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Structure and Conformational Analysis of 5,5-Bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane

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Abstract—The structure of 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane **1** has been studied by means of ^{1}H and ^{13}C NMR spectroscopy as well as X-ray diffraction analysis. The molecules of compound **1** exist in the chair conformation with the axially oriented phenyl group. The computer simulation using DFT approximation at the PBE/3ξ level has revealed the route of interconversion of the ring and the optimal conformation of the phenyl group corresponding to the data of X-ray diffraction analysis.

Keywords: 1,3-dioxane, 5,5-bis(halomethyl)-1,3-dioxanes, X-ray diffraction analysis, conformers, computer simulation

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Substituted 1,3-dioxanes are interesting due to special structural features and are widely applied as synthons in fine organic synthesis [2–4]. For example, 5,5-bis(halomethyl)-1,3-dioxanes can be easily converted into the mono- and diiodo-derivatives; the process proceeds stereoselectively, predominantly at the equatorial chloromethyl substituent [5].

The conformational behavior of formals of 5,5-bis(halomethyl)-1,3-dioxanes at room temperature is characterized by fast interconversion of the ring (at the NMR timescale) [6]. On the contrary, the molecules of 2-substituted analogs exist predominantly in the *chair* conformation with equatorial orientation of the substituent at the C^2 atom (C_e) [7, 8]. However, conformational behavior of the ketals of the same series has been scarcely studied. To fill in the gap, this study was devoted to investigation of the structure and conformational transformations of 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane using ^{1}H and ^{13}C NMR spectroscopy, X-ray diffraction analysis, and DFT simulation using the PBE/3ζ method implemented in PRIRODA software package [9].

The hitherto unknown 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane was synthesized via the condensation of 2,2-bis(bromomethyl)-1,3-propanediol with acetophenone (Scheme 1).

The results of X-ray diffraction investigation of the obtained ketal are summarized in Tables 1 and 2. The structure of the molecule of 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane corresponded to the *chair* conformation with the axial phenyl group (C_a, see figure). The planes of the aromatic ring and the O^1–O^5–C^3–C^{14} fragment were practically orthogonal. For the heteroatomic part of the heterocyclic ring, the

Scheme 1.

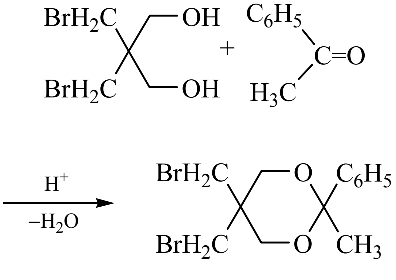


Table 1. Crystallographic data and details of X-ray diffraction experiment

Parameter	Value	Parameter	Value
Formula	$C_{13}H_{16}O_2Br_2$	Z	4
M	364.06	ρ_{calc}, mg/mm^3	1.693
T, K	293(2)	μ, mm^{-1}	5.665
Crystallographic system	Monoclinic	F(000)	720.0
Space group	$P2_1/c$	Indexes range	$-9 \le h \le 7$ $-26 \le k \le 20$ $-14 \le l \le 13$
a, Å	6.9219(4)	Number of reflections used for refinement/number of refined parameters	2777/145
b, Å	19.0319(11)	GOOF	1.090
c, Å	11.2114(8)	Final values of divergence factors for reflections with $I \ge 2\sigma(I)$	$R_1 = 0.0861$ $wR_2 = 0.1492$
β, deg	104.780(6)	Final values of divergence factors for all reflections	$R_1 = 0.1634$ $wR_2 = 0.1815$
V, Å^3	1428.09(16)	Residual electronic density, e/Å^{-3}	0.47/–1.01

values of the C–O bond lengths (1.416–1.430 Å) and bond angles (110°–113°) corresponded to conventional values. The interplane angles between the 1,3-dioxane ring fragments COO and COOC (α_1) as well as COOC and CCC (α_2) equaled 129.2(5)° and 130.7(5)°, respectively. It should be noted that the heteroatomic fragment of the molecule of the studied ketal was more folded as compared to 5,5-bis(bromomethyl)-2-phenyl-1,3-dioxane, the α_1 value for the latter being 120.1° [3]. The bromomethyl substituents, in accordance with the earlier performed quantum-chemical simulations [7], were in the *gauche*-position with respect to each other (see figure), in the conformation corresponding to the minimum of energy.

