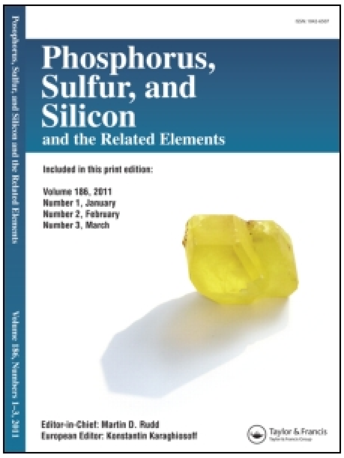

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N-PHOSPHORYL AMINO ACIDS AND PEPTIDES: PART III. THE CRYSTAL AND MOLECULAR STRUCTURE OF *N*-(*O,O*-DIISOPROPYL PHOSPHORYL)-*L*-ALANINE

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N-PHOSPHORYL AMINO ACIDS AND PEPTIDES: PART III. THE CRYSTAL AND MOLECULAR STRUCTURE OF *N*-(*O*,*O*-DIISOPROPYL PHOSPHORYL)-*L*-ALANINE

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(Received June 15, 1988)

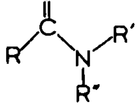
The crystal and molecular structure of *N*-(*O*,*O*-diisopropyl phosphoryl)-*L*-alanine (*N*-DIPP-Ala) has been determined by X-ray diffraction analysis and is compared with *N*-(*O*,*O*-diisopropyl phosphoryl)-trans-4-hydroxy-*D*,*L*-proline (*N*-Dipp-Hyp) and *N*-acyl amino acids reported in the literature. The compound crystallized in the tetragonal system with space group $P4_12_12_1$, $a = 15.571(2)$ Å, $b = 15.571(2)$ Å, $c = 12.392(3)$ Å, $V = 3.004.56$ Å^3, $Z = 8$, $Dc = 1.12$ g/cm^3. The structure was solved by direct and Fourier method and refined to a discrepancy index $R = 0.072$. The P—N bond length of N-DIPP-Ala (1.60 Å) was found to be shorter than that of *N*-DIPP-HYp (1.62 Å), but these two compounds share the same value of the P = O bond distance (1.47 Å). It is thus postulated that in addition to the resonance interaction between the nonbonding electrons of the nitrogen and the P═O π system in these two compounds, there might be another type of resonance interaction along the P—N bond which is proposed as N → P back donation effect. The conformation of the phosphoramide function in *N*-DIPP-Ala is favoured by the cis orientation of the P═O bond with respect to the N—H bond. This situation is in contrast with N-acyl amino acids in which the conformation of the carboxamide function is favoured by the trans orientation of the C═O bond with respect to the N—H bond.

Key words: X-ray diffraction analysis; *N*-(*O*,*O*-diisopropylphosphoryl)-*L*-alanine; *N*-(*O*,*O*-diisopropylphosphoryl)-trans-4-hydroxy-D,L-proline; comparison with *N*-acylaminoacids

INTRODUCTION

N-phosphorylated amino acids and small peptides have been shown to possess biological activities.[1–6] For example, derivatives of *N*-phosphoaspartic acid and their salts are useful for treating psychic and physic asthenia;[3] *N*-phosphoryl tripeptides can be used as anti-hypertension drugs[4–5] and inhibitors of bacterial collagenase.[6] It is likely that the phosphoryl group in these compounds might be, in part, responsible for their peculiar biological functions which are not possessed by other *N*-derivatives of these amino acids and peptides, for instance, *N*-acyl amino acids and peptides.

