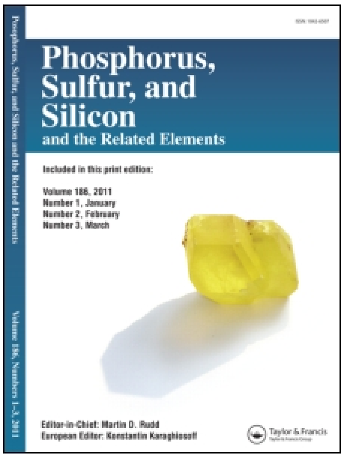
This article was downloaded by:
On: *29 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



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

N-PHOSPHORYL AMINO ACIDS AND PEPTIDES: PART V: O-ALKYL SUBSTITUTION EFFECTS ON THE ^{31}P-NMR SPECTRA OF PHOSPHORAMIDATES

Yi Chen[a]; Yu-Fen Zhao[a]; Ying-Wu Yin[b]; Xu-Qing Yang[b]
[a] Department of Chemistry, Tsinghua University, Beijing, China [b] Beijing Xing-da Scientific System Corporation, Tsinghua Yan Beijing, China

To cite this Article Chen, Yi , Zhao, Yu-Fen , Yin, Ying-Wu and Yang, Xu-Qing(1991) 'N-PHOSPHORYL AMINO ACIDS AND PEPTIDES: PART V: O-ALKYL SUBSTITUTION EFFECTS ON THE ^{31}P-NMR SPECTRA OF PHOSPHORAMIDATES', Phosphorus, Sulfur, and Silicon and the Related Elements, 61: 1, 31 — 39

To link to this Article: DOI: 10.1080/10426509108027334

URL: http://dx.doi.org/10.1080/10426509108027334

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur, and Silicon, 1991, Vol. 61, pp. 31–39
Reprints available directly from the publisher
Photocopying permitted by license only

© 1991 Gordon and Breach Science Publishers S.A.
Printed in the United Kingdom

N-PHOSPHORYL AMINO ACIDS AND PEPTIDES: PART V: O-ALKYL SUBSTITUTION EFFECTS ON THE ^{31}P-NMR SPECTRA OF PHOSPHORAMIDATES

YI CHEN and YU-FEN ZHAO*
Department of Chemistry, Tsinghua University, Beijing 100084, China

and

YING-WU YIN, XU-QING YANG
Beijing Xing-da Scientific System Corporation, Tsinghua Yan Beijing 100084, China

(Received December 10, 1990; in final form January 8, 1991)

The N-(O,O-dialkyl) phosphoryl derivatives of amines and amino acids demonstrated additive O- and N-alkyl substitution γ, δ and ε effects on the ^{31}P-NMR spectra. In general, the O-alkyl substitution generated much more profound influence than the N-alkylated one.

Key words: Additive steric effects; ^{31}P-NMR shifts; N-(O,O-dialkyl) phosphoryl amino acids; γ shielding effect.

Downloaded At: 15:41 29 January 2011

INTRODUCTION

The correlation of the steric effect on the ^{31}P-NMR for the phosphine, phosphonates and phosphate compounds had been reported.[1–5] Similar results had been extended to the phosphoramidates.[6] Among the above examples, only one of the three substitutents' consequence was considered. In this paper, both the O-alkyl and N-alkyl substitution were taken into account. It was found that for a phosphoryl compound, such as the phosphoramidate, the steric effect caused by the O-alkylation was much more profound than that which arises from the N-alkyl groups. Also, it indicated that these two effects were additive. For a O,O-dialkyl N-alkyl phosphoramidate the ^{31}P-NMR shift in ppm relative to 85% H_3PO_4 as standard may be calculated from the expression

$$^{31}\mathrm{P} = \delta\ \mathrm{parent} + [n_\beta\beta + n_\gamma\gamma + n_\delta\delta + n_\varepsilon\varepsilon]^{\mathrm{Oxygen}} + [n_\beta\beta + n_\gamma\gamma + n_\delta\delta + n_\varepsilon\varepsilon]^{\mathrm{Nitrogen}}$$

Indeed, this equation could be applied to five types of compounds, dialkyl phosphite, trialkyl phosphate, O,O-dialkyl-N-dialkyl phosphoramidate, O,O-dialkyl-N-alkyl phosphoramidate and the O,O-dialkyl N-phosphoryl amino acids. For each class of compound, the steric effects could be divided into two parts, the oxygen term and the nitrogen term where n is the number of the carbons on each position. The constants β, γ, δ and ε represent the extent of the steric effects on each position.

