40	60:40
trans-**IIb**	3.58	4.00	0.42	3.80	1.34	1.16	9.3	4.2	8.1	–		
cis-**IIIb**	3.69	3.76	0.07	4.04	1.87	1.06	9.5	4.7	4.8	0.9	62:38	68:32
trans-**IIIb**	3.49	3.90	0.41	3.73	1.43	1.17	9.2	4.2	8.0	–		
VI	3.60	4.00	0.40	–	1.95	–	10.2	4.3	–	–	–	–
cis-**IVb**	3.78	3.87	0.09	4.17	1.64	1.20	9.0	4.3	4.2	0.8	67:33	64:36
trans-**IVb**	3.63	3.98	0.35	3.82	2.00	1.29	8.0	4.2	8.0	–		
VII	3.63	3.99	0.36	–	2.01	–	8.7	3.9	–	–	–	–

[a] From the integral intensities of the C^4–CH_3 proton signals.

contrast to our previous conclusions [20, 21], we have to suggest here that 2,4,5-trisubstituted 1,3,2-dioxaborinanes are formed in a stereospecific fashion: Like with 4,5-disubstituted 1,3-dioxanes [18, 19], *threo* diols give exclusively *trans*, while *erythro* diols, exclusively *cis* isomers of cyclic boronic esters.

It is known that the *cis* and *trans* isomers of 5-alkyl-4-methyl-1,3-dioxanes have different configurations of the C^5 atom [18, 19], whereas those of compounds **Ib**–**IVb**, like with 5-isopropyl-2,2,4-trimethyl-1,3-dioxa-2-silacyclohexane [22], differ in the configuration of the C^4 atom. Thus fact can be explained either by weakened nonbonded interactions in organosilicon derivatives or by decreased number of such interactions in six-membered cyclic boronic esters containing an atom with a planar configuration (trigonal boron) in the 2 position of the ring [8]. In this case, the axial orientation of the C^4–CH_3 group in the *cis* isomers gets to be preferred over the axial orientation of of the alkyl group on C^5. Evidence for these conclusions comes from the relative energies of model 5-alkyl-2,4-dimethyl-1,3,2-dioxaborinanes **Ia**–**IVa**, estimated by the MM+ and AM1 methods. The potential energy surfaces for all the *trans* isomers (internal rotation of the substituent at C^5 was not included) show a single minimum corresponding to the *sofa* conformer having both 4- and 5-substituents equatorial (*S*-4*e*5*e*), while those for the *cis* isomers have two minima: *S*-4*e*5*a* and *S*-4*a*5*e*, the latter being the major one (Table 2).

Table 2. Relative energies of the *S*-4*a*5*e* and *S*-4*e*5*a* conformers of the *cis* isomers of esters **Ia**–**IVa**, kcal/mol[a]



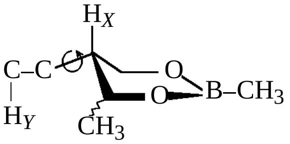
S-4*e*5*a* *S*-4*a*5*e*

R	ΔE = E(*S*-4*e*5*a*) – E(*S*-4*a*5*e*)	
	MM+	AM1
C_2H_5	0.7	1.5
C_3H_7	1.8	1.9
C_4H_9	1.1	1.2
CH_2=CH–CH_2	0.8	1.5

[a] For the most favorable conformation of group R, formed by internal rotation about the C^5–R bond.

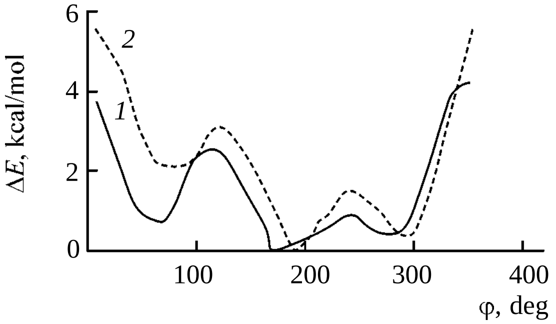
For a more detailed conformational assessment of the *cis* and *trans* isomers of compounds **Ib**–**IVb**, we calculated by the MM+ and AM1 methods with full geometry optimization the relative energies of 2-methyl derivatives **Ia**–**IVa**, varying the torsion angle of the substituent at the C^5 atom [torsion angle

Table 3. Minima and maxima (max) on the two-dimensional section curve of the potential energy surfaces of the *cis* and *trans* isomers of cyclic esters **Ia**–**IVa**, kcal/mol, at various torsion angles φ(H_XCCH_Y), deg

