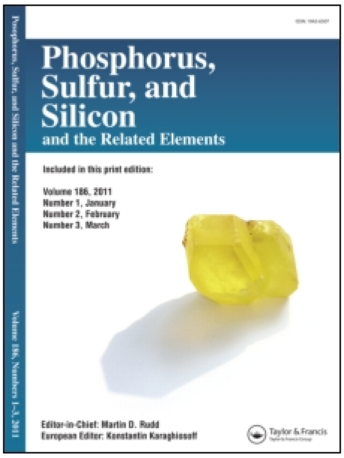

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CONFORMATIONAL ANALYSIS OF DIALKYL (2,5-DIALKYL PYRROLIDIN-2-YL)PHOSPHONATES AND DIETHYL(2,5,5-TRIMETHYL PYRROLIDIN-2-YL)PHOSPHONATE BY X-RAY ANALYSIS, NMR AND FORCE FIELD CALCULATIONS

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CONFORMATIONAL ANALYSIS OF DIALKYL (2,5-DIALKYL PYRROLIDIN-2-YL)PHOSPHONATES AND DIETHYL(2,5,5-TRIMETHYL PYRROLIDIN-2-YL)PHOSPHONATE BY X-RAY ANALYSIS, NMR AND FORCE FIELD CALCULATIONS

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Using force field calculations (MM2), ^{1}H, ^{13}C NMR spectroscopy and X-ray diffraction, conformational studies were performed on four substituted (pyrrolidin-2-yl) phosphonates **1–4**. According to force field calculations, one type of conformation (twist form around C^4 and C^5 atoms) was found to be strongly favoured for compounds **2–4** while for **1** an equilibrium between two envelope forms on the C^4 atom was established. ^{1}H NMR parameters obtained from simulations of spectra with the LAOCOON program as well Karplus relationships were in good agreement with the calculated geometries.

Key words: Dialkyl(pyrrolidin-2-yl)phosphonates, conformational analysis, NMR studies, molecular mechanics, X-ray diffraction.

INTRODUCTION

In a previous paper, we described the synthesis of a new series of (pyrrolidin-2-yl) phosphonates.[1] These compounds are useful precursors of α-phosphorylated pyrrolin-1-oxydes, which were recently shown to be excellent traps of free radicals, particularly in biological *milieu.*[2] β-Phosphorylated pyrrolidinoxyl radicals, which can also be generated by oxydation of (pyrrolidin-2-yl) phosphonates,[3] are obtained in these spin trapping experiments and we have shown that EPR coupling constants of these radicals strongly depend on their conformation.[4] We are currently undertaking a conformational study on both different (pyrrolidin-2-yl) phosphonates and their corresponding nitroxides,[3c,5] and we describe in this paper the conformational study of four (pyrrolidin-2-yl) phosphonates **1–4** (Scheme I) performed using force field calculations, X-ray diffraction, and ^{1}H NMR spectroscopy.

The energy differences between twist and envelope forms of cyclopentane are so small that no favoured conformation[6] exists for the molecule. However, introduction of substituents[7–9] and/or heteroatoms[10–14] clearly modify the conformational equilibrium of five membered rings.

Conformational studies have been carried out on pyrrolidine ring derivatives of

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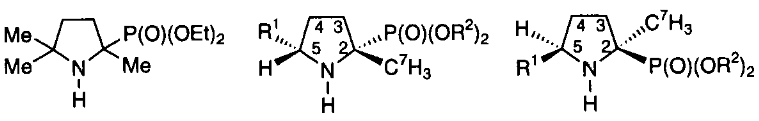
†To whom correspondence should be addressed.

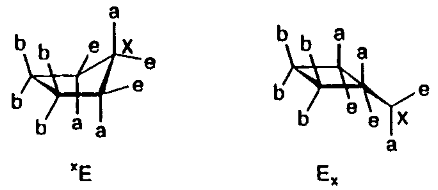


1 **2** **3-4**

	R^1	R^2
2	C^6H_3	$CH\ (CH_3)_2$
3	C^6H_3	CH_2CH_3
4	$C^6H\ (CH_3)_2$	CH_2CH_3

* In this scheme, only the diastereomers of compounds **2-4**, isolated in solid state and studied by X-ray diffraction, are shown.

SCHEME I



• a= axial, e= equatorial, b= bisectional or isoclinal.

