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A comparative theoretical investigation on the hydride transfer process of trans and gauche conformers of phenylethylamine and norepinephrine with lumiflavin

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The deamination of phenylethylamine (PEA) and norepinephrine (NOR) to corresponding aldehyde and ammonia by the enzyme human monoamine oxidase is one of the most important concerns in neurobiochemistry due to its involvement in several neurological diseases and complications. In this work concerted hydride transfer mechanism for trans and gauche conformers of PEA/NOR have been investigated by density functional theory (DFT) methods using B3LYP/DFT-D3 and MP2 functional with standard split valance basis set 6-31g. This computational work provides the first evidence that could support the easier feasibility of deamination of gauche conformer of hMAO substrates over trans-substrate. The results provide some interesting energetic insights on the direct hydride transfer mechanism; the activation energy barrier for trans and gauche PEA/NOR are compared, in which gauche conformation is always preferred over trans conformers which thus suggesting that the deamination of monoamine neurotransmitters are highly dependent on the conformational preference of substrate molecules which may be useful in conformation based drug/inhibitor design for human monoamine oxidase.

Keywords: Density functional theory, neurotransmitter, hydride transfer mechanism, structural conformation, lumiflavin.

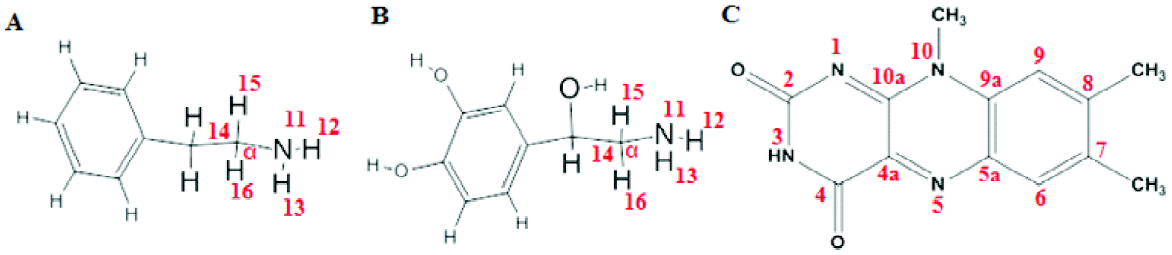
Introduction

The phenylethylamine (PEA) and norepinephrine (NOR) are two important neutrotransmitter molecules which are acting as chemical messenger in the synaptic cleft[1] and making communication between the nerve cells. However, excess of these molecules are degraded by flavoenzyme monoamine oxidase (MAO) present in nerve cells through hydride transfer mechanism involving Flavin Adenine Dinucleotide (FAD)[2]. Generally the trans conformer of the molecules is thought to be preferred in the interaction with MAO[3], however MD-simulation studies of their complexes with that enzyme have also indicated the presence of gauche conformers where the alkylamine side chain was stabilized by intramolecular N-H···π (aromatic ring) interaction[4]. So concerning to the stability and intramolecular association it is also important to study the deamination mechanism of gauche conformer of the neurotransmitters by that enzyme through hydride transfer mechanism. However as lumiflavin is one of the simplest flavin compounds, so it is often used as model to study that electron transfer reactions[5] involving the neurotransmitters[6].

In this study, hydride transfer mechanism of both the trans and gauche conformers of phenylethylamine and norepinephrine molecules have been investigated by complexing them with lumiflavin moiety using DFT-D/B3LYP/6-31G and MP2/6-31G methods. This computational work provides the first evidence that could support the easier feasibility of deamination of gauche conformer of neurotransmitter molecules (PEA/NOR) compared to its trans form.

Materials and methods

To study the hydride transfer mechanism of the trans and gauche conformers of both norepinephrine and phenylethylamine molecules, four different model structures have been build (A, B, C, D). The Model A and B consist of trans and gauche phenylethylamine substrate along with lumiflavin, Model C and D consist of both the norepinephrine conformers along with lumiflavin. The trans and gauche conformers of the substrates were placed in close proximity to lumiflavin. Chemical structures of the substrates and lumiflavin moiety along with their numbering protocols are shown in Scheme 1.



Scheme 1. Structures alongwith the numbering scheme of atoms for (A) phenylethylamine, (B) norepinephrine and (C) lumiflavin.

The DL-find algorithm[7] was used for the optimization of all the reactant complexes (RC), transition states (TS) and product complexes (PC) using B3LYP and MP2 methods with standard split valance basis set 6-31g. As the standard DFT methods are inadequate to model long range dispersion effects, so dispersion corrections (DFT-D3)[8] have also been taken into account for all calculations. The B3LYP methods along with Grimme empirical dispersion correlation (B3LYP-D) claims to be in excellent agreement with experiment data's[9]. The solvation energies were added using the conductor-like Polarizable Continuum Models (C-PCM)[10,11], the standard value of dielectric constant $\varepsilon = 4$ was used to maintain the surrounding with protein and $\varepsilon = 80$ was chosen for modeling the system surroundings with water molecules. Nudged Elastic Band (NEB) method was used for searching the transition state and minimum energy paths between the stable reactant and product complexes[12]. The transition state structures were characterized by one imaginary frequency. Finally, natural bond orbital (NBO) analysis was done on the optimized RC, TS and PC structures to obtain the natural charges[13]. The quantum chemical calculations were performed with Gaussian 09[14], TeraChem v1.9[15,16], NWChem[17] computational programs.

Results and discussions

In the present study, concerted direct hydride transfer mechanism is considered for two different substrates phenylethylamine (PEA) and norepinephrine (NOR), where the former shows binding specifities with hMAO B, and the latter is specific for the other isoform of that enzyme hMAO A. The reactant, transition state and product complexes were optimized with DFT-D3/B3LYP/6-31g and MP2/6-31G level of theory with two different dielectric constants (ε) 4 and 80. In all cases, the gauche conformation of the substrates has endowed lower activation energy compared to trans form.

