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4-(2,3-Dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl), 4-(2,4-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl), and 4-(2,3,5-trichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl): conformational observations in the crystalline state

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Hydrogen bonding interactions displayed by three crystalline chloro-substituted 4-phenyl-1,4-dihydropyridine molecules 4-(2,3-Dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl), 4-(2,4-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis (methoxycarbonyl) and 4-(2,3,5-trichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis (methoxycarbonyl), suggests that, in contrast to previous observation, sp orientation of the 3 or 5 substituted carbonyl group accomodates hydrogen bonding to the carbonyl oxygen atom when polar orthosubstituents exist on the phenyl ring.

KEY WORDS: Hydrogen bonding; 1,4-dihydropyridine; calcium beta blockers; single crystal structures.

Introduction

1,4-Dihydropyridine derivatives (DHPs, Fig. 1) comprise a class of calcium antagonists which are widely marketed for use as vasodilators and in the treatment of angina and cardiac arrhythmia. DHPs inhibit the flow of extracellular Ca^{2+} ions through the voltage sensitive L-type calcium channels found in skeletal and cardiac smooth muscle.[1] Early work using rabbit skeletal muscle *trans*-tubule membrane established the amino acid sequence of a 29 residue moiety located in the $alpha_1$ subunit of such channels which appears to contain the receptor site.[2]

Structure activity relationship studies[3] have established certain conformational requirements for potency. An active DHP molecule (Fig. 1) should have its A ring in a flattened boat conformation (total planarity achieved by making ring A aromatic is detrimental to activity.[4,5] The B ring substituted at the four position should be found in a pseudo axial orientation and close to orthogonality with the C2—C3—C5—C6 basal plane of the DHP boat. Ortho and meta substituents on the B ring should point away from the A ring (prow position) and not back over the A ring. Electron withdrawing substituents on the B ring contribute to potency in relation to their position: ortho substituents improving potency more than meta ones; while para substitution has little effect. The carbonyl double bonds of the ester moieties at C3 and C5 of ring A are usually found to be coplanar with the conjugated C=C bonds of the A ring. This is to be expected because electron delocalization through the conjugated system increases the stability of the molecule. The conformation of the carbonyl groups of the ester moieties may be ap or sp relative to the near double bond of the DHP ring (Fig. 1).

Evaluation of the potential potency of a DHP molecule may be achieved by using molecular

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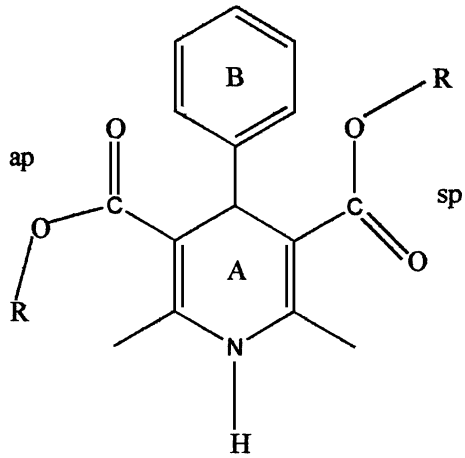

Fig. 1. View of the 1,4-dihydropyridine framework showing numbering, ring identification, and defining ap and sp orientation of carbonyl groups.

modeling to observe the strength of the interaction of docking of the drug into a receptor site. Early work using Sybyl[6] involved observation of the most favorable binding energies when a static DHP molecule was fit, B ring first, into a static receptor site. Comparison of these "best" binding strengths paralleled *in vivo* activity. Therefore Sybyl was widely applied to evaluate potential potency of DHP derivatives prior to synthesis.

Second-generation software[7,8] permits rotation about specified bonds of both drug and receptor site groups and thus a more realistic approach to the docked state of the molecule. However, these programs often do not agree on the way in which the drug is bound to the supposed receptor site nor on the specific location of the DHP receptor site. Thus one seeks other avenues to knowledge of modes of DHP interaction with polar environments as a basis for evaluation of the molecular modeling results and as a basis for understanding how to maximize binding efficiency by DHP design.

