DFT Study on the Stereoisomeric Effect of Amino-acid Side Chain on the Formation of Penta-coordinate Phosphorus Carboxylic-phosphoric Mixed Anhydride

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Abstract: - N-phosphorylamino-acids can self-catalyze and self-assemble into polypeptides and polynuleotides under mild condition. Both experimental and theoretical studies have shown that a pentacoordinate phosphorus intermolecular mixed carboxylic-phosphoric anhydride (IMCPA) is formed as the common intermediate in these reactions. In this paper, the mechanism of the formation of stereoisomeric penta-coordinate intermediates through different stereochemical reaction pathway is studied at B3LYP/6-311+G(d,p) level. The results show that amino-acid side chains have an obvious effect on the stereochemical specificity of the IMCPAs formation from N-phosphorylamino-acids.

Key-Words: - N-phosphorylamino-acids; Intermolecular mixed carboxylic-phosphoric anhydride; Stereoisomerism; Origin of life; DFT

1 Introduction

The origin of life, which involves cosmology, astrophysics, organic chemistry, molecular biology and mathematics, is one of the most difficult scientific puzzles to be solved [1,2]. In 1953, Urey and Miller performed their famous experiment which is widely accepted as a model of probiotic synthesis of amino-acids. Ferris and Orgel showed that cyanoacetylene is a major product of the action of an electric discharge in a mixture of methane and nitrogen and that cyanoacetylene is a plausible source of the pyrimidine bases. In 1980s, the first ribozyme was discovered by Cech in his study of tetrahymenathermophila, which initiated the RNA world hypothesis of the origin of life [3]. Organic phosphors compounds are also important evidences in the research of anchebiosis because of their multiple biochemistry actions in biosystem [4]. Experimental results show that N-phosphorylamino-acids can react to form esters, peptides, phosphoryl ester-exchanged products and phosphoryl group migration products under mild condition [5,6]. It is also found that N-phosphorylamino-acids could self-catalyze and self-assemble into polypeptides and polynuleotides simultaneously to form a basic system, which may combine the origin of nucleic acid and protein together and exchange energy and substances internally [7]. In these reaction systems, a kind of penta-coordinate phosphorus carboxylic-phosphoric mixed anhydride are proposed to be the common intermediate (Fig. 1) [8-11]. Quantum chemistry studies have been carried out to investigate the mechanism of the intramolecular mixed carboxylic-phosphoric anhydride (IMCPA) formation from N-phosphorylamino-acids, as well as the molecular structures and activities of the IMCPA and its analogue [12,13]. It has been verified that the IMCPA, which takes a TBP (trigonal bipyramidal) configuration, is situated at the relatively minimal point of the potential surface and that it can form in a non-synchronous concerted reaction pathway through a transition state with a hydrogen-bond-bridge structure. With the study on the recognition of α-amino-acids from β- and γ-amino-acids by N-phosphorylation, the formation of IMCPA from N-phosphoryl-α-amino acid is demonstrated to be energetically favorable [14,15]. This explains the experimental phenomena that only N-phosphoryl-α-amino acid can enjoy considerable self-activation under mild conditions, but N-phosphoryl-β-amino-acids and N-phosphoryl-γ-amino-acids can not.

Nevertheless, the stereochemistry involved in these reactions has not arouse enough attention in previous researches. Because the amino-acids making up natural proteins (except for glycine) are chiral, the IMCPAs formation reaction can generate two kinds of stereoisomers through different pathways (Fig. 2). This stereoisomerism may amplify the function of the chiral of amino-acids and may be handed on to the next reactions. So the stereochemical

effect of amino-acids on N-phosphoryl- amino-acids is prominent for the final formation of the whole chiral system of biomolecules. In this paper, the stereochemistry in the IMCPA formation from N-phosphorylamino-acids is investigated by means of DTF method.

