Tetrahedron. Vol. 30, pp. 2077 to 2086. Pergamon Press 1974. Printed in Great Britain

THE ROLES OF HETERO ATOMS IN SOLVOLYTIC REACTIONS—I

PREFERENTIAL EFFECT BY NITROGEN TO FACILITATE CARBONYL-OXYGEN CLEAVAGE OF ESTERS

S. IKEGAMI,* K. UOJI and S. AKABOSHI
Division of Pharmaceutical Chemistry, National Institute of Radiological Sciences, Anagawa, Chibashi, Japan

(*Received in Japan* 6 *July* 1973; *Received in the UK for publication* 20 *February* 1974)

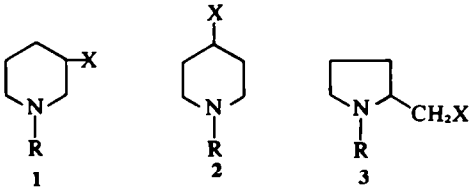
Abstract—3- and 4-Piperidinyl and 2-pyrrolidinylmethyl halides and *p*-nitrobenzoates were prepared. In the solvolysis, the remarkable difference in the effect of nitrogen on the two kinds of the leaving groups was observed. Halides underwent the solvolysis of S_N1 mechanism, whereas *p*-nitrobenzoates resulted in the preferential O–CO cleavage. The results of IR absorption of ester-carbonyl group and kinetic deuterium isotope effect suggested that in the solvolysis of the esters, an initial solvation may be important for the cleavage of a O–CO bond.

INTRODUCTION

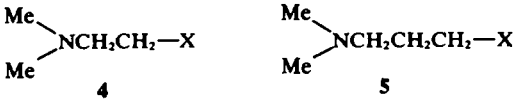
Past studies on the intramolecular catalysis of nitrogen to accelerate ester hydrolysis, particularly in biochemical and enzymological reactions, have led to an understanding of important roles of the N atom.[1] In addition to this catalysis, the N atom has the property of strong nucleophilicity to an electron deficient centre such as carbonium ion which is expected to result from solvolytic displacement reactions.[2] Nucleophilic reactions usually proceed through ammonium ions as intermediates and their rates depend on the stability of the ring size of intermediary ions.[3]

Although individual data on the participation by nitrogen in ester hydrolysis[1,4] and solvolytic displacement reactions[2] are available, information concerning the relationship between the two effects has not been well-established. Other interesting questions in this area concern an accurate comparison with the participation by other hetero atoms (S, O)[5,6] which offer different nucleophilicities.

Concerning transannular participation by hetero atoms, it is of interest to know whether nucleophilic participation exists in medium-sized heterocycles,[7] although the information of hetero atom-carbonyl interaction has become recently available.[8-11] The present study was designed to examine the nature of N-participation in a series of 5- and 6-membered heterocyclic systems (**1–3**) and similar chain systems (**4, 5**), in which two different derivatives, halides and *p*-nitrobenzoates, were prepared.

