Coupling constants $^1J(^{15}N,^{31}P)$ as a probe for the conformational equilibria of 2-amino-substituted 1,3,2λ^5-oxazaphosphinan-2-ones †

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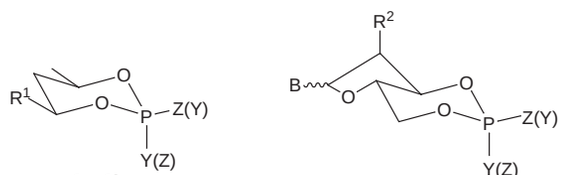
The ^{15}N NMR spectra of both P(2) diastereomers of the *trans*-fused 2-bis(2-chloroethyl)amino-3,4,4a,5,6,7,8,8a-octahydro-1,3,2λ^5-benzoxazaphosphinin-2-ones and their 3-methyl and 3-benzyl derivatives have been measured. Depending on the P(2) configuration, the coupling constants $^1J(^{15}N,^{31}P)$ vary markedly. The applicability of the coupling between exocyclic nitrogen and phosphorus for determination of the heteroring conformation is discussed.

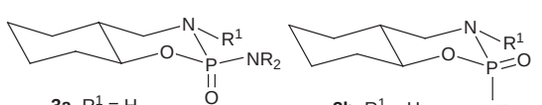
Introduction

It was shown by Stec and co-workers[1,2] that in the 2-Y-2-Z-1,3,2λ^5-dioxaphosphinanes the one-bond coupling constant between phosphorus and a Z nucleus ($I = \frac{1}{2}$, Z = ^{1}H, ^{13}C, ^{19}F or ^{77}Se) has a smaller absolute value when Z is in an axial compared to an equatorial position. The same relationship holds for nitrogen substituted dioxaphosphinanes,[3–6] *e.g.* **1a**,**b** and nucleotide analogues **2a**,**b**. Recently, Gudat *et al.*[7] employed ^1J(N,P)



1a, 1b **2a, 2b**

Y = O; Z = NR_2; R = H, Me, Ph; B = nucleotide base;
R^1 = H, Me; R^2 = H, OH, OBz



3a, R^1 = H
4a, R^1 = Me
5a, R^1 = CH_2Ph

3b, R^1 = H
4b, R^1 = Me
5b, R^1 = CH_2Ph

R = CH_2CH_2Cl

for the determination of the stereochemistry in nitrogen-phosphorus ring systems and Modro *et al.*[8] demonstrated a correlation between the bond angles at nitrogen and the ^1J(N,P) coupling constants.

The variations of ^1J(N,P) can be attributed to changes in nitrogen hybridization and/or N–P bond lengths.[5,8] The X-ray structures of **3a**[9] and **5a**[10] show the exocyclic nitrogen to be planar (sum of bond angles 358.5 and 359.9°) whilst the endocyclic nitrogen is more tetrahedral (in **5a** 348.4°); these geometries are typical for 1,3,2λ^5-oxazaphosphinanes with a heteroring chair conformation and an equatorial exocyclic nitrogen.[11,12] Axial nitrogens tend to adopt non-planar geometry to avoid 1,3-*syn*–axial interactions,[13,14] but if the heteroring adopts a twist-boat conformation, then both nitrogens can assume almost planar geometry.[15,16] The N–P bond has been noted to be longer for an axial than for an equatorial nitrogen,[5,13,14,17] this phenomenon usually being associated with an anomeric effect.[11,18] However, it has not been proven whether hybridization or the anomeric effect has the more pronounced effect on ^1J(N,P) values.

We earlier studied the conformations of oxazaphosphinanes **3**–**5** by means of ^{1}H, ^{13}C, ^{31}P, VT, 2D and NOE NMR methods—a multinuclear approach—and concluded that **3a**–**5a** exist solely in the chair–chair conformation, while **3b**–**5b** exist as mixtures of chair–chair and chair–twist-boat conformations.[19] However, since the use of ^3J(P,N,C,H) as a conformational probe is not straightforward, some uncertainty remained and the conformational equilibrium was therefore reinvestigated by analysis of ^1J(N,P) values.

Results and discussion

The 1,3,2λ^5-oxazaphosphinan-2-ones **3**–**5** were synthesized earlier.[19] Since the compounds were generally not available pure in sufficient quantity for natural abundance ^{15}N NMR by direct detection, spectra were recorded on samples containing a mixture of diastereomers. The stereochemistry of the diastereomers (known from previous work)[19] and relative isomeric concentrations were readily determined by phosphorus NMR.