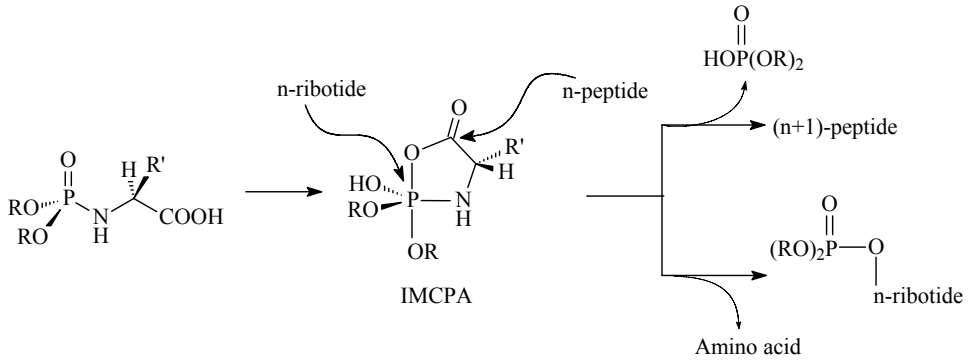

Fig.1 The reaction of N-phosphorylamino-acid to form peptide and ribotide with the proposed penta-coordinate phosphorus intermediate

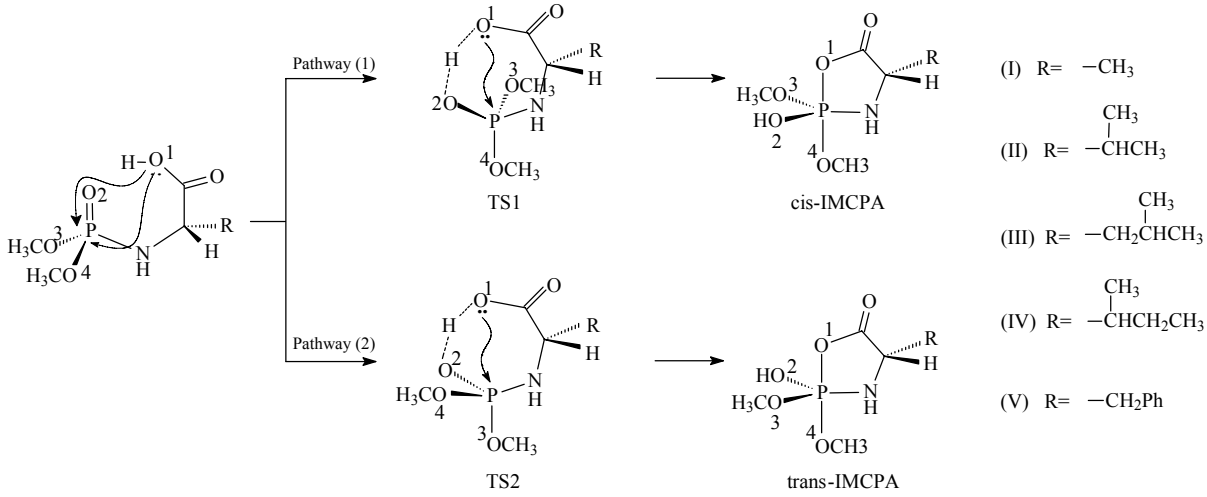

Fig. 2 The supposed mechanism of stereoisomeric IMCPAs formation from N-phosphorylamino-acids through two pathways

2 Computational methods

Dimethoxyl N-phosphoryl-L-α-amino-acids with nonpolar hydrocarbonyl group on α-carbon of the amino-acid are selected as the model reactants. They are N-(O,O'-Dimethyl)phosphoryl-alanine (DMP-Ala), N-(O,O'-Dimethyl)phosphoryl-valine (DMP-Val), N-(O,O'-Dimethyl)phosphoryl-leucine (DMP-Leu), N-(O,O'-Dimethyl)phosphoryl-isoleucine(DMP-Ile) and N-(O,O'-Dimethyl)phosphoryl-phenylalanine (DMP-Phe). As shown in Fig.3, stereoisomeric IMCPAs can be formed through two pathways. In pathway (1), the reaction is initiated by the attack of O1 on P through the plane defined by O2, N and O3. With the formation of O1-P bond, O2, N and O3 gradually go into coplane with P, and finally become the IMCPA with O1-P and O4-P as the two apical bonds. In pathway (2), O1 attacks P through the plane defined by O2, N and O4, and finally become the IMCPA with P-O2, P-O4, P-N as the three equatorial bonds and P-O1, P-O4 as the two apical bonds.

