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Structure-activity relationships in verapamil and analogues using molecular mechanics calculations *

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Summary

The most stable conformation of verapamil was determined theoretically using the MM2 (85) molecular mechanics program. The dihedral angles formed by the plane of the aromatic ring and the nitrile group were determined under the same conditions and with the same method. The energy barriers for rotation around the bond between the phenyl group and the α-carbon of the nitrile were determined for verapamil and six analogues using the 'driver' procedure. Greater conformational stability was related to the coplanar arrangement of the phenyl and cyano groups and the activity of these molecules as calcium antagonists.

Introduction

Verapamil (**1**) was developed in 1962 as a coronary vasodilator with antiarrhythmic and antihypertensive properties (Haas and Haertfelder, 1962). Not until a number of years later did it become known that its mechanism of action was associated with its ability to obstruct cellular calcium channels (Fleckenstein et al., 1967), whereupon studies were undertaken in order to elucidate the basic structural requirements for the action of this molecule.

The two benzene rings joined by a carbon chain whose central part bears a tertiary nitrogen, which due to being tertiary is almost completely protonated at physiological pH, appear to be essential characteristics for the activity of these compounds, whereas neither the position and nature of the aromatic substituents – although four or five methoxyl groups are optimal (Holtje and Baranowski, 1983; Mannhold et al., 1987; Soll et al., 1990) – nor even the phenylethyl portion, which may be replaced by an aryloxypropanolamine group (Laguerre et al., 1991), appears to be crucial.

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Abbreviation: verapamil, 5-[(*N*-(3,4-dimethoxyphenethyl)-*N*-methylamino)]-2-(3,4-dimethoxyphenyl)-2-isopropylvaleronitrile (IUPAC name).

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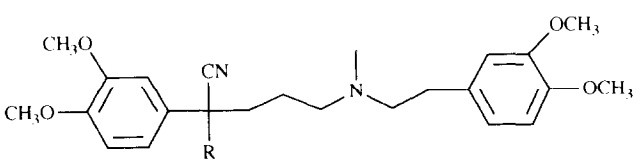
The pivotal position for the molecular activity is the quaternary benzylic carbon (Gualteri et al., 1985), where the presence of the nitrile group is practically an a priori requirement (Mannhold et al., 1986; Romanelli et al., 1989), although examples exist of compounds with moderate activity in which this nitrile group has been substituted by other functional groups with comparable electronic properties (Konig, 1987).

According to recent hypotheses (Kubinyi and Klebe, 1987), the receptor-binding affinity of verapamil derivatives is related to the molecule's capacity for adopting a conformation with coplanar cyano and phenyl groups.

Method

Verapamil is a molecule with many degrees of freedom. Although X-ray studies (Carpy et al., 1985) place the benzene ring and the cyano group in the same plane, we considered it convenient to carry out a theoretical study to determine the most stable conformers of this molecule and some analogues (Fig. 1), as well as the energy barriers for rotation around the bond between the phenyl group and the α-carbon to the cyano group (C13-C14 bond), and correlate these data with the



R	Compound
$CH(CH_3)_2$	1
H	2
CH_3	3
CH_2-CH_3	4
CN	5
$CH(CH_3)$-CH_2-CH_3	6
$C(CH_3)_3$	7

Fig. 1. Structures of the studied compounds.

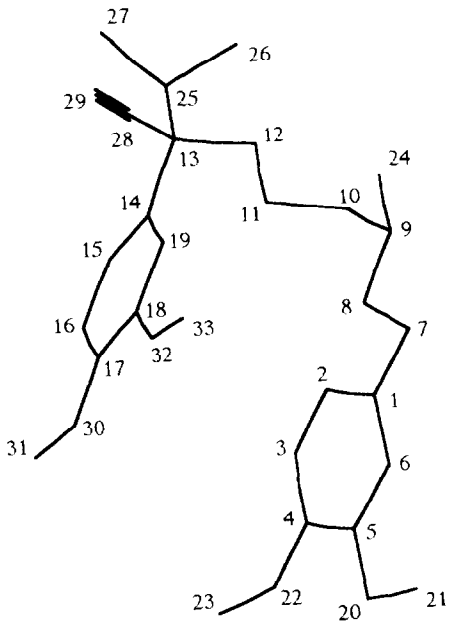


Fig. 2. Verapamil MM2(85) structure and atom numbering.

binding capicity to the specific receptors of the calcium channels. The binding affinity was used as biological activity parameter (Konig, 1987).

