Asian Journal of Chemistry Vol. 20, No. 5 (2008), 3331-3340

DFT Studies of the Molecluar Structure and Conformational Process of Tricyclic Antidepressants

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Trimipramine, imipramine, amitriptyline, desipramine and doxepine were subjected to *ab initio* (HF/6-31G(d)) and DFT ((b3lyp/6-31G(d) and (b3lyp/6-311+G(d)) computation. Molecular geometries and the activation energies for ring inversions were determined with full geometry optimizations. Results obtained reveals that the changes of side-chain conformation, the angle value between two phenyl rings and the type of N-amine on side-chain can be affected on drug activity.

Key Words: Tricyclic antidepressants, DFT calculation, Drug activity.

INTRODUCTION

The major schological drugs were discovered[1] in 1950s . Two types of these drugs are antipsychotic and antidepressant drugs. Chloropromazine is one of the most important antipsychotic compounds, which is derived from phenothiazine[2-6]. The successful performance of chloropromazine is caused the synthesis of another type of compounds with cyclic skeleton, which is expected to be used as antipsychotic characteristic in comparison with chloropromazine derivatives. But the result of experiments reveals that they are impressed a little effect in control of imaginations and they can be used as ideal antidepressant agent. These compounds are dibenzaphine derivatives[7-9]. Todays there are many synthesized psycho-therapy drugs that are similar to these compounds. For example whereas phenothiazine and thioxanthene compounds which have antipsychotic and nuroleptic activities but the derivaties of dibenzapine and dicycloheptadiene compounds are used as antidepressant and thymoleptic agents[10-12]. Also trimipramine (**1**), imipramine (**2**), amitriptyline (**3**), desipramine (**4**) and doxepine (**5**) are some antidepressant drugs which have been prepared by several methods[13-18]. As can be seen from **Scheme-I**, these antidepressant drugs have a seven member ring in the center which was surrounded by two aromatic rings. Different substituents which are joined to this ring affected on the drug activities and properties of these compounds and demonstrated

the relationships between structures and activities[19]. In this study we investigated the molecular structure of these compounds by using the *ab initio* and density functional theory methods. These calculations were done at HF/6-31G (d), b3lyp/6-31G (d) and b3lyp/6-311+G (d) level of theory. In addition, the energy barrier of inversion in seven member ring for these compounds was calculated and the relationship between their structures and drug activities were investigated.

CALCULATIONS

All calculations on trimipramine, imipramine, amitriptyline, desipramine and doxepine compounds were performed by using the Gaussian 2003 program pakage[20]. The global minima geometry of all compounds was fully optimized by using the Hartree-Fock (HF) method with the 6-31G(d) basis set and Beck's three-parameter hybrid method (B3LYP) with the 6-31G(d) and 6-311+G(d) basis sets. The nature of optimized geometries for global minima at the HF level has been checked with frequency calculations. In order to calculate the ring inversion energy barrier for global minima geometry, the geometry of transition state was also optimized.

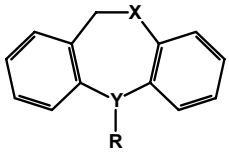
RESULTS AND DISCUSSION

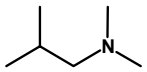
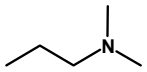
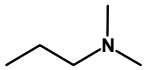
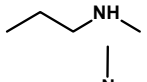
Since higher levels of theory are more reliable, therefore the majority of the discussion will be focused on the results which are obtained at the DFT level.

Molecular geometry of the stable structures: The geometrical parameters of trimipramine, imipramine, amitriptyline, desipramine and doxepine (**1-5**) were calculated with 6-31G(d) and 6-311+G(d) basis set and presented in Tables 1-3. The results of calculations were shown that the stable conformers for these compounds have similar geometries but their bond angles and dihedral angles could be change due to the effect of different factors. These substituents share a basic chemical structure comprising a three-ring core and an alkylamine side chain (**Scheme-I**).

The conformation of side chain conformation seems to be responsible for their various biological activities and linkage of nitrogen atom by a three-carbon atom chain to ring center, plays an important role in medicinal chemistry[21]. Due to the importance of side-chain, we first investigated the bond length, bond angle and dihedral angle of these compounds which was affected by the side-chain.

