ISSN 0027-1314, Moscow University Chemistry Bulletin, 2008, Vol. 63, No. 6, pp. 318–320. © Allerton Press, Inc., 2008.
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Conformation of 1,4-Dihydropyridine Calcium Channel Blockers and H-Bonds in a Crystal

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Received January 24, 2008

Abstract—A statistical analysis of conformations for flexible 1,4-dihydropyridine calcium channel blockers, which are derivatives of nifedipine, was performed on the basis of the data deposited with the Cambridge Crystallographic Data Centre. Inequality of N and C deviations from the root-mean-square plane of the heterocycle was verified. A correlation was established between the orientation of carbonyls and their ability to form H-bonds in a crystal.

DOI: 10.3103/S0027131408060023

Calcium channel blockers are mostly used for myocardial cells [1]. 1,4-Dihydropyridine derivatives include all compounds whose molecules contain a fragment of this type, but the only drugs now produced are nifedipine derivatives (Fig. 1a), for which nifedipine is the leader compound in accordance with the term used in [2].

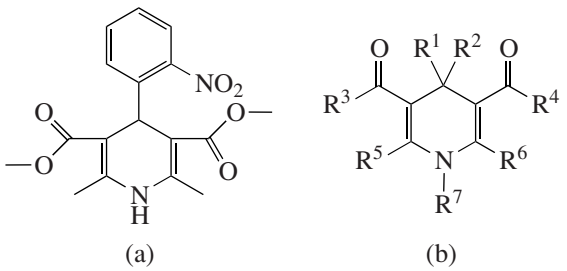
Fossheim et al., in their X-ray diffraction study [3] showed that the 1,4-dihydropyridine ring has a boat conformation. They also found a linear correlation between the deviations of the nitrogen atom and the saturated carbon atom, expressed through the mean torsion angles of rotation around the bond lines of these atoms; for the nitrogen atom, the deviation was smaller than for the carbon atom. Later, the equilibrium ring conformation was determined using molecular mechanics [4] and ab initio [5] calculations for a number of 1,4-dihydropyridine blockers, this conformation being nonplanar in all cases. Shishkin [6] inferred that the conformational behavior of the dihydropyridine ring is apparently dictated by the interplay between the 1,2-allyl stress and bond-angle stress at the saturated carbon atom, as well as the conjugation of the lone pair of the nitrogen atom with the π-system of the ring.

Fossheim [7] and Ramusino and Vari [8] thought that side ester groups are H-bonded to the receptor, and the orientation of these groups influences bioactivity. Therefore, conformation mapping for 1,4-dihydropyridine blockers can be of great importance for design of new drugs.

EXPERIMENTAL

The Cambridge Structure Database (CSD, version 5.28) was searched for structures containing a 1,4-dihydropyridine fragment. Of the 684 structures found, 681 correspond to compounds with a tricoordinated nitrogen atom. Of them, 409 structures contain an sp^3-hybridized carbon, while most of the other structures contain substituted 4-pyridone, which is not a calcium channel blocker, is an abundant aglycone in *N*-glycosides, and is used as a chelant in therapy. Of the sp^3-carbon structures, 291 contain two carbonyls in the positions 3 and 5; only 54 structures are not carbonylated in these positions. Of the dicarbonylated structures, 39 have a five-membered homo- or heterocycle in the position 4 and 217 have a six-membered cycle in this position; in 213 structures, the cycle is aromatic and in 202 structures this is substituted phenyl. Thus, nifedipine derivatives remain the best studied 1,4-dihydropyridines.

The reference structural fragment used in further search is shown in Fig. 1b. For characterizing the conformation of the dihydropyridine cycle, we chose dihedral angles (θ_N and θ_C for nitrogen and carbon atoms, respectively), which correspond to the deviation of ends (planes through three atoms) from the mean bottom plane (four atoms); for the boat conformation, this seems most illustrative. The orientation of carbonyls was set by torsion angles φ_1 and φ_2 in cases of statistically indistinguishable groups and χ and φ in cases



(a) (b)

Fig. 1. (a) Structural formula of nifedipine and (b) the reference fragment used in searching over the CSD (R^1, R^2, …, R^7 is any fragment).

