Study of 1,4-dihydropyridine type Ca^{2+} blockers by the methods of quantum chemistry

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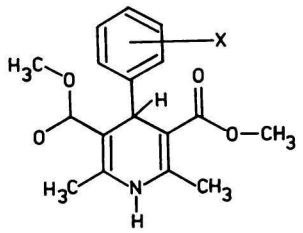
Rotation barrier for the rotation around the exocyclic C—C bond between aryl and 1,4-dihydropyridine ring in differently modified derivatives of nifedipine was calculated. The molecules investigated differ from each other in position and character of the substituent on the aromatic ring. A relatively high rotation barrier preventing the free rotation of aryl around the exocyclic C—C bond was found for all the derivatives with substituents in *ortho*, *meta*, and *para* positions. In active substances the rotation barrier is by one order higher than in inactive ones.

Вычислено значение ротационного барьера для вращения вокруг экзоциклической C—C связи между арильным и 1,4-дигидропиридиновым циклами в различных модифицированных производных нифедипина. Исследуемые молекулы взаимно отличаются положением и характером заместителя в ароматическом кольце. Относительно высокое значение ротационного барьера, препятствующее свободному вращению арила вокруг экзоциклической C—C связи, было найдено для всех производных с заместителями в *орто*, *мета* и *пара* положениях. В активных соединениях величина ротационного барьера на порядок выше, чем у неактивных соединений.

The therapeutic efficacy of differently modified 1,4-dihydropyridines as cardiovascular drugs is sufficiently known. These drugs inhibit the contractility of cells by blocking the passage of the Ca^{2+} ions through the slow calcium channel in the cell membrane. The finding that biological activity of 1,4-dihydropyridines is related to their conformation features led to the preparation of large number of derivatives with different effects. Similarly, great attention was paid to the relationships between the structure and activity [1—4], the quantum-chemical calculations of conformational behaviour of these drugs [5, 6] as well as to the X-ray structural analysis [7—10].

In our paper we deal with the conformational analysis of 2,6-dimethyl-3,5--dimethoxycarbonyl-4-(2-nitrophenyl)-1,4-dihydropyridine (nifedipine *I*) and



I X = 2-NO_2
II X = 3-NO_2
III X = 4-$N(CH_3)_2$
IV X = 4-CH_3

its three derivatives (*II*—*IV*) which differ from each other by character and position of the substituent on the benzene ring. The aim of our study was to investigate the relationship between the height of the rotation barrier and the pharmacological activity.

Methods

The semiempirical quantum-chemical method PCILO [11—14] was used. Calculations were performed by means of a version of the PCILO program with a gradientless optimizing procedure enabling to optimize any number of degrees of freedom for the system studied.

For initial conformations of particular derivatives the bond lengths and the valence angles according to *Hopfinger* [15] as well as the dihedral angles according to *Fossheim et al.* [2] were applied. Valence angles,dihedral angles, and bond lengths for all atoms in the 1,4-dihydropyridine ring, further valence angles and dihedral angles for both hydrogen atoms, and the carbon atoms in the methyl groups as well as the carbon and oxygen atoms in the methoxy groups were optimized. For the derivative *I*, the valence and dihedral angles of oxygen atoms in the NO_2 group on the benzene ring were also optimized. Altogether 41 geometrical parameters were optimized. The remaining geometrical parameters of each derivative were kept constant during calculation. When calculating the height of the rotation barrier the benzene ring was rotated around the C—C bond with 30° steps. All the above-mentioned geometrical degrees of freedom of each conformation were optimized.

Results and discussion

We were interested especially in the height of the rotation barrier for rotation around the simple C—C bond between the C-atoms of the benzene and of the 1,4-dihydropyridine ring. Therefore, derivatives with differently positioned substituent on the benzene ring [2] were chosen. The relative energies for diverse calculated derivatives with different angles of the internal rotation are given in Table 1. Here the minimum of the energy for each derivative was taken as zero.

Table 1

The relative energies for the conformers of the derivatives *I*—*IV* with different angles of the internal rotation

I		*II*		*III*		*IV*	
Dihedral angle/°	Energy / kJ mol^{-1}	Dihedral angle/°	Energy / kJ mol^{-1}	Dihedral angle/°	Energy / kJ mol^{-1}	Dihedral angle/°	Energy / kJ mol^{-1}
73.5	17.60	237.8	0.00	270.1	0.00	42.8	4.35
103.5	65.93	267.8	11.11	300.1	64.73	72.8	4.03
133.5	30807.72	297.8	464.65	330.1	289.56	102.8	2.72
163.5	25546.16	327.8	773.73	0.1	98.84	132.8	22.65
193.5	2418.69	357.8	998.46	30.1	20.00	162.8	28.62
223.5	78.50	27.8	64.02	60.1	9.91	192.8	16.76
253.5	0.00	57.8	4.57	90.1	9.54	222.8	0.00
283.5	1141.89	87.8	4.03	120.1	78.64	252.8	2.75
313.5	57420.40	117.8	436.36	150.1	292.22	282.8	13.86
343.5	103253.28	147.8	1892.75	180.1	91.49	313.8	8.14
13.5	1746.63	177.8	1089.49	210.1	8.54	342.8	59.47
		207.8	46.31	240.1	8.39	12.8	8:14