The DHP environment in the crystalline solid, where near neighbors are other identical molecules and perhaps some solvent molecules, is surely different from that of the environment of the receptor site. However, the process of crystallization, of maximizing hydrogen bonding, dipole—dipole, and van der Waals-type interactions within the assembling solid must mimic the behavior of maximizing these same interactions when a molecule approaches its docking site. Both are processes of molecular recognition, i.e., the DHP molecules response to potential interactions as it crystallizes must be similar to its behavior while docking. Thus it is worthwhile to examine

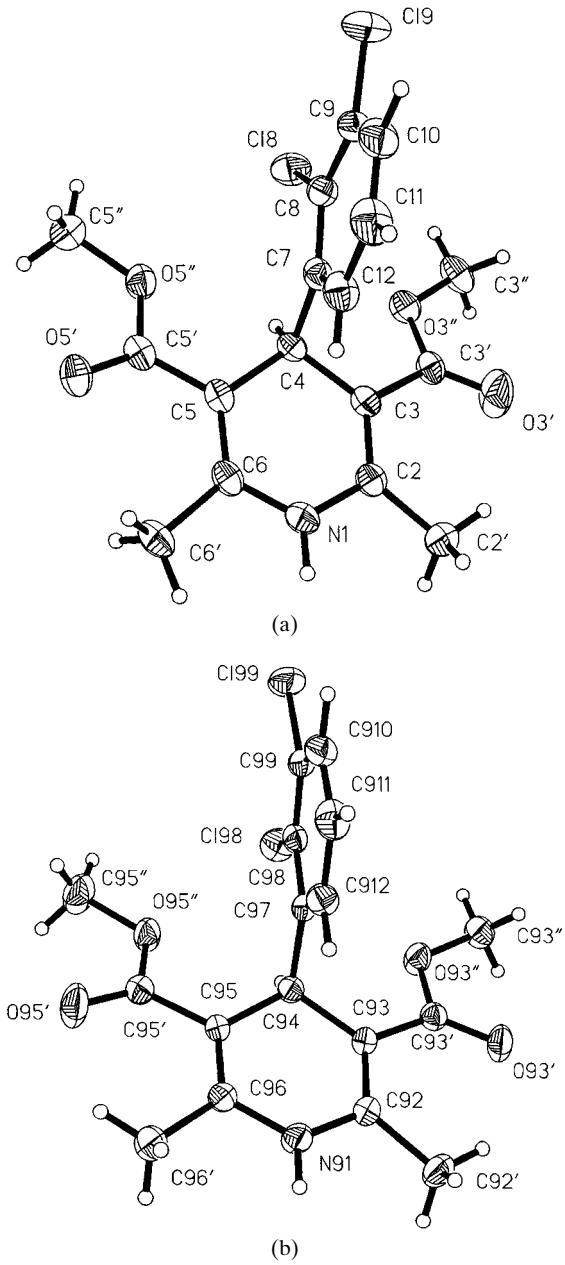

Fig. 2. (a, b) Projection views of the two molecules per asymmetric unit of 4-(2,3-Dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (ellipsoids are shown at the 50% probability level).

patterns of molecular interaction in the crystal as a guide to what to expect in the docked molecule. Of interest are patterns of rotation of carbonyl groups and/or the B ring in response to hydrogen bonding opportunities. Particularly useful to this end are examinations of series of DHP structures containing similar B-ring substituents because they offer

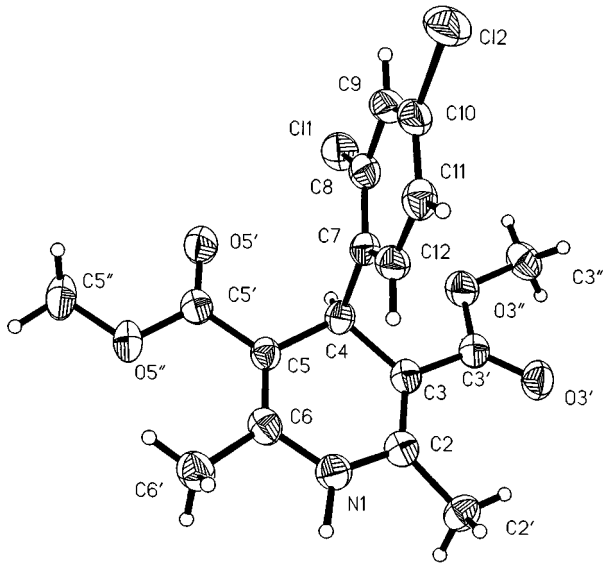

Fig. 3. Projection view of 4-(2,4-dichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (ellipsoids are shown at the 50% probability level).

multiple observations of the molecule adapting to its environment. We have prepared three DHP derivatives with chloro substituted B rings to further this investigation.

