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New 1,4-dihydropyridine derivatives with hetero and saturated B rings

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The single crystal structures of 4-(5-(1,3-benzodioxole)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**I**), 4-(3-pyridyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis (methoxycarbonyl) (**II**), 4-(3(1-methyl-1H-indole))-2,6-dimethyl-1,4-dihydropyridine-3, 5-bis(methoxycarbonyl) (**III**), and 4-cyclopentadienyl-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**IV**) suggest that these members of a calcium beta blocking family may dock with their receptor sites from the A ring end of the molecule.

KEY WORDS: Heterocycle; hydrogen bonds; 1,4-dihydropyridine; calcium beta blocker; structure; hetero 1,4-dihydropyridine derivatives.

Introduction

1,4-Dihydropyridine derivatives (DHPs) form a class of compounds widely prescribed for their antihypertensive activity.[1] They are thought to block calcium passage through the walls of smooth muscle by interaction with a receptor site in voltage-gated manner.[2] The attention paid to molecular modeling of the docking of rigid DHP derivatives with a particular rigid receptor site in the α_1 subunit of cardiac smooth muscle seemed to have led to a consistent view of the correlation of molecular conformation parameters with molecular activity.[3] However the lack of consistency seen on application of second generation molecular modeling programs that permit flexibility of drug and docking site[4] has led to the suspicion that the receptor site(s) may be other than that used widely for modeling experiments.

Thus, it is appropriate to seek other avenues of understanding of the characteristics of the DHP docking site and of drug interaction with it, i.e. of molecular recognition of the docking site. The crystallization process represents a form of molecular recognition in that the crystallizing molecule seeks interactions with other molecules on the surface of the growing crystal that are stronger than interactions with the solvent and that impose an orientation on the approach of the incoming molecule. Thus the molecule is driven energetically to align in a specific way with the molecules of the crystalline solid and to shed interactions with the solvent. These interactions must involve hydrogen bonding, dipole–dipole interactions, and Van der Waals interactions, in the order of decreasing strength.

Patterns of molecular recognition as seen in the resulting crystal structure may mimic recognition of binding site patterns. For a DHP molecule, these patterns involve variations in conformation of the A ring (Fig. 1), relative orientation of ring A

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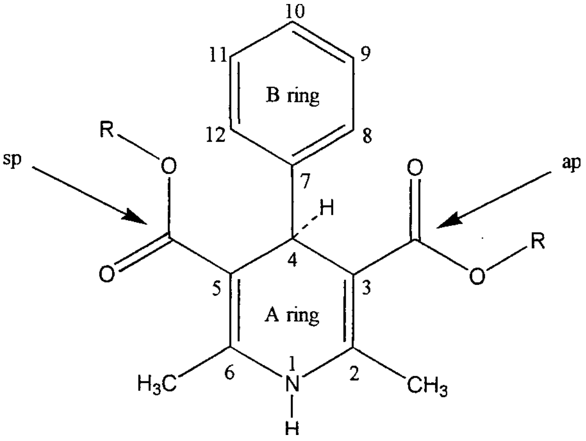

Fig. 1. General view of a 1,4-dihydropyridine framework, with numbering scheme and terminology of carbonyl conformation indicated.

to ring B, carbonyl orientation at C3 and C5, and hydrogen bonding involving the hydrogen atom of N1.

Previous work in this laboratory has shown that the presence of the hydrogen on N1 of the A ring is important for DHP potency.[5,6] Indeed, the aromatization of the A ring, which occurs on oxidation of 2-nitro-DHP, results in serious loss of pharmacological activity.[7]

Coplanarity of the carbonyl of the ester group with the conjugated double bond of the A ring is to be expected because of the stabilization gained by efficient charge delocalization. The esterification alkyl group should be small in volume for better DHP activity. Groups larger than isopropyl lead to a significant drop in the binding strength.[8–10]

Our previous work has shown that the carbonyl groups attached to C3 and C5 are preferentially in *ap* (antiperiplanar) conformation when hydrogen bonded, but *sp* (synperiplanar) otherwise.[11,12] There are, however, exceptions to this generalization. 4-(2,3-Dichlorophenyl)-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl), 4-(2,3,5-trichlorophenyl)-2,6-dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl) display *sp*, *sp* orientation of carbonyl groups, yet they display hydrogen bonding to one of the carbonyl groups. 4-(2,4-Dichlorophenyl)-2,6-dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl) is seen with the ester group attached at C5 in *ap* conformation and uninvolved in hydrogen bonding; however there is a hydrogen bond involving the C3-substituted carbonyl group that is in *sp* conformation.[13]

Normally the hydrogen-bonding donor is the N—H group of the A ring, and the carbonyl oxygen atom serves as acceptor. Hetero atoms of the B ring such as S and O have not been seen to participate in hydrogen bonding.[14,11] However, in one instance, a bifurcated hydrogen bond has been observed to form between the H1 of N1 and the oxygen atoms of two adjacent methoxy groups substituted on ring B.[12]

Previous work has shown that the orientation of an ortho substituent on the B ring in prow-forward or prow-backward conformation is easily reversed. Diethyl 4-(2,5-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate crystallized from nitrobenzene or urea is seen as the prow backwards rotamer.[12] Cystallized from ethanol, the prow forward rotamer is observed.[15] Furthermore, in DHP molecules with 2- and 3-thiophene groups serving as the B ring, both prow forward and prow backward orientations are seen.[14] The 2-chloro derivative has been found to crystallize, with both rotamers present in the same unit cell.[16]

Of interest is the effect of bulky B rings on crystal packing as an indication of possible interactive behavior with a receptor site. We have determined the single crystal x-ray structures of 4-(5-(1,2-benzodioxole)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**I**), 4-(3-pyridyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**II**), and 4-(3(1-methyl-1*H*-indole))-2, 6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**III**). For comparison purposes, we have determined the single crystal structure of a 4-cyclohexyl DHP derivative, 4-cyclohexyl-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**IV**) in which the B ring is totally devoid of polar groups.

