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Structure and Conformational Analysis of 5-Methyl-2,2-diphenyl-1,3-dioxane

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Abstract—The structure of 5-methyl-2,2-diphenyl-1,3-dioxane has been studied by ^1H and ^{13}C NMR spectroscopy and X-ray analysis. Its molecules in crystal, as well as in $CDCl_3$ and C_6D_6 solutions, have a *chair* conformation with equatorial methyl group. The conformational transformation pathways, ΔG^0_{298} value for the 5-methyl group in $CDCl_3$ and C_6D_6, and the optimal number of solvent molecules in the nearest solvation shell of 5-methyl-2,2-diphenyl-1,3-dioxane have been determined by quantum chemical calculations at the PBE/3ξ and RI-MP2/λ2 levels of theory and by comparing the theoretical and experimental vicinal spin–spin coupling constants.

Keywords: 1,3-dioxane, X-ray analysis, NMR, conformer, cluster model, computer simulation

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1,3-Dioxane ring is present in many biomolecules with a broad spectrum of pharmacological activity [1]; therefore, 1,3-dioxane derivatives are quite promising for the design of new medicines [2, 3]. In addition, substituted 1,3-dioxanes are widely used as reagents in fine organic synthesis [4–6], in particular in regioselective reactions in carbohydrate chemistry [7] and in the preparation of chiral carboxylic acids [8] and 1,3-diols [9]; furthermore, 1,3-dioxanes are classical models for conformational analysis [10]. The present work was aimed at studying the effect of the solvent nature and number of its molecules on the relative energy of particular minima on the potential energy surface of 5-methyl-2,2-diphenyl-1,3-dioxane (**1**) (cluster model) and its structure and conformations by using ^1H and ^{13}C NMR spectroscopy, X-ray analysis, and DFT quantum chemical calculations at the PBE/3ζ level of theory [11]; this computational method previously showed good results for 1,3-dioxane derivatives. In some cases, RI-MP2/λ2 calculations were performed using PRIRODA software [12].

5-Methyl-2,2-diphenyl-1,3-dioxane (**1**) has not been reported previously. It was synthesized by condensation of 2-methylpropane-1,3-diol with benzophenone (Scheme 1). The structure of compound **1** in crystal was determined by X-ray analysis (Fig. 1; see Experimental). It crystallized in space group $P2_1/n$ belonging to the monoclinic crystal system. The six-membered ring has a *chair* conformation with equatorial methyl group on C^5 and expected C–O bond lengths (1.410–1.430 Å) and bond angles in the heteroatom moiety (111–114°; Table 1) [10, 11].

The data of ^1H and ^{13}C NMR spectroscopy (Table 2) for solutions of **1** in $CDCl_3$ and C_6D_6, includ-

Scheme 1.

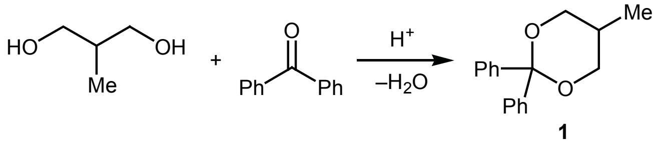

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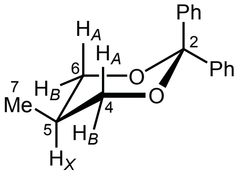
Table 1. Selected bond lengths (*d*) and bond angles (φ) in the molecule of 5-methyl-2,2-diphenyl-1,3-dioxane (**1**)

Bond	*d*, Å		Bond angle	φ, deg	
	calculated[a]	experimental		calculated[a]	experimental
$C^4–O^2$	1.430	1.410(2)	$O^1C^4O^2$	111.6	111.2(15)
$C^4–O^1$	1.430	1.416(2)	$C^4O^2C^7$	113.4	114.1(14)
$C^7–O^2$	1.430	1.430(2)	$C^4O^1C^{10}$	113.4	112.8(13)
$C^{10}–O^1$	1.439	1.426(2)	$C^7C^{15}C^{10}$	107.0	107.0(17)
$C^{16}–C^{15}$	1.529	1.515(3)	$C^{15}C^{10}O^1$	111.2	112.2(16)
$C^4–C^5$	1.531	1.513(3)	$C^{15}C^7O^2$	111.2	111.9(15)
$C^4–C^3$	1.546	1.545(3)	$C^3C^4C^5$	109.2	108.1(16)

[a] Calculated for the isolated molecule (C_{eq}) by the PBE/3ζ method.