SCHEME II

biological importance: for example, nicotine,[15,16] proline derivatives,[17,18] and peptides.[19] However, only a few pyrrolidine ring derivatives have been isolated in solid state, and thus X-ray geometries of these derivatives are very scarce.

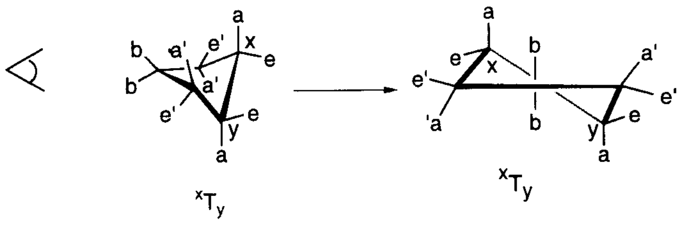
Many methods are used for conformational determination on gas and liquid phases. Electronic diffraction[10] is the most successful experimental approach used in gas phase, while in solution, Karplus type correlations between vicinal NMR coupling constants are mostly used.[7–9,12–22] Molecular mechanics calculations[20,23] and molecular orbital theory[8] have also been used to investigate the conformation of substituted pyrrolidine rings.

We present here a conformational study of α-phosphorylated pyrrolidine rings **1–4** (Scheme I) in solution, using NMR and molecular mechanic calculations; in addition, one diastereomer of each compound **2–4** has been isolated in solid state and its conformation established by X-ray diffraction (Scheme I).

FORCE FIELD CALCULATIONS

Molecular mechanics was employed to explore conformations of the substituted β-phosphorylated pyrrolidine rings[24] **1–4**, using the MM2[25] force field developed by Allinger and his co-workers.

For each compound, energy minimization has been carried out on 20 starting conformations: ten "twist" and ten "envelope" forms corresponding to the pseudorotation around the pyrrolidine ring. The nomenclature of the ring conformations,



* a= axial, e= equatorial, a'= pseudo-axial, e'= pseudo- equatorial; b= bisectional or isoclinal.

SCHEME III

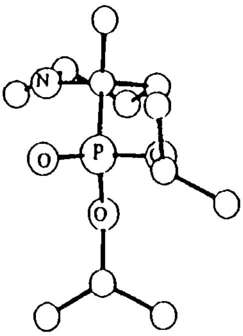


FIGURE 1 A view of the molecule **2** in the conformation $^{5}T_{4}$.

TABLE I

Results (energy,[a] population[b] and dihedral angles[c]) of energy minimization of compound **1**

Conformations	Energies	Populations	$NC^2C^3C^4$	$C^3C^2NC^5$	$H^{3a}C^3C^4H^{4a}$	$H^{3a}C^3C^4H^{4b}$	$H^{3b}C^3C^4H^{4a}$	$H^{3b}C^3C^4H^{4b}$	$H^{3a}C^3C^2P$	$H^{3b}C^3C^2P$	$C^4C^3C^2P$	C^5NC^2P
^4E	16.51-17.18	75	16.6/21.7	0.0/6.3	-41.1/-39.5	79.4/81.0	-159.1/-157.0	-38.6/-36.4	21.7/27.7	142.0/148.0	-101.0/-95.0	118.8/126.4
E_4	17.08-17.56	25	-26.9`/-18.9	-4.4/6.7	36.2/39.0	156.9/159.3	-81.7/-79.8	39.0/40.6	-30.0/-21.2	91.8/100.0	-147.1/-138.8	117.4/128.7

a: kcal/mol; b: per cent; c: degree. a and c: The lowest and highest values are given for the same type of conformers.

E for the envelope form (symmetry C_S) and T for half-chair or twist forms (symmetry C_2), originates from the one defined by Brutcher[26] for cyclopentane.

Compounds **2**, **3** and **4**, have been directly built up from their X-ray coordinates with the absolute configurations indicated on Scheme I. The twenty starting conformations were obtained using as a builder the GenMol[27] program developed by Pepe and Siri. In the case of the "envelope" forms E (Scheme II), four atoms of the ring are coplanar and the fifth one may be above or below this plane, thus giving rise to ten envelope conformations. For the "twist" forms T (Scheme III), two consecutive

TABLE II

Results (energy,[a] population[b] and dihedral angles[c]) of energy minimization of compound **2**