Experimental

4-(5-(1, 3-Benzodioxole))-2,6-dimethyl-1, 4-dihydropyridine-3,5-bis(methoxycarbonyl) (***I***): 1,3-Benzodioxole-5-carboxaldehyde (2.175 g, 14.5×10^{-3} mol), methyl acetoacetate (3.364 g, 29×10^{-3} mol), and concentrated ammonium hydroxide (1.015 g, 29×10^{-3} mol) were mixed in methanol and allowed to reflux for 5 h. The resulting yellow solution was concentrated by rotary evaporation and dried over $MgSO_4$. Crystals suitable for x-ray diffraction formed from the solution.

4-(3-Pyridyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**II**): 3-Formylpyridine (1.772 g, 16.56×10^{-3} mol), methyl acetoacetate (3.835 g, 33.12×10^{-3} mol), and concentrated ammonium hydroxide (1.160 g, 33.12×10^{-3} mol) were refluxed in methanol for 5 h. The resulting yellow solution was concentrated under reduced pressure and dried over $MgSO_4$, yielding crystals suitable for x-ray.

4-(3-(1-Methyl-1H-indole))-2,6-dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl) (**III**): 1-Methyl-1H-indole-3-carboxaldehyde (2.245 g, 14.12×10^{-3} mol), methyl acetoacetate (3.276 g, 28.24×10^{-3} mol), and concentrated ammonium hydroxide (0.985 g, 28.24×10^{-3} mol) were mixed in methanol and allowed to reflux for 5 h. Crystals suitable for x-ray diffraction formed from the yellow solution after concentration under reduced pressure.

4-Cyclohexano-2, 6-dimethyl-1, 4-dihydropyridine-3,5-bis(methoxycarbonyl) (**IV**): Cyclohexanocarboxaldehyde (1.58 g, 14.12×10^{-3} mol), methyl acetoacetate (3.276 g, 28.24×10^{-3} mol), and concentrated ammonium hydroxide (0.985 g, 28.24×10^{-3} mol) were mixed in methanol and allowed to reflux for 5 h, yielding a yellow solution that crystallized on standing.

Table 1. Crystallographic Data for Compounds **I**, **II**, **III**, and **IV**

Compound	**I**	**II**	**III**	**IV**
Molecular formula	$C_{18}H_{19}NO_6$	$C_{16}H_{18}N_2O_4$	$C_{20}H_{22}N_2O_4$	$C_{17}H_{25}NO_4$
CCDC deposit no.	CCDC-1003/6117	CCDC-1003/6118	CCDC-1003/6119	CCDC-1003/6120
Mass	345.3	302.3	354.4	307.4
a, Å	7.498(6)	8.525(5)	8.209(5)	9.451(3)
b, Å	9.698(6)	22.070(13)	10.524(4)	13.081(4)
c, Å	12.374(7)	8.996(9)	10.856(5)	13.923(6)
α, deg	100.90(2)	90.0	90.0	90.0
β, deg	97.49(3)	111.24(1)	95.56(1)	100.62(3)
γ, deg	99.73(3)	90.0	90.0	90.0
Z M	2	4	2	4
d, mg/m^3	1.336	1.273	1.261	1.207
Crystal system	Triclinic	Monoclinic	Monoclinic	Monoclinic
Space group	P1bar	$P2_1/c$	$P2_1$	$P2_1/c$
Diffractometer	Siemens P4	Siemens P4	Siemens P4	Siemens P4
Crystal size	0.2 × 0.3 × 0.1	0.05 × 0.1 × 0.1	0.2 × 0.2 × 0.2	0.2 × 0.2 × 0.2
θ range, deg	1.8–30.0	2.56–30.0	1.8–30.0	2.5–30.0
Reciprocal lattice segment	$-8 < h < 1; -10 < k < 10; -13 < l < 13$	$-1 < h < 11; -1 < k < 31; -12 < l < 12$	$-1 < h < 10; -1 < k < 13; -13 < l < 13$	$-1 < h < 10; -14 < k < 1; -15 < l < 15$
Reflections measured	3183	5656	2879	3431
Number of symmetry independent reflections	2525	4574	2394	2595
F_o/parameter	2525/228	4574/200	2394/236	2595/199
R [$I > 2\sigma(\mathbf{I})$]	6.50	5.87	5.17	6.27
Rw	8.5	8.74	7.57	7.39

X-ray crystallographic study

The collection of diffraction data using suitable crystals was accomplished using a Siemens P4 automated single crystal x-ray diffractometer equipped with monochromatized Mo Kα radiation (0.71073 Å) and a θ–2θ scan.[17] Cell constants were determined using the least-squares fit of the four diffractometer angles for an appropriate number of reflections (Table 1). The intensities of three standard reflections were monitored after every 97 reflections. Crystal decomposition was found to be insignificant. The structures were solved and refined using the programs SHELXS and SHELXL of the SHELX[18] package. Refinement of an extinction coefficient showed it to be insignificant. The hydrogen atoms of methyl groups C2′ and C6′ of **I**; C2′, C3″, C5″, and C6′ of **II**; and C2′, C3″, C5″, and C6′ of **III** showed a rotational disorder. The two sets of hydrogen positions associated with each methyl group, which were apparent from a difference Fourier synthesis, were refined with 50% occupancy factors in the final cycles of refinement.