The present calculation results reveals that the distance of N-side chain to the center ring (r_8, r_9) is 4.91 and 5.62 Å, respectively in desipramine, which is shorter than another compounds (Table-1). This means that the side-chain is twised toward rings in desipramine, whereas in other compounds the values of r_8 and r_9 are larger and the side-chain is oriented along the



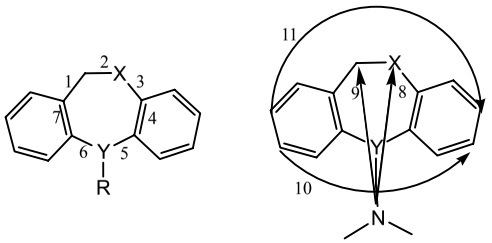
No.	X	Y	R	Ec_{50} mg/μL [Ref. 22]
1	CH_2	N		0.090
2	CH_2	N		0.030
3	CH_2	CH		0.025
4	CH_2	N		0.012
5	O	CH		0.030

Scheme-I

rings. The calculated dihedral angles show that the values of ϕ_2 and ϕ_3 in desiperamine are lower than other compounds and the values of ϕ_5 and ϕ_6 are increased in this compound, which is the result of direction of side-chain toward aromatic ring (Table-3).

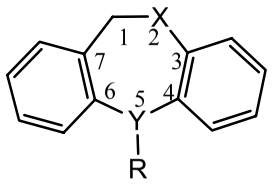
The compounds which contain the side-chain with secondary amine have more antidepressant activity than the tertiary analogues. Imipramine has tertiary amine side chain which is exhibited relativity lower activity than desipramine with secondary amine side chain. The change of dihedral angles (ϕ) and bond angles (θ) values confirmed this subject. The values of θ_1, θ_2 and θ_3 in desipramine were larger than imipramine, whereas other bond angles of the center ring in imipramine is increased (Table-2). The values of θ_9-θ_{12} in side chain of desipramine increased in comparison imipramine. Also the values of dihedral angles of ϕ_5 and ϕ_6 increased in desipramine and the dihedral angle ϕ_2 decreased in this compound. Furthermore ϕ_{11}-ϕ_{14} angles in desipramine were less than imipramine. The sign of the ϕ_8 and ϕ_9 angles in desipramine are opposite to imipramine, which shows the differences in side chain directions in these compounds. Also, the presence of substitute on side chain can be affected on the value of tortional and bond angles. Whereas in trimipramine a methyl group exist on side chain, in imipramine this group is omitted. It was also observed, the changes of angles is related to the structure of side chain. Therefore the bond angles of central ring, specially the θ_5 value, decreased in trimipramine. As can be seen in Table-2, the bond angles of side chain (θ_8, θ_{10} and θ_{11}) are decreased

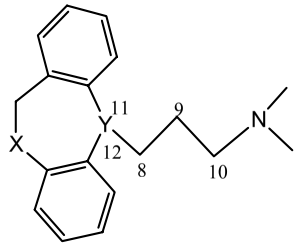
TABLE-1
OPTIMIZED BOND LENGTHS FOR THE STABLE CONFORMERS OF COMPOUNDS **1-5** OBTAINED AT THREE LEVELS OF THEORY



Levels	X	Y	R	r_1	r_2	r_3	r_4	r_5	r_6	r_7	r_8	r_9	r_{10}	r_{11}
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	1.508	1.530	1.524	1.398	1.423	1.430	1.395	7.06	7.53	6.60	7.29
	CH_2	N	$(CH_2)_3N(CH_3)_2$	1.508	1.529	1.522	1.397	1.428	1.428	1.394	7.51	6.95	6.76	7.42
HF/6-31G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	1.509	1.532	1.526	1.339	1.502	1.497	1.395	7.77	6.88	6.74	7.34
	CH_2	N	$(CH_2)_3NH(CH_3)$	1.506	1.530	1.525	1.401	1.426	1.427	1.394	5.56	4.91	6.50	7.17
	O	CH	$CH(CH_2)_2N(CH_3)_2$	1.506	1.408	1.354	1.398	1.501	1.496	1.394	7.75	7.00	6.83	7.30
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	1.508	1.537	1.524	1.414	1.437	1.438	1.407	7.58	7.10	6.73	7.39
	CH_2	N	$(CH_2)_3N(CH_3)_2$	1.506	1.537	1.522	1.414	1.429	1.434	1.406	7.53	7.03	6.92	7.55
B3LYP/6-31G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	1.509	1.538	1.526	1.414	1.499	1.495	1.408	7.86	6.98	6.85	7.44
	CH_2	N	$(CH_2)_3NH(CH_3)$	1.504	1.536	1.525	1.417	1.430	1.432	1.406	5.61	4.91	6.69	7.34
	O	CH	$CH(CH_2)_2N(CH_3)_2$	1.504	1.432	1.369	1.416	1.497	1.493	1.407	7.85	7.08	6.90	7.37
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	1.506	1.536	1.528	1.411	1.436	1.437	1.404	7.58	7.09	6.71	7.38
	CH_2	N	$(CH_2)_3N(CH_3)_2$	1.505	1.535	1.521	1.412	1.427	1.433	1.404	7.47	6.98	6.91	7.54
B3LYP/6-311+G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	1.508	1.536	1.525	1.411	1.497	1.494	1.405	7.83	6.93	6.81	7.41
	CH_2	N	$(CH_2)_3NH(CH_3)$	1.503	1.434	1.524	1.415	1.429	1.431	1.404	5.62	4.92	6.50	7.17
	O	CH	$CH(CH_2)_2N(CH_3)_2$	1.503	1.435	1.368	1.413	1.497	1.493	1.404	7.82	7.04	6.87	7.34