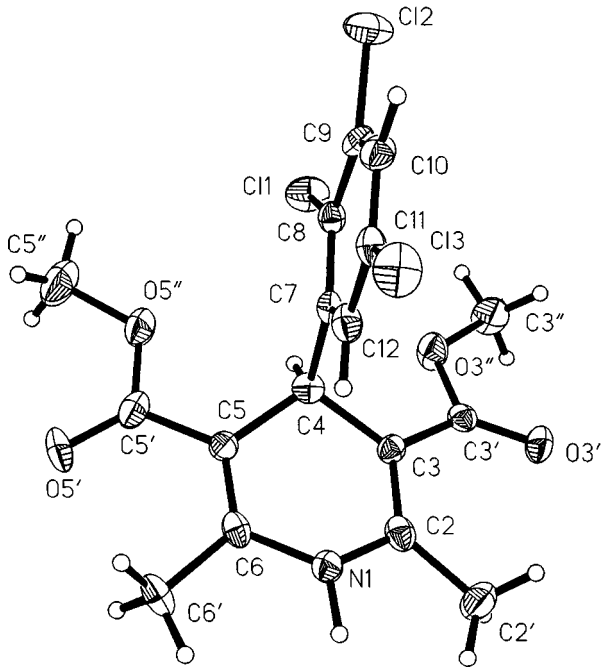

Fig. 4. Projection view of 4-(2,3,5-trichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (ellipsoids are shown at the 50% probability level).

Experimental synthesis

4-(2,3-Dichlorophenyl)-2,6-dimethyl-1,4-dihydopyridine-3,5-bis (methoxy carbonyl) (I)

2,3-Dichlorobenzaldehyde (5 g, 2.86×10^{-2} mol), methyl acetoacetate (6.635 g, 5.72×10^{-2} mol), and 2.002 g (5.72×10^{-2} mol) of concentrated ammonium hydroxide were mixed in 40 ml of methanol and refluxed for 12 hr. The methanol was then removed by rotary evaporation leaving a yellow solid which was dissolved in acetonitrile. The solution was dried over $MgSO_4$. Yellow crystals formed upon slow evaporation of the acetonitrile solution.

4-(2,4-Dichlorophenyl-2,6-dimethyl-1,4-dihydropyridine-3,5-bis (methoxycarbonyl) (II)

2,4-Dichlorobenzaldehyde (5 g, 2.86×10^{-2} mol), methyl acetoacetate (6.635 g, 5.72×10^{-2} mol), and 2.002 g (5.72×10^{-2} mol) of concentrated ammonium hydroxide were mixed in 40 ml of methanol and refluxed for 12 hr. The methanol was then removed under reduced pressure and the yellow solid which remained was dissolved in acetonitrile and the solution dried over $MgSO_4$. Yellow crystals formed on standing.

4-(2,3,5-Trichlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis (methoxycarbonyl) (III)

2,3,5-Trichlorobenzaldehyde (3 g, 1.44×10^{-2} mol), methyl acetoacetate (3.341 g, 2.88×10^{-2} mol), and 1.008 g (2.88×10^{-2} mol) of concentrated ammonium hydroxide were mixed in 40 ml of methanol and heated under reflux for 12 hr. The methanol was then removed by rotary evaporation and the residual yellow solid dissolved in acetonitrile and the solution dried over $MgSO_4$. Yellow crystals formed upon slow evaporation of the acetonitrile solution.

X-ray crystallography

Single crystals of (I), (II), and (III) were mounted on a Siemens P4 automated single-crystal diffractometer. Data were collected (Table 1) and corrected for Lorentz, polarization, and background effects.[9] The intensities of 3 standard reflections were

