APPLICATION OF EMPIRICAL AND QUANTUM-CHEMICAL COMPUTATIONAL METHODS IN THE DETERMINATION OF THE FREE CONFORMATIONAL ENERGY OF SUBSTITUENTS IN 1,3-DIOXANES

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The advantages and disadvantages of empirical and quantum-chemical methods for the determination of the free conformational energy of methyl and phenyl substituents at the $C_{(4)}$ and $C_{(5)}$ atoms of the ring in the molecules of 1,3-dioxanes are analyzed.

Keywords: 1,3-dioxane, conformational equilibrium, free conformational energy.

The most widely used methods for the determination of the free conformational energy of substituents in the molecules of 1,3-dioxanes and other six-membered 1,3- and 1,3,2-heterocycles involve study of the equilibrium parameters of the stereoisomers or the NMR spectra of the slow transformations, requiring direct integration of the signals from the various conformers [1, 2]. However, the laborious nature of the first method, which requires isolation of the individual stereoisomers, and the relatively rare possibility of observing the signals of the separate conformers in the second case makes it urgent to seek other approaches to solution of the problem. It is known that the conformational behavior of the molecules of most monosubstituted 1,3-dioxanes is described fairly correctly by a scheme of binary *chair–chair* equilibrium [1-4]. In this case the ΔG^0 value can be estimated by means of an equation [5] resting on the weighted-mean (experimental ${}^{3}J_{AX}$ and ${}^{3}J_{BX}$) and standard (J_{aa}, J_{ae}, J_{ae} , J_{ea} , and J_{ee} for the alternative conformers with contents N and 1 - N) spin–spin coupling constants.

$${}^{3}J_{AX} + {}^{3}J_{BX} = N (J_{aa} + J_{ae}) + (1 - N) (J_{ea} + J_{ee});$$

$$\Delta G^{0} = -RT \ln N/(1 - N)$$

In this connection the aim of the present work was to assess the applicability of the empirical and quantum-chemical methods (in terms of the HyperChem software package) for determination of ΔG^0 for the substituents in 1,3-dioxane by calculating the torsion angles between the corresponding protons (the data of the optimum geometry of the equatorial and axial *chair* conformers K_e and K_a) and the corresponding standard spin–spin coupling constants. The latter were determined by means of the modified equations of Karplus [7] (A) and [8] (B) using data on the electronegativity of the atoms and the groups in the investigated ethane fragment from [9, 10]. The 1,3-dioxanes 1-4 were chosen as subjects for investigation.

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TABLE 1. The Calculated Torsion Angles (φ) between the Protons, the Spin—Spin Coupling Constants, and the Parameters of the Conformational Equilibrium (N, ΔG^0) of the Molecules of 1,3-Dioxanes 1-4 at 293 K



R	Calculation method	Conformer*	φ _{AX} , deg.	φ _{BX} , deg.	Equation of SSCC	Calculated S ${}^{3}J_{AX}$	SSCC, Hz^{*2} ${}^{3}J_{BX}$	N	ΔG^0 , kcal/mol	Δ, %* ³
1	2	3	4	5	6	7	8	9	10	11
5-CH3	MM^+	K _e K	174.1 50.0	53.7 70.0	А	11.7	5.1 2.7	0.84	1.0	11
		$K_e \\ K_a$	50.0	70.0	В	11.3 4.9	4.4 2.5	0.92	1.4	56
	CNDO	$egin{array}{c} { m K}_e \ { m K}_a \end{array}$	166.8 45.5	51.3 70.4	А	11.6 3.8	5.4 2.7	0.81	0.9	0
		K _e K _a			В	10.9 5.5	4.7 2.5	0.92	1.4	56
	INDO	$egin{array}{c} { m K}_e \ { m K}_a \end{array}$	167.6 46.2	51.3 70.6	А	11.6 3.7	5.4 2.7	0.81	0.9	0
		$egin{array}{c} K_e \ K_a \end{array}$			В	10.9 5.4	4.7 2.5	0.92	1.4	56

