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Molecular Orbital Study of the Conformational Properties of Phenothiazines

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The conformation of the side-chain attached to N_{10} of the phenothiazine ring system is investigated by the molecular orbital PCILO method. It is shown that this conformation depends on the folding of the ring along the S–N central axis. The theoretical results are in very satisfactory agreement with the available X-ray crystallographic data on chlorpromazine, thiethylperazine, diethazine and mopazine.

La conformation de la chaîne latérale partant du N_{10} du noyau phenothiazinique est étudiée par la méthode PCILO. Les résultats montrent que cette conformation dépend notablement du degré de pliage de la molécule le long de l'axe S–N central. Les prédictions théoriques sont en excellent accord avec les données expérimentales provenant de l'étude cristallographique de la chlorpromazine, la thiethylperazine, la diethazine et la mopazine.

Die Konformation der Seitenkette am N_{10} des Phenothiazinringsystems wird mit der PCILO-Methode untersucht. Es wird gezeigt, daß diese Konformation von der Stellung des Rings entlang der zentralen S–N Achse abhängt. Die theoretischen Ergebnisse stimmen sehr gut mit den vorhandenen kristallographischen Daten von Chlorpromazin, Thiethylperazin, Diethazin und Mipazin überein.

Introduction

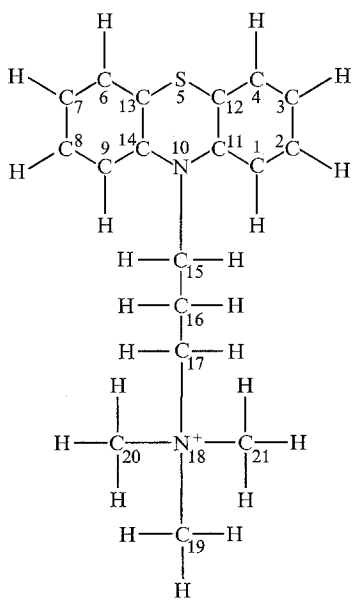
Phenothiazine derivatives have numerous pharmacological activities, the best known being their action as tranquilizers [1]. Quantum-mechanical calculations have contributed to the knowledge of the electronic properties of these compounds [2] and have, in particular, attracted attention to their electron-donor properties and their ability to participate in charge-transfer complexes [3, 4]. In fact, a theory was proposed [5] linking the tranquilizing activity of phenothiazines to their ability to act as electron donors. As might have been expected, it is not universally adopted (see e.g. the discussion after Ref. [2], at the 2nd International Symposium on "The Action Mechanism and Metabolism of Phychoactive Drugs Derived from Phenothiazine and Structurally Related Compounds", hold in Paris in October 1967).

Whatever the significance of the electronic properties of the phenothiazine ring for the pharmacological activity of phenothiazine drugs, it has long been realized that this activity depends also on the geometrical and conformational properties of these compounds. In a previous publication [6] we have studied quantum-mechanically one aspect of these properties namely the folding of the phenothiazine ring system along the central S–N axis. The present paper is devoted to the study of another, at least as and possibly more important aspect

of these properties namely the conformational arrangement of the side chain attached to the N atom with respect to the folded ring. The mutual interlationship of these two properties is also investigated to some extent.

The Method

This paper forms a part of a general investigation of conformational properties of pharmacological drugs and in particular of drugs composed of side chains attached to aromatic rings. The method utilized is the PCILO (Perturbative Configurational Interaction using Localized Orbitals) method [7], which is a refined all-valence electrons procedure going beyond the self-consistent field approximation by incorporating an appreciable part of correlation energy. It has been used succesfully for a large study of the conformational properties of the constituents of proteins (see e.g. [8, 9]) and nucleic acids [10, 11] and of a series of pharmacological drugs: acetylcholine and its agonists [12], serotonine [13], histamine [14], phenylethylamines [15], barbiturates [16], monoaminooxidase inhibitors [17] etc.



I

The calculations have been carried out on the model compound *I*, composed of the phenothiazine ring and the typical dimethylaminopropyl side chain, which, however, for reasons of computational simplification, was taken in the cationic $-N^+(CH_3)_3$ form. The geometrical input data (bond length and angles) were taken following the crystallographic indications of [18].

The calculations on the conformation of the side chain with respect to the ring were carried out for two preselected values of the angle of folding φ of the ring system along the S–N central axis: $\varphi = 140°$, a popular value derived already a long time ago on the basis of dipole moment measurements [19] and observed recently in X-rays studies of a number of phenothiazines (*vide infra*) and $\varphi = 160°$ corresponding to a flattened ring found recently in one such study (*vide infra*).