Table 1. Crystal Data for Compounds I, II, and III

Compound	I	II	III
CCDC Deposit no.	CCDC-1003/5956	CCDC-1003/5957	CCDC-1003/5958
Formula	C17 H17 Cl2 N O4	C17 H17 Cl2 N O4	C17 H16 Cl3 N O4
Molecular weight	370.22	370.22	404.66
Crystal system	Triclinic	Monoclinic	Monoclinic
Space group	$P1$bar	$P2_1/c$	$P2_1$
a, Å	9.809(4)	10.951(10)	8.654(4)
b, Å	12.714(7)	11.358(11)	10.206(5)
c, Å	16.071(9)	14.77(3)	10.463(5)
α, °	112.36(3)		
β, °	91.40(3)	97.58(8)	90.45(4)
γ, °	101.72(3)		
V, Å^3	1803.4(16)	1821(5)	924.1(8)
Z	4	4	2
D_{cal}, Mg m^{-3}	1.364	1.351	1.454
Temperature, K	301	301	301
$F(000)$	768	768	416
Crystal size, mm	0.05 × 0.1 × 0.1	0.1 × 0.1 × 0.1	0.05 × 0.1 × 0.3
Lattice determination	44 reflections $4.908 < \theta < 14.288$	48 reflections $4.994 < \theta < 12.674$	32 reflections $7.716 < \theta < 12.718$
μ, mm^{-1}	0.380	0.376	0.517
Data collection range	$3.5 < 2\theta < 48.82$	$3.5 < 2\theta < 45.44$	$3.5 < 2\theta < 53.74$
Range of indices	h, −11 to 1; k, −14 to 14; l, −18 to 18	h, −1 to 11; k, −1 to 11; l, −16 to 16	h, −10 to 1; k, −12 to 1; l, −13 to 13
Scan type	θ–2θ	θ–2θ	θ–2θ
Scan range (θ–2θ)	1.20	1.20	1.20
Scan speed, °/min	Variable 10 to 30	Variable 10 to 30	Variable 10 to 30
Reflections measured	7053	2973	3677
Unique reflections	5906	2324	2185
R_{int}	8.19	3.82	4.43
Weighting scheme	calc $w = 1/[\sigma^2(F_o^2) + (0.1127P)^2 + 0.2222P]$ where $P = (F_o^2 + 2F_c^2)/3$	calc $w = 1/[\sigma^2(F_o^2) + (0.2000P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3$	calc $w = 1/[\sigma^2(F_o^2) + (0.0372P)^2 + 0.0000P]$ where $P = (F_o^2 + 2F_c^2)/3$
$R(I > 2\sigma(I))$	6.17	5.83	5.98
Goodness of fit	1.026	1.001	1.00
Number of parameters	434	220	231
Maximum peak in final ΔF map, eÅ^{-3}	0.39	0.23	0.27
Minimum peak in final ΔF map, eÅ^{-3}	−0.29	−0.28	−0.27

monitored after every 97 reflections. Crystal decomposition was found to be insignificant. Atomic positions were determined using SHELXS[10] and refined using full-matrix least squares (SHELXL[11]). Hydrogen positions were calculated and included in the final cycles of refinement in constrained positions and with fixed isotropic thermal parameters. Absorption corrections were not made due to the small value of the absorption coefficients (Table 1). Tables 2, 4, and 6 present positional parameters for (I), (II), and (III), respectively, which are the basis for the bond angles and distances of Tables 3, 5, and 7.

Discussion

There have been four observations of DHP derivatives with a single chloro substituent in the 2 or ortho position of the B ring reported in the literature, and three of them crystallize with the chloro substituent in the prow position and with sp, sp conformation of the carbonyl groups.[12–15]4-(2,3-Dichlorophenyl)-2, 6-dimethyl-1, 4-dihydropyridine -3,5-bis(methoxycarbonyl)(I), 4-(2,4-dichlorophenyl) -2,6-dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl)(II), and 4-(2,3,5-trichlorophenyl)-2,6-

Table 2. Atomic Coordinates (Å) and Equivalent Isotropic Displacement Coefficients (Å^2) for Compound I