^{1}H and ^{13}C NMR spectra demonstrate the conformational homogeneity of the molecules of 5,5-bis(bromomethyl)-2-phenyl-1,3-dioxane in solution. The assignment of the signals in the ^{1}H and ^{13}C NMR spectra was performed using the data of 1D and 2D spectroscopy (DEPT135, NOESY, COSYHH, and HSQC techniques). The methylene protons at the magnetically equivalent carbon atoms C^4 and C^6 of the heterocyclic ring were diastereotopic (Δδ 0.26 ppm)

Table 2. Selected bond lengths and bond angles in the molecule of 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane

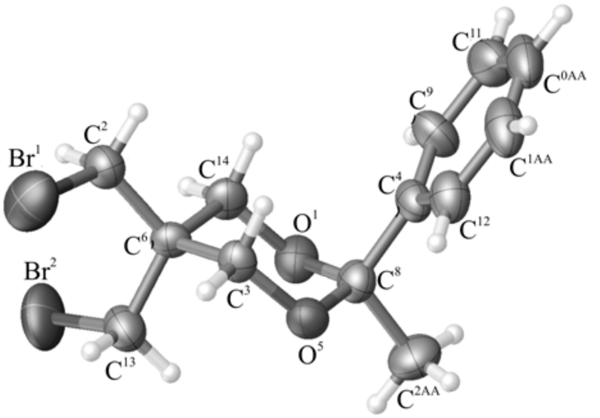
Bond	d, Å		Bond angle	φ, deg	
	calculation	experiment		calculation	experiment
$O^1–C^8$	1.434	1.416(8)	$C^{14}O^1C^8$	113.6	113.8(4)
$O^1–C^{14}$	1.432	1.423(7)	$C^3O^5C^8$	113.8	114.0(5)
$O^5–C^8$	1.435	1.430(7)	$O^1C^8O^5$	110.5	110.1(5)
$O^5–C^3$	1.431	1.426(7)	$O^1C^{14}C^6$	111.3	110.2(5)
$C^8–C^4$	1.538	1.530(8)	$O^5C^3C^6$	112.1	110.6(4)
$C^6–C^2$	1.525	1.521(8)	$C^3C^6C^{14}$	105.4	110.0(5)
$C^6–C^{13}$	1.529	1.532(8)	$C^6C^2Br^1$	114.1	113.6(4)
$C^2–Br^1$	1.989	1.955(6)	$C^6C^{13}Br^2$	114.1	113.9(5)
$C^8–C^{2AA}$	1.525	1.507(8)	$C^2C^6C^{13}$	113.1	113.0(5)

and appeared as doublets with ^2J = 10.7 Hz in the ^{1}H NMR spectrum. The methylene protons of the bromomethylene substituents at the C^5 atom of the ring were magnetically nonequivalent ($\Delta\delta$ = 0.90 ppm); the NOESY experiment showed that the protons of the axial CH_2Br group resonated in a lower field.

The obtained results were confirmed by the data of conformational analysis of 5,5-bis(bromomethyl)-2-phenyl-1,3-dioxane at the PBE/3ζ level. The potential energy surface (PES) contained three minimums (conformers C_e, C_a, and 2,5-*T*) and two transition states TS-1 and TS-2 (Scheme 2). The simulations were performed for the *gauche*-orientation of bromomethyl substituents at the C^5 atom of the heterocyclic ring.

The global minimum of the PES corresponded to the C_a form (Table 3). The simulated values of the bond lengths as well as bond and torsional angles were close to the data of the X-ray diffraction experiment (Table 2). The phenyl group, as in the case of the molecule in the crystal (see figure), was orthogonal to the O^1–O^5–C^3–C^{14} plane of the heterocyclic ring (see the atoms enumeration in the figure). Simulation of its internal rotation in the course of scanning over the C^{2AA}–C^8–C^4–C^{12} torsion angle (φ) resulted in appearance of a transition state in which the phenyl group was oriented along the bisector plane of the heterocyclic ring; the potential barrier for such rotation ($\Delta G^{\neq}_{298}$) was 11.1 kcal/mol.

The 2,5-*T* conformer showed the nearest local minimum to the C_a form, whereas the C_e form was the least stable. The transition states, *half-chair* conformations, differed in energy by 1.2 kcal/mol ($\Delta G^{\neq}_{298}$); the maximum height of the potential barrier (9.2 kcal/mol) was well consistent with the experimental data for 2-methyl-2-phenyl-1,3-dioxane [1]. Note also the absence of an intermediate 1,4-*twist* minimum on the PES, which is typical for the equilibriums of the molecules of unsubstituted as well as the 2-, 4-, 5-, 2,5-, and 4,4-substituted 1,3-dioxanes [4].

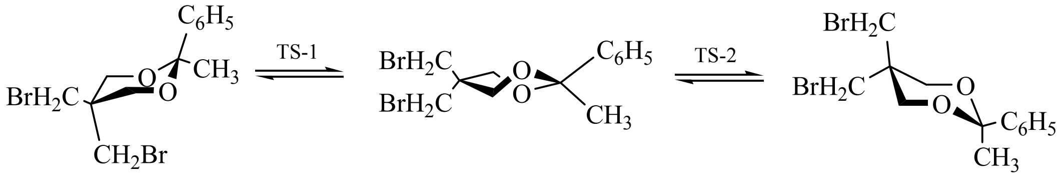


Structure of 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane molecule in the crystal.