1	2	3	4	5	6	7	8	9	10	11
	-	5		5	Ŭ	,	0		10	
	MINDO/3	Ke	150.9	37.6	А	10.2	7.5	0.70	0.5	44
		K _a	20.1	93.0		7.7	1.1			
		Ke			В	9.2	6.7	0.83	0.9	0
		Ka				8.8	1.8			
5-CH3	MNDO	Ke	159.4	41.8	Α	11.1	6.9	0.72	0.5	44
		Ka	30.9	85.8		6.1	1.3			
		Ke			В	10.2	6.1	0.81	0.9	0
		Ka				7.6	1.7			
	AM1	K _e	170.2	47.5	А	11.7	6.0	0.77	0.7	22
		Ka	42.9	79.6		4.2	1.8			
		Ke			В	11.1	5.2	0.85	1.0	11
		K _a				5.9	1.9			
	PM3	Ke	169.5	44.0	Α	11.5	6.6	0.74	0.6	33
		Ka	38.5	83.1		4.9	1.5			_
		K _e			В	10.8	5.7	0.82	0.9	0
		K_a				6.5	1.8			
	STO-3G	Ke	171.2	46.3	A	11.7	6.2	0.75	0.6	33
		K _a	68.3	53.3		1.2	5.1			
		Ke			В	11.2	5.4	0.81	0.8	11
		K_a				2.7	5.6			
$5-C_6H_5$	MM^+	K _e	176.3	55.6	A	11.1	5.1	0.90	1.3	30
		K _a	48.6	70.9		2.9	2.5	1.05		
		K _e			В	10.8	3.9	1.05	—	_
		K _a				4.8	2.3			1.0
	CNDO	K _e	168.3	52.9	A	11.0	5.5	0.87	1.1	10
		K_a	43.2	72.5	D	3.6	2.4	1.07		
		K _e			В	10.4	4.3	1.06	—	—
		K_a				3.0	2.2			

TABLE 1 (continued)

TABLE 1 (continued)
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1	2	3	4	5	6	7	8	9	10	1
$5-C_6H_5$	INDO	K _e	169.1	52.9	А	11.0	5.5	0.87	1.1	1
		K _a	44.4	72.2		3.5	2.4			
		Ke			В	10.5	4.3	1.04	—	-
		\mathbf{K}_{a}				5.4	2.2			
	MINDO/3	K _e	152.7	39.5	Α	9.8	7.4	0.73	0.6	4
		\mathbf{K}_{a}	14.3	98.6		7.8	1.5			
		Ke			В	8.9	6.1	1.02	—	-
		K_a				8.8	1.9			
	MNDO	Ke	161.2	43.5	А	10.6	6.9	0.75	0.6	
		K_a	22.2	94.2		6.7	1.4			
		Ke			В	9.9	5.5	0.95	1.7	
		K_a				8.2	1.7			
	AM1	Ke	172.0	49.1	А	11.1	6.1	0.81	0.9	
		K_a	37.0	85.1		4.5	1.5			
		Ke			В	10.6	4.8	0.96	1.8	
		\mathbf{K}_{a}				6.4	1.6			
	PM3	Ke	166.4	44.4	А	10.9	6.7	0.77	0.7	
		Ka	31.0	90.4		5.4	1.4			
		Ke			В	10.3	5.4	0.91	1.4	
		Ka				7.2	1.7			
4-CH ₃	MM^+	Ke	173.5	55.2	А	11.7	2.7	0.98	2.3	
,	/*	K _a	44.6	72.8		6.2	2.4			
		K K			В	11.3	4.2	0.84	1.0	
		IX _e V			_	57	23			

