

## PREFERRED CONFORMATION OF *m*-NITROPHENYLADAMANTYL PIPERIDINE ON THE BASIS OF POTENTIAL ENERGY CALCULATIONS

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In this paper, some of the conformational features of neuro-active molecule are presented. There have been quite a few studies carried out to calculate conformational properties of pharmacologically active molecules with respect to the mapping of receptors. During the course of present study the potential energy of non-bonded interaction for PAP (*m*-nitrophenyladamantyl piperidine) has been calculated. These calculations indicate that the drug has limited allowed conformations. It is speculated that the most feasible position for the drug to interact with the receptor would be at the minimum potential energy level.

### INTRODUCTION

Addiction of various psychoactive and opiates poses a global problem in general for the social infrastructure and in particular for the drug addicts[1].

Phencyclidine (PCP, Sernyl, angel, dust, peace pill) was synthesized as an analgesic, anesthetic for patients but later on withdrawn due to its addictive side effect such as delirium, hallucination, depression, coma and seizure[2,3].

In order to ascertain the stereo-selective nature of receptor, various models of drugs are selected to observe the effect of functional groups, their position in space and geometrical requirements for receptors[4]. These models could be of profound importance in comparing the energies and do establish the nature of agonists and antagonist of opiates and related compounds[5]. PAP is an analogue of PCP (*m*-nitrophenyl cyclohexyl piperidine) which exhibited the same pharmacological activity as that of PCP[6].

Potential energy calculations are carried out to ascertain possible conformation of phenyl, piperidine and adamantane group in PAP. Several programs were written in Basic language and Sord Computer was used throughout this work.

### THEORETICAL CALCULATIONS

The perspective view of PAP is shown in Fig. 1. In fixing the positions of atoms in the PAP residue, the coordinates used are the values reported by Thomas *et al*[10]

from X-ray diffraction studies. The conformation corresponding to  $(w_1, w_2) = (0, 0)$  is the one in which the atoms  $C^{11}-C^{10}$  of phenyl group are  $C^{10}-N^1$  of piperidine group are in the same plane. The rotations are considered to be positive when further end of the vector representing the bonds  $C^{10}-C^{11}$  and  $C^{10}-C^1$  rotates clockwise, proceeding along the chain. The adamantane ring is fixed due to its rigid structure.

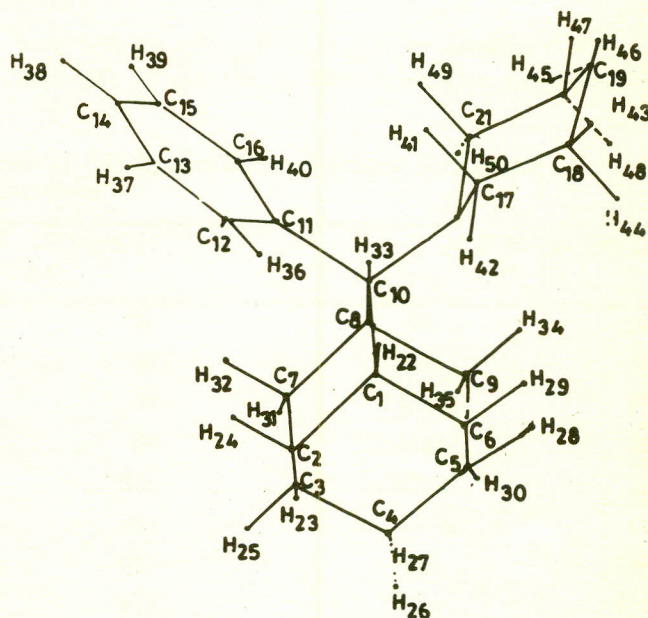


Fig. 1. Solid state structure of PAP.

In order to determine, allowed conformation in the PAP it is necessary to examine the contact distances between atoms in the residues namely Phenyl, piperidine and

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adamantane using criteria for minimum Van der Waals contact distances<sup>[11,12]</sup>. This can be done by calculating positions of the atoms in phenyl and piperidine for various values of  $w_1$  and  $w_2$ . The calculations can be extended with respect to adamantane (fixed residue of the PAP) for both phenyl and piperidine. The two fragments (phenyl and piperidine) in which C10 is taken as origin of coordinates of a system of axis OXYZ. The plane N<sup>1</sup>-C10-C11 which does not change for any rotation along  $w_1, w_2$ . If  $x, y, z$  and  $x_1, y_1, z_1$  are the coordinates of an atom before and after rotation, then the relation can be given as used by Ramakrishan *et al*<sup>[11]</sup>.

