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Stereochemistry of Seven-Membered Heterocycles: XLIII.* Steric Structure of Diastereoisomeric 8,8-Dichloro(dibromo)-4-R-3,5-dioxabicyclo[5.1.0]octanes

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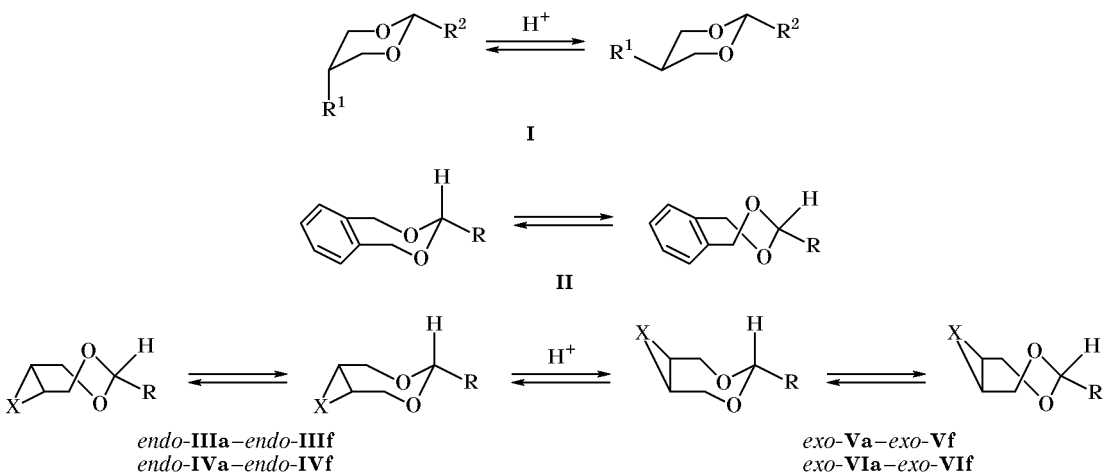
Abstract—Dichloro- and dibromocyclopropanation of 2-substituted 1,3-dioxacyclohept-5-enes according to Makosza resulted in formation of the corresponding 4-substituted 8,8-dichloro(dibromo)-3,5-dioxabicyclo-[5.1.0]octanes in good yields. Ultrasonic activation of the process considerably shortened the reaction time. According to the ^{13}C NMR spectra, the *chair–twist* equilibrium is essentially displaced toward the *chair* conformer for the *exo* isomers and toward the *twist* conformer for the *endo* structures. Similar results were obtained by AM1 semiempirical calculations which indicated that the CCl···O interaction largely determines the conformational equilibrium. The state of the diastereoisomer epimerization equilibrium depends on the size of the substituent at the acetal carbon atom.

1,3-Dioxanes **I** are six-membered cyclic saturated acetals which are classical models in stereochemical studies. Up to now, a great deal of experimental and theoretical data have been reported on equilibria of their *chair*-like conformations. Comparative analysis of conformational parameters of substituents in positions *2*, *4* (*6*), and *5* of 1,3-dioxanes and cyclohexane derivatives made it possible to elucidate the role of heteroatoms and formulate basic concepts concerning factors responsible for the state of *chair*(*ax*)–*chair*(*eq*)

Scheme 1.



III, **V**, X = CCl_2; **IV**, **VI**, X = CBr_2; R = H (**a**), Ph (**b**), Me (**c**), Et (**d**), *i*-Pr (**e**), *t*-Bu (**f**).

* For communication XLII, see [1].

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Table 1. ^{13}C NMR chemical shifts (δ_C, ppm) of compounds **III**–**VI** in $CDCl_3$ at 25°C

Compound no.	C^4	C^2, C^6	C^1, C^7	C^8	Substituent on C^4
IIIb	102.5	60.7	34.0	63.4	–[a]
IIIc	101.7	61.2	34.1	63.5	20.8
IIId	106.1	61.7	34.2	63.9	27.8, 9.3
IIIe	108.9	62.6	34.0	64.1	33.0, 18.0
IIIf	109.4	64.0	33.5	65.6	36.7, 25.4
IVb	103.5	63.6	36.9	36.4	–[a]
IVc	101.5	63.1	35.0	–[b]	21.3
IVd	106.1	63.5	34.7	–[b]	27.7, 9.2
IVe	108.5	64.4	34.5	–[b]	33.0, 18.3
IVf	109.2	66.1	33.7	–[b]	–[b], 25.2
IIIa–**Va**	102.3	70.6	36.1	67.9	–
Vb[c]	110.3	69.5	35.6	67.2	–[a]
Vc[c]	109.1	69.6	35.5	67.2	22.6
Vd	113.1	69.5	35.3	67.4	29.2, 9.5
Ve	116.1	69.7	35.6	67.5	34.1, 18.1
Vf[c]	118.6	70.3	35.9	66.9	37.9, 25.9
IVa–**VIa**	102.1	72.6	36.4	35.3	–
VIb[c]	110.0	71.2	35.8	35.1	–[a]
VIc[c]	109.2	71.9	35.6	35.0	22.5
VId	112.9	71.7	35.3	–[b]	29.0, 9.5
VIe	115.4	71.8	35.5	–[b]	33.9, 18.4
VIf[c]	118.5	72.5	36.9	36.0	36.4, 26.0

