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A QUANTUM CHEMICAL STUDY OF THE CONFORMATION OF ALINIDINE A NEW ANTI-ARRHYTHMIC AGENT

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Abstract

The conformation of alinidine a new and specific bradycardic agent was studied using MNDO method. It has been found that the rotation of both phenyl and imidazoline ring of this compound is restricted. Of two possible isomers of imidazoline ring, the one with NH in the *cis* position to allyl side chain is slightly more stable. On the other hand, the allyl group can rotate freely and at least six more conformers besides that of global minima has been identified. These calculations show that alinidine has a rather flexible structure and suggest that synthesis of more rigid analogs of this compound may be interesting from the structure-activity point of view.

Introduction

Alinidine (Fig.1) is a new anti-arrhythmic agent which is currently under clinical trial [1]. This compound is a derivative of clonidine and reduces the heart rate by a specific action on the sinus node [2,3]. The closely related compound, clonidine, does not possess such a specific bradycardic action [2]. It has been suggested that the bradycardic action of alinidine results from the inhibition of anionic membrane current in the sinus nodal cells [4].

The study of the conformation of clonidine and its analogs has provided useful information concerning the structure-activity relationship among these groups of compounds [5,6]. The present study was carried out to elucidate the conformation of alinidine by using quantum chemical methods to provide some information about its structure and compare that with that of clonidine.

Methods

Geometry of alinidine was optimized using the MOPAC program [7]. The initial geometry, which was constructed from standard bond lengths [and angles], was used as input to the semi-empirical all-valence electron molecular orbital method, NMDO [8]. Totally unconstrained geometry optimization was carried out. The resulting structure and its stereo-view were drawn by the aid of the MOLPLOT program [9].

In addition to finding the global minimum energy conformer resulting from the MNDO geometry optimization, a more detailed conformational energy study was carried out. The phenyl ring around C3N1 bond and the imidazoline ring around C2N1 bond (Fig.1) were rotated in 15 degree steps and the total energy of the molecule was calculated. The range of conformations which encompass 70%, 95%, [and 99%] of the molecules at 37°C were caluculated using a statistical mechanical procedure on the computed potential surface [10]. Briefly, this method proceeds as follows; first a probability map is calculated from the conformational energy map by taking an exponential Boltzmann factor for each point and drawing an exponential map. Then, from the exponential map it is possible to calculate a

Keywords; Alinidine, anti-arrhythmic agent, conformation, MNDO, Quantum chemistry

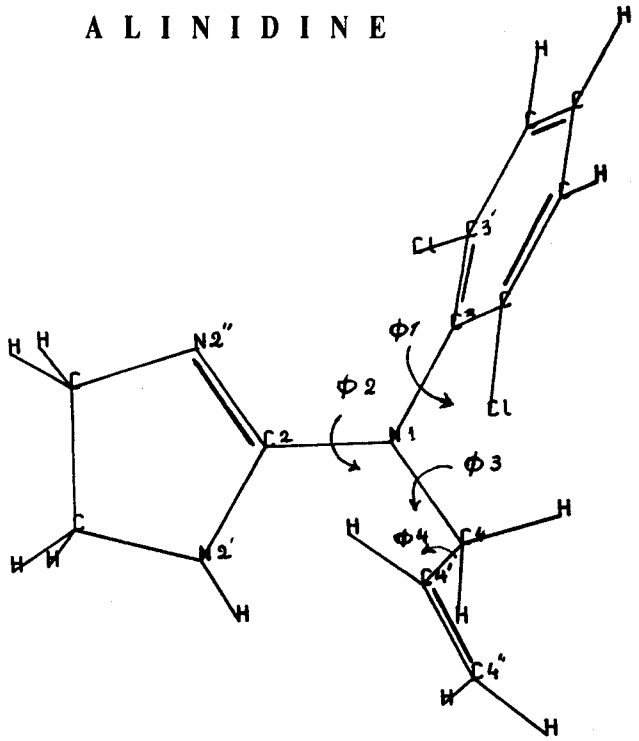

Figure. 1; The MIDO optimized structure of alinidine. φ1- φ4 indicates the possible axes of rotation in the alinidine molecule.

percentage map which can be used to indicate the regions of conformation within which any given percentage of molecules would be expected to be found at the physiological temperature of 37°C. The percentage map highlights the regions of like and improbable conformation for a given molecule at this temperature.