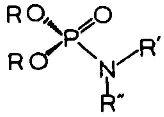
Phosphoric amides (**2a**) or imides (**2b**) can be considered as close structural analogues of carboxylic amides (**1a**) or imides (**1b**). Both systems are derived from the primary amine R'NH$_2$ or secondary imine R'R'NH, acylated by carboxyl and phosphoryl groups. However, as far as the bonding characteristics and structural effects are concerned, there are some intrinsical differences between (**1**) and (**2**). For example, the carbonyl center in (**1**) is planar while the phosphoryl center in (**2**) is not planar but tetrahedral. Consequently, the



(1)

(1a): R′=alkyl, R″=H

(1b): R′=R″=alkyl



(2)

(2a): R′=alkyl, R″=H

(2b): R′=R″=alkyl

conformational preference of the phosphoramide function in (**2**) might exhibit different behaviour as compared with the carboxamide function in (**1**). In view of this, it is probable that the determination of the molecular structures of N-phosphoryl amino acids and peptides will allow to make a comparison of the molecular structures between *N*-phosphoryl and *N*-acyl amino acids and peptides and will be helpful for the understanding of structure-activity relationships of *N*-phosphoryl amino acids and peptides.

As part of our interest in the structure-activity relationships of *N*-phosphoryl amino acids and peptides, we have reported the crystal and molecular structure of *N*-(*O,O*-diisopropyl phosphoryl)-trans-4-hydroxy-*D,L*-proline (*N*-DIPP-Hyp, **3**) which represents the type of *N*-phosphoryl imino acids, and made a comparison with *N*-acyl proline and hydroxyproline.[7] In this paper, we wish to report the crystal and molecular structure of *N*-(*O,O*-diisopropyl phosphoryl)-*L*-alanine (*N*-DIPP-Ala, **4**) which represents the type of *N*-phosphoryl amino acids, and the crystal and molecular structures between (**4**) and (**3**), and between (**4**) and N-acyl amino acids (**5**) are compared.

RESULTS AND DISCUSSION

The final atomic coordinates and equivalent isotropic temperature factors for compound (**4**) are given in Table I, and the selected bond lengths, selected bond angles and selected torsional angles calculated are shown in Tables II, III and IV, respectively. An ORTEP perspective view of the molecular structure of (**4**) including the numbering scheme is presented in Figure 1. It can be seen from the figure that the two isopropyloxy groups of this molecule in the crystals are inflexible. This is in contrast with *N*-DIPP-Hyp (**3**) in which one of the two isopropyloxy groups exhibits high flexibility in the crystals.[7]

It can be seen from Tables III and IV that the values of the bond angles around the nitrogen atom indicate the trigonal configuration of this atom, and the values of the torsional angles for O(1)—P—N—C(7) and O(1)—P—N—Hn atoms (−176·4° and 4·2° respectively) are in agreement with the near coplanarity of the phosphoramide function. It is thus suggested that the nonbonding electrons of the nitrogen are conjugated with the P═O π system. The effect of this conjugation can be reflected by the N—P bond length of 1.60 Å which is shorter than the typical P—N single bond length of 1.78 Å in the dipolar molecule of phosphoramidic acid H_3N^+—PO_3H^-.[8] It is interesting to note that this P—N bond length in (**4**) is shorter than that (1.62 Å) in (**3**).[9] It is likely that the resonance

TABLE I

Atomic coordinates ($\times 10^4$) and isotropic temperature factors ($\times 10^3$)

