CONFORMATIONAL ANALYSIS OF 2-PHENYL-1,3-DIAZABICYCLO[3.1.0]HEXANE

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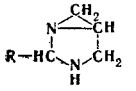
The 2-phenyl-1,3-diazabicyclo[3.1.0]hexane molecule was subjected to conformational analysis within the framework of the Westheimer method. The optimum conformations of two of its possible stereoisomers (endo and exo) were found, and the equilibrium concentrations of the latter were calculated and found to be 62 and 38%, respectively. The results of the calculations are in good agreement with the PMR spectroscopic data.

2-Substituted 1,3-diazabicyclo[3.1.0]hexanes (I) were recently synthesized [1], and some of their properties were studied. The I molecule is a new heterocyclic system containing condensed three-membered and five-membered rings with a nitrogen atom in common.



I

The conformational rigidity of bicyclic I ensures the existence of its 2-substituted derivatives in two isomeric forms (endo and exo), which can be easily distinguished by PMR spectroscopy [1, 2]. For some I, specifically, I ($R = C_6H_5$), the isomers can be isolated in pure form by repeated recrystallization [2]. However, crystals of 2-substituted I undergo reversible isomerization in solution or upon x-ray irradiation, as a result of which equilibrium is established between both forms [2]. The isomer ratio during equilibrium in solutions and the rate of establishment of equilibrium (the half-time of the transformation is tens of hours in solution) is determined by the nature of substituent R and the solvent. The results of a study of the mechanism and kinetics of the endo⇌exo isomerization of I will be published separately.

The aim of the present research was the exposure of the most stable conformations of I in the endo and exo forms and the determination of the equilibrium percentages of both stereoisomers by calculation within the framework of the Westheimer strain-energy method [3]. As the subject of our investigation we selected 2-phenyl-1,3-diazabicyclo[3.1.0]hexanes (Ia, $R = C_6H_5$), for which the isomerization and the conformational peculiarities have been studied in detail by PMR spectroscopy [2], which insures mutual checking and the supplementation of the results obtained by theoretical and experimental methods.

The calculations were made with a special program that permits fixing of any internal coordinates of the molecule. The optimization was accomplished by the fastest-descent method with variation of the torsion and valence angles. The interaction of the valence-nonbonded atoms was extrapolated with the exp-6 potential. The electrostatic interactions were disregarded. The parameters of the angles and the bond lengths of the three-membered ring of the molecule were assumed to be equal to the values for ethyleneimine [4].

*Deceased.

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TABLE 1. Torsion Angles for the Most Stable Conformer of the Endo Form of Ia

Atom No.	1	2	3	4	5	6	7	8	9	10	11	12
Angle	0	0	254	14	225	−15,3	138	258	3	−124	−35	1
Atom No.	13	14	15	16	17	18	19	20	21	22	23	24
Angle	62,4	134	120	0	−180	−180	0	−180	0	−180	0	−180

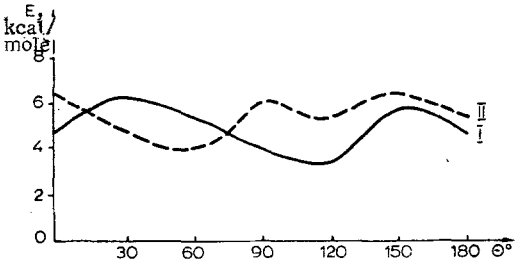

Fig. 1. Dependence of the conformation energy on θ: I) endo isomer; II) exo isomer.

In fact, this means a decrease in the conformational energies of the endo and exo forms of Ia to an identical strain energy of formation of the three-membered ring, which should not have a significant effect on the fundamental conclusions of this study.

For the remaining portion of the molecule all of the equilibrium valence angles were considered to be tetrahedral, except for the C−C−C angle, which is 112° [5]. The benzene ring was considered to be planar. The bond lengths corresponded to the generally accepted values [6]. The force constants of the deformation vibrations and the parameters of the functions that determine the van der Waals interactions of the nonvalence-bonded atoms were borrowed from the literature data [7-9], as were the barriers to rotation relative to the C−C and C−N bonds [10]. Inasmuch as accurate allowance for the interaction between the unshared electron pairs is impossible within the framework of the mechanical model, these interactions were disregarded.

