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

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Abstract—The structure of 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane was studied by ^{1}H and ^{13}C NMR spectroscopy and X-ray analysis. Its molecules in crystal adopt a *chair* conformation, whereas equilibrium between energy-degenerate *chair* invertomers exists in solution at room temperature. According to the low-temperature NMR data, the interconversion barrier amounts to 8.9 kcal/mol. The ring inversion path was simulated by DFT quantum chemical calculations using PBE/3ξ and (in some cases) RI-MP2/λ2 approximations, and the potential barrier to interconversion in different solvents was estimated by the cluster model. The calculated geometric parameters of the title compound were consistent with the experimental X-ray diffraction data, and the calculated interconversion barrier matched a cluster containing 5 molecules of methylene chloride in the nearest solvation shell of the substituted 1,3-dioxane molecule.

Keywords: 1,3-dioxane, X-ray analysis, conformer, interconversion barrier, cluster model, computer simulation.

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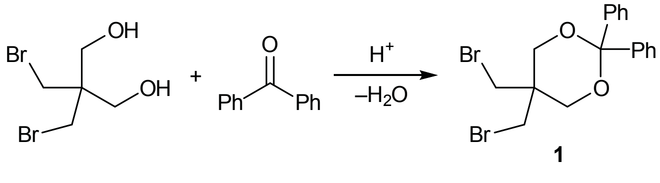
Substituted 1,3-dioxanes are classical models for conformational analysis; they are also used as reagents in fine organic synthesis [1–4]. Interest in 5,5-bis(halomethyl)-1,3-dioxanes is determined by the presence in their molecules of additional reaction centers, i.e., halogen atoms that can be replaced via nucleophilic substitution reactions [5]. The conformational behavior of 5,5-bis(halomethyl)-1,3-dioxanes at room temperature is characterized by fast (on the NMR time scale) inversion of the six-membered 1,3-dioxane ring [6, 7]; 2-substituted 5,5-bis(halomethyl)-1,3-dioxanes preferentially exist as *chair* conformers with the equatorial substituent on C^2 [8–11].

The present article reports the structure and conformational transformations of previously unknown 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane (**1**), which were studied by ^{1}H and ^{13}C NMR spectroscopy and X-ray analysis, as well as by DFT PBE/3ζ quantum chemical method (PRIRODA software [12]). This method showed good results for structurally related compounds [11]. In addition, the effect of the solvent nature and the number of its molecules in the solvation shell on the relative energies of minima and transition state on the potential energy surface (PES) of compound **1** was analyzed in the framework of the cluster model. A sample of dioxane **1** was synthesized by condensation of 2,2-bis(bromomethyl)propane-1,3-diol with benzophenone (Scheme 1).

The X-ray diffraction data for a single crystal of **1** are given in Experimental and were deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1 880 875). Compound **1** crystallizes in the noncentrosymmetric *P*1 space group of the triclinic crystal

Scheme 1.



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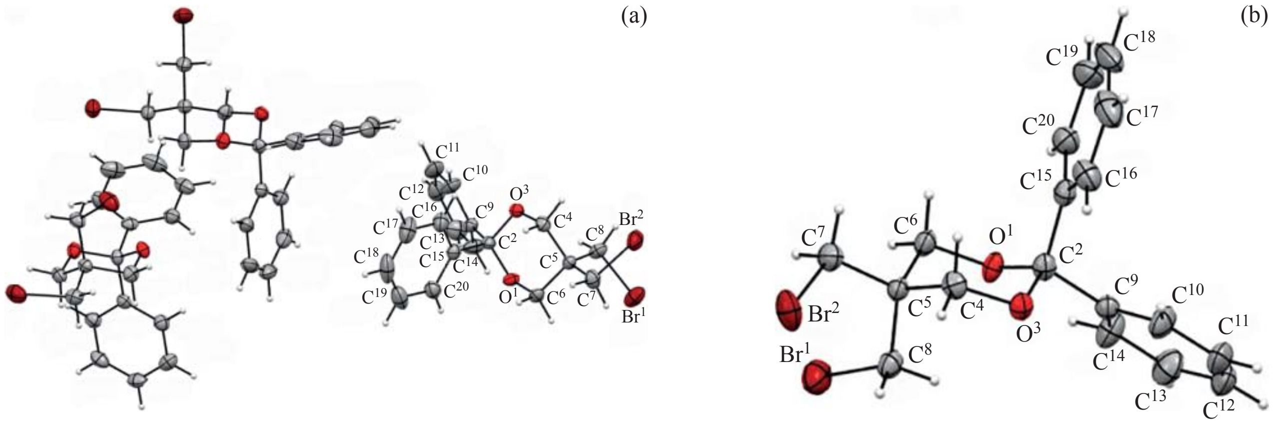