Atom	*X*	*Y*	*Z*	*U*
P	8035(1)	2922(1)	663(1)	70(1)
O(1)	8679(2)	2827(3)	1521(3)	84(1)
O(2)	7801(3)	2068(3)	65(3)	94(1)
O(3)	8302(3)	3500(3)	−312(3)	85(1)
O(4)	5022(3)	2895(4)	301(3)	118(1)
O(5)	5572(2)	2919(3)	1948(3)	89(1)
N	7163(3)	3333(3)	1102(3)	69(1)
C(1)	7711(5)	1246(4)	650(5)	107(2)
C(2)	6790(6)	975(5)	531(8)	163(2)
C(3)	8338(7)	655(5)	189(7)	174(2)
C(4)	9095(5)	3311(5)	−951(5)	112(2)
C(5)	8839(7)	3260(5)	−2058(6)	188(2)
C(6)	9729(5)	3985(6)	−727(8)	173(2)
C(7)	6389(4)	3465(4)	469(5)	82(1)
C(8)	6229(5)	4423(5)	269(7)	141(2)
C(9)	5628(3)	3055(4)	1004(5)	77(1)
Ho	4575(23)	2546(23)	678(26)	113(3)
Hn	7172(23)	3494(22)	1794(22)	78(3)
H(1)	7856(25)	1431(23)	1413(23)	101(3)
H(4)	9296(21)	2745(20)	−744(25)	75(3)
H(7)	6409(22)	3151(20)	−260(22)	69(3)
H(2a)	6689	788	−195	175(3)
H(2b)	6420	1451	694	302(3)
H(2c)	6674	512	1021	164(3)
H(3a)	8249	607	−575	193(3)
H(3b)	8273	100	517	215(3)
H(3c)	8907	867	325	343(3)
H(5a)	9331	3137	−2498	166(3)
H(5b)	8594	3799	−2274	107(3)
H(5c)	8420	2813	−2144	300(3)
H(6a)	10246	3869	−1125	205(3)
H(6b)	9856	3996	31	156(3)
H(6c)	9500	4530	−943	251(3)
H(8a)	5747	4491	−206	96(3)
H(8b)	6730	4674	−55	198(3)
H(8c)	6111	4704	943	180(3)

TABLE II

Selected bond lengths (Å) for *N*-DIPP-Ala

P—O(1)	1.469(4)	N—C(7)	1.453(7)
P—O(2)	1.565(4)	N—Hn	0.894(28)
P—O(3)	1.563(4)	C(1)—C(2)	1.502(13)
P—N	1.597(5)	C(1)—C(3)	1.459(12)
O(2)—C(1)	1.477(7)	C(4)—C(5)	1.430(10)
O(3)—C(4)	1.496(9)	C(4)—C(6)	1.467(12)
O(4)—C(9)	1.308(7)	C(7)—C(8)	1.532(10)
O(4)—Ho	1.000(35)	C(7)—C(9)	1.501(8)
O(5)—C(9)	1.192(7)		

TABLE III

Selected bond angles (degree) for *N*-DIPP-Ala

O(1)—P—O(2)	114.6(2)	N—C(7)—C(8)	11.1(5)
O(1)—P—O(3)	115.8(2)	C(8)—C(7)—C(9)	110.9(5)
O(2)—P—O(3)	100.7(2)	C(9)—O(4)—Ho	107.1(19)
O(1)—P—N	112.0(2)	O(4)—C(9)—O(5)	124.6(5)
O(2)—P—N	107.7(3)	O(4)—C(9)—C(7)	110.8(5)
O(3)—P—N	105.0(2)	O(5)—C(9)—C(7)	124.5(5)
P—O(2)—C(1)	121.7(3)	O(2)—C(1)—C(2)	106.6(6)
P—O(3)—C(4)	121.0(4)	O(2)—C(1)—C(3)	107.0(6)
P—N—C(7)	125.3(4)	C(2)—C(1)—C(3)	115.0(7)
P—N—Hn	115.2(24)	O(3)—C(4)—C(5)	106.8(7)
C(7)—N—Hn	119.5(24)	O(3)—C(4)—C(6)	108.4(6)
N—C(7)—C(9)	110.9(5)	C(5)—C(4)—C(6)	114.1(7)