The MM2 (85) molecular mechanics program (Tai and Allinger, 1988) was used to obtain the most stable conformers, and the barriers to rotation around the C13-C14 bond, estimated using the 'driver' procedure (Wiberg and Boyd, 1972).

Results and Discussion

The results yielded by molecular mechanics (Fig. 2) were compared with the only structural study known for this molecule, performed using X-ray diffraction on verapamil in the form of the hydrochloride (Carpy et al., 1985). The values determined through both techniques for the main geometrical features of the lowest energy conformer are listed in Table 1. The molecular conformation is essentially the same, the discrepancies being in the order of the experimental error except for some features involving N9 and its near neighbours, since this is protonated in the hydrochloride. The 8-9 distance is lengthened by 0.08 Å in the case of the hydrochloride in the

TABLE 1

Comparison between the verapamil MM2 main geometrical features and the corresponding X-ray data for its hydrochloride derivative (Carpy et al., 1985)

Feature	MM2(85)	X-ray
9–8	1.462	1.539(11)
9–10	1.464	1.528(11)
9–24	1.457	1.505(11)
13–12	1.547	1.543(12)
13–14	1.529	1.541(12)
13–25	1.560	1.573(12)
13–28	1.478	1.476(12)
7–8–9	115.3	109.1(7)
8–9–10	111.7	110.9(6)
12–13–14	108.1	111.0(7)
25–13–28	105.8	107.9(7)
25–13–12	111.8	110.9(7)
25–13–14	111.6	109.6(7)
28–13–14	110.4	108.3(7)
28–13–12	109.1	109.0(7)
2–1–7–8	100.4	94
1–7–8–9	−172.5	−172
7–8–9–10	−178.7	−178
8–9–10–11	−61.1	−56
9–10–11–12	−58.0	−74
10–11–12–13	178.0	168
11–12–13–14	−57.4	−66
12–13–14–15	99.3	119
11–12–13–28	62.7	53
11–12–13–25	179.3	172

Bond lengths are given in Å and angles in degrees.

solid phase and the angle 7-8-9 yielded by MM2 is 6.2° larger than that reported in the solid-phase results. As to the dihedral angles, the differences are only significant in the angle 9-10-11-12 (16°), which again involves N9, and in the torsion with respect to the C13-C14 bond, where the X-ray diffraction study indicates perfect coplanarity between the phenyl and cyano groups, whereas according to the MM2 data, there is a distortion of about 20°.

Taking into account the different phases in both studies and the fact that the X-ray diffraction work was carried out on the hydrochloride form, the discrepancies observed among the two techniques do not appear unreasonable, and it may be inferred that the MM2 method is applicable to the study of this kind of compounds.

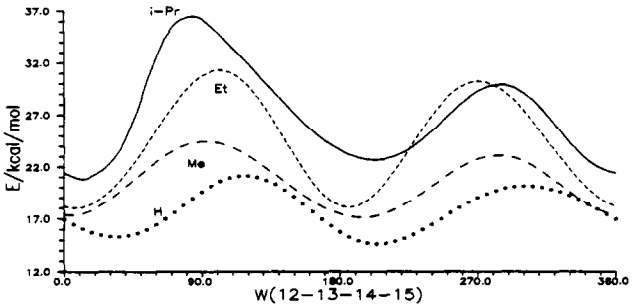


Fig. 3. Drivers around the C13-C14 bond for **1**, **2**, **3** and **4**.