Conformations	Energies	Populations	$NC^2C^3C^4$	$C^3C^2NC^5$	$H^{3a}C^3C^4H^{4a}$	$H^{3a}C^3C^4H^{4b}$	$H^{3b}C^3C^4H^{4a}$	$H^{3b}C^3C^4H^{4b}$	$H^{3a}C^3C^2P$	$H^{3b}C^3C^2P$	$C^4C^3C^2P$	C^5NC^2P	$H^{4a}C^4C^5H^5$	$H^{4b}C^4C^5H^5$
$^5T_4$	15.12-15.48	95.3	-15.8/-11.5	-15.4/-10.1	40.5/42.0	-81.6/-80.1	158.1/159.8	35.9/37.8	-22.0/-16.9	-142.8/-138.0	101.0/105.7	-135.5/-130.1	-169.8/-168.3	-47.8/-46.3
^4E	16.92-17.10	3.9	22.3/27.1	-6.8/0.1	-39.0/-37.2	-159.9/-158.3	79.8/80.9	-41.1/-40.1	24.1/29.4	-97.5/-92.6	141.3/146.2	-128.3/-122.1	-86.7/-84.4	34.4/36.9

a: kcal/mol; b: per cent; c: degree. a and c: The lowest and highest values are given for the same type of conformers.

TABLE III

Results (energy,[a] population[b] and dihedral angles[c]) of energy minimization of compound **3**

Conformations	Energies	Populations	$NC^2C^3C^4$	$C^3C^2NC^5$	$H^{3a}C^3C^4H^{4a}$	$H^{3a}C^3C^4H^{4b}$	$H^{3b}C^3C^4H^{4a}$	$H^{3b}C^3C^4H^{4b}$	$H^{3a}C^3C^2P$	$H^{3b}C^3C^2P$	$C^4C^3C^2P$	C^5NC^2P	$H^{4a}C^4C^5H^5$	$H^{4b}C^4C^5H^5$
$^4T_5$	14.62-15.32	99.3	12.0/15.8	10.3/14.3	-42.3/-40.3	80.0/81.7	-160.2/-157.8	-38.0/-35.9	17.1/21.5	137.9/142.4	-105.7/-101.3	129.5/134.5	169.2/170.1	47.2/47.9
E_4	16.84-16.88	0.6	-27.7/-24.4	4.5/7.8	38.7/39.3	159.6/160.0	-80.0/-79.6	40.9/41.1	-30.6/-28.1	91.4/93.7	-147.4/-145.1	126.3/129.4	86.0/87.4	-35.2/-33.6

a: kcal/mol; b: per cent; c: degree. a and c: The lowest and highest values are given for the same type of conformers.

atoms are respectively one below and one above the plane formed by the three others, thus another ten "twist" conformations to exist.

Then, for each compound **1–4** the twenty starting conformations have been minimized using the "dipole-dipole interaction" option of the MM2 force field. The minimized conformations were labeled E or T according to the values of their q and ϕ coordinates.[26]

For each compound **2–4**, minimization led to a large proportion (higher than 93 per cent) of conformer populations[28] belonging to twist forms ($^5T_4$ type for **2** and $^4T_5$ type for **3** and **4**) which exhibit very similar strain energies and geometries (Tables II–IV). All these conformations present an axial H^5 proton, and thus the R^1 group adopts an equatorial position while the phosphoryl and the methyl groups adopt a bisectional position (Scheme III and Figure 1). It is worth to note the similarity of the calculated dihedral angles, for the predominant conformations of compounds **2–4** (Tables II–IV). The minor conformations of compounds **2**, **3** and **4** correspond to ^4E, or E_4 geometries with an equatorial H^5 proton.

TABLE IV

Results (energy,[a] population[b] and dihedral angles[c]) of energy minimization of compound **4**

Conformations	Energies	Populations	$NC^2C^3C^4$	$C^3C^2NC^5$	$H^{3a}C^3C^4H^{4a}$	$H^{3a}C^3C^4H^{4b}$	$H^{3b}C^3C^4H^{4a}$	$H^{3b}C^3C^4H^{4b}$	$H^{3a}C^3C^2P$	$H^{3b}C^3C^2P$	$C^4C^3C^2P$	C^5NC^2P	$H^{4a}C^4C^5H^5$	$H^{4b}C^4C^5H^5$
$^4T_5$	16.44-17.28	92.5	8.7/18.2	16.4/17.6	-41.9/-38.7	79.8/82.9	-159.6/-156.3	-37.9/-34.6	13.6/22.1	134.4/143.0	-108.9/-100.8	128.7/137.2	168.0/170.3	42.4/47.9
^4E	17.11	7.3	18.1	7.3	-42.7	79.1	-160.9	-39.1	24.5	145.4	-98.4	126.0	168.7	46.2

a: kcal/mol; b: per cent; c: degree. a and c: The lowest and highest values are given for the same type conformers.