Downloaded At: 15:41 29 January 2011

RESULTS AND DISCUSSION

In Table I, the O-substitution steric effect on the ^{31}P-NMR chemical shift of the dialkyl phosphites **1–5** was first analyzed, as shown in Equation 1. The γ and δ constants were deduced from the differences between **1**, **2**, and **3**, as −1.6 ppm/carbon and 0.2 ppm/carbon respectively. These two values could also be derived from compounds **2**, **3** and **5**. The strong γ shielding effect might reflect an unusual conformation of the dialkyl phosphites **1–5**. In compound **4** there were two ε carbons, but the ε effect was not yielding to any shielding shift.

$$\begin{aligned} \delta\,^{31}P &= \delta\text{ parent} + n_\gamma\gamma + n_\delta\delta + n_\varepsilon\varepsilon \\ &= 10.4 + n_\gamma(-1.6) + n_\delta(0.2) \end{aligned} \tag{1}$$

When the temperature was raised from 25° to 60°, a 0.1 to 0.4 ppm upfield shift was observed for each dialkylphosphite **1–5**. It could be that the γ constant but not the δ constant is more sensitive to the temperature fluctuation. At higher temperature, the shielding effect increased. For the trialkyl phosphates **6–17**, the Equation 2 was derived as above. Since there were three β carbons on each of them, the β term was also put into the δ parent term. In order to fit most of the

TABLE I

O-Substitution effects on the ^{31}P-NMR shifts of $(RO)_2\overset{O}{\overset{\|}{P}}H$ $\delta\,^{31}P = 10.4 + n_\gamma(-1.6) + n_\delta(0.2)$

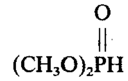
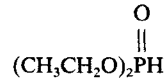
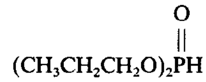
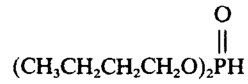
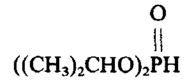
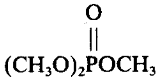
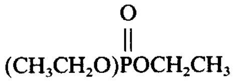
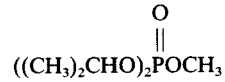
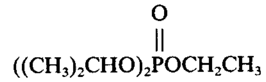
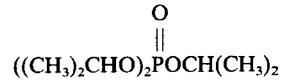
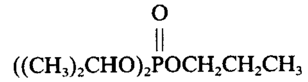
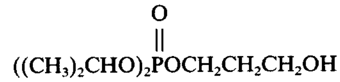
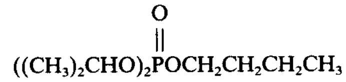
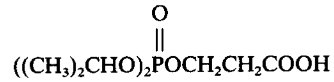
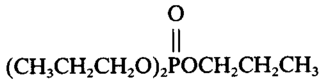
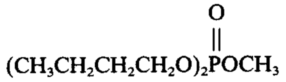
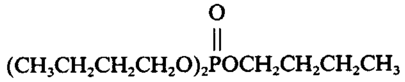
		The number of substituent			δ (ppm)		
Entry	Structure	n_γ	n_δ	n_ε	25°	60°	calc.
1	 $(CH_3O)_2\overset{O}{\overset{\|}{P}}H$	0	0	0	10.4	10.3	10.4
2	 $(CH_3CH_2O)_2\overset{O}{\overset{\|}{P}}H$	2	0	0	7.2	6.8	7.2
3	 $(CH_3CH_2CH_2O)_2\overset{O}{\overset{\|}{P}}H$	2	2	0	7.6	7.3	7.6
4	 $(CH_3CH_2CH_2CH_2O)_2\overset{O}{\overset{\|}{P}}H$	2	2	2	7.6	7.3	7.6
5	 $((CH_3)_2CHO)_2\overset{O}{\overset{\|}{P}}H$	4	0	0	4.2	3.9	4.0

TABLE II

O-Substitution effects on the ^{31}P-NMR shifts for $(R^1O)_2\overset{\overset{O}{\|}}{P}OR^2$ $\delta\ ^{31}P = 2.2 + n_\gamma(-1.0) + n_\delta(0.1) + n_\varepsilon(-0.1)$