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



Solvent	Proton	δ, ppm; *J*, Hz	Carbon atom	$δ_C$, ppm
$CDCl_3$	H_A	3.6 t	C^2	100.8
	H_B	4.1 q	C^4, C^6	67.9
	H_X	2.2 m	C^5	29.4
	CH_3	0.8 d; $^3J_{AX} = 11.3$; $^3J_{BX} = 4.4$	CH_3	13.2
	H_{arom}	7.3–7.6 m	C_{arom}	125.8–144.0
C_6D_6	H_A	3.4 t	C^2	101.0
	H_B	3.8 q	C^4, C^6	67.7
	H_X	1.8 m	C^5	29.5
	CH_3	0.3 d; $^3J_{AX} = 10.2$; $^3J_{BX} = 4.3$	CH_3	13.0
	H_{arom}	7.0–7.2 m	C_{arom}	126.4–144.8

ing two-dimensional NOESY, HH COSY, and HSQC experiments, also indicated preferential *chair* conformation of its molecules with equatorial orientation of the 5-methyl group. This follows from magnetic nonequivalence of methylene protons on C^4 and C^6 and spin–spin coupling constants $^3J_{AX}$ and $^3J_{BX}$.

The experimental data were confirmed by conformational analysis of dioxane **1** using PBE/3ζ and (for the isolated molecule) RI-MP2/λ2 approximations. Three energy minima were localized on the potential energy surface for compound **1**; these minima correspond to *chair* conformations with equatorial (C_{eq}) and axial (C_{ax}) methyl group and 2,5-*twist* conformer (2,5-*T*). Also, transition states TS1 and TS2 having half-*chair* conformation were identified (Scheme 2). The calculated bond lengths and bond and torsion angles in conformer C_{eq} were similar to those found experimentally by X-ray analysis (Table 1).

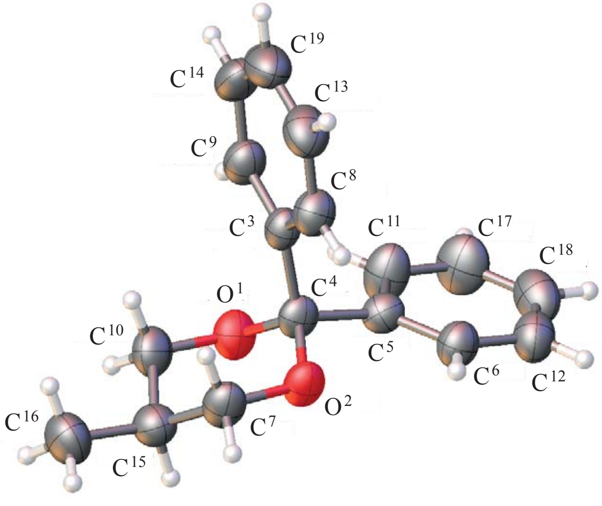
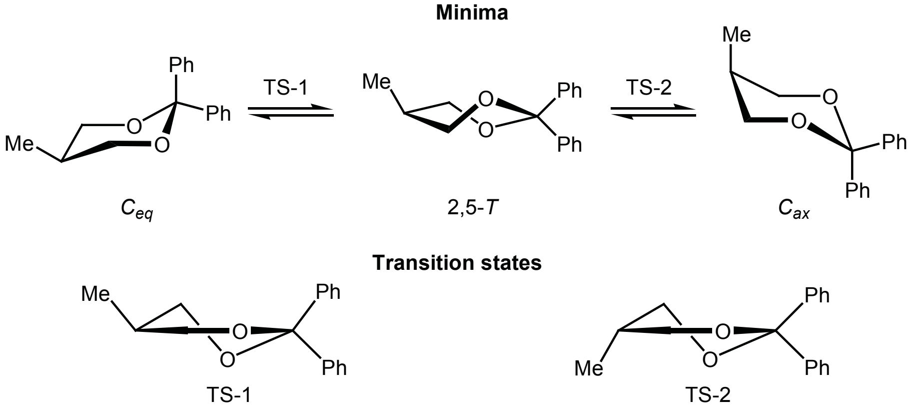