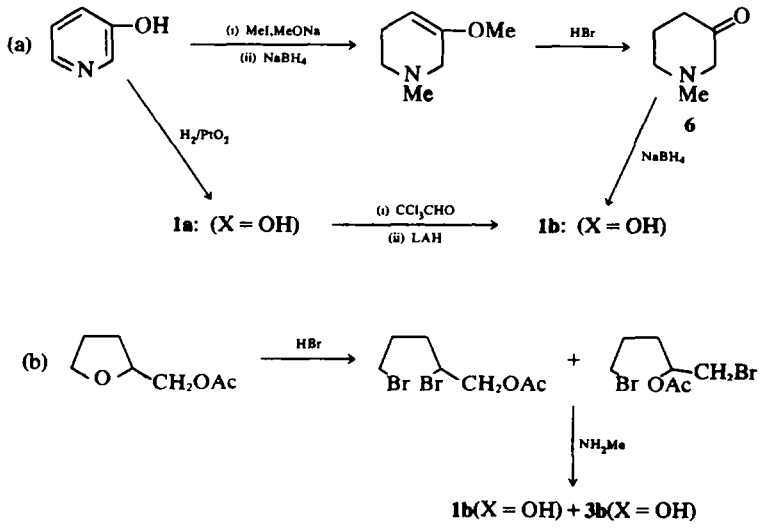


a: R = H
b: R = Me
X = Cl, Br, OPNB



RESULTS AND DISCUSSION

Synthesis of amino alcohols and their related compounds. 3-Piperidinol derivatives (**1a, 1b**) were synthesized from 3-pyridinol, which was prepared by Hofmann reaction of isonicotinamide followed by diazotization-decomposition of 3-aminopyridine (Scheme 1a).[12] As is shown in Scheme 1a, amino ketone (**6**) was prepared according to Lyles' procedure[13] and reduced with sodium borohydride to give the corresponding amino alcohol (**1b**) in a moderate yield. Alternatively, **1b** was prepared through Blicke's methylation[14] of 3-piperidinol (**1a**) provided by catalytic reduction of 3-pyridinol under low pressure.[15] Prolinol (**3a**) was synthesized from proline ester[16] or pyroglutamine ester[14] by sodium borohydride or LAH reduction. A more convenient synthesis of the amino alcohols (**1b, 3b**) was to prepare a mixture by the same route and then, to separate the individual compounds by fractional distillation using a Spinning Band Column (Scheme 1b). Tetrahydrofurfural acetate was treated with

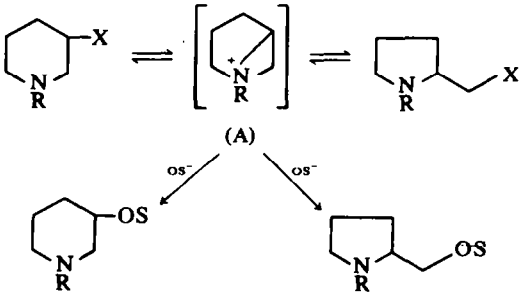


SCHEME 1.

hydrogen bromide to yield the two isomers of dibromo acetate in good yield, and cyclisation with methylamine gave a mixture of the amino alcohols in a ratio of 6 (**3b**):4 (**1b**).[17] These amino alcohols were separated by distillation under reduced pressure.

The amino alcohols (**1a**, **1b**, **2a**, **2b**, **3a**, **3b**) were halogenated under appropriate conditions to afford the corresponding chloro or bromo derivatives and all of the tertiary amino alcohols were converted to *p*-nitrobenzoates in THF solution.

Solvolysis rates. Nucleophilic participation by the amino group increases the rate considerably and usually forms reactive ammonium ion intermediates in the tertiary amine systems. The reactions of 2-haloethylamines in aqueous media have initially been investigated by Cohen[18] and Bartlett.[19] Similarly, in the cyclic system, many workers have since reported skeletal rearrangements by the displacement reactions of the 1-alkyl-3-chloropiperidine system (Scheme 2).[20-24] More recently, Hammer *et al.*[7] have obtained precise evidence for the existence of the bicyclic intermediate (A) from a detailed study in the case where R = Et.



SCHEME 2.

In the present study, the rate of solvolysis for the amino halides (chloride and bromide) was measured in methanol containing an equimolar amount of sodium methoxide and determined titrimetrically by silver nitrate solution using potassium chromate as an indicator. As is shown in Table 1, β-amino halides underwent the solvolysis with strong β-N-participation which is consistent with the reported mechanism;[2] that is, $8{\cdot}3 \times 10^4$ for **1a**, $3{\cdot}5 \times 10^4$ for **1b**, $5{\cdot}8 \times 10^7$ for **3a**, and $2{\cdot}4 \times 10^7$ for **3b** in rates relative to cyclohexyl chloride. Hammer[7a] observed a similar relative rate, $5{\cdot}5 \times 10^3$ (in 80% aq. ethanol at 80·5°) for the compound 1 (R = Et, X = Cl) and pointed out that this enhanced rate is due to the participation by nitrogen in the rate determining step.

It is interesting that **3b** (X = OPNB) was solvolysed about 1000 times faster than **1d** (X = OPNB). This may be explained in terms of the stereochemical difference of the structures. A similar phenomenon was observed for S-participation, but the ratio is much smaller.[5]

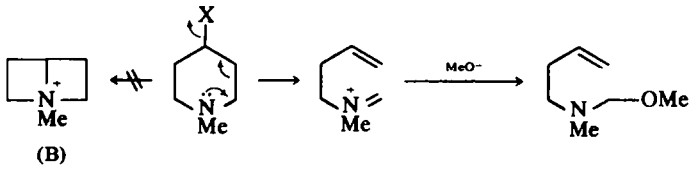
Rate acceleration of **2a** and **2b**, by factors of 490 and 214 respectively, would result from the fragmentation reaction[25] (Scheme 3), rather than N-participation of γ-type (B). This is characteristic of γ-aminoalkyl derivatives, whereas O- and S-containing compounds in a similar system undergo the solvolysis as slowly as cyclohexyl derivative where the reactions do not involve fragmentation.[5,6]

