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Dedicated to the memory of
Professor Eugen Segal (1933-2013)

PHENYL AND IMIDAZOLE RING ROTATION IN NEUTRAL AND PROTONATED DEXMEDETOMIDINE. A SEMIEMPIRICAL AND *ab initio* STUDY

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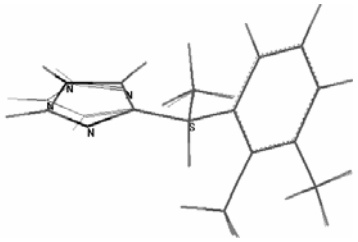
The alpha2 adrenergic receptor ligand (S)-dexmedetomidine (4-[(S)-1-(2,3-dimethyl-phenyl)-ethyl]-1*H*-imidazole), Dex is a selective agonist with many clinical applications acting on the α2 adrenergic receptor subtypes. The presence of an imidazole and a phenyl ring in molecular structure of Dex has a great importance for its potency. Both rings can contribute by their rotation to an efficient interaction with the amino acid residues from the ligand binding domain, LBD. At physiologic pH Dex can exist both in neutral and protonated ionization forms. In this paper we present results regarding conformational behavior to ring rotation, studied through 1D profiles obtained with AM1, PM3 and *ab initio* HF/6-31G**methods. 1D energy profiles for phenyl rotation have maxima of 50-2360 kcal/mol at the HF/6-31G** level, while those for rotation of imidazole ring have maxima of only 4-7 kcal/mol at T 298 K and p 1 atm. Quantum chemical studies suggest that the imidazole ring can easily rotate to adopt the best position in the LBD, while the 2,3-dimethyl ring has much more limited possibilities to rotation than the imidazole ring.



INTRODUCTION

Dexmedetomidine is a potent agonist of α2-adrenergic receptor (α2-AR) subtypes with neuroprotective effect.[1] Its therapeutic importance is associated with its predominant action in the central nervous system (CNS) where α2-ARs are pre and/or postsynaptically expressed. Several reviews regarding its clinical importance and its new future applications have been published.[2-6] It has sedative, analgesic and anxiolytic properties. Its sedative effect is different from that of opioids. The infusion of high doses of Dex does not lead to clinically significant respiratory depression, but rather to a decrease of the apnea/hypopnea index.[2,3] It causes a unique kind of sedation, acting on the subcortical areas, which resembles natural sleep.[4-6] Dex is a safe and effective adjunct in many clinical applications in adult and pediatric populations, including patients in operating room, in intensive care unit (ICU), postsurgical patients and patients who need sedation and/or analgesia for invasive and noninvasive procedures.[7,8] Sedation with a low dose of Dex appears to be safe and potentially

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efficacious for young healthy patients undergoing dental procedures.[9] Postoperative sedation with Dex was associated with significantly lower rates of postoperative delirium and lower care costs.[10] Dex is considered safe for up to 24 hours treatment of surgical patients, although occasional hemodynamic effects including bradycardia and hypotension have been reported.[11,12] Several studies explored its potential use for long-term treatment of critically ill patients in ICU.[5]

Dex was released on market in 1999 and gradually its importance has increased due to its positive effects in clinical applications in the adult, pediatric and geriatric populations, mainly because of its minimal respiratory depression.[8] Dex has recently been investigated for its potential in many other clinical treatments, including neuroprotection, cardioprotection and renoprotection, with promising results.[8]

In animal models Dex has positive effects against mortality and inflammatory responses to endotoxin-induced shock.[12] It produces inhibition of arginine vasopressin release, diuresis, and sympatholytic effects by activation of the G protein-coupled inwardly rectifying K^+ current and by suppression of hyperpolarization-activated currents in hypothalamus neurons.[13] It enhances the local anesthetic action of lidocaine[14] and has efficacy in decreasing the need for opioids, benzodiazepines, propofol, and other sedative medications.[15]