Fig. 1. Structure of the molecule of 5-methyl-2,2-diphenyl-1,3-dioxane (**1**) in crystal according to the X-ray diffraction data. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 50%.

Scheme 2.



Scheme 3.

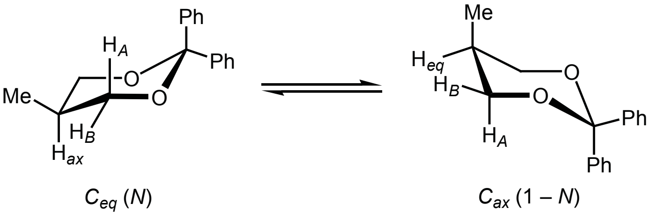


Table 3 contains the relative energies of all structures identified as stationary points on the PES for isolated molecule **1** and its clusters with solvent molecules (C_{eq} and C_{ax} conformers). These data suggest quite low concentrations of flexible structures. Therefore, the interconversion of molecules **1** can be reduced to binary equilibrium $C_{eq} \rightleftarrows C_{ax}$ (Scheme 3).

In this case, the relative concentrations of conformers C_{eq} and C_{ax} and the corresponding ΔG^0 value for the 5-methyl group can be estimated independently by using an approach based on the correlation between the experimental vicinal coupling constants $^3J_{AX}$ and $^3J_{BX}$ (from the ^{1}H NMR spectrum) and theoretical coupling constants (J_{Aax}, J_{Bax}, J_{Aeq}, J_{Beq}) for alternative conformers with mole fractions of N and $1 - N$, respectively. This approach was successfully applied previously to 5-substituted 1,3-dioxanes [11].

$$^3J_{AX} + {}^3J_{BX} = N(J_{Aax} + J_{Bax}) + (1 - N)(J_{Aeq} + J_{Beq});$$
$$\Delta G^0 = -RT\ln(N/1 - N).$$

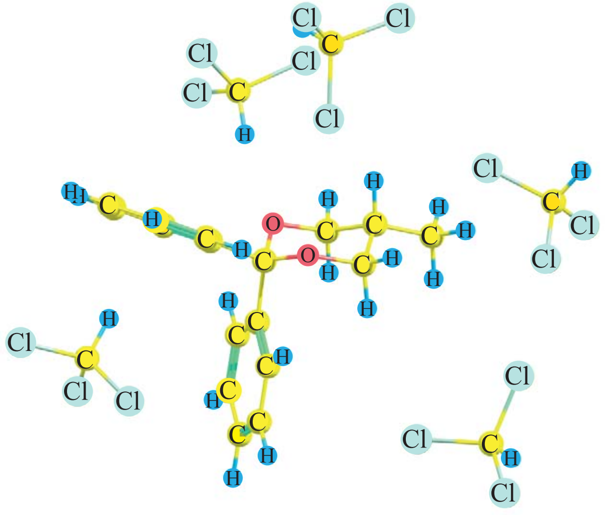


Fig. 2. Calculated structure of the cluster **1** (C_{eq})@5CHCl$_3$.