		The number of substituent			δ (ppm)	
Entry	Structure	n_γ	n_δ	n_ε	obs.	calc.
6	 $(CH_3O)_2\overset{\overset{O}{\|}}{P}OCH_3$	0	0	0	2.2	2.2
7	 $(CH_3CH_2O)\overset{\overset{O}{\|}}{P}OCH_2CH_3$	3	0	0	−1.0	−0.8
8	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}OCH_3$	4	0	0	−1.5	−1.8
9	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}OCH_2CH_3$	5	0	0	−2.8[a]	−2.8
10	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}OCH(CH_3)_2$	6	0	0	−3.5	−3.8
11	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}OCH_2CH_2CH_3$	5	1	0	−2.7[b]	−2.7
12	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}OCH_2CH_2CH_2OH$	5	1	1	−2.9	−2.8
13	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}OCH_2CH_2CH_2CH_3$	5	1	1	−2.9	−2.8
14	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}OCH_2CH_2COOH$	5	1	2	−3.5	−2.9
15	 $(CH_3CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}OCH_2CH_2CH_3$	3	3	0	−0.7	−0.5
16	 $(CH_3CH_2CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}OCH_3$	2	2	2	0.2	0.2
17	 $(CH_3CH_2CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}OCH_2CH_2CH_2CH_3$	3	3	3	−1.0	−0.8

[a] At 60°, a value of −2.8 ppm was also observed, no temperature effect.

[b] At 60°, a value of −2.7 ppm was also observed, no temperature effect.

Downloaded At: 15:41 29 January 2011

data in Table II, the γ, δ, and ε constants were chosen as -1.0 ppm/carbon, 0.1 ppm/carbon and -0.1 ppm/carbon respectively.

$$\begin{aligned}\delta\,^{31}\mathrm{P} &= \delta\,\text{parent} + n_\gamma\gamma + n_\delta\delta + n_\varepsilon\varepsilon \\ &= 2.2 + n_\gamma(-1.0) + n_\delta(0.1) + n_\varepsilon(-0.1) \qquad (2)\end{aligned}$$

It was found that except for compound **14**, where there was a carboxylic group present, all twelve compounds were correlated well by Equation 2 within the range of ±0.3 ppm. As compared to the dialkyl phosphite **1–5**, trialkyl phosphates **6–17**, showed much less γ shielding effect.

Previously, the N-alkylation substitution effect on the ^{31}P-NMR spectra of phosphoramidate compounds was reported.[6] It was found that for primary amine derivatives a -0.6 to -0.8 ppm/carbon γ effect was obtained. While for secondary amine phosphoramidates only a -0.15 ppm γ shielding shift was detected. In Tables III, IV and V, both the O-alkylation and N-alkylation substitution effects were investigated at the same time. By the same manner, from compounds **18–24** in Table III the γ constants for the oxygen and nitrogen substituents were -1.2 ppm/carbon and -0.15 ppm/carbon respectively. The δ constant for the oxygen term was 0.1 ppm/carbon and the nitrogen term was diminished.

$$\delta\,^{31}\mathrm{P} = 13.1 + [n_\gamma(-1.2) + n_\delta(0.1)]^{\mathrm{Oxygen}} + [n_\gamma(-0.15)]^{\mathrm{Nitrogen}} \qquad (3)$$

It is interesting to note that for each substituent on the phosphoryl group, its steric effect could be analyzed separately, then the total effects were additive. For example, Table IV shows the ^{31}P-NMR shifts for the phosphoramidates **25–33** derived from the primary amines. The N-alkylation and O-alkylation effects were elaborated to give Equation 4. Not only substitution on oxygen but also those on nitrogen exhibited substantial effects.

$$\begin{aligned}\delta\,^{31}\mathrm{P} = 13.2 &+ [n_\gamma(-1.3) + n_\delta(0.3)]^{\mathrm{Oxygen}} \\ &+ [n_\gamma(-0.8) + n_\delta(0.4) + n_\varepsilon(-0.4)]^{\mathrm{Nitrogen}} \qquad (4)\end{aligned}$$

For compounds **25–33** the experimental values were close to the calculated ones within ±0.4 ppm. Similar to Table I, there was also a temperature effect on the ^{31}P-NMR shift. But in Table III for those compounds without H-bonding, there was no such effect. Table V presents the ^{31}P-NMR data of the phosphoryl amino acids **34–44**, with different alkyl groups on the oxygen and nitrogen atoms. As discussed above, Equation 5 was designed for the amino acid derivativatives **34–44**.

