Stereochemical Dependence of $^2J_{PNC}$ Coupling Constants in *N*-Dialkyloxyphosphoryl Amino Acids and Other Phosphoramidate Compounds

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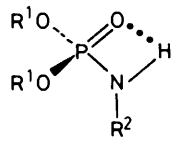
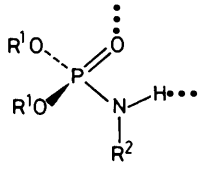
The geminal coupling constant $^2J_{PNC}$ in *N*-Dialkyloxyphosphorylamino acids and other phosphoramidate compounds is found to be small (<1 Hz) in the secondary amides (**1**)–(**5**) and (**9**)–(**16**) and larger (2.8–7.1 Hz) in the tertiary amides (**6**)–(**8**) and (**17**)–(**20**). IR studies on the secondary amides show that in solution these compounds favour the conformation in which the N–C bond is *anti* to P=O bond. The two-bond coupling constant $^2J_{PNC}$ in phosphoramidates is dependent on the conformation of the phosphoramide function. The $^2J_{syn}$ constant is affected by the changes in the bulk of the *N*-alkyl group, with $^2J_{syn}$ values successively increased on going from *N*-methyl to *N*-isopropyl.

The stereochemical dependence of the two-bond coupling constants $^2J_{PCH}$, $^2J_{PCC}$, and $^2J_{PNC}$ of organophosphorus(III) compounds and $^2J_{PCH}$ of phosphonates has been reported,[1–4] and the magnitude of the ^2J values has been proved to be useful in the evaluation of the conformations of these types of compounds.[5,6] However, little attention has been paid to the dependence of $^2J_{PCN}$ on the stereochemistry in phosphoramidates. In this paper, we wish to report the dependence of $^2J_{PNC}$ on the P–N conformation in phosphoramidates and *N*-dialkyloxyphosphorylamino acids.

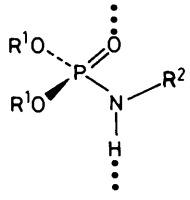
The P–N *Conformation and* $^2J_{PNC}$. Phosphoramidate compounds (**1**)–(**5**) (Table 1), and (**6**)–(**8**) were chosen to represent secondary and tertiary phosphorus(IV) amides,



(**1a**)–(**4a**)



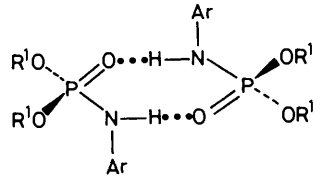
(**1b**)–(**4b**)



(**1c**)–(**4c**)

respectively. It can be seen from Table 1 that the $^2J_{PNC}$ constants are small (<1 Hz) in the secondary amides (**1**)–(**5**) and larger (2.8–5.5 Hz) in tertiary amides (**6**)–(**8**). These results are consistent with those observed in (**9**)–(**20**). Since compounds (**17**)–(**20**) (cyclic molecules) and (**6**)–(**8**) (acyclic molecules) have $^2J_{PNC}$ values of similar magnitude (2.8 Hz), we exclude the possibility that the larger $^2J_{PNC}$ constants in (**17**)–(**20**) as compared with those in (**9**)–(**16**) are affected by the presence of a ring structure (pyrrolidine ring) in each of the compounds (**17**)–(**20**). (Table 2).[7–9] X-Ray diffraction studies on compounds (**9**) and (**17**)[8] have demonstrated that the nitrogen configuration in these two compounds is trigonal and O=P–N–C are coplanar, with N–H *cis* to P=O in (**9**) (*cis* conformation), and N–C_δ *trans* to P=O in (**17**) (*trans* conformation).† The P–N–C bond angle in (**9**) and P–N–C_α, P–N–C_δ bond angles in (**17**) are 125.3, 123.8, and 122.0°, respectively. Since the magnitudes of the P–N–C bond angles in these two compounds is very similar, the possibility that the unequivalent $^2J_{PNC}$ constants in compounds (**9**)–(**16**) and (**17**)–(**20**) are caused by the structural changes at nitrogen (bond angles) is precluded. It is likely that the difference arises from the different conformation of the phosphoramide function in these compounds.