The mechanisms of stereoisomeric IMCPAs formed from each of these N-phosphorylamino-acids are studied at B3LYP/6-311+G(d,p) level. All molecular structures are full optimized and all transition states are located by QST2 method. The frequency calculations are performed for all stationary points to verify either that they are energy minimum with all positive frequencies or that the transition states with only one imaginary frequency. After transition states are obtained, intrinsic reaction coordinate (IRC) calculations are carried out to follow the reaction pathway in both directions, leading back to the N-phosphorylamino-acid as well as to the penta-coordinate phosphorus intermediate.

All calculations presented here are performed with GAUSSIAN 03 package [16] on a PC cluster.

3 Results and discussion

The optimized molecular structures of the five N-phosphorylamino-acids are shown in Fig. 3. The distance of O1···O2 in the molecular structures are all between 2.70Å~2.80Å and the angle of O1-H1-O2 is 172.1° averagely. There is an intramolecular hydrogen bond between the carboxyl group and the phosphoryl group. It can be seen that the hydroxyl group is on a favorable position for the nucleophilic attack of P after the proton shift through the intramolecular hydrogen bond. Moreover, in the five molecules, O1 is almost on the plane of O2-P-N, which divides the square pyramidal phosphate group equally. This structure suggests that the nucleophilic attack of P by O1 may proceeds from two sides of the phosphate group. When the reaction goes through pathway (1), O1 departs from the plane of O2-P-N and closes to the line of P-O4 gradually. In a similar way, when the reaction goes through pathway (2), O1 closes to the line of P-O3 gradually.

The optimized molecular structures of the IMCPAs and transition states are shown in Fig. 4. and the main structural parameters are listed in Table 1 (DMP-Ala is taken for an example). Both of the two IMCPAs are take TBP configuration, however, in the transition states, the phosphorus take square pyramidal (SPY) configuration. IRC calculations show that the N-P bond rotates obviously during the proton shift, but the rotation takes opposite directions. In pathway (1), the N-P bond rotates 22.8° clockwise; in pathway (2), it rotates 72.1° anti-clockwise (see Fig.4). The N-C1 bond also rotates obviously. The dihedral of P-N-C1-C2 is 79.2° in DMP-Ala, 16.2° in TS1 and 25.7° in TS2. In the molecular structures of the transition states, the two sides of the phosphate group are opened slightly and O1 is situated on the appropriate position for the attack of P.

Both of the two stereoisomers are constitute with a five-membered ring and the ring is almost planar. But on the two sides of plane of the ring, the spatial positions of substituent groups are distinctly different. In the molecule of cis-IMCPA isomer, which forms through pathway (1), the –CH3 on the α-carbon of the amino group and the –OCH3 on the equatorial bond are on the same side of the ring plane. In the molecule of trans-IMCPA isomer, which forms through pathway (2), the –CH3 of the amino group and the –OCH3 on the equatorial bond are on the different side of the ring plane.