Results and discussion

Projection drawings of the four structures are given in Fig. 2 on the basis of positional parameters of Tables 2, 4, 6, and 8. Tables 3, 5, 7, and 9 display selected bond angles and distances based on the final positional parameters.

In molecule **IV**, with a six-membered B ring in chair conformation containing no hetero atoms, the sum of the torsion angles of ring A (boat conformation) is 114.5°. The two structures with bulky fused rings substituted at C4, i.e. **I** and **III**, are seen with flatter boat conformations of the A ring (torsion angle sum $= 0^\circ$ for a totally flat ring and 240° for a boat of idealized conformation). Their torsion angle sums are 94.8° (**I**) and 108.1° (**III**). Structure **II**, in which the aromatic B ring has an unshared pair localized on the nitrogen atom in the meta position, is the most distorted from idealized boat geometry: torsion angle sum $= 78.6^\circ$.

For **IV**, the average plane of the cyclohexane ring subtends an angle of 81.9° with the base of the dihydropyridine ring (atoms C2, C3, C5, and C6). The fused and hetero B rings are seen in orientations closer to orthogonality with the basal plane of the boat: 93.3° (**I**), 88.5° (**II**), and 88.5° (**III**), suggesting that B ring bulk or the presence of hetero atoms in the B ring leads to more rigorous orthogonality.

The conformations of carbonyl groups substituted at C5 and C3 may be quantified by the C6—C5—C5′—O5′ and C2—C3—C3′—O3′ torsion angles, respectively. Values close to 0 indicate *sp* conformation, whereas those close to 180° denote *ap* conformation. Delocalization of charge over the conjugated C=C—C=O system normally insures that these angles remain close to their theoretical values. The absolute

Table 2. Atomic Coordinates and Equivalent Isotropic Displacment Coefficients (Å) for Compound **I**

Atom	x	y	z	U_{eq}[a]
N(1)	0.7867(5)	0.2921(4)	0.4190(3)	0.055(1)
C(2)	0.6539(6)	0.2438(5)	0.4810(4)	0.050(1)
C(2′)	0.7325(7)	0.1880(6)	0.5782(4)	0.062(1)
C(3)	0.4759(6)	0.2521(4)	0.4465(3)	0.045(1)
C(3′)	0.3252(6)	0.2203(5)	0.5104(4)	0.048(1)
C(3″)	0.2241(7)	0.1214(6)	0.6595(5)	0.074(2)
O(3′)	0.1698(4)	0.2428(4)	0.4857(3)	0.063(1)
O(3″)	0.3703(5)	0.1613(4)	0.5978(3)	0.069(1)
C(4)	0.4167(6)	0.2917(5)	0.3350(3)	0.047(1)
C(5)	0.5804(6)	0.3830(5)	0.3015(4)	0.048(1)
C(5′)	0.5417(7)	0.4749(5)	0.2224(4)	0.055(1)
C(5″)	0.3069(9)	0.5693(6)	0.1274(5)	0.078(2)
O(5′)	0.6517(5)	0.5397(4)	0.1762(3)	0.084(1)
O(5″)	0.3591(5)	0.4776(4)	0.2013(3)	0.066(1)
C(6)	0.7551(6)	0.3742(5)	0.3400(4)	0.051(1)
C(6′)	0.9301(7)	0.4466(5)	0.3078(5)	0.068(2)
C(7)	0.3324(6)	0.1548(4)	0.2449(3)	0.045(1)
C(8)	0.1401(6)	0.1039(4)	0.2254(4)	0.050(1)
C(9)	0.0703(7)	−0.0204(5)	0.1464(4)	0.055(1)
O(10)	−0.1129(5)	−0.0871(4)	0.1096(3)	0.075(1)
C(11)	−0.1098(9)	−0.2210(6)	0.0371(5)	0.081(2)
O(12)	0.0746(6)	−0.2170(4)	0.0128(3)	0.078(1)
C(13)	0.1813(8)	−0.0977(5)	0.0883(4)	0.058(1)
C(14)	0.3697(7)	−0.0499(5)	0.1048(4)	0.062(1)
C(15)	0.4433(7)	0.0775(5)	0.1837(4)	0.054(1)