The essential torsion angles to be investigated are $\tau_1(S_5–N_{10}–C_{15}–C_{16})$, $\tau_2(N_{10}–C_{15}–C_{16}–C_{17})$ and $\tau_3(C_{15}–C_{16}–C_{17}–N_{18})$. (We remind that the torsion angle τ of the atoms A–B–C–D is the angle between the planes ABC and BCD. Viewed from the direction of A, τ is positive for clockwise and negative for anticlockwise rotations. The value $\tau = 0°$ corresponds to the planar-*cis* arrangement of the bonds AB and CD. Usually the definition is applied to a series of bonded atoms. It is enlarged here to involve the non bonded S, N atoms.) The $N^+(CH_3)_3$ group was fixed in a staggered position following previous results [12–14].

The rotations about the torsion angles τ_1 and τ_2 were carried out with 30° increments. For τ_3, two preselected values of 180° and 60° were utilized. The calculations indicate that for both values of $\varphi = 140°$ and $\varphi = 160°$, the global minimum of the map obtained with $\tau_3 = 180°$ is about 30 kcal/mole lower than that of the map obtained with $\tau_3 = 60°$. Consequently, only the maps corresponding to $\tau_3 = 180°$ will be reproduced in this paper[1].

Results and Discussion

Fig. 1 represents the conformational energy map for compound *I* corresponding to the preselected values $\varphi = 140°$, $\tau_3 = 180°$. The map shows two practically equivalent global minima at:

$$\tau_1 = 30°, \quad \tau_2 = -60°,$$

and

$$\tau_1 = 30°, \quad \tau_2 = 180°.$$

In both conformations the β-CH_2 group leans towards one of the lateral benzene rings of the phenothiazine system. The two conformations differ, however, by the orientation of the further part of the side chain which points respectively toward and away from the ring system.

Fig. 2 represents the conformational energy map for the same compound *I*, corresponding to the preselected values $\varphi = 160°$, $\tau_3 = 180°$. This map shows three practically equivalent minima. To the previous minima at:

$$\tau_1 = 30°, \quad \tau_2 = -60°,$$

and

$$\tau_1 = 30°, \quad \tau_2 = 180°,$$

[1] The conformational energy maps corresponding to $\tau_3 = 60°$ show also a very restricted permissible conformational zone, with global minima always at $\tau_2 = 150°$ and $\tau_1 = \pm 30°$ for $\varphi = 140°$ and $\tau_1 = 180°$ for $\varphi = 160°$. There is also a local minimum at $\tau_2 = 150°$, $\tau_1 = 180°$ for $\varphi = 140°$ and at $\tau_2 = 150°$, $\tau_1 = \pm 30°$ for $\varphi = 160°$.

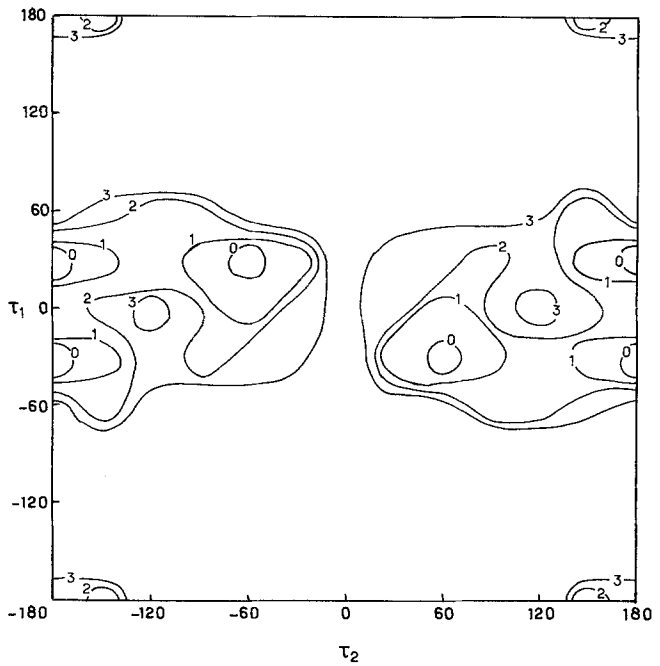


Fig. 1. Conformational energy map of phenothiazine I for $\varphi = 140°$, $\tau_3 = 180°$. Isoenergy curves in kcal/mole with respect to the global minimum taken as energy zero

