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ACID CATALYZED METHANOLYSIS OF N-SUBSTITUTED 2-AMINO-1,3,2-DIOXAPHOSPHORINANE-2-OXIDES, AN OBSERVATION OF RETENTION PROCESS

Toru Koizumi*, Yoshiko Kobayashi, and Eiichi Yoshii
Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University, Sugitani, Toyama 930-01, Japan

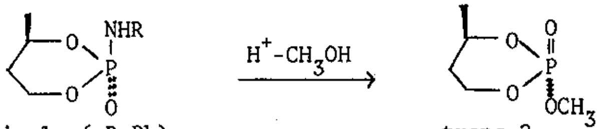
Acid catalyzed methanolysis of cis N-substituted 2-amino-1,3,2-dioxaphosphorinane-2-oxides revealed that H^+ catalyzed reaction proceeded by the complete inversion process while BF_3 catalysis proceeded by the intervention of retention process.

Contrasting to the well investigated solvolysis of phosphinamides[1], the stereochemical course of acid catalyzed P-N bond cleavage of phosphoramidates has been little studied. The inversion of configuration has been assumed[2] tacitly without strong stereochemical evidences. Recently Hall and Inch disclosed an exceptional case against the assumption in which the retention process was observed by the reaction of chiral O,S-dialkyl phosphoramidothioates with various alcohols, and pointed out the assumption is no longer justified.[3]

We here describe our results on the acid catalyzed methanolysis of

N-substituted 2-amino-1,3,2-dioxaphosphorinane-2-oxides which not only support their proposal but indicate that the course of the reaction is affected by the nature of the acid catalyst itself.

When cis N-substituted 2-amino-1,3,2-dioxaphosphorinane-2-oxides, cis 1a(R=Phenyl)[4] and cis 1b(R=CH_2Ph)[5], were treated with 1M H_2SO_4-MeOH for 22-24 hr under reflux, only trans 2-methoxy-1,3,2-dioxaphosphorinane-2-oxide(trans 2)[6] was obtained in a fair yield.



cis 1a (R=Ph)
1b (R=CH_2Ph)
trans 2

Similarly the corresponding trans amides[4,5] afforded cis methyl ester 2 exclusively but in poor yields under stronger reaction conditions. Since no isomerization between cis and trans ester 2 was observed under the reaction condition, the solvolysis of 1a, b must have proceeded through A-2 mechanism with complete inversion of configuration.

On the contrary, BF_3catalyzed methanolysis (2% or 20% BF_3 under reflux) of both cis and trans amides 1a,b did afford a mixture of cis and trans ester 2[7], though the ratios were susceptible to the structure of amides as shown in Table.

Since the control experiments of ester 2 with various cis/trans ratio(Table) indicate that the equilibrium lies far to the trans ester side(trans/cis ca 80)[8], the observed cis ester formation with the cis amides 1a, b should be interpreted as that arising mostly under kinetic control, and therefore indicates the participation of a retention process besides the inversion process.

Table BF_3 Catalyzed Methanolysis of N-Substituted 2-Amino- and 2-Methoxy-1,3,2-dioxaphosphorinane-2-oxides

Substrate		Reaction Conditions		trans/cis ratio
		BF_3 Concentration (%)	Reaction Time (hr of reflux)	of 2
cis amide	1a	2	50	21
	1b	2	25	3.3
trans amide	1a	20	120	0.40
	1b	20	22	0.24
methyl ester 2 (cis)		20	120	0.84
2(trans/cis 5.5)		2	120	11
2(trans/cis 29)		20	120	83
2(trans)		20	120	81

In those cases of the trans amides, it is not certain whether the solvolysis is merged with a retention process, because in this case the interpretation of the experimental results is complicated due to the difficulty in estimating the extent in which the more stable trans ester was formed directly by the solvolysis not by the isomerization of cis isomer.