TABLE IV

Selected torsional angles (degree) for *N*-DIPP—Ala

O(1)—P—O(2)—C(1)	39.6(0.6)	O(3)—P—O(2)—C(1)	164.6(0.5)
O(1)—P—O(3)—C(4)	56.6(0.5)	O(2)——P—O(3)—C(4)	−67.6(0.5)
O(1)—P—N—C(7)	−176.4(0.5)	O(1)—P—N—Hn	4.2(2.5)
O(2)—P—N—Hn	131.1(2.5)	O(3)—P—N—C(7)	57.1(0.5)
P—O(2)—C(1)—C(2)	116.0(0.6)	P—O(2)—C(1)—C(3)	−120.5(0.6)
P—O(3)—C(4)—C(5)	126.4(0.6)	P—O(3)—C(4)—C(6)	−110.3(0.6)
Ho—O(4)—C(9)—O(5)	−10.6(2.3)	N—P—O(2)—C(1)	−85.8(0.5)
P—N—C(7)—C(9)	125.8(0.5)	N—P—O(3)—C(4)	−179.4(0.4)
Hn—N—C(7)—C(9)	−54.9(2.7)	O(2)—P—N—C(7)	−49.5(0.5)
N—C(7)—C(9)—O(5)	25.1(0.9)	O(3)—P—N—Hn	−122.2(2.5)
C(8)—C(7)—C(9)—O(4)	79.0(0.7)	P—N—C(7)—C(8)	−110.5(0.6)
N—C(7)—C(9)—O(4)	−157.1(0.5)	Hn—N—C(7)—C(8)	68.9(2.6)
C(8)—C(7)—C(9)—O(5)	−98.8(0.8)	Hn—N—C(7)—H(7)	−168.5(3.2)

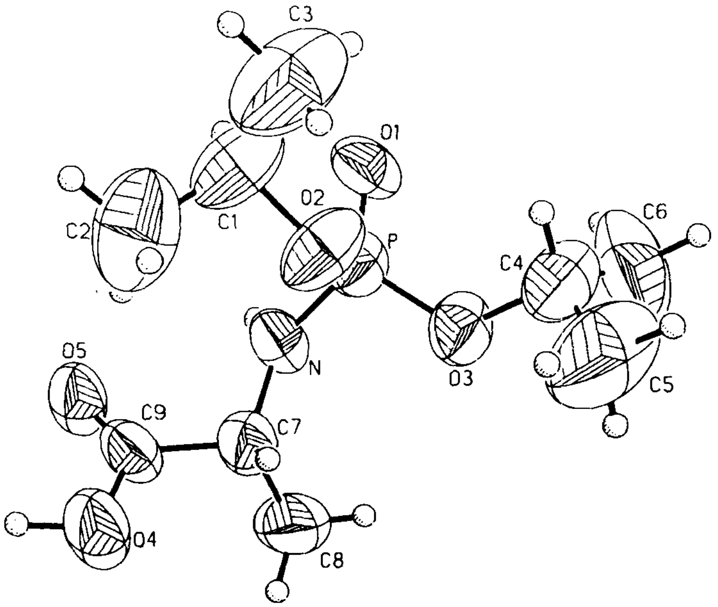
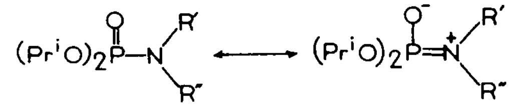
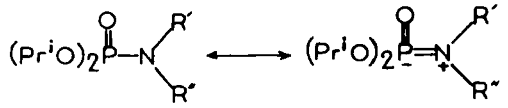


FIGURE 1. An ORTEP perspective view of the molecular structure of *N*-DIPP-Ala including the numbering scheme.



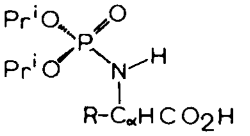
SCHEME 1

interaction between the nonbonding electrons of the nitrogen and the P=O π system (Scheme 1) in (**4**) might be more significant than in (**3**), which should result in the higher P—N bond order and at the same time, the lower P=O bond order in (4). However, these two compounds exhibit the same value of the phosphoryl bond distance (both 1.47 Å), pointing out the same bond order of this bond in (**3**) and (**4**). It is thus postulated that in addition to the resonance interaction between the nonbonding electrons of the nitrogen and the phosphoryl π system in these two compounds (Scheme 1), there might be another resonance interaction between N and P which is proposed as the N→P back donation effect[12-13] as illustrated in Scheme 2, and the contribution of the latter resonance to the P=O bond order is expected to be more important in (**4**) as compared with (**3**). This interpretation is supported by the fact that the P—N bond length in (**4**) lies within the range of the P—N bond lengths of 1.52–1.60 Å which are thought to be typical for a strong p_π–$d\pi$ back donation effect along the P—N bond in cyclotriphosphazenes.[14]