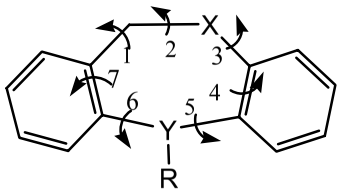
TABLE-2
OPTIMIZED BOND ANGLES FOR THE STABLE CONFORMERS OF COMPOUNDS **1-5** OBTAINED AT THREE LEVELS OF THEORY

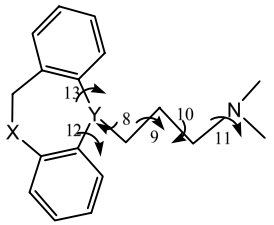




Levels	X	Y	R	θ_1	θ_2	θ_3	θ_4	θ_5	θ_6	θ_7	θ_8	θ_9	θ_{10}	θ_{11}	θ_{12}
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	111.666	118.417	126.560	124.761	116.436	121.075	119.406	118.126	111.672	114.316	118.261	116.272
HF/6-	CH_2	N	$(CH_2)_3N(CH_3)_2$	111.716	117.646	126.308	125.328	119.208	121.229	119.345	114.577	113.459	113.554	116.393	117.209
31G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	112.582	118.701	126.228	123.691	116.660	118.884	118.853	128.024	111.547	113.355	123.221	120.117
	CH_2	N	$(CH_2)_3NH(CH_3)$	112.229	118.352	126.408	121.517	115.544	117.720	118.512	114.064	116.901	116.407	117.626	117.529
	O	CH	$CH(CH_2)2N(CH_3)_2$	112.262	122.197	126.376	124.336	116.121	118.187	118.166	128.278	111.593	113.318	123.529	120.347
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	110.979	118.036	126.237	124.910	117.492	121.181	119.045	118.339	111.384	114.390	117.788	116.202
B3LYP/6-	CH_2	N	$(CH_2)_3N(CH_3)_2$	111.036	116.968	125.893	125.434	121.078	121.336	119.054	115.133	113.427	113.665	115.646	117.629
31G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	112.364	118.462	125.978	124.297	117.689	119.348	118.814	127.873	111.849	113.447	122.486	119.809
	CH_2	N	$(CH_2)_3NH(CH_3)$	112.124	117.940	126.445	122.654	117.654	118.553	118.686	113.873	116.739	117.198	117.129	117.538
	O	CH	$CH(CH_2)_2N(CH_3)_2$	112.421	120.428	126.676	124.998	116.842	118.704	117.977	128.082	111.959	113.404	122.937	120.206
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	111.097	118.126	126.225	124.855	117.385	121.144	119.017	118.485	111.496	114.392	117.905	116.239
B3LYP/6-	CH_2	N	$(CH_2)_3N(CH_3)_2$	111.160	117.026	125.906	125.387	121.233	121.280	119.062	115.286	113.674	113.599	115.956	117.898
311+G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	112.491	118.627	125.992	124.098	117.328	119.222	118.789	127.819	112.019	113.465	122.558	120.107
	CH_2	N	$(CH_2)_3NH(CH_3)$	112.058	117.885	126.371	122.703	117.853	118.687	118.642	113.955	116.647	117.008	117.141	117.627
	O	CH	$CH(CH_2)_2N(CH_3)_2$	112.397	120.665	126.681	124.798	116.563	118.606	117.995	128.070	112.085	113.420	122.882	120.438