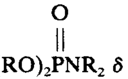
$$\begin{aligned}\delta\,^{31}\mathrm{P} = 9.7 &+ [n_\gamma(-0.9) + n_\delta(0.1)]^{\mathrm{Oxygen}} \\ &+ [n_\gamma(-0.6) + n_\delta(0.3) + n_\varepsilon(-0.3)]^{\mathrm{Nitrogen}} \qquad (5)\end{aligned}$$

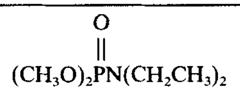
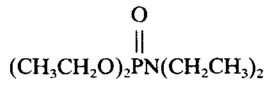
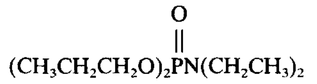
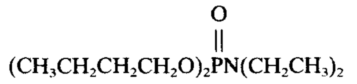
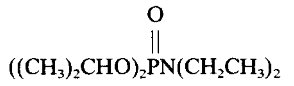
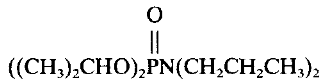
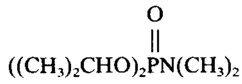
The contained N-alkyl substitution effect in Equation 5 for compounds **34–44** was consistent with that found in a previous paper where the oxygen term was fixed as the O,O-diisopropyl groups. For most straight chain amino acids a ±0.4 ppm deviation was obtained, when the detected data was compared to the calculated ones. But a 0.8 to 1.0 ppm deflection was observed for the ring amino acids compounds **40** and **41**. This indicates that ring conformation is entirely different

Downloaded At: 15:41 29 January 2011

Downloaded At: 15:41 29 January 2011

TABLE III

O- and N-substitution effects on the ^{31}P-NMR shifts of  $(RO)_2\overset{\overset{O}{\|}}{P}NR_2$ $\delta\,^{31}P = 13.1 + [n_\gamma(-1.2) + n_\delta(0.1)]^{oxygen} + [n_\gamma(-0.15)]^{nitrogen}$

		The number of substituent						
		oxygen			nitrogen		δ (ppm)	
Entry	Structure	n_γ	n_δ	n_ε	n_γ	n_δ	obs.	calc.
18	 $(CH_3O)_2\overset{\overset{O}{\|}}{P}N(CH_2CH_3)_2$	0	0	0	2	0	12.8	12.8
19	 $(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}N(CH_2CH_3)_2$	2	0	0	2	0	10.2	10.4
20	 $(CH_3CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}N(CH_2CH_3)_2$	2	2	0	2	0	10.3	10.6
21	 $(CH_3CH_2CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}N(CH_2CH_3)_2$	2	2	2	2	0	10.4	10.6
22	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}N(CH_2CH_3)_2$	4	0	0	2	0	8.3	8.0
23	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}N(CH_2CH_2CH_3)_2$	4	0	0	2	2	8.2	8.0
24	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}N(CH_3)_2$	4	0	0	0	0	8.6	8.3

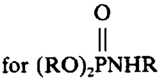
from the non ring's. Hence, a new Equation should replace Equation 5 in order to understand the steric effect on the ring. This area of research will be investigated in the future.

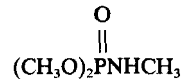
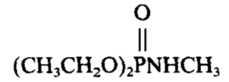
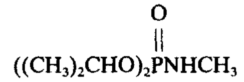
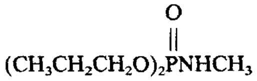
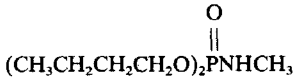
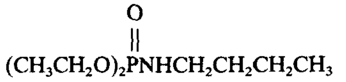
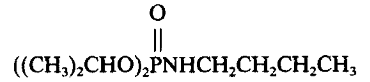
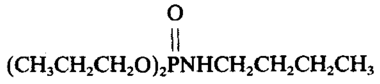
All the spectra were recorded in chloroform solutions. When the solvent was changed into polar solvent such as water, a 1.3 ppm downfield shift was observed for the N-diisopropyl phosphoryl alanine (Table VI). In basic condition, even more downfield shift occurred.