$$\begin{aligned}x_1 &= (M11)x + (M12)y + (M13)z \\y_1 &= (M21)x + (M22)y + (M23)z \\z_1 &= (M31)x + (M32)y + (M33)z\end{aligned}$$

where :-

$$M11 = a^2 + b^2 - c^2 - d^2, M12 = 2(bc - ad), M13 = 2(bd + ac)$$

$$M21 = 2(bc + ad), M22 = a^2 - b^2 + c^2 - d^2,$$

$$M23 = 2(cd - ab)$$

$$M31 = 2(bd - ac), M32 = 2(cd + ab),$$

$$M33 = (a^2 - b^2 - c^2 + d^2)$$

$$a = \cos(w/2), b = L \sin(w/2), c = M \sin(w/2),$$

$$d = N \sin(w/2)$$

L, M, N are the direction cosines of axis the of rotation.

The coordinates of H<sub>40</sub>, H<sub>41</sub>, H<sub>42</sub>, H<sub>43</sub> of PAP were evaluated after rotation through  $w_1, w_2$  (Fig. 1). The other

pairs are given in Figure-5. The interatomic distances were calculated for each pair. The coordinates were evaluated at an interval of 20° of  $w_1$  and  $w_2$ . Kitaigorodsky<sup>[9]</sup> function was used to calculate potential energy V after parameter variation ( $w_1, w_2$ ). The equation can be given by:-

$$V = 3.5 \left[ (-0.04/z^6) - 8600 \exp(-13z) \right]$$

$$\text{where } z = r_{ij}/r_0$$

$r_{ij}$  is the distance between interacting atoms  $i$  and  $j$ , and  $r_0$  is the equilibrium distance between the interaction atoms. The values of  $r_0$  are given elsewhere<sup>[11]</sup>. This equation is unique in that the value of V is different according to the value of  $r_0$  chosen for an interaction. Furthermore, there is only one parameter ( $r_0$ ) that requires to be specific for the calculation of total energy of non-bonded interactions.

## RESULTS

The non-bonded interaction energy for phenyl and piperidine is given in Fig. 4. The Fig. 4 indicates energy contours obtained for phenyl and piperidine residues in PAP. The Fig. 5 indicates interaction energy for various pairs of atoms of piperidine and adamantane, phenyl and adamantane.

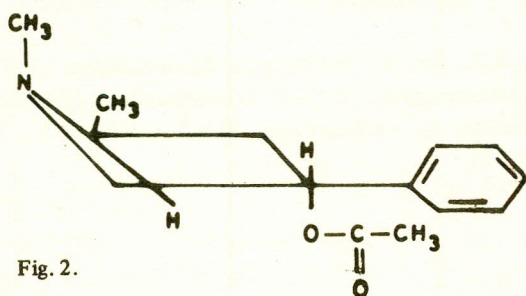
It is interesting to note that interaction energy for various pairs of atoms of piperidine and adamantane is high as compared to phenyl and adamantane, (Fig. 5). The potential energies for pairs of atoms are also given in Table-1

Table 1. Non bonded potential energies [9] for various pairs of atoms. Some of the values for the pairs of atoms are given below

a) Pair H34.H50 $w_1 = 0$		b) Pair H50..H29 $w_1 = 0$		c) Pair H42..H29 $w_1 = 0$	
w2	V <sup>9</sup>	w2	V <sup>9</sup>	W2	V <sup>9</sup>
0	-0.7	70	-0.6	240	-0.4
20	0.3	80	0.3	250	0.4
40	18.9	90	2.9	260	4.1
60	212.5	100	17.5	270	24.6
80	124.1	110	76.7	280	104.7
100	6.0	120	192.0	290	249.0
120	-0.9	130	217.3	300	257.3
		140	106.9	310	114.4
		150	28.2	320	27.8
		160	5.1	330	4.8
		170	0.6	340	0.5
		180	-0.3	350	-0.4

## DISCUSSION

It is evident from the calculations that there is limited allowed region for PAP. The energy diagrams (Fig. 4 & 5) for pair of atoms (Fig. 5) indicates that rotation of phenyl and piperidine residues in PAP is highly restricted. The possible allowed conformation is in the region  $w_1 = 340^\circ$  to  $360^\circ$  and  $0$  to  $10^\circ$  and ( $w_2 = 340^\circ$  to  $360^\circ$  and  $0-10^\circ$ ) (Fig. 5). It may be presumed that PAP in this conformation may interact with the receptor, while the rigid nature of the molecule due to adamantane ring, would help the molecule to acquire a better geometrical fit.



It is also expected that rigid nature of the molecule due to the presence of adamantane would show more activity than that of the molecule having any simple substituent. The requirement of a better geometrical fit with the receptor is of paramount importance as far as the potentiation effect of a drug is concerned, such as compound (Fig. 2) is reported to be twice as potent as morphine and ten times more effective than its enantiomer in the hot-plate procedure in mice [8].

