

## POTENTIAL ENERGY CALCULATIONS OF PIPERX AND DEXITIMIDE

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The conformations of piperx and dexitimide have been investigated. The present calculations suggest limited allowed conformations for both molecules. The calculations suggest that the largest differences in A and B are the internal rotations around bonds  $C_{17} - N_2$  and  $C_{17} - C_{18}$  for allowed conformations (dexitimide). The potential energy calculations indicate that there are serious type of overlapping for the pairs  $C_{13}-C_5$  and  $C_{13}-C_4$  at  $W_1 = 120^\circ$ . The allowed regions for the conformations is at  $W_1 = 0 - 120^\circ, 300-360^\circ$  (Wisanine).

**Key words:** Potential energy, Piperx, Dexitimide.

### INTRODUCTION

The hydrobromide of dexitimide, the pharmacological active enantiomer of ( $\pm$ )-benzetimide, crystallizes from 70 % alcohol as the hemihydrate. The crystals are triclinic, space group  $P_1$ , with  $a = 7.390$ ,  $b = 9.073$ ,  $c = 17.284 \text{ \AA}$ ,  $= 96.24^\circ$ ,  $\beta = 101.78^\circ$ ,  $\gamma = 81.28^\circ$  [1].

( $\pm$ )-Benzetimide-HCl, ( $\pm$ )-1-benzyl-4-(2,6-dioxo-3-phenyl-3-piperidyl) piperidine HCl [1], was a potent and persistent anticholinergic agent, acting in both the peripheral and the central nervous system. Its activity was completely due to the ( $\pm$ )-enantiomer dexitimide [2]. A comparative study was done by Van Wigngaarden *et al.* [3], on space filling models of agonists dexitimide, and other antagonists of acetylcholine resulted in the correct prediction of the S-configurations of dexitimide. Soudijn *et al.* [4] suggested dexitimide were bound stereospecifically to the acetylcholine binding site of the receptor with the hydrophilic part of the molecule.

An amide alkaloid (piper) was isolated from the root bark of the plant piper guineense (West African Black or Ashanti Pepper) by Addae Mensah, *et al.* [5]. It has been confirmed by X-ray analysis that piperx is a trans-2-cis-4-isomer of wisanine. The crystal data of trans-2-cis-4-isomer of wisanine shows orthorhombic unit cell having space groups Pca 2, with unit cell dimensions  $a = 16.907 \text{ \AA}$ ,  $b = 6.325 \text{ \AA}$ ,  $c = 15.007 \text{ \AA}$  [6].

The present work describes: The conformations of dexitimide and piperx.

### METHOD

The detailed mathematical calculations are given elsewhere [7].

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The molecule 'A' of the drug dexitimide is shown in Fig. 1.

The coordinates for the pairs  $C_{15}^{II} - C_{19}^I, C_{15}^{II} - C_{23}^I, C_{14}^{II} - C_{19}^I, C_{14}^{II} - C_{23}^I$  have been determined after rotation about the bonds  $C_{17}-C_{18}$  ( $W_1$ ) and  $C_{17}-N_2$  ( $W_2$ ). The numbers I and II represent the first and second rings of the molecules. The other molecule in the unitcell is molecule 'B'. In this case same procedure is adopted for the pairs. The structure is given in Fig. 2.

The perspective view of the isomer of wisanine is shown in Figure 5. The coordinates of the atoms  $C_{13}^I-C_4^{II}$  and  $C_{13}^I-C_5^{II}$  were evaluated after rotation about the bonds  $C_2-O_3$  ( $W_1$ ) and  $C_2-C_1$  ( $W_2 = 0$ ) ( $W_1'$  and  $W_2'$  are angle of rotations about the bonds  $C_2-O_3$  and  $C_2-C_1$  respectively).

### RESULTS AND DISCUSSION

Energy diagrams for the molecule A and B are given in Fig. 3 and 4 respectively.

The coordinates of the atoms for the pairs ( $C_{15}^{II}-C_{19}^I, C_{15}^{II}-C_{23}^I, C_{14}^{II}-C_{19}^I, C_{14}^{II}-C_{23}^I$  - molecule A) were evaluated after rotations about the bonds  $C_{17}-C_{18}$  ( $W_1$ ) and  $C_{17}-N_2$  ( $W_2$ ) respectively. Potential energies for individual pairs  $C_{15}^{II}-C_{19}^I, C_{15}^{II}-C_{23}^I, C_{14}^{II}-C_{19}^I, C_{14}^{II}-C_{23}^I$  for molecule A (Fig. 1) and  $C_{15}^{II}-C_{19}^I, C_{14}^{II}-C_{19}^I, C_{15}^{II}-C_{23}^I, C_{14}^{II}-C_{23}^I$  for molecule B (Fig. 2) were calculated.

