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Structure and conformational analysis of 5,5-bis(bromomethyl)-2-trichloromethyl-1,3-dioxane by XRD, NMR and computer simulation

Sh.Yu. Khazhiev[a], M.A. Khusainov[b], R.A. Khalikov[c], V.A. Kataev[c], T.V. Tyumkina[d], E.S. Mescheryakova[d], L.M. Khalilov[d], V.V. Kuznetsov[b,e,*]

[a] OAO ANK Bashneft, Ufa 450077, Russian Federation
[b] Ufa State Petroleum Technological University, Ufa 450062, Russian Federation
[c] Bashkirian State Medical University, Ufa 450008, Russian Federation
[d] Institute of Petrochemistry and Catalysis of Russian academy of Science, Ufa 450075, Russian Federation
[e] Ufa State Aviation Technical University, Ufa 450008 Russian Federation

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ABSTRACT

According to the NMR ^{1}H, ^{13}C and X-ray analysis data molecules of 5,5-bis(bromomethyl)-2-trichloromethyl-1,3-dioxane in the crystalline phase and in solution have a *chair* conformation with an equatorial trichloromethyl group. The route of conformational transformations for isolated molecule and for a cluster with five chloroform molecules, as well as a transition states and barriers to the internal rotation of the axial and equatorial trichloromethyl group have been established using DFT approximation PBE/3ξ.

1. Introduction

Substituted 1,3-dioxanes – classical objects of conformational analysis [1–4] – are used as reagents for fine organic synthesis [5–10], as well as for the creation of new promising bioactive compounds [11–17]. On the other hand, 5,5-bis(halomethyl)−1,3-dioxanes contain two additional reaction centers: halogen atoms – capable of entering into nucleophilic substitution reactions [4,18]. The appropriate formals at room temperature are characterized by the fast (in the NMR time scale) ring interconversion [18,19]. In the case of 2-substituted analogs, the *chair* form is realized with an equatorial substituent at the C-2 atom of the ring [20–22]. Thus, 5,5-bis (halomethyl)−1,3-dioxanes are potential reagents for organic synthesis and convenient models for studying the effect of substituents on the conformational properties of six-membered heterocyclic ring.

As a result, the presence of certain substituents and the conformational preference of 1,3-dioxanes have a noticeable effect on their biological activity [13–16], which determines the importance and relevance of structural studies of compounds of this class.

At the same time, it remains unclear how the nature of substituent at the C−2 atom of the 1,3-dioxane ring including bulk groups affects both the structural features of the ring itself in solid state and the dynamic characteristics of its conformational transformations in solutions. In this respect, of particular interest is the presence of the CCl_3 substituent at the C-2 atom of the 1,3-dioxane ring because of its electronic and structural features; in addition, the accumulation of halogen atoms in substituted 1,3-dioxanes leads to an increase in their bactericidal activity [13]. On the other hand, the development of solute–solvent interaction research strategy has resulted in two solvent models: implicit (continuum) and explicit (discrete); their comparative effectiveness has been discussed in recent publications [23–28]. Which of these approaches can be applied in computer simulation of the conformational properties of saturated six-membered heterocyclic compounds? It has been found recently that an explicit model makes it possible to obtain calculated results that are in good agreement with the experimental data. For example, in the case of cluster: 3-methyltetrahydro-1,3-oxazine@4 molecules of difluorodichloromethane – the calculated and experimental (NMR)

* Corresponding author at: Ufa State Petroleum Technological University, Ufa 450062, Russian Federation.
E-mail address: kuzmaggy@mail.ru (V.V. Kuznetsov).

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values of the pyramidal nitrogen inversion barrier coincide [29]. The presence of 8 molecules of chloroform in the first solvation shell of 2-isopropyl-5-methoxy-5-methyl-1,3,2-dioxaborinane leads to the good agreement between conformational behavior of this compound according to computational and NMR data [30]. The calculated potential barrier to the interconversion of the 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane in a cluster with five methylene chloride molecules is also close to the experimental NMR value of this parameter [31]. The further development of explicit model showed that the optimal number of solvent molecules in the nearest solvation shell of substituted 1,3-dioxanes is from 4 to 10 [22,32,33]. All mentioned above determined the goal of present investigation devoted to the conformational analysis (the study of minima and transition states between them on the potential energy surface) of a new 5,5-bis(bromomethyl)-2-chloromethyl-1,3-dioxane 1 using single crystal X-ray diffraction study, NMR (^{1}H and ^{13}C) spectral investigation, as well as a computer simulation within the DFT approximation PBE/3ζ using the explicit solvation model.

2. Experimental section

The melting point of synthesized compound 1 was measured in a liquid paraffin bath in the open capillary tube and was not calibrated. Elemental analysis was performed on the CarloErba 1108 CH analyzer and is within 0.3% of the calculated value. NMR spectra were recorded on a Bruker Avance 400 spectrometer with frequencies of 400.13 MHz (^{1}H) and 100.62 MHz (^{13}C) at room temperature. The chemical shifts δ were measured in ppm with respect to solvent (^{1}H: $CDCl_3$, δ = 7.26 ppm; ^{13}C: $CDCl_3$, δ = 77.16 ppm).