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

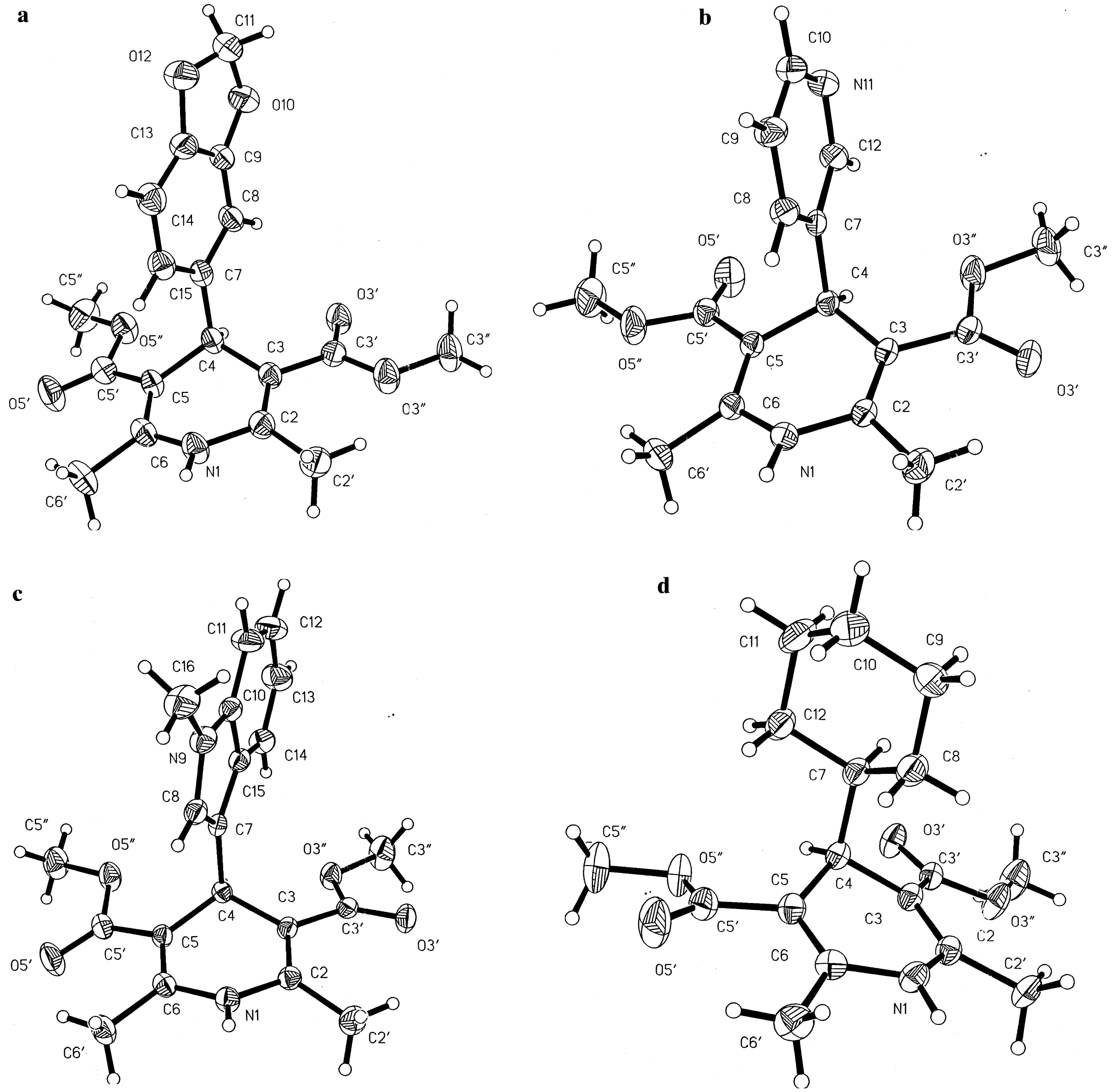

Fig. 2. Projection views with ellipsoids shown at the 50% probability level of (a) 4-(5-(1,2-benzodioxole)2,6-dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl) (**I**); (b) 4-(3-pyridyl)2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**II**); (c) 4-(3(1-methyl-1*H*-indole))-2, 6-dimethyl-1, 4-dihydropyridine-3, 5-bis(methoxycarbonyl) (**III**); (d) 4-cyclohexyl-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(methoxycarbonyl) (**IV**).

magnitudes of the values seen for the torsion angles C6—C5—C5′—O5′ and C2—C3—C3′—O3′ are 6.8° and 181.7° for **I**, 160.5° and 0.8° for **II**, 5.9° and 16.2° for **III**, and 26.2° and 169.9° for **IV**, respectively; this confirms the influence of electron delocalization upon carbonyl conformation. The respective conformations are thus *sp,ap* (**I**); *ap,sp* (**II**); and *sp,sp* (**III**); and *sp,ap* (**IV**). Molecules **I** and **IV** follow the expected pattern of the carbonyl atom not involved in hydrogen bonding being seen in *sp* conformation (torsion angle near 0°) whereas the carbonyl that is hydrogen bonded is seen in *ap* conformation (torsion angle near 180°). For **I**, H1A $\cdots$ O3′$(1 + x, y, z)$ 2.138 Å with a N1−H1a−O3′ angle of 168°. For **IV**, N1−H1a $\cdots$ O3′ $(x, \frac{1}{2} - y, -\frac{1}{2} + z)$ 2.116 Å with an angle 171.7°. This pattern is seen for the majority of published DHP structures and can be said to be indicative of hydrogen bonding causing *ap* orientation of the C=O group. Without hydrogen-bonding involvement, the group is mostly *sp*.

Structures **II** and **III** do not follow the pattern. For **II**, hydrogen bonding involves the N−H of the A ring as a donor and the pyridine nitrogen atom of the B ring of an adjacent molecule as the acceptor [H1a−N9 $(x, y, 1 + z)$ 2.131 Å with a N1−H1a $\cdots$ N11 angle of 157.5°]. Yet one