Fig. 1. (a) Asymmetric unit cell of 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane (**1**) containing three independent molecules; (b) molecule **1** with non-hydrogen atoms shown as thermal vibration ellipsoids with a probability of 50%.

system with a unit cell containing three independent molecules with similar geometric parameters (Fig. 1, Table 1). Molecules **1** in crystal have a *chair* conformation. The heteroatom moiety of the 1,3-dioxane ring is characterized by expected C–O bond lengths (1.410–1.431 Å) and bond angles in the range 110–114°. The torsion angles are also consistent with those typical of *chair* conformers (Table 1) [2, 11]. It should be noted that the bromomethyl substituents are oriented *gauche* with respect to each other (Fig. 1); as shown previously by quantum chemical calculations [13], this structure is more energetically favorable than alternative conformations of carbon–halogen bonds in the substituents on C^5 of 1,3-dioxanes.

The data of 1D and 2D ^{1}H and ^{13}C NMR spectroscopy (including NOESY, ^{1}H–^{1}H COSY, and HSQC techniques; Table 2) indicated that cyclic ketal **1** in different solvents at room temperature exists as an equilibrium mixture of invertomers. This followed from the fact that methylene protons of the dibromomethyl substituents and on the magnetically equivalent C^4 and C^6 atoms resonated as singlets. In the low-temperature ^{1}H NMR spectrum in CD_2Cl_2, the C^4H_2 and C^6H_2 protons appeared as a doublet with a coalescence temperature of 213 K. The corresponding signal splitting was observed in the ^{13}C NMR spectrum. On the basis of these data, the interconversion barrier was estimated at $\Delta G^{\neq}_{298}$ = 8.9 kcal/mol.

The experimental results were confirmed by conformational analysis of dioxane **1** in the PBE/3ζ and (for the isolated molecule) RI-MP2/λ2 approximations. Two minima corresponding to *chair* (*C*) and 2,5-*twist* conformers (2,5-*T*), as well as transition state (TS) with a half-*chair* conformation, were localized on the potential energy surface (Scheme 2). The calculated bond length and bond and torsion angles for structure *C* were fairly similar to those found experimentally by X-ray analysis (Table 1).

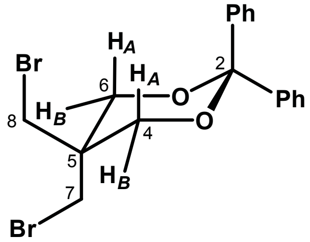
Table 3 contains the relative energies of all species corresponding to stationary points on the PES for the isolated molecule of **1**, as well as for some clusters with several solvents. The differences in the calculated energies of *C* and 2,5-*T* in clusters with solvents (PBE/3ζ, ΔG^{0}_{298}) are larger than that found for the gas

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

Bond	Bond length, Å		Bond angle	φ, deg		Torsion angle	τ, deg	
	calcd.	exptl.		calcd.	exptl.		calcd.	exptl.
Br^1–C^8	1.987	1.944(4)	$O^1C^2O^3$	110.6	110.3(3)	$C^4C^5C^6O^1$	54.9	55.3(4)
C^2–O^1	1.432	1.410(4)	$C^2O^1C^6$	113.5	114.0(3)	$C^6C^5C^4O^3$	–54.2	–55.3(4)
C^2–O^3	1.432	1.431(4)	$C^2O^3C^4$	113.7	114.1(2)	$C^2O^3C^4C^5$	56.9	58.1(4)
C^4–O^3	1.432	1.420(4)	$C^5C^6O^1$	111.2	110.4(3)	$C^2O^1C^6C^5$	–58.7	–57.3(4)
C^2–C^9	1.529	1.516(5)	$C^5C^4O^3$	111.9	111.7(3)	$C^4O^3C^2O^1$	–55.3	–56.1(4)
C^5–C^8	1.529	1.511(5)	$C^4C^5C^6$	105.2	104.8(3)	$C^6O^1C^2O^3$	56.4	55.5(4)

