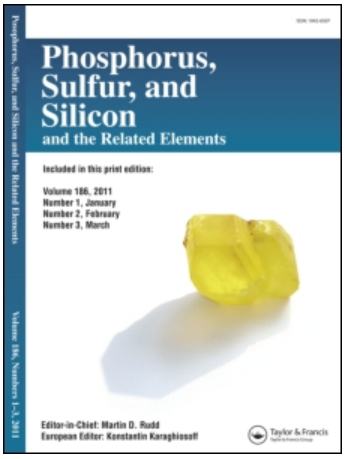

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N-PHOSPHORYL AMINO ACIDS AND PEPTIDES: PART IV: *N*-ALKYL SUBSTITUTION EFFECTS ON THE ^{31}P-Nmr SPECTRA OF PHOSPHORAMIDATES

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

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The correlations of the steric effect on the ^{31}P-NMR shifts showed that the *N*-(O,O-diisopropyl) phosphoryl derivatives of the primary amines and amino acids displayed significant γ, δ and ε effects. The phosphoryl derivatives of secondary amines only exhibited minute γ effect and the influence was almost extinguished beyond γ position.

Key words: Steric effect; *N*-(O,O-diisopropyl) phosphoramidate; ^{31}P-NMR shifts; γ shielding effect; δ deshielding effects.

INTRODUCTION

The correlations of the steric effect on the ^{31}P-NMR for various families of compounds had been studied. In general, the chain length and branch effects on the chemical shift can be interpreted in terms similar to those used for the ^{31}C- and ^{15}N-shifts. Quin reported that the ^{31}P-NMR shift for a compound in ppm relative to 85% H_3PO_4 as standard may be calculated from the expression

$$\delta^{31}P = \delta_{parent} + m\beta + n\gamma$$

where m is the number of β-carbons and n the number of γ-carbons.[1] It indicated that a β-carbon substituent was shown to deshield phosphorus, while a γ-carbon caused shielding. The effects are additive and good correlation was obtained for the phosphines. Li and Chesnut also applied the molecular mechanics to investigate these effects in the phosphonates and phosphate compounds.[2–5]

TABLE I

Substitution effects on the ^{31}P-NMR shifts for $(i\text{Pro})_2\overset{\overset{O}{\|}}{P}$—HNR (Dipp-NHR)

Entry	Structure	The number of substituent (ppm)					
		n_β	n_γ	n_δ	n_ε	obs.	calc.
1	Dipp-$NHCH_3$	1	0	0	0	8.1	8.1
2	Dipp-$NHCH_2CH_3$	1	1	0	0	7.3	7.3
3	Dipp-$NHCH(CH_3)_2$	1	2	0	0	6.5	6.5
4	Dipp-$NHCH_2CH_2CH_3$	1	1	1	0	7.9	7.9
5	Dipp-$NHCH_2CH_2CH_2CH_3$	1	1	1	1	7.5	7.5

TABLE II

Substitution effect on the ^{31}P-NMR shift for $(i\text{Pro})_2\overset{\overset{O}{\|}}{P}\text{—}NR_2$ (Dipp-NR_2)

Entry	Structure	The number of substituent (ppm) n_β	n_γ	n_δ	n_ε	obs.	calc.
6	Dipp-$N(CH_3)_2$	2	0	0	0	8.6	8.6
7	Dipp-$N(CH_2CH_3)_2$	2	2	0	0	8.3	8.3
8	Dipp-$N(CH_2CH_2CH_3)_2$	2	2	2	0	8.2	

TABLE III

Substitution effect on the ^{31}P-NMR for $(i\text{Pro})_2\overset{\overset{O}{\|}}{P}\text{—}NH\overset{\overset{R}{|}}{C}HCOOH$

