

Diethyl 4-(2,5-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, conformational change with solvent of crystallization

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The title compound, $C_{21}H_{27}NO_6$, has been crystallized from ethanol containing nitrobenzene and shows the phenyl ring, *B*, in an *ap* conformation. This structure may be compared with that of the molecule crystallized from ethanol alone, in which the *B* ring is seen in an *sp* conformation. The isolation of this rotamer has implications for the understanding of the docking of calcium beta-blocking dihydropyridine molecules with their receptor site.

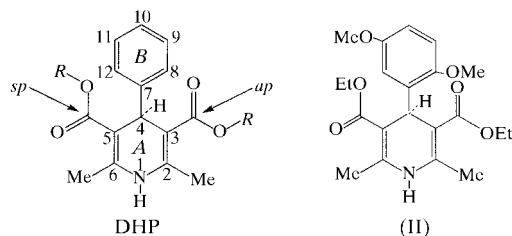
Comment

1,4-Dihydropyridine compounds (DHPs) are widely prescribed as calcium beta-blockers. Structure–activity relationship studies (Triggle *et al.*, 1989) of DHP molecules have indicated that certain conformational details correlate with high binding efficiency: ring *A* should be in a flattened boat form [however total planarity when the *A* ring is aromatic is detrimental to activity; Rowan & Holt (1995, 1996)]; ring *B* should be in a pseudo-axial position relative to the floor of the boat; rings *A* and *B* should display a nearly orthogonal relationship; electron-withdrawing substituents on the *B* ring improve activity in the order $o > m \gg p$; *ortho* substituents on the *B* ring should be in the prow or forward position and not projecting backwards over the *B* ring. The conformation of the ester carbonyl groups at C3 and C5 of ring *A* may be either *ap* or *sp* relative to the near double bond of the DHP ring.

Previous work in this laboratory suggests that carbonyl groups which are not involved in hydrogen bonding exist in an *sp* conformation (Caignan & Holt, 2000, 2001; Caignan *et al.*, 2000; Metcalf & Holt, 2000), whereas the molecule responds to a hydrogen-bonding opportunity by rotating the carbonyl group about the C3–C3' or C5–C5' bond to place the carbonyl group in an *ap* conformation.

The conformation of a crystallized molecule represents a structure of minimum energy in the environment of neighboring molecules. It does not necessarily represent the conformation of the molecule in its receptor site where the

neighbors are different molecules. However, the process of crystallization, of maximizing hydrogen bonding, dipole–dipole and van der Waals-type interactions within the solid, must mimic the behavior of a molecule approaching its docking site. Both are processes of molecular recognition.



In an effort to understand the range of conformational adjustments possible for DHP molecules as they recognize their receptor sites, we have embarked on a series of co-crystallization experiments, crystallizing DHP molecules from solutions including hydrogen-bond donors or acceptors.

We have previously reported the single crystal of diethyl 4-(2,5-dimethoxyphenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate, (I), crystallized from ethanol, for which the *ortho* or 2-methoxy substituent on the *A* ring is found in the prow position. When we recrystallized this material from ethanol containing nitrobenzene, we were surprised to isolate a rotamer (II) of the published molecule in which the *ortho* or 2-methoxy group is seen rotated back over the *A* ring.

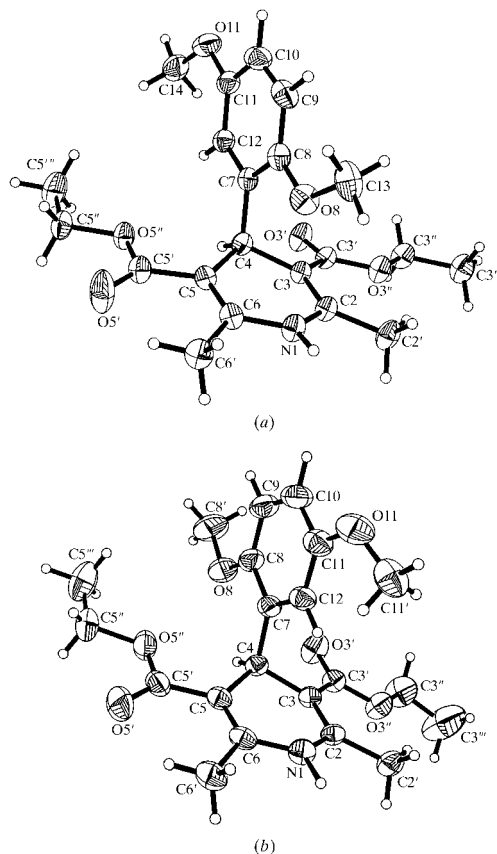


Figure 1
View of (a) the title compound and (b) compound (I), with ellipsoids shown at the 50% probability level. Only a single set of H-atom positions is shown for the disordered H-atom positions at C2', C3''' and C6'.