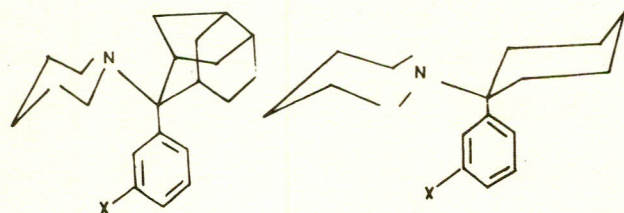


Fig. 3. PCP ( $x = H$ )  
NPCP ( $x = N_2O$ )  
(A)

PAP ( $x = H$ )  
NPAP ( $x = N_2O$ )  
(B)

Compounds possessing structure A and B and related derivatives are supposed to interfere with the cholinergic system [6] (Fig. 3)

It is believed that aromatic ring along with the ammonium group interacts with the receptor in the same way as that of acetyl group of acetylcholine (receptor). Compound

B is more active than compound A due to its rigid structure conforming to better attachment with the receptor. It is

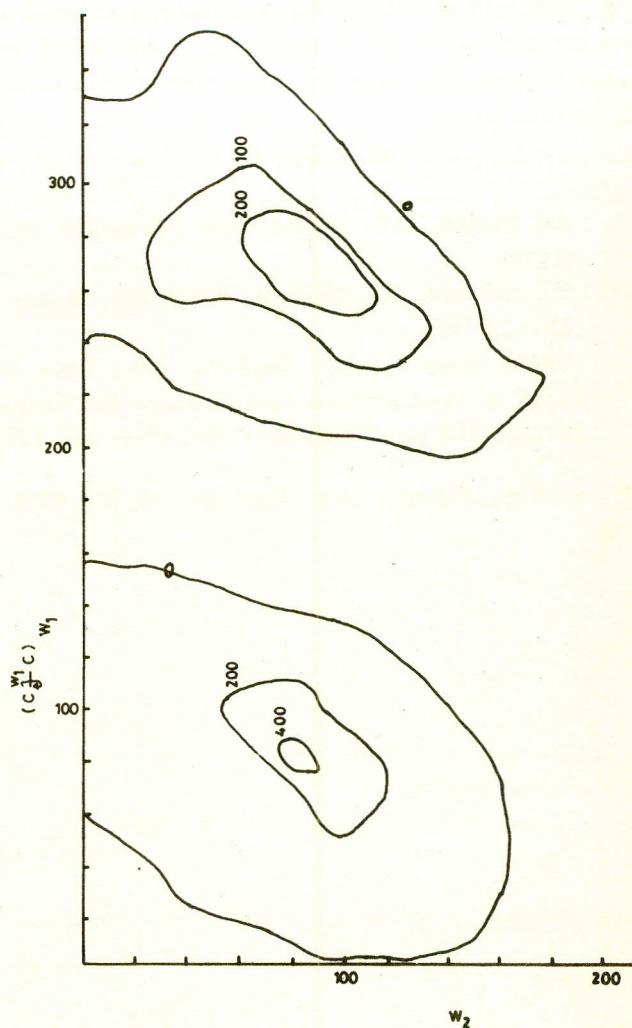


Fig. 4.

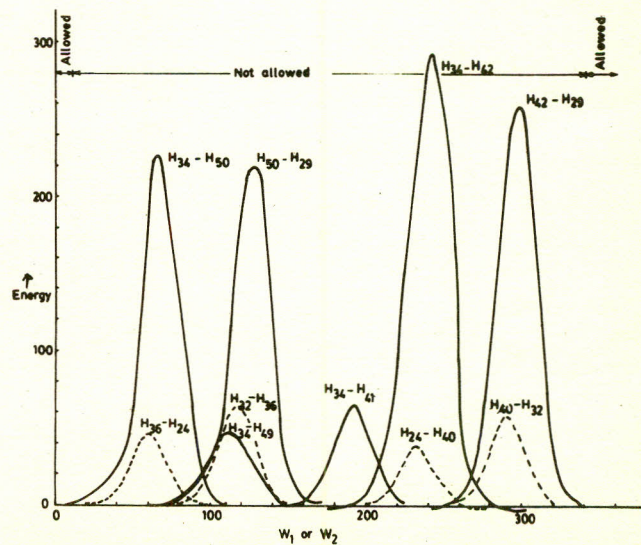


Fig. 5.

not necessary that a drug may interact with the receptor at the level of its most stable position with respect to energetics of the molecule<sup>[7]</sup>. It is expected that the technique of computation would be of great help in elucidating the mode of drug action with respect to stereospecific nature of the receptor.

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