2.1. Procedure for the synthesis of 5,5-bis(bromomethyl)–2-chloromethyl-1,3-dioxane 1

The sample of 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane 1 was obtained by condensation of 2,2-bis(bromomethyl)-1,3-propanediol with chloral (Scheme 1) using of a modified method [34].

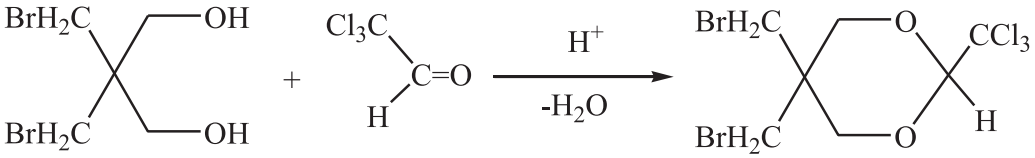
The 15 ml of conc. sulfuric acid was added to 7.0 g (0.043 mol) of chloral hydrate. The mixture was stirred for 10 min. Then the formed upper layer was transferred into a 250 ml round-bottom flask, mixed with 50 ml of benzene and 5.24 g (0.02 mol) of 2,2-bis(bromomethyl)-1,3-propanediol. The reaction mixture was stirred for 10 min, after that was added 2 ml of conc. sulfuric acid. The flask was connected to a reflux condenser through a Dean-Stark trap and reaction mixture was boiled until the release of water ceased (7 h). After cooling to room temperature, 8.4 g (0.1 mol) of sodium bicarbonate was placed in a flask and reaction mixture was stirred for 5 h. The precipitate was filtered off, washed twice with 20 ml of benzene and once with 20 ml of hexane. To the resulting white mass, 10 ml of ethanol was added and dissolved under weak heating. After cooling to 5 °C, the precipitate formed was filtered off and dried at 40 °C. Yield 0.94 g (12.6%), mp. 102.5–103.5 °C. Elemental analysis found (calculated)%: C 21.31 (21.46); H 2.17 (2.30).

2.2. X-ray crystallography

The colorless transparent crystal of 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane 1 having dimensions of 0.53 × 0.22 × 0.15 mm was chosen for intensity data collection in a XCalibur Eos automated four-circle diffractometer (Mo Kα radiation, λ 0.71073 Å; graphite monochromator; ω-scanning, 2θmax = 62°). The data were acquired and processed using CrysAlisPro version 1.171.36.20 (Oxford Diffraction). The structure was solved by the direct method and was refined by the full-matrix least-squares method in anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were localized by the difference Fourier synthesis and were refined in isotropic approximation. The calculations were performed using SHELX97 [35]. The thermal ellipsoid plot and packing were done using PLATON [36]. An independent part of the unit cell of crystals of compound 1 includes one molecule.

2.3. DFT calculations

Various approaches based both on *ab initio* and DFT methods are usually used as an appropriate computational approximations for simulation of the structural, electronic, and conformational properties of six-membered saturated heterocycles [4]. Some of the most useful among them are PBE and hybrid PBE approaches [37–39]. The PBE method is based on the principle of the generalized gradient approximation (GGA) and has proven itself well in the computational analysis of various molecular systems [40]. Our investigations are connected with the approximation PBE/3ζ (PRIRODA package [41]). The basis set of triple valence cleavage of 3ζ, developed by Laikov [42], is a full-electronic non-relativistic atomic basis of the Gaussian type, containing a diffuse part and polarization functions. According to the numerous examples [4,19–22,29–33] PBE/3ζ approximation correctly describes the structural, thermochemical and polar characteristics of saturated six-membered heterocycles of different classes. The initial geometry optimization of the acetal 1 (*chair* conformer) was carried out using the HyperChem package [43] (semiempirical approximation PM3), and then – within the framework of the method PBE/3ζ. The interconversion of the ring and the internal rotation of the CCl_3 substituent were simulated by scanning the corresponding torsion angles. The values of potential barriers were established using the procedure for searching for transition states within the PRIRODA package [41]. The fact that the stationary points of the potential energy surface belong to the transition states was confirmed by the presence of one imaginary frequency in the corresponding Hessian, and to the minima – by the absence of imaginary frequencies. The cluster 1@5$CHCl_3$ was initially formed by the virtual placement of chloroform molecules in the vicinity of the investigated 1,3-dioxane (equatorial *chair* conformer) using the HyperChem software, after which the resulting system was optimized within approximation PBE/3ζ and then – sequentially translated into other forms.



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Scheme 1. Synthesis of 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane 1.