Dimethyl *N*-phenylphosphoramidate (**5**) has been investigated by IR spectroscopy and it was found that the conformation in solution is that shown, due to the existence of hydrogen-bonded dimers.[10] Thus the ^{13}C NMR result provides definitive

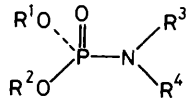


(**5**)

evidence that the small $^2J_{PNC}$ value (<1 Hz) is related to the *anti* orientation of the P=O and N–C group. As for (**1**)–(**4**), IR investigations on these compounds (Table 3) have shown that there are two N–H stretching vibration bands for each of the compounds in 10% chloroform solution. When the solution was diluted to a concentration of *ca.* 0.1%, the lower-frequency band (ν 3 230–3 260 cm^{-1}) completely disappeared. It is obvious that the higher-frequency band (ν 3 400–3 435 cm^{-1}) arises from the weakly electrostatically attracted species (**1a**)–(**4a**) (*cis* conformation), and the lower-frequency band results from the intermolecularly hydrogen-bonded species (**1b**)–(**4b**) (*cis* conforma-

† In a peptide chain, the conformation of the peptide unit containing a proline or hydroxyproline residue is defined as *cis* or *trans* conformations when the N–C_δ group is *cis* or *trans* to the C=O group respectively. By analogy, the conformation of the phosphoramide function in (**17**)–(**20**) is described as *cis* or *trans* when the N–C_δ group is *cis* or *trans* to the P=O group, respectively.

Table 1. ^{13}C NMR spectral data for the phosphoramidates (**1**)–(**8**).[a,b]



Compound	$R^1(R^2)$	R^3	R^4	δ (*J*/Hz)[a,b] R^1, R^2	R^3	R^4
(**1**)	$(CH_3)_2CH$	H	CH_3	70.5 (5.6)		27.6 (<1)
(**2**)	$CH_3CH_2CH_2CH_2$	H	CH_3	65.1 (5.6)		26.7 (<1)
(**3**)	$(CH_3)_2CH$	H	CH_2CH_3	70.1 (5.7)		36.1 (<1)
(**4**)	$(CH_3)_2CH$	H	$CH(CH_3)_2$	69.6 (4.9)		43.0 (<1)
(**5**)	CH_3	H	Ph(*ipso* C)	52.8 (3.4)		140.0 (<1)
(**6**)	$(CH_3)_2CH$	CH_3	CH_3	68.5 (6.5)	35.0 (2.8)	35.0 (2.8)
(**7**)	$(CH_3)_2CH$	CH_2CH_3	CH_2CH_3	69.5 (6.3)	38.8 (4.2)	38.8 (4.2)
(**8**)	$-CH_2CH_2-$	$CH(CH_3)_2$	$CH(CH_3)_2$	65.0 (2.3)	46.3 (5.5)	46.3 (5.5)

[a] Digital resolution 0.8 Hz. [b] The sign of $^2J_{PNC}$ constant was established to be positive by off-resonance ^1H irradiation.[3]

Table 2. Selected ^{13}C chemical shifts (δ) and ^{13}C–^{31}P coupling constants (*J*/Hz)[a] in the *N*-Dialkyloxyphosphoryl amino acids (**9**)–(**20**).[b,c]

