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Conformation of 1,4-dihydropyridine – planar or boat-like?

H.-J. Hofmann* and R. Cimiraglia

Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56100 Pisa, Italy

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The geometry of the 1,4-dihydropyridine molecule was completely optimized employing three different ab initio basis sets (6–31 G*, 4–31G, STO–3G). The most reliable 6–31G* basis set provides a very flat boat conformation which may easily undergo defolding to a planar ring arrangement. This result is discussed with respect to enzymatic redox cofactors and the pharmacological activity of dihydropyridine calcium antagonists.

NAD cofactor; NADH cofactor; Dihydropyridine; Theoretical conformational analysis

1. INTRODUCTION

A wide variety of derivatives of 1,4-dihydropyridine **1** is accessible by the famous Hantzsch synthesis [1]. In the last few years, some of them are used as so-called calcium channel antagonists and agonists reducing or enhancing the transmembrane calcium ion influx into cells [2]. X-ray studies indicate a flattened boat conformation for the 1,4-dihydropyridine ring in these derivatives. A correlation between the degree of flatness and the antagonistic activity was postulated, which demonstrates the influence of conformational factors [3,4]. The 1,4-dihydropyridine ring not only is an important constituent of the afore-mentioned drugs, but it also represents a decisive structure element of enzymatic oxidation-reduction cofactors of the nicotinamide-adenine-dinucleotide type (NAD/NADH and NADP/NADPH). Structure differences between the reduced and oxidized forms could be responsible for the regulation of the enzyme activity [5–7]. Whereas a planar arrangement should be distinctly favoured in the aromatic pyridinium part of the oxidized cofactor, the reduced 1,4-dihydropyridine part could be non-planar as in the calcium channel ligands or, even if planar, at least much more flexible. There are some speculations about the existence of a boat conformation in these cofactors [8–11]. However, X-ray data for some NADH model compounds show no essential deviations from planarity in the 1,4-dihydropyridine ring system [12–14] which was only recently reconfirmed by an excellent structure determination of two simple N-substituted dihydronicotinamides [15] in contrast to the situation in the calcium channel ligands. NMR data [16] of simple dihydropyridines indicate equivalence of the two C_4 protons, giving support either to a planar ring skeleton or, on the other hand, to rapid interconversion between two boat forms. Considering the numerous experimental and theoretical studies on 1,4-dihydropyridine derivatives at present available [17–19], the conformation of this ring remains an open problem. The 1,4-dihydropyridine molecule itself is rather unstable [21] and has not been subjected to experimental structure examinations until now.

It is the aim of this paper to obtain reliable structure information for this important compound by means of ab initio quantum chemical methods. These data may serve as reference points for the discussion of structural influences both in pharmacologically active dihydropyridine compounds

Correspondence address: R. Cimiraglia, Dipartimento di Chimica e Chimica Industriale, Università di Pisa, Via Risorgimento 35, I-56100 Pisa, Italy

* On leave from Sektion Biowissenschaften, Karl-Marx-Universität Leipzig, Talstraße 33, DDR-7010 Leipzig, GDR

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and in biochemical processes involving this structure.

2. DETAILS OF THE CALCULATIONS

Ab initio geometry optimization of various conformations of 1,4-dihydropyridine was performed at SCF level, employing three different basis sets (STO–3G, 4–31G, 6–31G* [22]) for comparison. The MONSTERGAUSS program package [23] was used in all cases. Optimization was stopped at values of the energy gradient less than 0.5×10^{-3} a.u.

3. RESULTS AND DISCUSSION

The optimized geometries of the most stable conformations of 1,4-dihydropyridine **1** (fig.1) obtained with various basis sets are collected in the tables 1–3. Whereas the STO–3G calculation provides a distinct boat conformation as the preferred one with the nitrogen and the methylene carbon atoms above the plane of the four double bond carbon atoms ($\alpha = 14.0°$, $\beta = 9.6°$), the 4–31G basis set result tends to a practically planar structure ($\alpha = 0.8°$, $\beta = 0.9°$). It is difficult to decide on the dihydropyridine structure based on these data considering the rather small STO–3G energy difference of $\Delta E = 9.3$ kJ/mol between boat and planar conformation indicating high conformational flexibility. Moreover, a stabilization of the planar conformation could be reached by maintaining a pyramid arrangement at the ring nitrogen. An STO–3G calculation of this conformation indicates indeed additional stabilization by $\Delta E = 3.4$ kJ/mol. Finally, the results could be influenced by the general tendency of minimal basis sets to overestimate and of split-valence basis sets to underestimate the degree of pyramidalization at nitrogen atoms [22], which is clearly brought out by the STO–3G and 4–31G results. The more extended 6–31G* basis set, including polarization functions, may be of sufficient quality to judge this problem. Based on this basis set, the boat conformation exhibited by STO–3G is confirmed. However, the angles $\alpha = 8.38°$ and $\beta = 5.44°$ are just in between the values estimated with STO–3G and 4–31G. The 6–31G* energy difference between boat and planar conformation amounts only to 2.7 kJ/mol which is reduced by another $\Delta E = 0.2$ kJ/mol assuming a pyramidal structure at the nitrogen atom in the planar ring arrangement. Thus, the boat form represents indeed an extremely flexible system, which may easily undergo defolding to the planar conformation along the line connecting the atoms N_1 and C_4. This is also

