Journal of Computer-Aided Molecular Design, 4 (1990) 403–409
ESCOM

J-CAMD 090

Theoretical models for the conformations and the protonation of triacetonamine

C. Ch. Navajas[a], L.A. Montero[b] and B. La Serna[c]

[a]*Facultad de Farmacia y Alimentos and* [b]*Facultad de Quimica, Universidad de la Habana, Ciudad de La Habana 10400, Cuba*
[c]*Academia de Ciencias de Cuba, Ciudad de La Habana 10200, Cuba*

Received 3 July 1989
Accepted 16 February 1990

Key words: Cancer; MNDO; MM2; COPEANE; Conformations; Triacetonamine; Vincubine

SUMMARY

In this paper we propose theoretical models for the conformations of triacetonamine and protonated triacetonamine (Vincubine, an anticancer chemotherapeutic agent) developed by quantum and molecular mechanics techniques. We discuss the theoretical factors which are involved in the stabilization of the conformations calculated by the MNDO, MM2 and COPEANE methods and show the relative percent abundance of each molecular shape. Graphic representations of the conformers are depicted.

INTRODUCTION

Cancer, and all of the chemical structures connected in some way with this disease, is a field of scientific work in which great interest exists. For our country, research in this area has been an important objective in recent years. It has led to the development of new chemotherapeutic agents, including Vincubine [hydrochloride of the 2,2,6,6-tetramethyl-4-piperidinone (protonated triacetonamine)], an alkaloid with antitumor activity that is currently undergoing phase II clinical trials. The agent has demonstrated analgesic and antipyretic activity in more than 90% of the treated patients showing little or no toxicity (Cuéllar, A., personal communication).

We have studied the molecular structure of triacetonamine with the aid of quantum and molecular mechanics techniques in order to construct a theoretical model of the molecular conformations with the purpose of initiating a QSAR study. We hope to define the mode of action of this agent and to assist the development of new and more potent derivatives for the treatment of cancer.

MATERIALS AND METHODS

All computer programs were run on both LTEL/24 (IBM-XT compatible) and MITAC MPC 2000 (IBM-AT compatible, 10 MHz) computers with graphics displays. Hard copy of all the structures was produced on an IBM compatible graphics printer. The language of the programs is FORTRAN-77 supported by the MS-DOS v. 3.20 operating system.

We used the semiempirical method MNDO (Modified Neglect of Diatomic Differential Overlap) to calculate structural properties such as heats of formation, relative total energies, ionization potentials, effective atomic charges, dipole moments and optimized molecular geometries. The method was chosen because of its reliability and relative trustworthiness [1].

We employed the COPEANE method (COordenadas y Potenciales Entre Atomos No Enlazados; coordinates and potentials between non-bonded atoms) [2] to calculate the degree of hydrogen bonding by means of ECEPP potentials [3]. The verification of other parameters was estimated by the former method. The program uses a non-bonded potential developed in a $[F[R^{-6}]+\exp(F'[-R])]$ series of dispersive and overlapping repulsive terms, respectively. The parameters were obtained from Allinger [4] and optimized for typical conformations. COPEANE uses one to five simultaneous geometrical parameter variations to optimize a molecular conformation. An electrostatic potential developed in terms of a $F''[R^{-1}]$ series was included in the calculations. Atomic charges for each conformation were obtained from the previous SCF MNDO runs. Further tests with the 1977 MM2 method [4] were likewise carried out.

TABLE 1
TOTAL ENERGY CALCULATED FOR EACH CONFORMATION OF TRIACETONAMINES (kJ mol^{-1})

	Triacetonamine			Vincubine
	Axial NH	Equatorial NH	dE[e]	
MNDO (dH_f)[b]				
Boat	−157.7	−163.8	−6.1	544.6
Chair	−164.9	−172.5	−7.6	534.8
dE[a]	−7.2	−8.7		−9.8
MM2 (E_s)[c]				
Boat	36.5	34.0	−2.5	196.3
Chair	26.2	23.3	−2.9	184.8
dE[a]	−10.3	−10.7		−11.5
COPEANE (E_{nb})[a]				
Boat	529.9	525.0	−4.9	679.9
Chair	535.1	523.6	−11.5	684.6
dE[a]	5.2	−1.4		4.7

[a] $E_{chair} - E_{boat}$.
[b] Heat of formation.
[c] Stretching energy.
[d] Non-bonded energy.
[e] $E_{equat.} - E_{axial}$.