Dex attenuates isoflurane-induced injury in the developing brain, providing neurocognitive protection.[16] Studies regarding the use of Dex for management of iatrogenic opioid abstinence syndrome (IOAS) show that Dex is effective and safe second-line agent for treatment and prevention of IOAS.[17] Dex positively modulates the depressant effects of ethanol, contributing to understanding the role of noradrenergic dysfunction in stress-related alcoholism.[18] It is a promising agent for the treatment of ICU-associated delirious agitation in patients undergoing mechanical ventilation.[19] Clinical doses of Dex inhibit diffuse noxious inhibitory control (DNIC) modulating the intrinsic pain inhibition system.[20]

Physiological and pharmacological effects of Dex are related to its molecular and electronic structure. The presence of the two flexible bonds in Dex makes possible more conformers, of which one or more may be bioactive forms of ligand, that is, the conformation taken by Dex in the interaction with the key amino acid residues from the binding site of the alpha2-AR subtypes. The rotation of the two rings could play an important role in the interaction of Dex with its target protein. The aim of this work is to study the imidazole and 2,3-dimethyl ring rotation of the neutral and protonated global minima of Dex using semiempirical MO and *ab initio*/HF methods.

METHODS

The structural characteristics, energy and thermodynamic properties of neutral and protonated Dex conformers have been determined by LCAO-MO-SCF restricted Hartree-Fock methods at semiempirical AM1 and PM3 and *ab initio* levels of theory using the HyperChem7.52 software.[21] The energy minima with respect to the nuclear coordinates were obtained by the simultaneous relaxation of all the geometric parameters and the optimized AM1 or PM3 geometries were minimized without any constraint in the potential energy surface at HF level, adopting the 6-31G** basis set. To include electron correlation effects, single point energies with second-order frozen core Mőller Plesset perturbation theory[22] at the HF/6-31G** geometries (MP2/6-31G**//HF/6-31G**) were evaluated. For all methods the geometry optimization was performed using the Polak-Ribiere conjugate gradient algorithm and a stop criterion of 0.01 kcal/Åmol or less for the RMS gradient. The optimized structural parameters were used in the vibrational frequency calculations at the HF levels to characterize local, and absolute minima or transition states. In order to evidence the possibility that certain Dex conformers to interconvert in other low energy conformers the 1D profiles of the potential energy of Dex conformers against the values of the $C_4C_6C_7C_8$ and $N_3C_4C_6C_7$ dihedrals were plotted. Potential energy in semiempirical MO methods is based on binding energy values. 1D profiles were obtained through rotation of the phenyl and imidazole rings by modifying the $C_4C_6C_7C_8$ and $N_3C_4C_6C_7$ dihedrals (see Fig. 1) between 0 and 360º with steps of 10 or 15º and performing single point calculations at the AM1, PM3 and HF/6-31G** levels by using the lowest energy conformers of neutral or protonated Dex. Thermodynamic properties for HF/6-31G** conformers have been obtained from single point calculations with Jaguar7.0 software implemented in Schrödinger suite 2010, Schrödinger, LLC, New York, NY.

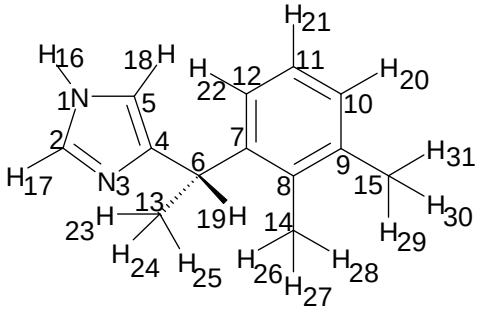


Fig. 1 – Structure and atom numbering in (S)-Dex.

