Theoretical Study of Molecular Structure, Tautomerism, and Geometrical Isomerism of Moxonidine: Two-Layered ONIOM Calculations

Milan Remko,*,† Owen A. Walsh,‡ and W. Graham Richards‡

Department of Pharmaceutical Chemistry, Comenius University, SK-832 32 Bratislava, Slovak Republic, and Physical and Theoretical Chemistry Laboratory, Oxford University, South Parks Road, Oxford, OX1 3QZ, United Kingdom

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The geometries of various tautomers and rotamers of moxonidine in both anionic and protonated forms were optimized using the two-layered ONIOM(B3LYP 6-311+G(d,p): AM1) method. The calculations showed that, in agreement with experiments, moxonidine exists in a more stable imino tautomer. The tautomer containing the amino group is less stable by about 19 kJ/mol. The computed stable conformation for the moxonidine species is characterized by the pyrimidine and imidazolidine rings being in the mutual gauche conformation to one another. In contrast to the parent neutral molecule of moxonidine, ionization caused considerable geometric changes in the anions compared to the neutral species. In the neutral form and anion of the parent drug, an intramolecular hydrogen bond stabilizes the structure and makes the most stable conformations more planar. The primary protonation site is the imidazolidine part of drug. The proton affinity of moxonidine was computed to be −1004 kJ/mol. The moxonidine base was found to be less lipophilic than the base of parent clonidine.

Introduction

Moxonidine (4-chloro-N-(4,5-dihydro-1H-imidazol-2yl)-6-methoxy-2-methyl-5-pyrimidinamine) is a new centrally acting anihypertensive drug that is widely used therapeutically.[1,2] Its action is mediated by imidazoline I1 receptors located in the rostral ventrolateral medula. Moxonidine binds with an affinity for the imidazoline I1 receptor that is 33 times more effective than its α_2-receptor binding affinity.[3] The discovery of new binding sites specifically recognizing the imidazoline structure or similar chemical structure, both in the brain and in certain peripheral tissues including the kidney, some of which participate in the control of blood pressure,[4,5] resulted in the development of a second generation of centrally acting antihypertensives[4−15] (moxonidine and rilmenidine). Moxonidine and rilmenidine are considered preferable over the classic α_2-adrenoreceptor stimulants (clonidine) because of their fewer side-effects. This may be explained on the basis of absent or weak affinity for the α_2-adrenoreceptor.[14] These new binding sites are now generally accepted as being receptors (imidazoline receptors). Second-generation agents moxonidine and rilmenidine are I1-receptor-selective ligands.[15]

Despite a great deal of pharmacological evidence for the imidazoline receptors at the plasma membrane, none of them have been identified using the techniques of molecular biology. The absence of experimental structural data of imidazoline receptors presents a challenge to the application of molecular modeling methods trying to obtain insight into the recognition and binding processes. Musgrave et al.[16] carried out conformational analysis of clonidine and several structurally diverse imidazoline ligands using a molecular mechanical force field. Physicochemical properties of clonidine and rilmenidine were investigated at the ONIOM:B3LYP level of theory.[17] In this paper, we have used large-scale theoretical quantum chemical calculations for the study of stable geometries of various tautomers and rotamers of moxonidine in both anionic and protonated forms. All structures investigated are shown in Figure 1. Of particular interest are the molecular geometries, tautomeric equilibria, acidities, proton afinities, and lipophilicities of the species. The results of theoretical studies of moxonidine were compared with similar calculations for clonidine and discussed with the present theories of action of these centrally acting antihypertensive agents.

Computational Details

The geometry of various tautomers and isomers of moxonidine (4-chloro-N-(4,5-dihydro-1H-imidazol-2yl)-6-methoxy-2-methyl-5-pyrimidinamine) and their ionized forms were completely optimized with the Gaussian 98 program,[18] using the two-layered ONIOM[19−21] method. The model system and real molecule (R) used for the two-layer ONIOM calculations are shown in Figure 2. The real system is the full moxonidine molecule; the model system (MS) is 2-amino-2-imidazoline. The calculations were performed for both amino and imino tautomers of parent drug and its model systems (Figure 2). The geometric parameters of model systems were taken from the values of real system, except for the terminal hydrogen, which is assumed to be along the N−C bond that is being replaced with an N−H distance of 1.012 Å. The small system (2-amino-2-imidazoline) contains the imidazoline receptor pharmacophore to be ionized and/or protonated.

