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Structure and Conformational Analysis of 5,5-Bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane

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Abstract—The structure of 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane has been studied by ^{1}H and ^{13}C NMR and X-ray diffraction. Molecules of the title compound exist in the *chair* conformation with equatorial orientation of the methoxyphenyl substituent. The dioxane ring inversion path, free conformational energy, and optimal conformation of the aryl group have been determined by computer simulation in terms of the DFT PBE/3ζ method. The calculation results are consistent with the X-ray diffraction data.

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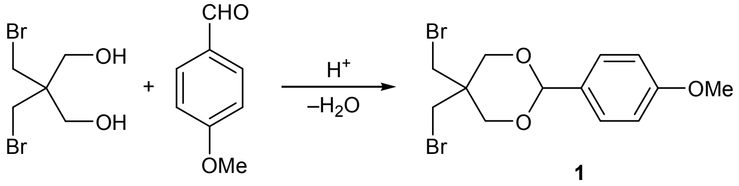
1,3-Dioxanes are used as reagents in fine organic synthesis and are classical model structures for conformational analysis [1–4]. 5,5-Bis(halomethyl)-1,3-dioxanes occupy a particular position among six-membered cyclic acetals due to the presence of additional reaction centers, i.e., halogen atoms capable of being replaced by nucleophiles. For example, bis(chloromethyl) analogs are relatively readily converted to mono- and diiodo derivatives; the reaction is stereoselective, and it involves mainly the equatorial chloromethyl group [5].

The conformational behavior of 5,5-bis(halomethyl)-1,3-dioxanes at room temperature is characterized by fast (on the NMR time scale) ring inversion [6, 7], while 2-substituted analogs preferentially adopt a *chair* conformation with equatorial orientation of the 2-substituent (C_{eq}) [8–10]. The present work was aimed at studying the structure and conformational transformations of previously unknown 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**1**) by ^{1}H and ^{13}C NMR, X-ray diffraction, and DFT PBE/3ζ calculations (PRIRODA software [11]).

A sample of **1** was prepared by condensation of 2,2-bis(bromomethyl)propane-1,3-diol with 4-methoxybenzaldehyde (Scheme 1). The structure of dioxane **1** was determined by X-ray analysis (see Experimental), and the results were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1813094). Molecule **1** has a *chair* conformation with equatorial orientation of the 4-methoxyphenyl group at C^2 (C_{eq}, Fig. 1). The aromatic ring and the $O^{14}C^{17}C^5O^{12}$ fragment of the 1,3-dioxane ring form a dihedral angle of 91.8°. The heteroatom part of the heterocycle is characterized by expected C–O bond lengths ranging

Scheme 1.



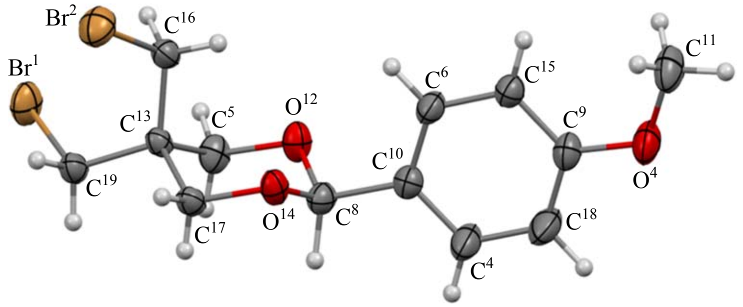


Fig. 1. Structure of the molecule of 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**1**) according to the X-ray diffraction data.