Alternatively, the allyl group around C4N1 and C4' C4 bonds (Fig. 1) was rotated and the total energy of the molecule was calculated as before. The range of conformations were calculated and presented as a percentage map (Fig.5). The position of local minima were determined from calculated energy surface and the structure of each conformer was drawn as described above.

Results and Discussion

The geometry of alinidine base was optimized by MNDO and results are shown in Figures 1 and 2 and Table I. Similar to clonidine, the phenyl ring adopts a rather perpendicular orientation with respect to the imidazoline ring. The bond length between N1 and C2 is less than that of N1 and C4 which indicates to some degree of conjugation between a lone pair electron of N1

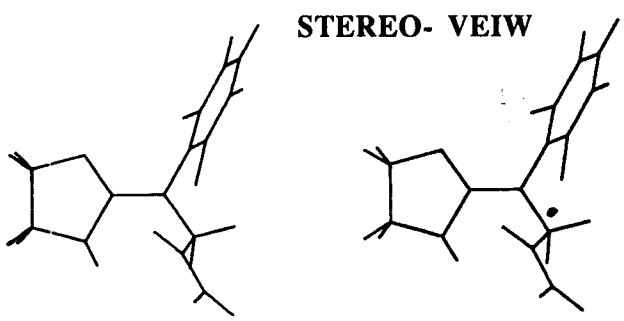

Figure. 2; Stereo-view of MNDO optimized alinidine molecule. The picture is drawn by the aid of MOLPLOT program [9].

Table I. Some important structural parameters of alinidine base in the gas phase state, calculated from MNDO optimized geometry. For the numbering see. **Figure 1.**

Bond length	A°
N1C2	1.400
N1C3	1.431
N1C4	1.478
C2N2'	1.437
C2N2"	1.314
C4C4'	1.510
C4'C4"	1.342

Bond angle	degrees
C2N1C3	117.5
C2N1C4	123.7
N1C2N2"	114.9
N2"C2N2'	123.6
C4'C4N1	115.2
C4"C4'C4	124.1

Dihedral angle	degrees
C3'C3N1C2	90.6
C4'C4N1C2	-60.7
C4"C4'C4N1	178.1

and N2"C2 double bond (bond order is slightly more than one).

Similar to what has been reported for clonidine [6], the rotation of phenyl group around C3N1 bond is rather restricted and the maximum free rotation at 37°C is +20 degrees (Fig. 3). There is a high energy barrier for the flopping of this ring, which is also comparable to clonidine [6].

The rotation of imidazoline ring around the C2N1 bond is also restricted (Fig. 4). Two possible isomer can

be attributed to the two minima on the potential surface (Fig. 4), one with NH group in *cis* position to allyl group (ϕ 2 =-17) and the other in the *trans* position (ϕ 2 = 165). Of these two, the *cis* isomer is slightly more stable and has a lower energy. It is interesting to find out how the restriction of this tautomerism will affect the biological activity of alinidine.

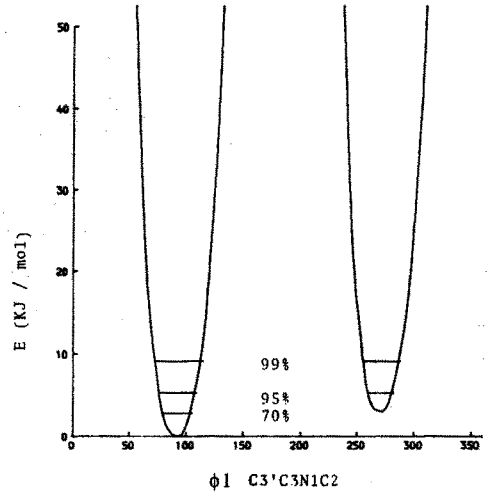

Figure. 3; The change in the energy of the alinidine molecule with respect to the rotation of phenyl ring. The bars indicate the conformational range where 70%, 95%, and 99% of the population of molecules are present at 37°C. ϕ1 is the dihedral angle of C3'C3N1C2 (for the numbering see Fig. 1).

