

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 ¹H and ¹³C 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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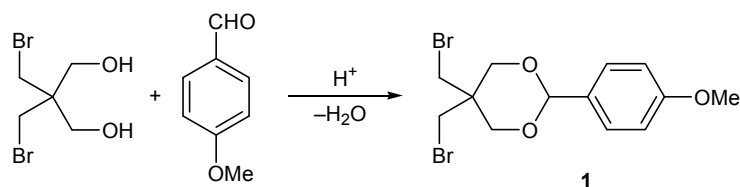
1,3-Dioxanes are used as reagents in fine organic synthesis and are classical model structures for conformational analysis [1–4]. 5,5-Bis(halomethyl)-1,3-dioxanes occupy a particular position among six-membered cyclic acetals due to the presence of additional reaction centers, i.e., halogen atoms capable 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 ¹H and ¹³C 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 C² (*C_{eq}*, Fig. 1). The aromatic ring and the O¹⁴C¹⁷C⁵O¹² 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.



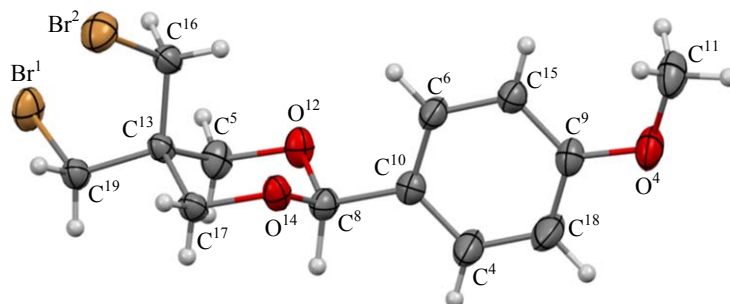


Fig. 1. Structure of the molecule of 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**1**) according to the X-ray diffraction data.

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 ⁸ O ¹²	110.6	110.0(4)	C ⁶ C ¹⁰ C ⁸ O 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 ⁴ C ¹⁰ C ⁸ O ¹⁴	140.8	120.2(6)
C ⁸ –O ¹²	1.432	1.420(6)	C ⁵ O ¹² C ⁸	110.8	110.9(4)	C ⁸ O 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 ⁵ O ¹²	111.8	111.5(4)	C ⁸ O ¹² C ⁵ C ¹³	58.6	59.7(6)
C ⁸ –C ¹⁰	1.504	1.497(7)	C ⁵ C ¹³ C ¹⁷	105.8	106.0(5)	C ¹⁵ C ⁹ O ⁴ C ¹¹	–0.1	6.4(9)

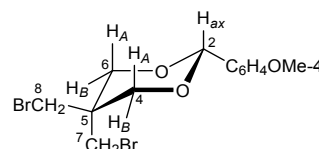
from 1.409 to 1.423 Å and bond angles close to 110°. The torsion angles are also typical of a *chair* conformation (Table 1) [2, 12]. The bromomethyl substituents are oriented *gauche* with respect to each other (Fig. 1); as shown previously by quantum-chemical calculations [9], such conformation possesses lower energy than alternative arrangement of the carbon–halogen bonds in the halomethyl groups on C⁵. 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 ¹H and ¹³C NMR spectra of **1** were assigned on the basis of one- and two-dimensional NMR experiments (DEPT 135, NOESY, ¹H–¹H COSY, and HSQC). Methylene protons on the magnetically equivalent C⁴ and C⁶ atoms of the heterocycle are diastereotopic ($\Delta\delta = 0.4$ ppm), and they resonate in the ¹H NMR spectrum as two doublets with a geminal coupling constant ²*J* of –11.8 Hz. Methylene protons of the bromomethyl substituents at C⁵ are also nonequivalent ($\Delta\delta = 0.7$ ppm); according to the NOESY data, the signals of the axial CH₂Br group are located in a low field (Table 2). The most downfield carbon signal in the ¹³C NMR spectrum was assigned to C² (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/3 ζ 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. ¹H and ¹³C NMR spectra (chemical shifts δ , δ_C) of 5,5-bis(bromomethyl)-2-(4-methoxyphenyl)-1,3-dioxane (**1**)



Proton	δ , ppm (² <i>J</i> , 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 ₂ Br (<i>ax</i>)	4.0 s	C ⁷	36.1
CH ₂ Br (<i>eq</i>)	3.3 s	C ⁸	34.6
CH ₃ O	3.8 s	OCH ₃	55.4