X-RAY CRYSTALLOGRAPHIC ANALYSIS OF OPTICALLY ACTIVE 1,3,2-DIAZAPHOSPHOLIDINE DERIVATIVES AND N→O MIGRATION REACTION OF PHOSPHORUS ATOM UNDER NEUTRAL CONDITIONS

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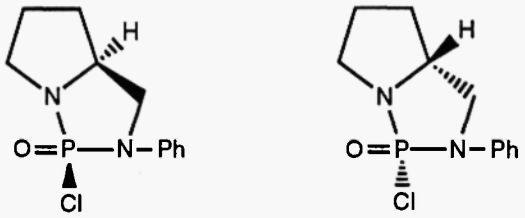
Abstract: X-Ray crystallographic analyses of optically active 2-chloro-1,3,2-diazaphospholidine 2-oxide derivatives were performed, and novel reaction of the chloro derivatives with chiral amino alcohols in organic solvent was proceeded to afford 1,3,2-oxazaphospholidine 2-oxide derivatives.

We reported about the determination of the absolute configuration and the evaluation of enatiomer excess of amines and alcohols by the use of optically active reagent 2-chloro-1,3,2-diazaphospholidine 2-oxide and ^{1}H and ^{31}P NMR spectroscopies in previously paper (1). The determination of conformation as well as configuration of 2-chloro-1,3,2-diazaphospholidine 2-oxide derivatives is very much interested in the standpoint why the reagent produces so large magnetically different field for enantiomeric materials as to assign them each other.

Pure 2-chloro-1,3,2-diazaphospholidine 2-oxides **1** and **2** were prepared by the diastereoselective reactions of corresponding (*S*)- and (*R*)-2-(anilinomethyl)pyrrolidine, respectively, with phosphoryl chloride in the presence of triethylamine at -78 ℃ quantitatively followed by simple purification of the products by column chromatography on silica gel (eluents: ethyl acetate / n-hexane = 2 / 1, v / v) (1).



1 **2**

Scheme 1.

These tentative stereochemical conclusion showing us that the reagents are excellent for determing the stereochemistry of such chiral substrated as alcohols and amines promoted us to carry out X-ray crystallographic analyses of 2-chloro-1,3,2-diazaphospholidine 2-oxide **2**. Rod-shaped crystals of **2** were grown from slow evaporation of a saturated solution in ethyl acetate. Precise lattice constants and three dimensional intensity data were collected on a RIGAKU AFC7R controlled by Stoe four circle diffractometer with Ni-filtered CuK α radiation. Phase determination was made by a direct method SHELXS (2) and expanded using fourier techniques (3). The CHARON drawing plot for compound **2** is shown by Fig. 1, and the summary of the crystallographic data is shown in Table 2. In Fig. 1, the P=O (1.456 Å) group is same direction with the hydrogen atom of stereogenic center on C5 of nomenclature, and P-Cl (2.047 Å) group is opposite direction with the hydrogen atom of stereogenic center on C5. From the results of X-ray crystallographic analysis, the correct structure of **2** is (2*R*,5*R*)-2-chloro-3-phenyl-1,3,2-diazaphosphabicyclo[3.3.0]octane 2-oxide. Conformation of pyrrolidine ring of chloride **2** has "envelope" conformation with C(3) deviating from the least-squares plane formed by C(2)-N(1)-C(5)-C(4), and the 1,3,2-diazaphospholidine 2-oxide ring has also "envelope" conformation with C(1) deviating from the least-squares plane formed by P(1)-N(1)-C(2)-C(1) in the solid state (4).

