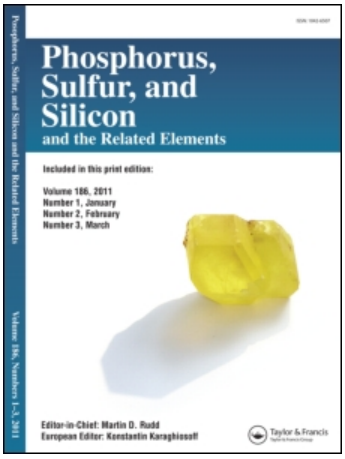


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Theoretical Prediction of ^{31}P NMR Chemical Shifts of Intermediates in Phosphoryl Ester Exchange and N → O Migration Reactions of Dialkyloxyphosphoryl Amino Acid

Chang-Guo Zhan

To cite this Article Zhan, Chang-Guo(1999) 'Theoretical Prediction of ^{31}P NMR Chemical Shifts of Intermediates in Phosphoryl Ester Exchange and N → O Migration Reactions of Dialkyloxyphosphoryl Amino Acid', Phosphorus, Sulfur, and Silicon and the Related Elements, 144: 1, 655 — 658
To link to this Article: DOI: 10.1080/10426509908546330
URL: http://dx.doi.org/10.1080/10426509908546330

Phosphorus, Sulfur and Silicon, 1999, Vol. 144-146, pp. 655-658
Reprints available directly from the publisher
Photocopying permitted by license only

Theoretical Prediction of ^{31}P NMR Chemical Shifts of Intermediates in Phosphoryl Ester Exchange and N → O Migration Reactions of Dialkyloxyphosphoryl Amino Acid

CHANG-GUO ZHAN

Department of Chemistry, Central China Normal University, Wuhan 430070, P. R. China and Radiation Laboratory, University of Notre Dame, Notre Dame 46556, USA

Based on a detailed *ab initio* study on the reaction mechanism of phosphoryl ester exchange and N → O migration reactions of dimethyloxyphosphoryl-threonine, *ab initio* GIAO magnetic shielding calculations have been carried out on the predicted stable intermediate and the corresponding reactant and product. The ^{31}P NMR chemical shift of the most stable penta-coordinate phosphorus intermediate has been predicted as about −71 ppm. The theoretical results may lead to a possible way to experimentally examine our predictions and to monitor the most stable intermediate during the reaction process.

Keywords: ^{31}P NMR chemical shift; phosphorylated amino acid; reaction mechanism

INTRODUCTION

Phosphorylated protein plays a vital role in many biological aspects because a large number of biological processes.[1-6] Numerous

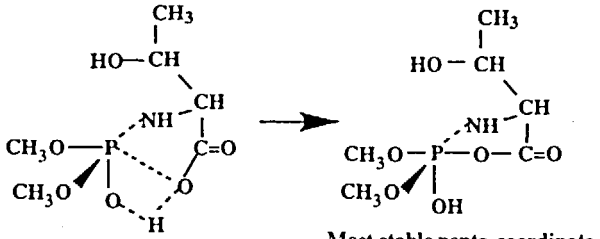
experimental studies on the structure-reactivity relationship about the phosphorylated amino acids have been carried out in order to understand the intrinsic relationship between the phosphoryl group and the amino acid residues in the proteins, and much attention has been focused on regulation effect of phosphoryl group on side chain of amino acid,[4-6] such as $(R'O)_2P(O)$-NHCH(COOH)CH(R)OH. The experimental results reveal an important fact that the side chains of the amino acids act as the relay device to modulate the chemical reactivity of the N-phosphoryl amino acids. It was found in the experimental studies[4-6] that in alcoholic media the phosphoryl ester exchanges took place with the concomitant phosphoryl transfer from amino to hydroxyl together with the peptide's formation reaction. This unusual reactivity could be blocked when the carboxyl group was protected as ester or the carboxyl group is replaced by something else.

Considered in this work is dimethyloxyphosphoryl-threonine, a simplified model system for studying the regulation effect of phosphoryl group on side chain of phospholated amino acid involving the three essential functional groups mentioned above. The goal of our work on this project is to understand the detailed reaction mechanism and to predict some characteristic properties of the stable intermediates which could be examined and monitored experimentally during the reaction process.