[a] Signals from aromatic carbon atoms are not given.
[b] Signals were not assigned.
[c] Chemical shifts for isolated diastereoisomers.

equilibrium in saturated six-membered carbo- and heterocycles [2–5]. It should be emphasized that the most fruitful method for stereochemical study of the above systems involves examination of the epimerization process [3, 6]. It is commonly accepted that epimerization equilibrium simulates conformational equilibrium; therefore, conformational energies of substituents can be determined [4].

Unlike 1,3-dioxanes, the *chair* and *twist* conformers of 2-substituted unsaturated seven-membered acetals **II** having a planar carbocyclic fragment (*cis*-butylene, *o*-xylylene, etc.) are characterized by similar energies [7–10]. The state of conformational equilibrium in six- and seven-membered acetals was found [4, 8] to be controlled by 1,3-repulsive interactions involving substituents.

3,5-Dioxabicyclo[5.1.0]octanes **III** also possess a planar carbocyclic fragment ($C^2C^1C^7C^6$). They can exist in solution as *chair* conformers with *exo*- and *endo*-oriented three-membered ring, as well as the corresponding *twist* conformers [11–17] (Scheme 1). The *chair*-like structures of these compounds may be regarded as analogs of 5_{eq}- and 5_{ax}-substituted 1,3-dioxanes, in which the three-membered ring is a specific substituent.

We have started systematic studies of hetero analogs of bicyclo[5.1.0]octanes. The present communication reports on the synthesis and steric structure of diastereoisomeric *endo*- (**III**, **IV**) and *exo*-8,8-dichloro(dibromo)-4-R-3,5-dioxabicyclo[5.1.0]-octanes (**V**, **VI**). In keeping with published data, the dichlorocyclopropanation of 2-substituted 1,3-dioxacyclohept-5-enes was performed according to Parham [14, 18] (dichlorocarbene genaration from chloroform by the action of potassium *tert*-butoxide [19]) or Seyferth [11, 12, 20]. The yields of the target products did not exceed 30%. The addition of dibromocarbene to 1,3-dioxacyclohept-5-ene was also characterized by a poor yield (~10%) [18].

Our attempt to apply the Wagner procedure to the same substrates (thermolysis of sodium trichloroacetate in benzene) was unsuccessful: no cyclopropanation product was formed at all. Replacement of the aromatic solvent by $CHCl_3$ in the presence of

benzyltriethylammonium chloride did not radically change the result: the yield was as low as 10%. Structurally related 5,6-disubstituted seven-membered acetals underwent dichlorocyclopropanation according to Makosza to give bicyclo[5.1.0]octanes in good yields [16, 21]. Under analogous conditions, we obtained dichloro- and dibromocyclopropanation products [17] in 50–70% yield. When the reaction was carried out under ultrasonic irradiation, the reaction time was shortened from 40 to 4 h.

According to the ^{13}C NMR spectra of the reaction mixtures, in all cases (R ≠ H) a mixture of diastereoisomers was obtained at a ratio of ~1 : 1. The adducts can readily be purified by vacuum distillation. An alternative version of the isolation of compounds **III**–**VIb**, **Vc**, and **Vf** is epimerization followed by recrystallization. In such a way we succeeded in isolating configurationally pure *exo* diastereoisomers. The structure of products **III**–**VI** was confirmed by the ^{13}C NMR spectra and elemental analyses. The adducts were assigned to the *endo* or *exo* series on the basis of the X-ray diffraction data for 2-phenyl-substituted acetals **Vb** [10, 11] and **VIb** [17]. Compounds **Vb** and **VIb** exist in crystal as *chair* conformers with *exo*-oriented cyclopropane rings. The ^{13}C NMR parameters of diastereoisomeric 8,8-dihalo-4-R-3,5-dioxabicyclo[5.1.0]octanes are given in Table 1.