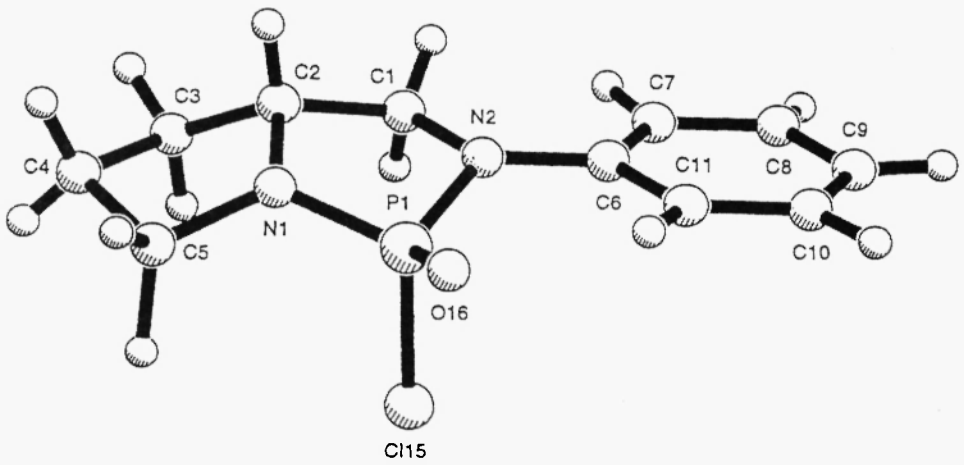
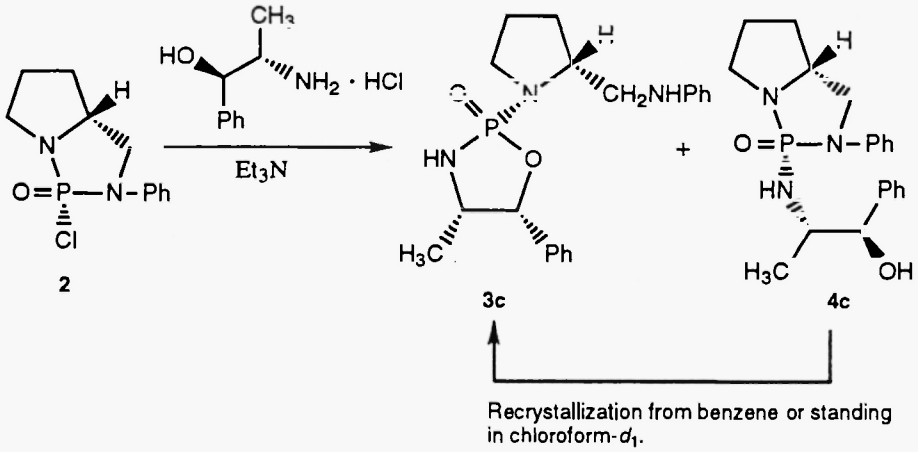


Fig. 1. X-Ray structure of (2R, 5R)-2-chloro-3-phenyl-1,3,2-diazaphosphabicyclo[3.3.0]octane 2-oxide (**2**).

We have reported a novel methodology to determine more conveniently and unambiguously the absolute configuration of amines or alcohols using ^{1}H NMR spectra than the other similar methods such as Mosher's ester method by the use of chlorides **1** and **2**, however, compounds having both amino and hydroxyl groups intramolecularly such as amino alcohol derivatives had not been examined. The reaction of chlorides **1** or **2** with optically active norephedrine hydrochloride in the presence of two equimolars amount of triethylamine in THF for 6 h at room temperature afforded 1,3,2-oxazaphospholidine 2-oxide derivatives **3** regioselectively as well as phosphamides **4** quantitatively (Scheme **2** and Table 1) (5). The structure determination of compounds **3** and **4** was very embarrassing

task by ^{1}H NMR spectrum data, because compounds **3** and **4** were isomer and these two products afforded little difference each other on their ^{1}H NMR spectra.



Scheme 2.

Table 1. Reaction of chloride **1** or **2** with optically active norephedrine hydrochloride.

chloride	norephedrine	product	ratio	chemical yield (%)
1	(1*R*, 2*S*)	**3a** / **4a**	90 / 10	98
1	(1*S*, 2*R*)	**3b** / **4b**	89 / 11	quant
2	(1*R*, 2*S*)	**3c** / **4c**	90 / 10	quant
2	(1*S*, 2*R*)	**3d** / **4d**	90 / 10	quant