Atom	x	y	z	U_{eq}[a]
N(1)	−0.0179(3)	0.6459(3)	−0.1666(2)	0.054(1)
C(2)	−0.0296(4)	0.7338(3)	−0.0828(3)	0.046(2)
C(2′)	−0.1183(5)	0.8133(4)	−0.0928(3)	0.061(2)
C(3)	0.0353(3)	0.7377(3)	−0.0054(2)	0.041(1)
C(3′)	0.0106(4)	0.8224(3)	0.0843(3)	0.047(2)
C(3″)	0.0165(5)	0.8609(4)	0.2424(3)	0.063(2)
O(3′)	−0.0373(4)	0.9071(3)	0.0982(2)	0.098(2)
O(3″)	0.0432(3)	0.7903(2)	0.1514(2)	0.055(1)
C(4)	0.1312(3)	0.6560(3)	−0.0057(2)	0.038(1)
C(5)	0.1231(4)	0.5585(3)	−0.1013(2)	0.041(1)
C(5′)	0.2009(4)	0.4683(3)	−0.1108(3)	0.045(2)
C(5″)	0.3225(4)	0.3855(4)	−0.0307(3)	0.066(2)
O(5′)	0.2308(3)	0.3991(2)	−0.1820(2)	0.059(1)
O(5″)	0.2415(3)	0.4683(2)	−0.0295(2)	0.056(1)
C(6)	0.503(4)	0.5592(3)	−0.1750(3)	0.046(2)
C(6′)	0.314(5)	0.4662(4)	−0.2721(3)	0.062(2)
C(7)	0.2834(3)	0.7306(3)	0.0294(3)	0.043(2)
C(8)	0.3566(4)	0.7498(3)	0.1124(3)	0.048(2)
Cl(8)	0.2856(1)	0.6791(1)	0.1815(1)	0.069(1)
C(9)	0.4896(4)	0.8260(4)	0.1414(3)	0.063(2)
Cl(9)	0.5776(2)	0.8584(1)	0.2476(1)	0.103(1)
C(10)	0.5548(5)	0.8779(4)	0.0860(4)	0.073(2)
C(11)	0.4879(5)	0.8565(4)	0.0025(4)	0.071(2)
C(12)	0.3505(4)	0.7837(3)	−0.0256(3)	0.056(2)
N(91)	0.6022(3)	0.6318(3)	0.3388(2)	0.050(1)
C(92)	0.4817(3)	0.5461(3)	0.3291(2)	0.042(1)
C(92′)	0.4473(4)	0.4510(4)	0.2334(3)	0.059(2)
C(93)	0.4100(3)	0.5532(3)	0.4024(2)	0.038(1)
C(93′)	0.2832(4)	0.4628(3)	0.3924(3)	0.042(2)
C(93″)	0.1086(4)	0.3885(4)	0.4687(3)	0.059(2)
O(93′)	0.2198(3)	0.3849(3)	0.3207(2)	0.061(1)
O(93″)	0.2367(3)	0.4732(2)	0.4727(2)	0.055(1)
C(94)	0.4561(3)	0.6537(3)	0.4971(2)	0.037(1)
C(95)	0.5992(3)	0.7341(3)	0.4983(2)	0.038(1)
C(95′)	0.6663(4)	0.8269(3)	0.5868(3)	0.046(2)
C(95″)	0.6557(5)	0.9011(4)	0.7466(3)	0.078(2)
O(95′)	0.7679(3)	0.9061(3)	0.5995(2)	0.086(2)
O(95″)	0.6017(3)	0.8142(3)	0.6565(2)	0.059(1)
C(96)	0.6608(4)	0.7221(3)	0.4209(2)	0.043(2)
C(96′)	0.7950(4)	0.7996(3)	0.4126(3)	0.056(2)
C(97)	0.3465(3)	0.7299(3)	0.5232(2)	0.038(1)
C(98)	0.2808(3)	0.7506(3)	0.6040(2)	0.043(1)
Cl(98)	0.3087(1)	0.6817(1)	0.6766(1)	0.061(1)
C(99)	0.1907(4)	0.8275(3)	0.6270(3)	0.050(2)
Cl(99)	0.1146(1)	0.8595(1)	0.7289(1)	0.078(1)
C(910)	0.1598(4)	0.8803(4)	0.5698(3)	0.059(2)
C(911)	0.2211(4)	0.8586(4)	0.4897(3)	0.061(2)
C(912)	0.3144(4)	0.7849(3)	0.4676(3)	0.048(2)

[a] Equivalent isotropic U defined as the one third of the trace of the orthogonalized V_{ij} tensor.

Table 3. Selected Bond Lengths (Å) and Angles (°) for Compound I

Bond lengths	
N(1)−C(2)	1.411(5)
N(1)−C(6)	1.367(6)
C(3′)−O(3′)	1.208(6)
C(3′)−O(3″)	1.344(6)
C(3′)−O(3″)	1.459(5)
C(5′)−O(5′)	1.235(4)
C(5′)−O(5″)	1.357(5)
C(5″)−O(5″)	1.437(6)
C(8)−Cl(8)	1.752(5)
C(9)−Cl(9)	1.754(5)
N(91)−C(92)	1.396(4)
N(91)−C(96)	1.391(4)
C(93′)−O(93′)	1.242(4)
C(93′)−O(93″)	1.348(5)
C(93″)−O(93″)	1.461(5)
C(95′)−O(95′)	1.215(5)
C(95′)−O(95″)	1.346(5)
C(95″)−O(95″)	1.451(4)
C(98)−Cl(98)	1.751(5)
C(99)−Cl(99)	1.756(4)
Bond angles	
C(2)−N(1)−C(6)	123.7(4)
C(3)−C(3′)−O(3′)	127.0(4)
C(3)−C(3′)−O(3″)	111.1(4)
O(3′)−C(3′)−O(3″)	121.8(4)
C(3′)−O(3″)−C(3″)	117.4(3)
C(5)−C(5′)−O(5′)	126.8(4)
C(5)−C(5′)−O(5″)	112.0(3)
O(5′)−C(5′)−O(5″)	121.2(4)
C(5′)−O(5″)−C(5″)	116.6(3)
C(93)−C(93′)−O(93′)	127.0(4)
C(93)−C(93′)−O(93″)	112.1(3)
O(93′)−C(93′)−O(93″)	120.9(3)
C(93′)−O(93″)−C(93″)	115.6(3)
C(95)−C(95′)−O(95′)	126.9(4)
C(95)−C(95′)−O(95″)	111.9(3)
O(95′)−C(95′)−O(95″)	121.1(3)
C(95′)−O(95″)−C(95″)	117.2(3)

dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl)(III) similarly crystallize with the chloride substituted in the ortho position in prow or forward position. The three chloride substituted molecules reported here are, thus, consistent with the dominant pattern evident from the literature.

Previous observations suggested that carbonyl groups would be found in sp conformation except when the carbonyl oxygen atom was involved in

Table 4. Atomic Coordinates (Å) and Equivalent Isotropic Displacement Coefficients (Å^2) for Compound II

Atom	x	y	z	U_{eq}[a]
N(1)	0.3764(3)	0.5591(3)	0.3031(2)	0.0660(9)
C(2)	0.4678(3)	0.4722(3)	0.3150(2)	0.0580(9)
C(2′)	0.5658(3)	0.4849(3)	0.25013)	0.0703(11)
C(3)	0.4643(3)	0.3883(3)	0.3811(2)	0.0542(9)
C(3′)	0.5532(3)	0.2894(3)	0.3913(3)	0.0579(9)
C(3′′)	0.6303(4)	0.1258(4)	0.4840(3)	0.0809(12)
O(3′)	0.6228(2)	0.2584(2)	0.3350(2)	0.0764(9)
O(3′′)	0.5492(2)	0.2277(2)	0.4711(2)	0.0709(8)
C(4)	0.3592(3)	0.3856(3)	0.4446(2)	0.0535(9)
C(5)	0.2828(3)	0.5011(3)	0.4353(2)	0.0539(9)
C(5′)	0.2052(3)	0.5187(3)	0.5107(3)	0.0585(9)
C(5′′)	0.0762(4)	0.6468(4)	0.5867(4)	0.0875(13)
O(5′)	0.1963(3)	0.4459(3)	0.5694(2)	0.0843(9)
O(5′′)	0.1489(3)	0.6259(2)	0.5110(2)	0.0854(10)
C(6)	0.2875(3)	0.5771(3)	0.3621(3)	0.0621(10)
C(6′)	0.2069(4)	0.6835(3)	0.3336(3)	0.0756(12)
C(7)	0.2740(3)	0.2773(3)	0.4188(2)	0.0538(9)
C(8)	0.2463(3)	0.1888(3)	0.4814(3)	0.0605(10)
C(9)	0.1657(3)	0.0950(3)	0.4536(3)	0.0691(11)
C(10)	0.1136(3)	0.0861(3)	0.3622(3)	0.0680(11)
C(11)	0.1416(3)	0.1693(3)	0.2967(3)	0.0645(10)
C(12)	0.2192(3)	0.2637(3)	0.3265(2)	0.0590(9)
Cl(1)	0.31444(10)	0.18982(9)	0.59730(7)	0.0786(6)
Cl(2)	0.01242(11)	−0.03260(10)	0.32836(11)	0.0950(7)

[a] Equivalent isotropic U defined as the one third of the trace of the orthogonalized V_{ij} tensor.

Table 5. Selected Bond Lengths (Å) and Angles (°) for Compound II

Atoms	Bond length
N(1)−C(2)	1.400(5)
N(1)−C(6)	1.405(5)
C(3′)−O(3′)	1.250(5)
C(3′)−O(3′′)	1.377(5)
C(3′′)−O(3′′)	1.456(5)
C(5′)−O(5′)	1.211(5)
C(5′)−O(5′′)	1.365(4)
C(5′′)−O(5′′)	1.476(6)
C(8)−Cl(1)	1.776(5)
C(10)−Cl(2)	1.775(4)
Bond angles	
C(3)−C(3′)−O(3′)	126.6(4)
C(3)−C(3′)−O(3′′)	112.2(3)
O(3′)−C(3′)−O(3′′)	121.1(3)
C(3′)−O(3′′)−C(3′′)	115.4(3)
C(5)−C(5′)−O(5′)	123.2(3)
C(5)−C(5′)−O(5′′)	114.9(3)
O(5′)−C(5′)−O(5′′)	121.8(3)
C(5′)−O(5′′)−C(5′′)	115.8(3)