In order to find out whether the effect of BF_3 to cause the retention process is valid to other phosphoramidates, the BF_3 catalyzed methanolysis of diastereomeric ethyl phenyl phosphoramidate[2a] of L-proline ethyl ester has been carried out. The product methyl ester was proved to be almost 100 % pure inversion product[9], suggesting the effect appears depending on the structure of the substrates, and that the six membered dioxaphosphorinane ring system might be responsible for this mechanistic change[10]. As Hall and Inch pointed out,[3] more experimental data are required to provide an unifying explanation for these changes in the stereochemical course of the reactions. The BF_3 catalyzed alcoholysis of other stereochemically defined phosphoramidates are along this line and are now being investigated in this laboratory.

References and Notes

1 a) T. Koizumi, Y. Kobayashi, and E. Yoshii, *Chem. Comm.*, 1974, 678. b) T. Koizumi, Y. Kobayashi, and E. Yoshii, *Chem. Pharm. Bull.*, **24**, 834(1976). c) T. Koizumi, Y. Kobayashi, and E. Yoshii, *Tetrahedron Lett.*, 1976, 2853. d) M. J. P. Harger, *Chem. Comm.*, 1973, 774.
e) M. J. P. Harger, *J. Chem. Soc., Perkin I*, 1977, 2057.
f) T. Koizumi, *J. Synthetic Organic Chem. Japan*, **34**, 137(1976).

2 a) T. Koizumi, Y. Kobayashi, H. Amitani, and E. Yoshii, *J. Org. Chem.*, **42**, 3459(1977). b) C. R. Hall, T. D. Inch, G. J. Lewis, and R. A. Chittenden, *Chem. Comm.*, 1975, 720. c) D. B. Cooper, C. R. Hall, and T. D. Inch, *Chem. Comm.*, 1975, 721. d) D. B. Cooper, J. M. Harrison, and T. D. Inch, *Tetrahedron Lett.*, 1974, 2697.

3 C. R. Hall and T. D. Inch, *Tetrahedron Lett.*, 1977, 3765.

4 *1a* was prepared by the reaction of anilinophosphorodichloridate with butane-1,3-diol. Cis(mp 170-173°) and trans(mp 158-159°) were separated by silica gel column chromatography and their structure

were assigned by the comparison of the mps with those reported.

W. J. Stec and A Okruszek, *J. Chem. Soc., Perkin I*, 1975, 1828.

5 1b was prepared by the reaction of benzylaminophosphorodichloridate with butane-1,3-diol and the isomers were separated by silica gel column chromatography. Configuration of each isomer(cis ; mp 105-108°, trans ; mp 41-43°) was tentatively assigned by the comparison of their ^{1}H-NMR, and IR spectra with those of 1a and was also confirmed by the above mentioned solvolytic reactivity.

6 Both cis and trans methyl esters were prepared according to the method described by Bodkin and Simpson.

a) C. L. Bodkin and P. Simpson, *J. Chem. Soc.(B)*, 1971, 1136.

b) C. L. Bodkin and P. Simpson, *J. Chem. Soc., Perkin II*, 1973, 676.

7 The mixtures of isomers were analyzed by glc(5% SE 30 on Chromosorb W 1m, Column temp. 130° cis ; R_t 5.2 min **trans** ; R_t 7.6 min).

8 Considering experimental errors due to the glc method, the value is just a rough estimate of equilibrium constant but is sufficient for the above discussion.

9 When diastereomeric amide ($[\alpha]_D$-45°) was treated with 4% BF_3-MeOH under reflux for 2 hr, methyl ethyl phenyl phosphate($[\alpha]_D$ -3.9°) was obtained. Considering the tacit assumption and the above experimental results (100% inversion with H^+ catalyzed methanolysis of 1a,b), operation of complete inversion process(not 100% retention process) is reasonable.

10 Similar observations were reported by Wadsworth in the substitution reactions of 5,5-disubstituted dioxaphosphorinane system.

a) W. S. Wadsworth, Jr., *J. Org. Chem.*, **38**, 2921(1973).

b) W. S. Wadsworth, Jr. and Y-G Tsay, *J. Org. Chem.*, **39**, 984(1974).

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