In the solvolysis of *p*-nitrobenzoates different results were observed, as there is an enormous difference in the physical parameters which are unexpectedly low values for the usual displacement reaction. The *p*-nitrobenzoyloxy group is a good leaving group for alcohols which correspond to stabilized carbocation and can be replaced in displacement reactions. Therefore, in the systems involving

Table 1. Rates of solvolysis of the amino halides in methanol[a]

Compd	First-order rate constant, $k \times 10^6$ sec-1 100°	75°	50°	25°	0°	ΔH‡ kcal/mole	ΔS‡ e.u.	Rel. rate at 50°
Cyclohexyl[b]			$4{\cdot}06 \times 10^{-4}$[c]					1·00
2-Aminoethyl[b]		259	16·9			23·7	−7·0	$4{\cdot}2 \times 10^4$
2-(Methylamino)ethyl[b]			112	9·89		17·9	−21	$2{\cdot}8 \times 10^5$
4 (X = Cl)			322	13·7		23·5	−1·8	$7{\cdot}9 \times 10^5$
1a (X = Br)			1,550[e]	107	4·55	19·9	−10	
			33·7[d]					$8{\cdot}3 \times 10^4$
2a (X = Br)		148	9·15			24·2	−6·9	
			0·199[d]					490
3a (X = Cl)			23,700[f]					$5{\cdot}8 \times 10^7$
1b (X = Cl)		276	14·1			25·9	−0·7	$3{\cdot}5 \times 10^4$
1b (X = Br)			648	31·5		22·5	−3·6	
2b (X = Cl)	28·6	1·94	0·0867[e]			27·1	−7·2	214
3b (X = Cl)			9,860[e]	619	23·4	20·6	−4·0	$2{\cdot}4 \times 10^7$

[a]Computer calculated rates using a least-squares program. [b]Chloride. [c]Rate calculated from the rate of the tosylate ($k = 4{\cdot}78 \times 10^{-6}$ sec-1 at 50°; W. Hückel and H. D. Sauerland, *Ann. Chem.* **592**, 190 (1955)) using a factor of $k_{R\text{-}Cl}/k_{R\text{-}OTs} = 8{\cdot}5 \times 10^{-5}$ (ethanolysis; H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.* **86**, 5008 (1964)). [d]Calculated rate for the chloride by use of $k_{Br}/k_{Cl} = 46$, which was observed for the 1-methyl-3-piperidinyl derivatives. [e]Rate extrapolated from the rates obtained at other temperatures. [f]Rate calculated using $k_{NH}/k_{NMe} = 2{\cdot}4$ observed for the 3-piperidinyl derivatives and k_{Br}/k_{Cl} described above.



(B)

SCHEME 3.

strong β-N-participation for displacement reactions, it is possible to leave the *p*-nitrobenzoyloxy anion similar to the process in halide and/or arenesulfonate. However, the solvolysis of β- and γ-amino alcohol *p*-nitrobenzoates resulted in the preferential cleavage of oxygen–carbonyl bond. The rates relative to cyclohexyl *p*-nitrobenzoate (rate calculated for S_N1 process) were $8{\cdot}9 \times 10^7$ for **1b** (X = OPNB), $1{\cdot}6 \times 10^{10}$ for **3b** (X = OPNB) and even compounds **2b** and **5** (X = OPNB) which could be expected to proceed through a fragmentation reaction were solvolysed 10^7–10^9 orders of magnitude faster than the cyclohexyl derivative (Table 2). The rate enhancement of **2b** and **5** being similar to those of **1b** (X = OPNB) and **3b** (X = OPNB) shows that the reaction does not proceed through a