Phenylethylamine:

In our earlier MD-simulation studies followed by quantum chemical calculations of protonated phenylethylamine complexed with hMAO B, the gauche conformation of PEA seems to be more stable than trans form in some of the snapshots[4], but till date no proper attention has been paid on the deamination mechanism for the gauche conformer of substrate. As the protonated form of substrate shows high energy barrier during the deamination by hydride transfer process compared to its neutral form[3], so in the present study we examine the preference of both the trans and gauche conformers of neutral PEA molecule. For studying the direct hydride transfer mechanism all the quantum chemical calculations are performed by placing the trans and gauche form of substrates near to lumiflavin moiety; the optimized reactant (RC), transition state (TS) and product complexes (PC) for the two PEA-conformers are shown in Figs. 1a and 1b.

In reactant complex, within the protein surrounding (ε = 4), the distance between (C14)Cα-N5 atoms is 3.57 Å for trans and 3.23 Å for gauche conformers, whereas in water surrounding (ε = 80) the values are 3.57 and 3.24 Å for the respective trans and gauche-PEA molecules with B3LYP-D3 method. The distance between (C14)Cα-N5 atoms with MP2 method, ε = 4 is 3.53 Å for trans and 3.22 Å for gauche conformers whereas for ε = 80 the values for respective trans and gauche-PEA are 3.55 and 3.22 Å which are given in Table 1. These values indicate the possibilities of relative easy transfer of hydride ion from Cα position of substrate to

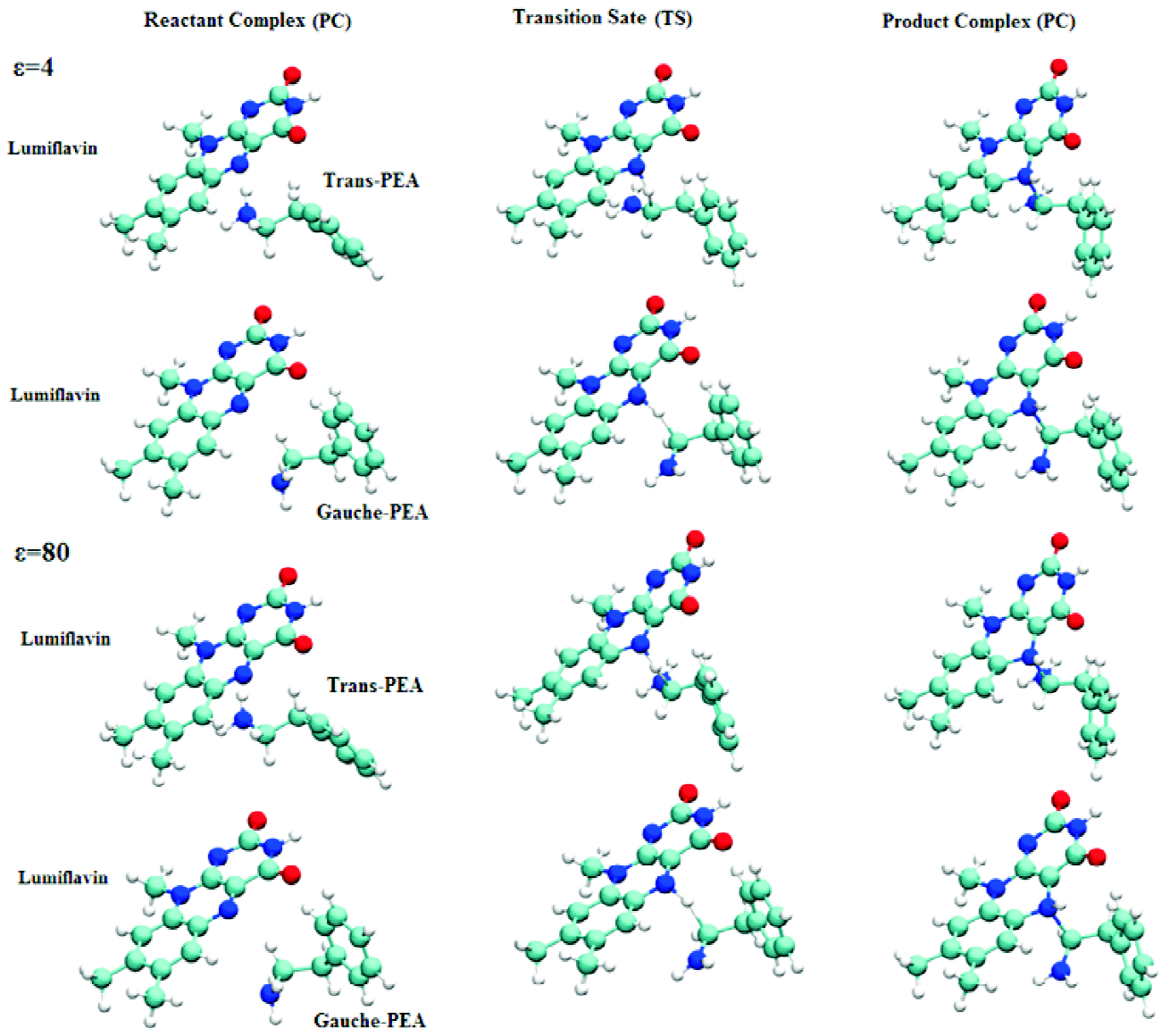


Fig. 1a. The optimized reactant, transition state and product complexes of trans and gauche phenylethylamine molecule with lumiflavin moiety using B3LYP/DFT-D3 method and 6-31g basis set with two different dielectric constants (ε) 4 and 80.

N5 atom of FAD in the gauche conformer compare to trans-form. Hereafter in the entire text, the bond lengths, charges and activation energies for the respective calculations of RC, TS and PC for the C-PCM, ε = 4 are mentioned first followed by ε = 80 and the data's with B3LYP-D3 method are mentioned without parentheses and MP2 method are given within parentheses.

