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A QUANTUM CHEMICAL STUDY OF STRUCTURE-ACTIVITY RELATIONSHIPS OF DIHYDROPYRIDINE CALCIUM ANTAGONISTS

M. Mahmoudian

Departmentof Pharmacology, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran.

W. G. Richards

Physical Chemistry Laboratory, Oxford University, Oxford, England

Abstract

Quantum chemical (MNDO) calculations have been used to elucidate the molecular properties and structure - activity relationships of dihydropyridine (DHP) type calcium antagonists. There is a good correlation between the net atomic charges on various atoms of the 4 - phenyl ring of dihydropyridines and pharmacological activity. Also, activity decreases with increasing free rotation of the phenyl ring. These results indicate that the binding of the 4 - phenyl ring to a rigid part of the receptor plays an important part in the activity of DHP calcium antagonists.

Introduction

Dihydropyridine (DHP) calcium antagonists of nifedipine analogues are one of the most recent and important groups of cardiovascular drugs [1, 2]. It is believed that they selectively inhibit the plasmalemmal Ca^{++} entry through voltage dependent calcium channels [3]. The structure - activity relationships of these compounds have been of interest and various methods have been applied to elucidate the structural requirements for the optimal activity [4-6].

Quantum chemical calculations can provide valuable information about the charge distribution in a molecule and its conformation [7]. These parameters are very important factors in the binding of a drug to its receptor. This study was carried out to elucidate the structural requirements for the activity of DHP calcium antagonists using quantum mechanical calculations at the MNDO level [8, 9].

Methods

Geometries of dihydropyridine analogues (Table 1) were optimized using the MOPAC program[8] starting with initial geometries constructed using standard bond length and angles [10]. These initial geometries were used as input to the semi - empirical all - valence electron molecular orbital method, MNDO [9]. Totally unconstrained geometry optimization was performed for all analogues except for nifedipine and 3' - nitro derivative, where the nitro group was constrained as in the crystal structure [11, 12]. It has been reported that MNDO calculations do not provide satisfactory results regarding the geometry of a nitro group attached to an aromatic ring [13].

The net atomic charges (Mulliken population analysis) on each atom of each compound were calculated by MNDO method [9] for the optimized structures.

The net atomic charges on the various atoms of DHP analogues were correlated with the pharmacological activity (- log IC50 of the negative inotropic effect on the heart [4]), by computerized regression analysis. The validity of the regressions was judged by; i) the standard deviation, s; ii) the F-test value; iii) the level of significance, p; and iv) the correlation coefficient, r.

Key words: Quantum chemistry, Structure - activity, nifedipine, calcium

Conformational studies

In addition to finding the minimum energy conformer resulting from the MNDO geometry optimization, a more detailed conformational energy study was made to determine the relationship of the conformation of the DHPs molecules to their biological activity. The phenyl ring of each of the ortho substituted DHPs (Table II) was rotated in 15° steps with respect to the rest of the molecule and the total energy of the molecule calculated. The range of conformations which encompass 99% of the molecules at 37°C are calculated using a statistical mechanical procedure on the computed potential surface [14]. The range of this angle was taken as a measure of the free rotation of the phenyl ring with respect to the rest of the molecule. This degree of free rotation of 4 - phenyl ring in various DHP analogues was correlated with the biological activity.

Results

The relationship between the biological activity and net atomic charges

Calculation of the net atomic charges showed that the charges on the DHP ring and carbomethoxy side chains do not vary significantly with respect to the substitution of the phenyl ring. However, the charges on the various carbon atoms of the phenyl ring do vary with respect to substitution (Table I). A good correlation was obtained between the pharmacological activity, expressed as - log IC50 (4), and the net atomic charges on the various carbon atoms of 4 - phenyl ring of the ortho and para substituted DHPs as shown in the equations 1 to 6.