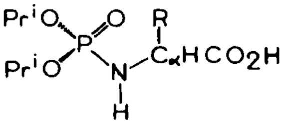


SCHEME 2

Since the phosphoramide group in (**4**) is coplanar, there are two possibilities for the orientation of the P=O bond with respect to the N—H bond, namely, the cis orientation (cis conformation, **4a**) and the trans orientation (trans conformation, **4b**). It is interesting to find that the phosphoramide function of (**4**) is favoured by

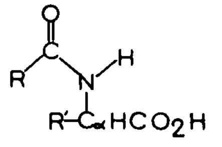


(4a)

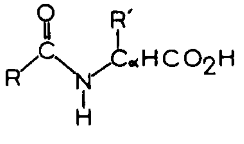


(4b)

the cis conformation in the crystals. This situation is in contrast to that in N-acyl amino acids (**5**) in which the trans conformation (**5b**) is more preferable over the cis conformation (**5a**). A possible reason for this difference of conformational preference between (**4**) and (**5**) is that in compound (**5**) the trans conformation (**5b**) is more stable than the cis conformation (**5a**) due to the steric crowding between the R group and the C_α group in (**5a**),[13] while in compound (**4**) the cis conformation (**4a**), with the projection of the N—C_α bond bisecting the



(5a)



(5b)

Pr^iO—P—OPr^i angle, should not suffer such steric effect as the analogous conformation (**5a**).

Hydrogen Bonding. In compound (**3**), no hydrogen bonding was observed in the crystals. However, there exist two types of intermolecular hydrogen bonding in the crystals of compound (**4**) and the hydrogen bonding data are given in Table V. One type of hydrogen bonding (type I) occurs between the P═O of one molecule (molecule A) and the O—H of another molecule (molecule B) as illustrated in Figure 2. The other type of hydrogen bonding (type II) is the two symmetric C═O · · · H—N hydrogen bonds between one molecule (molecule A) and the third molecule (molecule C). The O(1) · · · O(4′) and O(5) · · · N″ or N · · · O(5″) distances (2.52 Å and 2.96 Å respectively) reveal that the type I of hydrogen bonding is much stronger as compared to the type II of hydrogen bonding.

TABLE V

Hydrogen bonding data for *N*-DIPP-Ala

Type I	O(1) · · · Ho′ (Å)	1.56	O(4′)—Ho′ · · · O(1) (°)	160
	O(4′) · · · O(1) (Å)	2.52		
Type II	O(5) · · · Hn″ O(5″) · · · Hn (Å)	2.13	O(5) · · · Hn″—N″ N—Hn · · · O(5″) (°)	155
	O(5) · · · N″ N · · · O(5″) (Å)	2.96		

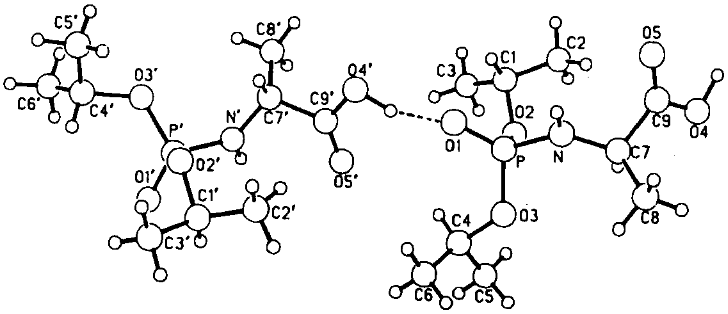


FIGURE 2. A perspective view of the hydrogen bonded pair of N—DIPP—Ala.