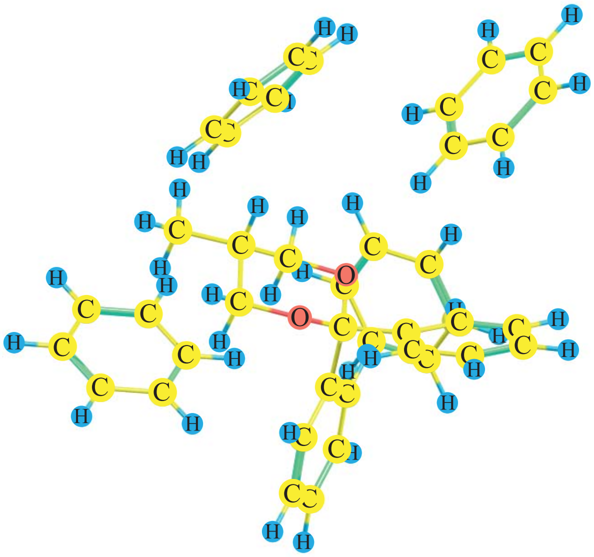


Fig. 3. Calculated structure of the cluster **1** (C_{eq})@4C$_6$H$_6$.

Table 3. Energy parameters of conformational transformations of 5-methyl-2,2-diphenyl-1,3-dioxane (**1**) relative to the C_{eq} conformer according to PBE/3ζ calculations

Solvent	Conformation	ΔG^0_{298} ($\Delta G^{\neq}_{298}$), kcal/mol
–	C_{ax} [a]	0.60
–	2,5-*T* [a]	3.10
–	C_{ax}	1.33
–	2,5-*T*	1.84
–	TS1	(7.15)
–	TS2	(7.82)
3 $CHCl_3$	C_{ax}	1.11
5 $CHCl_3$	**C_{ax}**	**1.45**
	TS1	(5.53)
	TS2	(7.76)
7 $CHCl_3$	C_{ax}	2.71
10 $CHCl_3$	C_{ax}	2.16
3 C_6H_6	C_{ax}	2.36
4 C_6H_6	**C_{ax}**	**0.83**
	TS1	(5.42)
	TS2	(7.82)
5 C_6H_6	C_{ax}	1.87
6 C_6H_6	C_{ax}	2.47
7 C_6H_6	C_{ax}	0.75
8 C_6H_6	C_{ax}	4.79

[a] Calculated by the RI-MP2/λ2 method.

The theoretical coupling constants were calculated by the modified Karplus equation [13] from the torsion angles (optimized values) between the corresponding C–H bonds in the conformers involved in binary equilibrium.

In all the examined clusters, the average calculated torsion angles for vicinal protons in conformers C_{eq} and C_{ax} (PBE/3ζ) were as follows (±0.5°): $\varphi_{Aax} = 175.4°$, $\varphi_{Bax} = 54.9°$, $\varphi_{Aeq} = 47.4°$, $\varphi_{Beq} = 73.6°$. The coupling constants calculated by the Karplus equation [13] ($J_{Aax} = 11.7$, $J_{Bax} = 4.9$, $J_{Aeq} = 3.6$, $J_{Beq} = 2.3$ Hz) and the corresponding experimental values (Table 2) were used to determine the free conformational energy (ΔG^0_{298}) of the 5-methyl group in **1**. The ΔG^0_{298} values were 1.45 kcal/mol for $CHCl_3$ and 0.84 kcal/mol for C_6H_6. Comparison of these values with the calculated data for all clusters (Table 3) showed a good agreement with a cluster formed by molecule **1** and five chloroform molecules in the nearest solvation shell (Fig. 2). In the case of benzene, the calculated ΔG^0_{298} value conformed to the clusters containing four and seven solvent molecules, **1**@4C_6H_6 and **1**@7C_6H_6. However, the former should be thermodynamically more stable due to the presence of a lower number of solvent molecules in the nearest solvation shell (Fig. 3). The calculated activation barrier for the transformation $C_{eq} \rightleftarrows C_{ax}$ corresponds to transition state TS2; the experimental barriers to similar conformational transitions of substituted 1,3-dioxanes in polar and nonpolar solvents range from 8 to 10 kcal/mol [10].

The proposed approach makes it possible to estimate the real number of solvent molecules in the first solvation shell of a solute. This approach was successfully applied previously to clusters of 2,2,5,5-substituted 1,3-dioxanes with various solvent molecules [14, 15]. It should also be noted that no intermediate 1,4-*twist* minimum typical of conformational equilibria of unsubstituted 1,3-dioxane and 2-, 4-, 5-, 2,5-, and 4,4-substituted 1,3-dioxanes [11] was localized on the potential energy surface of 5-methyl-2,2-diphenyl-1,3-dioxane (**1**).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer (Germany) at

400.13 and 100.62 MHz, respectively, from solutions in $CDCl_3$ and C_6D_6 (99.5–99.8%, Sigma–Aldrich) using the residual proton and carbon signals of the solvent as reference.