For **3a** and **b**, the endocyclic nitrogens (NH) were readily detected (and thus distinguished from the exocyclic nitrogens) by both INEPT [1/(4*J*)] and DEPT (45°) pulse sequences, using a one-bond *J*(N,H) constant of 90 Hz. For the exocyclic nitrogens and the nitrogens in the other compounds (**4** and **5**), long-range coupling was utilized. The approach applied was to search for the resonances in a sample by the acquisition of INEPT or DEPT spectra with an appropriate *J* constant (*e.g.* 1–7 Hz), together with variation of such parameters as the 3rd and 4th delays in the case of INEPT [*e.g.* 1/(5*J*)-4/(5*J*)] or the final proton irradiation pulse in the case of DEPT (*e.g.* 20–45°) until at least the two doublets (due to ^{31}P coupling) from the major isomer, if not all four resonances from a mixture of two isomers, had been detected, though not necessarily in the same spectrum.

When all four resonances were not readily detected in one sample, then another sample with an increased relative concentration of the minor isomer was utilized. A second sample also enabled the assignment of the resonances to their respective compounds as this could not, based on peak intensities, be determined from a series of spectra from one sample. It was, however, readily apparent from the acquisition of spectra under otherwise identical conditions (pulse sequence, delays, *etc.*) on samples with different relative isomer concentrations. Distinction between the endo- and exo-cyclic nitrogens in the methyl

† Previously known as 1,3,2-oxazaphosphorinan-2-ones.

Table 1 ^{15}N NMR data for studied 1,3,2-oxazaphosphinanes

	$\delta_{N(1)}$	^1J[P,N(1)]/Hz[a]	$\delta_{N(3)}$	^1J[P,N(3)]/Hz[a]
3a	−360.19	42.7	−367.25	20.6
3b	−360.16	28.0	−371.66	26.3
4a	−364.45	42.3	−374.77	19.6
4b	−360.33	34.1	−379.58	30.1
5a	−363.31	41.8	−361.48	19.8
5b	−359.73	31.7	−364.69	29.9

[a] The sign of the coupling constant was not determined.

and benzyl isomers (**4** and **5**) was accomplished using selective, long-range INEPT (also with variation of *J*). For example, irradiation of the β-methylene protons of the sidechain readily gave a response for the exocyclic nitrogen. The endocyclic nitrogen was generally much more difficult to detect by this method with selective irradiation at the methyl/benzyl, H4 or H4a protons.

Thus, whilst these polarization transfer experiments resulted in the quick acquisition of spectra when conditions were optimal (20–40 min, depending on the concentration, *vs.* overnight accumulation for single-pulse excitation), many spectra needed to be acquired to find all the resonances, requiring appreciable operator effort and spectrometer time; increased operator experience did not markedly reduce this process.

The ^{15}N chemical shifts and coupling constants ^1J(N,P) are listed in Table 1. Change of the N(3) substituent from hydrogen to methyl or benzyl produced the expected several ppm upfield and downfield shifts, respectively, in both series. It is of significance though, that N(3) for the **b** isomers only resonates 3.2–4.8 ppm upfield and N(1) 0.0–4.1 ppm downfield relative to their **a** counterparts. These very narrow shift ranges for N(1) and N(3), together with the fact that the coupling constant N(1)–P differs substantially between pairs of isomers, makes it tempting to postulate that the ^1J(N,P) values are more dependent on N–P bond length than on nitrogen hybridization.

The coupling constant between exocyclic nitrogen N(1) and phosphorus is almost constant (41.8 to 42.7 Hz) in **3a**–**5a**, indicating the orientation of the bis(2-chloroethyl)amino group to be the same in all three compounds. The endocyclic nitrogen–phosphorus coupling also remains relatively constant in this series (19.6 to 20.6 Hz). The nature of the substituent on endocyclic nitrogen N(3) appears to have minimal effect on either coupling.

By contrast, for the **b** isomers there are clear variations in both couplings. The exocyclic nitrogen–phosphorus couplings have smaller absolute values than those in the **a** isomers, whilst conversely the endocyclic nitrogen–phosphorus couplings have larger absolute values. If a mean value of 42.3 Hz (calculated from **3a**–**5a**, for which the pure chair–chair conformation was assigned earlier)[19] is used to characterize the exocyclic N,P coupling constant when the N(1)–P bond is purely equatorial and a calculated value of 26.9 Hz for an axial N(1)–P bond [using the ^1J(N,P) of **3b** for which a 93% chair–chair/7% chair–twist-boat equilibrium was estimated in an earlier study],[19] then the percentage populations can be calculated from eqn. (1).

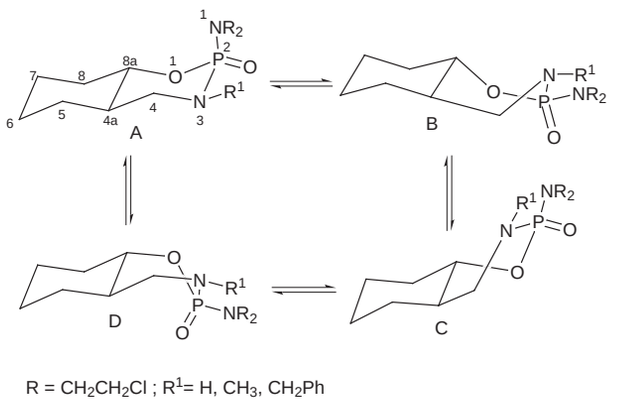
$$\text{percentage(chair–twist-boat)} = [^1J\text{(N,P) (obs.)} - 26.9]/[42.3 - 26.9] \times 100 \quad (1)$$