Table 3. Bond Lengths (Å) and Angles (deg) for Compound **I**

N(1)−C(2)	1.405(6)	C(3′)−C(3)−C(4)	114.8(4)
N(1)−C(6)	1.394(6)	C(3)−C(3′)−O(3′)	123.7(4)
C(2)−C(2′)	1.502(6)	C(3)−C(3′)−O(3″)	114.5(4)
C(2)−C(3)	1.368(6)	O(3′)−C(3′)−O(3″)	121.8(4)
C(3)−C(3′)	1.484(6)	C(3′)−O(3″)−C(3″)	116.5(4)
C(3)−C(4)	1.532(6)	C(3)−C(4)−C(5)	110.2(4)
C(3′)−O(3′)	1.231(5)	C(3)−C(4)−C(7)	110.0(3)
C(3′)−O(3″)	1.347(5)	C(5)−C(4)−C(7)	112.1(3)
C(3″)−O(3″)	1.457(6)	C(4)−C(5)−C(5′)	118.2(4)
C(4)−C(5)	1.538(6)	C(4)−C(5)−C(6)	120.7(4)
C(4)−C(7)	1.542(6)	C(5′)−C(5)−C(6)	121.1(4)
C(5)−C(5′)	1.476(6)	C(5)−C(5′)−O(5′)	127.0(5)
C(5)−C(6)	1.357(6)	C(5)−C(5′)−O(5″)	111.8(4)
C(5′)−O(5′)	1.219(6)	O(5′)−C(5′)−O(5″)	121.2(5)
C(5′)−O(5″)	1.366(6)	C(5′)−O(5″)−C(5″)	116.2(4)
C(5″)−O(5″)	1.453(5)	N(1)−C(6)−C(5)	119.4(4)
C(6)−C(6′)	1.518(6)	N(1)−C(6)−C(6′)	113.2(4)
C(7)−C(8)	1.416(6)	C(5)−C(6)−C(6′)	127.4(4)
C(7)−C(15)	1.409(6)	C(4)−C(7)−C(8)	119.2(4)
C(8)−C(9)	1.375(6)	C(4)−C(7)−C(15)	121.3(4)
C(9)−O(10)	1.392(6)	C(8)−C(7)−C(15)	119.5(4)
C(9)−C(13)	1.391(7)	C(7)−C(8)−C(9)	117.6(4)
O(10)−C(11)	1.438(7)	C(8)−C(9)−O(10)	128.0(5)
C(11)−O(12)	1.448(7)	C(8)−C(9)−C(13)	122.5(5)
O(12)−C(13)	1.391(6)	O(10)−C(9)−C(13)	109.5(4)
C(13)−C(14)	1.386(7)	C(9)−O(10)−C(11)	105.5(4)
C(14)−C(15)	1.399(6)	O(10)−C(11)−O(12)	108.2(4)
C(2)−N(1)−C(6)	123.4(5)	C(11)−O(12)−C(13)	104.9(4)
N(1)−C(2)−C(2′)	113.1(4)	C(9)−C(13)−O(12)	110.3(5)
N(1)−C(2)−C(3)	117.9(4)	C(9)−C(13)−C(14)	121.2(4)
C(2′)−C(2)−C(3)	129.0(4)	O(12)−C(13)−C(14)	128.4(5)
C(2)−C(3)−C(3′)	123.8(4)	C(13)−C(14)−C(15)	117.2(5)
C(2)−C(3)−C(4)	121.4(4)	C(7)−C(15)−C(14)	122.0(5)

Table 4. Atomic Coordinates and Equivalent Isotropic Displacment Coefficients (Å) for Compound **II**

Atom	x	y	z	$U_{\mathrm{eq}}{}^{a}$
N(1)	0.4075(2)	0.6256(1)	1.0689(2)	0.041(1)
C(2)	0.5473(2)	0.6528(1)	1.0521(2)	0.042(1)
C(2′)	0.6274(3)	0.7007(1)	1.1782(3)	0.061(1)
C(3)	0.5972(2)	0.6358(1)	0.9294(2)	0.039(1)
C(3′)	0.7528(2)	0.6603(1)	0.9137(2)	0.045(1)
C(3″)	0.9201(3)	0.6563(1)	0.7489(4)	0.070(1)
O(3′)	0.8512(2)	0.6970(1)	0.9999(2)	0.072(1)
O(3″)	0.7756(2)	0.6361(1)	0.7839(2)	0.061(1)
C(4)	0.4884(2)	0.5935(1)	0.7966(2)	0.036(1)
C(5)	0.3641(2)	0.5574(1)	0.8509(2)	0.037(1)
C(5′)	0.2897(2)	0.5044(1)	0.7479(3)	0.045(1)
C(5″)	0.0603(4)	0.4345(1)	0.6544(4)	0.087(1)
O(5′)	0.3518(2)	0.4803(1)	0.6613(2)	0.076(1)
O(5″)	0.1393(2)	0.4864(1)	0.7518(2)	0.071(1)
C(6)	0.3277(2)	0.5749(1)	0.9809(2)	0.041(1)
C(6′)	0.2091(3)	0.5443(1)	1.0499(3)	0.058(1)
C(7)	0.3917(2)	0.6292(1)	0.6437(2)	0.035(1)
C(8)	0.2731(2)	0.6732(1)	0.6435(2)	0.042(1)
C(9)	0.1822(2)	0.7039(1)	0.5025(2)	0.050(1)
C(10)	0.2150(3)	0.6904(1)	0.3653(2)	0.050(1)
N(11)	0.3312(2)	0.6498(1)	0.3618(2)	0.053(1)
C(12)	0.4165(2)	0.6198(1)	0.4995(2)	0.046(1)