TABLE-3
OPTIMIZED TORSIONAL ANGLES FOR THE STABLE CONFORMERS OF COMPOUNDS **1-5** OBTAINED AT THREE LEVELS OF THEORY





Levels	X	Y	R	ϕ_1	ϕ_2	ϕ_3	ϕ_4	ϕ_5	ϕ_6	ϕ_7	ϕ_8	ϕ_9	ϕ_{10}	ϕ_{11}	ϕ_{12}	ϕ_{13}
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	65.968	61.461	10.510	-1.746	50.302	-69.726	5.208	82.873	54.756	-175.567	163.213	-105.253	83.295
HF/6-	CH_2	N	$(CH_2)_3N(CH_3)_2$	66.148	-65.231	14.568	-0.494	45.342	-66.193	5.020	69.926	65.595	-171.549	166.388	-95.479	75.549
31G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	70.832	-62.599	7.218	0.095	50.828	-67.750	0.911	-0.489	118.897	-178.299	162.056	-68.519	51.087
	CH_2	N	$(CH_2)_3NH(CH_3)$	69.109	-56.864	2.756	-1.258	59.470	-75.423	1.719	-57.423	-63.673	-61.774	97.108	-41.446	25.077
	O	CH	$CH(CH_2)_2N(CH_3)_2$	71.575	-68.111	12.05	0.379	46.246	-61.442	0.656	0.356	118.246	-177.619	162.506	-63.297	47.788
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	66.079	-65.292	13.101	0.263	46.202	-68.957	6.808	80.694	53.873	-176.351	164.799	-102.765	78.178
B3LYP/6-	CH_2	N	$(CH_2)_3N(CH_3)_2$	66.168	-69.690	17.515	2.105	39.556	-64.028	6.298	69.584	64.649	-168.669	168.471	-88.847	66.708
31G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	70.626	-64.835	9.490	0.767	47.852	-66.122	1.429	-0.728	120.040	-177.834	164.626	-65.150	47.014
	CH_2	N	$(CH_2)_3NH(CH_3)$	69.504	-60.526	6.563	-0.53	54.445	-71.637	1.601	-55.324	-62.069	-61.907	92.479	-39.183	22.240
	O	CH	$CH(CH_2)_2N(CH_3)_2$	72.713	-69.001	11.796	2.255	43.517	-59.893	0.138	-0.104	118.515	-177.326	164.963	-59.821	44.115
	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	66.018	-64.974	12.747	0.199	46.562	-69.175	6.801	80.376	54.286	-176.378	164.312	-103.061	78.419
B3LYP/6-	CH_2	N	$(CH_2)_3N(CH_3)_2$	66.374	-69.296	16.811	2.584	39.468	-63.790	5.852	68.257	63.460	-163.996	169.549	-87.125	64.843
311+G(d)	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	70.479	-63.942	8.448	0.826	48.763	-66.895	1.522	-0.779	120.393	-177.352	164.148	-66.463	48.576
	CH_2	N	$(CH_2)_3NH(CH_3)$	69.464	-61.366	7.715	-1.005	54.068	-71.343	1.802	-55.056	-62.525	-62.086	93.651	-39.497	22.309
	O	CH	$CH(CH_2)_2N(CH_3)_2$	72.382	-68.435	11.298	2.067	44.366	-60.766	0.462	-0.105	119.524	-176.719	164.514	-61.383	45.572

in imipramine relative to trimipramine. The dihedral angles ϕ_1-ϕ_4 in imipramine is increased, whereas the ϕ_5-ϕ_7, ϕ_8, ϕ_{10}, ϕ_{12} and ϕ_{13} are decreased relative to trimipramine.

The changes in bond length, bond angles and torsional angles in the center ring of these compounds can be affected on their drug activities. We found a correlation between drug activity and bond length in these compounds. This correlation exists between r_4 and Ec_{50} (effective drug concentration), therefore the value of r_4 in desipramine (with high drug activity) was higher than other investigated compounds.

According to the present calculations, the value of θ_1 in trimiprame (with the lowest drug activity) is decreased and the θ_4 angle of this compound is increased relative to other compounds. In the other hand the value of θ_4 in desipramine is lower than other compounds.