RESULTS

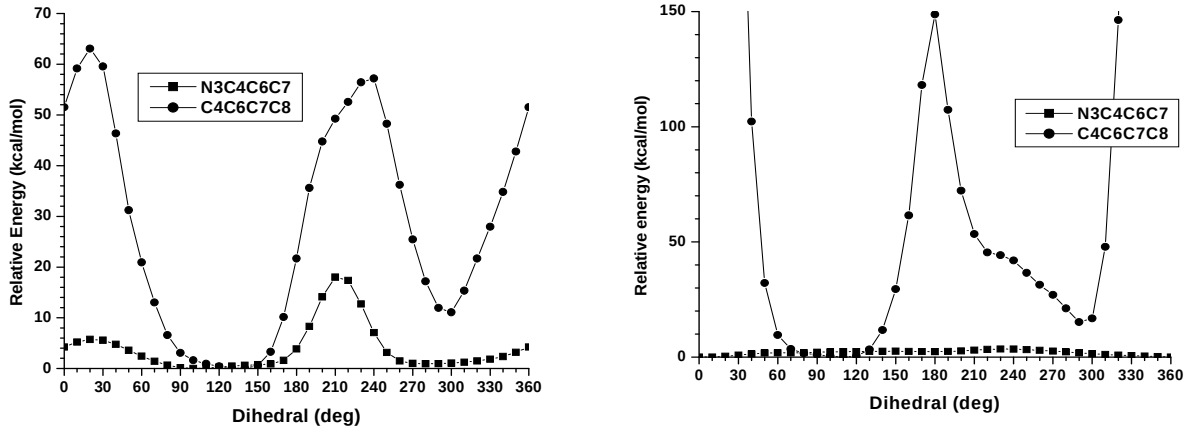
Except for PM3 (protonated Dex), the other quantum mechanics methods used in this study were not able to reproduce the global minimum determined experimentally by X-ray diffraction spectrum.[23]

1D profiles of the potential or total energy obtained from semiempirical and *ab initio*/HF calculations are depicted in Figs. 2-5 It results from Figs. 2-5 that both semiempirical and *ab initio*/HF methods give similar 1D profiles of potential or total energy of neutral and protonated Dex, in which there are two or three minima and two or three maxima.

AM1 method gives the simplest shape of the 1D profiles of potential energy both for neutral and protonated conformers (Fig. 2). From Table 1 it results that the rotation of the $N_3C_4C_6C_7$ dihedral gives AM1 neutral conformers with energies between 0 and 18 kcal/mol higher than the energy of the AM1 neutral global minimum conformer, while the rotation of the $C_4C_6C_7C_8$ dihedral gives AM1 neutral conformers with energies between 0 and 63 kcal/mol higher than the energy of the AM1 neutral global minimum conformer. The differences between the energy the two maxima and the one of the global minimum are 5.7 and 18 kcal/mol for the imidazole ring rotation, and 63.1 and 57.2 kcal/mol for the 2,3-dimethlphenyl ring rotation. Thus in AM1 neutral conformers the imidazole ring can rotate much easier than the 2,3-dimethylphenyl ring.

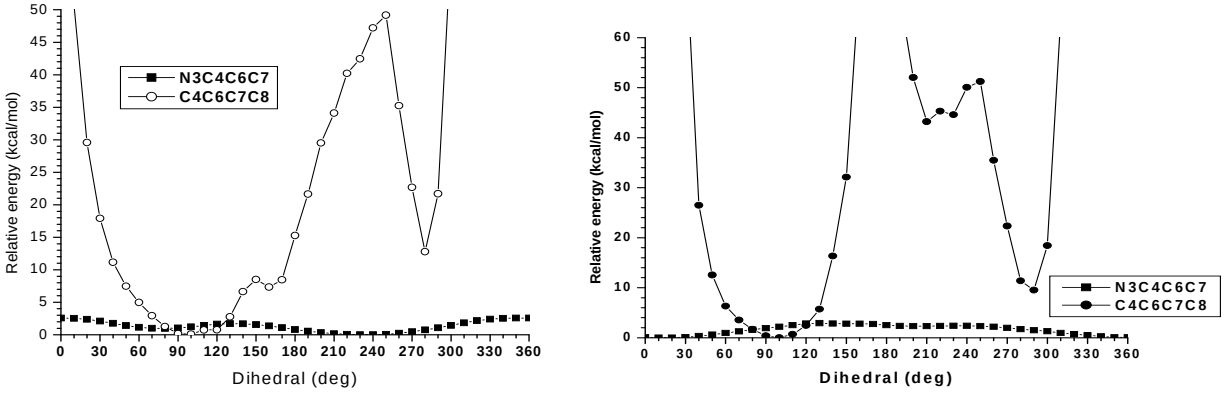
In protonated Dex the rotation of the $N_3C_4C_6C_7$ dihedral gives AM1 protonated conformers with energies between 0 and 3.5 kcal/mol higher than the energy of the AM1 protonated global minimum conformer, while the rotation of the $C_4C_6C_7C_8$ dihedral gives AM1 protonated conformers with energies between 0 and 1177 kcal/mol higher than the energy of the AM1 protonated global minimum conformer. The differences between energies of the two maxima and the one of the global minimum are 2.5 and 3.5 kcal/mol for the imidazole ring rotation and 148.8 and 1177.2 kcal/mol for the 2,3-dimethlphenyl ring rotation. These data show that the rotation of the imidazole ring in AM1 protonated conformers is easier than in AM1 neutral conformers, while rotation of the 2,3-dimethylphenyl ring is easier in AM1 neutral conformers than in protonated ones.