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

Table 5. Bond Lengths (Å) and Angles (deg) for Compound **II**

N(1)−C(2)	1.390(2)	C(2)−C(3)−C(4)	121.1(2)
N(1)−C(6)	1.397(2)	C(3′)−C(3)−C(4)	117.1(2)
C(2)−C(2′)	1.520(3)	C(3)−C(3′)−O(3′)	127.8(2)
C(2)−C(3)	1.371(3)	C(3)−C(3′)−O(3″)	110.5(2)
C(3)−C(3′)	1.484(4)	O(3′)−C(3′)−O(3″)	121.7(2)
C(3)−C(4)	1.535(3)	C(3′)−O(3″)−C(3″)	117.6(2)
C(3′)−O(3′)	1.221(2)	C(3)−C(4)−C(5)	111.0(1)
C(3′)−O(3″)	1.360(3)	C(3)−C(4)−C(7)	111.1(1)
C(3″)−O(3″)	1.448(2)	C(5)−C(4)−C(7)	110.0(1)
C(4)−C(5)	1.540(2)	C(5′)−C(5)−C(6)	125.3(2)
C(4)−C(7)	1.541(3)	C(6)−C(5)−C(4)	121.3(2)
C(5)−C(5′)	1.485(3)	C(5′)−C(5)−C(4)	113.3(2)
C(5)−C(6)	1.369(3)	C(5)−C(5′)−O(5′)	124.1(2)
C(5′)−O(5′)	1.211(2)	C(5)−C(5′)−O(5″)	114.1(2)
C(5′)−O(5″)	1.355(2)	O(5′)−C(5′)−O(5″)	121.8(2)
C(5″)−O(5″)	1.452(3)	C(5′)−O(5″)−C(5″)	116.8(2)
C(6)−C(6′)	1.522(2)	N(1)−C(6)−C(5)	119.7(2)
C(7)−C(8)	1.401(2)	N(1)−C(6)−C(6′)	112.5(2)
C(7)−C(12)	1.404(3)	C(5)−C(6)−C(6′)	127.8(2)
C(8)−C(9)	1.399(3)	C(8)−C(7)−C(12)	116.9(2)
C(9)−C(10)	1.392(3)	C(8)−C(7)−C(4)	120.5(2)
C(10)−N(11)	1.345(3)	C(12)−C(7)−C(4)	122.6(2)
N(11)−C(12)	1.360(3)	C(7)−C(8)−C(9)	119.9(2)
C(2)−N(1)−C(6)	123.0(2)	C(8)−C(9)−C(10)	118.5(2)
N(1)−C(2)−C(2′)	112.9(2)	C(9)−C(10)−N(11)	123.3(2)
N(1)−C(2)−C(3)	119.9(2)	C(10)−N(11)−C(12)	117.3(2)
C(2′)−C(2)−C(3)	127.2(2)	C(7)−C(12)−N(11)	124.0(2)
C(2)−C(3)−C(3′)	121.7(2)		

Table 6. Atomic Coordinates and Equivalent Isotropic Displacment Coefficients (Å) for Compound **III**

Atom	x	y	z	U_{eq}[a]
N(1)	0.3044(3)	0.6629	0.4939(2)	0.039(1)
C(2)	0.3599(4)	0.5468(4)	0.4521(3)	0.036(1)
C(2′)	0.5121(5)	0.4995(5)	0.5278(4)	0.056(1)
C(3)	0.2715(4)	0.4868(4)	0.3568(3)	0.033(1)
C(3′)	0.3216(4)	0.3607(4)	0.3121(3)	0.035(1)
C(3″)	0.2355(6)	0.1835(5)	0.1847(5)	0.070(1)
O(3′)	0.4566(3)	0.3108(4)	0.3339(2)	0.051(1)
O(3″)	0.1994(3)	0.3054(4)	0.2394(2)	0.047(1)
C(4)	0.1224(4)	0.5538(4)	0.2875(3)	0.031(1)
C(5)	0.0467(4)	0.6481(4)	0.3738(3)	0.035(1)
C(5′)	−0.1288(4)	0.6801(5)	0.3510(3)	0.042(1)
C(5″)	−0.3712(5)	0.6531(6)	0.2138(4)	0.068(1)
O(5′)	−0.2072(3)	0.7481(5)	0.4132(3)	0.071(1)
O(5″)	−0.1994(3)	0.6223(4)	0.2472(2)	0.052(1)
C(6)	0.1440(4)	0.7051(4)	0.4667(3)	0.038(1)
C(6′)	0.0978(5)	0.8141(5)	0.5487(4)	0.049(1)
C(7)	0.1743(4)	0.6221(5)	0.1722(3)	0.034(1)
C(8)	0.2471(4)	0.7401(5)	0.1673(3)	0.040(1)
N(9)	0.2880(4)	0.7667(4)	0.0493(3)	0.045(1)
C(10)	0.2403(4)	0.6646(5)	−0.0260(3)	0.041(1)
C(11)	0.2565(5)	0.6461(6)	−0.1530(3)	0.061(1)
C(12)	0.1954(6)	0.5337(6)	−0.2052(4)	0.066(1)
C(13)	0.1197(6)	0.4426(6)	−0.1365(4)	0.063(1)
C(14)	0.1051(5)	0.4598(5)	−0.0101(3)	0.047(1)
C(15)	0.1688(4)	0.5719(4)	0.0472(3)	0.037(1)
C(16)	0.3626(6)	0.8840(5)	0.0091(5)	0.067(1)

