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DFT Study on One-carbon Unit Transfer from 1,10-CH^+-tetrahydroquinoxaline to Methylamine

Chuan Song QI, Da Cheng FENG*, Hua Yang WANG, Zheng Ting CAI

Institute of Theoretical Chemistry, Shandong University, Jinan 250100

Abstract: Density Functional Theory (DFT) method was used in this paper to study one-carbon transfer from 1,10-tetrahydroquinoxaline, an analogue of tetrahydrofolic acid, to methylamine. This reaction can be completed *via* two paths. From the computation result we can conclude that a general-acid catalysis exists in this reaction. By computation we find DFT has its limitation in describing a newly incorporated structure with a unit charge.

Keywords: Density Functional Theory (DFT), folate cofactor, tetrahydroquinoxaline, one-carbon unit transfer.

Enzymatic one-carbon unit transfer reaction has a significant function in the biosynthesis of purine, glycine and histidine and metabolism of cell as well as the transformation from ATP to ADP[1]. One-carbon unit transfer reaction requiring folate cofactor continues to attract great interests owing to its significance for designing novel chemotherapeutic agents and anticancer drugs[2-5].

In this paper, we select the reaction of 1,10-CH^+-tetrahydroquinoxaline, an analogue of tetrahydrofolic acid, and methylamine as a study target to study their reaction process and mechanism in detail. 1,10-CH^+-tetrahydroquinoxaline reacting with methylamine can complete one carbon unit transfer and lead to formylated methylamine by hydrolysis. We present a generally accepted mechanism for this one-carbon unit transfer (see **Figure 1**) based upon experimental results of H4folate and its models[6-9] as well as the theoretical studies[10] of imidazolidine model complex. First, the two reactants combine to form intermediate **b**. The proton H11(or H12) linking to N10 in intermediate **b** migrates to N7 (or N1) atom to form intermediate **Ic** (**IIc**). Then C8N7(C8N1) bond of the five-member ring in **Ic** (**IIc**) breaks apart to form **I d** (**IId**) which can produce formylated methylamine by hydrolysis, thus complete the entire one-carbon transfer from 1,10-CH^+-tetrahydroquinoxaline to methylamine.

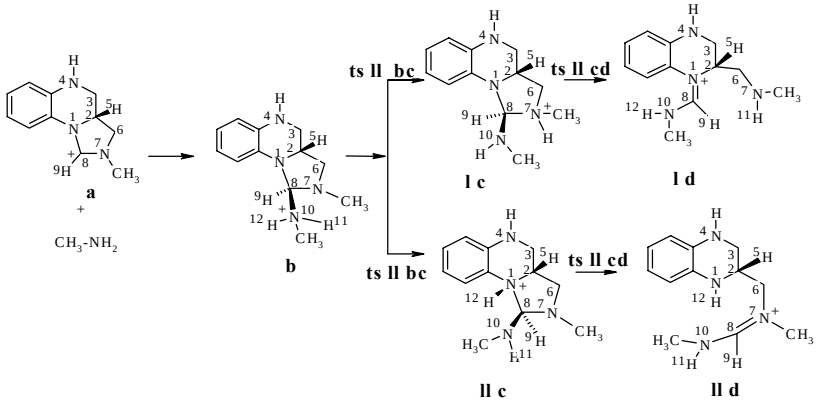
Methods

The structures of reactants, intermediates and transition states have been optimized with

*E-mail: fdc@sdu.edu.cn

B3LYP/6-31G* method and the most stable conformations as well as their energies at every stationary point have been figured out. Frequency calculations of all stationary points have been performed and all transition states have been identified by analyzing the vibrational models of their one and only imaginary frequencies.

Figure 1 Reaction mechanism of the one-carbon unit transfer of the article



Results and Discussion

The main geometric data of all optimized stationary points are listed in **Table 1** from which one can find that the five-member imidazolidine ring of **a** is almost planar. C8 atom in it has more positive charge than the others (the NBO charges of N1, C6, N7, C8 is -0.3706, -0.2651, -0.3893 and 0.3637 respectively), so it is easier to be attacked by nucleophilic N atom of methylamine (NH_2CH_3). In principle, there are two ways for methylamine to attack C8 atom of **a** to form R- and S- chiral conformation of C8 respectively. In this paper we only discuss the case that the new formed chiral atom C8 is in R-configuration (see **Figure 1 b**).

Methylamine attacking C8 atom of **a** can form intermediate **b** in which C8 and N10 has a stronger bond interaction. But it can not be obtained using B3LYP/6-31g* and other DFT method such as MPW1PW91/6-31g* and PW91PW91/6-31g*. The DFT method has its limitation in describing a dissociation (or incorporated) behavior of the system[11]. So an alternative electron correlation method MP2 with the same basis set has been used to the same intermediate. We named the optimized intermediate with MP2 method as **b'** in which the N10C8 bond length is 1.572 Å, it means there are four atoms linking to N10 atom in **b'**, so one proton attaching to it will migrate to keep N10 in normal state of linking to three atoms. The proton migrates to N7 atom or N1 atom *via* transition state **tsIbc** and **tsIIbc**, respectively (**I** denoting proton H11 migrating to N7 and **II** to N1) to form intermediates **Ic** or **IIc**. After proton migration, there will be four atoms interacting with N7 (N1) atom by bonds, thus one of the bonds will break to make N7 (N1) maintaining its normal state. By analyzing the structure data one can find

bond N7C8 (N1C8) is more prone to break than the others around N7 (N1) atom to lead the imidazolidine ring breaking. The ring cleavage process of **c** passes through transition state **tscd** to form intermediate **d**. From the NBO charge of **Id** and **IId** one can find that the unit positive charge mainly delocalized on N1, C8 atoms to form formimidoyl amine salt which can hydrolyze to formylmethylamine.