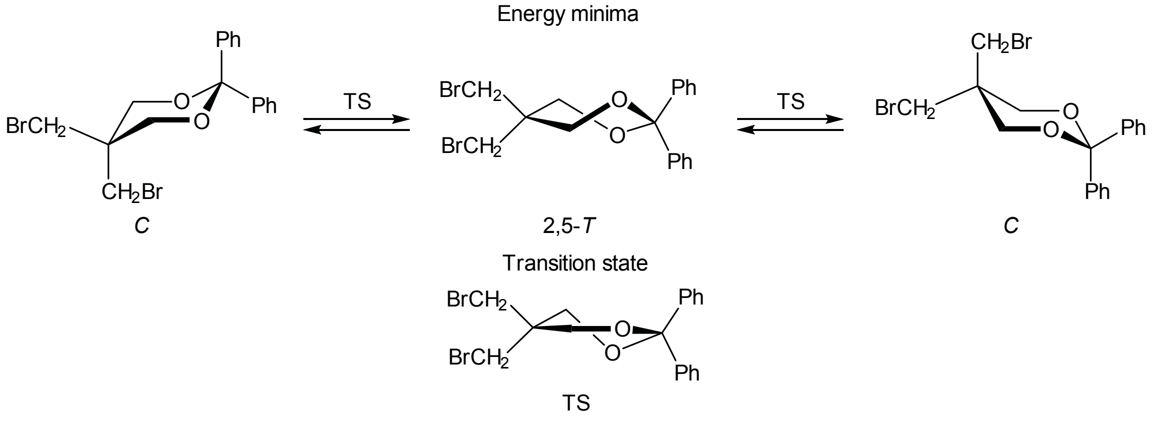
[a] Calculations were performed for the *chair* conformer in the gas phase using PBE/3ζ approximation.

Table 2. ^{1}H and ^{13}C NMR spectra of 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane (**1**)



Solvent	Proton	δ, ppm	Carbon atom	δ_C, ppm
$CDCl_3$	CH_2Br	3.6 s	C^2	101.8
	CH_2O	4.0 s	C^4, C^6	66.5
	C_6H_5	7.3–7.6 m	C^5	38.0
			C^7, C^8	35.5
			C_{arom}	126.4–140.9
$CDCl_2$, 298 K	CH_2Br	3.6 s	C^2	101.6
	CH_2O	4.0 s	C^4, C^6	66.4
	C_6H_5	7.3–7.5 m	C^5	37.9
			C^7, C^8	35.6
			C_{arom}	126.2–141.2
$CDCl_2$, 213 K	CH_2Br	3.6 d	C^2	101.2
	CH_2O	3.9 s	C^4, C^6	66.2
	C_6H_5	7.3–7.5 m	C^5	37.9
			C^7, C^8	35.3, 36.7
			C_{arom}	124.6–128.3
DMSO-d_6	CH_2Br	3.4 s	C^2	100.9
	CH_2O	3.9 s	C^4, C^6	66.6
	C_6H_5	7.3–7.5 m	C^5	37.3
			C^7, C^8	36.2
			C_{arom}	125.9–141.1
C_6D_6	CH_2Br	3.1 s	C^2	101.9
	CH_2O	3.6 s	C^4, C^6	66.2
	C_6H_5	7.0–7.5 m	C^5	37.8
			C^7, C^8	35.5
			C_{arom}	126.6–141.9

Scheme 2.