The two levels of theory used for energy calculations are the density functional theory[22,23] (DFT) at the Becke3LYP level[24−26] with the polarized triple-split valence 6-311+G(d,p) basis set (the High level, H) and the semiempirical AM1 method[27] for the low level (L) of theory. Previous studies have shown[28,29] that Becke3LYP relative energies are in excellent agreement

* Corresponding author. E-mail: remko@fpharm.uniba.sk.
† Comenius University.
‡ Oxford University.

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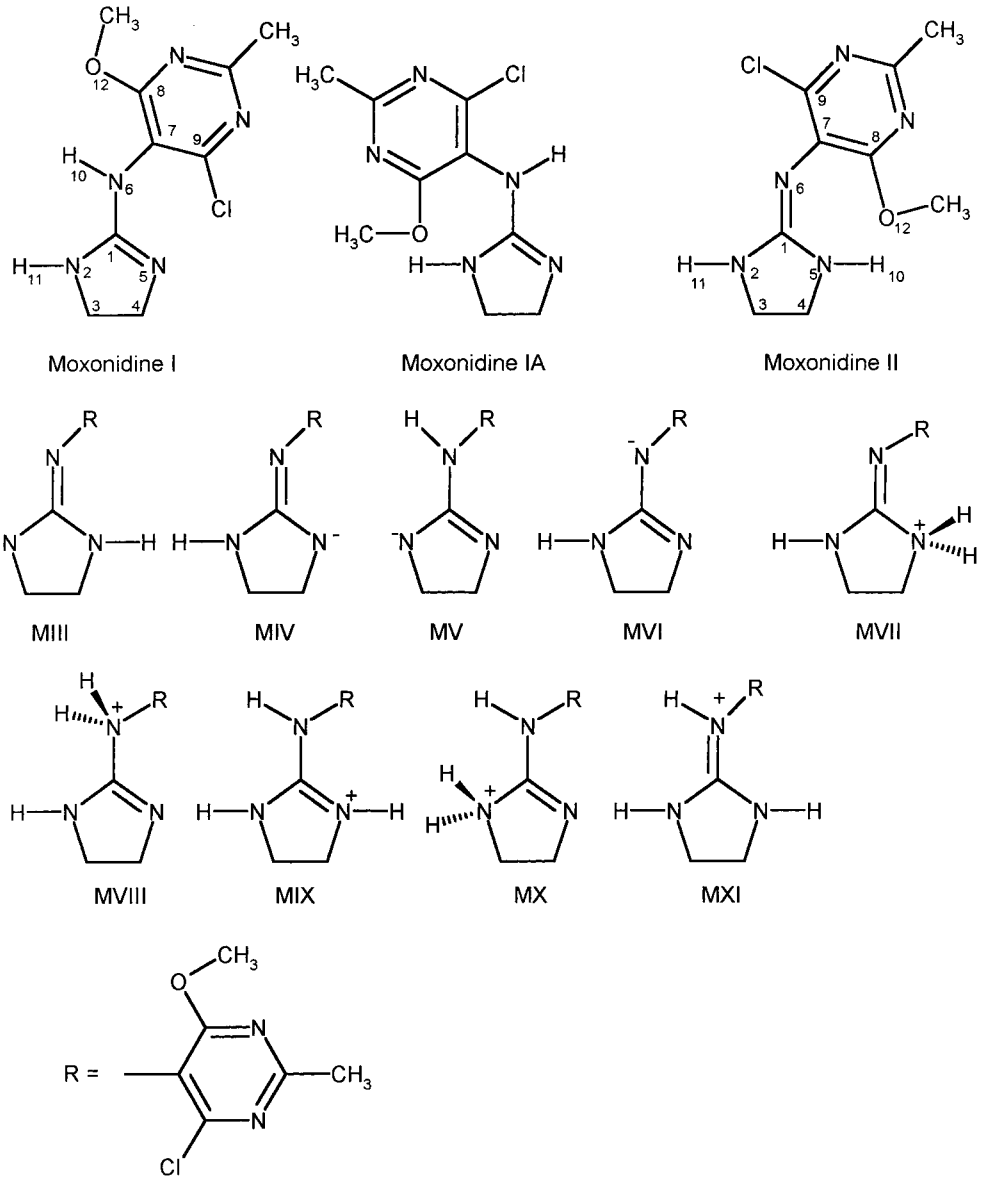