Table 6. Atomic Coordinates (Å) and Equivalent Isotropic Displacement Coefficients (Å^2) for Compound III

Atom	x	y	z	U_{eq}[a]
N1	0.1932(6)	0.0858	0.4900(5)	0.0397(16)
C2	0.1368(8)	0.2058(10)	0.4495(6)	0.0398(18)
C2′	−0.0005(9)	0.2524(11)	0.5234(7)	0.061(2)
C3	0.2119(7)	0.2689(9)	0.3524(6)	0.0299(16)
C3′	0.1579(8)	0.4014(9)	0.3116(6)	0.0332(18)
C3′′	0.2316(10)	0.5886(10)	0.1874(8)	0.060(2)
O3′	0.0322(6)	0.4521(8)	0.3309(4)	0.0511(14)
O3′′	0.2659(6)	0.4597(8)	0.2383(5)	0.0514(14)
C4	0.3518(8)	0.2091(9)	0.2860(5)	0.0316(15)
C5	0.4287(8)	0.1035(9)	0.3726(6)	0.0318(16)
C5′	0.5907(9)	0.0721(10)	0.3511(7)	0.046(2)
C5′′	0.8024(9)	0.1083(13)	0.2099(9)	0.077(3)
O5′	0.6738(7)	0.0014(10)	0.4174(6)	0.081(2)
O5′′	0.6448(6)	0.1318(8)	0.2469(5)	0.0571(15)
C6	0.3431(8)	0.0436(10)	0.4644(7)	0.0349(18)
C6′	0.3960(9)	−0.0702(10)	0.5495(7)	0.054(2)
C7	0.3036(7)	0.1527(9)	0.1542(6)	0.0308(16)
C8	0.3569(7)	0.2063(10)	0.0398(6)	0.0317(16)
Cl1	0.4881(2)	0.3344(6)	0.03289(16)	0.0560(6)
C9	0.3003(8)	0.1548(10)	−0.0779(6)	0.0389(18)
Cl2	0.3542(3)	0.2239(7)	−0.22308(16)	0.0709(8)
C10	0.1987(9)	0.0468(10)	−0.0800(7)	0.044(2)
C11	0.1546(8)	−0.0049(9)	0.0344(7)	0.0365(18)
Cl3	0.0284(2)	−0.1415(7)	0.0339(2)	0.0612(6)
C12	0.2046(8)	0.0456(9)	0.1495(7)	0.041(2)

[a] Equivalent isotropic U defined as the one third of the trace of the orthogonalized V_{ij} tensor.

Table 7. Selected Bond Lengths (Å) and Angles (°) for Compound III

Bond lengths	
N(1)−C(2)	1.383(9)
N(1)−C(6)	1.395(9)
C(3′)−O(3′)	1.222(8)
C(3′)−O(3′′)	1.352(8)
C(3′′)−O(3′′)	1.450(9)
C(5′)−O(5′)	1.229(9)
C(5′)−O(5′′)	1.336(9)
C(5′′)−O(5′′)	1.440(9)
C(8)−Cl(1)	1.733(7)
C(9)−Cl(2)	1.742(7)
C(11)−Cl(3)	1.770(7)
Bond angles	
C(3)−C(3′)−O(3′)	127.8(7)
C(3)−C(3′)−O(3′′)	110.2(6)
O(3′)−C(3′)−O(3′′)	121.8(7)
C(3′)−O(3′′)−C(3′′)	117.9(6)
C(5)−C(5′)−O(5′)	126.9(8)
C(5)−C(5′)−O(5′′)	111.7(7)
O(5′)−C(5′)−O(5′′)	121.4(7)
C(5′)−O(5′′)−C(5′′)	118.8(7)

hydrogen bonding. In that case, the carbonyl group would be turned to ap conformation. For example, 4-(2-pyrrolyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl), 4-(3-furyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) 4-(3-bromo-2-furyl)-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl),[16] 4-(5-(1,3-benzodioxole) 2,6-dimethyl-1,4-dihydropyridine-3,5-bis (methoxycarbonyl), 4-(3-pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl),[17] 4-(2,5-dimethoxyphenyl)-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-bis-(ethoxycarbonyl), and 4-(3,4-dimethoxyphenyl)-2, 6-dimethyl-1, 4 -dihydropyridine-3, 5-bis(ethoxycarbonyl) [18] crystallize with carbonyl conformations, sp and ap; with only the ap conformer being involved in hydrogen bonding.

