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Clonidine Base: Evidence for Conjugation of Both Ring Systems

C. M. MEERMAN–VAN BENTHEM, K. VAN DER MEER,[1] AND J. J. C. MULDER[2]

Department of Theoretical Organic Chemistry, University of Leiden, Leiden, The Netherlands

P. B. M. W. M. TIMMERMANS AND P. A. VAN ZWIETEN

Department of Pharmacotherapy, University of Amsterdam, Plantage Muidergracht 24, Amsterdam, The Netherlands

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SUMMARY

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Complete neglect of differential overlap (CNDO/2) calculations were performed for clonidine base. For the ground state geometry the C—N and C$=$N distances of the ring junction proved to be 1.397 and 1.319 Å, respectively. For the angle C—N$=$C a value of 111.5° was calculated. For the angle between both rings we found a value of about 34°, indicating a nonperpendicular structure for this molecule.

INTRODUCTION

As a consequence of the interest in the structure-activity relationship of centrally acting phenyliminoimidazolidines we are investigating clonidine (Catapresan, 2-[(2,6 - dichlorophenyl)imino]imidazolidine HCl), which is the most potent drug in this series (Fig. 1).

The main cardiovascular effect of intravenously administered clonidine is a strong fall in arterial blood pressure, accompanied by bradycardia. This pronounced decrease in pressure is of central nervous origin. Clonidine is presumed to excite central *alpha* adrenergic receptors (for reviews see refs. 1–3).

It is well established that in general it is the base which passes across lipid layers before reaching its site of action. Under physiological conditions (pH 7.4) clonidine ($pK_a = 8.2$) exists about 85% in the protonated form, leaving about 15% for the free base (4). We will not consider here the question which of the two is the active form.

The hypotensive activity in this series of compounds proves to diminish greatly upon various substitutions. The rather subtle differences in steric factors can hardly explain the experimental data. We have considered the possibility of participation of electronic factors, which requires nonperpendicularity of both ring systems. In order to investigate this possibility we performed CNDO/2[3] calculations on clonidine base.

CALCULATIONS

From spectroscopic studies (ultraviolet, NMR, infrared) it has been concluded that at room temperature clonidine base pos-

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[2] To whom inquiries should be addressed.

[3] The abbreviation used is: CNDO/2, complete neglect of differential overlap.

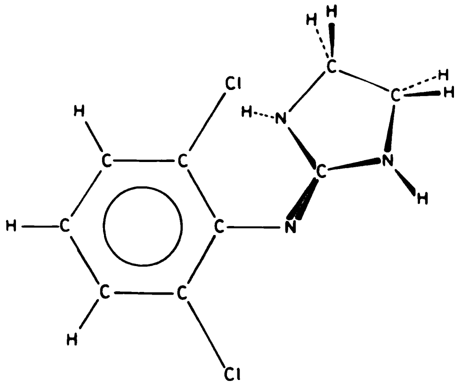

FIG. 1. *Clonidine base*

sesses a structure with an exocyclic double bond (5–7), for which a perpendicular position of both rings has been suggested (6, 8, 9). This presumption, however, is in contradiction to what may be called chemical intuition; for a nonperpendicular structure the cyclic guanidine moiety is conjugated with the phenyl moiety. In principle this kind of interaction leads to a gain in energy, if steric factors are not prohibitive. The magnitude of this prohibition is difficult to estimate from molecular models.

We have attempted to establish the equilibrium geometry of clonidine base by calculating it by means of the CNDO/2 program (10) in its original parametrization. This program has repeatedly proved to be very reliable for ground-state molecules under normal circumstances (11).

In our calculations standard bond lengths and angles were used. The parameters chosen for our geometry optimization are (a) the angle θ between the plane which contains the phenyl group and the plane containing the cyclic guanidine group, (b) the distance r_s, which is the formally single phenyl-nitrogen bond, (c) the distance r_d, which is the formally double nitrogen-imidazolidine bond, and (d) the phenyl-nitrogen-imidazolidine angle α (see Fig. 2). These parameters completely describe the geometry of the bridge, vital for conjugation. As the effect of ring puckering for the 5-membered ring is thought to be neligible, a planar structure for this ring was adopted.

The positions of the hydrogen atoms linked to the nitrogen atoms deserve special attention. As is generally known for the NH_3 molecule, two ground-state conformations are possible. These conformations may be characterized by the position of 1 hydrogen atom, which can be situated below or above the plane formed by the 3 other atoms. The same applies to our molecule. For each calculated conformation the one chosen was that in which the hydrogen atom has the longer distance from the nearest chlorine atom.

RESULTS AND DISCUSSION

By energy optimization of the ground-state equilibrium geometry, the following values of the four parameters were found: $\theta = 34°$, $r_s = 1.397$ Å, $r_d = 1.319$ Å, and $\alpha = 111.5°$. Of course, all eight geometries ($\alpha = 111.5°$ or $360° - 111.5°$ and $\theta = 34°$, $180° \pm 34°$, $360° - 34°$) are minima. Subsequently we calculated a potential surface for optimal r_s and r_d by varying the angular parameters. The results are shown in Fig. 3. As CNDO/2 calculations neglect inner-shell electrons, the calculated energies possess only a relative value. We scaled them with respect to the energy of the equilibrium geometry, which was chosen as a zero point. Figure 3 is a cross section of the complete potential surface. As can be seen from this figure, clonidine base proves to be more stable in a nonperpendicular conformation.