The (amino)N11-C4a bond length is observed to be higher 4.92 and 4.93 (4.88 and 4.89) Å in gauche form of the molecule compared to its trans-form in which the values are 3.94 and 3.95 (3.88 and 3.90) Å, which thus suggesting the impossibilities of gauche-PEA to follow the polar nucleophilic (path) or mechanism. The dihedral angle about N11-C_{α}-Cβ-C_{γ} atoms is 179.75° and 179.38° (177.97° and 178.14°) for trans and –53.17° and –53.46° (–55.61° and –56.32°) in gauche-PEA. It is interesting to observe an intramolecular N-H···π interaction between the amino nitrogen and aromatic π-ring of PEA in optimized RC gauche conformer where the

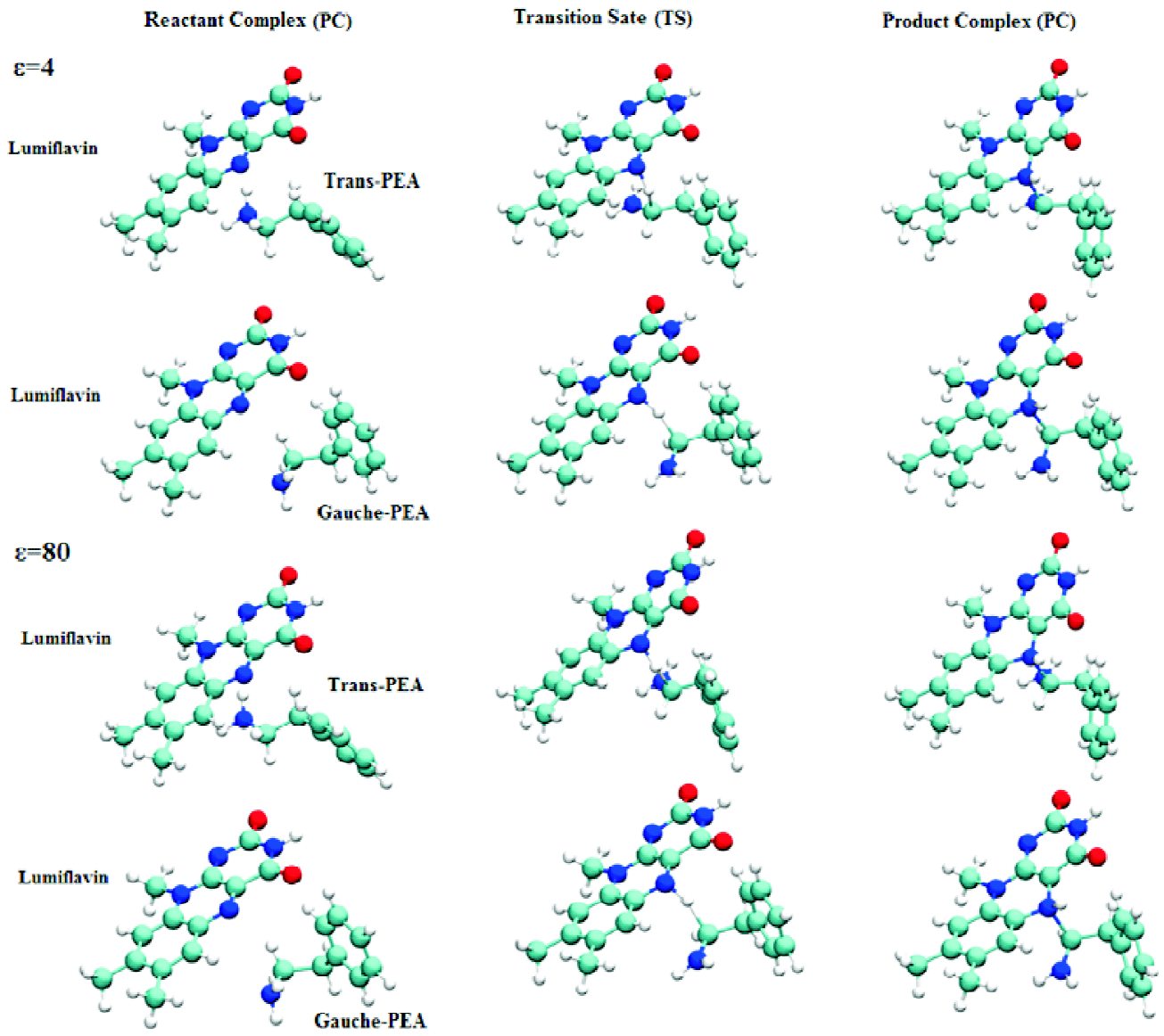


Fig. 1b. The optimized reactant, transition state and product complexes of trans and gauche phenylethylamine molecule with lumiflavin moiety using MP2 method and 6-31g basis set with two different dielectric constants (ε) 4 and 80.

distances are 3.26 and 3.27 (3.27 and 3.28) Å.

In the rate determining step of chemical reaction, during the abstraction of Hα as hydride ion form Cα position of PEA, the activation energy for trans conformer 27.035 and 28.303 (28.331 and 28.625) kcal/mol is observed to be ~1.9 and 3.55 (3.21 and 3.81) kcal/mol higher than the gauche conformer of PEA (Fig. 2), these results indicate the preference of gauche conformer to follow the direct hydride transfer path compared to trans- form of PEA. The transition states are marked with an imaginary frequency of 792i and 728i (784i and 758i) cm^{-1} for trans and 755i and 688i (754i and 702i) cm^{-1} for gauche-PEA.

In transition state the H^- ion donation is associated with the loosening or stretching of C14-H15 bond length from 1.10 to 1.60 and 1.10 to 1.60 (1.08 to 1.60 and 1.08 to 1.59) Å in trans and 1.09 to 1.59 and 1.09 to 1.62 (1.07 to 1.58 and

Table 1. The interatomic distances (Å) and charges |e| for some selected atoms of optimized reactant, transition state and product complexes of flavin-PEA using C-PCM/DFT-D3/B3LYP/6-31g and C-PCM/MP2/6-31g level of theory