Structures (I), (II), and (III) do not follow this pattern. Structures (I) and (III) display sp, sp orientation of carbonyl groups, yet they display hydrogen bonding involving an sp carbonyl group: 4-(2,3-dichlorophenyl)-2, 6-dimethyl-1, 4-dihydropyridine-3,5-bis(methoxycarbonyl)(I) crystallizes with both molecules displaying sp, sp conformation of the carbonyl groups substituted on the A ring. Torsion angles, molecule 1, C2—C3—C3′—O3′, −17.2(8)° C6—C5—C5—O5′ 13.3(8)°; Molecule 2, −9.8(8)° and 8.5(8)°, respectively. (N1—H1a···O93′($-x, 1-y, -z$) 2.133(1) Å, angle 157.9(3)° and N91—H91a···O5′ ($1-x, 2-y, -z$) 2.095(1) Å, angle 168.7(3)°

Similarly (III) has both carbonyl groups in sp orientation (torsion angles, −19.2(5)° and −8.0(5)°) and N1—H1a···O3′, ($-x, -1-y, 1-z$) 2.114(1) Å, angle 157.1(5)°.

4-(2, 4-Dichlorophenyl)-2, 6-dimethyl-1, 4-dihy dropyridine-3,5-bis(methoxycarbonyl)(II) is seen with the ester group attached at C5 in ap conformation (torsion angle 174.1(3)°) while the C3 substituted ester group is seen in sp conformation (torsion angle −13.7(3)°). The carbonyl group substituted at C5 (ap) is not involved in hydrogen bonding; however, there is a hydrogen bond involving the C3 substituted carbonyl group (sp): N1—H1···O3′ ($1-x$, 0.5 + y, $0.5-z$) 1.958(1) Å (angle 172.5(3)°).

As expected, (I), (II), and (III) exist in the crystalline state with the A ring in flattened boat conformation. The sums of the absolute values of the torsion angles are 30.4(5) and 25.3(5)° for (I), 51.2(3)° for (II), and 88.2(5)° for (III) indicating increased deviation from planarity of the ring in the series. The theoretical total is zero for a totally planar ring and 240° for an idealized boat conformation.

All three structures show the plane of the B ring nearly perpendicular to the plane of the A ring; interplanar angles, 91.2(3), 92.8(3) (I) 88.5(5) for (II), and 90.7(3)° for (III). This is in agreement with the literature discussion of ortho substituents allowing little variation from orthogonal positioning of the two rings. Each of the three structures (including both molecules of the asymmetric unit of (I)) has a chloro substituent in the ortho position of the B ring.

Consistent with the patterns observed in other DHP derivatives, ether oxygen atoms of 3- and 5-substituted ester groups are not involved in hydrogen bonding. Nor are hydrogen bonds observed to involve the halide atoms substituted on the B ring.

There are two conclusions to be drawn from these observations. First, the influence of a large atom bearing multiple electron pairs substituted on the ortho position of the B ring leads to a preference for near orthogonality of the A and B rings and for sp conformation of the carbonyl groups. Second, sp conformation does not preclude hydrogen bonding involving the carbonyl atoms in the crystal.

Indeed, it should be noted that 4-(2-chlorophenyl)-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-bis (methoxycarbonyl) has been observed with two molecules per asymmetric unit, one of which has the 2-chloro substituent in the prow position and carbonyl groups in sp and ap conformation, whereas the other molecule has the chloride in folded back orientation and ap, ap conformation of the carbonyl groups.[19] Thus not only are the carbonyl groups fluxional but also the B ring orientation is reversible without extraordinary energy cost.

The implications for docking site geometry appear to be that ortho substitution of electronegative atoms on the B ring increases calcium blocking efficiency, but not via hydrogen bonding to these groups. There may be dipole, dipole interaction of the ortho substituent with the receptor site. This interaction appears insufficient to represent the totality of DHP interaction with the binding site. Hydrogen bonding must be involved. Molecular recognition of the docking site must, therefore, involve hydrogen bonding to the hydrogen atom at N1 and hydrogen bonding to one or more of the oxygen atoms of the carbonyl groups substituted at C3 and C5. Perhaps these carbonyl groups, which appear to be capable of relatively free rotation from ap to sp conformation, hydrogen bond to the receptor site in a conformation intermediate between ap and sp. The loss of calcium blocking efficiency on oxidation of the A ring to a pyridine moiety

with attendant loss of the hydrogen atoms at C4 and N1 is strongly supportive of this view. These conclusions argue that the binding site previously identified is incorrect.

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