Relative energies and dihedral values for minimum and maximum points are summarized in Table 1.



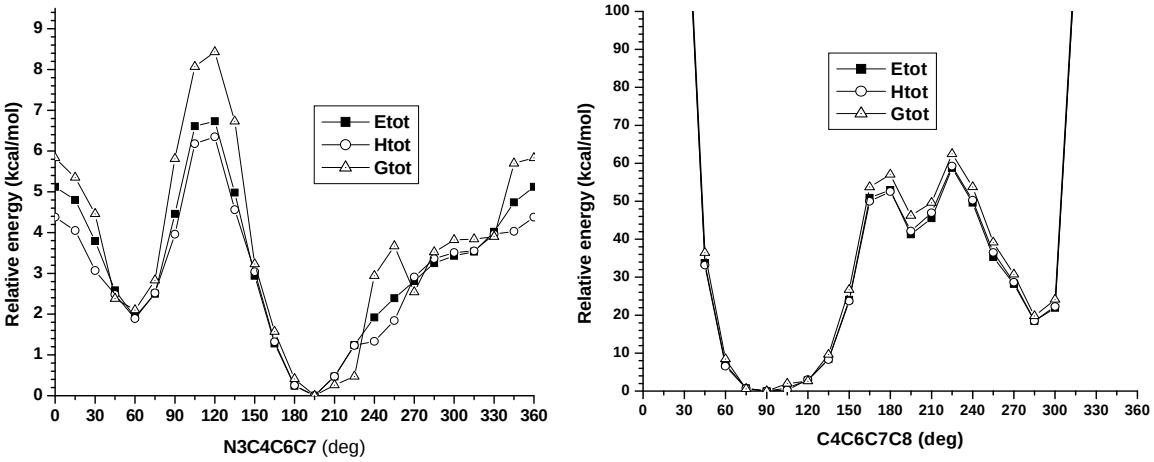
(a) (b)

Fig. 2 – 1D profile of the AM1 relative potential energy of the (a) neutral and (b) protonated Dex obtained through the rotation with steps of 10º of the two flexible bonds of Dex.



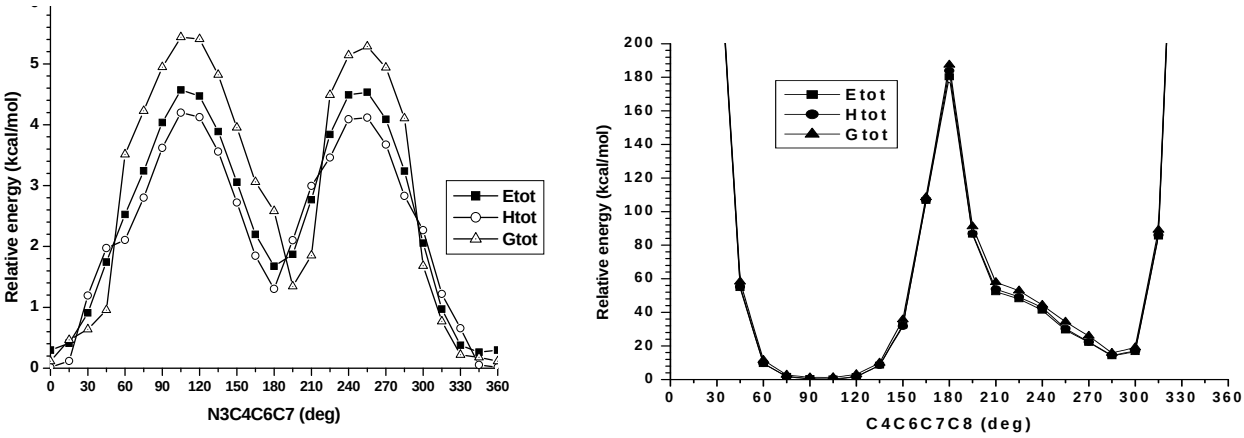
(a) (b)