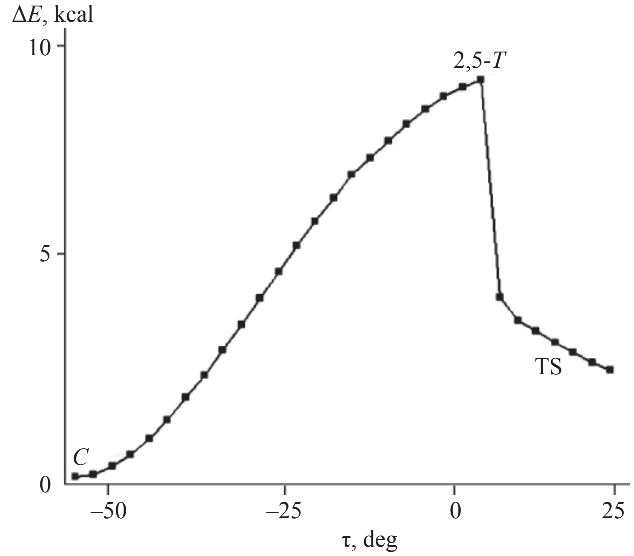


Fig. 2. Plot of the energy of the cluster **1**@5CH_2Cl_2 versus torsion angle $O^3C^4C^5C^6$ at 0 K.

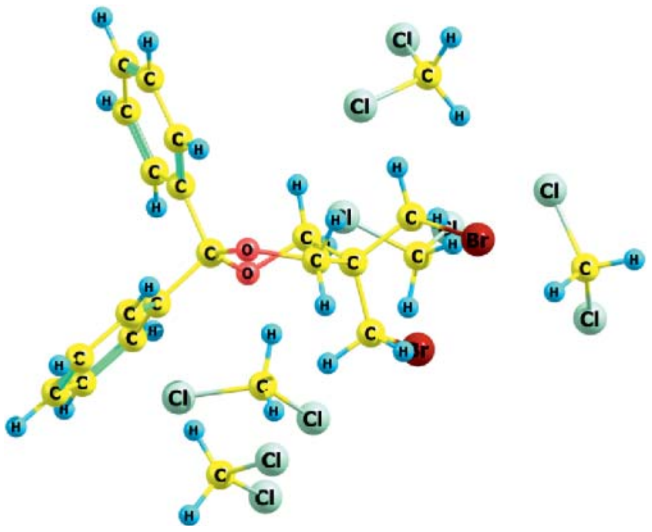


Fig. 3. Transition state for the interconversion of the cluster **1**@5CH_2Cl_2.

phase. The barrier to interconversion ($\Delta G^{\neq}_{298}$) also increases in going to cluster models. The calculated and experimental $\Delta G^{\neq}_{298}$ values for the cluster **1**@5 CH_2Cl_2 are fairly similar (8.9 and 8.33 kcal/mol, respectively). Figure 2 shows the energy of **1**@5 CH_2Cl_2 plotted against the torsion angle $O^3C^4C^5C^6$. Thus, it is highly likely that the first solvation shell includes 5–6 methyylene chloride molecules (Fig. 3). We previously showed that a probable number of solvent molecules in clusters with saturated heterocyclic molecules such as 1,3-dioxanes [14] and tetrahydro-1,3-oxazines [15] should not exceed 10 under standard conditions. Ac-

Table 3. Energy parameters of conformational transformations of 5,5-bis(bromomethyl)-2,2-diphenyl-1,3-dioxane (**1**), calculated by the PBE/3ζ method

Solvent	Conformer	$-E_0$,[a] hartree	ΔE^0_0 ($\Delta E^{\neq}{}_0$), kcal/mol	ΔH^0_{298} ($\Delta H^{\neq}_{298}$), kcal/mol	ΔG^0_{298} ($\Delta G^{\neq}_{298}$), kcal/mol	ΔS^0_{298} ($\Delta S^{\neq}_{298}$), kal mol^{-1} K^{-1}
–	*C*	5993.778232	0	0	0	0
–	2,5-*T*	5993.776440	1.12	1.21	0.41	2.67
–	(TS)	5993.766142	(7.59)	(7.37)	(7.06)	(1.04)
–	*C*[b]	5990.487591	0	0	0	0
–	2,5-*T*[b]	5990.484313	2.06	2.14	1.23	3.04
–	(TS)[b]	5990.472571	(9.04)	(9.22)	(8.60)	(2.10)
5 $CHCl_3$	*C*	13087.561564	0	0	0	0
	2,5-*T*	13087.560206	0.85	0.91	0.78	0.43
	(TS)	13087.550008	(7.25)	(6.98)	(7.72)	(–2.48)
5 CH_2Cl_2	*C*	10790.348269	0	0	0	0
	2,5-*T*	10790.344978	2.07	2.16	0.86	4.38
	(TS)	10790.335995	(7.70)	(7.41)	(8.33)	(–3.07)
10 CH_2Cl_2	*C*	15586.918992	0	0	0	0
	2,5-*T*	15586.916788	1.38	1.38	1.78	–1.37
	(TS)	15586.906675	(7.73)	(7.31)	(9.67)	(–7.91)
5 C_6H_6	*C*	7153.408643	0	0	0	0
	2,5-*T*	7153.406458	1.37	1.36	2.45	–3.67
	(TS)	7153.394712	(8.74)	(8.36)	(10.57)	(–7.44)

[a] With a correction for zero-point vibrational energy.