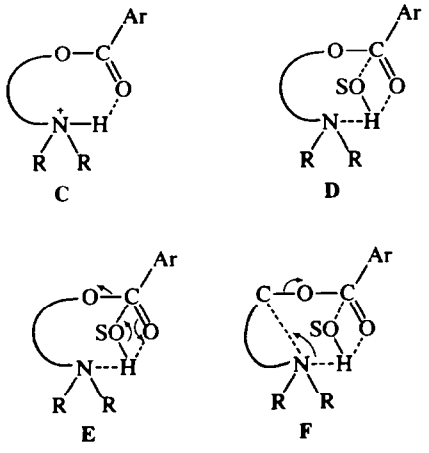
Table 2. Rates of solvolysis of N-containing alkyl and cycloalkyl *p*-nitrobenzoates in 80% aqueous acetone[a]

p-Nitrobenzoate	First-order rate constant, $k \times 10^6$ sec-1 150°	125°	100°	75°	50°	ΔH‡ kcal/mole	ΔS‡ e.u.	Re. rate at 50°
Cyclohexyl					$2{\cdot}8 \times 10^{-9}$[b]			1·00
1b (X = OPNB)		44·7	10·0		0·253[c]	16·9	−37	$8{\cdot}9 \times 10^7$
2b (X = OPNB)	3·63	1·37			0·0302[c]	12·2	−55	$1{\cdot}1 \times 10^7$
3b (X = OPNB)				228	45·0	13·8	−36	$1{\cdot}6 \times 10^{10}$
4 (X = OPNB)			463	123	26·4[c]	13·0	−39	$9{\cdot}3 \times 10^9$
5 (X = OPNB)			117	30·4	6·40[c]	13·2	−41	$2{\cdot}3 \times 10^9$

[a]All rates were calculated with a computer using a least-squares program. [b]Rate of the *p*-nitrobenzoate calculated using a factor of $k_{Ts}/k_{PNB} = 6{\cdot}6 \times 10^8$, which was determined by intervening the rate of the chloride in a cyclohexyl system ($k_{Cl}/k_{Ts} = 8{\cdot}5 \times 10^{-5}$ (ethanolysis); H. C. Brown and M.-H. Rei, *J. Am. Chem. Soc.* **86**, 5008 (1964). $k_{Cl} = k_{PNB} = 5{\cdot}6 \times 10^4$ for the 1-methylcyclohexyl derivatives (hydrolysis in 80% aqueous acetone)). [c]Rate extrapolated from the rate data at higher temperatures.

S_N1 mechanism but is an attack of a solvent anion on the carbonyl carbon. The products of solvolysis support the cleavage of oxygen–carbonyl bond which is consistent with rate data.

Studies concerning intramolecular catalysis of nitrogen to facilitate ester hydrolysis[26] have been done using an acetate ester in which the system is unable to promote the formation of a carbonium ion.[1] Thus, the rate of solvolysis of amino alcohol acetate is influenced by hydrolysis proceeding through the cleavage of the oxygen–acyl bond. The acidic hydrolysis of amino alcohol acetate results in an increase of the rate by a factor of about 1000,[27a] and this rate acceleration may be explained by the formula (C) of which the carbonyl carbon increases the positive charge and this is more easily attacked by a solvent anion in S_N2 reaction. As an explanation of this rate enhancement several authors[27b-d] have proposed these same arguments. Likewise, the solvolysis in a neutral medium, depending upon the pk_a value of the substrate, may be brought about by an intramolecular H-bond resulting from a proton of the solvent in dissociation. If the reaction is catalysed by a proton, although observed rate would be slower, a plot of the pseudo-first-order expression should not be linear but a curve, because of the change of the ionic strength by an acid generated as the reaction proceeded. Hence, the fact that the reaction proceeded as a linear of pseudo-first-order plot up to 80%, indicates that the hydrolysis is not catalysed by the acid generated and suggests that initially a hard solvation (**D**) is formed, which promotes the oxygen–acyl fission (**E**) but not the displacement-type reaction (**F**).[28]



The intramolecular catalysis of the neighbouring amino group for facilitation of ester hydrolysis classified by Bruice[1a] is defined as follows: (1) intramolecular nucleophilic catalysis; (2) intramolecular general-base catalysis; (3) intramolecular general-acid specific-base catalysis. The mechanism 1 can be excluded for the present subject because it does not involve the transfer of a proton in the transition state, so that a deuterium kinetic solvent isotope effect should not be observed. The mechanisms 2 and 3 may account for the preferential cleavage of O–CO bond. Since the mechanism 3 involves the reaction of charged ions, it should be sensitive to the ionic strength of the solvent, so that it may be important in acidic hysrolysis. In a neutral hydrolysis, the mechanism 2 would be rather favorable and profitable to fast rate of hydrolysis. However, considering the selective fission of a O–CO bond in the present systems in which competitive cleavages are possible, a process to go to the transition state seems to be more important.