The molecular mechanics results obtained for **1** were very different from those obtained for **2–4** (Table I). For **1**, conformations of the ^4E type represent 75 per cent of the conformer population, while the other 25 per cent are represented by E_4 envelope forms (Table I).

NMR STUDIES

To explore the conformations of compounds **1–4** in solution (C_6D_6), we analyzed their NMR spectra. However, the H^{3x} (x = a or b) and H^{4y} (y = a or b) hydrogens (Figure 2) exhibited second-order signals even at 600 MHz, and thus needed to be simulated using the LAOCOON[29] program. The initial parameters were determined from the experimental spectra with the help of several double resonance experiments. The final parameters are given in Tables V and VI, and as can be seen in Figure 2, good agreements were obtained between observed and calculated spectra.

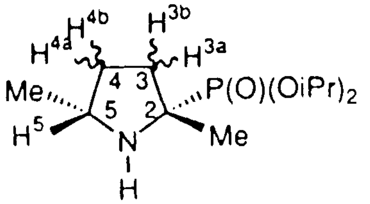
Low values of $^3J_{H^{3a}H^{4b}}$ and large values of $^3J_{H^{3a}H^{4a}}$ and $^3J_{H^{3b}H^{4a}}$ for compounds **2–4** (Table VI), suggest that their predominant conformers have $H^{3a}—C^3—C^4—H^{4b}$ dihedral angles close to 90° (Scheme IV).[15,16]

These NMR result agree with our force field calculations (for compound **2**, the calculated values of $H^{3a}—C^3—C^4—H^{4b}$ were in the range -81.6 to $-80.1°$) and that allowed us to reasonably assume that in the series **2–4** the same type of conformation is largely predominant either in the absence of solvent or in benzene solution. Then, taking in account only the lowest energy conformer, we found[30] for compounds **2–4** a very good Karplus relationship (1) (Figure 3), between the experimental vicinal coupling constants $J_{H^{3x}H^{4y}}$ and the corresponding calculated dihedral angles θ.

$$^3J_{H^{3x}H^{4y}} = A \cos 2\theta + B \cos\theta + C \qquad (1)$$

$$A = 3.25 \pm 0.30;\ B = 0.97 \pm 0.27;\ C = 6.93 \pm 0.19.$$

A Karplus relationship (2) has been established by Rabiller[21] for the $^3J_{C^5P}$ coupling