Entry	Structure	The number of substituent (ppm) n_γ	n_δ	n_ε	obs.	calc.
9	Dipp-$NHCH_2COOH$	1	2	0	6.1	6.1
10	Dipp-$NHCH(CH_3)COOH$	2	2	0	5.5	5.5
11	Dipp-$NHCH(CH(CH_3)_2)COOH$	2	4	0	6.1	6.1
12	Dipp-$NHCH(CH_2OH)COOH$	2	3	0	5.7	5.8
13	Dipp-$NHCH(CH_2SH)COOH$	2	3	0	5.5	5.8
14	Dipp-$NHCH(CH_3CHOH)COOH$	2	4	0	6.1	6.1
15	Dipp-$NHCH(CH_3CHCH_2CH_3)COOH$	2	4	1	5.9	5.9
16	Dipp-$NHCH(CH_2CH(CH_3)_2)COOH$	2	3	2	5.6	5.2
17	Dipp-$NHCH(CH_2COOH)COOH$	2	3	2	5.2	5.2
18	Dipp-$NHCH(CH_2CH_2COOH)COOH$	2	3	1	5.4	5.5

In this paper, we would like to extend the study to three types of compounds, namely, O,O-diisopropyl *N*-alkyl phosphoramidate class I (Table I), O,O-diisopropyl *N*,*N*-dialkyl phopshoramidates class II (Table II) and the O,O-diisopropyl *N*-phosphoryl amino acids class III (Table III). It was found that not only the β and γ effects but also the long distance δ and ε substitution effects were observed. Since for each type of compounds, different comformation were adopted in solution, three general equations were designed respectively.

Among these three types of compounds the *N*-phosphoryl amino acids is the most striking series in which no matter whether the side chain of the amino acids is alkyl, hydroxyl, thiol or carboxyl group the equation is fitted well.

RESULTS AND DISCUSSION

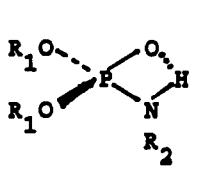
Previously, we had reported the synthesis of novel compounds *N*-O,O-diisopropyl phosphoryl amino acids, amino acid esters and dipeptides by using diisopropyl phosphite and carbon tetrachloride as the phosphorylation reagents.[6,7] The crystal and molecular structure of *N*-Dipp-Alane, and *N*-Dipp hydroxyl-proline had been determined by X-ray diffraction analysis.[8,9] In addition, the conformation of the *N*-Dipp amino acids were investigated by the ^{13}C-NMR spectra.[10] ^{31}P-NMR is a powerful technique to trace the reaction as well as a reliable tool to study the structures of the phosphorus. The steric effect on the ^{31}P-NMR shifts of three families of the diisopropyl phosphoramidates were examined. In Table I, the ^{31}P-NMR shifts of phosphorylated primary amine derivatives *N*-Dipp-NHR **1–5** are seen to respond to the additive deshielding effect by β and δ carbons and shielding by γ and ε carbons as expressed by Equation 1, where the n_β, n_γ, and n_ε are the carbons' number at various position.

$$\begin{aligned}\delta^{31}\mathrm{P} &= \delta_{\text{parent}} + n_\beta\beta + n_\gamma\gamma + n_\delta\delta + n_\varepsilon\varepsilon \\ &= 7.8 + n_\beta(0.3) + n_\gamma(-0.8) + n_\delta(0.6) + n_\varepsilon(-0.4)\end{aligned} \quad (1)$$

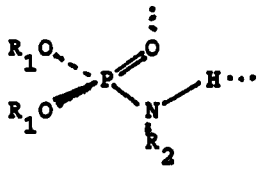
From Table I, in order to fit the Equation 1, δ_{parent} was adopted as 7.8 and β constant was chosen as 0.3. Similarly, the γ constant was deduced as -0.8 from the difference between **1** and **2**, which was consistent with the results by comparing **2** and **3**. By the same manner, the δ and ε were also derived from **4** and **2** or **5** and **4** as 0.6 and -0.4 respectively. From Equation 1, it seems that for the first series of compounds **1–5** the γ, δ and ε effects are much more profound than the β effect. On the contrary, Table II showed that the phosphorylated secondary amines **6–8** only exhibited small γ (-0.15) effect and almost no effect beyond γ substitution. Hence a much simpler Equation 2 was worked out. This distinctive deviation of Equation 2 from Equation 1 might suggest that the conformations for class I compounds **1–5** are distinguished from those for class II, **6–8**.