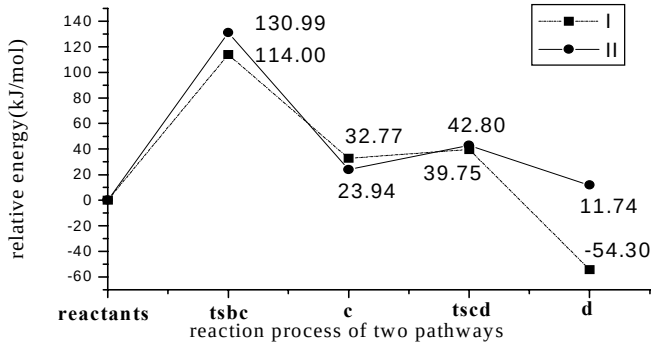
The energy fluctuant of the whole process of the two paths are shown in **Figure 2**. For N1, N7 atoms have different steric hindrance in each path, the relative energy of proton migrating transition state of path **I** is less than that of path **II**. From **c** to **d** the reaction needs overcomes 6.98kJ/mol (path **I**) or 18.86 kJ/mol (path **II**) energy barrier to complete the process of five-member-ring imidazolidine cleavage. The relative energy curves of the two reaction paths show that the difference is not obvious on the same stationary point of the two paths and both of the maximum reaction energy barriers are presented in proton migrating step. The whole energy curve indicates that both the pathways are probable and they compete with each other in reaction and path **I** is more favorable.

Table1 Structure data of all stationary points in the reaction*

	a	**b′**	**tsI bc**	**Ic**	**tsIcd**	**Id**	**tsIIbc**	**IIc**	**tsIIcd**	**IId**
Bond length(Å)										
N7C8	1.324	1.425	1.514	1.595	1.965	--	1.403	1.430	1.418	1.323
N1C8	1.318	1.420	1.397	1.426	1.384	1.334	1.542	1.695	1.895	3.397
N1H12	--	--	--	--	--	--	1.337	1.024	1.022	1.021
N7H11	--	--	1.326	1.027	1.019	1.021	--	--	--	--
N10H12	--	1.029	1.023	1.016	1.013	1.057	1.334	--	--	--
N10H11	--	1.029	1.343	--	--	--	1.022	1.011	1.013	1.013
Bond angle(°)										
C2C6N7	103.2	106.1	103.5	103.4	108.6	112.1	105.5	106.3	108.3	116.3
C8N1N2	110.1	109.6	111.6	111.3	116.5	121.3	106.4	102.3	102.2	--
C2N1H12	--	--	--	--	--	--	116.3	107.6	109.3	109.3
N1H8N10	--	107.0	116.2	116.6	119.4	125.6	93.1	116.0	110.8	--
C8N10H11	--	105.2	75.0	--	--	--	109.6	115.2	116.4	112.9
C8N10H12	--	108.2	109.7	110.6	117.3	117.7	76.2	--	--	--
C8N7H11	--	--	76.7	102.0	110.9	--	--	--	--	--
Dihedral angel(°)										
C2N1C8N7	1.0	0.4	-19.8	-30.7	-34.6	--	4.3	43.2	14.2	--
N1C8N7C6	-3.0	15.3	-2.7	5.4	40.1	--	15.1	-43.8	10.2	--
C2C6N7C8	3.6	-24.6	22.3	19.3	-32.3	--	-28.4	29.6	-32.1	-99.8
C6N7C8H9	176.1	145.8	124.9	122.8	158.2	--	143.1	61.2	112.8	-173.4
C6N7C8N10	--	-100.2	-121.1	-116.9	-82.4	--	-86.5	-166.1	-108.6	6.3
N7C8N10H11	--	156.5	--	--	--	--	-150.3	-161.2	-165.5	-177.2
N1C8N10H12	--	51.7	9.2	13.3	-14.3	-9.7	-6.7	--	--	--

* The structure of **b′**is optimized by MP2/6-31G*

Figure 2 Relative energy of the whole reaction along two paths



Conclusion

Both pathways of the whole reaction undergo following steps: methylamine attacking **a**, proton migrating, imidazolidine decomposing. Proton migrating is the rate-limiting step because it has higher energy barrier than other steps. It denotes that this type of reaction needs general acid-base catalysis. This is consistent with the analysis of the one-carbon transfer reaction of 1,10-CH^+-THF and 1,5-CH^+-tetrahydroquinoxaline[9] as well as some folate cofactor models[6-8]. By calculation we also find DFT has its limitation for describing a newly incorporated structure with the unit charge.

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