Figure 1. Structure and atom labeling in the moxonidine species studied.

with high-level ab initio results. The amine ↔ imine tautomerism of simpler models of antihypertensive drugs (2-amino-2-imidazoline, 2-amino-2-oxazoline and 2-amino-2-thiazoline) has been recently studied using the Becke3LYP/6-311+G(d,p) DFT, MP2/6-311+G(d,p), and CBS-Q model chemistries.[30] At each of the foregoing levels of theory, the amino tautomer has been computed to be more stable than the imino tautomer.

The integrated energy for the two-layered ONIOM approach is defined as[19]

$$E(\text{ONIOM2}) = E(\text{High,Model}) + E(\text{Low,Real}) - E(\text{Low,Model}) = E(\text{High,Model}) + \Delta E(\text{Low,Real}\leftarrow\text{Model}) \quad (1)$$

where

$$\Delta E(\text{Low,Real}\leftarrow\text{Model}) = E(\text{Low,Real}) - E(\text{Low,Model})$$

The gas-phase acidity ΔE(A) was defined as the energy of deprotonation ΔE(ONIOM) for reaction (A)

$$\text{AH(g)} \rightarrow \text{A}^-\text{(g)} + \text{H}^+\text{(g)} \quad \text{(A)}$$

The energy of deprotonation, ΔE, at $T = 0$ K was computed using eq 2

$$\Delta E(\text{A}) = E_{\text{ONIOM}}(\text{A}^-) - E_{\text{ONIOM}}(\text{AH}) \quad (2)$$

where E stands for the total energies of the stable conformations of acid and its anion. The enthalpy of deprotonation, ΔH,[298] was computed using eqs 3 and 4

$$\Delta H^{298}(\text{A}) = \Delta E^{298}(\text{A}) + \Delta(pV) \quad (3)$$

$$\Delta E^{298} = [E^{298}_{\text{ONIOM}}(\text{A}^-) + {}^3/_2RT] - E^{298}_{\text{ONIOM}}(\text{AH}) \quad (4)$$

where E^{298} stands for the total energies of the stable conformations of acids and their anions (including the thermal energy correction at $T = 298.15$ K). In eq 3, we substituted $\Delta(pV) = RT$ (1 mol of gas is obtained in reaction A). Notice that there is an inverse relationship between the magnitude of the ΔE and the strength of the acid. The more positive the value of ΔE is, the weaker the acid will be. The gas-phase basicity was defined

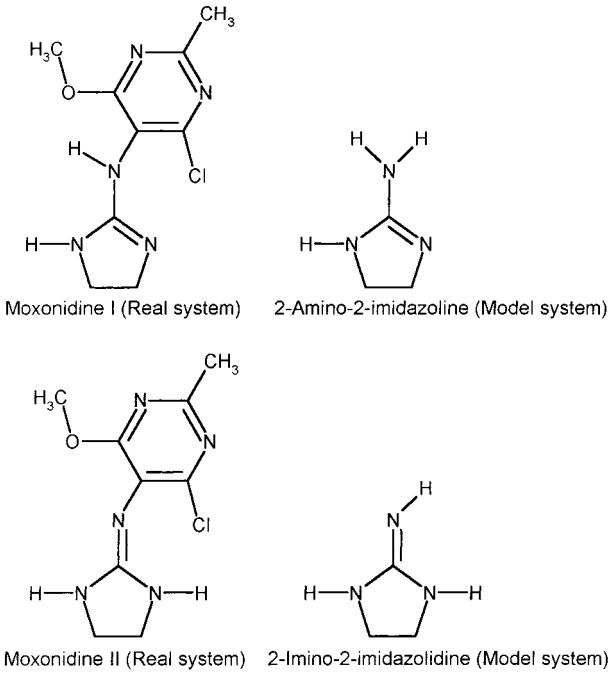

Figure 2. Two sites of systems used for the ONIOM-2 calculation: the full (real) system (moxonidine) and the model systems (2-amino-2-imidazoline, 2-amino-2-imidazolidine).