Direct nucleophilic participation by nitrogen in displacement reactions requires that the nonbonded electrons of the N atom are bare or a state corresponding to it. The preferential cleavage of the oxygen–acyl bond may reveal that the unshared electrons are not free to nucleophilic participation. Therefore, it is considered that in nearly neutral hydrolysis, the driving force of the preferential cleavage must be a solvation. Such solvation makes nucleophilic participation (**F**) more difficult and permits an easier attack on a carbonyl carbon with a solvent in a process going to the transition state (**E** or mechanism 2). The IR carbonyl frequencies suggest the importance of such an initial solvation. The relationship of nitrogen effects between the stability of carbonium ion at a reaction centre and the probability of oxygen–acyl bond cleavage is the subject in the next paper.[29]

Solvent isotope effect. Solvent isotope effects should be a particularly valuable source of information of a reaction mechanism, in attempting to learn more about the role of a solvent in solvolysis.[30]

p-Nitrobenzoates of the amino alcohols (**1b**, **2b**, **3b**, **4**) were solvolysed in 80% D_2O-acetone and their rates are summarized in Table 3, together with the data in 80% H_2O-acetone. It was observed that solvent deuterium effect was more pronounced in the esters solvolysed rapidly than in the esters more slowly solvolysed.

The solvent isotope effects reported for the hydrolysis of alkyl halides are $k_H/k_D = 1{\cdot}2$–$1{\cdot}3$ and for alkyl benzenesulfonates $1{\cdot}08$–$1{\cdot}11$.[31] As an interesting observation for the hydrolysis of t-butyl chloride, the isotope effect decreases from 1·35 in H_2O vs D_2O to 1·05 in 60% dioxane–40% H_2O vs D_2O.[32] Considering these results, it may be said that kinetic solvent isotope effects we observed are relatively large values.

Solvent isotope effects (k_{H_2O}/k_{D_2O}) are temperature-dependent, but their magnitudes vary with substrates in solvolysis. The effect we observed in the solvolysis of the *p*-nitrobenzoates decreases with increasing temperature. However, it also is in constant variation with the logarithms of rate ratios (Fig 1). Such variation of kinetic

Table 3. Summary of solvolysis rates of N-containing alkyl and cycloalkyl *p*-nitrobenzoates in 80% H_2O- and D_2O-acetone[a]

p-Nitrobenzoate	Temp., °C	$k_D \times 10^6$[b]	$k_H \times 10^6$[c]	k_H/k_D	k_H rel. at 50°[d]
3b (X = OPNB)	75	144	228	1·58	1,490
4 (X = OPNB)	100	305	463	1·52	870
1b (X = OPNB)	125	37·1	44·7	1·21	8·4
2b (X = OPNB)	150	3·60	3·63	1·01	1·0

[a] All rates were calculated with a computer. [b] Rate in 80% D_2O-acetone. [c] Rate in 80% H_2O-acetone. [d] Relative rates in 80% H_2O-acetone at 50°.

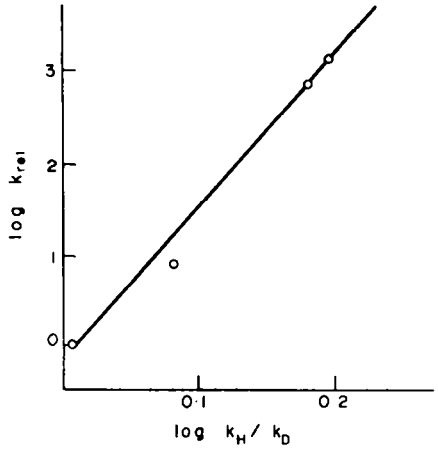


Fig 1. Plot of log k_{rel} vs log k_H/k_D in hydrolysis of the *p*-nitrobenzoates (**1b**, **2b**, **3b**, **4** (X = OPNB)) in 80% H_2O–acetone and D_2O–acetone.

deuterium solvent effect would be a first example and indicates the intervention of a solvent in the transition state. Consequently, it may be concluded that this type of solvent effect is very much influenced by temperature, so that the initial state solvation (D) would be important for oxygen–acyl cleavage to amino esters.