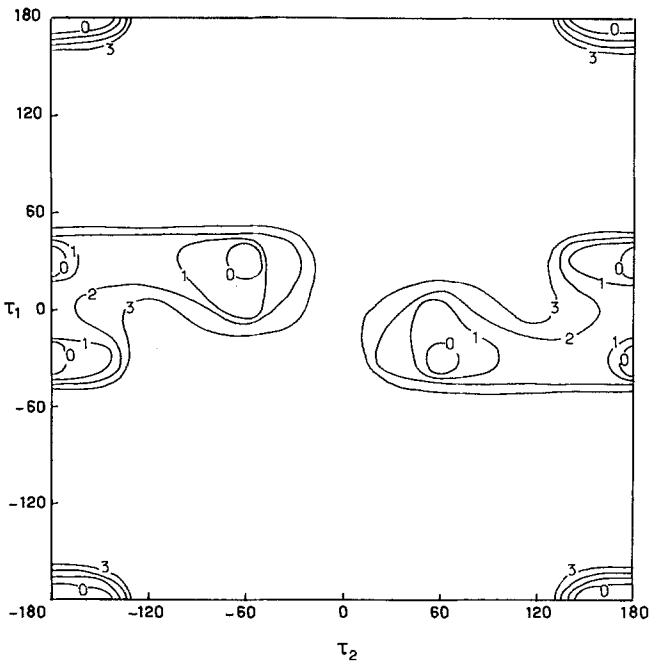


Fig. 2. Conformational energy map of phenothiazine I for $\varphi = 160°$, $\tau_3 = 180°$. Isoenergy curves in kcal/mole with respect to the global minimum taken as energy zero

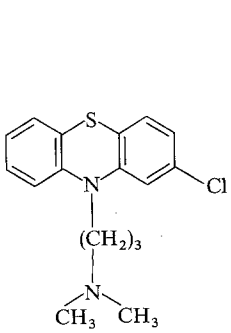
is now added a third minimum at:

$$\tau_1 = 180°, \quad \tau_2 = 180°.$$

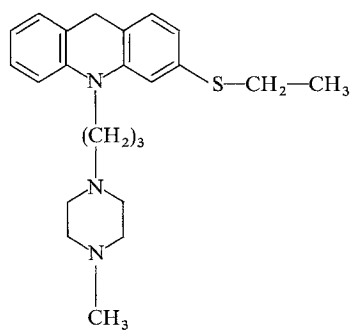
The flattening of the ring has therefore the effect of producing a new stability zone corresponding to an *all-trans* arrangement of the side chain with respect to the ring.

It must be stressed that the calculations indicate that, fundamentally, the conformation with $\varphi = 160°$ is about 30 kcal/mole less stable than the conformation with $\varphi = 140°$. Although the results refer, of course, only to the model compound and moreover *in vacuum*, this difference is sufficiently pronounced to justify the expectation that phenothiazines should exist preferentially with $\varphi = 140°$, in which case they should adopt the overall conformations predicted for this form. Nevertheless, should the ring system be induced for some reasons (other substituents at the ring susceptible to interact with the side-chain, crystal packing forces, solvent effects, etc.) to adopt a more flattened shape, around $\varphi = 160°$, a third overall conformation appears possible.

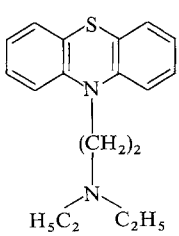
We may now turn to the few available experimental data in order to compare them with the theoretical results. These data come from recent X-ray crystallographic studies on some simple phenothiazine derivatives: chlorpromazine (II) [18, 20], thiethylperazine (III) [21], diethazine (IV) [22] and mopazine (V) [18]. The experimental values of the angles φ, τ_1 and τ_2 in these compounds are shown in Table 1.



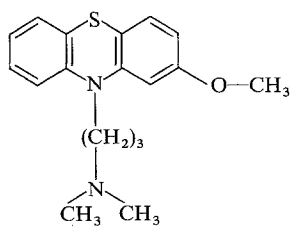
II



III



IV



V

Table 1. X-ray crystallographic results

Molecule	φ	τ_1	τ_2	Ref.
Chlorpromazine	139.4°	−34.5°	−160°	[20]
Chlorpromazine	139.5°	34.6°	164°	[18]
Thiethylperazine	139°	−32°	175°	[21]
Diethazine	138°	38°	171°	[22]
Mopazine	157.7°	178.8°	175.5°	[18]

The agreement between the theoretical results and the experimental data is extremely striking. Three of the four compounds studied have their angle of folding φ in the vicinity of 140° and the three of them exhibit a conformation of their side chain very close to the theoretical global minimum predicted for $\tau_1 = 30°$, $\tau_2 = 180°$. This correspondance is even observed for diethazine (IV) whose side chain only contains two CH_2 groups indicating thus that the principal conformational features of the side chain do not seem to depend too drastically on the length of the chain. On the other hand one compound, mopazine, investigated experimentally in the form of mopazine maleate with therefore environmental factors of prominent importance, presents a folding angle close to the value of 160°. It is particularly striking that this compound, and this compound alone, shows a conformation of the side chain near $\tau_1 = \tau_2 = 180°$ corresponding thus to the third, new global minimum specific for the higher value of φ. This situation clearly indicates the important influence of the degree of folding of the ring system upon the conformation of the side chain.

Conclusion

The results indicate once more the reliability of the PCILO method for the evaluation of molecular conformations. They indicate a far reaching selectivity in the overall conformations susceptible to be adopted by phenothiazine drugs and the interrelation of the conformations of the side chain with the magnitude of folding of the phenothiazine ring system.

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