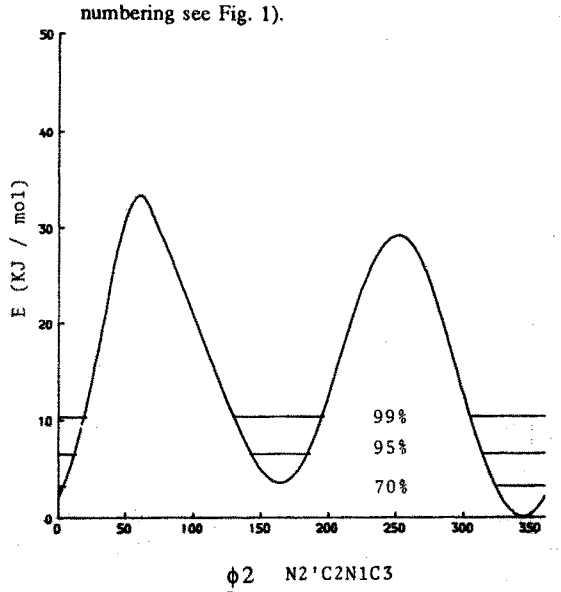

Figure. 4; The change in the energy of the alinidine molecule with respect to the rotation of imidazoline ring. The bars indicate the conformational range where 70%, 95%, and 99% of the population of molecules are present at 37°C. ϕ2 is the dihedral angle of N2'C2N1C3 (for the numbering see Fig. 1).

It was found that the allyl group is rather flexible and can adopt many conformations all of which can convert to each other very easily (Fig. 5). On the calculated energy surface, at least six more local minima corresponding to six conformers besides that of global minima were identified. The relative energy of these conformers are shown in Table II.

In conclusion, the phenyl and imidazoline groups of alinidine show many characteristics similar to that of clonidine. Therefore, these groups are not responsible for the difference in the activity of these two compounds. However, the additional allyl group of alinidine is rather flexible with respect to the rest of the molecule and can adopt many conformations. The modification of this group will affect the distribution of these conformers and will provide some evidence to decide which of the above mentioned conformers is the active one.

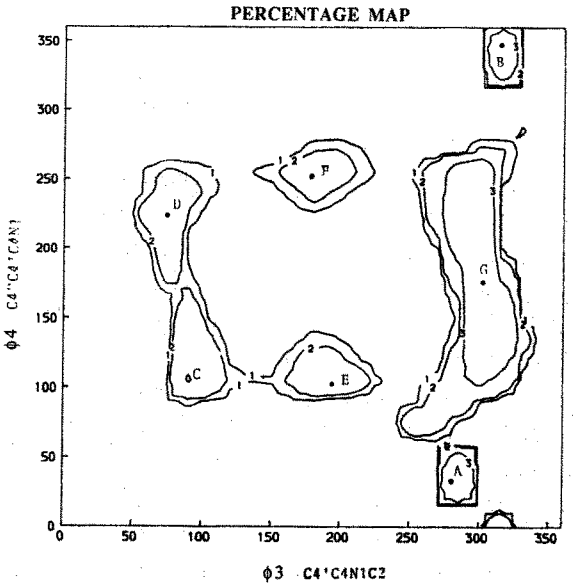

Figure . 5; The percentage map of possible conformations of alinidine molecule with respect to the changes in the position of allyl group calculated from the potential energy surface. ϕ3 is the dihedral angle of C4'C4N1C2 and ϕ4 is the dihedral angle of C4''C4'C4N1 (for the numbering see Fig. 1). Contours 1, 2, and 3 refer to the conformational ranges where respectively 99%, 95% and 70% of the population of molecules are present at 37°C. G indicates the position of the global minimum and A-F refer to other local minima. For the value of dihedral angles see Table II.

Table II. Relative energies of various alinidine conformers with respect to global minimum

Conformer	Dihedral of C4'C4N1C2	Dihedral of C4"C4'C4N1	E Kj/mol
Global minimum	300	178	0.0
A	285	30	1.04
B	315	345	1.67
C	90	105	5.31
D	75	225	6.12
E	195	105	6.43
F	180	255	6.58

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