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

Table 7. Bond Lengths (Å) and Angles (deg) for Compound **III**

N(1)−C(2)	1.395(5)	C(3)−C(3′)−O(3′)	126.3(3)
N(1)−C(6)	1.394(4)	C(3)−C(3′)−O(3″)	111.3(3)
C(2)−C(2′)	1.512(5)	O(3′)−C(3′)−O(3″)	122.4(3)
C(2)−C(3)	1.361(5)	C(3′)−O(3″)−C(3″)	116.7(3)
C(3)−C(3′)	1.485(5)	C(5)−C(4)−C(7)	110.7(3)
C(3)−C(4)	1.543(5)	C(5)−C(4)−C(3)	110.3(3)
C(3′)−O(3′)	1.228(4)	C(7)−C(4)−C(3)	109.9(3)
C(3′)−O(3″)	1.347(4)	C(4)−C(5)−C(5′)	119.4(3)
C(3″)−O(3″)	1.456(5)	C(4)−C(5)−C(6)	119.5(3)
C(4)−C(5)	1.538(4)	C(5′)−C(5)−C(6)	121.1(3)
C(4)−C(7)	1.539(4)	C(5)−C(5′)−O(5′)	127.2(3)
C(5)−C(5′)	1.476(5)	C(5)−C(5′)−O(5″)	111.6(3)
C(5)−C(6)	1.363(5)	O(5′)−C(5′)−O(5″)	121.3(3)
C(5′)−O(5′)	1.211(4)	C(5′)−O(5″)−C(5″)	115.5(3)
C(5′)−O(5″)	1.360(5)	N(1)−C(6)−C(5)	119.4(3)
C(5″)−O(5″)	1.458(5)	N(1)−C(6)−C(6′)	113.6(3)
C(6)−C(6′)	1.523(5)	C(5)−C(6)−C(6′)	127.0(3)
C(7)−C(8)	1.381(5)	C(4)−C(7)−C(8)	127.3(3)
C(7)−C(15)	1.453(5)	C(4)−C(7)−C(15)	127.1(3)
C(8)−N(9)	1.385(5)	C(8)−C(7)−C(15)	105.5(3)
N(9)−C(10)	1.384(5)	C(7)−C(8)−N(9)	111.2(3)
N(9)−C(16)	1.463(5)	C(8)−N(9)−C(10)	108.0(3)
C(10)−C(11)	1.412(5)	C(8)−N(9)−C(16)	126.3(3)
C(10)−C(15)	1.421(5)	C(10)−N(9)−C(16)	125.6(3)
C(11)−C(12)	1.385(7)	N(9)−C(10)−C(11)	129.5(4)
C(12)−C(13)	1.397(7)	N(9)−C(10)−C(15)	108.2(3)
C(13)−C(14)	1.401(6)	C(11)−C(10)−C(15)	122.4(4)
C(14)−C(15)	1.410(5)	C(10)−C(11)−C(12)	116.9(4)
C(2)−N(1)−C(6)	122.8(3)	C(11)−C(12)−C(13)	122.0(4)
N(1)−C(2)−C(2′)	113.0(3)	C(12)−C(13)−C(14)	121.2(4)
N(1)−C(2)−C(3)	119.1(3)	C(13)−C(14)−C(15)	118.5(4)
C(2′)−C(2)−C(3)	127.8(3)	C(7)−C(15)−C(10)	107.2(3)
C(2)−C(3)−C(3′)	121.3(3)	C(7)−C(15)−C(14)	133.9(3)
C(2)−C(3)−C(4)	119.9(3)	C(10)−C(15)−C(14)	118.9(3)
C(3′)−C(3)−C(4)	118.7(3)		

carbonyl group, uninvolved in hydrogen bonding, is seen in *ap* conformation.

In structure **III**, the carbonyl oxygen atom O3′ is involved in a hydrogen bond [H1a—O3′ 2.114 Å, $1 - x, \frac{1}{2} + y, 1 - z$, with a N1—H1a—O3′ angle of 172.7°], and yet the carbonyl group is seen in *sp* orientation. This is rare in reported DHP structures. The observation of *sp*,*sp* conformation has been mostly attributable to the presence of an additional hydrogen bonding site in the molecule and thus the lack of involvement of either of the carbonyl oxygen atoms. For example, 4-(3-nitrophenyl)-2,6-dimethyl-1,4-dihydropyridine-3-methyl-5-(1-phenylmethyl)-3-piperidinyl ester) hydrochloride[19] and YM-09730 hydrochloride [(3*S*)-1-benzyl-3-pyrrolidinyl methyl(4*S*)-2,6-dimethyl-4-(*m*-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate hydrochloride][20] do not involve the carbonyl oxygen groups in hydrogen bonding because of the presence of a better receptor (Cl^-).

Structure **II** may be compared to a structural observation of 4-(3-pyridyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(ethoxycarbonyl)[21] in which both carbonyl groups are seen in *sp* conformation. Hydrogen atoms were not located in this structure and thus the influence of hydrogen bonding on carbonyl conformation cannot be assessed.

There are also two reported observations of 4-(2-pyridyl) DHP derivatives that differ in esterification groups. Both crystallize with the 2-pyridyl

Table 8. Atomic Coordinates and Equivalent Isotropic Displacment Coefficients (Å) for Compound **IV**