Table 1. Selected bond lengths and bond and torsion angles in the molecule of 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**1**)

Bond	Bond length, Å		Bond angle	ω, deg		Torsion angle	τ, deg	
	calculated	experimental		calculated	experimental		calculated	experimental
$Br^1–C^{19}$	1.989	1.951(5)	$O^{14}C^8O^{12}$	110.6	110.0(4)	$C^6C^{10}C^8O^{12}$	80.5	62.7(7)
$C^5–O^{12}$	1.429	1.423(6)	$C^{17}O^{14}C^8$	110.8	112.8(4)	$C^4C^{10}C^8O^{14}$	140.8	120.2(6)
$C^8–O^{12}$	1.432	1.420(6)	$C^5O^{12}C^8$	110.8	110.9(4)	$C^8O^{14}C^{17}C^{13}$	–59.4	–59.1(3)
$C^8–O^{14}$	1.425	1.409(7)	$C^{13}C^{17}O^{14}$	111.6	110.0(4)	$O^{14}C^{17}C^{13}C^5$	52.9	54.0(6)
$C^{13}–C^{16}$	1.529	1.507(8)	$C^{13}C^5O^{12}$	111.8	111.5(4)	$C^8O^{12}C^5C^{13}$	58.6	59.7(6)
$C^8–C^{10}$	1.504	1.497(7)	$C^5C^{13}C^{17}$	105.8	106.0(5)	$C^{15}C^9O^4C^{11}$	–0.1	6.4(9)

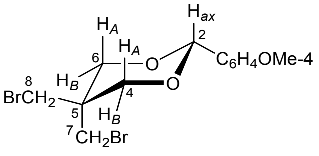
from 1.409 to 1.423 Å and bond angles close to 110°. The torsion angles are also typical of a *chair* conformation (Table 1) [2, 12]. The bromomethyl substituents are oriented *gauche* with respect to each other (Fig. 1); as shown previously by quantum-chemical calculations [9], such conformation possesses lower energy than alternative arrangement of the carbon–halogen bonds in the halomethyl groups on C^5. The methoxy group is almost coplanar with the aromatic ring: the corresponding torsion angle is 6.4°.

The NMR data (Table 2) indicated high conformational homogeneity of molecules **1** in solution. Signals in the ^{1}H and ^{13}C NMR spectra of **1** were assigned on the basis of one- and two-dimensional NMR experiments (DEPT 135, NOESY, ^{1}H–^{1}H COSY, and HSQC). Methylene protons on the magnetically equivalent C^4 and C^6 atoms of the heterocycle are diastereotopic ($\Delta\delta$ = 0.4 ppm), and they resonate in the ^{1}H NMR spectrum as two doublets with a geminal coupling constant ^2J of –11.8 Hz. Methylene protons of the bromomethyl substituents at C^5 are also nonequivalent ($\Delta\delta$ = 0.7 ppm); according to the NOESY data, the signals of the axial CH_2Br group are located in a low field (Table 2). The most downfield carbon signal in the ^{13}C NMR spectrum was assigned to C^2 (δ_C 102.3 ppm); it showed a correlation with 2-H$_{ax}$ (δ 5.4 ppm) in the HSQC spectrum.

The obtained results were confirmed by conformational analysis of molecule **1** in terms of the DFT PBE/3ζ approximation. Four minima were localized on the potential energy surface of this compound, namely conformers C_{eq} (**A**, **B**), C_{ax}, and 2,5-*T*, as well as two transition states TS-1 and TS-2 (Scheme 2). The calculated bond lengths and bond and torsion angles were fairly similar to the corresponding experimental values determined by X-ray analysis (Table 1).

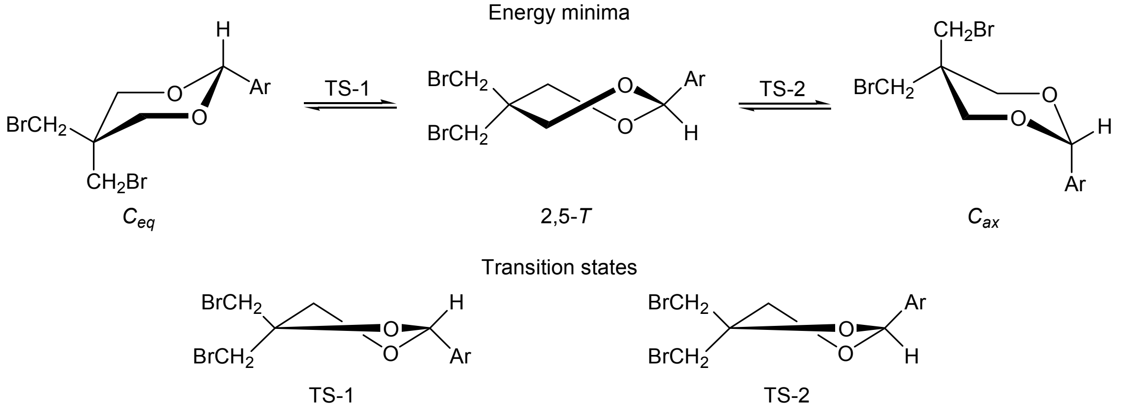
Structures **A** and **B** resulting from internal rotation of the 4-methoxyphenyl group are almost degenerate