	B3LYP-D3/6-31G											
	ε = 4						ε = 80					
	Trans-PEA			Gauche-PEA			Trans-PEA			Gauche-PEA		
	RC	TS	PC	RC	TS	PC	RC	TS	PC	RC	TS	PC
Distance (Å)												
C14-H15	1.10	1.60	2.24	1.09	1.59	2.25	1.10	1.60	2.24	1.09	1.62	2.25
N5-H15	2.86	1.13	1.03	2.25	1.13	1.03	2.87	1.13	1.03	2.25	1.13	1.03
N11-C14	1.46	1.36	1.39	1.47	1.37	1.38	1.46	1.36	1.39	1.47	1.37	1.38
N5-C14	3.57	2.58	1.72	3.23	2.62	1.76	3.57	2.57	1.72	3.24	2.64	1.77
C4-C4a	1.49	1.45	1.42	1.48	1.44	1.42	1.49	1.45	1.42	1.48	1.44	1.42
N5-C4a	1.31	1.38	1.45	1.31	1.38	1.46	1.31	1.38	1.45	1.31	1.38	1.46
N11-C4a	3.94	3.26	2.99	4.92	4.40	3.81	3.95	3.25	2.97	4.93	4.43	3.80
N1-C10a	1.31	1.33	1.33	1.32	1.33	1.33	1.31	1.33	1.33	1.32	1.33	1.33
Charge |e|												
C4a	0.072	–0.025	–0.135	0.071	–0.016	–0.131	0.072	–0.050	–0.135	0.072	–0.017	–0.131
N5	–0.323	–0.477	–0.485	–0.324	–0.502	–0.489	–0.323	–0.520	–0.485	–0.325	–0.508	–0.490
N11	–0.922	–0.805	–0.874	–0.930	–0.787	–0.862	–0.922	–0.775	–0.873	–0.928	–0.783	–0.860
C14	–0.264	–0.127	0.138	–0.282	–0.105	0.127	–0.264	–0.057	0.138	–0.281	–0.095	0.127
H15	0.203	0.338	0.479	0.257	0.388	0.473	0.204	0.372	0.480	0.255	0.390	0.473
N1	–0.580	–0.600	–0.611	–0.586	–0.600	–0.607	–0.580	–0.604	–0.611	–0.586	–0.601	–0.607
	MP2/6-31G											
Distance (Å)												
C14-H15	1.08	1.60	2.09	1.07	1.58	2.10	1.08	1.59	2.09	1.07	1.61	2.10
N5-H15	2.83	1.13	1.01	2.33	1.13	1.01	2.85	1.13	1.01	2.33	1.12	1.0
N11-C14	1.44	1.36	1.38	1.45	1.37	1.38	1.44	1.36	1.38	1.45	1.37	1.38
N5-C14	3.53	2.57	1.59	3.22	2.62	1.58	3.55	2.57	1.59	3.22	2.64	1.58
C4-C4a	1.47	1.45	1.39	1.46	1.44	1.39	1.46	1.45	1.39	1.46	1.44	1.39
N5-C4a	1.28	1.38	1.44	1.27	1.37	1.44	1.27	1.38	1.44	1.27	1.38	1.44
N11-C4a	3.88	3.25	2.73	4.88	4.39	2.49	3.90	3.24	2.73	4.89	4.42	3.66
N1-C10a	1.29	1.32	1.31	1.29	1.32	1.31	1.29	1.32	1.31	1.29	1.32	1.31
Charge |e|												
C4a	0.033	–0.177	–0.210	0.023	–0.137	–0.216	0.034	–0.176	–0.210	0.023	–0.142	–0.216
N5	–0.279	–0.548	–0.516	–0.271	–0.529	–0.513	–0.279	–0.545	–0.515	–0.271	–0.544	–0.513
N11	–0.955	–0.837	–0.932	–0.961	–0.860	–0.942	–0.955	–0.838	–0.932	–0.961	–0.852	–0.942
C14	–0.220	–0.146	0.202	–0.240	–0.085	0.201	–0.220	–0.142	0.202	–0.240	–0.109	0.020
H15	0.193	0.332	0.50	0.252	0.354	0.495	0.193	0.332	0.501	0.251	0.354	0.495
N1	–0.692	–0.737	–0.730	–0.699	–0.731	–0.724	–0.691	–0.737	–0.730	–0.699	–0.733	–0.725

1.07 to 1.61) Å in gauche-PEA. Charges on the C14 atom is observed to decrease from –0.264 to –0.127 and –0.264 to –0.057 (–0.220 to –0.146 and –0.220 to –0.142) |e| and from –0.282 to –0.105 and –0.281 to –0.095 (–0.240 to –0.085 and –0.240 to –0.109) |e| in the respective trans and gauche-PEA. Transfer of H^- ion to N5 atom of lumiflavin moiety has increased the negative charge over that nitrogen atom from –0.323 to –0.477 and –0.323 to –0.520 (–0.279 to –0.548 and –0.279 to –0.545) |e| in trans and from –0.324 to –0.502 and –0.325 to –0.508 (–0.271 to –0.529 and –0.271 to