The molecular graphics program MOLGRA was used to generate structural representations of the different conformations.

In all cases, we employed programs developed or adapted for personal computers by the Theoretical and Computational Chemistry group at the Faculty of Chemistry of Havana University [5]. The package is entitled TC-HABANA.

RESULTS

Triacetonamine

The first step consisted of optimizing the geometry and the total energy of the molecular conformations by the MNDO molecular orbital procedure. Charges calculated by this method were

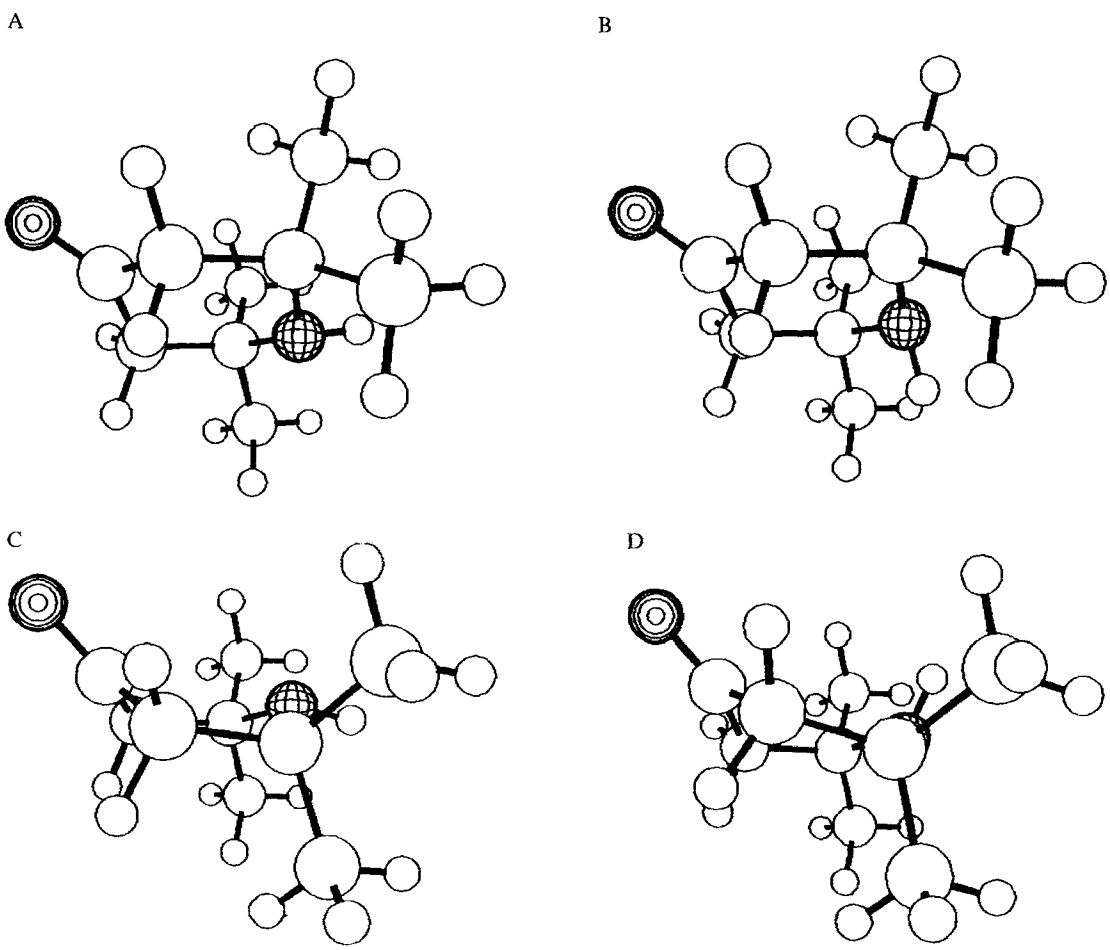


Fig. 1. Representation of the conformations in the molecule of triacetonamine. A: chair with equatorial NH; B: chair with axial NH; C: boat with equatorial NH; D: boat with axial NH.

