



Conformational preferences in 2-alkyl, 2-alkanoyl and 2-aroyle-2-oxo-1,3,2-oxazaphosphorinanes

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Abstract—A series of 2-alkyl-, 2-alkanoyl- and 2-aroyle-2-oxo-1,3,2-oxazaphosphorinanes bearing *N*-benzyl, *N*-benzhydryl and *N*-trityl substituents are prepared and their conformational preferences in solid phase are discussed. © 2001 Published by Elsevier Science Ltd.

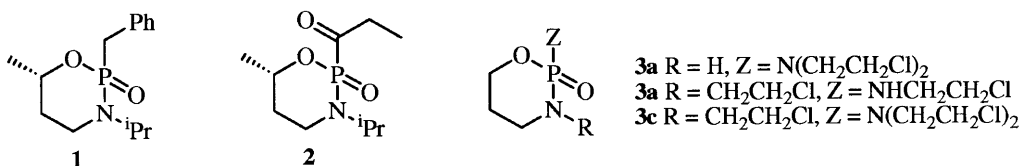
Study of the conformation of 2-oxo-1,3,2-oxazaphosphorinanes is important for three reasons. The conformation of 2-oxo-1,3,2-oxazaphosphorinanes is the basis of a number of models which predict asymmetric reactions of chiral phosphoramidates such as **1**¹ and **2**.² Secondly, it is of basic interest to understand the effect on the conformational properties arising from the replacement, and substitution, of the carbon atoms of a cyclohexane ring by heteroatoms.³ Lastly, this ring system is found in a number of anticancer drugs (cyclophosphamide **3a**, isophosphamide **3b**, trophosphamide **3c**) and therefore an understanding of this ring's preferred conformation contributes to the interpretation of these drugs' structure–activity relationships (Scheme 1).⁴

Previous studies on the solid and solution state structures of 2-oxo-1,3,2-oxazaphosphorinanes have revealed important information about the conformational preferences of this ring system. These studies have concentrated on ring systems in which the phosphorus atom is substituted with electronegative groups such as OMe,^{3a} Cl,^{3b} and NR₂.^{3c} Bentrude has studied ring systems with

phenyl or hydrogen substituents on the nitrogen atom (which was found to be trigonal).^{3a,c} Denmark has reported oxazaphosphorinanes with *i*-Pr and *t*-Bu substituents on the nitrogen atom (which was found to be pyramidal).^{2b} In this paper, we reveal further influences of the *N*-substituent and the *P*-substituent on the solid state structure of this ring system.

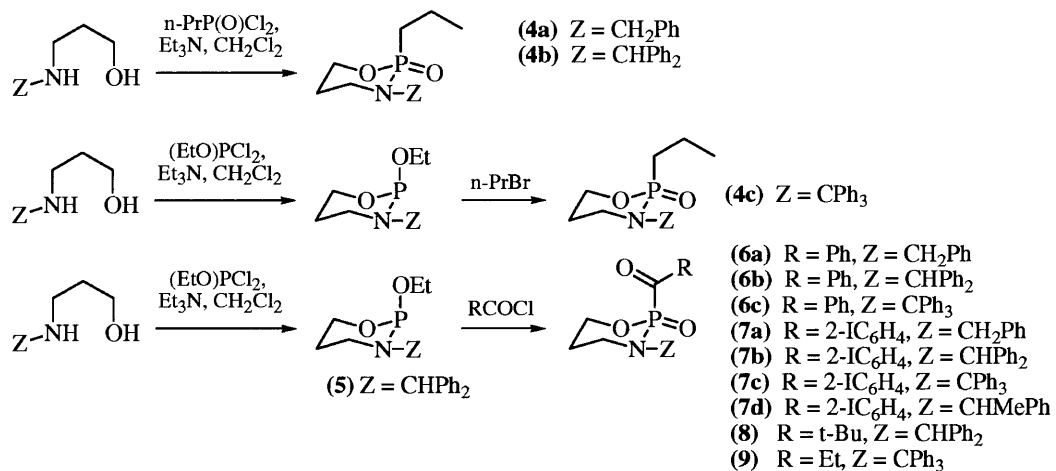
2-Propyl-2-oxo-1,3,2-oxazaphosphorinanes bearing *N*-benzyl and *N*-benzhydryl substituents (**4a** and **4b**, respectively) were prepared from the reaction of *N*-benzyl and *N*-benzhydrylpropanolamine with propanephosphonic dichloride.^{1,2}

2-Alkanoyl- and 2-aroyle-2-oxo-1,3,2-oxazaphosphorinanes bearing *N*-benzyl, *N*-benzhydryl and *N*-trityl substituents (**6–9**) were prepared by the Arbuzov reaction of the corresponding acid chlorides and 2-ethoxy-oxazaphosphorinanes (Scheme 2). Intermediate 2-ethoxy-1,3,2-oxazaphosphorinanes, such as **5**, were found to be predominantly of one configuration, presumably with the OEt in an axial position. 2-Propyl-2-oxo-1,3,2-oxaza-



Scheme 1.