as the energy of protonation (ΔE) for reaction B

$$B(g) + H^+(g) \rightarrow BH^+(g) \qquad (B)$$

The energy of protonation, ΔE(PA), at T= 0 K was computed using eq 5

$$\Delta E(\mathrm{PA}) = E_{\mathrm{ONIOM}}(BH^+) - E_{\mathrm{ONIOM}}(B) \qquad (5)$$

where E stands for the total energies of bases and their cations. The enthalpy of protonation, ΔH,[298] was computed using eqs 6 and 7

$$\Delta H^{298} = \Delta E^{298} + \Delta(pV) \qquad (6)$$

$$\Delta E^{298} = E^{298}_{\mathrm{ONIOM}}(BH^+) - [E^{298}_{\mathrm{ONIOM}}(B) + {}^3/_2\, RT] \qquad (7)$$

where E^{298} stands for the total energies of bases and their cations (including thermal energy correction at T = 298.15 K). In eq 3, we substituted $\Delta(pV) = -RT$ [1 mol of gas is lost in reaction B].

It has been shown[19,20,31−34] that the integrated MO approach, ONIOM, provides an ideal method for accurate calculations for large systems, for such molecules accurate calculations are often too expensive and out of reach. The proton affinity, acidity values, and tautomeric equilibria computed using density functional theory[35−40] are as effective as high-level ab initio results and are in good agreement with the corresponding experimental data.

Results and Discussion

Geometries. The total ONIOM energies, enthalpies, and Gibbs energies of all calculated species are listed in Table 1. An analysis of the ONIOM(B3LYP 6-311+G(d,p):AM1 level of theory) optimized species revealed that these are minima since frequency analysis revealed that each molecule's Hessian matrix had no negative eigenvalues, thus demonstrating that there were no imaginary frequencies present. Important geometrical parameters are given in Table 2. The neutral structures **MI**, **MIA**, and **MII** show a distinctly nonplanar configuration in the C(3)−C(4) moiety of the imidazoline ring. This ring adopts a half-chair conformation. The geometry of the aminoimidazoline moiety is different in the amino and imino tautomers. Some trends are apparent: (i) The C(1)−N(6) single bond in amino tautomers is about 0.1 Å longer than the C(1)═N(6) double bond in corresponding imino species. (ii) The C(1)−N(2) and N(2)−C(3) bonds of the aminoimidazoline ring are shortened upon tautomerization (by about 0.02 Å). (iii) The valence angles of the imidazoline ring change considerably upon tautomerization. (iv) The sp^3 hybridized nitrogen atoms of the **MI**, **MIA**, and **MII** tautomers are slightly pyramidal. The arrangement of bonds about the sp^2 hybridized bridging nitrogen atoms is nearly planar. The imidazoline and pyrimidine rings in the moxonidine tautomers and isomers studied are stabilized by the favorable electrostatic interaction (via intramolecular hydrogen bond) of the electropositive hydrogen and negatively charged heteroatoms. This occurrence is also witnessed by the short intramolecular N−H...X (X = N and O) hydrogen bonds in these molecules (Table 2), which are much less than the sum of the van der Waals radii of the atoms[41] (2.75 and 2.7 Å for H···N and H···O contacts, respectively). The structure of the N(2)−C(1)−N(6)−C(7) part of the molecules is similar for the same tautomers of neutral drug. For the angle between the imidazoline and pyrimidine rings in moxonidine tautomers **MI**, **MIA** and **MII** (dihedral angle C(1)−N(6)−C(7)−C(8), Table 2), a value within a relatively large interval of about 45−110° was found, indicating a nonplanar structure for this molecule.

TABLE 1: ONIOM Energies, Enthalpies, and Gibbs Energies (hartrees/molecule) of Moxonidine Species Studied

species	energy + ZPE[a]	enthalpy[b]	gibbs energy[b]
MI	−282.629 397	−282.613 303	−282.674 615
MIA	−282.628 727	−282.612 534	−282.675 976
MII	−282.638 610	−282.622 708	−282.683 291
MIII	−282.093 757	−282.077 810	−282.139 153
MIV	−282.092 207	−282.076 331	−282.136 926
MV	−282.060 316	−282.044 379	−282.105 234
MVI	−282.089 934	−282.073 967	−282.135 080
MVII	−282.971 498	−282.955 287	−283.016 116
MVIII	−282.952 937	−282.936 576	−282.999 301
MIX	−283.017 588	−283.001 033	−283.063 215
MX	−282.964 323	−282.948 884	−283.010 735
MXI	−283.017 585	−283.001 032	−283.063 219

[a] At T = 0 K. [b] At T = 298.15 K.