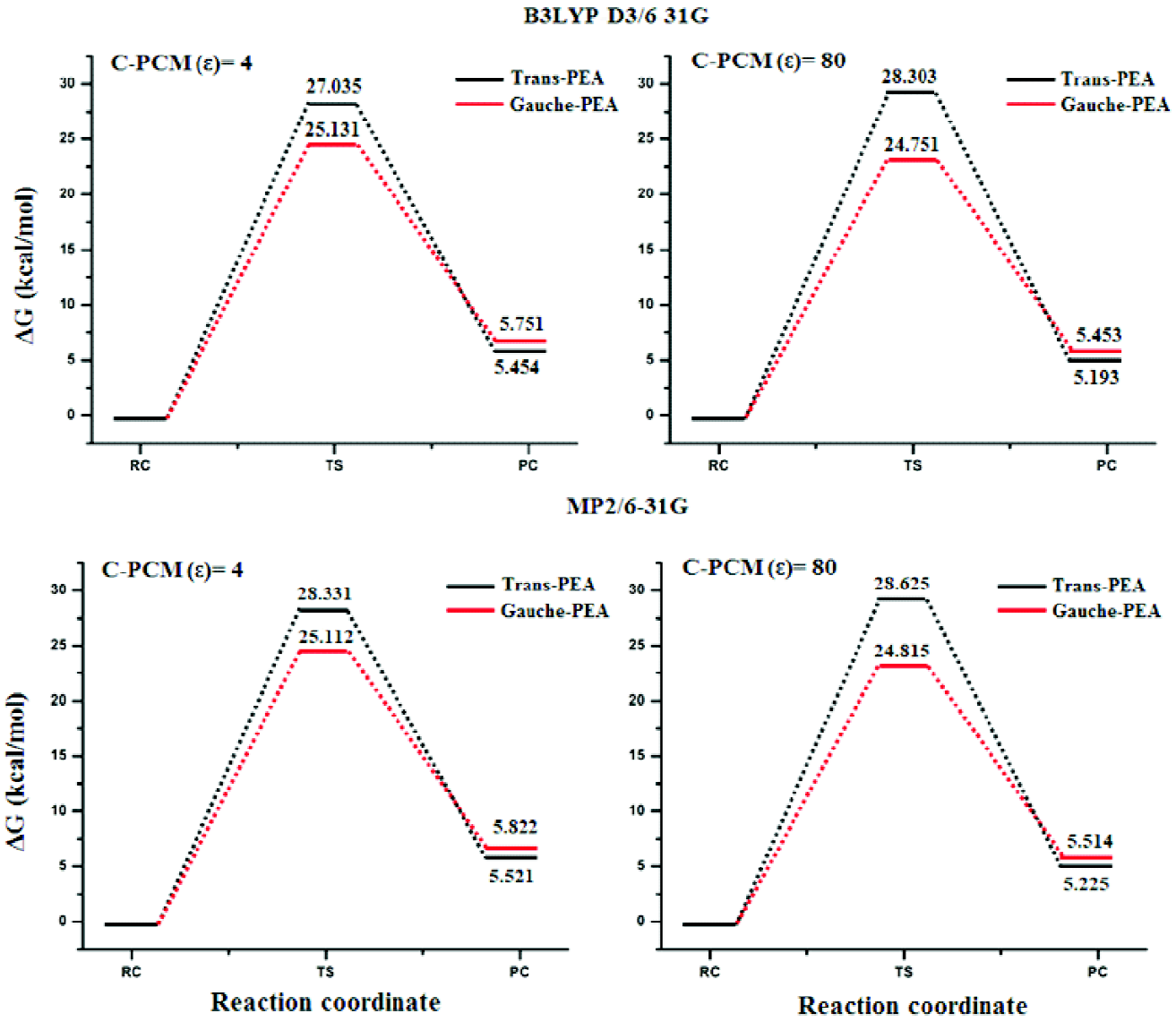


Fig. 2. Relative energy barriers for the trans and gauche-PEA degradation by direct hydride transfer mechanism.

–0.548) |e| in gauche-PEA. Again, the hydride ion transfer from Cα of substrate has caused the shortening of bond length between the amino (N11) and C14 atoms from 1.46 to 1.36 and 1.46 to 1.36 (1.44 to 1.36 and 1.44 to 1.36) Å in trans and from 1.47 to 1.37 and 1.47 to 1.37 (1.45 to 1.37 and 1.45 to 1.37) Å in gauche-PEA. In PEA the dihedral angle about N11-C_α-Cβ-C_γ is found to be –175.66° and –177.05° (–174.62° to –175.47°) for trans and –35.08° and –35.13° (–41.56° to –41.98°) for gauche-PEA, with (N11)N-H···π (substrate) distance of 3.18 and 3.17 (3.19 to 3.18) Å.

Norepinephrine:

The norepinephrine molecule is structurally unlike to phenylethylamine due to presence of three hydroxyl groups, two in aromatic ring and the other is covalently attached with β-carbon atom. Considering the promising stability of gauche-PEA compare to trans-form, we select the norepinephrine molecule to check their conformational preference, so two other model systems C and D are build, which are consist of