Infrared carbonyl frequency. Carbonyl absorptions are sensitive to both chemical and physical effects. Many factors are involved in determining the precise frequency of a given carbonyl group R_2CO.[33] Field effects which alter the force constant are chemical and should be considered before assessing the nitrogen effect.

Carbonyl stretching bands of the *p*-nitrobenzoates were observed both in carbon tetrachloride and in the presence of 5 equimolar amounts of methanol. The procedure is described in the Experimental. If a protic solvent interacts with amino unshared electrons and ester carbonyl, the addition of methanol should affect the carbonyl frequency. As is shown in Table 4, carbonyl stretching bands of the *p*-nitrobenzoates measured in methanol–carbon tetrachloride revealed at lower wave number by 1 cm-1 than the absorptions in carbon tetrachloride. On the other hand, carbonyl bands of methyl and cyclohexyl *p*-nitrobenzoates appeared at the same wave number in both solvent systems. S- and O-containing compounds, skeletally similar to **1**, have the absorptions in slightly different deviation. Apparently, methanol has a greater effect on carbonyl stretching frequency in amino esters and this effect would result from the solvation which methanol produces between the amino and ester carbonyl groups (**D**).

The states for the mechanism 2 and 3 are of the near transition state, high energy level, whereas the observation of CO frequency represents the state

Table 4. Infrared carbonyl frequencies of *p*-nitrobenzoates[a]

p-Nitrobenzoate	$\nu_{C=O}$ (cm-1) in CCl_4	$\nu_{C=O}$ (cm-1) in MeOH–CCl_4	$\Delta\nu_{C=O}$ (cm-1)[b]
6[c]	1732·9	1732·9	0·0
4 (X = OPNB)	1730·4	1729·7	0·7
3b (X = OPNB)	1730·1	1729·1	1·0
8[d]	1729·9	1729·7	0·2
9[e]	1727·9	1727·7	0·2
1b (X = OPNB)	1726·9	1725·9	1·0
2b (X = OPNB)	1724·9	1723·9	1·0
7[f]	1723·0	1723·0	0·0

[a] See the Experimental for the measurement. [b] $\Delta\nu_{C=O} = \nu_{C=O}$ in CCl_4–$\nu_{C=O}$ in MeOH–CCl_4. [c] Methyl *p*-nitrobenzoate. [d] Tetrahydro-3-pyranyl *p*-nitrobenzoate. [e] Tetrahydro-3-thiopyranyl *p*-nitrobenzoate. [f] Cyclohexyl *p*-nitrobenzoate.

Table 5. Product distribution of solvolysis in methanol[a]

Compd	1b (X = OMe)	1b (X = OH)	3b (X = OMe)	3b (X = OH)	2b (X = OH)	10[b]	11[c]
1b (X = Cl)	32·5		61·5			6·0	
2b (X = Cl)						13	87
3b (X = Cl)	30·5		69·6				
1b (X = OPNB)[d]		100					
2b (X = OPNB)[d]					100		
3b (X = OPNB)[d]				100			

[a] Solvolysis was carried out in MeOH containing an equimolar amount of MeONa for the chlorides and in MeOH for the *p*-nitrobenzoates. [b] 1-Methyl-1,2,5,6-tetrahydropyridine. [c] N-Methyl-N-methoxymethyl-3-butenylamine. [d] Methyl *p*-nitrobenzoate was obtained quantitatively.

of the change for CO band at near ground state or fairly stable interconversion in the interaction with a solvent. Consequently, the initial solvation would supply a favorable pass on going to the more stable transition state such as **E** or mechanism 2.

Products on solvolysis. Solvolysis for product study was carried out by the same procedure as adopted for the measurement of rates. A number of products was determined by GLPC analysis and structures were characterized spectroscopically by PMR and mass spectra after trapping on GLPC. Results for N-methyl derivatives **1b–3b** (X = Cl, OPNB) are summarized in Table 5. All amino halides and *p*-nitrobenzoates gave quantitatively products on gas chromatographical analysis and all products were obtained clearly as completely separable peaks. Equivocal results concerning products for the amino halides (**1a**, **3a**) could be obtained, but only one product, 1-azabicyclo[3.1.0]hexane, was characterized by PMR and mass spectra after trapping on GLPC, which was given in 30% and 70% yields from **1a** and **3a** respectively.