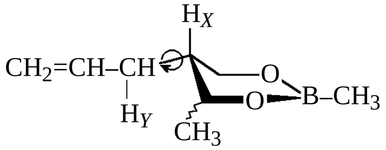


Comp. no.	MM+		AM1		Comp. no.	MM+		AM1	
	φ	Δ*E*	φ	Δ*E*		φ	Δ*E*	φ	Δ*E*
cis-**Ia**	299	0.0	45	0.0	*cis*-**IIIa**	300	0.0	189	0.0
	50	0.1	300	0.3		171	0.4	294	0.3
	160	2.5	155	2.3		81	2.6	88	2.2
	0	2.9 (max)	0	1.4 (max)		235	3.1 (max)	238	1.4 (max)
	120	4.1 (max)	120	3.1 (max)		115	4.6 (max)	119	3.2 (max)
	240	5.8 (max)	235	5.3 (max)		0	7.0 (max)	0	5.5 (max)
trans-**Ia**	61	0.0	52	0.0	*trans*-**IIIa**	60	0.0	60	0.0
	176	0.2	341	0.6		180	0.2	340	0.4
	335	1.4	180	1.0		340	1.5	180	1.0
	0	2.1 (max)	0	0.8 (max)		0	2.1 (max)	0	0.6 (max)
	120	4.0 (max)	120	2.7 (max)		120	4.2 (max)	120	2.7 (max)
	240	5.6 (max)	240	4.3 (max)		240	5.8 (max)	240	4.3 (max)
cis-**IIa**	300	0.0	42	0.0	*cis*-**IVa**	184	0.0	189	0.0
	55	0.3	300	0.3		300	0.3	293	0.4
	160	2.5	150	2.3		78	2.2	80	2.1
	0	2.9 (max)	0	1.3 (max)		236	3.6 (max)	239	1.5 (max)
	120	4.2 (max)	120	3.1 (max)		115	4.2 (max)	120	3.1 (max)
cis-**IIa**	240	5.9 (max)	240	5.4 (max)		0	6.1 (max)	0	5.5 (max)
trans-**IIa**	60	0.0	50	0.0	*trans*-**IVa**	56	0.0	170	0.0
	180	0.1	320	0.5		177	0.2	276	0.4
	340	1.3	180	1.0		288	0.5	66	0.7
	0	1.9 (max)	0	1.0 (max)		244	2.6 (max)	241	0.9 (max)
	120	4.0 (max)	120	2.7 (max)		100	3.8 (max)	108	3.8 (max)
	240	5.6 (max)	240	4.3 (max)		0	5.9 (max)	0	4.2 (max)

φ(H_XCCH_Y)]. The base conformations of the *trans* and *cis* isomers were taken to be *S*-4*e*5*e* and *S*-4*a*5*e*, respectively. The resulting data listed in Table 3 and depicted in the figure (with ester **IVa** as example) show that rotation of equatorial



Plots of the total energies of the (*1*) *trans* and (*2*) *cis* isomers of ester **IVa** vs. torsion angle φ(H_YCHC^5H_X).



IVa

substituent R gives rise to equilibria between the *sofa* and *half-chair* (*HC*-1 and *HC*-2) conformers with different degrees of distortion of separate fragments of the heteroring.

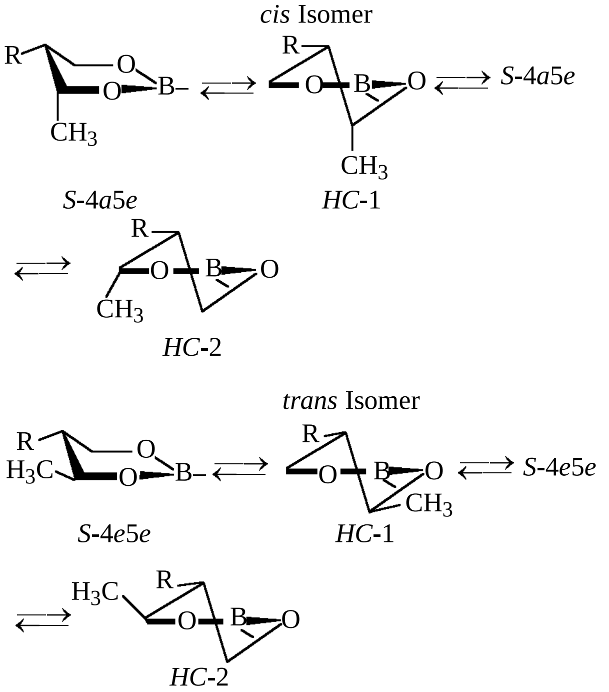
The two-dimensional section of the potential energy surface, reflecting changes in potential energy