Compounds **3** and **4** were separated by HPLC on silica gel (eluent: $CHCl_3$ / CH_3OH = 20 / 1, v / v; ratio: **3a-d** / **4a-d** = ca. 90 / 10). When the mixture of compounds **3a-d** and **4a-d** was recrystallized from benzene by a usual manner or from $CDCl_3$ by spontaneous evaporation of the solvent at room temperature for 3-4 days, all compounds **4a-d** efficiently converted into the isomeric 1,3,2-oxazaphospholidine 2-oxide derivatives **3a-d** (checked by HPLC), respectively, thus X-ray crystallographic analysis of compounds **3** was attempted to elucidate the structure. The crystal of compound **3c** was grown from slow evaporation of solution in a mixture of chloroform-hexane. Phase determination was made by a direct method MULTAN88 (6) and expanded using fourier techniques. The CHARON drawing plot for compound **3c** is shown by Fig. 2. A summary of the crystallographic data for **3c** is shown in Table 2.

Fig. 2 shows that all of the stereogenic centers of chloride **2** and introduced nucleophile (1*R*, 2*S*)-norephedrine are retained during the conversion of 4c into 1,3,2-oxazaphospholidine 2-oxide 3c, and that compound 3c form an intramolecular hydrogen bonding (1.75 Å) between the oxygen atom of the P=O group and the hydrogen atom of the anilino group in the solid state. Ring opening reactions of 1,3,2-oxazaphospholidine 2-oxides are well known to take place under basic conditions such as Grignard reagents, sodium alkoxide as well as in aqueous acid solutions (7)-(11), and N-phosphorylated amino acids undergo nitrogen to oxygen atom migration reactions, a special kind of hexa-coordinate (12), simultaneously, as reported by Zhao et al (13)-(15), however, those of 1,3,2-diazaphospholidine 2-oxides have not been known. The reaction of bis(dimethylamino)phosphoryl chloride with (1*R*, 2*S*)-norephedrine hydrochloride in the presence of two equimolars amount of triethylamine afforded three products, i.e., 1,3,2-oxazaphospholidine 2-oxide derivatives 5 and 6, and 7 (Scheme 3), which were separated each other by HPLC on silica gel (ratio: ca. 5 / 6 / 7 = 40 / 30 / 30).

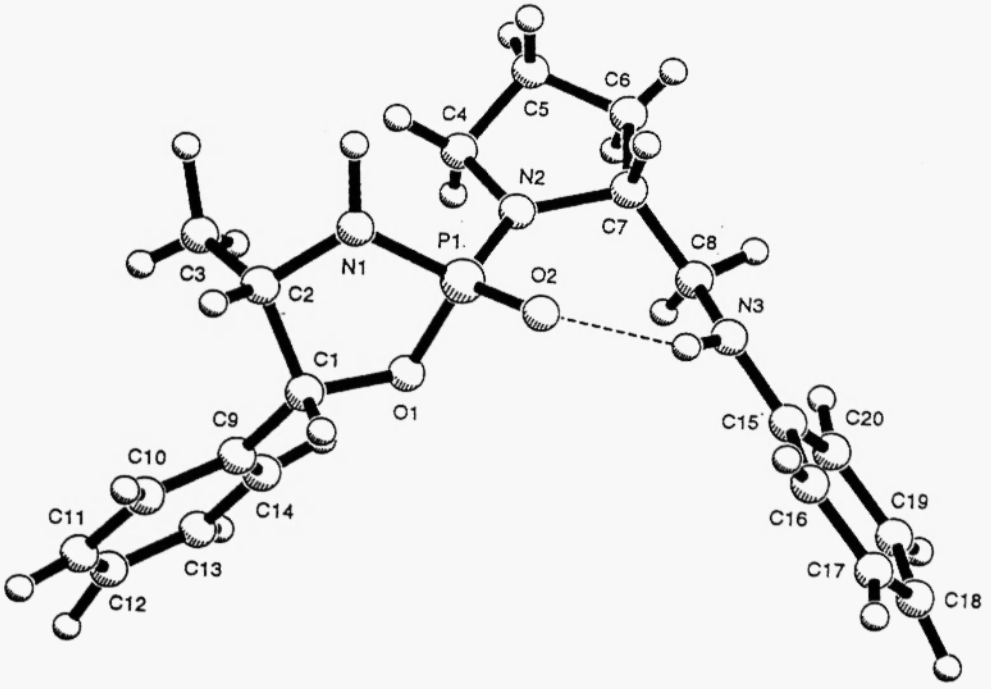
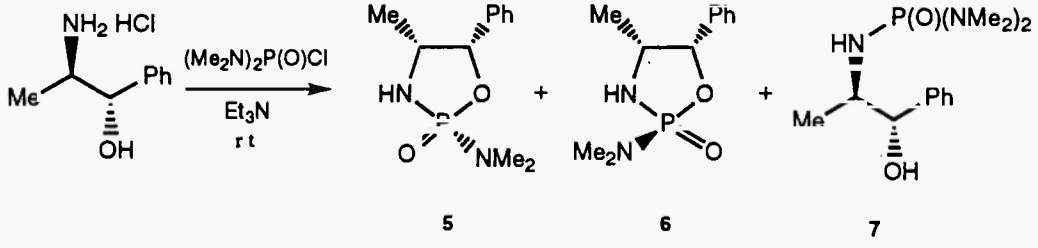