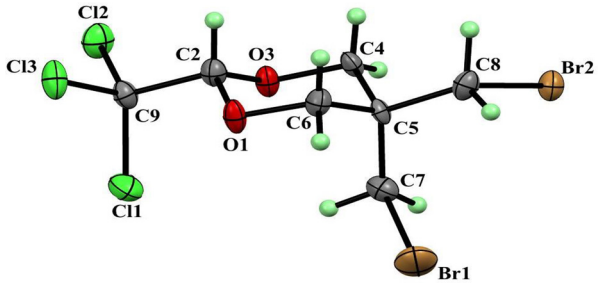


Fig. 1. The crystal structure of the dioxane 1 molecule in the representation of atoms by thermal vibration ellipsoids (p = 50%).

3. Result and discussion

Comprehensive structural analysis of dioxane 1 assumed the study of its structure both in the solid state and in chloroform solution, using the data of X-ray diffraction analysis, NMR and quantum chemical calculations.

3.1. X-ray crystal structure of compound 1

The molecules of the investigated acetal 1 form monoclinic crystals with the space group $P2_1/c$. The PLATON diagram shows 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane 1 exists in the *chair* conformation and CCl_3 substituent at C-2 of the 1,3-dioxane ring occupies equatorial position (Fig. 1).

The corresponding crystallographic details are given in Table 1 and selected bond length, as well as bond and torsion angles – in Table 2.

It should be stressed that heteroatomic part of the ring is characterized by the expected C–O bond lengths (1.391–1.436 Å) and bond angles close to 110–113°. The torsion angles also correspond to those observed in the *chair* conformation of 1,3-dioxane ring (Table 2) [1, 4, 20–22,31.32]. Besides that, it is necessary to note the characteristic *gauche* arrangement of bromomethyl substituents at C-5 atom of 1,3-dioxane ring (Fig. 1). According to the data of quantum chemical calculations, this conformation corresponds to the minimum energy in comparison with the alternative forms of carbon-halogen bonds in bis(halomethyl) fragment [44].

Bulky substituent CCl_3 has a noticeable effect on the ring puckering of 1,3-dioxane. This is clearly demonstrated by a comparison of the interplanar angles of the compound 1 and 5,5-dibromomethyl-2-phenyl-1,3-dioxane 2 [20] according to the results of X-ray analysis (Fig. 2). The corresponding angles in the carbon part of the ring almost coincide, while in the heteroatomic fragment are differ by almost 7° [dioxane 1: 126.9 (5°), dioxane 2: 120.1 (12°)].

Table 1
Crystal data and refinement strategy of compound 1.

Parameters	Values
Empirical formula	$C_7H_9Br_2Cl_3O_2$
Formula weight	391.31
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, $P2_1/c$
Unit cell dimensions	a = 8.3451(4) Å; b = 11.1745(7) Å;
Volume	c = 13.0164(10) Å; α =90°; β =95.218(6)°; γ =90°
Z, Calculated density	1208.78(13) Å^3
Absorption coefficient	4, 2.150 g/cm^3
F(000)	7.341 mm^{-1}
Crystal size	752.0
2Θ range for data collection	0.53 × 0.22 × 0.15 mm
Index ranges	4.902 to 58.286°
Reflections collected	$-11 \le h \le 6$, $-10 \le k \le 14$, $-17 \le l \le 17$
Independent reflections	5478
Data/restraints/parameters	2709 [R_{int} = 0.1021, R_{sigma} = 0.1806]
GOOF	2709/0/163
Final R indexes [I>=2σ (I)]	0.925 R_1 = 0.0730, wR_2 = 0.1100
Final R indexes [all data]	R_1 = 0.1488, wR_2 = 0.1375
Largest diff. peak/hole	0.74/−1.03 e Å^{-3}

Table 2
Selected bond lengths (Å) as well as bond and torsion angles (°) of dioxane 1 (data from X-ray diffraction analysis and PBE/3ζ calculation*).

Bond length		Bond angles	
Calculation	Experiment	Calculation	Experiment
C^2-O^1		O^1-C^2-O^3	
1.408	1.393(8)	112.1	112.9(6)
C^2-O^3		C^2-O^1-C^6	
1.408	1.391(9)	110.4	111.8(5)
C^6-O^1		C^2-O^3-C^4	
1.435	1.436(8)	110.2	111.3(6)
C^4-O^3		O^3-C^4-C^5	
1.434	1.436(8)	111.1	110.4(5)
C^2-C^9		O^1-C^6-C^5	
1.551	1.545(9)	111.7	110.5(7)
C^9-Cl^{12}		C^4-C^5-C^6	
1.797	1.758(7)	105.9	107.6(6)
C^8-Br^2		C^7-C^5-C^8	
1.986	1.938(8)	113.2	113.0(6)

Torsion angles	
Calculation	Experiment
C^2-O^1-C^6-C^5	
−59.3	−55.9(9)
C^2-O^3-C^4-C^5	
57.7	58.0(8)
C^6-O^1-C^2-O^3	
63.2	58.9(9)
C^4-O^3-C^2-O^1	
−62.3	−59.7(8)
C^4-C^5-C^6-O^1	
53.0	53.5(8)
C^6-C^5-C^4-O^3	
−52.4	−54.5(8)

* The calculation results are given for the molecule of dioxane 1 in vacuum.