The ionization and/or protonation of the parent moxonidine molecules brought about changes in geometry in the vicinity of reaction centers (Table 2). The stable conformers of the ionized species **MIII**, **MIV**, and **MV** and protonated structures **MVII**, **MVIII**, **MIX**, and **MX** are stabilized by intramolecular hydrogen bonds between the N−H group hydrogens and proton-acceptor nitrogen and oxygen atoms (Table 2). Compared to the parent free base of drug, the C(1)−N(6) double bond of protonated imino tautomers **MIII**, **MIV**, **MV**, and **MIX** is longer by about 0.05−0.1 Å. Thus, upon ionization of parent drugs, this bond looses double bond character. The ionization of the thermodynamically stable imino tautomer of moxonidine does not greatly change the pyrimidine−N−imidazolidine valence angle C(1)−N(6)−C(7). However, the N(6)−C(7) bond in the ionized imino tautomers **MIII** and **MIV** is substantially shortened. This bond exhibits, in these species, double bond character and is conjugated with the pyrimidine group. In the anions **MIII** and **MVI** the nonplanarity of the molecular structure is caused by the rotation about the torsion angle N(2)−C(1)−N(6)−C(7) (Table 2).

TABLE 2: Selected Structural Parameters of the Moxonidine Tautomers and Ionized Species Studied

	moxonidine										
parameter[a]	**MI**	**MIA**	**MII**	**MIII**	**MIV**	**MV**	**MVI**	**MVII**	**MVIII**	**MIX**	**MX**
d[C(1)−N(2)]	1.403	1.398	1.380	1.296	1.426	1.330	1.423	1.355	1.374	1.340	1.554
d[C(1)−N(5)]	1.276	1.281	1.385	1.425	1.298	1.321	1.297	1.542	1.254	1.333	1.249
d[N(5)−H]			1.011	1.014				1.022			
d[N(5)−H]								1.029			
d[N(2)−H]	1.012	1.013	1.009		1.011		1.012	1.010	1.012	1.009	1.025
d[N(2)−H]											1.023
d[N(2)−C(3)]	1.477	1.476	1.459	1.469	1.457	1.469	1.465	1.457	1.492	1.478	1.516
d[C(3)−C(4)]	1.554	1.549	1.538	1.544	1.546	1.560	1.546	1.533	1.560	1.544	1.549
d[C(1)−N(6)]	1.406	1.393	1.302	1.408	1.388	1.443	1.406	1.263	1.506	1.351	1.378
d[C(4)−N(5)]	1.471	1.470	1.467	1.468	1.469	1.472	1.470	1.513	1.485	1.476	1.458
d[N(6)−C(7)]	1.419	1.410	1.407	1.336	1.350	1.399	1.334	1.411	1.450	1.421	1.425
d[N(6)−H]	1.018	1.014				1.017			1.032	1.016	1.018
d[N(6)−H]									1.030		
Θ[C(1)−N(2)−C(3)]	105.0	104.8	110.8	106.8	106.0	102.0	105.5	115.5	104.0	110.3	102.6
Θ[N(2)−C(3)−C(4)]	101.3	100.6	100.7	104.8	99.3	104.2	99.5	101.7	101.6	101.7	102.5
Θ[N(2)−C(1)−N(5)]	117.6	117.1	107.1	113.8	113.1	123.5	113.8	104.0	121.6	110.9	112.6
Θ[C(3)−C(4)−N(5)]	105.8	105.3	101.0	99.4	104.7	104.2	105.2	102.5	106.0	101.6	106.0
Θ[C(1)−N(5)−C(4)]	106.3	105.9	110.0	104.9	107.0	102.2	106.8	106.5	104.7	110.9	111.9
Θ[N(2)−C(1)−N(6)]	115.8	120.2	121.5	126.0	114.4	115.4	118.8	129.2	116.7	123.6	113.4
Θ[C(1)−N(6)−C(7)]	118.1	123.9	121.8	124.2	125.3	121.2	126.1	124.9	113.6	121.4	117.3
Φ[C(1)−N(2)−C(3)−C(4)]	−18.8	−22.8	−27.0	−18.4	−29.1	−16.1	−28.6	26.6	−13.8	−18.5	18.6
Φ[N(2)−C(3)−N(4)−N(5)]	18.7	23.7	30.9	29.7	29.4	19.9	28.1	−30.3	13.1	20.3	−20.5
Φ[C(3)−C(4)−N(5)−C(1)]	−11.6	−15.8	−24.9	−30.1	−19.3	−15.3	−17.4	26.1	−7.3	−17.4	14.5
Φ[C(3)−N(2)−C(1)−N(6)]	−165.8	−170.6	−167.1	−173.6	−155.6	−172.4	−167.1	168.6	−175.5	−168.2	176.6
Φ[N(2)−C(1)−N(6)−C(7)]	−172.1	27.7	−178.6	−113.6	−157.0	−158.0	90.5	177.8	176.6	−167.1	179.6
Φ[C(1)−N(6)−C(7)−C(8)]	110.6	44.5	58.1	2.0	26.2	115.9	178.4	59.9	98.6	107.0	103.5
Φ[C(1)−N(6)−C(7)−C(9)]	−72.9	−136.5	−129.8	−178.7	−158.5	−69.6	−2.7	−130.1	−79.0	−79.2	−79.9
d[N(6)−H...O(12)]	2.425					2.421					
d[N(6)−H...N(5)]		2.501			2.421				2.318	2.598	2.494
d[N(5)−H...O(12)]			2.227	2.432				2.111			
d[N(2)−H...O(12)]		2.363									

