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遗传密码子起源的化学模型研究与芳基氧化
磷的合成研究

A Chemical Model for Genetic Code Origin and Study on the
Synthesis of Aryl Phosphine Oxide

王 涛

指导教师姓名: 赵玉芬 教 授

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**A Chemical Model for Genetic Code Origin and
Study on the Construction of C-P Bond**

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Tao Wang

Dissertation Supervisor: Prof. Yu-Fen Zhao

Department of Chemical Biology, Xiamen University

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摘 要

遗传密码子的起源问题是世界上重大的科学问题,一直受到整个科学界关注和探索。从遗传密码子表中分析得出三联体遗传密码子中,氨基酸的编码与遗传密码三联体中间的核苷有直接关系。无机磷作为前生源条件下可能存在的缩合试剂,对研究生命起源过程具有重要意义。

本文建立了简单的化学模型(氨基酸、核苷和磷试剂)。将苯丙氨酸和核苷转变成N,O-BTMS- α -苯丙氨酸和O-TMS-核苷,三氯氧磷作为核苷和氨基酸的活化剂来研究氨基酸成肽与核苷之间的关系,进一步研究密码子起源的化学机理。使用UV和MRM双重定量产物苯丙-苯丙二肽方法对模型进行研究,相关系数R均在0.999以上,样品的RSD(%)均小于2%。质谱定量的实验结果与色谱定量的实验结果相互印证,苯丙氨酸在核苷A和U的存在下产生的二肽量高于核苷G、C的影响。通过六配位磷模型的理论分析,当第1位碱基(A/G/C/U)固定时,第2位碱基为U, XpaaY过渡态的生成焓最低,佐证了原始密码子三联体主要由第2位碱基来编码,苯丙氨酸的密码子为UUU和UUC。因此本论文的理论验证了密码子第2位碱基的重要性,可以推断此化学模型对研究前密码子起源是合理的。

天文学者发现太阳系中存在与地球类似的行星,为了考察这类行星上是否存在某种生命形态,多种因素如磁场、水、温度、辐射、重力的改变被考虑是否为地外生命存在的必要条件。重力作为一个非常重要的外界因素是科学家一直关注的问题。由于空间条件的限制,我们采用大梯度超导磁体模拟空间重力环境(失重和超重)来研究密码子能否被准确翻译,初步探索了核苷对氨基酸成肽的影响。

在过去的二十年,过渡金属催化C-P键交叉偶联反应在生物、医药、材料和催化领域中的广泛应用引起了越来越多科研工作者的关注。本文开展了一种新颖的、高效的钨催化三芳基钨与P(O)-H化合物交叉偶联构建C-P键的新方法。该方法反应条件相对温和,对空气、水不敏感,操作简便可实现高产率的制备。三芳基钨作为原子经济性的绿色偶联试剂首次运用到过渡金属催化构建各种芳基氧化膦,芳基膦酸酯和芳基次膦酸酯化合物。此外,我们对反应提出了较为合理的反应机理并首次运用DFT密度泛函理论对三芳基钨与P(O)-H偶联的反应机理进

行研究。

关键词：肽；磷试剂；强磁重力环境；HPLC-MS；铋化合物

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Abstract

The origin of the genetic code has been recognized as one of the most important scientific problems, which has attracted increasing attention and exploration. The genetic code is a triplet code. Inorganic phosphorus compounds probably played the key role as condensation reagents for peptide formation in prebiotic evolution, which is of great significance to the study on the origin process of life.

In considering the chemical origins of life, there is a significant "chicken and egg" problem, with regard to which came first, since both seem to require the pre-existence of the other. What is the interaction between them? How did this relation influence the chemical evolution? Why did nature choose the present genetic code? These are very important questions in the study of origin of life. However, there was no example combining theoretical and experimental tests for the model for the origin of the genetic code origin mentioned before. There is a considerable need for an experimental model for the study of the origin of genetic code. Based on our research in the area of the origins of genetic coding and phosphorus chemistry, we have therefore developed a simplified chemical model for the study of the origins of the genetic code. Three components α -amino acid, phosphorus compounds and nucleosides (A/G/C/U) could form a simple system as a chemical model for the genetic code. Peptide yields could be determined quantitatively by HPLC-MS, and were found to vary in the presence of nucleosides due to presumed stereochemically interaction. Herein, we report an α -amino acid, nucleoside and phosphorus oxychloride, three-component model system, that coexist in aprotic solvents. Differences of dipeptide yields are related to the types of nucleosides. These provide a basis for the study of the putative pre-codon phase. In our chemical model system, the dipeptides and dinucleotides are generated simultaneously, thus connecting amino acid and nucleoside chemistry, and offer a new perspective in the study of the origin of life. Within this model system, the amino acids and nucleosides was replaced by

N,O-bis(trimethylsilyl)- α -amino acids and O-(trimethylsilyl)-nucleosides. POCl₃ was chosen as the optimized phosphorous reagent that could mediated N,O-bis(trimethylsilyl)- α -amino acids and O-(trimethylsilyl)-nucleosides, and oligomerize into dipeptides in aprotic solvents. Phenylalanine amino acid was transformed into (Phe-Phe) dipeptide in a much higher yield under the presence of uridine and phosphorus reagent than under the presence of either guanosine or cytidine. These experimental results were well-confirmed with the theoretical calculation results, indicating that this chemical model is reasonable for the pre-coding proposal and uridine is the contemporary code for phenylalanine. In addition, HPLC-MS-MRM was applied in this system for the double-check of the dipeptide yield.