3.2. NMR spectral analysis of compound 1

The data of ^{1}H and ^{13}C NMR spectroscopy indicate a high conformational homogeneity of 5,5-bis(bromomethyl)-2-trichloromethyl-1,3-dioxane in solution ($CDCl_3$) (Figs. 3 and 4, Table 3).

This follows from the diastereotopic nature of methylene protons at magnetically equivalent carbon atoms C-4 and C-6 of the heterocyclic ring ($\Delta\delta$ 0.41 ppm), which appear in the ^{1}H NMR spectrum as two doublets with a geminal constant of ^{2} J −11.9 Hz. The methylene protons of the bromomethyl substituents at the C-5 atom of the ring are magnetically nonequivalent ($\Delta\delta$

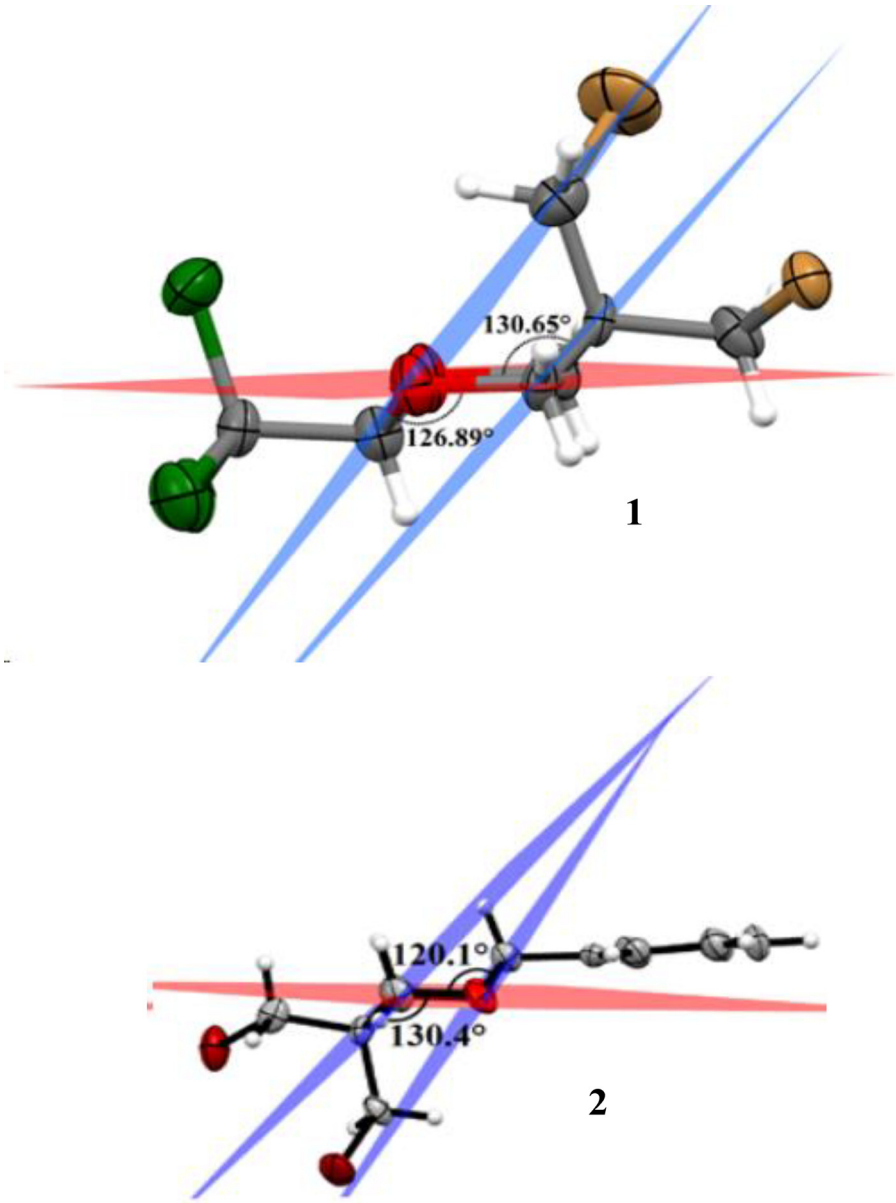


Fig. 2. Interplanar angles in 1,3-dioxane molecules 1 and 2.