It should be noted that ^{13}C NMR spectroscopy turned out to be very informative for analysis of the steric structure of 1,3-dioxa-5,6-benzocycloheptenes **II** [10]. The authors obtained "frozen" spectra of the *chair* and *twist* conformers of a series of 2-substituted acetals. Analysis of the ^{13}C NMR spectra of the four series of compounds (**III**–**VI**) showed that in all cases signals from carbon atoms of *exo* diastereoisomers **V** and **VI** appear in a weaker field, the maximal difference in the chemical shifts being observed for the C^4 and C^2/C^6 atoms ($\Delta\delta_C$ = 9 ppm). Let us consider the chemical shifts of C^2/C^6. These atoms are located in the γ-position with respect to the substituent on C^4. The chemical shifts of C^2/C^6 in *exo*-dichlorides **V** range from 69.5 to 70.3 ppm, and the corresponding interval for dibromides **VI** is 71.2–72.5 ppm. In the *endo*-isomer series, the chemical shifts of the same carbon atoms are δ_C 61.2–64.0 and 63.1–66.1 ppm, respectively. The benzyl carbon signals of the *chair* and *twist* conformers of **II** are located at δ_C 74.7–76.3 and 67.6–70.4 ppm, respectively. Comparison of the chemical shifts of C^2/C^6 in the series of compounds **III** and **V** and **IV** and **VI** and of benzyl carbon atoms in the spectra of phthalyl acetals **II** suggests that the *chair*–*twist* equilibrium for the *exo*-isomers is displaced toward the *chair* form and that the *twist* conformer predominates in the *endo* series. Compounds **IIIa**–**VIa** (R = H) should be assigned the *chair* structure, for the chemical shifts of C^2/C^6 (δ_C 70.6 and 72.6 ppm) are similar to those of the 4-R derivatives. Moreover, the ^1H NMR spectra of acetal **Vb** and 8,8-dichloro formal **Va** in the temperature range from 20 to –80°C did not reveal conformational heterogeneity of these compounds.

Table 2. Gibbs energies (ΔG^0, kcal/mol) for the epimerization equilibrium of the *endo* and *exo* isomeric adducts of dichloro- (**A**) and dibromocarbene (**B**) to 2-R-1,3-dioxacyclohept-5-enes in carbon tetrachloride

R	A	B
Ph	0.72	0.41
Me	1.45	1.17
i-Pr	1.37	1.29
t-Bu	–[a]	–[a]

[a] No *endo* isomer was detected by ^{13}C NMR spectroscopy.

In order to elucidate steric structure of bicyclic acetals, we have resorted to AM1 semiempirical calculations. This procedure was found to be appropriate as applied to 2-substituted 1,3-dioxacyclohept-5-enes [1, 22]. 8,8-Dichloro acetals **IIIa** and **Va** are the most representative models for studying specific features of steric structure. 4-Substituted derivatives, in principle, could give rise to no more than two conformers due to high conformational energy of substituents at the acetal carbon atom in the *chair*(*a*)–*chair*(*e*) equilibrium [8]. The calculated heats of formation of the *chair* conformers with *endo*- and *exo*-oriented dichlorocyclopropane moieties and of the *twist* form are –76.1, –78.8, and –77.6 kcal/mol, respectively. Analysis of the AM1 geometric parameters of the conformers showed that the *endo* structure and flexible conformation are unfavorable because of repulsion between the *endo*-oriented chlorine and oxygen atoms. The distance between the latter is shorter than the sum of their van der Waals radii (3.15 and 3.12 Å, respectively). In the *chair*-like *endo* isomer, repulsion between the chlorine and two oxygen atoms leads to increase of the OCC angles by 5.9° with respect to the *exo* isomer (111.1°). In the *twist* conformer, the OCC angles are 109.7 and 114.0°.