REACTION MECHANISM

We have also studied the detailed reaction mechanism with HF/6-31G(d,p) method followed by MP2/6-31G(d,p) energy calculation.[7,8] We have found two reaction paths for the N → O migration reaction from $(CH_3O)_2P(O)$-NHCH(COOH)CH(CH_3)OH (**1a**) to $(CH_3O)_2P(O)$-OCH(CH_3)CH(NH_2)COOH (**1c**).[7] and, also, two paths for the corresponding ester exchange reaction. For each of the two kinds of reactions, the reaction path with lower energy barrier is always associated with participation of the carboxyl group as an intramolecular catalyst. Due to participation of the carboxyl group, the highest energy barrier for the migration reaction changes from 58.0 kcal/mole to 51.1 kcal/mole, and that for the ester exchange reaction

changes from 46.4 kcal/mole to 35.0 kcal/mole. Both kinds of reactions have a common penta-coordinate phosphorus intermediate (**1e**) through a transition state (**1d**). **1e** has been predicted as the most stable one of intermediates existing in the reaction process, and its energy calculated is only about 1.1 kcal/mole higher than the corresponding reactant.[8] One can also see that in the presence of base, this most stable penta-coordinate phosphorus intermediate may lose a proton to form the hexa-coordinate phosphorus intermediate anion (**1b**).[4-7]



Transition state (1d)

Most stable penta-coordinate phosphorus intermediate (1e)

^{31}P NMR CHEMICAL SHIFTS

We have further carried out *ab initio* GIAO magnetic shielding calculation on the most stable penta-coordinate phosphorus intermediate and the hexa-coordinate phosphorus intermediate anion at HF/6-311+G(d,p)//HF/6-31G(d,p) level. The same level of GIAO procedure has also been performed on the reactant, product and H_3PO_4 (used as the reference of the ^{31}P NMR chemical shift). The ^{31}P NMR chemical shifts calculated for the most stable penta-coordinate phosphorus intermediate (**1e**) and the hexa-cooordinate phosphorus intermediate (**1b**) are -71 and -138 ppm, respectively. Changing HF/6-31G(d,p) geometry into MP2/6-31G(d,p) geometry, the changes of the calculated ^{31}P NMR chemical shift for the hexa-coordinate phosphorus[9] are within 0.2 ppm.

It may be helpful for the estimation of the ^{31}P NMR chemical shifts of the hexa-coordinate phosphorus intermediates in the similar reactions to compare our calculated ^{31}P NMR chemical shifts of the **1a** and **1c** with the experimental data reported for the analogous

dialkyloxyphosphoryl amino acids. The experimental ^{31}P chemical shift of N-diisopropyloxyphosphoryl-threonine (**2a**) was reported as 6.1 ppm, which is very close to our calculated ^{31}P NMR chemical shift 4.9 ppm of **1a**. The experimental ^{31}P chemical shift of O-butyloxyisopropyloxyphosphoryl-threonine (**3c**) was reported as -2.8 ppm which can reasonably compare with our calculated ^{31}P NMR chemical shift -6.6 ppm **1c**. It is expected that this prediction will help the experimentalists to look for the signals and to confirm the reaction mechanism by a further experimental NMR study using a powerful high-resolution ^{31}P NMR technique.

CONCLUSION

In summary, ^{31}P NMR chemical shift of the most stable penta-coordinate phosphorus intermediate has been predicted as about -71 ppm, which could be observed experimentally during reaction process. ^{31}P NMR chemical shift of the hexa-coordinate phosphorus intermediate anion, which may exist in solution of strong base, has also been predicted as about -138 ppm.

References

[1] P. Cohen *ed., Recently Discovered Systems of Enzyme Regulation by Reversible Phosphorylation* (Elsevier, New York, 1980).
[2] A. J. Zaug, J. R. Kent, and T. R. Cech, *Science,* **224,** 574 (1984).
[3] U. Yarden, and A. Ullrich, *Annu. Rev. Biochem.,* **57,** 443 (1988).
[4] C. B. Xue, Y. W. Yin, and Y. F. Zhao, *Tetrahedron Lett.,* **29,** 1145 (1988).
[5] Y. M. Li, and Y. F. Zhao, *Phosphorus, Sulfur and Silicon.,* **76,** 15 (1993).
[6] Y. F. Zhao, Y. M. Li, Y. W. Yin, and Y. C. Li, *Sci. China,* **36,** 145 (1993).
[7] C.-G. Zhan, and S. Iwata, *Chem. Phys. Lett.,* **247,** 401 (1995); **253,** 372 (1996).
[8] C.-G. Zhan, to be submitted.
[9] C.-G. Zhan, and S. Iwata, *Chem. Lett.,* 3 (1997).