$$Y = -\log IC50 = 6.715 + 6.916\,C1 - 1.577\,I\,para \quad n = 8, r = 0.99, s = 0.149, F(2, 5) = 122, p < 0.001 \qquad \text{Eq. 1}$$

$$Y = -\log IC50 = 6.237 - 2.548\,C2 - 1.854\,I\,para \quad n = 8, r = 0.98, s = 0.22, F(2, 5) = 54.8, p < 0.001 \qquad \text{Eq. 2}$$

$$Y = -\log IC50 = 6.572 + 6.655\,C3 - 1.703\,I\,para \quad n = 8, r = 0.98, s = 0.176, F(2, 5) = 86.6, p < 0.001 \qquad \text{Eq. 3}$$

$$Y = -\log IC50 = 6.198 - 2.101\,C4 - 1.705\,I\,para \quad n = 8, r = 0.96, s = 0.29, F(2, 5) = 30.6\ p < 0.001 \qquad \text{Eq. 4}$$

$$Y = -\log IC50 = 6.711 + 9.176\,C5 - 1.689\,I\,para \quad n = 8, r = 0.98, s = 0.194, F(2, 5) = 70.9, p < 0.001 \qquad \text{Eq. 5}$$

$$Y = -\log IC50 = 5.809 - 20.976\,C6 - 1.600\,I\,para \quad n = 8, r = 0.99, s = 0.146, F(2, 5) = 127, p < 0.001 \qquad \text{Eq. 6}$$

Here y is the pharmacological activity (- log IC50); Cn, is the net atomic charge on the nth atom of the phenyl ring; and I para is an indicator term for the presence of para substituent.

As can be seen from the equations and Fig. 2, the best correlation is obtained between the biological activity and the charges on the C6′ of the phenyl ring. It was necessary to include on indicator term (I para) for para substituted compounds to obtain a correlation which includes the para substituted analogues. The addition of the data for meta substituted analogues to the regression analysis did not improve the correlation.

The conformation studies

The MNDO - optimized structure of various substituted 4 - phenyl DHPs were comparable to the published crystal structures [11, 12]. The main features are a rather flat DHP ring and a phenyl ring in the plane perpendicular to and bisecting the DHP ring. The major difference was the orientation of the carbonyl groups. While, in the crystal structures this group is orientated in the same plane as the dihydropyridine ring, MNDO calculations indicate an orientation perpendicular to the DHP ring.

More detailed analysis of the conformation of the phenyl ring by calculating the energy of the molecule as a function of the rotation of the phenyl ring showed that the position of this group is rather rigid with respect to the rest of the molecule especially when a bulky group, such as methyl, nitro, or trifluoromethyl, is present at ortho position (Table II). A representative graph of the energy against the rotation of the phenyl ring is shown in Fig. 3 for nifedipine.

The calculations also showed that a conformer where ortho - substituent oriented on the top of DHP ring (dihedral of C6. C1. C4. H4″; $\varphi = 0$) was not favored (Table II and Fig. 3).

A good correlation but with negative slope was found between the degree of free rotation of phenyl group and the biological activity of ortho substituted DHPs as shown in equation 7 and Fig 4.

$$Y = -\log IC50 = 7.413 - 0.0302\,\theta n = 6, r = 0.81, s =$$

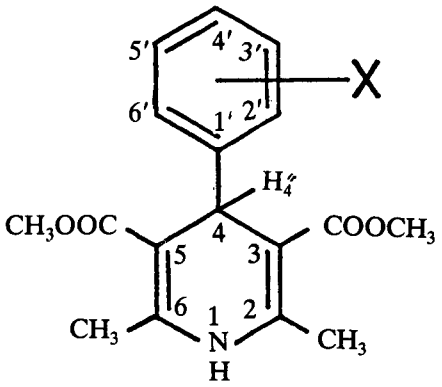

Fig. 1. The structure of dihydropyridine calcium antagonists.