Fig. 3 – 1D profile of the PM3 relative potential energy of the (a) neutral and (b) protonated Dex obtained through the rotation with steps of 10º of the two flexible bonds of Dex.



(a) (b)

Fig. 4 – 1D profile of the HF/6-31G** relative energy of neutral Dex conformers obtained through the rotation with steps of 15º of dihedrals: (a) $N_3C_4C_6C_7$ and (b) $C_4C_6C_7C_8$.



(a) (b)

Fig. 5 – 1D profile of the HF/6-31G** relative energy of the protonated Dex conformers obtained through the rotation with steps of 15º of dihedrals: (a) $N_3C_4C_6C_7$ and (b) $C_4C_6C_7C_8$.

Table 1

Dihedral (deg) and relative energy (ΔE) values for minimum and maximum points of neutral and protonated Dex conformers obtained through rotation of the $N_3C_4C_6C_7$ and $C_4C_6C_7C_8$ dihedrals

Method	Ionization form	Dihedral name	Minimum (deg)	Minimum ΔE	Maximum (deg)	Maximum ΔE
		N3C4C6C7	100	0.00	20	5.73
	Neutral		280	0.93	210	18.01
	(a)	C4C6C7C8	140	0.02	20	63.09
AM1			300	11.08	240	57.19
		N3C4C6C7	0	0.03	150	2.54
	Protonated		180	2.35	230	3.50
	(b)	C4C6C7C8	110	0.02	0	1177.19
			290	15.21	180	148.76
		N3C4C6C7	80	0.98	130	1.72
	Neutral		240	0.01	350	2.57
	(a)	C4C6C7C8	100	0.10	250	49.18
			160	7.33	150	8.51
PM3			280	12.78	330	279.50
		N3C4C6C7	20	0.01	130	2.91
	Protonated		200	2.33	240	2.39
	(b)	C4C6C7C8	100	0.01	170	120.36
			210	43.20	250	51.23
			290	9.52	350	1263.24
		N3C4C6C7	60	1.93	0	5.12
	Neutral		195	0.00	120	6.73
	(a)	C4C6C7C8	90	0.00	0	760.89
			195	41.25	180	52.96
6-31G**			285	18.46	225	58.78
		N3C4C6C7	180	1.41	105	4.31
	Protonated		345	0.00	255	4.27
	(b)	C4C6C7C8	105	0.076	0	2364.26
			285	13.82	180	180.04

ΔE (in kcal/mol) is the difference between the energy of each point and the energy of the global minimum; its values for the neutral and protonated Dex conformers are: AM1 neutral -3226.45, and protonated -3140.57; PM3 neutral -3251.92, and protonated -3163.75; HF/6-31G** neutral -383113.64; and protonated -383363.88; the correlation energy from single point MP2/6-31G** calculations decreases the conformer energy with -2.1696 u.a. or -1361.45 kcal/mol, but the relative energies remain those from HF/6-31G** calculations.