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Scheme 2.

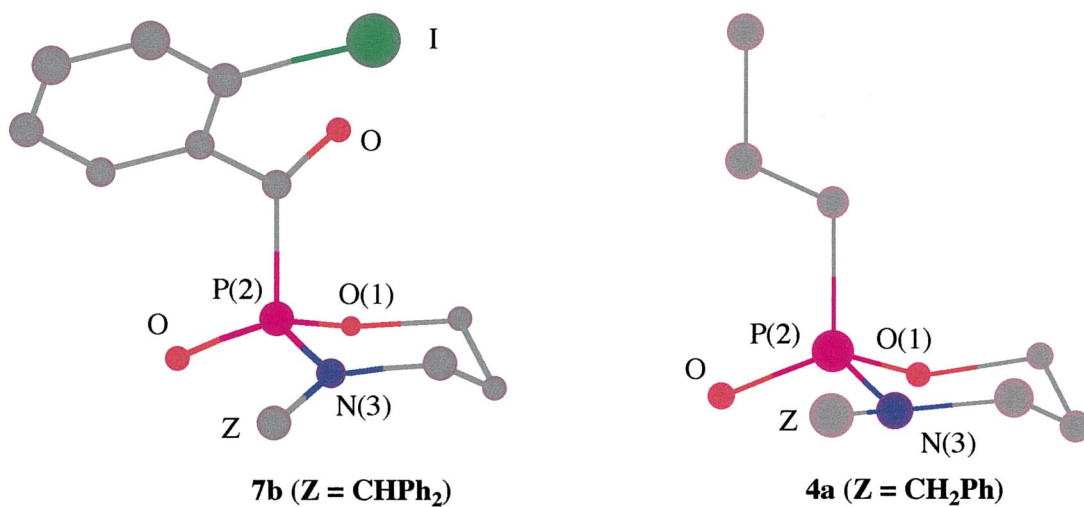


Figure 1.

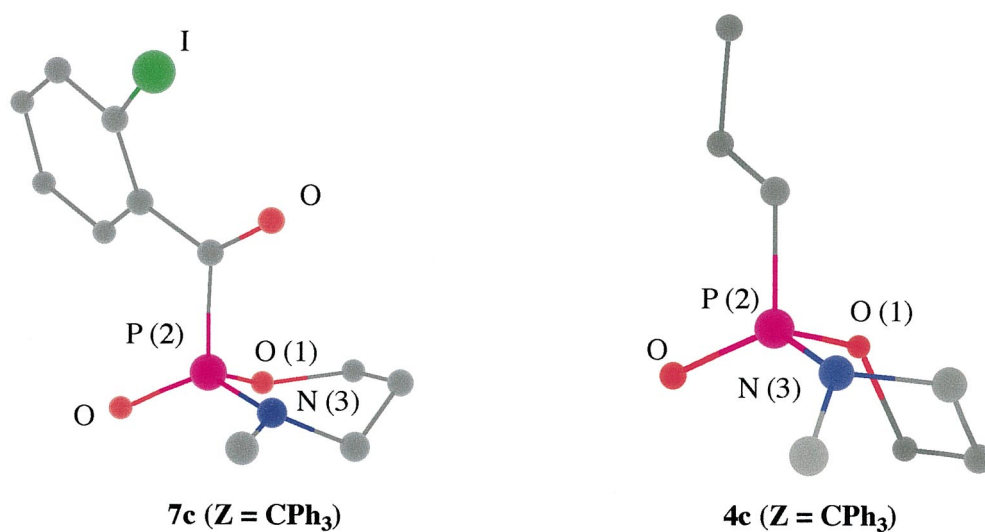


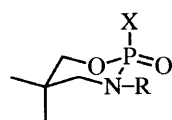
Figure 2.

Table 1.