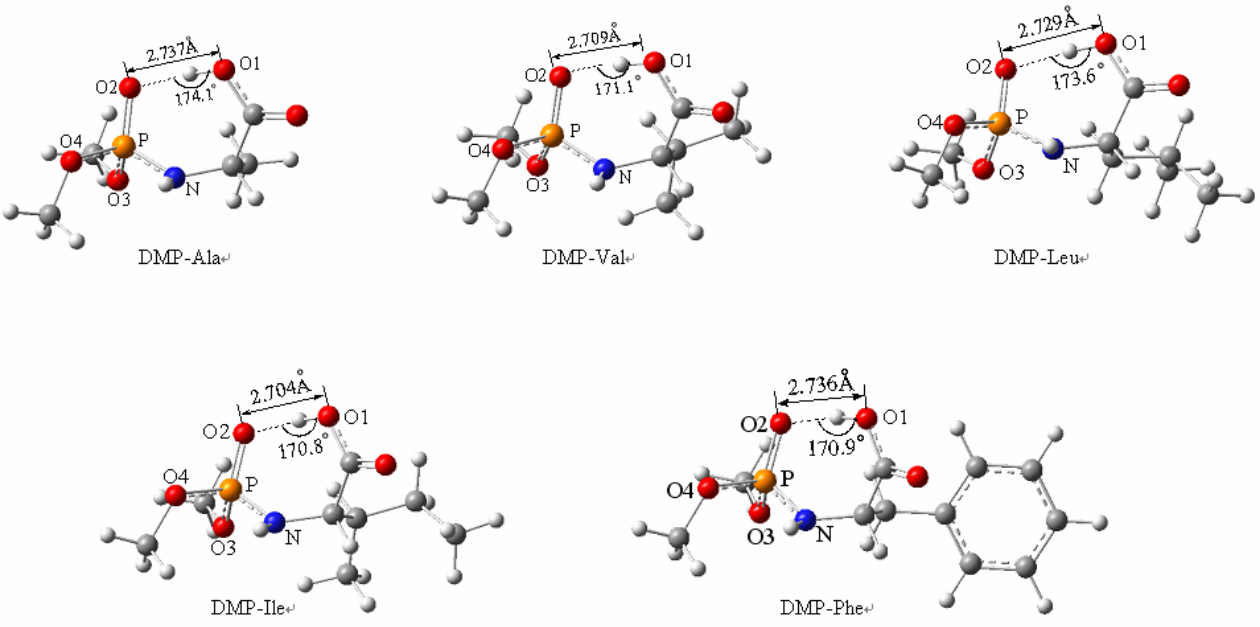

Fig. 3. The optimized molecular structures of six N-phosphorylamino-acids obtained from B3LYP/6-311+G(d,p) calculation