[a] Bond lengths in Å and bond angles and dihedral angles in deg.

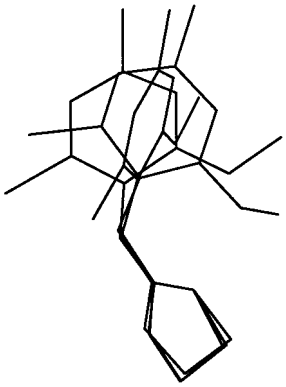

Figure 3. Molecular superimposition of the minimum-energy conformations of moxonidine (**MII)** and its ionized (**MIII)** and protonated (**MIX)** forms. For simplicity, the hydrogen atoms are omitted.

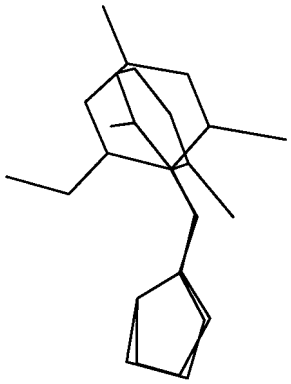

Figure 4. Molecular superimposition of the minimum energy conformations of moxonidine and clonidine. For simplicity, the hydrogen atoms are omitted.

The superposition of the optimized most stable tautomer **MII** of moxonidine and its ionized (**MIII)** and protonated (**MIX**) species is shown in Figure 3. The moxonidine base adopts the geometry in which the dihedral angle between the imidazoline and pyrimidine rings is 58.1°. The non coplanarity of these rings in clonidine-like imidazolidines is, according to the current theories of the interaction of these drugs with adrenergic receptors, a prerequisite for their biological activity.[42,43] Clonidine (2-[2,6-dichlorophenyl)imino]imidazolidine) and its analogues exhibit geometries close to that of norepinephrine[44] and act mainly via the stimulation of alpha 2-adrenoreceptors[45] (α 2 theory). The corresponding superposition of moxonidine on the ONIOM optimized structure of clonidine taken from ref 17 (Figure 4) shows that the imidazolidine parts of these drugs are very close in geometry, suggesting this part of drug could interact with the same receptor site(s). The more hydrophilic pyrimidine group of the moxonidine does not occupy common space with the phenyl ring of clonidine. Thus, it is probable that the spatial arrangement and the character of the pyrimidine part of moxonidine fits better the physicochemical nature of the imidazoline receptor area involved in ligand binding. This steric molecular-shape difference between moxonidine and clonidine antihypertensives may be one of the factors for their different pharmacological profile. Moxonidine possesses much greater selectivity toward nonadrenergic imidazoline receptors.[5,15] Great structural differences were also observed for most stable ionized and protonated species of moxonidine (Figure 3). The proposed active conformation for moxonidine is characterized by the pyrimidine and imidazoline rings not being planar to one another.