Table 2. ^{1}H and ^{13}C NMR spectra (chemical shifts δ, δ_C) of 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**1**)



Proton	δ, ppm (^2J, Hz)	Carbon	δ_C, ppm
H_{ax}	5.4 s	C^2	102.3
H_A	3.9–3.8 d (11.8)	C^4, C^6	71.9
H_B	4.3–4.2 d (11.8)	C^5	37.4
CH_2Br (*ax*)	4.0 s	C^7	36.1
CH_2Br (*eq*)	3.3 s	C^8	34.6
CH_3O	3.8 s	OCH_3	55.4

Scheme 2.



Ar = 4-$MeOC_6H_4$.

in energy (Fig. 2, Table 3). However, the planes of the aromatic ring and $O^{14}C^{17}C^{5}O^{12}$ fragment in conformer **A** form a dihedral angle of 96°, which is close to the X-ray diffraction data (91.8°), whereas the same moieties in conformer **B** are almost coplanar. The calculated (PBE/3ζ) potential barrier to internal rotation of the equatorial aryl group ($\Delta G^{\ne}_{298}$, TS 2-Ar) in conformer C_{eq} is 2.0 kcal/mol, and the barrier for the rotation of the methoxy group in C_{eq} (**A**, TS OCH_3) is 4.2 kcal/mol (Table 3). Thus, molecules **1** in the gas phase at room temperature are characterized by restricted rotation of both substituents.

Conformers C_{ax} and 2,5-*T* have fairly similar energies (ΔG^{0}_{298}). The energies of the transition states (*half-chair* conformers) differ by 1.7 kcal/mol ($\Delta G^{\ne}_{298}$); the highest potential barrier (11.0 kcal/mol) is very consistent with the experimental data for 1,3-dioxanes [2]. It should also be noted that no intermediate energy minimum (1,4-*twist*) typical of conformational equilibria of unsubstituted and 2-, 4-, 5-, 2,5-, and 4,4-substituted 1,3-dioxanes [12] was localized on the potential energy surface of compound **1**.

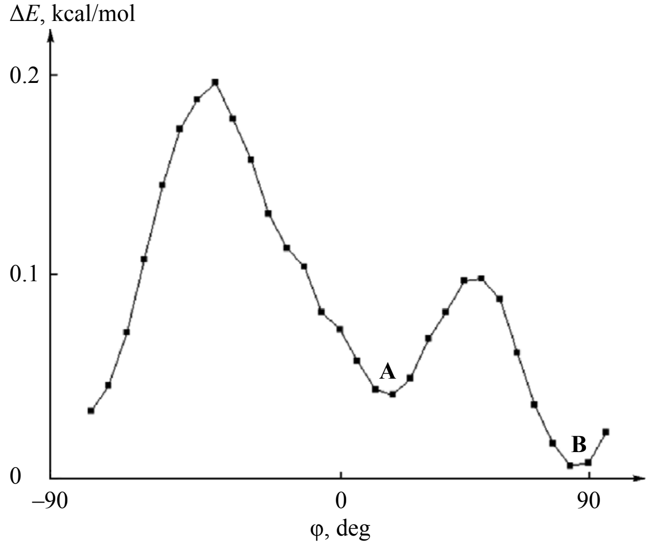


Fig. 2. Energy profile for internal rotation of the phenyl group (dihedral angle $H^{a}C^{2}C_{arom}C'_{arom}$) in the C_{eq} conformer of 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**1**) at 0 K.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 400.13 and 100.62 MHz, respectively, from solutions in $CDCl_3$; the chemical shifts were measured relative to the residual proton and carbon signals of the solvent.