Let α be kept to its optimal value of 111.5°. When θ is varied two effects with opposite impact on the potential surface are present: conjugation and repulsion. Conjugational effects are responsible for the energy lowering for decreasing θ. For low values of θ the NH···Cl repulsion grows very large, resulting in a net increase in energy. A compromise is found for $\theta = 34°$. For small values of θ and α (the

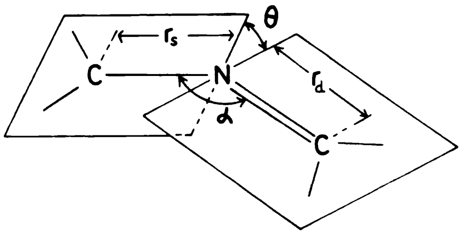

FIG. 2. *Schematic diagram of four parameters*

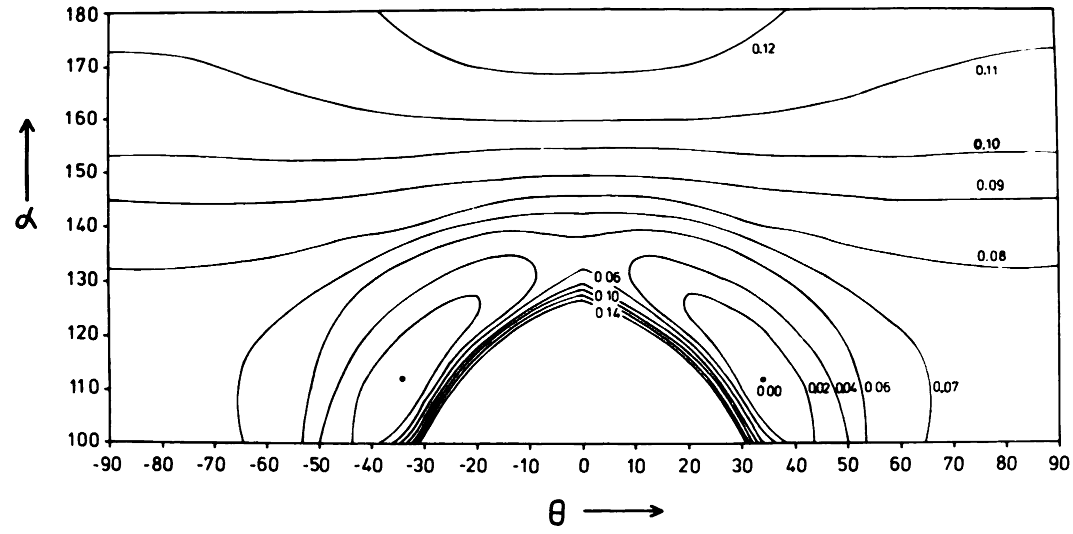

FIG. 3. *Energy contours as a function of θ and α for r_s = 1.397 Å and r_d = 1.319 Å*
Energies are given in atomic units relative to the energy of the equilibrium geometry.

TABLE 1

Comparison between energies calculated with r_s = 1.397 and r_d = 1.319Å, and energies calculated with optimal values for r_s and r_d at corner points of Fig. 3

α	θ	r_s	r_d	Energy
		Å	Å	*a.u.*
100°	90°	1.407	1.319	0.0738
100°	90°	1.397	1.319	0.0740
180°	90°	1.36	1.29	0.1075
180°	90°	1.397	1.319	0.1117

middle lower part of Fig. 3) the nitrogen and chlorine cores penetrate each other. This corresponds to physically irrelevant structures, whose energy contours are not shown. Because of a slightly incorrect representation of the atomic orbitals, as well as neglect of certain nonvanishing integrals, CNDO calculations somewhat underestimate the nonbonded repulsions. Such an interaction is present here in the N—H···Cl system. For this reason the optimal value of θ could be slightly larger than the calculated 34°.

In order to investigate the applicability of Fig. 3 we recalculated the optimal values of r_s and r_d. As can be seen from Table 1, the energies in Fig. 3 are not sensitive to these small changes in r_s and r_d.

Until now we have considered only structures containing an sp^2-hybridized bridging nitrogen atom. We also investigated the possibility that an allene-like structure of clonidine base could be stable. In this conformation a linear *sp*-hybridized bridging nitrogen atom is present. This structure is shown in Fig. 4. In our parametrization this situation corresponds to α = 180° and θ = 90°. This corner point with E = 0.1075 atomic unit is a saddle point on the surface; θ = 90° is the optimal value for θ if α is kept to 180°, but this conformation is unstable with respect to a decrease in α. Without an activation barrier the molecule reaches some smaller value of α where it is no longer resistant to a decrease in θ as well. After this the molecule can reach the calculated equilibrium geometry.

CONCLUSION

We have investigated the ground-state geometry of clonidine base by calculations with the CNDO/2 program. Our results indicate that the earlier presumptions that the two ring systems have a perpendicular structure are incorrect. The minimum energy is found for a nonperpendicular structure, which enables the cyclic guanidine moiety to be conjugated with the phenyl moiety. An allene-like structure does not

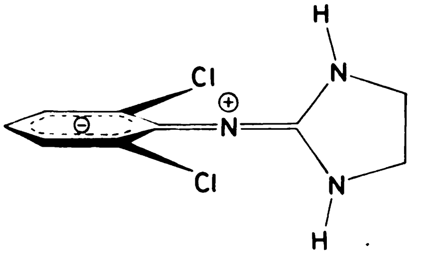

FIG. 4. *Allene-like structure of clonidine base*

correspond to a minimum but to a saddle point on the potential surface.

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