$$\delta^{31}\mathrm{P} = 8.0 + n_\beta(0.3) + n_\gamma(-0.15) \quad (2)$$

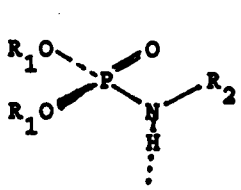
Indeed, the IR study evidently indicated that only the class I compounds but not class II were capable of forming the intra- as well as the inter-molecular hydrogen bonding, scheme I.[10] The N—H stretching frequency for the inter-molecular hydrogen bonding (**1b–5b**) or (**1c–5c**) is in the range of 3230–3260 cm^{-1} which is diminished as the concentration changed from 10% chloroform solution to 0.1%. However, under the same diluted condition, the N—H stretching at 3400–3425 cm^{-1} for intra-molecular hydrogen bonding (**1a–5a**) did persist. The strong hydrogen bondings reinforced the molecules in a rigid conformation in which the bond rotation around the P—N is relatively frozen as compared to that for the class II compounds where the P—N single bond rotation is not prohibited. Of course, there might be many factors to cause the difference in ^{31}P-NMR chemical



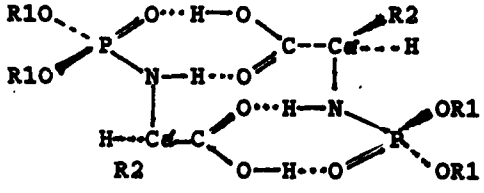
(1a)-(5a)



(1b)-(5b)



(1c)-(5c)



(9a)-(18a)

SCHEME I

shifts,[11-12] but judging from the reasons discussed above, the intrinsic hydrogen bond difference between class I and II compounds could account for the diverse behavior of the steric effect on the ^{31}P-NMR shift. For most of the class III compounds *N*-Dipp-amino acids (Table III), Equation 3 was derived where the carboxyl group was counted as one γ atom and two δ atoms. It is interesting to note that the agreement with experimental values is close and often within experimental error ± 0.3 ppm, in spite of the side chains.

$$\delta^{31}\mathrm{P} = 6.1 + n_\gamma(-0.6) + n_\delta(0.3) + n_\varepsilon(-0.3) \qquad (3)$$

For example, the analogous compounds **12** and **13** gave similar chemical shift, in spite of hydroxy or thiol groups being present on the γ-carbon. It had been discovered, that as the class I compounds, the *N*-Dipp amino acids also formed hydrogen bonded dimers as **9a–18a** (Scheme I) which were not changed even upon dilution to 0.1% in chloroform as investigated by IR.[10] Therefore, a relatively rigid conformer might predominate in solution. Consequently, the long distance steric effect was observed. But as compared to class I, these effects were smaller.

CONCLUSION

The steric effects on the ^{31}P-NMR spectra of three families of *N*-alkyl phosphoramidates were analyzed by three equations. Among them, the phosphorylated primary amines showed the greatest long distance γ, δ and ε effects, of which the γ constant is close to 1.0 ppm/carbon. The *N*-Dipp amino acids also followed the same rule but with smaller parameters. In contrast to them, the phosphorylated

secondary amines only exhibited a very small γ effect and almost no effect beyond the γ position.

EXPERIMENTAL

Methods. The ^{31}P-NMR spectra were taken on a JEOL FX-100 spectrometer at 40 MHz with probe temperature 25°C by broad band decoupled technique with 85% H_3PO_4 as external reference. The concentrations of the samples were 25% in $CDCl_3$ in 5 mm tubes.

Materials. Compounds **1–18** were prepared from the corresponding amines or amino acids and the dialkyl phosphites.

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