Compound	$\delta_{C=O}$ (^3J)	δ_{C_α} (^2J)[d]	δ_{C_β} (^3J)	δ_{C_γ} (^3J)	δ_{C_δ} (^2J)[d]
(**9**) N-DIPP-Ala	175.8 (10.9)	49.7 (1.0)	20.8 (2.4)		
(**10**) N-DBP-Ala	175.8 (10.8)	49.5 (<1)	20.6 (<1)		
(**11**) N-DIPP-Abu	174.2 (7.4)	54.4 (<1)	26.7 (<1)		
(**12**) N-DIPP-Gly	172.7 (14.8)	42.3 (<1)			
(**13**) N-DIPP-Ile	174.2 (4.3)	57.9 (<1)	38.6 (4.4)		
(**14**) N-DIPP-Leu	175.8 (4.0)	52.5 (<1)	43.6 (5.5)		
(**15**) N-DIPP-Phe	174.2 (5.9)	55.3 (<1)	39.8 (4.4)		
(**16**) N-DIPP-Val	174.4 (4.1)	59.1 (<1)	31.6 (5.5)		
(**17**) N-DIPP-Hyp	175.1 (<1)	59.1 (5.4)	39.1 (8.8)	71.0 (6.3)	54.8 (3.5)
(**18**) N-DIPP-Pro	174.8 (<1)	60.3 (6.8)	30.6 (8.7)	25.2 (7.8)	46.8 (3.9)
(**19**) N-DIPP-ProOCH_2Ph	174.0 (<1)	60.3 (7.1)	31.3 (8.0)	25.1 (7.9)	46.9 (3.7)
(**20**) N-DBP-Pro	175.3 (<1)	59.6 (6.5)	30.8 (8.6)	25.0 (8.7)	46.6 (4.2)

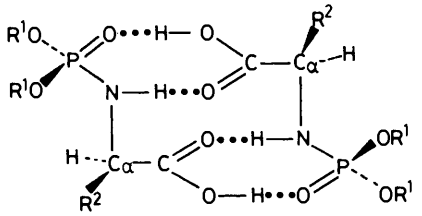
[a] Digital resolution 0.7 Hz. [b] Abbreviations used: DIPP = di-isopropyloxyphosphoryl; DBP = dibutyloxyphosphoryl; Abu = 2-aminobutyric acid; Hyp = *trans*-4-hydroxy-L-proline. [c] The di-isopropyl group in each *N*-DIPP amino acid has chemical shifts at *ca.* 71 and 23 ppm, and the dibutyl group in (**2**) and (**12**) at *ca.* 66, 32, 18, and 13 ppm. [d] The sign of $^2J_{PNC}$ constant was determined to be positive by off-resonance ^1H irradiation.[3]

Table 3. N–H stretching frequency ν_{NH} for Compounds (**1**)–(**4**) and (**9**)–(**16**) in chloroform.

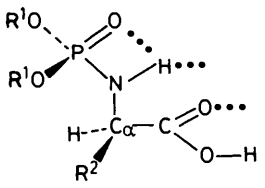
Compound	ν_{NH}/cm^{-1} [a] 10% solution		0.1% solution	
(**1**)	3 260	3 435		3 430
(**2**)	3 260	3 435		3 430
(**3**)	3 235	3 405		3 405
(**4**)	3 230	3 400		3 400
(**9**)	3 290	3 395	3 285	3 395
(**10**)	3 290	3 395	3 285	3 395
(**11**)	3 292	3 396	3 288	3 396
(**12**)	3 295	3 398	3 290	3 398
(**13**)	3 288	3 393	3 286	3 392
(**14**)	3 286	3 392	3 286	3 390
(**15**)	3 285	3 390	3 285	3 390
(**16**)	3 285	3 390	3 285	3 390

[a] The population of the species at higher frequencies relative to that of the lower frequencies in (**1**)–(**8**) is in the range 5–10%, and 20–30% in (**9**)–(**16**), in 10% solution.