TABLE 2
RELATIVE ABUNDANCE ACCORDING TO BOLTZMANN DISTRIBUTION CALCULATED FOR THE CONFORMATIONS OF TRIACETONAMINE AND VINCUBINE

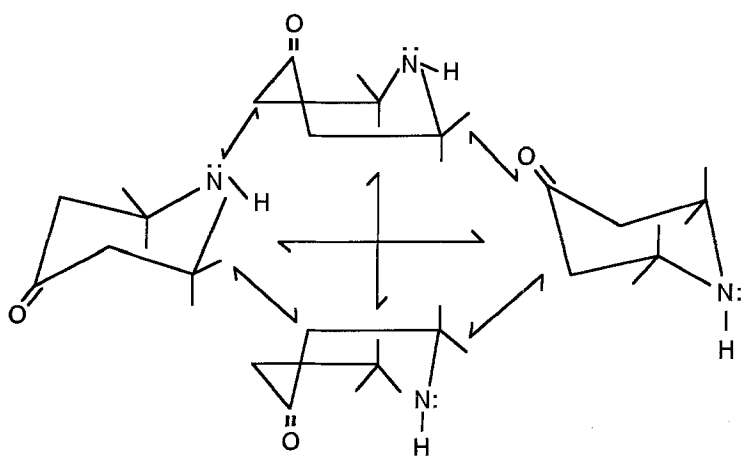
Conformation	% Abundance		
	MNDO	MM2	COPEANE
Triacetonamine			
Equatorial chair	91.8	74.4	59.5
Axial chair	4.8	24.1	0.7
Equatorial boat	3.1	1.2	34.6
Axial boat	0.3	0.4	5.2
Vincubine			
Chair	97.8	98.9	13.9
Boat	2.2	1.1	86.1

used to reoptimize geometries by the MM2 method and to calculate non-bonded potentials by COPEANE.

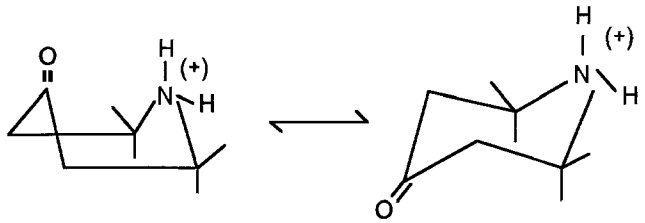
Results are shown in Table 1. The corresponding structures are displayed in Fig. 1. The stability order of the different conformations (based on the calculated conformational energies) by both MNDO and MM2 methods is:

'chair' with equatorial NH >
'chair' with axial NH >
'boat' with equatorial NH >
'boat' with axial NH.

Energy differences on the 'boat'-'chair' conformations are about 7–11 kJ/mol. However, COPEANE non-bonded potentials disagree with the MM2 and MNDO calculations resulting in the stability order given in Table 1. It appears that the axial H interaction with ring methyl groups is being treated differently for COPEANE than for MM2. It must be noted that COPEANE calcula-



Scheme 1. Conformational equilibrium in the molecule of triacetonamine.



Scheme 2. Conformational equilibrium in the molecule of Vincubine.

tions do not use optimized bonding parameters as does MM2. The method uses instead the MNDO-optimized ring geometry to obtain non-bonded potentials. On the other hand, covalent potentials are ignored by COPEANE, while they are taken into account explicitly in MM2 and implicitly in MNDO.