In summary, the data of the X-ray diffraction analysis, NMR spectroscopy, and computer simulation solidly proved the conformational homogeneity of the molecules of 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane existing in the *chair* conformation with the axial phenyl group.

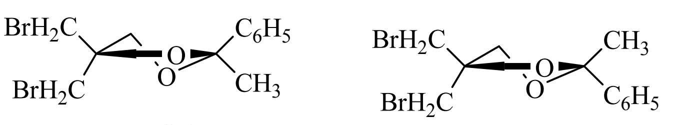
Scheme 2.

Minimums



C_a 2,5-*T* C_e

Transition state



TS-1 TS-2

Table 3. Energy parameters of conformational transformations of 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane molecule according to the data of PBE/3ζ simulations

Conformers	$-E_0$[a], Hartree	ΔE°_0, kcal/mol ($\Delta E^{\neq}_0$)	ΔH°_{298}, kcal/mol ($\Delta H^{\neq}_{298}$)	ΔG°_{298}, kcal/mol ($\Delta G^{\neq}_{298}$)	ΔS°_{298}, cal mol^{-1} K^{-1} ($\Delta S^{\neq}_{298}$)
C_a	5802.274495	0	0	0	0
C_e	5802.269567	3.1	3.2	2.6	1.9
2,5-T	5802.270376	2.6	2.6	2.1	1.7
TS-1	5802.261527	(8.1)	(7.9)	(8.0)	(–0.4)
TS-2	5802.258974	(9.7)	(9.5)	(9.2)	(1.2)
Rotation 2-Ph (C_a)	5802.262507	(10.1)	(9.5)	(11.1)	(–5.5)

[a] With ZPE.

EXPERIMENTAL

NMR spectra were registered using a Bruker Avance 400 spectrometer operating at 400.13 (^{1}H) and 100.62 (^{13}C) MHz, in $CDCl_3$ with residual protons of the solvent used as internal reference. X-ray diffraction analysis was performed using an XCalibur Eos automated four-circle diffractometer (graphite monochromator, MoK_α radiation, λ = 0.71073 Å, ω-scanning, $2\theta_{max}$ = 62°). Collection and processing of the data were performed using CrysAlis^{Pro} 1.171.36.20 software (Oxford Diffraction Ltd.). The structures were solved via the direct method and refined by full-matrix least square method under anisotropic approximation for non-hydrogen atoms. Hydrogen atoms were localized from the differential Fourier synthesis and refined under isotropic approximation. The calculations were performed using SHELX97 software [10]. The structural data were deposited at the Cambridge Crystallographic Database Center (CCDC 1849061).

Preliminary geometry optimization of the C_a conformer of 5,5-bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane was performed using AM1 method implemented in HyperChem 8.0 software [11]. The obtained structure was investigated using PBE/3ζ method (PRIRODA [9]). Simulation of conformational transformations of the phenyl group in the C_a conformer was performed by geometry optimization with varying the C^{2AA}–C^8–C^4–C^{12} torsion angle from 0° to 180°; simulation of interconversion of the ring was performed by scanning over the transannular CCCO torsion angle from –60° to 60°. The values of potential barriers were found by the transition states search procedure using PRIRODA software package. The correspondence of the PES stationary points to the transition states was confirmed by the presence of a single imaginary frequency in the corresponding Hessian, whereas no imaginary frequencies were found for the points corresponding to the minimum.

5,5-Bis(bromomethyl)-2-methyl-2-phenyl-1,3-dioxane was prepared via a method adopted from Ref. [12], by refluxing an equimolar mixture (0.01 mol each) of 2,2-bis(bromomethyl)-1,3-propanediol with acetophenone in the presence of 0.1 g of *p*-toluenesulfonic acid. Yield 73%, mp 96–97°C (hexane–ethanol 1 : 1). ^{1}H NMR spectrum, δ, ppm: 1.58 s (3H, CH_3), 3.12 s (2H, CH_2Br_{eq}), 3.63 d (2H, H^A, J = 10.7 Hz), 3.89 d (2H, H^B, J = 10.7 Hz), 4.02 s (2H, CH_2Br_{ax}), 7.29–7.44 m (5H, C_6H_5). ^{13}C NMR spectrum, δ, ppm: 31.5 (C^2), 36.1 (C^{13}), 37.5 (C^6), 66.1 ($C^{3,14}$), 101.4 (C^8), 126.5 (C^p), 128.2 (C^m), 129.0 (C^o), 139.4 (C^{ipso}). Found, %: C 42.79; H 4.33; Br 44.01. $C_{13}H_{16}Br_2O_2$. Calculated, %: C 42.85; H 4.39; Br 43.95.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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