Table 4. Calculated coupling constants (Hz) and parameters of the conformational equilibrium (N, ΔG^0, kcal/mol) of the *cis* isomers of esters **Ia**–**IVa** at 293 K

$$\underset{N}{S\text{-}4a5e} \rightleftarrows \underset{1-N}{S\text{-}4e5a}$$

Conformer	Equation[a]	MM+					AM1					ΔG^0, mean
		$^3J_{AX}$	$^3J_{BX}$	$^3J_{A'X}$	N	ΔG^0	$^3J_{AX}$	$^3J_{BX}$	$^3J_{A'X}$	N	ΔG^0	
I, *S*-4*a*5*e*	A	11.6	4.8	4.2	0.841	0.97	11.7	5.3	4.8	0.759	0.67	0.8
S-4*e*5*a*		2.1	3.6	1.7			3.5	2.3	2.3			
S-4*a*5*e*	B	11.4	4.1	4.3	0.863	1.07	11.3	4.6	4.9	0.750	0.64	
S-4*e*5*a*		3.7	3.2	3.4			5.2	2.2	4.2			
II, *S*-4*a*5*e*	A	11.6	4.8	4.2	0.836	0.95	11.7	5.3	4.7	0.757	0.66	0.8
S-4*e*5*a*		2.5	3.1	1.6			3.5	2.2	2.4			
S-4*a*5*e*	B	11.4	4.1	4.3	0.854	1.03	11.3	4.6	4.8	0.736	0.60	
S-4*e*5*a*		4.2	2.8	3.2			5.6	2.2	4.2			
III, *S*-4*a*5*e*	A	11.6	4.8	4.2	0.879	1.16	11.7	5.3	4.8	0.796	0.79	1.0
S-4*e*5*a*		2.1	3.5	1.8			3.5	2.3	2.3			
S-4*a*5*e*	B	11.4	4.1	4.3	0.914	1.38	11.3	4.6	4.9	0.804	0.82	
S-4*e*5*a*		3.8	3.1	3.6			5.2	2.2	4.2			
IV, *S*-4*a*5*e*	A	11.6	4.9	4.0	0.771	0.71	11.7	5.4	4.9	0.679	0.44	0.5
S-4*e*5*a*		2.1	3.6	1.7			3.4	2.3	2.3			
S-4*a*5*e*	B	11.4	5.4	4.1	0.679	0.44	11.2	4.6	5.0	0.645	0.35	
S-4*e*5*a*		3.8	3.1	3.4			5.2	2.2	4.1			

[a] quations for calculation of coupling constants: A [24] and B [25].



with rotation of the C^5–R group by 360°, has three minima corresponding to *sofa* (or a slightly distorted *sofa*) and three maxima corresponding to distorted *sofa* or *half-chair* forms; the relative energies of the forms depend on their substituent R. Points on ascending and descending branchs of the curves (see figure) relate to continuously changing set of *half-chair* or distorted *sofa* conformations. Thus, the *cis* and *trans* isomers of esters **I**–**IV** at room temperature are conformationally inhomogeneous, which is associated with internal rotation of the substituent at the C^5 atom and, in the *cis* isomers, in addition, by the equilibrium: *S*-4*a*5*e* ⟷ *S*-4*e*5*a* (Table 2). To estimate ΔG^0 for this equilibrium (Table 4), we made use of an approach relating weighted mean (experimental) and standard, for conformers *S*-4*a*5*e* and *S*-4*e*5*a*, coupling constants [23].

$$^3J_{AX} + {}^3J_{BX} + {}^3J_{A'X}$$
$$= N(J_{aa} + J_{ae} + J_{a'e'}) + (1 - N)(J_{ea} + J_{ee} + J_{e'e'}).$$

The standard coupling constants were calculated using known modifications of the Karplus equation (A [24] and B [25]), with the reported electronegativities of the substituents in the ethane fragment [26] and the optimized torsion angles between corresponding protons. The resulting data (Table 4) give evidence for the expected prevalence of form *S*-4*a*5*e* in the mixture; at the same time, the fraction of the alternative, *S*-4*e*5*a* conformer for *cis*-2-alkyl-5-allyl-4-methyl-1,3,2-dioxaborinanes **IVa** and **IVb** points to comparable conformational Gibbs energies of the C^4–CH_3 and C^5–C_3H_5 substituents in 1,3,2-dioxaborinanes.

Our present data contribute to the stereochemistry of unsymmetrically substituted 1,3,2-dioxaborinanes and open the way to predicting conformational compositions of such molecules with several chiral centers.

EXPERIMENTAL

Gas chromatography was performed on a Tsvet-126 chromatograph with a flame-ionization detector, columns 3000 × 4 mm, packings 5% OV-17 on Chromaton N-Super and 5% DC-550 on Chromaton NAW-HMDS, carrier gas argon. The ^{1}H NMR spectra were measured on a Bruker AM-250 spectrometer at 250 MHz in 10% solutions in $CDCl_3$ relative to TMS (internal reference).

Compound **IIIb** has been described in [27]. Cyclic esters **Ib**, **IIb**, and **IVb** as a stereoisomeric mixture we obtained by a common procedure [1] in an yield of 70–75%. 5-Ethyl-2-isopropyl-4-methyl-1,3,2-dioxaborinane (**Ib**), bp 61–63°C (8 mm), n_D^{20} 1.4288; 2-isopropyl-4-methyl-5-propyl-1,3,2-dioxaborinane (**IIb**), bp 72–73°C (8 mm), n_D^{20} 1.4329; 5-allyl-2-isobutyl-4-methyl-1,3,2-dioxaborinane (**IVb**), bp 80–82°C (5 mm), n_D^{20} 1.4442.

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