According to preliminary calculations, the skew boat conformation is energetically more favorable by 1.5-2 kcal/mole than the chair conformation for both forms of 2-phenyl-1,3-diazabicyclo [3.1.0]hexane. This is due to the appearance of additional strain in the Ia molecule in the chair conformation associated with deformation of the $C_6C_9C_{11}$ and $N_4C_6H_7$ angles and also to the decrease in the distance between the H_7H_{13} and H_3H_5 atoms.* Consequently, both the endo and exo forms of Ia should exist primarily in the skew boat conformation, and this is confirmed by PMR spectroscopic data.

In our search for the optimum conformation of the Ia molecule in both forms we established a dependence of the strain energy of the bicyclic compound on the angle of rotation of the benzene ring relative to the $N_1C_2C_{14}$ plane. Angle θ was varied from 0 to 180°. The dependences obtained are presented in Fig. 1.

For the most stable rotational conformers of the endo form of Ia the strain energies are 5.08 and 3.87 kcal/mole, and the angles are 0 and 120°, respectively. The barriers to interconversion are less than 2.5 kcal/mole, which is in agreement with the PMR regarding the rapid rotation of the benzene ring relative to the C_2-C_{14} bond.

The calculated valence angles of the most stable configuration of the endo form ($\theta = 120°$) are presented in Fig. 2. The torsion angles are presented in Table 1.

The most characteristic features of the three-dimensional structure reduce to the following: the C_6C_9 bond makes an angle of 3° with the plane of the $C_2N_4C_6$ atoms, and the C_9-C_{11} bond makes an angle of 35° with the plane of the $N_4C_6C_9$ atoms. The spatial orientation of the benzene ring is determined by the angle between the plane of the $N_1C_2N_4$ atoms and the C_2C_{14} bond, which is 120°.

*The numbering of the atoms is shown in Fig. 2.

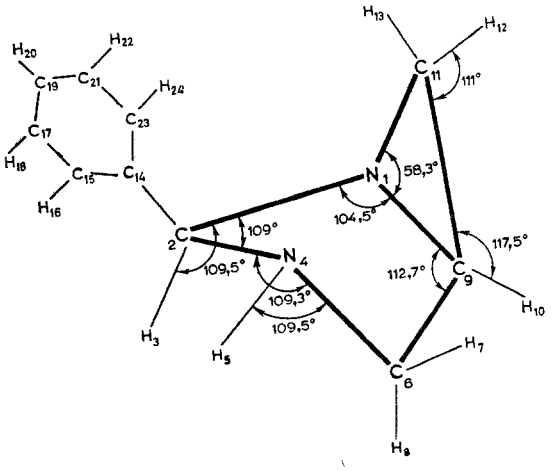

Fig. 2. Calculated geometry for the most stable conformation of the endo form.

A similar analysis of the calculated values for the exo form of Ia indicates the presence of two stable conformers with angles of rotation (θ) of 60 and 120° separated by a barrier of less than 2.5 kcal/mole (E_{str} = 4.20 and 5.88 kcal/mole, respectively). The geometry of the bicyclic framework of this isomer is extremely close to the geometry of the endo form. The greatest difference between them consists in an increase of 3° in angle $C_9H_{11}H_{13}$ for the exo form.

In order to determine the equilibrium percentages of the endo and exo forms of 2-phenyl-1,3-diazabicyclo[3.1.0]hexane in solution we estimated their average strain energies. Statistical averaging over all of the conformation gives 4.01 kcal/mole for the endo form and 4.29 kcal/mole for the exo form.

The difference in energies is due to the small change in most of the components. In particular, additional (as compared with the endo form) repulsions between the C_9, C_{14}, and H_{16} and the H_5 and C_{14} atoms appear in the exo form.

Using the Boltzmann distribution and the above-indicated calculated strain energies of the endo and exo forms we showed that the equilibrium mixture should contain 62% of the former and 38% of the latter. Allowance for the entropy of mixing does not affect the equilibrium percentage. The results are in agreement with the PMR data [2]. Under equilibrium conditions (at 36°), the experimentally determined percentages of the endo and exo forms are 54% and 46%, respectively.

Thus the use of the Westheimer method for the establishment of the most favorable configuration of the 2-phenyl-1,3-diazabicyclo[3.1.0]hexane molecule proved to be extremely fruitful. The results constitute a basis for a deeper understanding of the experimental and, above all, spectroscopic data. However, the final conclusion regarding the details of the three-dimensional structure of I can be drawn on the basis of x-ray diffraction studies, the results of which will be published in the future.

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