1	2	3	4	5	6	7	8	9	10	11
	CNDO	K _e	162.6	47.2	А	11.3	3.8	0.86	1.1	61
		$egin{array}{c} \mathbf{K}_a \\ \mathbf{K}_e \\ \mathbf{K}_a \end{array}$	36.4	/9.4	В	7.4 10.5 6.8	1.8 5.3 1.9	0.79	0.8	71
	INDO	K _e K _a	163.0 36.5	47.9 79.0	А	11.4 7.4	3.7 1.8	0.86	1.1	61
		$egin{array}{c} { m K}_e \ { m K}_a \end{array}$			В	10.6 6.8	5.2 1.9	0.79	0.8	71
	MNDO	K _e K _a	156.3 25.0	39.6 90.5	А	10.8 8.7	5.0 1.2	0.75	0.6	79
		$egin{array}{c} { m K}_e \ { m K}_a \end{array}$			В	9.9 8.3	6.4 1.7	0.68	0.4	86
	AM1	$egin{array}{c} { m K}_e \\ { m K}_a \end{array}$	169.8 37.2	51.0 81.2	A	11.6 7.3	3.3 1.6	0.90	1.3	54
		$K_e \\ K_a$			В	6.7	4.7 1.8	0.79	0.8	71
	PM3	$K_e \\ K_a$	166.6 31.9	49.9 84.5	A	11.6 8.0	3.5 1.4	0.86	1.1	61
		K _e K _a			В	10.9 7.4	4.9 1.7	0.78	0.7	75
	STO-3G	K _e K _a	172.7 42.7	53.5 72.6	A	11.7 6.5	3.0 2.4	0.93	1.5	46
		$K_e \\ K_a$			В	11.2 5.9	4.4 2.3	0.82	0.9	68
4-C ₆ H ₅	MM^{+}	K _e K _a	176.9 48.3	57.1 67.8	A	11.1 5.2	2.9 2.9	0.98	2.3	19
		$egin{array}{c} { m K}_e \ { m K}_a \end{array}$			В	10.8 4.9	3.7 2.6	0.91	1.3	54

TABLE 1 (continued)

2	3	4	5	6	7	8	9	10	11
CNDO	Ke K	163.2 38.4	47.8 77 4	А	10.7	4.0	0.87	1.1	61
	$egin{array}{c} \mathbf{K}_a \ \mathbf{K}_a \end{array}$	50.4	//	В	10.1 6.2	4.9 1.9	0.84	1.0	65
INDO	$egin{array}{c} { m K}_e \ { m K}_a \end{array}$	164.0 38.4	49.0 77.2	А	10.8 6.5	3.9 2.0	0.87	1.1	61
	$egin{array}{c} { m K}_e \ { m K}_a \end{array}$			В	10.1 6.2	4.8 1.9	0.85	1.0	65
MNDO	$egin{array}{c} { m K}_e \\ { m K}_a \end{array}$	156.8 13.3	40.2 101.5	А	10.2 8.9	5.1 1.6	0.71	0.5	82
	$egin{array}{c} { m K}_e \ { m K}_a \end{array}$			В	9.4 8.9	6.0 1.8	0.68	0.4	86
AM1	$egin{array}{c} { m K}_e \\ { m K}_a \end{array}$	171.4 40.3	52.6 77.6	А	11.1 6.3	3.4 2.0	0.90	1.3	54
	$egin{array}{c} { m K}_e \ { m K}_a \end{array}$			В	10.6 6.0	4.3 1.9	0.86	1.1	61
PM3	$egin{array}{c} { m K}_e \ { m K}_a \end{array}$	166.8 33.6	50.2 82.7	А	10.9 7.1	3.7 1.6	0.88	1.2	58
	$egin{array}{c} { m K}_e \ { m K}_a \end{array}$			В	10.3 6.9	4.6 1.7	0.84	1.0	65
	2 CNDO INDO MNDO AM1 PM3	$\begin{array}{c c} 2 & 3 \\ \hline CNDO & K_e \\ K_a \\ K_e \\ K_a \\ INDO & K_e \\ K_a \\ K_e \\ K_a \\ MNDO & K_e \\ K_a \\ K_e \\ K_a \\ AM1 & K_e \\ K_a \\ K_a \\ K_e \\ K_a \\ K_$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	$\begin{array}{c c c c c c c c c c c c c c c c c c c $

* During minimization in terms of the MINDO/3 method the K_a conformer of compounds 3 and 4 was transformed into the K_e form.