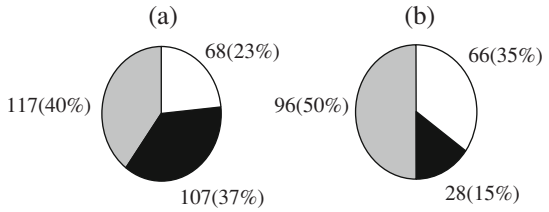


Fig. 2. Circular distribution diagram for *syn* and *anti* species (a) among all structures with the reference fragment and (b) among the structures with an acyclic carbonyl carbon atom. The sectors corresponding to the *anti–anti* species are dark gray, those corresponding to *syn–anti* species are light gray, and those corresponding to *syn–syn* species are unshaded.

where only the first carbonyl was H-bonded. N···O and H···O distances in intermolecular N–H···O contacts were denoted as *D* and *d*, respectively. The resulting numerical values of parameters were processed using the Vista program package [10].

RESULTS AND DISCUSSION

In the absence of steric influences, the proportion of the *anti–anti*, *syn–syn*, and *syn–anti* carbonyl orientations should roughly be 1 : 1 : 2. For the initial reference fragment (Fig. 2a), this proportion is heavily spoiled in favor of the *anti–anti* orientation; this is explained by the multiplicity of structures in which the carbonyl carbon atom enters the cycle. Therefore, to exclude these structures, cyclicity was forbidden in further searching. Figure 2b shows that the *syn–syn* form dominates over the *anti–anti* form, apparently because of the influence of the bulky aromatic substituent.

In about 45% of the structures, either with or without a normalized N–H bond length, there are short H···O contacts, according to Bondi [11] (Figs. 3a, 3b). However, it is common knowledge that the fraction of H-bonded channel blocker structures is actually much greater, and a search over short N···O distances verified this. In the case at hand (Fig. 3c), the bound of our accepted short distances does not completely correspond to the sum of the van der Waals radii; however, structures are known in which the N···O distance for a topologically evident H-bond exceeds this sum [12].

Figure 4b shows the torsion angle distribution for the above short distances (Fig. 3c). The a priori probability of finding carbonyl in the *syn* position from the general sample (Fig. 4a) is about 0.61, whereas the probability derived from the partial sample for an H-bonded carbonyl (Fig. 4b) is about 0.33. This implies a correlation between the existence of an H-bond and carbonyl *anti*-orientation: an H-bond prefers orientation. The correlation of the fractions of *anti–anti* species in the general and partial samples (11 and 10%, respectively) proves the lack of correlation between the existence of an H-bond and the steric influence of the bulky aromatic substituent; in other words, this substituent by no means hinders H-bonding.

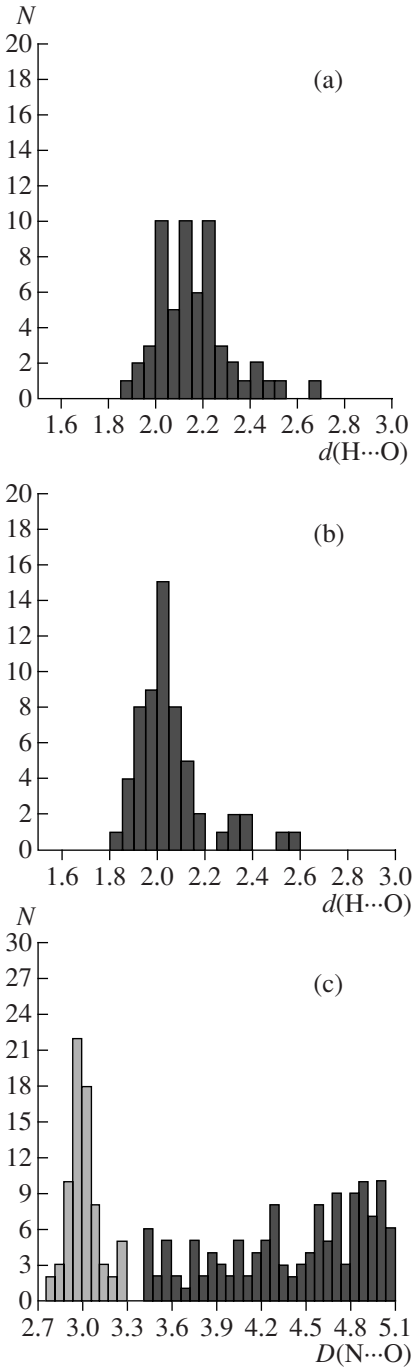


Fig. 3. (a, b) d (H···O) < $R_H + R_O$ bar diagrams among the structures with (a) an unfixed N–H distance and (b) a fixed N–H distance (1.009 Å). (c) D(N···O) < $R_N + R_O + 2.0$ Å bar diagram for structures with R^7 = H. The region corresponding to the accepted bound of the H-bond lengths is light gray.