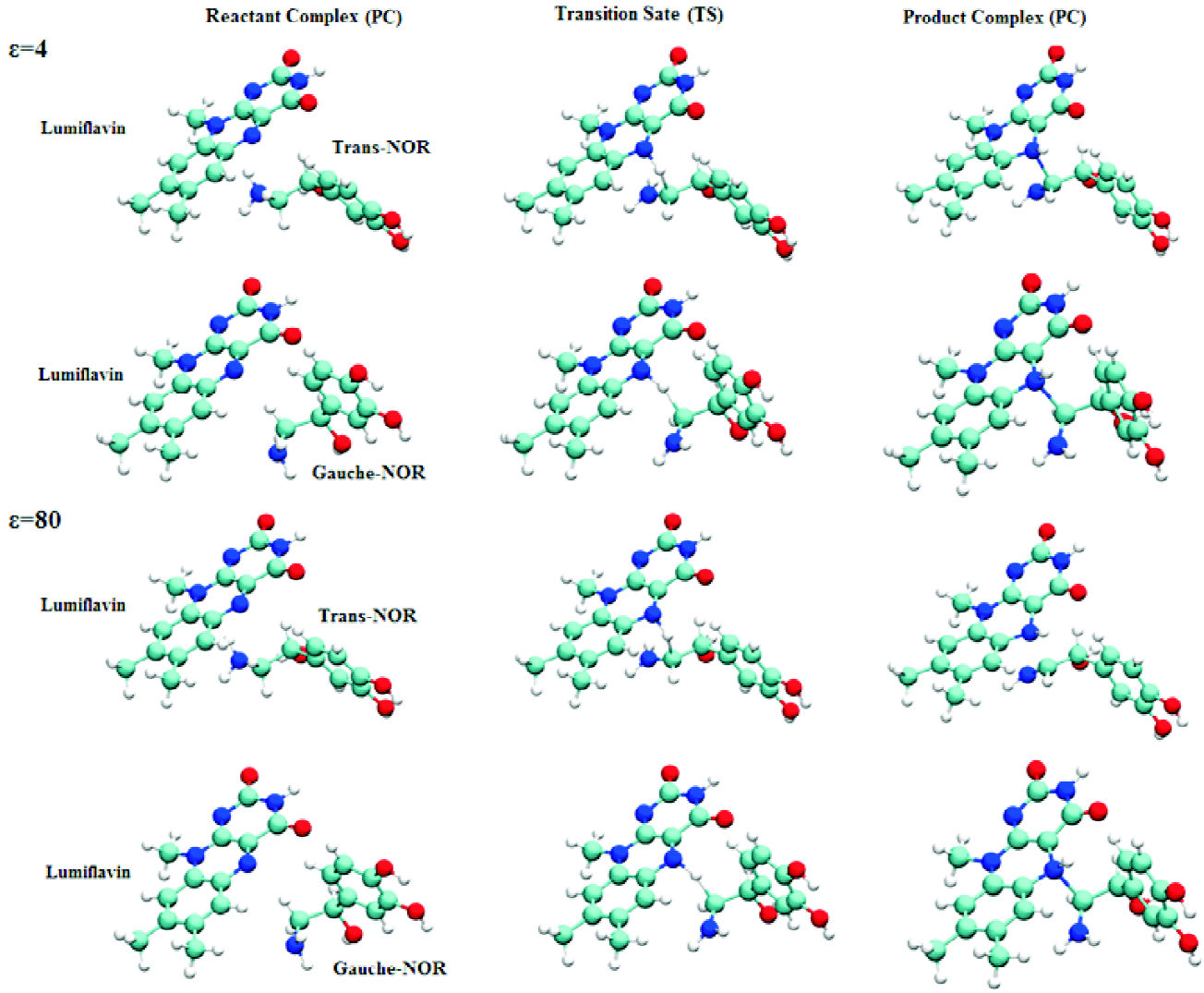


Fig. 3a. The optimized reactant, transition state and product complexes of trans and gauche norepinephrine molecule with lumiflavin moiety using B3LYP/DFT-D3 method and 6-31g basis set with two different dielectric constants (ε) 4 and 80.

trans and gauche-NOR alongwith the lumiflavin moiety of FAD. The reactant, transition state and product complexes are optimized (Figs. 3a and 3b) following the same methodologies and basis set as are considered for phenylethylamine molecule.

In RC, the C14-N5 distances are 3.55 and 3.54 (3.44 and 3.44) Å for trans and 3.25 and 3.25 (3.24 and 3.28) Å for gauche-NOR (Table 2). The dihedral angle about N11-C_{α}-Cβ-C_{γ} atoms is –172.0° and –172.92° (–176.09° and –176.26°) for trans and –54.23° and –54.51° (–55.95° to –55.25°) in case of gauche conformer. It is also interesting to observe the intramolecular N-H···π interaction between the amino nitrogen and π-electron cloud of catechol ring of NOR in the optimized RC gauche conformer, which could provide some extra stability to that conformer where the distances are found to be 3.29 (3.28 and 3.29) Å. During the transfer of a hydride ion from C14 to N5 atom of lumiflavin the associated energy barrier is 31.270 and 31.129 (30.446 and 30.345) kcal/mol for trans-NOR, however relatively low energy barrier 24.944 and 24.105 (25.126 and 25.231) kcal/mol is ob-

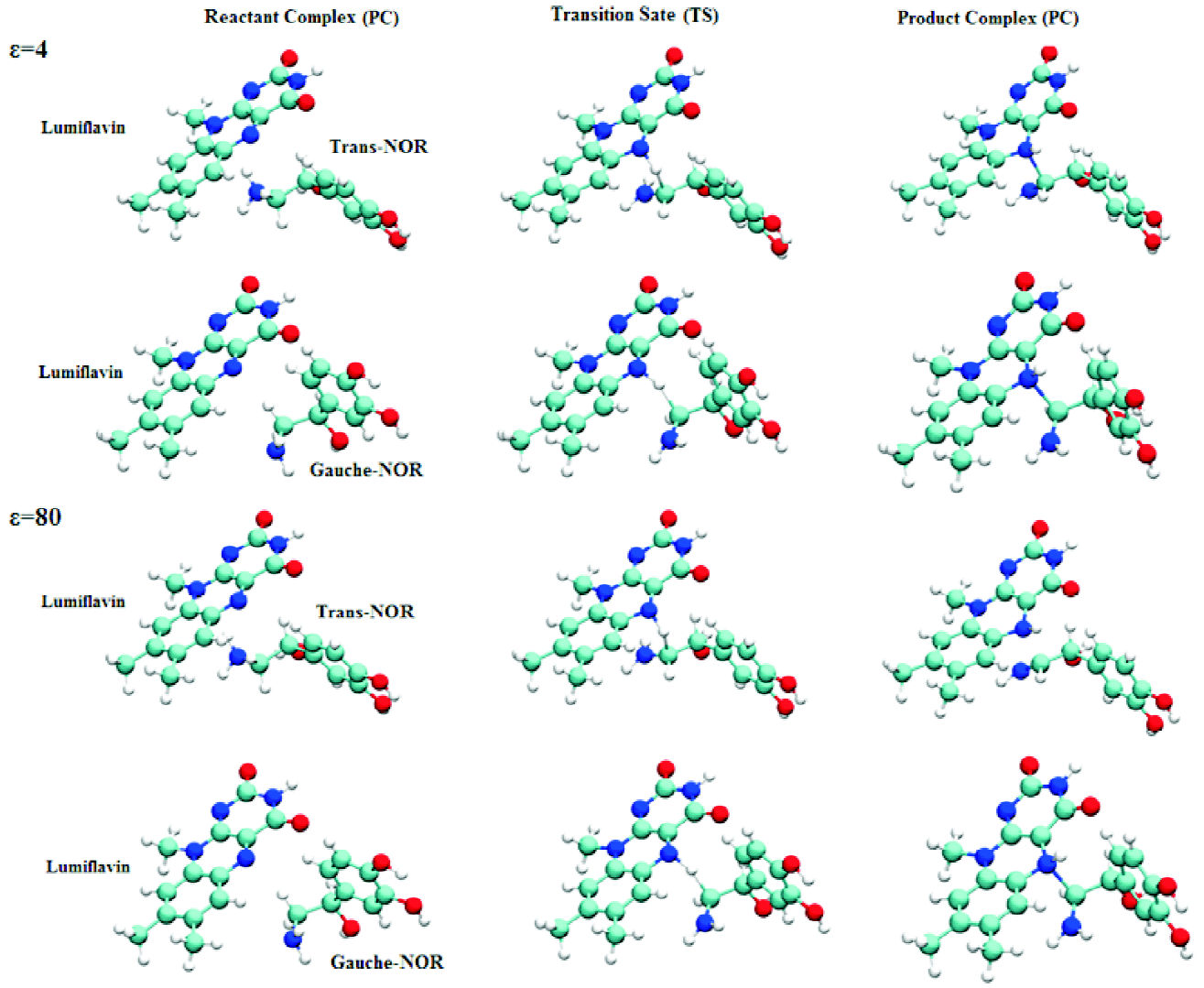


Fig. 3b. The optimized reactant, transition state and product complexes of trans and gauche norepinephrine molecule with lumiflavin moiety using MP2 method and 6-31g basis set with two different dielectric constants (ε) 4 and 80.

served in case of gauche-NOR (Fig. 4) indicating preference of gauche-NOR over trans-form.