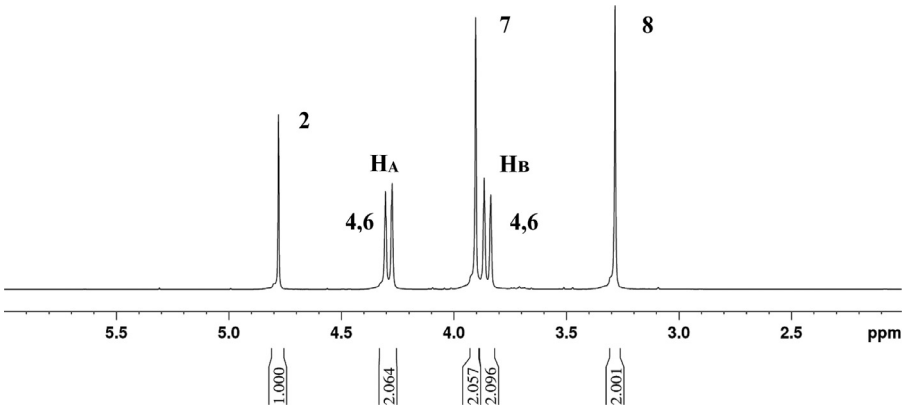


Fig. 3. NMR ^{1}H spectrum of 1,3-dioxane 1.

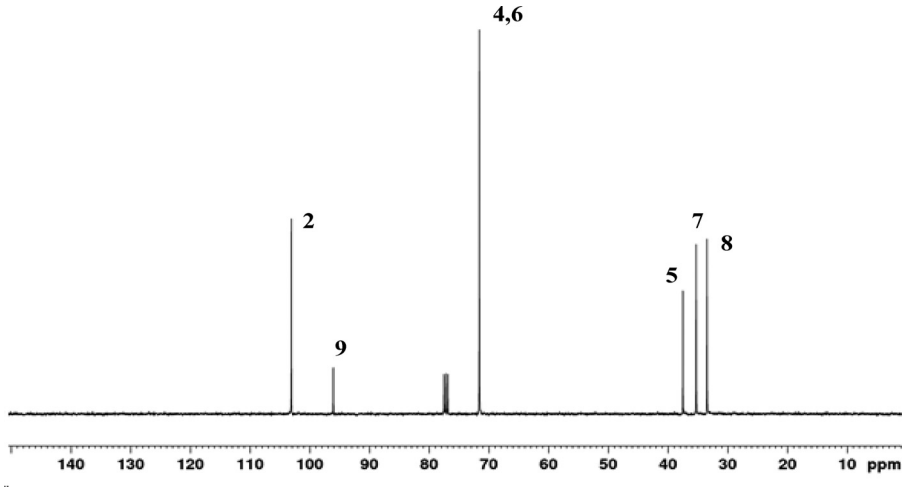


Fig. 4. NMR ^{13}C spectrum of 1,3-dioxane 1.

0.62 ppm). In this case, earlier, on the examples of a series of 5,5-bis (bromomethyl)-2-aryl-1,3-dioxanes using a NOESY experiment, it was found that the signal of the protons of the axial CH_2Br group as well as appropriate ^{13}C [$C_{(7)}CH_2$] appears in a weaker field [20–22,32]. The assignment of ^{13}C signals was unambiguously performed using DEPT-135 spectra; their values are typical for the compounds of this class [20–22,32].

3.3. Conformational analysis of dioxane 1 using DFT approximation PBE/3ζ

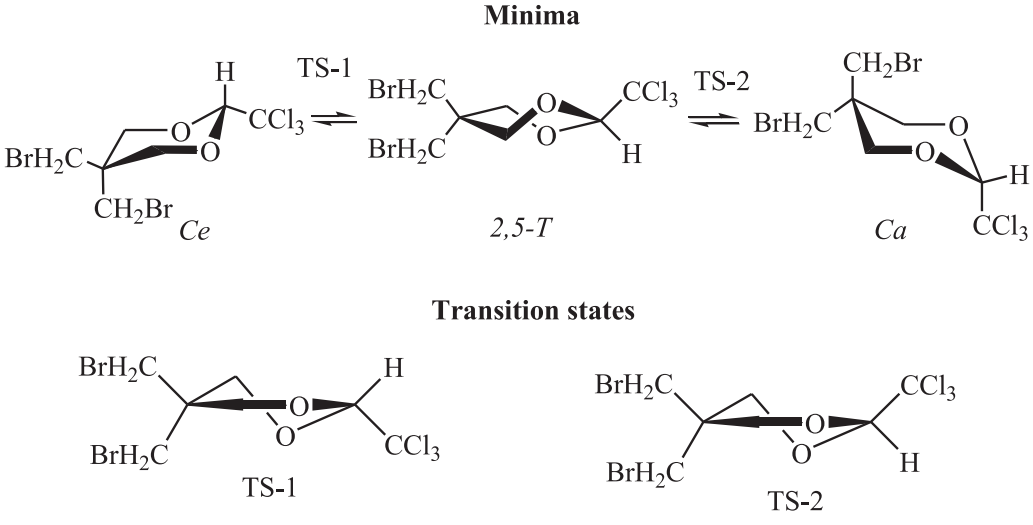
As is known, the aim of the conformational analysis of a particular compound is to search for minima and transition states between them on the potential energy surface. It was found according to the PBE/3ζ results that the main minimum on the potential energy surface of dioxane 1 corresponds to the conformer of the equatorial *chair* (*Ce*), which is in equilibrium with the local minima corresponding to the forms of axial *chair* (*Ca*) and *2,5-twist* (*2,5-T*) with the participation of transition states TS-1 and TS-2 corresponding to the *half chair* conformations (Scheme 2).