Since the amino chlorides (**1b**, **3b**) gave the same products in similar ratios, the main process in solvolysis is the formation of fairly stable bicyclic aziridinium intermediates (**A**), then the nucleophilic attack of a solvent anion (Scheme 2). Solvolysis of **3b** proceeds through a more stable transition state by 0·5 kcal/mole in free energy of activation than that of **1b**. Probably, steric factors cause this difference in the energy.

Products in solvolysis of amino alcohol *p*-nitrobenzoates in MeOH were skeletally unchanged alcohols produced from oxygen–acyl fission and the fragment of the leaving group was quantitatively obtained as methyl *p*-nitrobenzoate. This fact shows that the solvolysis must proceed entirely by oxygen–carbonyl cleavage caused by an attack of a solvent on the carbonyl carbon.

CONCLUSION

It is clear that compounds having halogen at the β-position from nitrogen are generally reactive in displacement reactions. Even medium-sized N-containing heterocycles, solvolysis proceeds at a fast rate, through the formation of relatively stable bicyclic aziridinium intermediate with strong transannular nitrogen participation. Though the system investigated here for the halides provides the neighbouring nitrogen participation for reactions easy proceeding in S_N1 mechanism, intramolecular catalysis by nitrogen in ester solvolysis becomes energetically more favored, where the initial solvation is an important role, and gives rise to preferential cleavage between oxygen and carbonyl bond by overwhelming CO carbon attack by the solvent.

EXPERIMENTAL

All m.ps were taken by a capillary tube and are corrected. B.ps are uncorrected. PMR spectra were taken in $CDCl_3$ by a Varian 100 Mc (HA-100) spectrometer and chemical shifts are represented in ppm from TMS as an internal standard. Mass spectra were measured by a reservoir method on a Hitachi RMS-4 mass spectrometer employed with 70 eV of the chamber voltage and 70 μA of the target current.

Preparation of amino chloride hydrochlorides

(**a**) To a soln of amino alcohol (50 mmol) or its hydrochloride dissolved or suspended in 50 ml of $CHCl_3$ was added 1·5–3·0 equimolar amounts of $SOCl_2$ under ice-cooling. The mixture was refluxed for 2 h. Then removal of an excess of $SOCl_2$ and the solvent by an aid of a rotary evaporator left a solid, which was recrystallised from isoPrOH or Me_2CO to give fairly pure amino chloride hydrochloride in the following yield: Yield, % (recrystn. solvent); 37% for **1b** (X = Cl), m.p. 185–186° (isoPrOH), Lit[21] reports m.p. 187–188°. 30% for **2b** (X = Cl), m.p. 160–162° (Me_2CO), Lits report b.p. 94–96°/13 mmHg[34] and 49°/10 mmHg[35] for the free base. 55% for **3b** (X = Cl), m.p. 143–146° (Me_2CO), Lits report m.p. 144°,[21] 151–153°,[14] 148–149°,[36] 164–165°.[37]

(**b**) The procedure similar to the method **a** was adopted for the chlorination of ethanol amine and its methyl derivative using benzene or toluene as a solvent instead of $CHCl_3$. There were obtained $H_2NCH_2CH_2Cl$·HCl in 39% yield, m.p. 144–146° (isoPrOH), Lit, m.p. 147–147·5°[38] and $MeNHCH_2CH_2Cl$·HCl in 69% yield, m.p. 107–109° (isoPrOH), Lit, m.p. 108–112°.[39]

Preparation of amino bromide hydrobromides

Bromination was carried out basically according to Bowden's procedure[40] for the preparation of **2a** (X = Br).

A soln of 30 mmoles of amino alcohol dissolved in 20% aq HBr soln was concentrated to dryness under reduced pressure. Owing to complete removal of water, a residue was dissolved in hot EtOH and the solvent was evaporated *in vacuo* to give amino alcohol hydrobromides. After dryness in a vacuum desiccator, PBr_3 (18·5 mmol) was added and the mixture was refluxed for 10 min. After cooling, an excess of PBr_3 was removed under reduced pressure and then a residue was washed with Et_2O several times and recrystallised from isoPrOH to yield amino bromide hydrobromide. Yield and elemental analysis are shown in Table 6.