The calculated population of each conformation at 37°C given in Table 2 agrees with the relative percentages given by Testa in 1979 for the same isomers [6] and reflects the different balance existing among the 4 conformers analyzed [7] (see Scheme 1).

Protonated triacetonamine (Vincubine)

As with the neutral structure, the first step was optimization of the conformations (2 in this case) using the techniques described. The results are shown in Table 1.

According to the calculated values the 'chair' conformation is more stable than the 'boat' at least for MNDO and MM2. The results of the equilibrium of these conformers (Scheme 2) at 37°C – as relative population percentages – are shown in Table 2.

TABLE 3
TOTAL ENERGY CALCULATED FOR EACH CONFORMATION OF PIPERIDONE (kJ mol^{-1})

	Piperidone			Protonated piperidone
	Axial NH	Equatorial NH	dE	
MNDO (dH_f)				
Boat	−175.0	−178.9	−3.9	545.7
Chair	−182.7	−186.4	−3.7	537.5
dE	−7.7	−7.5		−8.2
MM2 (E_s)				
Boat	−24.8	−31.0	−6.2	154.2
Chair	−38.8	−45.8	−7.0	137.3
dE	−14.0	−14.8		−16.9
COPEANE (E_{nb})				
Boat	271.6	255.1	−16.5	418.2
Chair	263.5	246.8	−16.7	409.5
dE	−8.1	−8.2		−8.7

DISCUSSION

Due to the lack of experimental data on the conformational equilibrium for triacetonamines, we approximated the energies by treating substances closely related to triacetonamines: cyclohexane, cyclohexanone, and piperidine. We also calculated the values for piperidone by the same methods as shown in Table 3.

For cyclohexane the energy difference between 'chair' and 'boat' is about 43.9 kJ/mol [8], similar to the value for piperidine (43.5 kJ/mol). This result shows that substitution of a methylene group by an NH group does not affect the energy [6]. For cyclohexanone an energetic barrier of 25.1 kJ/mol is reported. The value is explained by the ease of rotation about an sp2-sp3 bond relative to the sp3-sp3 bond. Hyperconjugation is the probable cause in this latter case. These values are similar to the energetic barriers for rotation of CH_2 and NH groups when bonded to CH_3.

The relative percentages agree with the results of Blackburne et al. in 1975 [7] which refer to the stability of the conformations of piperidine.

The calculations for piperidone carried out by the same approach as for triacetonamines and Vincubine, show (Table 3) a clear preference for the 'chair' conformation. In this case all methods agree qualitatively. MM2 differs slightly with respect to the MNDO and COPEANE values. The present agreement of COPEANE energies with the other methods reinforces the above hypothesis concerning its underestimation of axial $-H...CH_3-$ non-bonded interactions. They are absent in this molecule.

In addition we calculated the total energy for the system assuming a hydrogen bond potential between the axial hydrogen of the NH group and the oxygen for the 'boat' conformation of Vincubine. A simple molecular model suggests this conformation to be improbable. The total energy obtained for the molecule with the hydrogen bond (535.6 kJ/mol) is confirmatory with an energy 5.4 kJ/mol higher than that for the 'boat' with the axial NH. This result yields a relative population of 11% and 89% for the first and second species, respectively. Figure 2 displays the optimized conformers of protonated triacetonamine.

From the molecular shapes of triacetonamine and Vincubine (Figs. 1 and 2), it is clear that both 'chair' and 'boat' conformer bond angles differ from those obtained for the cyclohexanone mole-

