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NEIGHBORING ARYL GROUP PARTICIPATION IN NITROUS ACID DEAMINATIONS OF L-PHENYLALANINE ETHYL ESTER AND ITS p-NITRO AND p-METHOXY DERIVATIVES

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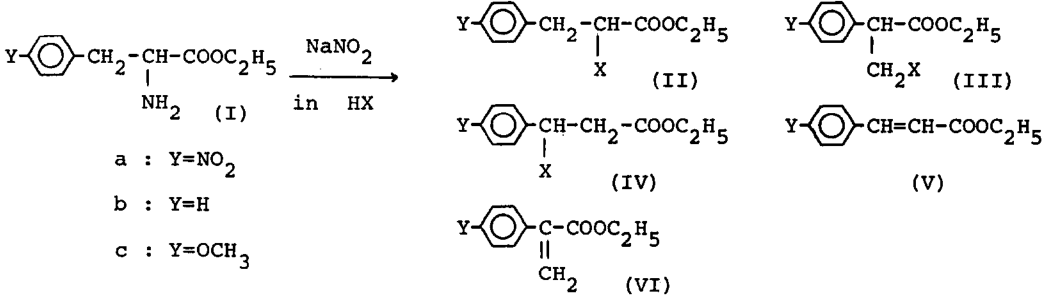
Detailed examinations on the stereochemistry of nitrous acid deamination of L-phenylalanine ethyl ester (Ib) in CH_3COOH have shown that migration (IIIb and IVb, $X=OCOCH_3$) and elimination (Vb) products are obtained along with the corresponding substitution product (IIb, $X=OCOCH_3$).$^{1)}$ Successive investigations on this reaction have revealed that the pattern of the reaction (yields of products and their stereochemical results) is highly dependent both on the solvent employed and on the substituent attached on the aromatic ring, with which the present paper concerns.



a : $Y=NO_2$

b : $Y=H$

c : $Y=OCH_3$

HX : $N\text{-}H_2SO_4$, CH_3COOH, CF_3COOH

The reactions were carried out as follows: To a solution of optically pure L-amino acid ethyl ester (Ia, Ib, or Ic) in $N\text{-}H_2SO_4$, CH_3COOH, or CF_3COOH were added 1.1 molar equivalents of sodium nitrite in portions within ca. 5 hr at room temperature. After standing overnight, a mixture of neutral reaction products was obtained by working up as usual. Determinations of the product ratios were made by vpc or nmr. Optical rotations of the products were determined after deriving them to their corresponding acetoxy esters (II, III, and IV, $X=OCOCH_3$) followed by separation. The results are shown in the Table.

Starting Material Y	Solvent (HX) / Product	$N-H_2SO_4$ (X=OH)		CH_3COOH ($X=OCOCH_3$)		CF_3COOH ($X=OCOCF_3$)	
		Yield (%)	Stereo-chemistry 4)	Yield (%)	Stereo-chemistry 4)	Yield (%)	Stereo-chemistry 4)
NO_2 1) (Ia)	IIa	39	40 Inv	35	10 Inv	25	48 Ret
	IIIa	trace		8		9	
	IVa	16	∿0	19	8 S	27	∿0
	Va	32		30		18	
H 2,3) (Ib)	IIb	24	43 Inv	26	11 Inv	11	66 Ret
	IIIb	26	72 Inv	24	35 Inv	50	87 Inv
	IVb	33	22 S	35	70 S	28	6 R
	Vb	18		14-16		3	
OCH_3 2) (Ic)	IIc	15	37 Inv	21	8 Inv	8	80 Ret
	IIIc	54	76 Inv	31	61 Inv	52	88 Inv
	IVc	25	5 S	21	23 S		
	Vc	5		21			
	VIc			5		39	

1) Yields of products were determined by nmr. 2) Yields of products were determined by vpc. 3) Data of the reaction in CH_3COOH are taked from ref. 1. 4) Values represent optical purity in net. Inv=Inversion. Ret=Retention. R and S represent absolute configuration.