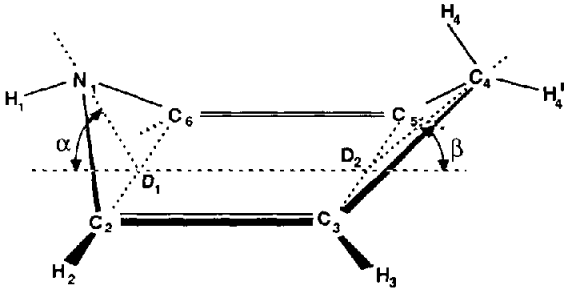

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Table 1

Bond lengths of the optimum conformations of 1,4-dihydropyridine **1** using various basis sets

Bond lengths[a]	6–31G*[b]	4–31G[c]	STO–3G[d]
N_1C_2	1.395	1.388	1.439
C_2C_3	1.321	1.322	1.312
C_3C_4	1.511	1.512	1.523
N_1H_1	0.995	0.987	1.028
C_2H_2	1.075	1.071	1.085
C_3H_3	1.075	1.072	1.081
C_4H_4	1.091	1.089	1.094
C_4H_4'	1.090	1.089	1.092

[a] See fig.1, all values in Å
[b] $E_{tot} = -247.823188$ a.u.
[c] $E_{tot} = -247.465395$ a.u.
[d] $E_{tot} = -244.784783$ a.u.

Table 2

Bond angles of the optimum conformations of 1,4-dihydropyridine **1** using various basis sets

Bond angle[a]	6–31G*	4–31G	STO–3G
$\angle C_2N_1C_6$	116.95	119.03	114.74
$\angle N_1C_2C_3$	123.28	122.53	123.22
$\angle C_2C_3C_4$	122.63	122.67	122.58
$\angle C_3C_4C_5$	110.11	110.56	110.36
$\angle H_1N_1D_1$	146.81	178.49	134.61
$\angle (N_1N_1C_2)$	(115.95)	(120.47)	(112.25)
$\angle H_2C_2C_3$	121.96	122.11	122.68
$\angle H_3C_3C_2$	118.85	119.26	120.00
$\angle H_4C_4D_2$	127.59	127.37	127.17
$\angle (H_4C_4C_3)$	(110.45)	(110.22)	(110.18)
$\angle H_4'C_4D_2$	127.11	127.31	126.81
$\angle (H_4'C_4C_3)$	(110.22)	(110.20)	(110.01)

[a] See fig.1, bond angles in degrees

Table 3

Torsion and folding angles in the optimum conformations of 1,4-dihydropyridine 1 using various basis sets

Torsion angle[a]	6–31G*	4–31G	STO–3G
$\angle N_1C_2C_3C_4$	−1.53	0.09	−2.53
$\angle C_2C_3C_4C_5$	−6.46	−1.01	−11.37
$\angle C_3C_4C_5C_6$	6.46	1.01	11.37
$\angle N_1C_2C_3H_3$	177.44	180.00	177.20
$\angle C_4C_3C_2H_2$	−179.46	−179.90	−179.70
$\angle H_2C_2C_3H_3$	−0.49	0.03	0.03
$\angle C_6N_1C_2C_3$	10.03	0.96	16.86
α	8.38	0.81	14.05
β	5.44	0.85	9.57

[a] See fig.1, angles in degrees

a possibility for ring conversion into the alternative boat conformation which is of interest in case of 4-substituted dihydropyridine derivatives. Based on the corresponding calculations, the possibility of an alternative path via envelope and chair conformations can be excluded because of the strong distortion of the double bonds in the chair arrangement. The general preference of a highly flexible boat conformation of the 1,4-dihydropyridine ring is also maintained in 3,5-dicarboxy- and 4-phenyl-substituted derivatives, respectively, which are more similar to the biologically active compounds (Hofmann and Cimiraglia, unpublished).

4. CONCLUSIONS

The determination of a highly flexible boat conformation for 1,4-dihydropyridine contributes to an understanding of the various X-ray data for numerous derivatives, which indicate both boat and planar arrangements of the ring system. Obviously, substituent effects and, above all, crystal forces influence the structure in the solid state.

Some conclusions may be drawn from these results both for the drugs mentioned above and the enzyme cofactors. At first, correlations between ring puckering and pharmacological activity of calcium channel influencing drugs should not be overestimated considering the very small energy difference between the possible conformations. Secondly, the considerable structure differences between 1,4-dihydropyridine and its aromatic oxidation product with respect to the ring arrangement and its flexibility may influence the binding behaviour of the two cofactor forms, the redox potential and, in turn, the selectivity toward different substrates and the transmission of effects in the enzyme molecule by induction of conformational changes. Such possibilities were generally suggested by various authors [5–7] and especially discussed for flavins [5].

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