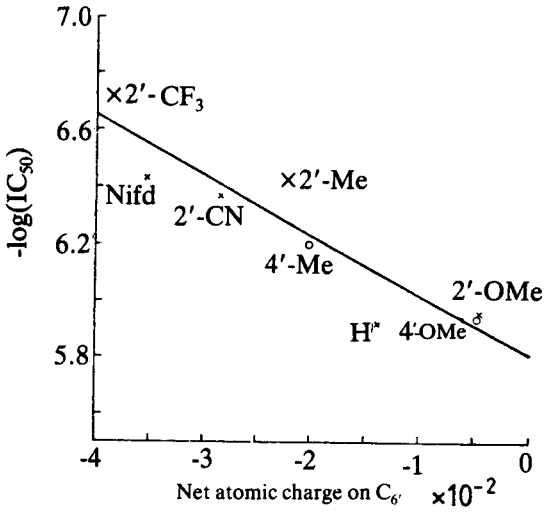

Fig. 2. The relationship between the net atomic charge on C_6. of the 4 - phenyl ring of DHPs and their biological activity. The biological activity (ordinate) is expressed ad -log(IC_{50}) of the negative inotropic effect on the heart (4).

$0.201, F(1, 4) = 7.64, p < 0.05$ Eq. 7

This indicates that the activity increases as the position of phenyl ring becomes more rigid with respect to the rest of the molecule.

Discussion

These data clearly demonstrate that the conformation of the aromatic ring with respect to the other part of the molecule plays an important part in the biological activity of the DHP calcium antagonists. Our calculation shows that the phenyl ring of DHP

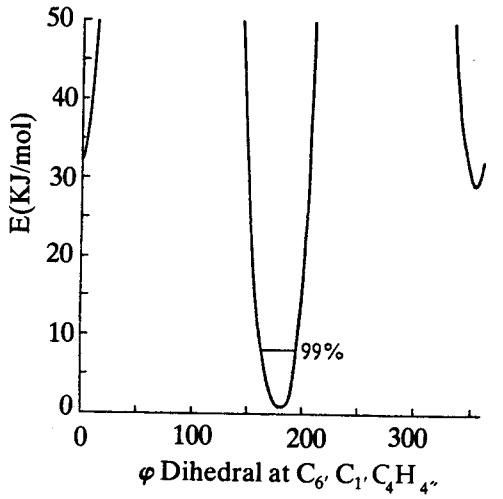

Fig. 3. The change in the energy of the nifedipine molecule wit respect to rotation of the 4 - phenyl ring. The bar indicates th conformational range where 99% of the population of molecules ar present at 37°C. φ is the dihedral of C_6. C_1. C_4H_4 - (for the numberin see Fig. 1)

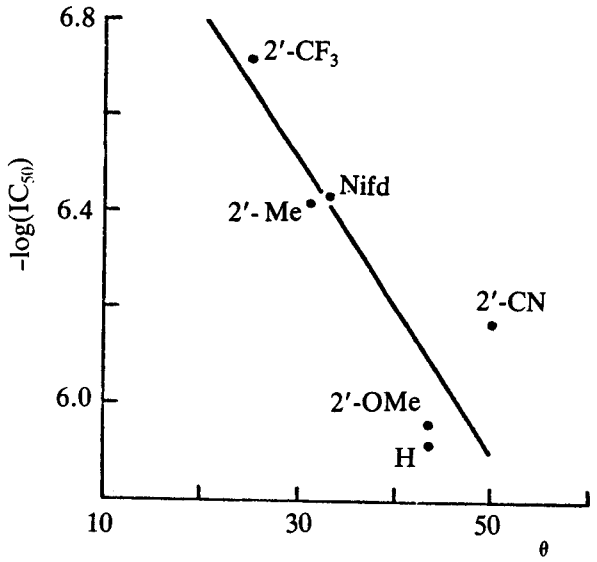

Fig. 4. The relationship between the free rotation of the 4 - phenyl ring (8) of the DHP calcium antagonists and the biological activity. The biological activity (ordinate) is expressed as -log(IC_{50}) of the negative inotropic effect on the heart.

calcium antagonists is oriented in a plane perpendicular to and bisecting the DHP ring. The ortho substituent is placed away from the DHP ring and synperiplanar to the hydrogen atom at the 4 position (Fig. 3, Table II). This is in agreement with NMR studies [15] which showed that the synperiplanar conformer is the predominant conformer in the 2' - methyl DHP. Similar results have been obtained from

TABLE I. The net atomic charges on the various atoms of the 4-phenyl ring of DHP analogues. For numbering see Fig. 1.

