Crystal Structure of the Dihydropyridine Ca^{2+} Antagonist Felodipine. Dihydropyridine Binding Prerequisites Assessed from Crystallographic Data

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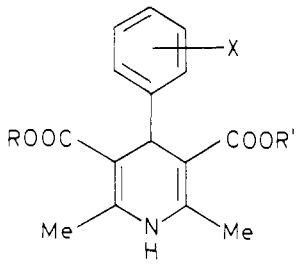
The molecular structure of the dihydropyridine Ca^{2+} antagonist felodipine (ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate) has been determined by X-ray crystallographic methods. The dihydropyridine ring in this potent smooth muscle relaxant is among the flattest found in such structures. This is in qualitative agreement with previous investigations of dihydropyridine Ca^{2+} antagonists; deviations from planarity in the dihydropyridine ring are generally smallest in the most active compounds. Hydrogen-bonding patterns observed in the crystal lattices of several dihydropyridine Ca^{2+} antagonists are compared. Antiperiplanar carbonyl groups are partly shielded from forming hydrogen bonds in compounds with relatively bulky ortho phenyl substituents. Conformational prerequisites for a favorable hydrogen-bonding geometry toward a receptor site may thus involve synperiplanar carbonyl groups.

Felodipine (ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate) belongs to the class of dihydropyridine (DHP) Ca^{2+} antagonists with the structural formula shown below. Pharmacological



effects of the title compound are characterized by tissue selectivity. It is a potent vasodilator, with only minor cardiodepressant effects.[1] These compounds are generally believed to exert their inotropic and vasomotor effects by blocking transmembrane Ca^{2+} influx,[2-4] although other mechanisms of action also have been proposed.[1]

Structural studies of several nifedipine (R = R' = Me; X = 2-NO_2) derivatives have shown that the flatness of the DHP ring is a significant structural parameter in describing the variance in pharmacological activity for ortho and meta phenyl substituted compounds.[5-7] Deviations from planarity in the DHP ring are smallest in compounds that are most active in inhibiting contractions in smooth muscle preparations. The crystal structure of felodipine has been determined as a part of further structural studies of DHP Ca^{2+} antagonists.

Experimental Section

Crystals of the title compound were grown by slow evaporation from a 2-propanol solution. Unit cell parameters were obtained by a least-squares fit of the diffractometer (SYNTEX P$\bar{1}$) settings for 15 general high order reflections. Crystallographic and experimental data are given in Table I. The diffraction intensities were measured by the $\theta/2\theta$ scan procedure using graphite monochromatized Mo Kα radiation (λ = 0.71 069 Å). The measured intensities were corrected for Lorentz and polarization effects but not for absorption.

Table I. Crystallographic and Experimental Data

formula	$C_{18}H_{19}Cl_2NO_4$
molecular wt	384.26
a(esd), Å	12.086 (3)
b, Å	12.077 (2)
c, Å	13.425 (2)
α, deg	90
β(esd), deg	116.13 (1)
γ, deg	90
space group	$P2_1/c$
Z	4
density (calculated), g cm^{-3}	1.45
μ, cm^{-1}	3.90
crystal dimensions, mm^3	0.45 × 0.40 × 0.20
temperature, °C	~-150
2θ range, deg	2.5-65.0
no. of independent measurements	5734
no. of intensities $I > 2.5\sigma(I)$	4221
R(usual)	0.063
R(weighted)	0.064

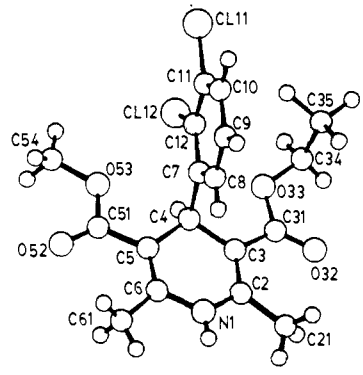


Figure 1. A schematic drawing of ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (felodipine).

The structure was solved by MULTAN[8] and refined by least-squares techniques. Final R values are given in Table I. The computer programs used are described by Groth.[9] Final positional parameters are given in Table IV (see paragraph at the end of paper concerning supplementary material). Thermal parameters and structure factors are available from the author.

Results and Discussion

Figure 1 shows a schematic drawing of the molecule with the adopted atomic labeling scheme. Bond distances do not differ much from values found in analogous DHP