The calculated structural parameters of the *Ce* form are relatively close to the data of the X-ray structural experiment (Table 2). The relative energies of all forms corresponding to stationary points on the potentional energy surface for the isolated dioxane molecule 1, as well as for the cluster 1@ $5CHCl_3$, are presented in Table 4.

In all cases, the nearest to the *Ce* form local minimum corresponds to the *2,5-T* conformer, and the most labile is *Ca* form. In accordance with the previously stated considerations (see the introduction) a cluster with five chloroform molecules, $1@5CHCl_3$, was considered (Fig. 5). All computational procedures for this system were similar to those for the isolated molecule of dioxane 1.

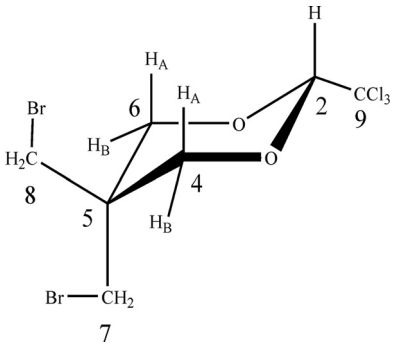
The routes of conformational transformation of acetal 1: *Ce*↔*2,5-T*↔*Ca* – in the cluster $1@5CHCl_3$ (relative energy of explicit model as a function of torsion angles) are clearly shown in Figs. 6 and 7. It should be noted that the expected asymmetric character of the obtained curves reflects noticeable differences in energy between the investigated conformers, as well as between each of them and the transition state.

The calculation data indicate that the values of ΔG^0_{298} for isolated molecule of dioxane 1 and for the cluster with chloroform in the case of the *Ca* conformer are close (Table 4). Chloroform belongs to the low-polarity solvents (ε 4.8), and, although the calculated dipole moment of the conformer *Ce* (μ 2.64 D) is noticeably higher than of *Ca* (μ 0.87 D), the solvent should not significantly affect the shift of the conformational equilibrium. Besides that, it should be noted that the experimental value of the free conformational energy of substituent CCl_3 at the C-2 atom in 1,3-



Scheme 2. Conformational transformations of the dioxane 1 molecule.

Table 3
^{1}H and ^{13}C NMR data of dioxane 1.



Protons	^{1}H, δ ppm	Carbon atoms	^{13}C, δ ppm
$C^{(2)}$-H	4.78 (s)	C^9	96.1
H_A	3.85 (d) (−2 J 11.9 Hz)	C^2	103.1
H_B	4.26 (d) (−2 J 11.9 Hz)	C^4, C^6	71.6
CH_2Br (a)	3.90 (s)	C^5	37.5
CH_2Br (e)	3.28 (s)	C^7	35.3
		C^8	33.5

dioxanes is unknown. However, the calculated values of this parameter, obtained both for dioxane 1 and 1@5CHCl$_3$, is relatively close to ΔG^0_{298} of 2-isopropyl-1,3-dioxane (4.2 kcal/mol [1]).

At the same time, the form *2,5-T* in cluster becomes more labile in comparison with that in vacuum. Using the dependence: $\Delta G = -RT \ln (N_1/N_2)$, it can be shown that the ratio of the populations of the conformers *Ce:2,5-T:Ca* at 298 K is (%) 99.7:0.2:0.1, respectively. It confirms the conformational homogeneity of the molecules of investigated dioxane 1 in solution according to the NMR results (Table 3).

The presence of a solvent increases the barriers to interconversion of the heterocyclic ring and, in most cases, the barriers to the internal rotation of the CCl_3 substituent ($\Delta G^{\neq}_{298}$, Table 4). The symmetric character of the dependence of the potential energy of the system 1@5CHCl$_3$ (conformer *Ce*) from the torsion angle H-C-C–Cl, which describes the internal rotation of group CCl_3 is shown in Fig. 8.

For an isolated molecule of dioxane 1, the value of $\Delta G^{\neq}_{298}$ of the internal rotation of the axial CCl_3 group is higher than that of the equatorial one; however, in the case of cluster 1@5CHCl$_3$, an inverse relationship is observed (Table 4).