CONCLUSION

The N- and O-alkylation substitution effects on the ^{31}P-NMR of five types of phosphorus compounds have been studied. Among them, the dialkyl phosphite

TABLE IV

O- and N-substitution effects on the ^{31}P-NMR shifts for  $(RO)_2\overset{\overset{O}{\|}}{P}NHR$ $\delta\ ^{31}P = 13.2 + [n_\gamma(-1.3) + n_\delta(0.3)]^{oxygen} + [n_\gamma(-0.8) + n_\delta(0.4) + n_\varepsilon(-0.4)]^{nitrogen}$

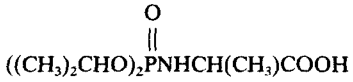
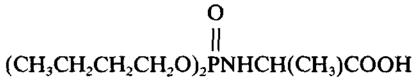
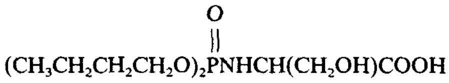
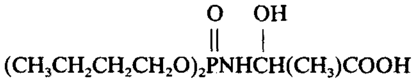
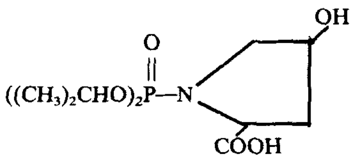
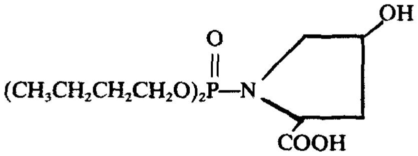
		The number of substituent						δ (ppm)		
		oxygen			nitrogen			obs.		calc.
Entry	Structure	n_γ	n_δ	n_ε	n_γ	n_δ	n_ε	25°	60°	
25	 $(CH_3O)_2\overset{\overset{O}{\|}}{P}NHCH_3$	0	0	0	0	0	0	13.2	13.0	13.2
26	 $(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}NHCH_3$	2	0	0	0	0	0	10.2	10.1	10.6
27	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}NHCH_3$	4	0	0	0	0	0	8.1	8.0	8.0
28	 $(CH_3CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}NHCH_3$	2	2	0	0	0	0	11.1	11.0	11.2
29	 $(CH_3CH_2CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}NHCH_3$	2	2	2	0	0	0	11.1	11.0	11.2
30	 $(CH_3O)_2\overset{\overset{O}{\|}}{P}NHCH_2CH_2CH_2CH_3$	0	0	0	1	1	1	12.2	11.9	12.4
31	 $(CH_3CH_2O)_2\overset{\overset{O}{\|}}{P}NHCH_2CH_2CH_2CH_3$	2	0	0	1	1	1	9.6	9.4	9.8
32	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}NHCH_2CH_2CH_2CH_3$	4	0	0	1	1	1	7.5	7.3	7.2
33	 $(CH_3CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}NHCH_2CH_2CH_2CH_3$	2	2	0	1	1	1	10.0	9.9	10.4

showed greatest γ effect, -1.6 ppm/carbon. Within the same type of compound, the O-alkyl substitution gave a much more profound γ substitution steric effect than that from the substitution on the nitrogen. But for the O,O-dialkyl-N-phosphoryl amino acids, both terms were comparable. Each steric effect could be analyzed separately and the total results were additive. These empirical equations might have potential for ^{31}P-NMR spectra study.

Downloaded At: 15:41 29 January 2011

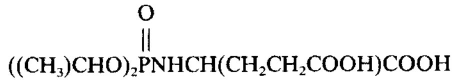
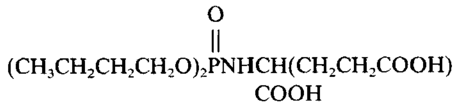
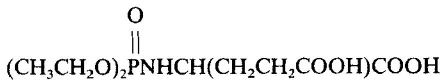
TABLE V

O- and N-substitution effects on the ^{31}P-NMR shifts for $(RO)_2\overset{\overset{O}{\|}}{P}NH\overset{\overset{R^1}{|}}{C}HCOOH$ δ $^{31}P = 9.7 + [n_\gamma(-0.9) + n_\delta(0.1)]^{oxygen} + [n_\gamma(-0.6) + n_\delta(0.3) + n_\varepsilon(-0.3)]^{nitrogen}$

		The number of substituent						(ppm)		
		oxygen			nitrogen			obs.		calc.
Entry	Structure	n_γ	n_δ	n_ε	n_γ	n_δ	n_ε	25°	60°	
34	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}NHCH(CH_3)COOH$	4	0	0	2	2	0	5.5	5.3	5.5
35	 $(CH_3CH_2CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}NHCH(CH_3)COOH$	2	2	2	2	2	0	7.1	6.8	7.5
36	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}NHCH(CH_2OH)COOH$	4	0	0	2	3	0	5.6	5.4	5.8
37	 $(CH_3CH_2CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}NHCH(CH_2OH)COOH$	2	2	2	2	3	0	7.4	7.3	7.8
38	 $((CH_3)_2CHO)_2\overset{\overset{O}{\|}}{P}NHCH(CH_3)(OH)COOH$	4	0	0	2	4	0	6.0	5.8	6.1
39	 $(CH_3CH_2CH_2CH_2O)_2\overset{\overset{O}{\|}}{P}NH\overset{\overset{OH}{|}}{C}H(CH_3)COOH$	2	2	2	2	4	0	7.8	7.7	8.1
40		4	0	0	3	3	0	4.4	4.2	5.2
41		2	2	2	3	3	0	6.2	5.9	7.2