The results indicate serious types of collisions for the following pairs:

- (i)  $C_{15}^{II}-C_{19}^I$  at  $W_1 = 280^\circ$  and  $W_2 = 300^\circ$ ,
- (ii)  $C_{15}^{II}-C_{23}^I$  at  $W_1 = (0-20^\circ, 220-360^\circ)$  and  $W_2 = 20 - 120^\circ$ ,
- (iii)  $C_{14}^{II}-C_{19}^I$  at  $W_1 = 160^\circ$  and  $W_2 = 100^\circ$ ,
- (iv)  $C_{14}^{II}-C_{19}^I$  at  $W_1 = 160^\circ$  and  $W_2 = 280^\circ$ .

Similarly the results for the molecule B showed serious types of collisions for the following pairs:

(i)  $C_{15}^{II}-C_{19}^I$  at  $W_1 = 200^\circ$  and  $W_2 = 260^\circ$ .

(ii)  $C_{14}^{II}-C_{19}^I$  at  $W_1 = 80^\circ$  and  $W_2 = 260^\circ$

(iii)  $C_{15}^{II}-C_{23}^I$  at  $W_1 = 200^\circ$  and  $W_2 = 80^\circ$ .

(iv)  $C_{14}^{II}-C_{23}^I$  at  $W_1 = 80^\circ$  and  $W_2 = 80^\circ$

The total potential energies (i.e.  $EV_{ij}$ ) were then calculated for both molecules (A,B). The contour maps for molecule A and B are given in Fig. 3 and 4 respectively.

The allowed regions are indicated outside the zero contour for molecules A (Fig. 3) and molecule B (Fig. 4). The potential energy for the structure of wisanine for the pairs  $C_{13}^I-C_4^{II}$  and  $C_{13}^I-C_5^{II}$  is given in Fig. 6.

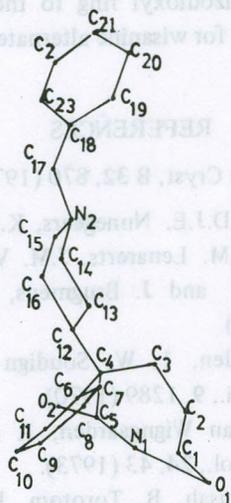


Fig. 1. 010 projection of dexitimide (molecule A).

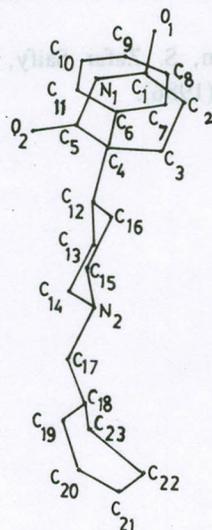


Fig. 2. 010 projection of dexitimide (molecule B).

The total potential energy of the molecule A and B are given in Fig. 3 and Fig. 4 respectively. The present calculations suggest limited allowed conformations for both the molecules. (Fig. 3 and Fig. 4, area outside zero contour). However the allowed conformation (area outside zero contour) for the molecule A is at the left side of the Fig. 3 while for the molecule B is at the right side of the Fig. 4. This indicates differences in the conformation of molecule A and molecule B. Therefore the largest differences in A and B are the internal rotations around  $C_{17}-N_2$  and  $C_{17}-C_{18}$  for allowed

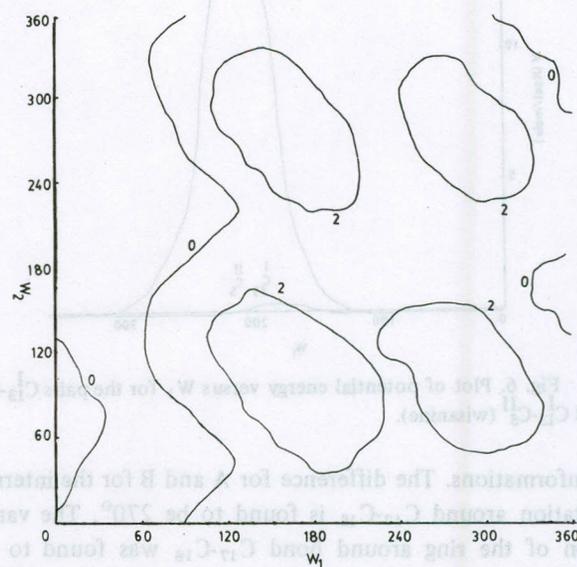


Fig. 3. Total energy contours for dexitimide (molecule A). The units of energy are Kcal./mole.