The calculated value of the main barrier to interconversion TS-2 in the cluster 1@5CHCl$_3$ (11.1 kcal/mol) is close to the experimental value of this parameter for 5,5-dimethyl-1,3-dioxane (11.0–11.2 kcal/mol [1]). Another interesting feature of the thermodynamics of conformational transformations of studied acetal in a cluster is the negative values of the entropy changes ΔS^0_{298}. In addition, in all cases, the change in the activation entropy $\Delta S^{\neq}_{298}$ is also less than zero (Table 4). This reflects the prominent role of solvation effects and indicates an increased sensitivity of transition states to spatial requirements. It should also be noted that the potential energy surface of investigated acetal does not contain an intermediate *1,4-twist* minimum, which is typical for the confor-

Table 4
Energy parameters of conformational transformations of dioxane 1 according to the PBE/3ζ.

Compound	Conformer	ΔG^0_{298} ($\Delta G^{\neq}_{298}$) kcal/mol (a)	ΔS^0_{298} ($\Delta S^{\neq}_{298}$) cal/mol K (a)
1	*Ca*	4.49	0.34
	2,5-T	2.86	0.78
	TS-1	(7.40)	(−1.48)
	TS-2	(8.22)	(−1.43)
	Ce (CCl_3 internal rotation)	(7.41) (b)	(−6.05) (b)
	Ca (CCl_3 internal rotation)	(9.98) (b)	(−6.15) (b)
1@5CHCl$_3$	*Ca*	4.54	−1.70
	2,5-T	3.64	−1.88
	TS-1	(8.82)	(−6.71)
	TS-2	(11.12)	(−11.63)
	Ce (CCl_3 internal rotation)	(8.19) (b)	(−8.07) (b)
	Ca (CCl_3 internal rotation)	(6.47) (b)	(−8.25) (b)
2 [20]	*Ca*	3.3	−2.6
	2,5-T	3.40	1.0
	TS-1	(9.3)	(0.5)
	TS-2	(11.0)	(−2.2)

(a) relatively to the conformer *Ce*.
(b) relatively to the ground state of given conformer.

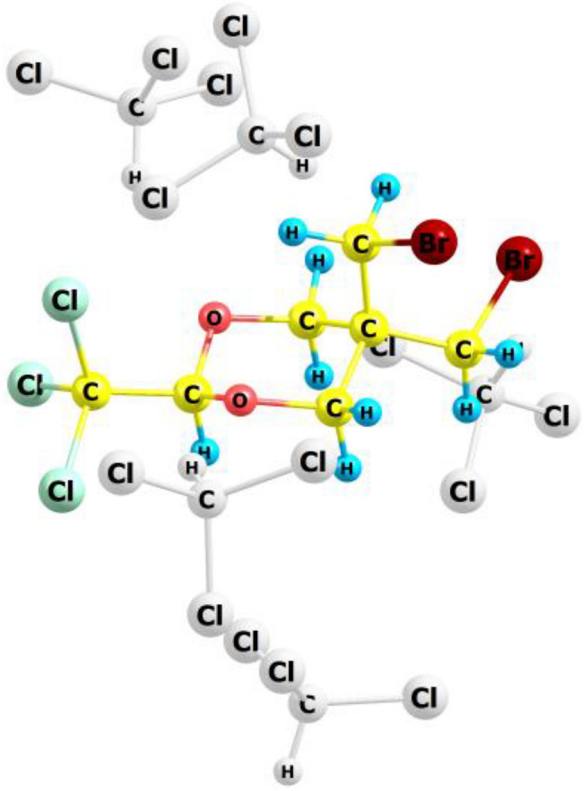


Fig. 5. Optimized structure of cluster 1@5CHCl$_3$ (conformer *Ce*).

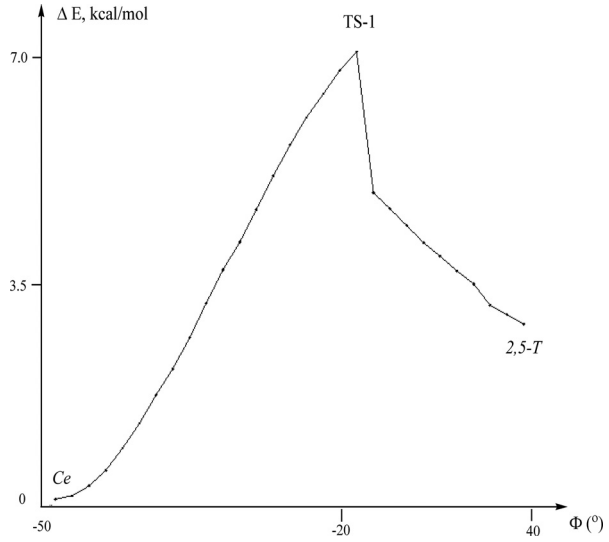


Fig. 6. Relative energy of 1@5CHCl$_3$ as a function of torsion angle C-C-C–O (Φ) at 0 K; transformation *Ce* ↔ TS-1 ↔ *2,5-T* (the relative energy of the *Ce* form is taken as zero).