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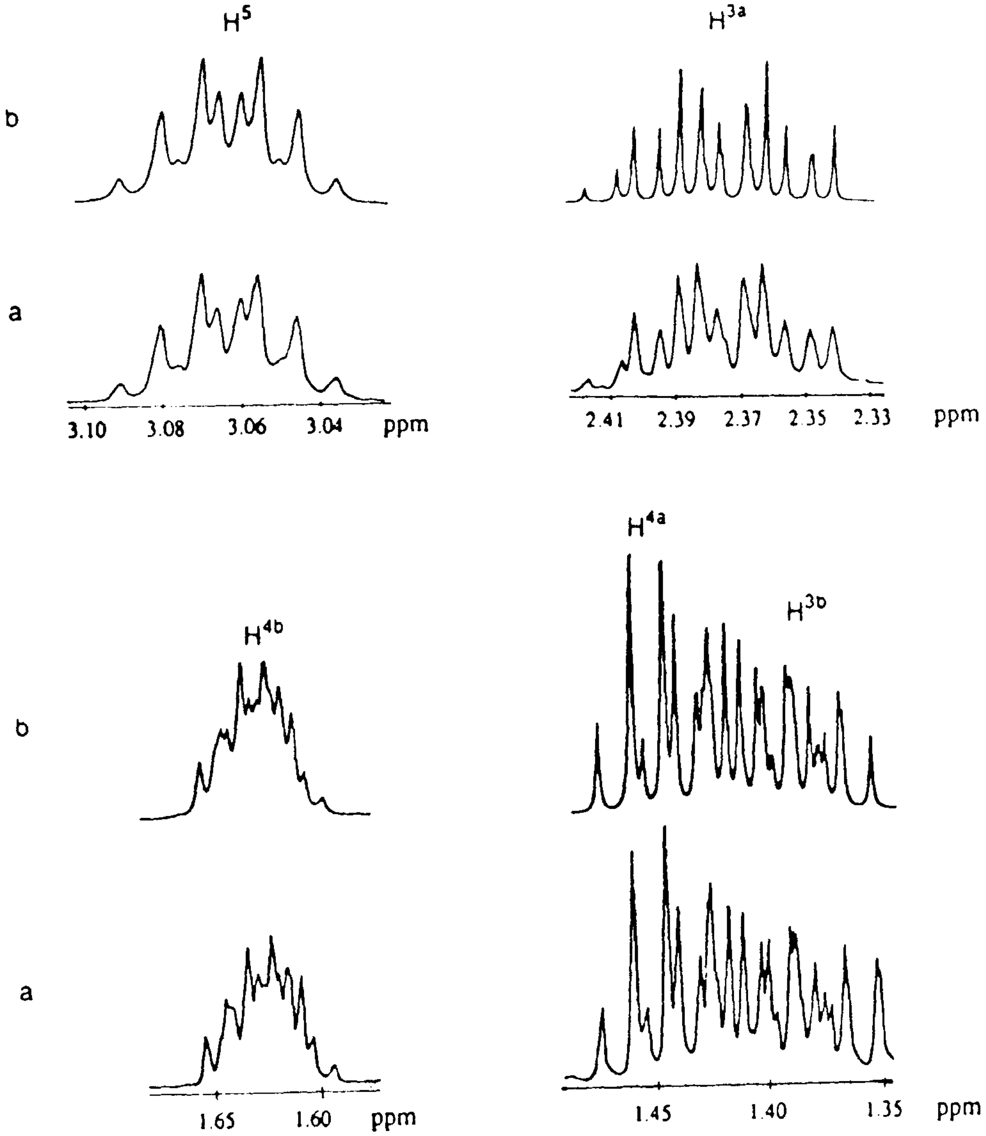
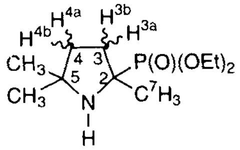


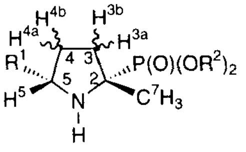
FIGURE 2 ^{1}H spectra (600 MHz) of compound **2**: (a) experimental spectrum; (b) computer-simulated spectrum.

TABLE V

^{1}H chemical shifts (ppm), in C_6D_6 for compounds **1–4**



1



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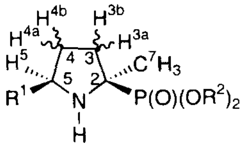


3-4

	H^{3a}	H^{3b}	H^{4a}	H^{4b}	$H(C^5)$	C^7H_3	R^1		R^2	
1	2.45	1.59	1.41	1.77	/	1.30	CH_3 0.98		CH_2 4.10	CH_3 1.10
2	2.37	1.38	1.44	1.62	3.06	1.30	CH_3 1.03		CH 4.74	CH_3 1.22
3	2.37	1.39	1.41	1.62	3.09	1.34	CH_3 1.02		CH_2 4.10	CH_3 1.11
4	2.37	1.39	1.59	1.61	2.64	1.33	CH_3 0.85	CH 2.69	CH_2 4.09	CH_3 1.13

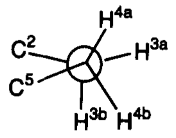
TABLE VI

^{1}H coupling constants* (Hz), in C_6D_6 for compounds **1–4**

	$J_{H^{3a}H^{4a}}$	$J_{H^{3a}H^{4b}}$	$J_{H^{3b}H^{4a}}$	$J_{H^{3b}H^{4b}}$	$J_{H^{4a}H^{5}}$	$J_{H^{4b}H^{5}}$	$J_{H^{3a}P}$	$J_{H^{3b}P}$	$J_{H^{3a}H^{3b}}$	$J_{H^{4a}H^{4b}}$
1	7,29	7,29	7,16	6,49	/	/	15,76	14,77	-12,84	-11,94
2	9,06	3,83	8,74	8,06	8,86	6,18	15,67	14,52	-12,81	-12,11
3	8,73	4,10	8,34	7,78	8,37	6,11	15,27	15,37	-12,80	-11,80
4	8,73	3,81	8,19	7,99	8,26	8,56	14,81	16,58	-12,78	-12,05