Tautomeric Equilibria. The relative energies (at $T = 0$ K), enthalpies, and Gibbs energies of various moxonidine species with respect to the most stable structures of drug are reported

TABLE 3: Relative Energies, Enthalpies, and Gibbs Energies (kJ/mol) of the Moxonidine Species at 298.15 K (Figure 1)

no.	ΔE^a	ΔH	ΔG
	Neutral Moxonidine		
MII	0	0	0
MIA	25.9	26.7	19.2
MI	24.2	24.7	22.8
	Anions		
MIII	0	0	0
MIV	4.1	3.9	5.9
MVI	10.0	10.1	10.7
MV	87.8	87.7	89.1
	Cations		
MIX	0	0	0
MXI	0	0	0
MVII	121.0	120.1	123.7
MX	139.8	139.4	137.8
MVIII	169.7	169.2	167.8

[a] At $T = 0$ K and correction for zero-point energy.

TABLE 4: ONIOM Gas-Phase Acidities and Basicities of Moxonidine and Clonidine

reaction	ΔE^a (0 K) (kJ/mol)	ΔH^{298} (kJ/mol)	ΔS^{298} (J/K.mol)	ΔG^{298} (kJ/mol)
	Moxonidine			
MII $- H^+ \rightarrow$ MIII	1430.5	1436.8	6.7	1434.8
MII $- H^+ \rightarrow$ MIV	1434.6	1440.7	0.3	1440.6
MII $+ H^+ \rightarrow$ MIX	−995.0	−999.5	14.0	−1003.7
	Clonidine[b]			
CII $- H^+ \rightarrow$ CV	1430.4	1435.9	−5.2	1437.5
CII $- H^+ \rightarrow$ CIV	1431.6	1437.3	−2.9	1438.2
CII $+ H^+ \rightarrow$ CVII	−991.6	−996.5	8.7	−999.1

[a] Including zero-point energy correction. [b] Values taken from ref 17.

in Table 4. The moxonidine molecules were considered in two sets of tautomeric amino (**MI** and **MIA**) and imino structures (**MII**) and the anions in several sets (**MIII**, **MIV**, **MV**, and **MVI**) and cations **MVII**−**MXI**. The tautomeric imino form is substantially more stable by about 20 kJ/mol than the amino tautomers. Of two possible amino conformers of moxonidine, the **MIA** structure is the most stable (by about 3 kJ/mol). The computed relative stability of the two tautomers of moxonidine (Table 3) corresponds well to the conclusions reached using experimentally observed data[46] (NMR spectroscopy) where, in cyclic substituted amidines, the predominant tautomer is in the imino form. Tautomeric equilibria are strongly dependent on the environment surrounding tautomers. However, previous theoretical studies[47] on the tautomerism of the structuraly related molecule clonidine have shown that the iminoimidazoline tautomer is, in a vacuum, the most stable species and that the solvent (water) does not change the relative stability of individual tautomers of this drug.

Moxonidine contains both an acidic N−H group and basic nitrogen center and thus may undergo protonation and/or deprotonation reactions. Table 4 details the acidities and basicities of moxonidine. With respect to the possible existence of several stable rotational conformers and tautomers of the moxonidine (Table 1), the enthalpy of deprotonation and/or protonation between two arbitrary species may be calculated. Only the differences between the most stable species can have physical meaning and can be compared with experiments. Of the four possible anionic forms of moxonidine (**MIII**−**MVI**), the anion **MIII** of the imino structure **MII** is thermodynamically most stable. However, the ionization of the other hydrogen of the amino group of the tautomer **MII** of moxonidine results in the anion **MIV** with similar geometry and almost the same stability (the calculated population ratio for these two stable anions at 310.2 K is 91:9). The computed acidity of moxonidine (1435 kJ/mol) indicates that this drug is weak acid.