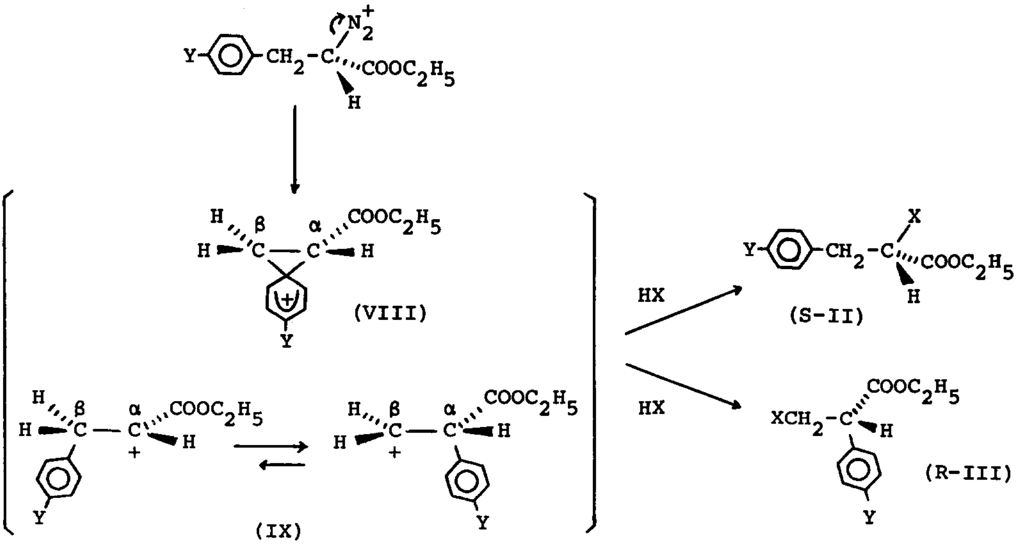
It has become apparent that the pattern of the reaction differs considerably as follows:

(1) The pattern of the reaction changes with the change of the solvent employed. Particularly interesting is the reactions in CF_3COOH. Thus, the stereochemical courses of the substitution products (IIa, IIb, and IIc) are relatively high net retention in CF_3COOH, in contrast to net inversion in $N-H_2SO_4$ and CH_3COOH. This phenomenon is at variance with the general recognition 2) that substitution reactions in the deaminations of α-amino acid esters proceed with net inversion. On the other hand, both the yields and the degree of inversion of aryl migration products (IIIb and IIIc) in CF_3COOH are shown to be higher than those in the other solvents ($N-H_2SO_4$ and CH_3COOH).

(2) The pattern of the reaction changes with the change of the substituent attached on the aromatic ring. Introduction of the electron-donating substituent is found to raise both the yields and the degree of inversion of aryl migration products. Thus, among the three α-amino acid esters (Ia, Ib, and Ic) examined, p-methoxy-L-phenylalanine ethyl ester (Ic) is found to give aryl migration products (IIIc) in the highest yields. Moreover, the degree of inversion of aryl migration products (IIIc) is found to be high in all solvents.

The mechanism of the deamination of L-phenylalanine ethyl ester (Ib) in CH_3COOH has already been discussed.[1)] In the case of the present investigation, therefore, the effects of two factors, i.e., solvent and p-substituent, must be considered. As to the solvent, CF_3COOH has become recognized as a unique solvent for its very low nucleophilicity and relatively high ionizing power.[3)] On the other hand, the substituent at p-position of the aromatic ring is far remote from the reaction site, and is considered to show little effect sterically, but to show considerable effect electronically in changing the nucleophilic character of the aryl group.

Therefore, the two points mentioned above are considered to be rationalized by evaluating the changes in the nucleophilicities of both the solvent and the aryl group that are nucleophiles in the present deamination reactions.



Thus, the generation of cation in a solvent of very low nucleophilicity is expected to cause the attack of neighboring aryl group to the cationic center from the backside of the leaving group to produce an unsymmetrical phenonium ion (VIII) or its stereochemically equivalent equilibrating pair of cations (IX). The reaction of solvent (HX) at α-position of VIII or IX is expected to give the substitution product (S-II) with retention of configuration, while the reaction at β-position is expected to give the aryl migration product (R-III) with inversion of configuration. This mechanism seems to be operative predominantly in the present deaminations in CF_3COOH. Increase in the nucleophilicity of the aryl group is also considered to enhance the aryl group participation.

The results of the present study4) clearly demonstrate that aryl groups exhibit so strong neighboring group participation in the deaminations in CF_3COOH as to overcome the control of conformational populations of the ground state,5) especially in the reaction of p-methoxy-L-phenylalanine ethyl ester (Ic).

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