The earth-like planet was found in the solar system, and that there may also be some kind of life on the planet. There could be many factors conditionality within the origin of life, such as magnetism, water, temperature, radiation, gravity and so on. But gravity could be one of the key factors. Hence, the experiment about the effect of gravity on the peptide formation in the presence of nucleoside was preliminary exploration.

Transition-metal-catalyzed carbon-phosphorus bond formation by cross-coupling reaction has attracted increasing attention in the last two decades due to its wide applicability in biological, pharmaceutical, material and catalytic sciences. This manuscript describes a novel and highly efficient Pd-catalyzed cross-coupling of environmentally benign triarylbiaryls with a variety of P(O)-H compounds resulting in the C-P formation, which proceeded smoothly without exclusion of moisture or air, with high atom-economy, operational simplicity of the procedure and good to high yield. To the best of our knowledge, this method is the first example of transition-metal-catalyzed cross-coupling of triarylbiaryls with P(O)-H compounds leading to various aryl-phosphorus compounds. This work provides a general and powerful methodology for the preparation of various valuable arylphosphonates, arylphosphinates and arylphosphine oxides, which would be very useful in synthetic programs. In addition, density functional theory calculations were carried out to

investigate the reaction mechanism in this paper and this work may open a new avenue to the C-P bond formation.

Keywords: peptide; phosphorous reagent; high magneto-gravitational; HPLC-MS; bismuth compounds

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主要符号缩写表

符号	英文含义	中文含义
A	Adenosine	腺苷
BAPPO	4,4'-[(Phenylphosphinylidene)bis(4,1-phenyleneoxy)]bisbenzenamine	4,4'-[(苯基亚膦酰)双(4,1-苯氧基)]双苯胺
Bpy	2,2'-Bipyridine	2,2'-联吡啶
BTMS	Bis-(trimethylsilyl)	二-(三甲基硅基)
C	Cytidine	胞苷
DFT	Density functional theory	密度泛函理论
DIPPH	<i>O,O'</i> -diisopropyl phosphite	二异丙基氢亚磷酸酯
DMF	<i>N,N</i> -dimethylformamide	<i>N,N</i> -二甲基甲酰胺
DMSO	Dimethylsulfoxide	二甲亚砜
DMEDA	<i>N,N'</i> -Dimethylethanediamine	<i>N,N'</i> -二甲基乙二胺
DOPO	6H-dibenz(C,E)(1,2)oxaphosphorin-6-oxide	9,10-二氢-9-氧杂-10-磷杂菲-10-氧化物
Dppp	1,3-Bis(diphenylphosphino)propane	1,3-双(二苯基膦)丙烷
ESI-MS	Electrospray Ionization Mass Spectrometry	电喷雾电离质谱
FT-MS	Fourier transform -mass spectrometer	傅立叶变换质谱计
FWHM	Full width at half maximum	半高宽
G	Guanosine	鸟苷
HMDS	Hexamethyldisilazane	六甲基二硅胺烷
HPLC-MS	High Performance Liquid Chromatography mass spectrometry	高效液相色谱质谱仪

HR-MS	High resolution mass spectrometry	高分辨质谱
IRC	Intrinsic reaction coordinate	内禀反应坐标
ISS	International Space Station	国际空间站
LOI	Limiting oxygen index	极限氧指数
LUMO	Lowest unoccupied molecular orbital	最低空轨道
Lys	Lysine	赖氨酸
MALDI	Matrix assisted laser desorption ionization	基质辅助激光解析电离
MRM	Multiple reaction monitoring	多反应监测
NBS	<i>N</i> -bromosuccinimide	<i>N</i> -溴代丁二酰亚胺
NMM	<i>N</i> -methylmorpholine	<i>N</i> -甲基吗啉
P ₃ m	Trimetaphosphate	偏三聚磷酸盐
PCM	Polarizable continuum model	极化连续介质模型
phen	Phenanthroline	菲罗啉
phe	Phenylalanine	苯丙氨酸
pro	Proline	脯氨酸
py	Pyridine	吡啶
PyBroP	Bromo(tripyrrolidin-1-yl)phosphonium hexafluorophosphate	三吡咯烷基溴化磷六氟磷酸盐
R.T.	Room Temperature	室温
SCRF	Self-consistent reaction field	自洽反应场
SRM	Selected reaction monitoring	选择性反应监测
THF	Tetrahydrofuran	四氢呋喃
TLC	Thin layer chromatography	薄层色谱
TMEDA	Tetramethylethylenediamine	<i>N,N,N,N</i> -四甲基乙二胺
TMS	Trimethylsilyl	三甲基硅基
TS	Transition state	过渡态
U	Uridine	尿苷

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