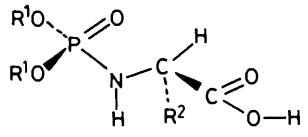
tion) or (**1c**)–(**4c**) (*trans* conformation) which are transformed into (**1a**)–(**4a**) upon dilution. This result is in contrast with compound (**5**). Since it is difficult to determine which species corresponds to the lower frequency band, (**1b**)–(**4b**) (*syn* conformation) and (**1c**)–(**4c**) (*anti* conformation), both being suitable candidates, the relationship between the observed $^2J_{PNC}$ values (≤ 1 Hz) for these compounds and the *anti* orientation of the N–C group with respect to the P=O group must be treated with caution. Considering the substitution effect on the magnitude of $^2J_{PNC}$, there is another possibility that significant differences in the $^2J_{PNC}$ values between the secondary amides (**9**)–(**16**) and (**1**)–(**5**) and the tertiary amides (**17**)–(**20**) and (**6**)–(**8**) may be created by changing from N–H to N–R (R = alkyl) in the amine moiety. However, the ^{13}C NMR result for 2-ethoxy-5-iodo-3-methyl-2-oxo-1,3,2-oxa-azaphosphorinane (**21**) (a tertiary amide)[11] demonstrated that no splitting was observed for the *N*-methyl and N–C_4 carbons, implying that an N–C carbon in tertiary amides does not necessarily have a larger $^2J_{PNC}$ value. This phenomenon might be explained by the fact that it is impossible for both *N*-methyl and N–C_4 groups to be *syn* to the P=O group from a stereochemical point of view, which thus provides the evidence that $^2J_{PNC}$ constant is larger only when the N–C group is *syn* to the P=O group. Moreover the IR studies on (**9**)–(**16**) in chloroform solution (Table 3) have revealed that in addition to the existence of a small amount (*ca.* 5–10%) of weakly electrostatically attracted species (ν = 3 390–3 398 cm^{-1}),[8] these compounds exist mainly as hydrogen-bonded dimers; in 10% solution the N–H stretching frequency



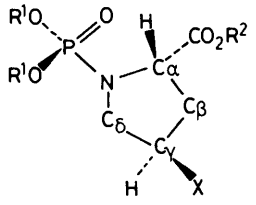
(9a)–(16a)



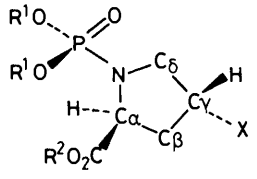
(9b)–(16b)



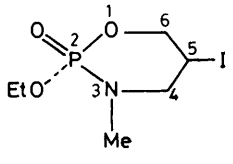
(9c)–(16c)



(17a)–(20a)



(17b)–(20b)



(21)

at *ca.* 3 285–3 295 cm^{-1}, which is typical for hydrogen-bonded phosphoramidates,[12,13] was unchanged upon dilution (0.1% solution). Phosphoramidates and phosphinic amides have been reported to exist as hydrogen-bonded dimers in solution.[10–14]

Compounds (**9**)–(**16**), owing to the presence of an extra carboxy group which is also capable of hydrogen bonding to form dimers, might take the forms (**9a**)–(**16a**). Other forms of hydrogen bonding are excluded since they lead to the formation of polymeric aggregates which cannot exist in highly dilute solution.[10] From the IR studies, it is proposed that the *cis* conformation, which is stabilized by the hydrogen-bonded dimeric structures (**9a**)–(**16a**) and the weakly electrostatically attracted structures (**9b**)–(**16b**), predominates in solution while the population of the *trans* conformation (**9c**)–(**16c**) is extremely low. For compounds (**17**)–(**20**) where there is no possibility of hydrogen-bonded forms, the *trans* conformations (**17a**)–(**20a**) in the solid state might also exist in equilibrium with the *cis* conformation in solution, and rotation around the P–N bond is not restricted at room temperature as reported for analogous compounds.[15]