EXPERIMENTAL

N-DIPP-Ala (**4**) was prepared according to the previous procedures described by Y-F. Zhao *et al*,[7,15] and the physical data of this compound are analogous to those reported in the literature.[7]

Single crystals of good quality for X-ray analysis were obtained by the crystallization from the mixed solvent system of ethyl acetate and n-hexane. The crystals belong to the tetragonal system, space group $P4_12_12_1$, $a = 15.571(2)$ Å, $b = 15.571(2)$ Å, $c = 12.392(3)$ Å, $V = 3004.56$ Å, $Z = 8$, $Dc = 1.12\ g/cm^3$, $\mu(Mo\ K_\alpha) = 1.82\ cm^{-1}$, $\lambda = 0.71069$ Å.

A crystal with approximate dimensions 0.46 × 0.46 × 0.30 mm was mounted on a Nicolet R3m/E four-circle diffractometer using graphite-monochromated Mo $K\alpha$ radiation.

The cell parameters were determined by least-square technique from the measured 2θ angles of 25 reflections with 2θ angles above 25°. Intensities were measured in the ω scan mode within the range $3° \leq 2\theta \leq 45°$. The scanning speed was varied according to the intensity, from 4° to 29.3°/min. Two standard reflections were monitored every 60 reflections. Their intensities indicated no counter or crystal instability.

2258 independent reflections were collected with tetragonal mode ($K \leq H$). The intensity data, after scaling, were corrected for Lorentz and polarization factor. Empirical absorption corrections were based on the ψ scan of six reflections. 1647 reflections with $i > 2.5\sigma(I)$ were considered to be observed and used for structure refinement.

The structure was solved by direct and Fourier method. After a few cycles of refinement, all nonhydrogen atoms were located with $R = 0.14$ for isotropic thermal parameters. Eight hydrogen atoms were located in a difference Fourier map. Other hydrogen atoms were located theoretically. Further refinement, including hydrogen positional and isotropic thermal parameters, was converged at final R factors $R = 0.072$.

All calculations were carried out with the SHELXTL program on an Exlipse S140 computer.

ACKNOWLEDGEMENT

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REFERENCES

1. J. Nordmann, G. Mattioda, and G. Loiseau, French Patent M7690, (1970).
2. J. Nordmann and G. Mattioda, French Patent M3936, (1966).
3. S. A. Laboratoires Sobio, French Patent M6430, (1968).
4. S. Sakakibara, Y. Yugari, and S. Hasimoto, European Patent EP 0085488 A2.
5. Ajinomoto Co., Inc., Japanese Patent 60 28 991, (1985).
6. R. E. Galardy and D. Grobelny, U.S. Patent 4,558,034, (1985).
7. Y.-W. Yin, B.-M. Chen, C.-B. Xue, and Y.-F. Zhao, *Phosphorus Sulfur*, **36,** (1988).
8. E. Holiles, D. E. C. Corbridge, and B. Raistrick, *Acta Crystallogr.*, **6,** 621 (1953); D. W. J. Cruickshank, *J. Chem. Soc.*, 5858 (1961).
9. The carboxamide C—N bond length in *N*-acyl amino acids is equal to the carboximide C—N bond length (1.32 Å) in *N*-acyl imino acids.[10–11] We thus exclude the possibility that the longer P—N bond length in (**3**) as compared with (**4**) is caused by the substitution of N—H group in (**4**) with the *N*-alkyl group in (**3**).
10. R. E. Marsh and J. Donahue, *Advan. Protein Chem.*, **22,** 235 (1967).
11. G. N. Ramachandran and V. Sasisekharan, *Advan. Protein Chem.*, **23,** 283 (1968), and references therein.
12. R. F. Husdon, "Structure and Mechanism in Organophosphorus Chemistry", Academic Press, London, (1965), Chapter 3.
13. M. P. du Plessis, T. A. Modro, and L. R. Nassimbeni, *J. Org. Chem.*, **47,** 2313 (1982).
14. D. E. C. Corbridge, "The Structural Chemistry of Phosphorus", Amsterdam: Elsevier, (1974), p. 333.
15. G.-J. Ji, C.-B. Xue, J.-N. Zeng, L.-P. Li, W.-G. Chai, and Y.-F. Zhao, *Synthesis*, **6,** 444 (1988).