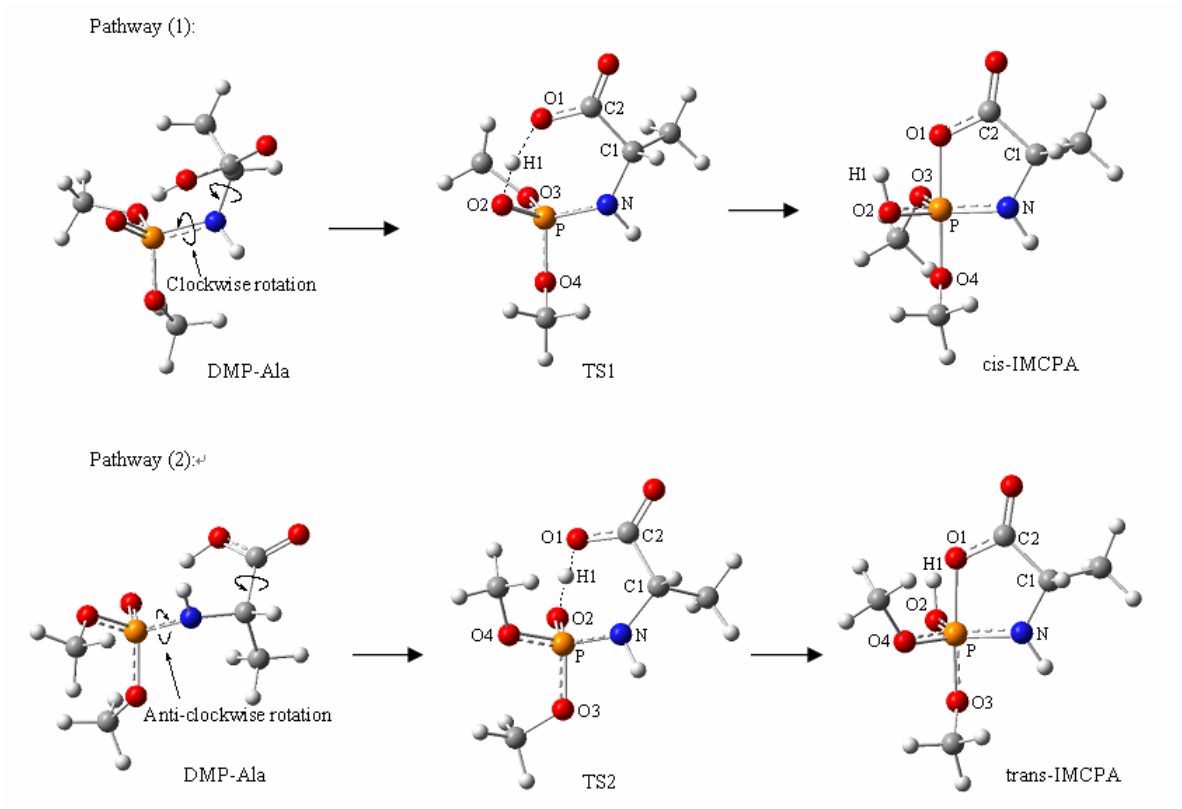

Fig. 4. The molecular structures of transition states and IMCPAs formed from N-phosphoryl-alanine obtained with B3LYP/6-311+G(d,p) optimization

Table 1 Main structural parameters of the transition states and the IMCPAs formed from N-phosphoryl-alanine obtained with B3LYP/6-311+G(d,p) calculation

	TS1	cis-IMCPA	TS2	trans-IMCPA
Bond /Å				
O1···H1	1.402	2.044	1.402	2.052
O2-H1	1.075	0.969	1.078	0.969
O1···O2	2.371	2.366	2.381	2.389
P-O1	2.549	1.798	2.572	1.834
P-O2	1.563	1.633	1.563	1.625
P-O3	1.587	1.619	1.596	1.652
P-O4	1.600	1.669	1.595	1.622
P-N	1.641	1.671	1.638	1.671
Angle /°				
O1-P-O2	65.4	87.1	65.1	87.1
O1-P-O3	87.8	87.0	168.5	175.5
O1-P-O4	170.6	178.3	89.8	91.0
O1-P-N	76.8	86.6	75.9	85.6
O2-P-O3	113.2	115.1	107.8	89.8
O2-P-O4	107.2	92.4	112.3	115.2
N-P-O2	115.9	123.6	117.2	123.6
N-P-O3	114.3	120.4	101.1	93.3
N-P-O4	102.6	92.4	114.7	120.8
O1···H1-O2	145.9	97.0	147.2	98.1

Table 5-6 (Continued)

	TS1	cis-IMCPA	TS2	trans-IMCPA
Dihedral /°				
O1-P-N-C1	-9.7	-8.7	-20.5	-2.9
O2-P-N-C1	-63.6	-92.9	31.3	80.7
P-N-C1-C2	16.2	9.4	25.7	2.9
N-C1-C2-O1	-12.6	-4.5	-8.9	-0.9
O2-P-O3-N	136.2	169.5	123.5	123.6
O2-P-O4-N	116.5	94.5	135.0	172.2
O2-P-O3-O4	110.6	96.3	110.9	93.6
O1···H1-O2-P	10.8	-1.8	-1.6	0.1
O1···O2-P-N	59.8	83.9	-57.3	-82.8

The computed relative energies of the penta-coordinate phosphorus intermediates and the transition states are listed in Table 2. The relative energy of the cis-IMCPAs is lower than that of the trans-IMCPAs formed from the same N-phosphoryl-amino-acid. Contrary, the activation energies of pathway (1) are higher than that of pathway (2) for a same N-phosphorylamino-acid. Fig. 5 shows the schematic energy profile of cis- and trans-IMCPA formed from N-phosphoryl-leucine, as well as the optimized geometries of the penta-coordinate phosphorus intermediates and the transition states. The results show that the cis-IMCPA isomer, which is more stable than the trans-IMCPA isomer, can be formed if the reaction surmounts the higher energy barrier of pathway (1).