Compounds (I) and (II) crystallize with the *A* ring in the flattened boat form. The sum of the absolute values of the six successive torsion angles of the *A* ring is 91.0 (4)°; this sum is 78.8 (4)° for rotamer (II). The theoretical values of these totals are zero if the ring is totally flat and 240° if the six-membered ring is in the classic boat form. Thus, both rotamers display flattened *A* rings. In (I), near orthogonality between the *B* ring and the base of the flattened boat is indicated by the angle of 88.3 (3)° between the plane of atoms C7–C12 of the *B* ring and the plane of atoms C2, C3, C5 and C6 of the base of the boat conformation of the *A* ring. Rotamer (II) shows a 92.6 (4)° angle between these planes.

Both rotamers show near coplanarity of the carbonyl C=O bonds with the conjugated double bond of the DHP ring. The torsion angles C6–C5–C5′–O5′ and C2–C3–C3′–O3′ are –0.2 (3) and –176.2 (3)° for (I), and 3.5 (6) and 166.4 (3)° for the rotamer. These torsional angles indicate *sp* and *ap* conformations at C5 and C3, respectively, for both rotamers.

Thus, the two rotamers show nearly identical molecular conformation despite the differing orientations of the bulky methoxy group in the *ortho* position on the *B* ring.

In both rotamers, the carbonyl group at C3 is seen in an *ap* conformation, and is hydrogen bonded to the H atom of the amino group of an adjacent molecule. In the folded back rotamer, the hydrogen-bonding details are N1–H1A···O3′(1 + *x*, *y*, *z*) 2.21 Å, N–H1A···O3′ 161° and N1···O3′ 3.073 (3) Å.

There have been only two other observations of rotamers in the DHP family. 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 a folded-back orientation and an *ap,ap* conformation of the carbonyl groups (Rovnyak *et al.*, 1988).

An examination of two 4-(2-thiophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-bis(alkoxycarbonyl) compounds, which differ only in the identity of the alkoxy group (methyl or ethyl), has shown both an *ap,ap* carbonyl orientation and the *ortho*-sulfur group predominately in the prow position when the esterification group is methyl, but an *sp,ap* orientation of the carbonyl groups and a roughly 50/50 prow/folded-back over the *A* ring orientation of the bulky sulfur group when the esterification group is ethyl (Caignan *et al.*, 2000).

These results indicate that DHP molecules which bear *ortho* substituents or bulky hetero atoms in the *ortho* position of the *B* ring can freely change between prow-forward and folded-back rotamers. Rotation of the *B* ring does not influence carbonyl orientation nor the degree of orthogonality between the *A* and *B* rings. Thus, docking of DHP molecules in their receptor may involve either of the two rotamers.

Experimental

An ethanol solution (40 ml) of 2,5-dimethoxybenzaldehyde (6.4 g, 0.0386 mol), ethyl acetoacetate (10.036 g, 0.0772 mol) and ammonium hydroxide (2.027 g, 0.0579 mol) was refluxed for 6 h. Aceto-

nitrile was added to the resulting immiscible liquids, following which all solvent was removed under reduced pressure. The remaining solid was recrystallized from methanol giving large yellow cubes of rotamer (I). This crystalline material was dissolved in nitrobenzene and allowed to stand for 30 d. Large yellow rhombs were observed to form (rotamer II).

Crystal data

$C_{21}H_{27}NO_6$	$D_x = 1.298 \text{ Mg m}^{-3}$
$M_r = 389.44$	Mo $K\alpha$ radiation
Monoclinic, $P2_1/c$	Cell parameters from 21 reflections
$a = 7.640 (2) \text{ \AA}$	$\theta = 5.0\text{--}10.7^\circ$
$b = 8.606 (6) \text{ \AA}$	$\mu = 0.10 \text{ mm}^{-1}$
$c = 30.307 (17) \text{ \AA}$	$T = 293 (2) \text{ K}$
$\beta = 90.25 (3)^\circ$	Rhomb, yellow
$V = 1992.7 (19) \text{ \AA}^3$	$0.20 \times 0.15 \times 0.15 \text{ mm}$
$Z = 4$	

Data collection

Syntex P4 four-circle diffractometer	$h = -8 \rightarrow 1$
$\theta/2\theta$ scans	$k = -10 \rightarrow 1$
4802 measured reflections	$l = -35 \rightarrow 35$
3380 independent reflections	3 standard reflections
2030 reflections with $I > 2\sigma(I)$	every 97 reflections
$R_{\text{int}} = 0.079$	intensity decay: none
$\theta_{\text{max}} = 24.7^\circ$	

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0609P)^2 + 0.7570P]$
$R(F) = 0.057$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.113$	$(\Delta/\sigma)_{\text{max}} < 0.001$
$S = 1.03$	$\Delta\rho_{\text{max}} = 0.02 \text{ e \AA}^{-3}$
3380 reflections	$\Delta\rho_{\text{min}} = -0.02 \text{ e \AA}^{-3}$
253 parameters	
H-atom parameters constrained	

H-atom positions were calculated using idealized geometry and a C–H distance of 0.97 Å. H atoms H1A and the disordered H-atom positions at C2′, C3′′ and C6′ were located from a difference Fourier synthesis and then constrained to idealized geometry.

Data collection, cell refinement and data reduction: *XSCANS* (Siemens, 1991). program(s) used to solve structure: *SHELXS97* (Sheldrick, 1990); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *XP* (Siemens, 1990).

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: FR1330). Services for accessing these data are described at the back of the journal.

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