The MM2(85) results show that through rotation around the 13-14 bond the compounds of the series interconvert between two conformers (Figs 3 and 4). The energy difference between them depends fundamentally on the volume of the substituent group present on C13: when this is bulky (isopropyl, isobutyl and *t*-butyl; compounds **1**, **6** and **7**, respectively) the difference is significant (between 1.2 and 2.8 kcal/mol) whereas it is very low (below 0.3 kcal/mol) with less bulky substituents (hydrogen, methyl, ethyl and cyano; compounds **2**, **3**, **4** and **5**, respectively). In each case the localized conformers displace the cyano group less than 30° with respect to the plane of the benzene ring (Table 2).

In the values obtained for the rotational barriers around the 13-14 bond, a distinction is made between a lower energy barrier (ΔE_1), that once surpassed allows the compound to leave the most stable conformation, and a higher energy barrier (ΔE_2), which impedes complete rotation around the bond (Table 2). ΔE_1 may be taken as a measure of the compound's capacity for intercon-

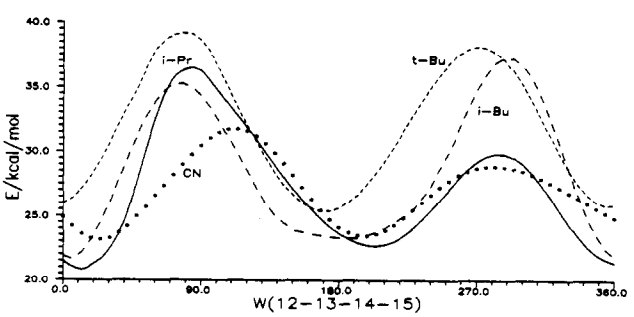


Fig. 4. Drivers around the C13-C14 bond for **1**, **5**, **6** and **7**.

TABLE 2

Torsion angles that give the disposition of the phenyl group with respect to the cyano (degrees), energy barriers [ΔE_1, lower barrier; ΔE_2, higher barrier (see text and Figs 3 and 4)] and $\Delta\epsilon$ energy differences between the conformers (all in kcal/mol) found for the compounds under study

Molecule	C28-C-C-C19/ C28-C-C-C15	ΔE_1	ΔE_2	$\Delta\epsilon$
1	20/200	6.7	15.2	2.8
2	30/210	4.7	6.3	0.0
3	20/190	6.2	7.9	0.1
4	0/180	11.9	12.8	0.3
5	30/200	5.6	7.2	0.3
6	20/210	10.7	15.6	1.8
7	0/170	13.5	14.5	−1.2

version between the two 'almost' coplanar arrangements, the coplanarity being responsible for the affinity that a particular substance shows for the receptors of calcium channels (Kubinyi and Klebe, 1987).

The biological activity of the compounds in which the structure-activity relationship was studied, determined using the 'capacity-for-binding-to-the-receptor' parameter, is in decreasing order **6, 1, 4, 5, 2** (Konig, 1987).

The results suggest that, with regard to the biological activity, it is not only the coplanarity of the benzene ring and the cyano group that is important, but also, possibly, the relative steric position of the cyano group with respect to the aromatic ring when the latter is not symmetrically substituted, as in the cases studied. Compounds **1** and **6** have the greatest capacity for binding to the receptor and are also those which show by far the greatest energy difference between the two most stable conformers, implying that one of the conformers, specifically that with the cyano group '*cis*' to the '*meta*' methoxyl, is much more abundant (and hence, presumably more active) than the other.

In compound **1** the favoured conformer is thermodynamically more stable than that of compound **6** (conformational energy differences of 2.8 and 1.8 kcal/mol, respectively), and hence would appear to be the most active. In fact, compound **6** is more active, probably because of the fact that, despite having the lowest energy conformer, it is kinetically much more stable than compound **1** ($\Delta E_1 = 10.7$ and 6.7 kcal/mol, respectively). This indicates that the mean time each molecule stays in this conformer is greater, facilitating its interaction with the receptor.