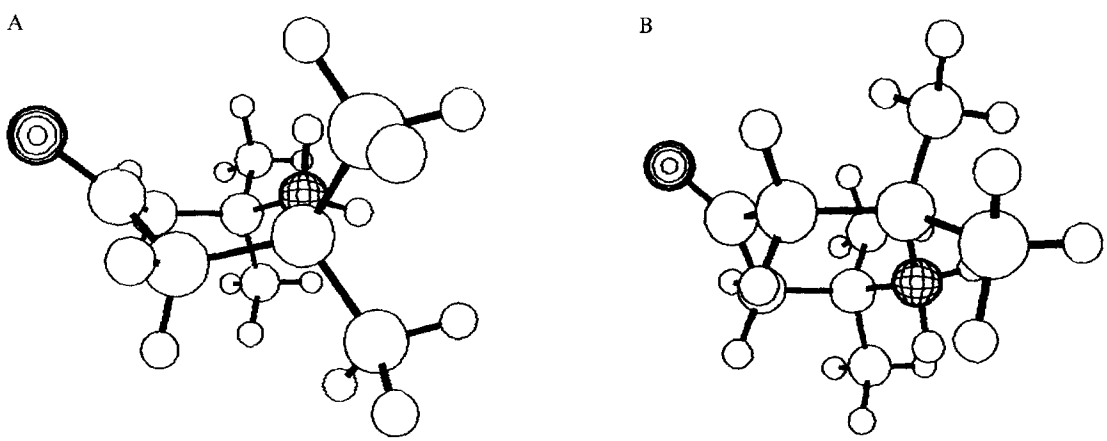


Fig. 2. Representation of the conformations in the molecule of Vincubine. A: boat; B: chair.

cule [6]. In our case, the values of the bond angles are more 'open', and indicate that the 'chair' and the 'boat' forms are 'softened' (i.e., they become more closely related to the ring plane). This is possibly a result of the steric hindrance present in the methyl groups within the molecule.

The former conclusion is in complete agreement with the ^1H NMR spectrum reported [9] for Vincubine. Two singlets are very clearly observed: one in the high field region at about 1.8 ppm (delta scale) corresponding to 12 protons from 4 equivalent methyl groups; and one at lower field, at about 2.8 ppm, corresponding to 4 equivalent methylene protons. The spectral data possibly explain the ease of interconversion of these conformations.

CONCLUSIONS

Theoretical methods for the construction of models of biologically active molecules permit an adequate approximation of probable structures that participate in physiological processes. In our case, the building of a theoretical conformational model and subsequent optimization of the geometry provides a satisfactory result for the molecular structure of alkaloids such as triacetonamine.

The concordance between the calculated energy values and the spectroscopic data will allow us to use these structures as a basis for further studies of the interaction between molecules and receptor, and to establish indices of activity on the basis of electronic properties computed in the same way.

ACKNOWLEDGEMENTS

We recognize the suggestions of referees, which have been very important for the improvement of this paper. We recognize, also, the financial aid of UNESCO for the hardware facilities.

REFERENCES

1 Boyd, D.B., Drug Inf. J., 17 (1983) 121.
2 Montero, L.A., La quimica computacional en Cuba. In II. Congreso de la Sociedad Cubana de Quimica, Santiago de Cuba, 1985, p. 34.
3 Momany, F.A., Carruthers, L.M., McGuire, R.F. and Scheraga, H.A., J. Phys. Chem., 78 (1974) 1595.
4 a. Allinger, N.L., Adv. Phys. Org. Chem., 13 (1976) 1.
b. Allinger, N.L., J. Am. Chem. Soc., 99 (1977) 8127.
5 Montero, L.A., Alvarez, J.R., del Bosque, J.R., Gonz lez, M.C., Cano, R. and Rodriguez, M.C., Folia Chim. Theor. Lat., (1988) 33.
6 Testa, B., Principles of Organic Stereochemistry, Marcel Dekker, New York, Basel, 1979, p. 217.
7 Blackburne, I.D., Katritzky, A.R. and Takeuchi, Y., Acc. Chem. Res., 8 (1975) 300.
8 Bocourt, R., Eliel, E.L. and Allinger, N.L. (Eds.) Topics in Stereochemistry, Vol. 8, Wiley, New York, NY, 1974, pp. 159–224.
9 Cuéllar, A. and O'Farrill, H., Rev. Cub. Farm., 9 (1975) 151.