With the data on steric structure of diastereoisomers of the two series in hand, we performed their epimerization in order to obtain information on the effects of the 4-substituent and dihalocyclopropane fragments on the configurational and conformational composition of the compounds under study. It might

Table 3. Melting (or boiling) points and elemental analyses of 4-R-substituted 8,8-dichloro- and 8,8-dibromo-3,5-dioxabicyclo[5.1.0]octanes

R	mp, °C, or bp, °C (*p*, mm), n_D	Found, %		Formula	Calculated, %	
		C	H		C	H
8,8-Dichloro-4-R-3,5-dioxabicyclo[5.1.0]octanes						
Me[a]	63–64	42.45	5.12	$C_7H_{10}Cl_2O_2$	42.64	5.08
Et	110–118 (5×10^{-1}), n_D^{24} = 1.4907	44.20	5.91	$C_8H_{12}Cl_2O_2$	45.52	5.73
i-Pr	89–91 (5×10^{-1}), n_D^{20} = 1.4915	47.37	5.99	$C_9H_{14}Cl_2O_2$	48.02	6.27
t-Bu[a]	75–76, 90–91 (5×10^{-1})	52.65	7.80	$C_{10}H_{16}Cl_2O_2$	50.42	6.72
8,8-Dibromo-4-R-3,5-dioxabicyclo[5.1.0]octanes						
Me[a]	96–98	29.52	3.32	$C_7H_{10}Br_2O_2$	28.8	3.24
Et	110–120 (6×10^{-1}), n_D^{25} = 1.5338	–[b]	–	$C_8H_{12}Br_2O_2$	–	–
i-Pr	141–145 (3×10^{-1}), n_D^{24} = 1.5408	–[c]	–	$C_9H_{14}Br_2O_2$	–	–
t-Bu[a]	86–87	36.76	4.63	$C_{10}H_{16}Br_2O_2$	36.58	4.88

[a] Pure *exo* diastereosomers.
[b] Found, %: Br 53.20. Calculated, %: Br 53.27.
[c] Found, %: Br 53.00. Calculated, %: Br 50.89.

be expected that, other conditions being equal, the configurational equilibrium will be determined by the size of the substituent on C^4. In other words, the pattern should be qualitatively similar to that observed for acetals of the 1,3-dioxacyclohept-5-ene series and seven-membered heterocycles **II**. Table 2 contains the Gibss energies of the epimerization equilibria. These data indicate that the fraction of the *endo* diastereoisomer having a *twist* conformation of the seven-membered ring decreases as the size of the 4-substituent increases. Thus we have an unambiguous proof for the existence of 1,3-interaction between the 4-substituent and hydrogen atoms on C^2 (C^6) in the flexible form.

The data obtained by studying the epimerization process do not allow us to determine the difference in the conformational properties of dichloro- and dibromocyclopropane fragments, whereas the existence of equilibria involving the *chair* and *twist* conformers suggest conformational heterogeneity of the *exo* isomers (except for the *tert*-butyl derivatives) with considerable prevalence of the *chair*-like conformers.

EXPERIMENTAL

The ^{13}C NMR spectra were recorded on Varian Unity-300 (75.43 MHz) and Bruker WP-200 spectrometers (50.46 MHz) in $CDCl_3$. The chemical shifts were measured relative to the solvent signals. A UZDN-A setup with an operating frequency of 22 kHz was used for ultrasonic activation. AM1 semiempirical calculations were performed with the aid of MOPAC 6 software [23–25]; geometry optimization was accomplished with a gradient norm of 0.1. In all cases, second derivatives matrices were calculated, and imaginary frequencies were absent.

4-Substituted 8,8-dichloro(dibromo)-3,5-dioxabicyclo[5.1.0]octanes III–VI (*general procedure***).** A 50% aqueous solution (14 g) of sodium hydroxide was added dropwise over a period of 2 h to a solution of 43.5 mmol of the corresponding 2-substituted 1,3-dioxacyclohept-5-ene and 0.3 g of benzyltriethylammonium chloride in 27.6 ml of $CHCl_3$ (or 30.5 ml of $CHBr_3$) under vigorous stirring and cooling in an ice bath. The mixture was stirred for 6 days at room temperature, diluted with methylene chloride, and washed with water. The organic layer was separated and dried over Na_2SO_4. If the emulsion did not divide into layers, the mixture was passed through a glass filter. The products were purified by vacuum distillation (0.1 mm) or recrystallization from hexane–ethanol (10 : 1) after epimerization. The yields were 50–70%. The physical constants and elemental analyses of the products are given in Table 3. When the reaction was carried out under ultrasonic activation (UZDN-A), the temperature was maintained at

25°C, the amounts of the reactants being the same. The yields of the target products were no less than 50% in 4–6 h.

General procedure for epimerization. A catalytic amount of *p*-toluenesulfonic acid was added to a 10% solution of an isomer mixture in CCl_4, and the mixture was kept for a week at 25 ± 2°C. The progress of the reaction was monitored by the ^{13}C NMR spectra (the isomer ratio was determined from the peak intensity ratio of the acetal and methylene carbon signals).

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