The X-ray diffraction data for compound **1** were obtained at 293(2) K with an XCalibur Eos four-circle automated diffractometer (USA); 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} (Oxford Diffraction, version 1.171.36.20). 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. All calculations were performed using SHELX97 [16]. Crystallographic parameters and X-ray diffraction experiment data: monoclinic crystal system, space group $P2_1/n$; unit cell parameters: $a = 15.636(5)$, $b = 6.2367(13)$, $c = 15.804(7)$ Å; $\beta = 116.03(4)°$; $V = 1384.8(9)$ Å^3; $Z = 4$; $\rho_{calc} = 1.220$ g/cm^3; $\mu = 0.078$ mm^{-1}; $F(000) = 544.0$; scan range $4.892 < \theta < 58.228°$, $-14 \le h \le 21$, $-8 \le k \le 7$, $-21 \le l \le 10$; number of independent reflections 3193 ($R_{int} = 0.0408$); $R_1 = 0.0578$, $wR_2 = 0.1237$ for reflections with $I_{hkl} > 2\sigma(I)$; $R_1 = 0.1110$, $wR_2 = 0.1570$ for all independent reflections; goodness of fit $S = 1.000$; residual electron density peaks $\Delta\rho_{min}/\rho_{max} = 0.16/-0.18$ $\bar{e}$Å^{-3}. The complete set of X-ray diffraction data for compound **1** was deposited to the Cambridge Crystallographic Data Centre (CCDC entry no. 1988349).

Initial geometry optimization of molecule **1** was done using HyperChem 8.0 (AM1) [17], and its structure was then optimized by the PBE/3ζ method or in the RI-MP2/λ2 approximation (PRIRODA [12]) for the isolated molecule. The ring interconversion was simulated by varying the torsion angle CCCO from –60 to 25°. The potential barriers were determined by the transition state search algorithm implemented in PRIRODA software. Stationary points on the potential energy surface were identified as transition states by the presence of one imaginary frequency in the corresponding Hessian matrices, and as minima, by the absence of imaginary frequencies. Model solvation clusters were assembled by successively placing solvent molecules in the vicinity of molecule **1** using PRIRODA procedures, and the resulting systems were optimized by the PBE/3ζ method.

The modified Karplus equation is as follows [13]:

$$
{}^3J_{HH} = P_1\cos^2\varphi + P_2\cos\varphi + P_3 \\
+ \sum\Delta\chi_i[P_4 + P_5\cos^2(\xi_i\varphi + P_6|\Delta\chi_i|)].
$$

Here, $\Delta\chi_i$ is the difference in the electronegativities of substituents in the corresponding ethane fragment and hydrogen atom; φ is the calculated torsion angle for coupled protons; ξ_i is equal to –1 or 1, depending on the orientation of substituents on carbon atoms in the ethane fragment, and the parameters P_1–P_6 depend on the degree of substitution of the ethane fragment. In our case, the number of substituents is 3 (O, CH_2, CH_3), and $P_1 = 13.22$, $P_2 = -0.99$, $P_3 = 0$, $P_4 = 0.87$, $P_5 = -2.46$, $P_6 = 19.9°$. The electronegativities were taken from [18].

5-Methyl-2,2-diphenyl-1,3-dioxane (1). A mixture of equimolar amounts of 2-methylpropane-1,3-diol (Sigma–Aldrich) (0.02 mol, 1.8 g) and benzophenone (3.64 g) in 50 mL of benzene contaning 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 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 2.7 g (53%), mp 114–115°C. Found, %: C 80.36; H 7.11. $C_{17}H_{18}O_2$. Calculated, %: C 80.31; H 7.09.

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CONFLICT OF INTEREST

The authors declare the absence of conflict of interest.

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