Rotation of the $N_3C_4C_6C_7$ dihedral in neutral Dex gives PM3 conformers with energies between 0 and 2.6 kcal/mol higher than the energy of the PM3 neutral global minimum conformer. On the 1D potential energy profile resulted through the rotation of the $C_4C_6C_7C_8$ dihedral there are three minima (0.1, 7.33, 12.78 kcal/mol) and three maxima (49.2, 8.5, 279.5 kcal/mol). This rotation gives PM3 neutral conformers with energies between 0 and 280 kcal/mol higher than the energy of the PM3 global minimum of neutral Dex. Thus for the imidazole ring rotation in neutral Dex the differences between PM3 energies of the two maxima and the one of the global minimum are 1.7, and 2.6 kcal/mol, while for the 2,3-dimethlphenyl ring rotation the PM3 differences between energies of the three maxima and the one of the global minimum are 49.2, 8.5, and 279.5 kcal/mol respectively. These data also show an easier rotation of the imidazole ring in PM3 neutral conformers than the one of the 2,3-dimethylphenyl ring.

Rotation of the $N_3C_4C_6C_7$ dihedral gives PM3 protonated conformers with energies between 0 and 2.9 kcal/mol higher than the energy of the PM3 protonated global minimum. Although the 1D profiles for the $C_4C_6C_7C_8$ dihedral rotation in PM3 protonated conformers does not resembles with the one of PM3 neutral conformers, both profiles have three minima and three maxima. When the $C_4C_6C_7C_8$ dihedral is rotated the obtained PM3 protonated conformers have energies with 0 up to 1263 kcal/mol higher than the energy of the PM3 global minimum of protonated Dex. Thus for the imidazole ring rotation in protonated Dex the differences between PM3 energies of the two maxima and the one of the global minimum are 2.4, and 2.9 kcal/mol, while for the 2,3-dimethlphenyl ring rotation the PM3 differences between energies of the three maxima and the one of the global minimum are 120.4, 51.2, and 1263.2 kcal/mol respectively. Thus the PM3 results show that the rotation of the imidazole ring is equally easy both for the PM3 neutral and protonated conformers, while the rotation of the 2,3-dimethylphenyl ring is more difficult for the PM3 protonated conformers in comparison with neutral ones.

In Fig. 4 1D profile of HF/6-31G** total energy, Etot, of neutral Dex conformers is plotted along with 1D profiles of total enthalpy, Htot (calculated as sum of total internal energy (SCFE+ZPVE+U) and pV), and total Gibbs free energy, Gtot, calculated as Htot-TS, where T is 298 K and S is entropy in cal/mol.

From Fig. 4 (a) and (b) it can be seen that the rotation of the $N_3C_4C_6C_7$ dihedral give similar shapes for Etot and Htot 1D profiles, but Gtot has an additional maximum of 3.67 kcal/mol at a value of 255º of the $N_3C_4C_6C_7$ dihedral, and a very close minimum of 2.54 kcal/mol at a value of 270º of the $N_3C_4C_6C_7$ dihedral. Rotation of the $N_3C_4C_6C_7$ dihedral (Fig 4 (a)) gives HF/6-31G** neutral conformers with total energy minima between 0 and 1.93 kcal/mol and maxima between 5.12 and 6.73 kcal/mol higher than the HF/6-31G** energy of the neutral global minimum, while rotation of the $C_4C_6C_7C_8$ dihedral (Fig. 4 (b)) gives HF/6-31G** neutral conformers with Etot minima between 0 and 41.25 kcal/mol and maxima between 53 and 761 kcal/mol higher than the HF/6-31G** energy of the neutral global minimum. Rotation of the $C_4C_6C_7C_8$ dihedral has three minima (0, 18.5, 41.3 kcal/mol) and three maxima (53.0, 58.8, 761.0 kcal/mol). The shapes of 1D profiles of Etot, Htot and Gtot are similar for the rotation of this dihedral. 1D profile of Etot resembles with the 1D profile of the PM3 protonatd Dex obtained through rotation of the $C_4C_6C_7C_8$ dihedral. Thus for the imidazole ring rotation in neutral Dex the differences between HF/6-31G** total energies of the two maxima and the one of the global minimum are 5.1, and 6.7 kcal/mol, while for the 2,3-dimethlphenyl ring rotation the HF/6-31G** differences between energies of the three maxima and the one of the global minimum are 58.8, 53.0, and 760.9 kcal/mol respectively.