TABLE 5: Calculated Partition Coefficients (Clog *P*) for Amino and Imino Tautomers of Moxonidine and Clonidine

compound	clog *P*
moxonidine amino tautomer	2.04
imino tautomer	1.90
clonidine amino tautomer	2.95
imino tautomer	2.81

Moxonidine contains several basic centers, each of these being possible protonation sites. Concerning the potential protonation of the two principal protonation sites (imidazoline and pyrimidine rings), the proton affinities for most stable tautomer **MII** of this drug were determined using the semiempirical quantum chemical AM1 method. The results clearly demonstrate that the imidazoline ring is the first protonation center. The protonation energy difference between the imidazoline and pyrimidine nitrogens was higher than 20 kJ/mol. Structures **MVII**−**MXI** were used to study the protonation processes at the three distinct protonation sites of the imidazoline moiety using the ONIOM approach. For all drugs studied, the protonation of the N-3 nitrogen atom of the aminoderivatives **MIA** and the N-6 atom of the imino structure **MII** (Figure 1) resulted in one stable structure **MIX**. Conformer **MXI** optimized to the **MIX** conformation. The **MIX** conformer was found to be most stable protonated form of moxonidine. Under physiological conditions (pH 7.4), clonidine-like drugs are almost present in their protonated forms.[48−50] The free base of parent drugs is responsible for the penetration through lipid layers to reach the site of action. There are, however, indications[42] that it is rather the protonated form which interacts with the biological receptors (α-adrenergic receptors) and therefore represents the active species. According to our calculations, moxonidine and clonidine are almost equally basic compounds (Table 4). The primary protonation site is the imidazoline part of drugs.

Lipophilicity. It is well established that, in general, it is the base which passes across lipid layers to reach the drug's site of action.[51] The lipophilicity of centrally acting antihypertensives is one of decisive physicochemical parameters which is responsible for their ability to penetrate the hydrophobic domain of the cell membrane. Because the bases of antihypertensives are more membrane-permeant, they account for most of the bulk passage of drug through membrane hydrophobic barriers. The lipophilicity of a drug is usually measured as *P*, the partition coefficient of the molecule in the water−octanol system. Table 5 contains the Clog *P* of both tautomeric forms of moxonidine and clonidine. Calculation of Clog *P* was carried out using atomic parameters derived by Ghose, Pritchett and Crippen[52,53] and program HyperChem 5.0.[54] The more lipophilic clonidine molecule contains a large hydrophobic domain in its phenyl ring. The different hydrophobicity of moxonidine in comparison with clonidine is probably one of the factors accounting for their different affinities to the α_2-adrenergic and imidazoline receptors. It is well-known[5,55] that moxonidine, contrary to clonidine, prefers interaction with I1 imidazoline receptors.

Conclusions

This theoretical study set out to determine stable conformations, tautomeric equilibria, gas-phase reactivity, and lipophilicity of moxonidine for which a relatively small amount of experimental physicochemical data exists, considering its phar-

macological importance. Using the theoretical methods the following conclusions can be drawn.

i. Moxonidine prefers a structure with an exocyclic double bond (imino form).

ii. One of the characteristics of moxonidine was the nonexistence of any conjugative electronic interaction between pyrimidine and imidazolidine rings. The computed stable conformation for moxonidine species is characterized by the pyrimidine and imidazolidine rings being in the mutual gauche conformation. This conformation is stabilized by the favorable intramolecular hydrogen bond between the N−H group of the imidazolidine group and the oxygen atom of the methoxy group of the pyrimidine part of drug.

iii. The primary protonation site is imidazolidine part of moxonidine. Moxonidine is practically an equally basic drug to its parent clonidine.

iv. The moxonidine base was found to be less substantially lipophilic than the base of clonidine.

One of most important characteristics of centrally acting antihypertensive drugs is their different selectivity by blockade of α_2-adrenoreceptors and imidazoline receptors. The substantially higher affinity of moxonidine toward I1 imidazoline receptors in comparison with clonidine could be explained by its lower lipophilicity and the different spatial arrangement of the biologically active conformation. Moxonidine and clonidine aromatic groups adopt a different conformation. It is probable that the spatial arrangement of moxonidine fits better the physicochemical nature of the imidazoline I1 receptor involved in ligand binding. The results of molecular modeling of clonidine and moxonidine may stimulate, therefore, further experimental and theoretical investigations on the molecular mechanism of centrally acting antihypertensives.

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