Analogue	-log(IC_{50})[4]	Net atomic charge on atom;					
		$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	$C_{5'}$	$C_{6'}$
H	5.92	-.1043	-.0355	-.0623	.-0454	-.0598	-.0148
2'-oMe	5.96	.-1032	0.1320	-.1003	-.0265	-.0769	-.0045
2'-CN	6.37	-.0455	0.0079	-.0191	-.0565	-.0322	-.0285
2'-Me	6.42	-.0734	-.0752	-.0538	-.0536	-.0622	-.0212
2'-NO_2*	6.43	-.0157	-.0464	-.0018	-.0573	-.0172	-.0353
2'-CF_3	6.72	-.0153	-.1361	-.0043	-.0607	-.0183	-.0370
3'-oMe	5.80	-.0851	-.0452	0.0892	-.0628	-.0504	-.0241
3'-NO_2	6.24	-.1097	0.0339	-.0884	0.0265	-.0778	- 0.0328
4'-oMe	4.34	-.1031	-.0273	-.0738	0.1082	-.0773	-.0047
4'-Me	4.60	-.0901	-.0408	-.0461	-.0861	-.0430	-.0202

* nifedipin

X-ray studies [11, 12].

MNDO calculations also showed that free rotation of the phenyl is restricted, especially when a bulky group is present at ortho position (Table II). This restriction of free rotation of phenyl ring will result in an increase in pharmacological activity (Fig. 4).

The importance of a bulky group at ortho position has already been demonstrated from the correlation between the biological activity and the minimum width of substituent at ortho position [4, 6]. Our calculation shows that this effect of ortho substitution is to a large extent due to restriction of the rotation of the phenyl group. In agreement with our results, Seidel et al. [5] have shown that in the rigid DHP analogues the activity decreases when the phenyl ring deviated from an orientation perpendicular and bisecting the DHP ring.

The relationship between the conformation and biological activity has also been shown for the other part of the DHP molecule. Mahmoudian and Richards [16] have shown that the orientation of the side chain of DHP determines whether a compound posseses agonist or antagonists activity.

Our calculations show that not only the conformation, but also the electronic properties of the phenyl ring play an important part in the biological activity of the DHP calcium antagonists (Eqs. 1-6, and Fig. 2). It is interesting to note that the slopes of the indicator term for para substituent has a negative value. This is in agreement with previous QSAR studies which show that a hydrogen at para position of the phenyl ring is required for maximum activity (6). From these data we can conclude that the phenyl ring binds to a rather rigid part of the receptor, possibly through electrostatic interaction with a complementary aromatic ring of an amino-acid residue. However, until the DHP receptor is isolated and its structure is determined, the nature of DHP binding site remains speculative.

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TABLE II. The range of possible conformations and the degree of free rotation of the 4- phenyl group in o substituted DHPs at 37°C.
φ i the dihedral angle of C_6. C_1. C_4 H_4. (for numbering see Fig. 1).
θ is the degree of free rotation of phenyl group at 37°C.

Analogue	Activity -log(IC_{50})[4]	Ranges of torsion angles encompass 99% of the population of molecules at 37°C.	Degree of free rotation of phenyl group
		φ	θ
H	5.92	-22 to +22 +159 to +202	43
2'-oMe	5.96	-4 to +5 +154 to +197	43
2'-CN	6.37	-7 to +7 +158 to +203	45
2'-CH_3	6.42	+164 to +195	31
Nifedipine	6.43	+163 to +197	33
2'-CF_3	6.72	+168 to +193	25

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