This hypothesis finds further support in explaining the much greater activity of compound **4** compared to compounds **2** and **5**. Although the dihedral angles and the energy differences between the conformers, are very similar, the energy barriers of compound **4** are very high ($\Delta E_2 = 12.8$ and $\Delta E_1 = 11.9$ kcal/mol), therefore, the molecules are stable in each conformation, particularly in the most active one, and have more time to interact with the receptor.

References

Carpy, A., Leger, J.M. and Melchiore, C., Structure of α-isopropyl-α-[(*N*-methyl-*N*-homoveratryl)-γ-aminopropyl]-3,4-dimethoxyphenylacetonitrile hydrochloride. Verapamil. *Acta Crystallogr. Sect C: Cryst. Struct. Commun.*, 41 (1985) 624–627.

Fleckenstein, J.A., Kammermeier, H., Doring, H. and Freund, H.J., Zum Wirkungs-Mechanismus neuartiger Koronardilatoren mit gleichzeitig Sauerstoff-einsparenden, miokard-Effekten, Prenylamin und Iproveratril. *Z. Kreislaufforsch.*, 56 (1967) 716–744.

Gualteri, F., Teodori, E., Bellucci, C., Pesce, E. and Piacenza, G., SAR Studies in the field of calcium(II) antagonists. Effect of modifications at the tetrasubstituted carbon of verapamil-like compounds. *J. Med. Chem.*, 28 (1985) 1621–1628.

Haas, H. and Haertfelder, G., α-Isopropyl-α-[γ-(*N*-methyl-*N*-homoveratrylamino)propyl]-3,4-dimethoxyphenylacetonitrile, a compound with coronary-dilating activity. *Arzneimittel-Forschung*, 12 (1962) 549–558.

Holtje, H.D. and Baranowsky, P., Theoretical investigations of interactions of verapamil derivatives. *Arch. Pharm.*, 316 (1983) 154–160.

Konig, H., Calcium antagonists of verapamil type – Chemical aspects. *Actual. Chim. Ther.*, 14 (1987) 99–117.

Kubinyi, H. and Klebe, G., Structure activity relationships of calcium antagonist. Plenary lectures, Vth Congress of the Spanish Society of Therapeutical Chemistry. 1st Spanish-Portuguese Congress of Therapeutical Chemistry, Santiago de Compostela, September 1987.

Laguerre, M., Boyer, C., Carpy, A., Panconi, E., Cognic, F. and Vaugien, B., Antagonistes calciques. I. Remplacement du groupe diméthoxy-3,4-phénylèthyle du vérapamil. *Eur. J. Med. Chem.*, 25 (1991) 351–359.

Mannhold, R., Holtje, H.D. and Koke, V., Importance of nitrile substitution for the Ca antagonistic action of verapamil. *Arch. Pharm.*, 319 (1986) 990–998.

Mannhold, R., Bayer, R., Ronsdorf, M. and Martens, L., Comparative QSAR studies on vasodilatory and negative inotropic properties of ring-varied verapamil congeners. *Arzneimittel-Forschung* 37 (1987) 419–424.

Romanelli, M.N., Gualtieri, F., Mannhold, R. and Chiarini, A., A search for calcium-channel activators in the verapamil series. *Il Farm. Ed. Sci.*, 44 (1989) 449–464.

Soll, R.M., Parks, J.A., Rimele, T.J., Heaslip, R.J., Woddan, A., Oshiro, G., Grimes, D. and Asselin, A., The synthesis and pharmacological evaluation of indole congeners of the calcium entry blocker verapamil. *Eur. J. Med. Chem.*, 25 (1990) 191–196.

Tai, J.C. and Allinger, N.L., Molecular mechanics calculations on conjugated nitrogen-containing heterocycles. *J. Am. Chem. Soc.*, 110 (1988) 2050–2055.

Wiberg, K.B., and Boyd, R.H., Application of strain energy minimization to the dynamics of conformational changes. *J. Am. Chem. Soc.*, 94 (1972) 8426–8430.