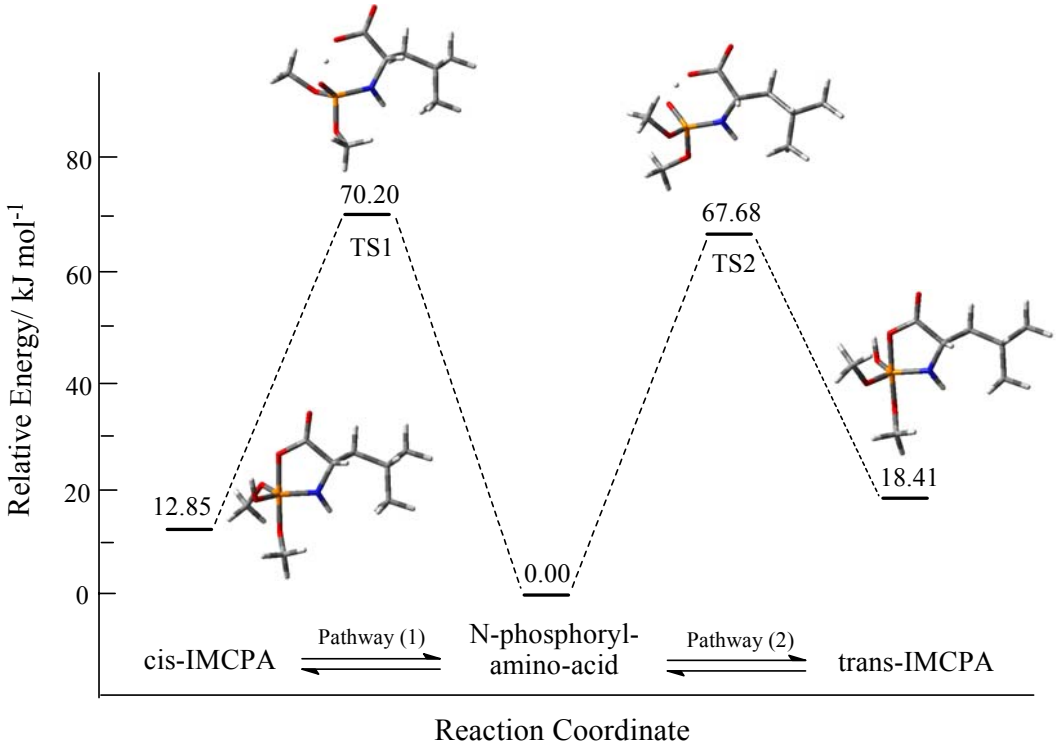

Fig.5 Schematic energy profile of cis- and trans-IMCPA formation from N-phosphoryl-leucine

Table 2 The relative energies of the IMCPAs and the transition states computated at B3LYP/6-311+G(d,p) level (kJ/mol)

		DMP-Ala	DMP-Val	DMP-Leu	DMP-Ile	DMP-Phe
Pathway (1)	TS1	75.78	71.65	70.20	81.71	62.33
	cis-IMCPA	17.69	13.91	12.85	21.81	8.09
Pathway (2)	TS2	74.45	67.09	67.68	75.69	62.29
	trans-IMCPA	23.73	19.43	18.41	27.40	14.13
Δ E	ETS1-ETS2	1.33	4.56	2.52	6.02	0.04
	Ecis-Etrans	-6.04	-5.52	-5.56	-5.59	-6.04

4 Conclusion

The results of the theoretical study show that the activation energy of the reaction pathway (1) by which the cis-IMCPA formed is higher than that of the pathway (2) by which the corresponding trans-IMCPA formed. However, all the cis-IMCPAs are more stable than their trans isomers. In any case, it is evidenced that the reaction has some stereo-selectivity, which may retain and even magnify the chirality of amino-acids in the following reactions and finally affect the stereo chemical characters of the biomolecular system. As common accepted, when prebiotic chemical evolution occurred approximately 4 thousand million years ago, the prebiotic "soup", where chemical reactions proceeded, was very hot. Under that condition, the reaction were thermodynamic controlling, in other words, the cis-IMCPA might be favorable.

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