The transition state was identified by the presence of a single imaginary frequency of 704i and 849i (703i and 842i) cm^{-1} for trans and 684i and 898i (692i and 878i) cm^{-1} for gauche norepinephrine.The intramolecular N-H$\cdots\pi$ interaction between the amino nitrogen and catechol ring of gauche-NOR in the optimized TS is found to be 3.18 and 3.17 (3.18 and 3.18) Å.The C14-N5 bond length shortens to 2.58 and 2.57 (2.57 and 2.57) Å for trans and 2.61 and 2.62 (2.61 and 2.67) Å for gauche-NOR and the atomic charge on C_β (C14) has been decreased from –0.302 to –0.091 and –0.302 to –0.122 (–0.259 to –0.190 and –0.259 to –0.129) |e| for trans and from –0.303 to –0.131 and –0.304 to –0.158 (–0.262 to –0.143 and –0.262 to –0.118) |e| for gauche, whereas it increased from –0.324 to –0.517 and –0.325 to –0.501 (–0.286 to –0.536 and –0.285 to –0.494) |e| and from –0.336 to –0.497 and –0.337 to –0.485 (–0.287 to –0.516 and –0.287 to –0.522) |e| on the N5 atom of FAD in the respective trans and gauche conformers of norepinephrine.

Table 2. The interatomic distances (Å) and charges |e| for some selected atoms of optimized reactant, transition state and product complexes of flavin-NOR using C-PCM/DFT-D3/B3LYP/6-31g and C-PCM/MP2/6-31g level of theory

	B3LYP-D3/6-31G											
	ε = 4						ε = 80					
	Trans-NOR			Gauche-NOR			Trans-NOR			Gauche-NOR		
	RC	TS	PC	RC	TS	PC	RC	TS	PC	RC	TS	PC
Distance (Å)												
C14-H15	1.10	1.60	2.39	1.09	1.58	2.27	1.10	1.54	2.44	1.09	1.52	2.27
N5-H15	2.80	1.14	1.03	2.19	1.13	1.03	2.79	1.18	1.03	2.20	1.18	1.03
N11-C14	1.47	1.36	1.35	1.46	1.37	1.37	1.47	1.37	1.35	1.46	1.38	1.37
N5-C14	3.55	2.58	1.93	3.25	2.61	1.82	3.54	2.57	1.99	3.25	2.62	1.82
C4-C4a	1.49	1.45	1.42	1.48	1.44	1.42	1.49	1.46	1.42	1.48	1.44	1.42
N5-C4a	1.31	1.38	1.43	1.31	1.38	1.46	1.31	1.37	1.43	1.31	1.37	1.46
N11-C4a	3.95	3.37	3.34	5.06	4.39	3.83	3.99	3.37	3.36	5.06	4.41	3.83
N1-C10a	1.31	1.33	1.33	1.32	1.33	1.33	1.31	1.33	1.33	1.32	1.33	1.33
Charge |e|												
C4a	0.074	–0.044	–0.124	0.075	–0.013	–0.127	0.074	–0.035	–0.120	0.075	-0.004	-0.128
N5	–0.324	–0.517	–0.513	–0.336	–0.497	–0.496	–0.325	–0.501	–0.520	–0.337	-0.485	-0.496
N11	–0.940	–0.761	–0.815	–0.918	–0.771	–0.831	–0.940	–0.775	–0.803	–0.918	-0.780	-0.832
C14	–0.302	–0.091	0.119	–0.303	–0.131	0.115	–0.302	–0.122	0.119	–0.304	-0.158	0.115
H15	0.223	0.370	0.463	0.252	0.387	0.469	0.223	0.357	0.461	0.252	0.371	0.469
N1	–0.576	–0.603	–0.607	–0.585	–0.600	–0.608	–0.576	–0.603	–0.608	–0.585	-0.599	-0.608
	MP2/6-31G											
Distance (Å)												
C14-H15	1.08	1.60	2.10	1.07	1.57	2.11	1.08	1.53	2.10	1.07	1.85	2.11
N5-H15	2.74	1.13	1.0	2.23	1.13	1.0	2.72	1.17	1.0	2.25	1.04	1.0
N11-C14	1.45	1.38	1.37	1.44	1.37	1.37	1.45	1.36	3.03	1.44	1.35	1.37
N5-C14	3.44	2.57	1.59	3.24	2.61	1.58	3.44	2.57	1.59	3.28	2.67	1.58
C4-C4a	1.47	1.45	1.38	1.46	1.43	1.39	1.47	1.45	1.38	1.46	1.42	1.39
N5-C4a	1.27	1.38	1.44	1.27	1.37	1.44	1.27	1.37	1.44	1.27	1.38	1.44
N11-C4a	3.81	3.36	2.68	5.06	4.38	3.65	3.80	3.37	2.67	5.07	4.42	3.65
N1-C10a	1.28	1.32	1.31	1.29	1.32	1.31	1.28	1.32	1.31	1.29	1.32	1.31
Charge |e|												
C4a	0.038	–0.164	–0.202	0.032	–0.127	–0.215	0.038	–0.144	–0.202	0.032	–0.160	–0.216
N5	–0.286	–0.536	–0.515	–0.287	–0.516	–0.514	–0.285	–0.494	–0.515	–0.287	–0.522	–0.512
N11	–0.971	–0.823	–0.928	–0.950	–0.847	–0.936	–0.971	–0.848	–0.928	–0.950	–0.795	–0.937
C14	–0.259	–0.09	0.183	–0.262	–0.043	0.189	–0.259	–0.029	0.184	–0.262	–0.218	0.189
H15	0.212	0.329	0.498	0.242	0.351	0.492	0.212	0.314	0.498	0.241	0.395	0.492
N1	–0.685	–0.735	–0.730	–0.697	–0.728	–0.723	–0.685	–0.731	–0.730	–0.697	–0.735	–0.723

The preference of gauche conformers over transduring hydride transfer mechanism may be due to the intramolecular N-H$\cdots\pi$ non-covalent interaction between the amino terminal and aromatic ring of the gauche form of substrate. Such interactions for monoamine neurotransmitter molecules has been explicitly studied by theoretical and experimental methods where the gauche form is found to have lower energy barrier when compared to their trans counter partners due to N-H$\cdots\pi$ interaction[18,19].