Downloaded At: 15:41 29 January 2011

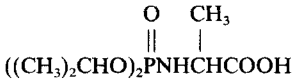
TABLE V (*Continued*)

		The number of substituent						(ppm)		
		oxygen			nitrogen			obs.		calc.
Entry	Structure	n_γ	n_δ	n_ε	n_γ	n_δ	n_ε	25°	60°	
42	 $((CH_3)CHO)_2\overset{O}{\overset{\|}{P}}NHCH(CH_2CH_2COOH)COOH$	4	0	0	2	3	1	5.4[a]		5.5
43	 $(CH_3CH_2CH_2CH_2O)_2\overset{O}{\overset{\|}{P}}NHCH(CH_2CH_2COOH)COOH$	2	2	2	2	3	1	7.5[b]		7.5
44	 $(CH_3CH_2O)_2\overset{O}{\overset{\|}{P}}NHCH(CH_2CH_2COOH)COOH$	2	0	0	2	3	1	7.5[b]		7.3

[a] In $CDCl_3$.
[b] In d_6-DMSO.

Downloaded At: 15:41 29 January 2011

TABLE VI

Solvent effects on the ^{31}P-NMR shifts for  $((CH_3)_2CHO)_2\overset{O}{\overset{\|}{P}}NH\overset{CH_3}{\overset{|}{C}}HCOOH$

Solvent:	$CHCl_3$	H_2O	N_aHCO_3	$N(C_2H_5)_3$
δ (ppm)	5.45	6.78	7.63 7.39 (trace)	8.2

EXPERIMENTAL

Methods: The ^{31}P-NMR spectra were taken on a JEOL FX-100 spectrometer at 40 MHz with probe temperature at 25°C by broad band decoupled technique with 85% H_3PO_4 as external reference. The concentrations of the samples were 25% in $CHCl_3$ in 5 mm tubes.

Materials: Compounds **6–44** were synthesized from the corresponding alcohol, amines or amino acids and the dialkyl phosphites.[7–12]

ACKNOWLEDGEMENTS

This work is supported by the Chinese National Science Fund 2860227, 2890068, a Scientific Grant from Tsinghua University and the Chinese National Science and Technology Committee Fund (89)-157 for YFZ.

REFERENCE

1. L. D. Quin and J. J. Breen, *Org. Magn. Reson.*, **5**, 17 (1973).
2. S. Li and D. B. Chesnut, *Mag. Reson. Chem.*, **23**, 625 (1985).

3. S. Li and D. B. Chesnut, *Mag. Reson. Chem.*, **24,** 93 (1986).
4. D. B. Chesnut and W. P. Johnson, *J. Mag. Reson.*, **65,** 110 (1985).
5. S. Li, Z. Y. Cheng and C. Y. Yuan, *Zhong Guo Ke Xue,* **B, 2,** 136 (1989).
6. Y. W. Yin, B. Z. Zhang, C. B. Xue, Y. Chen and Y. F. Zhao, *Phosphorus, Sulfur, and Silicon,* 1991 in press.
7. G. J. Ji, C. B. Xue, J. N. Zeng, L. P. Li, W. G. Chai and Y. F. Zhao, *Synthesis,* 444 (1988).
8. C. B. Xue, Y. W. Yin and Y. F. Zhao, *Tetrahedron Letters,* **29,** 1145 (1988).
9. J. N. Zeng, C. B. Xue, Q. W. Chen and Y. F. Zhao, *Bioorganic Chem.*, **17,** 434 (1989).
10. Y. W. Yin, B. M. Chen, C. B. Xue and Y. F. Zhao, *Phosphorus, Sulfur,* **39,** 131 (1989).
11. C. B. Xue, J. Z. Wu, Y. W. Yin and Y. F. Zhao, *Phosphorus, Sulfur, and Silicon,* **42,** 149 (1989).
12. C. B. Xue, J. Z. Wu, Y. W. Yin and Y. F. Zhao, *J. Chem. Soc., Perkin Trans.*, **II,** 431 (1990).

Downloaded At: 15:41 29 January 2011