*The ^{1}H coupling constants J_{HC^7P}, J_{OCHCH3}, $J_{OCH2CH3}$ are equivalent for the products **1-4**. J_{H^5CH3}= 6.2, J_{HC^7P} =15.4, J_{OCHCH3} = 6.1 and $J_{OCH2CH3}$= 7.1Hz. The ^{1}H coupling constant J_{H^5CH3} is equivalent for the products **2** and **3**. J_{H^5CH3}= 6.2Hz.

constants in a series of diethylphosphonocarbethoxy 4-pyrrolidines (Scheme V). Using this relation, and the dihedral angle values derived from our molecular mechanics calculations, we obtained the coupling constants listed in Table VII. Again, the good agreement observed between calculated and experimental values, supports the cal-



SCHEME IV Newman projection along the C^3C^4 axis.

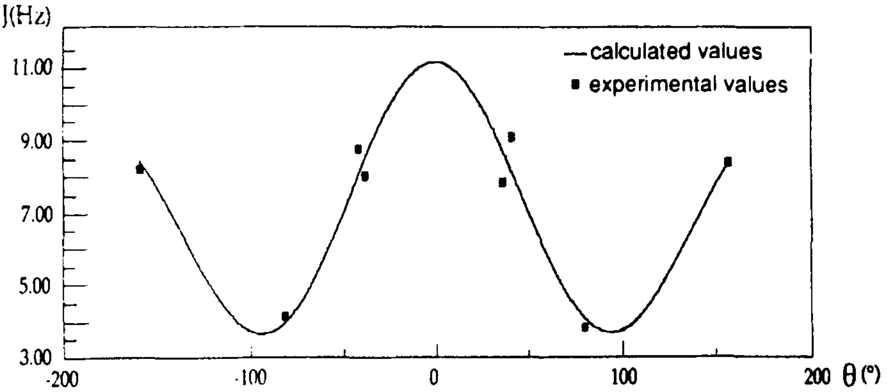
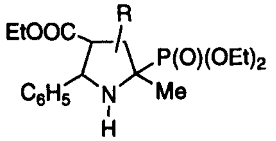


FIGURE 3 Plot of $^3J_{H^3,H^4}$ coupling constants against the corresponding Karplus dihedral angles.



SCHEME V

TABLE VII

Calculated and experimental ^{13}C coupling constants $^3J_{C^5P}$ (Hz) for the compounds **2–4**

	2	3	4
Exp.	11.50	11.10	10.40
Calc.*	12.60	12.90	12.80

*Weighted average values calculated from twenty minimized conformations.

culated geometries which indicated a bisectional position for the phosphoryl group in the lowest energy conformations of compounds **2–4**.

$$^3J_{C^5P} = 12.25 - 1.76\cos\theta + 7.86\cos 2\theta \qquad (2)$$

The Karplus relationship (1), was also used to calculate the coupling constants $^3J_{H^4,H^5}$. We obtained (Table VIII) a good agreement between calculated and experi-

TABLE VIII

Calculated and experimental coupling constants ${}^3J_{H^{4x}H^5}$ (Hz) for compounds **2–4**

	$J_{H^{4a}H^5}$		$J_{H^{4b}H^5}$	
	Exp.	Calc.*	Exp.	Calc.*
2	8.86	9.20	6.18	7.20
3	8.37	9.15	6.11	7.35
4	8.26	9.10	8.56	7.50

*These values have been calculated using the dihedral angles of the lowest energy conformation obtained by force field calculations[35].

TABLE IX

Calculated and experimental coupling constants ${}^3J_{C^5P}$ and ${}^3J_{H^{3x}H^{4y}}$ (Hz) for the compound **1**

	J_{C^5P}	$J_{H^{3a}H^{4a}}$	$J_{H^{3a}H^{4b}}$	$J_{H^{3b}H^{4a}}$	$J_{H^{3b}H^{4b}}$
Exp.	9.05	7.29	7.29	7.16	6.49
Calc.*	10.85	8.60	7.30	8.30	5.10

*Weighted averaged values for the ${}^4E$ and E_4 conformations.