Table 2

The population of the particular stable conformers at 37 °C

Derivative	Angle/°	Energy of the stable conformers kJ mol^{-1}	Population %
I	73.5	− 707272.26	0.11
	253.5	− 707289.86	99.89
II	237.8	− 707346.74	71.79
	57.8	− 707342.71	15.04
III	270.1	− 659756.18	89.15
	90.1	− 659746.64	2.20
IV	102.8	− 604355.88	15.99
	222.8	− 604358.60	45.90
	312.8	− 604350.46	1.95

According to Boltzmann's relation the relative portions of particular stable conformers at a temperature of 37 °C were calculated (Table 2). Both calculations, that of relative population of the single conformers and that of width of the internal rotation interval (valid for 99 % of molecules) were based on the assumption that the energy may acquire continuous values. At chosen values of temperature T and of ratio $N(\varepsilon_k)/N$, indicating the portion of molecules with energy below or equal to ε_k, the actual value of ε_k may be established. Then, from the known dependence of energy on the angle of internal rotation

$$\varepsilon = \varepsilon(\vartheta) \tag{1}$$

and by solving the unequality

$$\varepsilon(\vartheta) \leqslant \varepsilon_k \tag{2}$$

it may be possible to reveal the intervals of the angle which at the given temperature is accessible to the chosen portion of molecules. Dependence (*1*) is expressed in tabular form; to obtain a smooth curve a continuous function should be superimposed over the points. From among diverse possibilities we have chosen the method enabling easily to respect the periodicity of the angle dependence

$$\varepsilon(\vartheta) = \frac{\sum_i \frac{\varepsilon_i}{D(\vartheta_i, \vartheta)}}{\sum_i \frac{1}{D(\vartheta_i, \vartheta)}} \tag{3}$$

where the sum is going *via* the values listed in the table, ε_i are the listed energies corresponding to the angles ϑ_i and $D(\vartheta_i, \vartheta)$ is a measure of the distance between points ϑ and ϑ_i. In our case it may be chosen

$$D(\vartheta_i, \vartheta) = w^q \tag{4}$$

where

$$w = |\vartheta_i - \vartheta| \quad \text{if} \quad |\vartheta_i - \vartheta| \leqslant \pi \tag{5}$$

or

$$w = 2\pi - |\vartheta_i - \vartheta| \quad \text{if} \quad |\vartheta_i - \vartheta| > \pi \tag{6}$$

and ϑ, ϑ_i gain the values from the interval $\langle 0, 2\pi \rangle$. By selection of the exponent in eqn (*4*) and the interval of summation in eqn (*3*) it is to be achieved that the tendency of approximation (*3*) to create false extremes is depressed. Unequality (*2*) was then solved numerically, the widths of availability intervals obtained are given in Table 3.

Table 3

The Ca^{2+} blocking activity data of the derivatives and some calculated parameters

Derivative	Activity[a]	Rotation barrier / kJ mol^{-1}	Interval/°[b]	Population[c] / %
I	100	30807.7	58.9	99.9
II	130	1773.7	69.5	71.8
III	0.005	289.46	72.9	89.2
IV	0.5	13.86	110.6	45.9

a) According to *Fossheim et al.*; *b*) the width of the interval of the internal rotation which is possible for 99 % of the molecules at the temperature of 37 °C; *c*) the population of the most stable conformer at 37 °C.

Table 3 contains following data about the derivatives studied: *a*) The Ca^{2+} entry blocking activities [2]; *b*) the calculated heights of rotation barriers; *c*) the widths of the internal rotation interval at 37 °C available for 99 % of the molecules of the given substance. Populations of the conformers most stable at 37 °C are given in Table 3. For each of the drugs studied at least two stable conformations in respect to their internal rotation barrier have been amounted.

Energetically more convenient conformations for both, *ortho* and *meta* derivatives are those in which the substituent on the benzene ring is in *cis* position with the H-atom on the saturated C-atom of the 1,4-dihydropyridine ring. NMR studies of 1,4-dihydropyridine type Ca^{2+} blockers in solutions [6] support these findings. Also X-ray diffraction studies [2, 16] gave very similar results for the conformations of these compounds in crystals.

Owing to small number of the drugs investigated, a quantitative calculation of correlations gives minor sense. When evaluated qualitatively, our results revealed that at body temperature the relative portion of most stable conformers does not correlate with their biological effect.

On the contrary, the rotation barrier of active drugs is by one order higher than that of inactive substances. A high rotation barrier is obviously needed to secure that during interaction with receptor the molecule may persist in a conformation needed for the given type of the interaction.

The compounds studied are divided into two dichotomic groups, low- and high-effective compounds. Similarly, according to height of the rotation barrier they may be divided into compounds with a low and with a high rotation barrier, whereby the numerical value of height of the barrier is not taken into account. Accordingly, in our case we have two high-effective compounds with a high barrier and two low-effective compounds with a low barrier. By standard evaluation of the four-field table [17] reflecting this situation we revealed that in spite of low number of compounds investigated, the utterance: "the high rotation barrier is related to presence of a given pharmacological activity" is true with a probability of 5/6.

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