[b] RI-MP2/λ2 calculation.

cording to both calculated (Table 3) and experimental data, there is some effect of the solvent on the $\Delta G^{\neq}_{298}$ value. In particular, the $\Delta G^{\neq}_{298}$ value for the closest analog of **1**, 5,5-dimethyl-2,2-diphenyl-1,3-dioxane, in carbon disulfide solution is 9.6 kcal/mol [2].

It should also be noted that no intermediate minimum (1,4-*twist* conformer) typical of conformational equilibria of unsubstituted and 2-, 4-, 5-, 2,5-, and 4,4-substituted 1,3-dioxanes [11] was localized on the PES of compound **1**.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (Germany) at 400.13 and 100.62 MHz, respectively, using $CDCl_3$, CD_2Cl_2, DMSO-d_6, and C_6D_6 as solvents; the chemical shifts were measured relative to residual proton and carbon signals of the solvent. All solvents for NMR experiments had a purity of 99.5–99.8% (Sigma–Aldrich). The X-ray diffraction data for compound **1** were obtained at 293(2) K on 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 the difference Fourier synthesis and were refined in isotropic approximation. The calculations were performed using SHELX97 [16]. Triclinic crystal system, space group $P\bar{1}$; unit cell parameters: a = 9.8063(5) Å, b = 11.4309(4) Å, c = 23.4002(15) Å; α = 90.864(4), β = 91.837(4), γ = 102.439(4)°; V = 2559.5(2) Å^3; Z = 6; ρ_{calc} = 1.659 mg/mm^3; μ = 4.755 mm^{-1}; F(000) = 1272.0; scan range $4.54 < \theta < 58.52°$; $-10 \le h \le 12$, $-13 \le k \le 15$, $-27 \le l \le 29$; number of independent reflections 11 759 (R_{int} = 0.0289); goodness of fit S = 0.976; final divergence factors: R_1 = 0.0477, wR_2 = 0.0788 [reflections with $I_{hkl} > 2\sigma(I)$]; R_1 = 0.1170, wR_2 = 0.0969 (all independent reflections); maximum and minimum residual electron density peaks $\Delta\rho_{min}/_{max}$ 0.66/–0.74 $\bar{e}$/Å^3.

The geometric parameters of the *chair* conformer of **1** were preliminarily optimized by the AM1 method (HyperChem 8.0) [17] and then by the PBE/3ζ method, as well as in the RI-MP2/λ2 approximation (PRIRODA [12]) for the isolated molecule. The ring inversion was simulated by scanning the CCCO torsion angle in the range from –60 to 25° (Fig. 2). The potential barriers were determined by the transition state search algorithm implemented in PRIRODA. Stationary points on the PES were identified as transition states by the presence of one imaginary frequency in the corresponding Hessian matrix, and as minima, by the absence of imaginary frequencies therein. Model clusters were built up by successively placing solvent molecules in the vicinity of molecule **1** using HyperChem, and the resulting structures were then optimized in the PBE/3ζ approximation.

5,5-Bis(bromomethyl)-2,2-diphenyl-1,3-dioxane (1). An equimolar mixture of 2,2-bis(bromomethyl)-propane-1,3-diol (0.02 mol, 5.24 g; Sigma–Aldrich) and benzaldehyde (3.64 g) in benzene (50 mL) containing *p*-toluenesulfonic acid (0.1 g) was heated under reflux in a flask equipped with a Dean–Stark trap until water no longer separated. The mixture was cooled and washed with 5% aqueous sodium hydrogen carbonate (10 mL) and water (2×10 mL), the solvent was distilled off, and the residue was recrystallized twice from 95% ethanol. Yield 0.85 g (10%), mp 78–79°C.

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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