mental values which confirmed the axial position of hydrogen H^5 in the predominant conformers. Moreover, this axial position is consistent with the relatively large values of ${}^3J_{H^{4a}H^5}$ and ${}^3J_{H^{4b}H^5}$ coupling constants.[15,16,31,32]

For **1**, NMR results differ from those obtained for compounds **2–4**, especially the coupling constants $J_{H^{3x}H^{4y}}$ being the same order of magnitude (Table VI). According to force field calculations many conformations of the ${}^4E$ (75%) or E_4 (25%) type must be considered for **1**. We have supposed that these conformations were also present in solution and using the Karplus relationships (1) and (2), we calculated the weighted averaged coupling constants $J_{H^{3x}H^{4y}}$ and J_{C^5P}. We found a reasonably good agreement between calculated and experimental values (Table IX) which supported our assumptions.

CRYSTAL STRUCTURE

According to X-ray diffraction results, compounds **2–4** adopt an envelope conformation close respectively to the ${}^5E$ or E_5 (**3** and **4**) geometries with the R^1 group in equatorial position (C^6—C^5—N—C^2 ≅ 160°). Selected bond length and angle values are given in Table X. In the solid state, the rings conformations differ from those determined by NMR and molecular mechanics studies. Due to the small energy difference between the different conformations, the crystal-packing effects should be preponderant in solid state favoring the ${}^5E$ or E_5 conformations with a bisectional phosphoryl group.

TABLE X

Selected bond length and angle values for compounds **2–4**

	2	**3**	**4**
Bond lengths (Å)			
N - C(2)	1.479 (6)	1.490 (5)	1.490 (5)
C(2) - C(3)	1.563 (7)	1.553 (3)	1.550 (6)
C(3) - C(4)	1.516 (7)	1.497 (6)	1.475 (7)
C(4) - C(5)	1.502 (7)	1.510 (6)	1.519 (8)
C(5) - N	1.462 (6)	1.468 (3)	1.469 (5)
C(2) - P	1.804 (5)	1.804 (2)	1.806 (4)
Bond angles (°)			
C(5) - N - C(2)	107.4 (4)	109.5 (3)	109.5 (3)
N - C(2) - C(3)	104.4 (3)	104.7 (3)	104.7 (3)
C(2) - C(3) - C(4)	105.1 (4)	105.8 (4)	105.8 (4)
C(3) - C(4) - C(5)	104.5 (4)	106.6 (4)	106.6 (4)
C(4) - C(5) - N	103.2 (4)	102.9 (4)	102.9 (4)
Torsional angles (°)			
N - C(2) - C(3) - C(4)	-0.33 (0.50)	2.89 (0.34)	7.18 (0.47)
C(2) - C(3) - C(4) - C(5)	23.23 (0.54)	-24.95 (0.36)	-24.70 (0.54)
C(3) - C(4) - C(5) - N	-37.89 (0.53)	37.83 (0.35)	32.75 (0.51)
C(4) - C(5) - N - C(2)	38.83 (0.51)	-36.77 (0.34)	-28.43 (0,45)
C(5) - N - C(2) - C(3)	-23.74 (0.48)	21.19 (0.31)	13.71 (0,42)
P - C(2) - N - C(5)	-142.27 (0.33)	138.99 (0.21)	132.37 (0.28)

CONCLUSION

Using MM2 calculations and extensive NMR studies we were able to determine the preferred conformations of a series of dialkyl(pyrrolidin-2-yl)phosphonates **1–4**. For compounds **2**, **3** and **4**, conformers close to ideal $^{5}T_{4}$ (compound **2**) and $^{4}T_{5}$ (compounds **3** and **4**) conformations are largely predominant. In these conformers the H^{5} hydrogen is axial and the phosphoryl group bisectional. For compound **1**, 75% and 25% of the conformers are close respectively to ideal ^{4}E and E_{4} conformations. In the solid state, crystal-packing effects are predominant and E_{5} conformation is adopted by compounds **3** and **4** while compound **2** adopts an ^{5}E conformation.

EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were performed on Brucker AM X 400 spectrometers. The NMR spectra are referenced to internal tetramethylsilane. ^{1}H NMR spectra were analyzed with the LAOCOON-3 computer program. The maximum error in the chemical shifts and coupling constants of calculated spectra is 0.09 Hz.

The synthesis of **1–4** have been previously reported in the following references: **1**,[3a] **2**,[1] **3**[1,33] and **4**.[34]

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