The X-ray diffraction data were obtained with an XCalibur Eos automated four-circle diffractometer (Mo K_{α} radiation, λ 0.71073 Å, graphite monochromator, ω-scanning, $2\theta_{max} = 62°$). The data were acquired and processed using CrysAlis^{Pro} (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 difference Fourier syntheses, and their positions were refined in isotropic approximation. The calculations were performed using SHELX97 [13]. Crystallographic data and parameters of the X-ray diffraction experiment: temperature 293(2) K, monoclinic crystal system, space group $P2_1/c$; unit cell parameters: $a = 14.7130(8)$, $b = 8.4871(5)$, $c = 11.3429(6)$ Å; $\beta = 91.844(5)°$; $V = 1415.66(14)$ Å^3; $Z = 4$, $d_{calc} = 1.783$ mg/mm^3; $\mu = 5.724$ mm^{-1}; $F(000) = 752.0$; θ range 5.54–58.198°; $-19 \le h \le 10$, $-11 \le k \le$

Table 3. Energy parameters of conformational transformations of 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**1**) according to PBE/3ζ calculations

Structure	$-E_0$,[a] hartree	ΔE_0^0 ($\Delta E_0^{\neq}$), kcal/mol	ΔH_{298}^0 ($\Delta H_{298}^{\neq}$), kcal/mol	ΔG_{298}^0 ($\Delta G_{298}^{\neq}$), kcal/mol	ΔS_{298}^0 ($\Delta S_{298}^{\neq}$), cal mol^{-1} K^{-1}
C_{eq}, **A**	5877.436997	0.01	0	0	0
C_{eq}, **B**	5877.436974	0	0.01	0.08	–0.3
C_{ax}	5877.432858	2.6	2.5	3.4	–3.0
2,5-*T*	5877.431091	3.7	3.7	3.2	1.9
TS-1	5877.421975	9.4	9.1	9.4	–1.0
TS-2	5877.419970	10.7	10.4	11.1	–2.3
C_{eq}, TS 2-Ar	5877.436732	0.2	–0.4	2.0	–8.2
C_{eq}, **B**, TS OCH_3	5877.431052	3.7	3.4	4.2	–2.8

[a] Corrected for zero-point vibrational energy.

6, –14 ≤ l ≤ 15; number of independent reflections 3258 (R_{int} = 0.0260); final divergence factors: R_1 = 0.0565, wR_2 = 0.1426 [reflections with $I > 2\sigma(I)$]; R_1 = 0.1027, wR_2 = 0.1757 (all independent reflections); goodness of fit S = 0.978; $\Delta\rho_{\min/\max}$ 1.16/–0.85 $\bar{e}$ Å^{-3}.

The geometric parameters of conformers C_{eq} and C_{ax} of dioxane **1** were initially optimized by the AM1 method (HyperChem 8.0 [14]), and the optimized structures were then analyzed at the DFT PBE/3ζ level (PRIRODA [11]). Conformational transformations of the aryl group in C_{eq} were simulated by geometry optimization upon variation of the torsion angle $H_{ax}C^2C_{\text{arom}}C'_{\text{arom}}$ from –90 to 90° (Fig. 2); the ring inversion was simulated by scanning the endocyclic torsion angle CCCO in the range from –60 to 60°. The potential barriers to internal rotation were determined by the transition state search procedure implemented in PRIRODA. Stationary points on the potential energy surface were identified as transition states by the presence of one imaginary frequency in the corresponding Hessian matrix, and as energy minima, by the absence of imaginary frequencies therein.

5,5-Bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (1). An equimolar (0.1 mol) mixture of 2,2-bis(bromomethyl)propane-1,3-diol and 4-methoxybenzaldehyde in 300 mL of benzene containing 0.1 g of *p*-toluenesulfonic acid was refluxed in a flask equipped with a Dean-Stark trap until water no longer separated. The mixture was cooled and washed with a 5% solution of $NaHCO_3$ (2×50 mL), the solvent was distilled off, and the residue was recrystallized from ethanol. Yield 73%, mp 117–118°C.

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