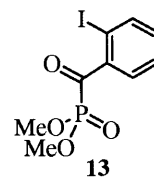
	4a	7b	4c	7c	8	7d
\angle C4–N–P (°)	118(0.5)	119(0.4)	114(0.7)	117(0.0)	120(0.7)	120(0.7)
\angle Z–N–P (°)	117(0.5)	120(0.9)	132(0.0)	124(0.6)	117(0.0)	121(0.3)
\angle C4–N–Z (°)	115(0.5)	119(0.3)	114(0.0)	114(0.2)	120(0.9)	117(0.9)
\angle O–P–N (°)	103(0.2)	105(0.4)	101(0.1)	103(0.6)	105(0.6)	106(0.0)
\angle O=P–N (°)	113(0.4)	114(0.9)	115(0.0)	118(0.9)	114(0.6)	115(0.4)
\angle O=P–O (°)	112(0.6)	113(0.5)	116(0.3)	111(0.0)	112(0.4)	113(0.4)
\angle O=P–C (°)	112(0.0)	113(0.0)	114(0.4)	113(0.5)	114(0.4)	110(0.0)
\angle O–P–C (°)	104(0.0)	103(0.0)	98(0.4)	100(0.9)	100(0.7)	101(0.6)
\angle N–P–C (°)	110(0.9)	105(0.9)	109(0.7)	106(0.8)	107(0.9)	108(0.4)
\angle C6–O–P (°)	119(0.1)	121(0.9)	115(0.4)	125(0.6)	122(0.8)	119(0.9)
P=O (Å)	1.47(8)	1.46(9)	1.47(1)	1.46(7)	1.47(0)	1.47(3)
P–O (Å)	1.60(1)	1.57(4)	1.59(5)	1.59(0)	1.58(1)	1.57(5)
P–N (Å)	1.66(6)	1.64(1)	1.67(6)	1.64(7)	1.64(0)	1.62(8)
P–C (Å)	1.80(1)	1.86(4)	1.79(1)	1.88(8)	1.87(2)	1.87(0)
Dev. ^a PNC5C6 (Å)	0.06(4)	0.07(5)			0.07(7)	0.10(0)
Dev. ^a OC6NC4 (Å)	0.02(1)	0.00(2)			0.00(3)	0.04(1)
Dev. ^a OPNC4 (Å)			0.07(3)	0.00(3)		
Dev. ^a OC4C5C6 (Å)			0.10(7)	0.12(8)		
Dih. ^b O=P–C=O (°)	NA	132(0.1)	NA	156(0.8)	176(0.0)	115(0.0)

^a Deviation from plane.

^b Dihedral angle.



10 (X = NMe₂); R = H
11 (X = OMe); R = Ph
12 (X = NHPh); R = H



Scheme 3.

phosphorinane bearing an *N*-trityl substituent, **4c**, was similarly prepared from 1-bromopropane and the corresponding 2-ethoxy-oxazaphosphorinane.^{1,2}

Drawings of the solid state conformations of a selection of these compounds are shown (Figs. 1 and 2, phenyl groups are omitted for clarity) and a selection of bond angles, dihedral angles and bond lengths are given (Table 1). In all cases, the N(3) atom is planar and the bond angles about the O(1) atom suggests that this atom is also trigonal. This observation is in direct contrast to that observed by Denmark for compound **1**,¹ but in agreement with that reported by Bentrude for compounds such as **10** and **11**.^{3a,c}

In all compounds synthesised by us, whether *P*-alkyl, *P*-alkanoyl or *P*-aroyl, the P=O bond is placed in an equatorial position. The equatorial preference for the P=O bond was previously observed by Bentrude^{3c} for compounds such as **12**, and was attributed in this compound to an *endo* anomeric effect arising from overlap of the N(3) *p* orbital and P–X anti-bonding (σ^*) orbital. Interestingly, our observation suggests that an equatorial preference for the P=O bond is also applicable when X is not an electronegative atom, for instance carbon. Furthermore, the P(O)–C(O) bond

length is quite similar in **7a–d** and **13** (where it is 1.850 Å)⁵ suggesting no significant interaction between the respective lone pairs on nitrogen and oxygen with σ^* of P(O)–C(O) bonds.

Furthermore, the P(O)–C(O) bond length is slightly longer than that of P(O)–CH₂, presumably due to repulsion between bonded pairs, but nevertheless suggesting no significant interaction between the respective π or π^* systems of the C=O and P=O bonds.

One of the most important differences in these systems arises from the ring conformation of the *N*-benzyl and *N*-benzhydryl derivatives, and that of the *N*-trityl derivatives. In the *N*-benzyl (including α -methylbenzyl) and *N*-benzhydryl derivatives, the oxazaphosphorinane ring adopts a *pseudo*-chair conformation (Scheme 3). The deviation from the true chair conformation arises from the planarity of the nitrogen atom and, to a lesser extent, the oxygen atom. Consequently, O(1)–N(3)–(C4)–C(6) are near planar (deviation from plane ca. 0.002 Å for **7b**). However, in *N*-trityl derivatives, the conformation is *pseudo*-boat with P(2)–O(1)–N(3)–(C4) near planar (deviation from plane ca. 0.003 Å for **7c**). In other words, the introduction of a bulkier *N*-trityl substituent forces the relative position of C(5) and C(6)

atoms to change, resulting in a conformational change in the oxazaphosphorinane ring.

Finally, it should be noted that all 2-alkanoyl- and 2-aroyle-2-oxo-1,3,2-oxazaphosphorinanes analysed during this work had a *gauche* or *anti* relationship between the P=O and C=O bonds. This is presumably to minimise dipolar interactions between the two bonds as observed in α -diketones.

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