Atom	*x*	*y*	*z*	$U_{eq}{}^{a}$
N1	0.0965(3)	0.2684(2)	0.5845(2)	0.0433(8)
C2	0.1954(4)	0.2239(3)	0.6587(3)	0.0379(9)
C2′	0.3450(4)	0.2170(3)	0.6341(3)	0.0510(11)
C3	0.1511(4)	0.1948(3)	0.7423(3)	0.0362(9)
C3′	0.2447(4)	0.1604(3)	0.8320(3)	0.0391(9)
C3″	0.4751(5)	0.1056(5)	0.9125(3)	0.0730(15)
O3′	0.2040(3)	0.1478(2)	0.9096(2)	0.0523(8)
O3″	0.3827(3)	0.1433(2)	0.8253(2)	0.0575(9)
C4	−0.0084(4)	0.1967(3)	0.7472(3)	0.0374(9)
C5	−0.0821(4)	0.2813(3)	0.6821(3)	0.0397(9)
C5′	−0.2064(4)	0.3343(3)	0.7090(3)	0.0489(11)
C5″	−0.3216(5)	0.3787(5)	0.8407(4)	0.087(2)
O5′	−0.3029(4)	0.3766(3)	0.6540(3)	0.0829(11)
O5″	−0.2044(3)	0.3292(2)	0.8060(2)	0.0602(9)
C6	−0.0332(4)	0.3079(3)	0.5998(3)	0.0417(10)
C6′	−0.1029(5)	0.3801(4)	0.5219(3)	0.0599(12)
C7	−0.0805(4)	0.0906(3)	0.7233(3)	0.0408(10)
C8	−0.0768(5)	0.0516(3)	0.6206(3)	0.0531(12)
C9	−0.1480(5)	−0.0531(3)	0.6013(4)	0.0631(13)
C10	−0.3020(5)	−0.0525(4)	0.6206(3)	0.0654(13)
C11	−0.3035(5)	−0.0159(4)	0.7237(4)	0.0678(14)
C12	−0.2361(4)	0.0898(3)	0.7404(3)	0.0522(11)

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

Table 9. Bond Lengths (Å) and Angles (deg) for Compound **IV**

N1−C6	1.382(5)	C2−C3−C4	119.8(3)
N1−C2	1.387(5)	C3′−C3−C4	114.5(3)
C2−C3	1.361(5)	O3′−C3′−O3″	120.4(4)
C2−C2′	1.518(5)	O3′−C3′−C3	123.9(3)
C3−C3′	1.462(5)	O3″−C3′−C3	115.7(3)
C3−C4	1.522(5)	C3′−O3″−C3″	116.2(3)
C3′−O3′	1.223(4)	C5−C4−C3	109.5(3)
C3′−O3″	1.343(4)	C5−C4−C7	112.9(3)
C3″−O3″	1.446(5)	C3−C4−C7	112.0(3)
C4−C5	1.517(5)	C6−C5−C5′	120.4(4)
C4−C7	1.554(5)	C6−C5−C4	120.1(3)
C5−C6	1.357(5)	C5′−C5−C4	119.5(3)
C5−C5′	1.471(5)	O5′−C5′−O5″	121.8(4)
C5′−O5′	1.211(5)	O5′−C5′−C5	126.7(4)
C5′−O5″	1.348(5)	O5″−C5′−C5	111.5(4)
C5″−O5″	1.441(5)	C5′−O5″−C5″	116.3(4)
C6−C6′	1.496(6)	C5−C6−N1	118.9(4)
C7−C8	1.525(5)	C5−C6−C6′	127.0(4)
C7−C12	1.532(5)	N1−C6−C6′	114.1(3)
C8−C9	1.528(6)	C8−C7−C12	109.4(3)
C9−C10	1.527(6)	C8−C7−C4	114.5(3)
C10−C11	1.516(6)	C12−C7−C4	111.6(3)
C11−C12	1.522(6)	C7−C8−C9	112.2(3)
C6−N1−C2	122.5(3)	C8−C9−C10	111.6(4)
C3−C2−N1	118.8(3)	C11−C10−C9	110.1(4)
C3−C2−C2′	128.5(4)	C10−C11−C12	110.8(4)
N1−C2−C2′	112.7(3)	C11−C12−C7	111.7(3)
C2−C3−C3′	125.7(3)		

group turned back over the DHP ring and with the 2-pyridyl nitrogen atom serving as an acceptor for a hydrogen donated by N1 of a neighboring molecule.[22] Thus the pyridyl ring is capable of rotation.

The structure of ethyl-methyl-2,6-dimethyl-4-(2, 3-methylenedioxyphenyl)-1, 4-dihydro-3, 5-pyridinecarboxylate[23] differs from **I** in the attachment of the fused oxo ring at the ortho and meta position of the B ring and not at the meta and para position as in **I**. In this structure the carbonyl group substituted at C6 is turned *ap* and is involved in hydrogen bonding. The carbonyl group at C3 is seen in *sp* conformation as usual.

Conclusion

Comparison of the structural details of **I**, **II**, and **III** with those of **IV** shows that the substitution of bulky fused ring systems or ring systems containing hetero atoms at C4 tend to flatten the boat conformation of the A ring. Furthermore, these factors lead to greater mutual orthogonality of the A and B rings and also to greater coplanarity of the carbonyl groups with their adjacent double bonds. The general expectation of hydrogen bonding involving a carbonyl group oxygen in *ap* conformation appears to be confirmed, but it becomes apparent that bulky groups at the ortho position as in **III**, or ortho substituents such as chloride[15], with large numbers of unshared pairs of electons can lead to hydrogen bonding to carbonyl oxygen atoms in *sp* conformation. The implications for docking geometry are these: the lack of observation of hydrogen bonding activity of any type involving halide or O, or S atoms of the B ring suggests that this ring is largely uninvolved in receptor site recognition except perhaps as a space filling moiety. The consistent observation of N1—H as a hydrogen bonding donor and of carbonyl group oxygen atoms as hydrogen bonding acceptors, plus the observation that both carbonyl atoms and B rings are capable of rotation to *sp* and "folded back" conformations, respectively, suggests that the DHP molecule may interact with its receptor site from the N1 end of the A ring and not via the B ring being driven head first into the receptor site[3] as has been assumed in the past.

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