The most correlation between torsional angles and drug activity was related to ϕ_2 (R = -0.954). As can be seen in Table-3, the value of ϕ_2 in desipramine was lower than the other compounds. On the other hand, the direction of side chain in respect to one aromatic ring can be affected on the value of dihedral angles, as in desipramine which the side-chain twisted toward the aromatic rings two dihedral angles ϕ_2 and ϕ_3 were decreased and ϕ_5 and ϕ_6 were increased in comparison with other investigated compounds. There are also two additional steric parameters which were affected on the tricyclic structure of these compounds. One important steric parameter which affected on the structure and drug activity is the angle between two planes of aromatic rings which is named angle of flexure (β)[23] (Table-4). As this angle became lower, the molecule was more bent and thymoleptic characteristic was increased. As two aromatic rings became closer, the values of r_{10} and r_{11} which indicate the distances between two aromatic rings, were decreases (Table-1). The results of calculation in the present study shows that in desiperamine which has the highest antidepressant activity the values of r_{10} and r_{11} are lower than other compounds, while in imipiramin which has mainly neuroleptic activity the values of r_{10} and r_{11} are higher than other compounds.

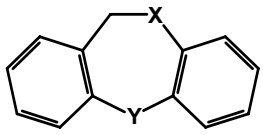
Another parameter that can be affected on drug activity is the torsional angle (γ). This angle shows the value of torsion of two aromatic rings to gather of them. As can be seen from Table-4, the angle of torsion in desipramine is decreased, whereas trimipramine has higher value than the other compounds. Therefore, when the amount of γ is decreased, the antidepressant activity is increased.

Energetics of ring inversion: The barrier of ring inversion is studied in the case of compounds without side chain. One structural features of these compounds in association of the saturated ring which fused to benzene ring. This ring can not be considered as cycloheptane or its heterocyclic

TABLE-4
OPTIMIZED ANGLES OF FLEXURE AND TORSION FOR THE STABLE CONFORMERS OF COMPOUNDS **1-5** OBTAINED AT THREE LEVELS OF THEORY

Level	X	Y	R	β	γ
HF/6-31G(d)	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	29.06	18.59
	CH_2	N	$(CH_2)_3N(CH_3)_2$	29.01	18.01
	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	29.36	15.38
	CH_2	N	$(CH_2)_3NH(CH_3)$	30.73	14.31
	O	CH	$CH(CH_2)_2N(CH_3)_2$	29.70	14.57
B3LYP/6-31G(d)	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	29.05	19.25
	CH_2	N	$(CH_2)_3N(CH_3)_2$	29.02	20.94
	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	29.32	16.46
	CH_2	N	$(CH_2)_3NH(CH_3)$	30.41	15.37
	O	CH	$CH(CH_2)_2N(CH_3)_2$	29.64	15.48
B3LYP/6-311+G(d)	CH_2	N	$CH_2CH(CH_3)CH_2N(CH_3)_2$	29.04	19.31
	CH_2	N	$(CH_2)_3N(CH_3)_2$	29.02	19.09
	CH_2	CH	$CH(CH_2)_2N(CH_3)_2$	29.35	16.33
	CH_2	N	$(CH_2)_3NH(CH_3)$	30.34	15.43
	O	CH	$CH(CH_2)_2N(CH_3)_2$	29.66	15.48

analogues in a boat conformation because it has two carbon-carbon double bond. The so-called 'twist-boat' conformation has been considered to be the most likely structure. This ring is expected to exist in two interconvertible enantiomeric forms with a boat transition state. Therefore, we investigated the ring inversion in compounds of **6**, **7** and **8** in **Scheme-II**. These structures are optimized at RHF/6-31G (d), the results of calculation reveals that the most stable conformation for these compounds is twist-boat conformation.



No.	X	Y
6	CH_2	NH
7	CH_2	CH_2
8	O	CH_2

Scheme-II

The degenerate interconversion of twist-boat with its mirror image takes place *via* the boat transition state (Fig. 1). The calculated strain energy barrier for this process in compounds **6-8** are 56.4, 13.7 and 13.1 kJ mol^{-1}, respectively. The calculated strain energy barrier for compounds **7** and **8** are almost equal and it is not expected to be observed by dynamic NMR experiments even at -180 °C.

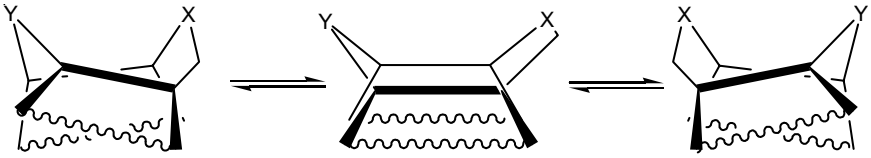


Fig. 1. Ring inversion in compounds **6-8**

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(*Received*: 12 February 2007; *Accepted*: 28 January 2008) AJC-6257