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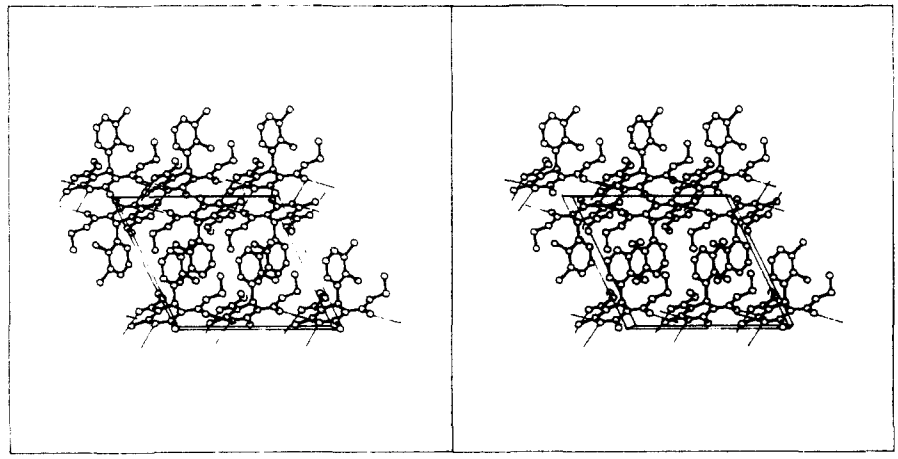

Figure 2. A stereoscopic drawing of the molecular packing arrangement as seen down the *b* axis. Hydrogen atoms are omitted for clarity.

Table II. Selected Torsion Angles

dihedral angle	deg
C31-O33-C34-C35	-97.1 (3)
C34-O33-C31-C3	169.2 (2)
C54-O53-C51-C5	-179.7 (2)
C2-N1-C6-C5	-6.2 (4)
C6-N1-C2-C3	7.6 (4)
N1-C2-C3-C4	3.8 (3)
C21-C2-C3-C31	-0.2 (4)
C2-C3-C4-C5	-14.2 (3)
C2-C3-C31-O32	2.0 (4)
C3-C4-C5-C6	15.5 (3)
C3-C4-C7-C8	-61.4 (3)
C3-C4-C7-C12	118.7 (2)
C4-C5-C6-N1	-6.3 (4)
C51-C5-C6-C61	-3.0 (4)
C6-C5-C51-O52	-0.1 (4)

structures.[5-7] Selected torsion angles may be found in Table II. As shown by the magnitude of the C3-C4-C7-C8 torsion angle, the plane of the phenyl ring approximately bisects the DHP ring. This interring orientation is preferred in all investigated ortho phenyl substituted derivatives, mainly because it minimizes steric strain imposed by the ortho phenyl substituent and the 3,5-diester groups. The present conformation, where the 2,3-dicloro substituents points away from the DHP ring, is also found to be predominant in solution.[10]

Because comparable pharmacological data are lacking, it is not known how well the title compound will fit the previously published regression line,[6] relating DHP ring puckering and the ability to inhibit contractile response in smooth muscle preparations. However, the reported potent smooth muscle relaxant properties of felodipine agrees with the fact that the DHP ring in this compound is among the flattest found in such structures. Deviations from planarity in the DHP ring, defined as the sum of the numeric values of the six intraring torsion angles, range from 52.1° to 112.5° in the investigated nifedipine derivatives as compared to the value 53.6° found in the title compound. To what extent the puckering of the DHP ring can explain the variance in pharmacological activity in DHPs with different ester groups is currently being investigated further in structural studies of a series of nisoldipine (R = Me, R′ = *i*-Bu; X = 2-NO_2) derivatives.

The carbonyl groups in felodipine are twisted in the same direction, both being synperiplanar (*sp*) to the ring double bonds. This conformation of the carbonyl groups (designated *sp,sp*) has also been found in other DHP structures,[5,11] although the conformation where the carbonyl groups are twisted in opposite directions (*ap,sp*)

Table III. Hydrogen-Bonding Parameters in DHP Ca^{2+} Antagonists

compd[a]	acceptor[b]	N···O, Å	H···O, Å	N-H···O, deg
I	O32	2.944	2.14	157
II	O32	2.964	2.05	168
III	O32	3.014	2.17	170
IV	O32	2.977	2.18	171
V	O32	2.945	2.11	167
VI	O32	2.953	2.07	165
VII	O32	2.990	2.19	172
VIII	O32	2.979	2.11	178
IX	O52	3.028	2.16	172
X	O52	2.943	2.05	164
XI	O52	3.293	2.50	157
XII[c]	O32	2.973	2.31	154
	O52	2.983	2.22	147
XIII	O32	3.155	2.67	119
	O52	3.237	2.43	163
XIV[d]	O92	3.101		