Effect of the Nature of the N-*Alkyl Group on* $^2J_{PNC}$.—It can be seen from Tables 1 and 2 that the $^2J_{anti}$ values in (**9**)–(**16**) and in (**1**)–(**5**) are little affected by the nature or the *N*-alkyl groups, with $^2J_{anti} \leqslant 1$ Hz in these compounds. However, it can be seen from Table 1 that the $^2J_{PNC}$ values for the N–C carbons in (**6**)–(**8**) successively increase on going from *N*-methyl to *N*-isopropyl. This indicates that the magnitude of $^2J_{syn}$ is much affected by the changes in the bulk of the *N*-alkyl group; the more bulky the coupled carbon is, the greater the $^2J_{syn}$ value becomes. It can be seen from Table 2 that owing to the steric crowding, the replacement of the dibutoxy groups in (**20**) with the di-isopropoxy groups in (**18**) results in a decrease in the population of conformer (**18b**) with an increase in (**18a**), which reflects in an enlargement of 0.3 Hz in $^2J_{PNC_\alpha}$. It is interesting to find that the $^2J_{PNC_\gamma}$ value changed from 5.4 to 4.8 Hz and the $^2J_{PNC_\delta}$ value, from 3.5 to 3.8 Hz in (**17**) when the temperature was raised from ambient (18 °C) to 50 °C. This change reflects the increase in the population of the *cis* conformer (**17b**) at the higher temperature, thus the *trans* conformer (**17a**) is energetically more stable than the *cis* conformer (**17b**).

In conclusion, the value of $^2J_{PNC}$ in phosphoramidates is dependent on the stereochemistry of the phosphoramide function, namely, the dihedral angle θ between the N–P=O and P–N–C groups. The small $^2J_{PNC}$ value ($\leqslant 1$ Hz) is related to the *anti* orientation (θ = 180°) and the larger $^2J_{PNC}$ value ($\geqslant 4.6$ Hz) is related to the *syn* orientation θ = 0°) of the P=O and N–C groups. It is obvious that the observed $^2J_{PNC}$ values in a particular compound $(R^1O)_2P(O)NR^2R^3$ will be determined by the relative populations of the *cis* and *trans* conformers in solution if R^2 is not equal to R^3, and therefore they can be used for the conformational evaluation of the phosphoramide function in phosphoramidates.

Experimental

Methods.—^{13}C NMR spectra were taken on a Varian XL 300 FT NMR spectrometer at 50.309 MHz. The concentrations were about 15–20% in $CDCl_3$ in 10 mm tubes. All spectra were recorded at a probe temperature of 18 °C unless otherwise indicated. Chemical shifts are reported in ppm relative to internal $CDCl_3$ at δ 77.0 ppm. Off-resonance experiments were performed using the technique described by Simonnin *et al.*[3] IR spectra were obtained on a Shimadzu 430 spectrophotometer in chloroform solution with an NaCl cell of 0.1 mm length.

Materials.—Compounds (**9**)–(**18**) and (**20**) were prepared from the corresponding amino acids and dialkyl phosphite using the procedures described by Zhao *et al.*[7] Compounds (**19**) and (**1**)–(**7**) were made according to Todd's method.[16]

Ethane-1,2-*diyl* N,N-*Di-isopropylphosphoramidate* (**8**).[17]—To a solution of di-isopropylamine (2.0 g, 20 mmol) and triethylamine (10.1 g, 100 mmol) in dry tetrahydrofuran (20 cm^3) cooled in an ice bath, was added dropwise ethylene chloro-

phosphite (2.5 g, 20 mmol). After a few hours of stirring, a solution of iodine (5.6 g, 22 mmol) in tetrahydrofuran–water (10/5 cm^3) was added while the mixture was cooled in an ice bath. After a further 10 min of stirring, the reaction mixture was extracted with ethyl acetate (3 × 20 cm^3), and the organic layer was washed with dilute HCl (3 × 20 cm^3) and water (3 × 20 cm^3). Drying (Na_2SO_4) and solvent evaporation gave (**8**) as an oil (2.6 g, 65%).

Acknowledgements

This work is supported by the Chinese National Science Fund (2860227) for Y-F. Z. and the postdoctorate fellowship for C-B. X.

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Paper 8/01760C
Received 4*th May* 1988
Accepted 30*th June* 1989