^{*2} Experimental spin–spin coupling constants: dioxane $\mathbf{1} - {}^{3}J_{AX} = 10.5$ and ${}^{3}J_{BX} = 4.5$; dioxane $\mathbf{2} - {}^{3}J_{AX} = 10.5$ and ${}^{3}J_{BX} = 4.6$; dioxane $\mathbf{3} - {}^{3}J_{AX} = 11.8$ and ${}^{3}J_{BX} = 2.5$; dioxane $\mathbf{4} - {}^{3}J_{AX} = 11.3$ and ${}^{3}J_{BX} = 2.6$ Hz. ^{*3} $\Delta = (|\Delta G^{0} - \Delta G^{0}_{p}|/\Delta G^{0}_{p}) \times 100\%$, where ΔG^{0}_{p} – is the free conformational energy, established by the configuration

equilibrium method [1, 2]: 0.9 (for 5-CH₃), 1.0 (for 5-C₆H₅), 2.8 (for 4-CH₃) and 2.85 kcal/mol (for 4-C₆H₅).



The results of the determination of ΔG^0 of the substituents at 293 K are presented in Table 1. It is easy to see that for the formals 1 and 2 the best agreement with the data from the configuration isomerization method [1, 2] (the smallest value of Δ) is observed with the use of AM1, CNDO, INDO, and Eq. (A). Correct values for the free conformational energy of the 5-CH₃ group were also obtained in the PM3, MNDO, and MINDO/3 methods with Eq. (B). In the case of the substituted analogs **3** and **4** the ΔG^0 values closest to the data from an independent experiment were only obtained by means of the empirical MM⁺ method and Eq. (A). Thus, the accuracy of reproduction of the optimum geometry of forms K_e and K_a in terms of the employed methods of calculation is determined to an appreciable degree by the position of the substituting group. An important factor that was not considered is also the specific dependence of ΔG^0 of the substituent (particularly Ph) on the dielectric characteristics of the medium [11, 12]. (All the calculations were made for an isolated molecule in a vacuum.) Nevertheless, with allowance for the above-mentioned restrictions the proposed approach opens up a possibility for relatively simple determination of the ΔG^0 values of alkyl and aryl substituents at the C₍₄₎ and C₍₅₎ atoms of the ring in the molecules of 1,3-dioxanes by means of separate calculation methods and the experimental spin-spin coupling constants from the ¹H NMR spectra of cyclic formals. A similar solution is possible in the case of other six-membered 1,3- and 1,3,2-heterocycles and, in particular, substituted 1,3-dioxa-2-silacyclohexanes [13, 14] and 1,3,2-dioxaborinanes [15, 16].

EXPERIMENTAL

The parameters of the ¹H NMR spectra of 5-methyl-1,3-dioxane **1** were described in [17]. The ¹H NMR spectra of the formals **2-4** were determined on a Bruker AM-300 spectrometer at 300 MHz for 10% solutions of the investigated compounds in deuterochloroform with TMS as internal standard.

1,3-Dioxanes 2 and 3. These compounds were obtained with yields of 64 and 56% respectively by condensation of the respective 1,2-diols with paraform in the presence of catalytic amounts of p-toluenesulfonic acid.

Formal 4. The formal was obtained with a yield of 70% by the reaction of styrene with paraform in the presence of sulfuric acid. The physicochemical constants of compounds **3** and **4** agreed with data in [18].

5-Phenyl-1,3-dioxane (2). Bp 110-112°C (8 mm Hg), n_D^{20} 1.5331.

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