Fig. 2. X-Ray structure of 1,3,2-oxazaphospholidine 2-oxide 3c (the dotted line shows the intramolecular hydrogen bonding).

The structures of 1,3,2-oxazaphospholidine 2-oxides 5 and 6 were clearly assigned by ^{1}H NMR spectroscopy on the basis of coupling pattern of C4-H with the phosphorus atom (compound 5: δ = 4.01 ppm; J_{HH} = 6.4 and 1.6 Hz, and J_{PNCH} = 13.5 Hz. compound 6: δ = 3.92 ppm; J_{HH} = 6.5 and 1.6 Hz, and J_{PNCH} = 21.1 Hz) and that of C5-H (compound 5: δ = 5.73 ppm; J_{HH} = J_{POCH} = 6.8 Hz. compound 6: δ = 5.52 ppm; J_{HH} = 2.7 and J_{POCH} =

Table 2. Summary of the crystallographic data for the 2-chloro-1,3.2-diazaphospholidine 2-oxide 2 and 1,3,2-oxazaphospholidine 3c.

	Compound 2	Compound 3c
Formula	$C_{11}H_{14}ClPO$	$C_{20}H_{26}N_3PO_2$
Crystal color	color less	color less
Crystal size (mm)	0.2× 0.2× 0.3	0.2× 0.2× 0.3
Crystal system	orthorhombic	monoclinic
Space group	$P2_12_12_1$ (#19)	C2 (#5)
a (Å)	12.3358	24.668
b (Å)	14.4813	7.282
c (Å)	6.8458	11.227
V ($Å^3$)	1222.9	2003.3
β (degree)		95.586
Z	4	4
ρ (calc.) [g cm^{-3}]	1.394	1.231
μ (CuK α, cm^{-1})	38.51	13.64
R (%)	4.2	3.7
wR (%)	4.3	2.6
F(000)	536	792



5 6 7

Scheme 3. Reaction of bis(dimethylamino)phosphoryl chloride with (1*R*, 2*S*)-norephedrine.

5.9 Hz). On the other hand, the signal of the N-CH of compound 7 was observed as complicated coupling pattern with the phosphorus and the signal of the HO-CH for 7 did not couple with the phosphorus atom. The stereo chemistries at the phosphorus atom of compounds 5 and 6 were ambiguously assigned by ^1H NMR, where the C4-H and C5-H of 5 (δ , 4.01 and 5.73 ppm) resonated at the lower magnetic field than that of 6 (δ , 3.92 and 5.52 ppm) did by 1,3-diaxial deshielding effect with the P=O group (16)-(17). From these experimental results, it may b e concluded that 2-chloro-1,3,2-diazaphospholidine 2-oxides having cyclic N-P(O)-N bond moiety may favor to convert into 1,3,2-oxazaphospholidine 2-oxides by the reaction with protic reagents such as amino alcohols, and 1,3,2-diazaphospholidines 4 transcribes the absolute configuration at phosphorus atom into oxazacyclophosphamides 3.

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(4) Selected torsion angles for compound **2**; C(2)-N(1)-C(5)-C(4) = -7.7° , N(1)-C(5)-C(4)-C(3) =29.7° , C(3)-C(2)-N(1)-C(5) = -17.3° , P(1)-N(1)-C(2)-C(1) = 6.9° , N(2)-P(1)-N(1)-C(2) = 11.2° , N(1)-C(2)-C(1)-N(2) = -24.3° .