The θ_N–θ_C dependence for all 409 structures containing a dihydropyridine moiety (the linear regression factor R = 0.9; the slope is 0.52) verifies the earlier observed correlation [3] and the inequality of the devi-

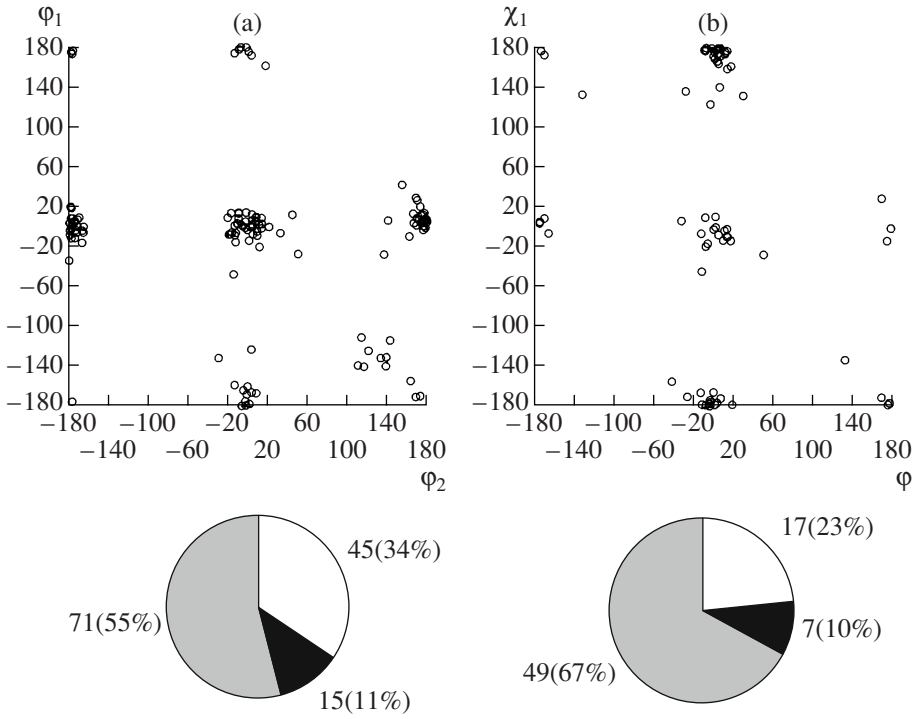


Fig. 4. Two-dimensional torsion angle distribution diagram and circular distribution diagram for *syn* and *anti* species (a) in the general sample of structures with R^7 = H (without errors and uncertainties, $R < 0.1$) and (b) in a sample with an H-bond. χ is the torsion angle for the H-bonded group. The sectors of the circular diagrams are colored to correspond to coloring in Fig. 2.

ations of C and N atoms from the plane of the cycle. This inequality is explained by the conjugation of the nitrogen lone pair with the π-system of double bonds in the cycle.

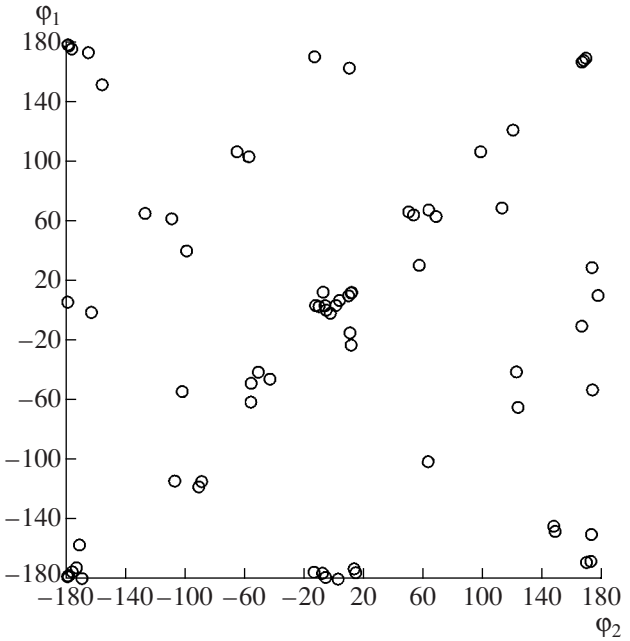


Fig. 5. Two-dimensional torsion angle distribution diagram for 3,5-dicarbonylated pyridines with an acyclic carbonyl carbon atom.

Comparing the torsion angle diagrams for dicarbonylated dihydropyridine and pyridine (Fig. 5), we infer a possible conjugation of C=O and C=C double bonds in carbonylated dihydropyridine; in Fig. 4a, there are regions of points with φ_1 near –120°, corresponding to amides with spoiled conjugation.

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