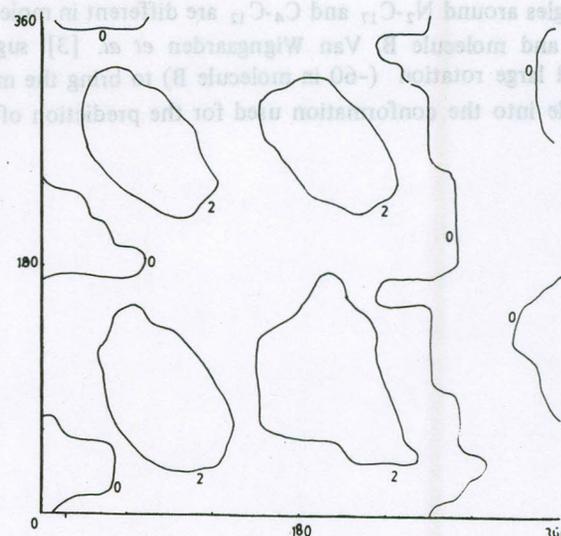


Fig. 4. Total energy contours for dexitimide (molecule B). The units of energy are Kcal./mole.

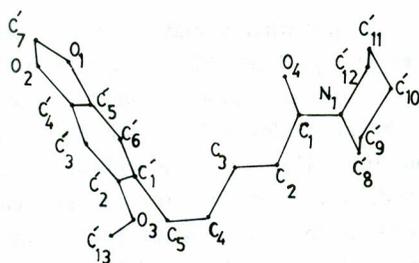
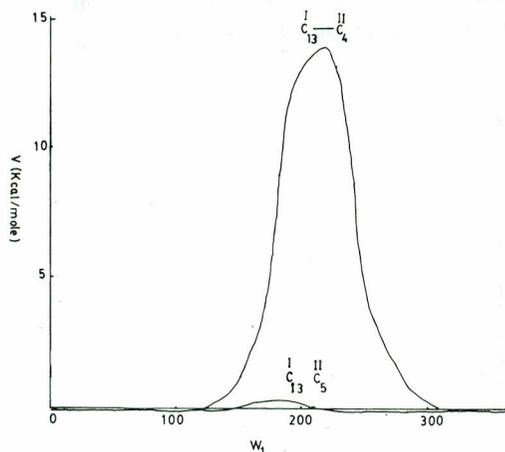


Fig. 5. Structure of wisanine.

Fig. 6. Plot of potential energy versus  $W_1$  for the pairs  $C_{13}^I-C_4^{II}$  and  $C_{13}^I-C_5^{II}$  (wisanine).

conformations. The difference for A and B for the internal rotation around  $C_{17}-C_{18}$  is found to be  $270^\circ$ . The variation of the ring around bond  $C_{17}-C_{18}$  was found to be  $270^\circ$  in molecule B from the conformation of molecule A. The internal rotations around  $C_4-C_{12}$  have not been calculated. Earlier workers suggested that the torsion angles around  $N_2-C_{17}$  and  $C_4-C_{12}$  are different in molecule A and molecule B. Van Wigngaarden *et al.* [3] suggested large rotation ( $-60^\circ$  in molecule B) to bring the molecule into the conformation used for the prediction of the

absolute conformation on the basis of receptor theory. Modern concept of drug — design and receptor model imparts a significant role in understanding the mode of action of biologically active molecule at cellular level. Present study is an extension of the work which is being carried out in our laboratory.

The coordinates of the atom  $C_{13}$  (Wisanine) have been calculated after rotation along the bond,  $C_2-O_3$  ( $W_1$ ) and contacts ( $W_2$ ) have been calculated for the pairs  $C_{13}^I-C_4^{II}$  and  $C_{13}^I-C_5^{II}$ . The results are given in Figure 6. The regions which are allowed for the pairs lies at  $W_1 = 0-20^\circ$  and  $300^\circ$  to  $360^\circ$ . These regions suggest that there is some flexibility in these pairs to bind with the respective receptors. The present calculations indicate that there appears to be decrease in the c-c-c-bond angles in the pentadiene chain from the benzodioxyl ring to the piperidine ring. However, the values for wisanine alternate in the c-c-c-bond angles.

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