The 1D profile of the HF/6-31G** Etot obtained through rotation of the $N_3C_4C_6C_7$ dihedral in protonated Dex is almost symmetrical. This rotation gives HF/6-31G** protonated conformers with Etot minima between 0 and 1.41 kcal/mol higher than the total energy of the HF/6-31G** protonated global minimum. The maxima are also low, their Etot values being around 4.3 kcal/mol above the Etot value of the HF/6-31G** protonated global minimum, while the rotation of the $C_4C_6C_7C_8$ dihedral gives HF/6-31G** protonated conformers with Etot minima between 0 and 13.8 kcal/mol higher than the total energy of the HF/6-31G** protonated global minimum. The shape of 1D profile of HF/6-31G** Etot obtained through rotation of the $C_4C_6C_7C_8$ dihedral in protonated global minimum conformer resembles well with the 1D profile of the AM1 potential energy of the protonated Dex obtained through the rotation with steps of 10º of the $C_4C_6C_7C_8$ dihedral. The maxima resulted from the rotation of the $C_4C_6C_7C_8$ dihedral are very high, having Etot values between 180 and 2364 kcal/mol above the Etot of the HF/6-31G** protonated global minimum. Thus for the imidazole ring rotation in protonated Dex the differences between HF/6-31G** energies of the two maxima and the one of the global minimum are both of 4.3 kcal/mol, while for the 2,3-dimethlphenyl ring rotation the HF/6-31G** differences are 180.0, and 2364.3 kcal/mol respectively. Again the rotation of the imidazole ring is much easier than the one of the 2,3-dimetyl ring both for the HF/6-31G** neutral and protonated Dex conformers.

From HF/6-31G** calculations resulted six optimized neutral conformers, five in fundamental states and one in a transition state. Total energy, values of $N_3C_4C_6C_7$ and $C_4C_6C_7C_8$ dihedrals, the values of the lowest vibrational frequency for global minimum (GM) and transition state (TS) conformers and the energy difference (ΔE) between the Etot of the TS and GM conformers are presented in Table 2.

Table 2

Values of Etot, dihedrals, and lowest vibration frequency in neutral HF/6-31G** GM and TS conformers

	Etot	N3C4C6C7	C4C6C7C8	v_0 (cm^{-1})	ΔE
GM	-383113.64	191.979	86.63	32.67	
TS	-383108.95	1.75	88.16	-52.51	4.7

Inspecting Table 2 one can notice that the $C_4C_6C_7C_8$ dihedral values in GM and TS conformers are very close, while the values of the $N_3C_4C_6C_7$ are very different. In Fig. 6 one can see the perfect superposition of the two conformers except the imidazole rings.

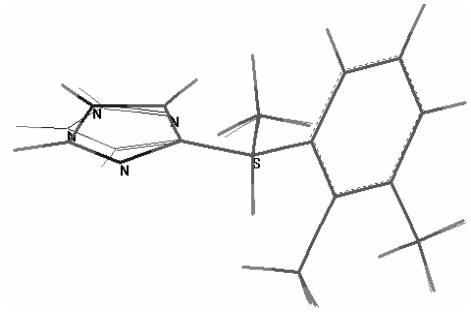


Fig. 6 – Superposition of the global minimum of neutral Dex (thick bonds) and a transition state conformer, both optimized at HF/6-31G** level.

The difference, ΔE, between the total energy of TS and GM conformers is 4.7 kcal/mol. Because *ab initio* HF methods generally overestimate the barrier to rotation values, the obtained value of the rotation barrier for the imidazole ring in neutral Dex could be less than 4.7 kcal/mol. Unfortunately, no one optimized Dex neutral conformer has values of the $N_3C_4C_6C_7$ dihedral close to the one from GM conformer and for this reason an energy barrier to rotation of the 2,3-dimethylphenyl ring could not be estimated.