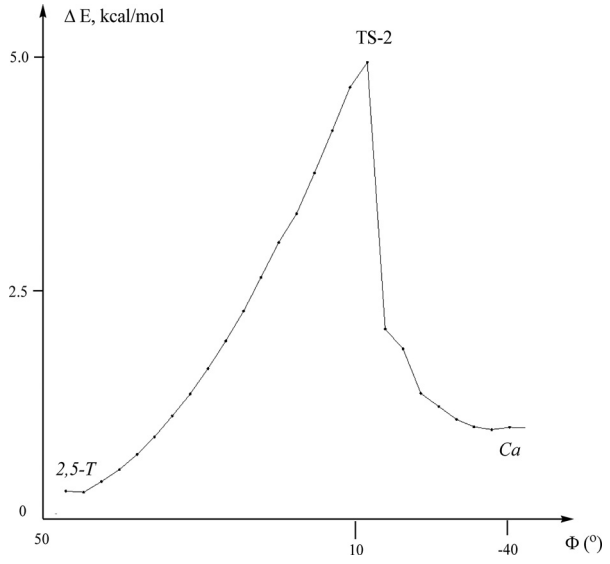


Fig. 7. Relative energy of 1@5CHCl$_3$ as a function of torsion angle O-C-O–C (Φ) at 0 K; transformation *2,5-T* ↔ TS-2 ↔ *Ca* (the relative energy of the *2,5-T* form is taken as zero).

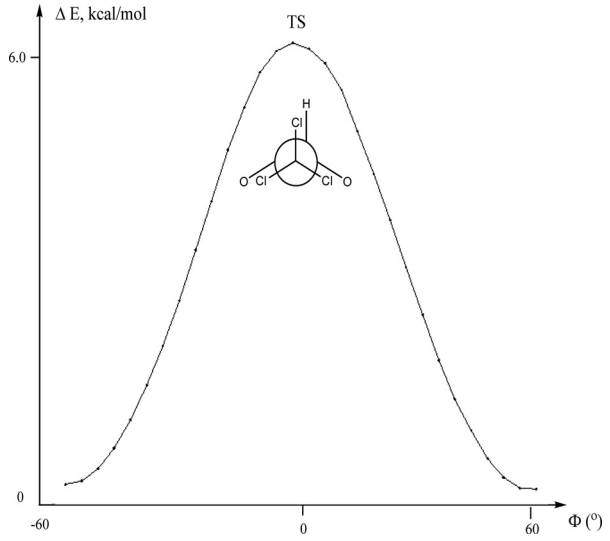


Fig. 8. Relative energy of 1@5CHCl$_3$ as a function of torsion angle H-C-C–Cl (Φ) at 0 K; internal rotation of CCl_3 substituent at C-2 atom (the relative energy of the ground state of the form *Ce* is taken as zero).

mational equilibrium of unsubstituted 1,3-dioxane, as well as of 2-, 4-, 5-, 2,5-, and 4,4-substituted 1,3-dioxanes [4].

The data on the dynamics of conformational transformations of dioxane 1 and 5,5-dibromomethyl-2-phenyl-1,3-dioxane 2 [20] (for the isolated molecule) show that the bulky substituent CCl_3, in comparison with the phenyl group, increases the relative energy of the local minimum *Ca*, lowers the energy of the *2,5-T* form, and noticeably reduces the potential barriers to ring interconversion (Table 4).

4. Conclusion

In summary, the structure of a new 5,5-bis(bromomethyl)-2-trichloromethyl-1,3-dioxane 1 according to the results of NMR ^{1}H, ^{13}C and X-ray analysis corresponds to the conformation of *chair* with the equatorial CCl_3 substituent. The route of conformational transformations of isolated molecule of acetal 1 and cluster 1@5CHCl$_3$ using DFT approximation PBE/3ξ (explicit model), includes, in addition to the equatorial *chair* (main minimum on the surface of the potential energy) local minima of *2,5-twist* and a *chair* with axial CCl_3 group, as well as transitional states, corresponding to the forms of a *half-chairs*. The calculative barriers to the internal rotation of CCl_3 substituent in equatorial and axial conformers of dioxane 1 were also identified. The bulky substituent CCl_3, in comparison with the phenyl group (dioxane 2), increases the interplanar angle in the heteroatomic part of the ring and noticeably affects the parameters of the conformational dynamics of dioxane 1.

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Additional information

Crystallographic data as .cif files for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Center with CCDC 2,086,414 for the molecule 1.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Sh.Yu. Khazhiev: Formal analysis. **M.A. Khusainov:** Methodology, Conceptualization. **R.A. Khalikov:** Formal analysis. **V.A. Kataev:** Investigation. **T.V. Tyumkina:** Investigation, Validation. **E.S. Mescheryakova:** Investigation, Validation. **L.M. Khalilov:** Methodology. **V.V. Kuznetsov:** Conceptualization, Software, Writing – review & editing.

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Supplementary materials

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