(5) Selected spectroscopic data for **3a** [the product obtained from reaction of compound **1** with (1*R*, 2*S*)-(-)-norephedrine]; δ H (270 MHz; $CDCl_3$) 0.78 (3H, d, *J* = 6.2 Hz), 1.62-2.01 (4H, m), 2.97 (1H, dd, *J* = 3.9 and 13.2 Hz), 3.17-3.79 (5H, m), 5.39 (1H, dd, *J* = 6.2 Hz and 3.5 Hz), 6.69 (1H, d, *J* = 6.2 Hz), 7.01-7.11 (10H, m); δ P (36.10 MHz; $CDCl_3$) 27.19. For **3b** [the product obtained from reaction of compound **1** with (1*S*, 2*R*)-(+)-norephedrine]; δ H (270 MHz; $CDCl_3$) 0.67 (3H, d, *J* = 6.5 Hz),1.66-1.95 (4H, m), 3.01 (1H, dd, *J* = 6.8 and 13.5 Hz), 3.15-3.30 (3H, m), 3.44 (1H, dd, *J* = 4.1 and 12.2 Hz), 3.84-4.08 (2H, m), 5.65 (1H, d, *J* = 6.2 Hz), 6.55 (1H, d, *J* = 8.1 Hz), 6.99-7.14 (10H, m); δ P (36.10 MHz; $CDCl_3$) 25.83. For **3c** [the product obtained from reaction of compound **2** with (1*R*, 2*S*)-(-)-norephedrine]; δ H (270 MHz; $CDCl_3$) 0.75 (3H, d, *J* = 6.5 Hz), 1.83-2.03 (4H, m), 2.95 (1H, dd, *J* = 3.9 and 13.2 Hz), 3.12 (1H, dd, *J* = 5.9 and 12.2 Hz), 3.25-3.39 (2H, m), 5.75 (1H, d, *J* = 6.2 Hz), 6.64 (2H, d, *J* = 6.4 Hz), 7.19-7.39 (10H, m); δ P (36.10 MHz; $CDCl_3$) 25.83. For **3d** [the product obtained from reaction of compound **2** with (1*S*, 2*R*)-(+)-norephedrine]; δ H (270 MHz; $CDCl_3$) 0.79 (3H, d, *J* = 6.5 Hz), 1.83-2.06 (4H, m), 2.98 (1H, dd, *J* = 3.9 and 13.2 Hz), 3.18-3.59 (4H, m), 3.82-3.98 (2H, m), 5.55 (1H, dd, *J* = 6.2 and 3.5 Hz), 6.65 (1H, d, *J* = 6.5 Hz), 7.09-7.38 (10H, m); δ P (36.10 MHz; $CDCl_3$) 27.19. For **6**; δ H (270 MHz; $CDCl_3$) 0.88 (3H, d, *J* = 6.5 Hz), 1.76 (1H, brs), 2.80 (6H, d, *J* = 10.5 Hz), 3.92 (1H, ddq, *J* = 6.5, 1.6 and 21.1 Hz), 5.52 (1H, dd, *J* = 2.7 and 5.9 Hz), 7.24-7.39 (5H, m); δ P (36.10 MHz; $CDCl_3$) 28.25. For mixture of **5** and **7**: δ H (270 MHz; $CDCl_3$) 0.76 (3H, d, *J* = 6.4 Hz for **5**), 1.03 (3H, d, *J* = 6.8 Hz for **7**), 2.02 (1H, brs for **5** and **7**), 2.72 (12H, d ×2, *J* = 10.3 Hz for **7**), 2.84 (6H, d, *J* = 10.3 Hz for **5**), 3.54-3.64 (1H, m for **7**), 4.01 (1H, ddq, *J* = 6.4, 1.6 and 13.5 Hz for **5**), 5.60 (1H, d, *J* = 7.02 Hz for **7**), 5.73 (1H, d, *J* = 6.8 Hz for **5**), 7.23-7.41 (aroma).

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