Also in case of protonated Dex, no transition state conformer has values of the $N_3C_4C_6C_7$ or $C_4C_6C_7C_8$ dihedral close to the value of the corresponding dihedral from the global minimum conformer and therefore the estimation of rotation barriers to the rotation of imidazole and/or 2,3-dimethylphenyl rings in HF/6-31G** protonated conformers was not possible.

Semiempirical and *ab initio*/HF methods give similar results regarding the rotation of imidazole and 2,3-dimethylphenyl rings. The easy rotation of the imidazole ring is of great importance for the interaction between the key residue D3.32 (from the α_2 adrenergic receptor LBD) and the H_{16} atom attached to N1 nitrogen atom, or the N3 nitrogen atom from the imidazole ring in neutral Dex conformers. Other possible interaction of protonated Dex conformers implies the proton H^+_{32} attached to N3 nitrogen atom from the protonated imidazole ring. Easier imidazole rotation means better interaction with the target protein and thus better potency.

CONCLUSIONS

Conformational changes in 1D profiles of potential/total energy resulted through the rotation of imidazole and 2,3-dimethylphenyl rings of neutral and protonated Dex were studied by using semiempirical, and *ab initio*/HF calculations.

For neutral Dex the AM1 method gives 1D profiles with differences between energies of the two maxima and the one of the global minimum of 5.7 and 18 kcal for the imidazole ring rotation and 57.2 and 63.1 kcal/mol for the 2,3-dimethlphenyl ring rotation, while for protonated Dex the AM1 method gives 1D profiles with differences between energies of the two maxima and the one of the global minimum of 2.5 and 3.5 kcal/mol for the imidazole ring rotation and 148.8 and 1177.2 kcal/mol for the 2,3-dimethlphenyl ring rotation. Thus the AM1 method allows an easier rotation of the imidazole ring either in AM1 neutral or AM1 protonated conformers than the one of the 2,3-dimethylphenyl ring. The rotation of the imidazole ring in AM1 protonated conformers is easier than in AM1 neutral conformers, while the rotation of the 2,3-dimethylphenyl ring is easier in AM1 neutral conformers than in protonated ones.

For neutral Dex the PM3 method gives 1D profiles with two minima and two maxima for the rotation of the C4-C6 bond (corresponding to imidazole ring rotation), and three minima and three maxima for the rotation of the C6-C7 bond (corresponding to 2,3-dimethylphenyl ring rotation). The differences between energies of the two maxima and the one of the global minimum are 1.7 and 2.6 kcal/mol for the imidazole ring rotation and 49.2, 8.51, and 279.5 kcal/mol for the 2,3-dimethlphenyl

ring rotation. The same number of minima and maxima are obtained from 1D profiles of protonated Dex. For the imidazole ring rotation in protonated Dex the differences between PM3 energies of the two maxima and the one of the global minimum are 2.4, and 2.9 kcal/mol, while for the 2,3-dimethlphenyl ring rotation the PM3 differences between energies of the three maxima and the one of the global minimum are 120.4, 51.2, and 1263.2 kcal/mol respectively. Thus PM3 method allows almost the same easy rotation of the imidazole ring in PM3 neutral or protonated conformers, while the rotation of the 2,3-dimethylphenyl ring is more difficult in PM3 protonated conformers than the one in neutral conformers.

For neutral Dex the HF/6-31G** method gives 1D profiles similar to those obtained for the PM3 protonated conformers, while for protonated Dex the HF/6-31G** method gives 1D profiles similar to those obtained for the AM1 protonated conformers. The imidazole rotation needs between 5.1 and 6.7 kcal/mol in neutral conformers, while in protonated conformers needs around 4.3 kcal/mol. The rotation of 2,3-dimethylphenyl ring is much more difficult, needing around 60 up to 760 kcal/mol in neutral conformers and 180 up to 2364 kcal/mol in protonated conformers.

A rotation barrier of 4.7 kcal/mol was estimated for the rotation of the imidazole ring in HF/6-31G** neutral conformers of Dex.

All methods used in this work lead to similar conclusions regarding the easy imidazole rotation, and its implication in the Dex potency.

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