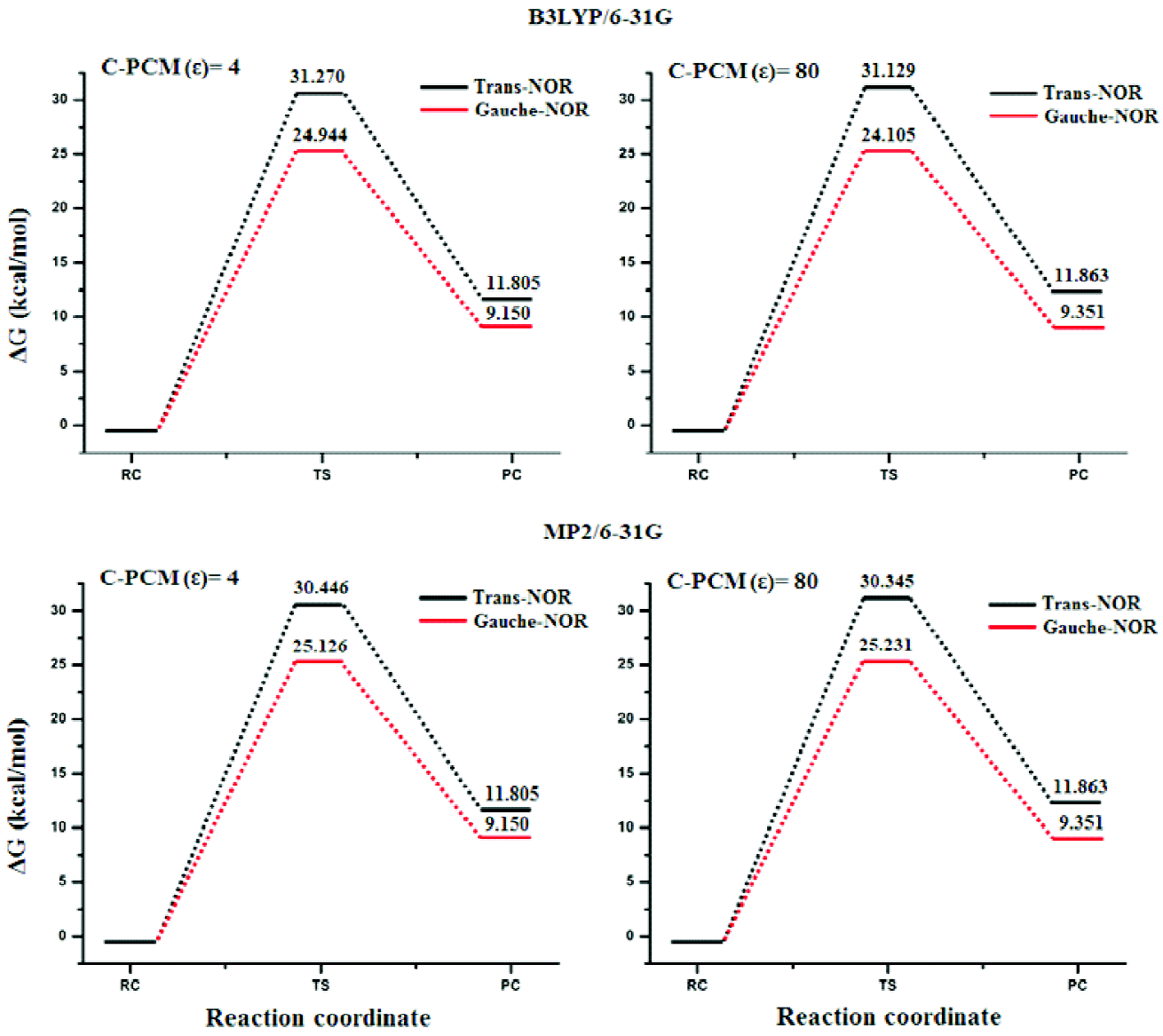


Fig. 4. Relative energy barriers for the trans and gauche-NOR degradation by direct hydride ion transfer mechanism.

Conclusion

In the present study, concerted hydride transfer mechanism for trans and gauche conformers of phenylethylamine/norepinephrine have been investigated using density function theory and second-order Møller-Plesset perturbation theory with two different dielectric constants (ε) 4 and 80. The activation energy profiles for the deamination of trans and gauche substrates have shown the preference of gauche conformation over trans form of PEA/NOR. The inter or intra-atomic bond lengths, distances and charges on atoms in the respective RC, TS and PC seem to be similar for both the trans and gauche conformers but we believe differences in activation energy barrier associated to trans and gauche substrates may be due to the intramolecular N-H···π non-covalent interaction between the amino terminal and aromatic ring of the gauche form of substrate. The present study indicates that the deamination of monoamine is highly dependent on the conformational preference of substrate mol-

ecule at the active site of enzyme which may be useful in conformation based drug/inhibitor design for human monoamine oxidase.

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Abbreviations

PEA: Phenylethylamine, NOR: Norepinephrine, FAD: Flavin Adenine Dinucleotide, hMAO: human Monoamine oxidase, C-PCM: conductor-like Polarizable Continuum Models, DFT: Density Functional Theory, MP2: Second-order Møller-Plesset perturbation theory, RC: Reactant complex, PC: Product complex, TS: Transition state.

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