[a] I = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-phenyl-1,4-dihydropyridine.[6] II = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(3-methylphenyl)-1,4-dihydropyridine.[6] III = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(3-nitrophenyl)-1,4-dihydropyridine.[6] IV = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(3-cyanophenyl)-1,4-dihydropyridine.[5] V = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(4-methylphenyl)-1,4-dihydropyridine.[6] VI = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(4-nitrophenyl)-1,4-dihydropyridine.[6] VII = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-[4-(dimethylamino)phenyl]-1,4-dihydropyridine.[5] VIII = diethyl 2,6-dimethyl-4-phenyl-1,4-dihydro-3,5-pyridinedicarboxylate.[12] IX = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(2-nitrophenyl)-1,4-dihydropyridine (nifedipine).[5] X = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(2,4-dinitrophenyl)-1,4-dihydropyridine.[6] XI = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-[2-(trifluoromethyl)phenyl]-1,4-dihydropyridine.[7] XII = 2,6-dimethyl-3,5-bis(methoxycarbonyl)-4-(pentafluorophenyl)-1,4-dihydropyridine.[5] XIII = ethyl methyl 1,4-dihydro-2,6-dimethyl-4-(2,3-dichlorophenyl)-3,5-pyridinedicarboxylate (felodipine). XIV = neopentyl (trimethylsilyl)methyl 2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydro-3,5-pyridinedicarboxylate[11] (the corresponding symmetric neopentyl and (trimethylsilyl)methyl dicarboxylates are shown to be structurally isomorph with XIV). [b] The carbonyl groups are twisted in opposite directions (*ap,sp*) in compounds I–XI. In the remaining compounds XII–XIV they are twisted in the same direction (*sp,sp*). [c] In this compound there are two molecules in the asymmetric unit. The carbonyl oxygens in molecule 2 do not participate in hydrogen bonding. N1 of molecule 2 is hydrogen bonded to O52 of molecule 1. [d] Hydrogen positions are not given in the paper.

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occurs most frequently. It may be noted that the *ap,sp* conformation is favored statistically as it can be achieved in two ways. The fact that both conformations are observed in a variety of crystalline environments strongly suggests that they do not differ much in terms of energy. Therefore, it is expected that the conformation with the highest receptor affinity is accessible to all compounds. This solid-state conformational difference between the compounds should therefore be irrelevant to questions concerning their pharmacological activity. Consistent with this, the one nifedipine derivative (R = R′ = Me; X = 2, 3, 4, 5, 6-F) that adopts the *sp,sp* conformation fits the DHP ring puckering model as well as any of the other compounds.

A weak bifurcated hydrogen bond is formed between N1 (donor) and the carbonyl oxygen atoms O32 and O52 of two neighboring molecules. A stereoscopic drawing of the molecular packing arrangement is given in Figure 2. Intermolecular hydrogen bonding parameters may be found in Table III together with values found in other DHP derivatives. In all compounds except one (XIV), the carbonyl oxygen atom(s) acts as hydrogen-bond acceptor(s). Extensive investigations of hydrogen-bonding patterns in organic crystals show that the ether oxygen (C–O–C) in esters very seldom participates in hydrogen bonding, suggesting it is a much poorer hydrogen-bond acceptor.[13] In compound XIV the hydrogen-bond acceptor is an oxygen atom of the 3-nitro phenyl ring substituent.

Table III shows that the hydrogen bonds are all relatively weak, partly due to the shielding effect of the methyl groups in the DHP ring. Both O32 and O52 are involved in hydrogen bonding in molecules adopting the *sp,sp* conformation. Molecules adopting the *ap,sp* conformation form linear chains of hydrogen-bonded molecules involving either O32 or O52 as acceptor atom. O32 acts as acceptor when the phenyl ring has only hydrogen atoms in the ortho position in the phenyl ring, whereas O52 acts as acceptor in compounds with ortho phenyl substituents. In all investigated compounds the ortho substituent points away from the DHP ring. This difference in hydrogen-bonding geometry is therefore mainly caused by the shielding effect of the ortho substituent, making the *ap* carbonyl group less accessible to hydrogen-bond formation.

The significance of the conformation of the ester groups for DHP receptor binding can only be assessed indirectly due to lack of structural information about the receptor site. However, the observed hydrogen-bonding patterns discussed above suggest that hydrogen bonding involving an *ap* carbonyl group and a receptor site donor atom would be hindered by relatively bulky ortho substituents. Provided optimum DHP receptor binding involves utilization of the hydrogen-bonding possibilities presented by the carbonyl groups and the DHP nitrogen atom, the fact that binding affinity is enhanced by ortho phenyl substituents[14] will disfavor the *ap,sp* conformation as the receptor active conformer. In this case the prerequisites for a favorable hydrogen-bonding geometry would best be fulfilled when the *sp,sp* conformation is adopted. Both carbonyl groups are then easily accessible to hydrogen bonding, regardless of the nature and position of the phenyl ring substituent.

If synperiplanar carbonyl groups are a common feature of DHP antagonists, it is interesting to note that in the DHP agonist ethyl 4-[2-(difluoromethoxy)phenyl]-1,4,5,7-tetrahydro-2-methyl-5-oxofuro[3,4-*b*]pyridine-3-carboxylate (CGP 28 392)[15] one ester group is locked into a rigid ring structure with the carbonyl group antiperiplanar. This suggests that the difference between agonist and antagonist response may be partly associated with this conformational difference.

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Supplementary Material Available: Fractional atomic coordinates (Table IV), intramolecular bond distances (Table V), and intramolecular bond angles (Table VI) (3 pages). Ordering information is given on any current masthead page.

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