This results in 47% of the chair–twist-boat conformation (Scheme 1, form B) for **4b**, and 31% for **5b** (Table 2). Both of these values are considerably larger than those calculated in our previous study: 32% for **4b** and 16% for **5b**.[19] However, in the previous study we assumed that a change in the heteroring conformation interchanges the magnitudes of the couplings between the C-4 protons and phosphorus, an assumption which is not necessarily valid. This is evidenced by the sum of the couplings ^3J[P,H(4)] decreasing from the **a** to the **b** series

Table 2 Percentages of twist-boat conformations for **b** isomers calculated from different coupling constants

	^3J(P,N,C,H) (%)[a]	^3J(P,N,C,H) (%)[b]	^1J[P,N(1)] (%)[b]
3b	7	9	—
4b	32	45	47
5b	16	23	31

[a] From ref. 19. [b] Values from the present article.



Scheme 1 Possible heteroring conformations for P–N axial diastereomers

(4 Hz for **3**, 6.4 Hz for **4** and 6.8 Hz for **5**),[19] and if this is accounted for by subtracting this difference from the larger coupling,[20] then proportions of the chair–twist-boat conformation can be re-evaluated as: 9% for **3b**, 45% for **4b** and 23% for **5b**. The value for **4b** is now in much better agreement with the result from this study, although the percentage for **5b** is still substantially lower. Since the chair–twist-boat populations calculated using exocyclic ^1J(N,P) values exhibit much the same trend as found previously,[19] it can clearly be used to estimate conformational equilibria.

Although we cannot separate hybridization and bond length changes as the cause(s) for the variation in the exocyclic ^1J(N,P), because both are expected to vary only according to ring conformational changes, a reliable probe results. This was not the case for the endocyclic ^1J(N,P). It is possible that N(3)R^1 substituent reorientation concomitant with the ring conformational change perturbs the magnitude of the endocyclic N–P coupling by also affecting nitrogen hybridization, thus making nitrogen hybridization also dependent on the nature of the N(3) substituent [N(3)H was noted to change from equatorial to axial on going from **3a** to **3b**].[19] However, the same trend is present in that the magnitude of this coupling increases when the conformation of the heteroring changes from a chair to a twist-boat.

Use of the coupling constant ^1J(N,P) to estimate conformational equilibria has some advantages. Firstly, it is not necessary to separate the diastereomers completely if, as in this case, the stereochemical assignments can be made by means of ^{31}P NMR. Secondly, the interpretation of the data is far easier in comparison to the multinuclear approach, where many shifts and couplings need to be examined. Thirdly, despite the low receptivity of the ^{15}N nucleus, the overall experimental time was shorter than required for conducting all the necessary 1D, 2D, and VT NMR experiments. However, it is important to note the limitations of this approach. A series of compounds is required to obtain meaningful results, since there is a lack of general reference data in the literature. A differentiation can be made only between chair and non-chair conformations; it is not feasible to ascertain which of the non-chair conformations is responsible for the observed changes in the coupling constants (Scheme 1, forms B, C and D). The amount of compound required for acquisition of the spectra in a reasonable time is

considerably larger than that needed for ^{1}H or ^{13}C NMR. Finally, in the ^{15}N NMR approach we could not obtain an experimental value for ^{1}J(N,P) for a purely axial N(1)–P bond and use of the percentage of chair–twist-boat conformation for **3b** from previous work to adjust the aforementioned coupling value makes the present approach dependent on the multinuclear one. Both approaches, the multinuclear one and the ^{1}J(N,P)-based one, have their limitations and it is not possible to ascertain which method gives the more reliable result, but the results given by the two approaches agree reasonably well within the experimental limits.

Experimental

Spectra were acquired on a JEOL Alpha 500 NMR spectrometer equipped with a 5 mm tunable probe operating at 202.47 MHz for ^{31}P and 50.688 MHz for ^{15}N. 1D nitrogen spectra were acquired with broad-band proton decoupling, spectral widths of 25 kHz consisting of 32k data points (digital resolution 0.76 Hz per point), zero-filled to 128k and processed with an exponential weighting window function of 0.25 Hz prior to Fourier transformation. In the case of normal single-pulse excitation, acquisition was achieved with inverse-gated decoupling, a 60° flip angle and a pulse recycle time of 20.7 s. For the polarization transfer experiments, the pulse recycle time was reduced to 4.3 s. Spectra were recorded on samples in $CDCl_3$ at 25 °C and typical concentrations (total) ranged from 100–400 mg per 0.5 ml. The nitrogen spectra were referenced externally to 90% formamide in [$^{2}H_6$]DMSO, assigned as −298 ppm.

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