Preparation of amino alcohol p-*nitrobenzoates*

To a soln of amino alcohol (10 mmol) in 10 ml of THF was added a soln of *p*-nitrobenzoyl chloride (10 mmol) dissolved in 10 ml of THF under ice-cooling with stirring. Although white solid came out within 5 min, the mixture was continually stirred at room temperature overnight. A solid obtained by filtration was recrystallised from iso-PrOH to give pure *p*-nitrobenzoate hydrochloride. Yield and analytical data are summarized in Table 7.

Free bases of *p*-nitrobenzoates, for the purpose of kinetical use, were obtained by extraction with Et_2O from alkalined aqueous soln and used without further purification.

Cyclisation of dibromoamyl acetate with methylamine

To a soln of NH_2CH_3 in EtOH (0·8M in 400 ml), prepared by treatment of 170 g of NH_2CH_3·HCl with alkali (NaOH, 200 g), was added 144 g (0·5M) of dibromoamyl acetate and the mixture was heated under reflux for 15 h. To the cold reaction mixture was added 50 ml of conc HCl and the mixture was concentrated to dryness under reduced pressure. Residual solid was treated with 200 ml of 25% NaOH and refluxed for 1 h. Continuous extraction with Et_2O for 3 days, dryness of the extract and evaporation gave a yellow oil, which was distilled under reduced pressure to yield 22·1 g of a mixture of **1b** (X = OH) and **3b** (X = OH), b.p. 73–81°/15 mmHg. The mixture was separated by redistillation using Teflon Autoannular Spinning Band distillation apparatus (Nester/Faust): **1b** (X = OH), 12·4 g, b.p. 98°/48 mmHg; **3b** (X = OH), 6·8 g, b.p. 92°/48 mmHg. Both alcohols were showed to be more than 99% purity on GLPC analysis.

Rate measurements. Methanol and acetone were purified according to Fieser's procedure.[42] The solvent to be used for the solvolysis of halides, 0·04 N MeONa in MeOH, was prepared by adding commercial 28% MeONa–MeOH soln and a factor was determined by titration with 0·02 N HCl soln. The solvent for the solvolysis of *p*-nitrobenzoates was made up by mixing 80 parts by volume of acetone with 20 parts by volume of water at 20°.

Rate measurements were usually carried out in the method using sealed ampoules except those at 0° and 25°. Samples of halides of *p*-nitrobenzoates were weighed in to 50 ml volumetric flasks in such a weight that solns would be obtained in 0·02 molar concentration, then filled to 50 ml with the solvents. Aliquots (2 ml) were pipetted from the flask at a constant temperature into ampoules. The sealed ampoules were immersed in the constant temperature bath controlled to ± 0·03° and individual ampoules were removed at recorded times and plunged into ice-cold water. After 5–10 mins "zero time" sample was removed, placed in 8 ml of 0° acetone and titrated immediately with A(0·02 N $AgNO_3$ soln using 3 drops of 5% K_2CrO_4 soln as in indicator) for kinetic run of halides or B (0·02 N NaOH soln using 5 drops of 0·1% bromothymol blue in 80% aqueous Me_2CO soln) for hydrolysis of *p*-nitrobenzoates. At appropriate intervals of time, seven to nine additional aliquots were removed and titrated. "Infinity" ampoules were removed after more than 10 times the calculated half-lives and usually two were taken for each run. In the measurement at 0° and 25°, the solvent, about 30 ml, was placed in a long necked 50 ml flask, brought to bath temperature, and 25 ml, pipetted from the fiask, were transferred to another flask containing samples weighed to be obtained in 0·02 molar solns and the solns were mixed rapidly by vigorous agitation. Aliquots, usually eight 2 ml portions of a reaction soln were pipetted directly from the long necked reaction flask at recorded times and placed in 8 ml of 0° acetone and titrated in a manner aforementioned. The rate constants were calculated by the usual first-order expression, $k_1 = 1/t \cdot \ln(a - x_0/a - x)$ using a computer programmed with least squares. Calculation of the physical parameters, enthalpy and entropy of activation, was also done from Eyring's equation of absolute reaction rate theory using a computer (TOSBAC 3400). Rate measurements of hydrolysis in D_2O were carried out in the solvent prepared by mixing 20 parts by volume of 99·8% pure deutero water with 80 parts by volume of purified acetone.

Measurement of C=O *vibration of* p-*nitrobenzoate*

Hitachi-Perkin Elmer Model 225 (Grating) was used as an infrared spectrometer. Measurements were carried out in CCl_4 (extra pure reagent grade) soln of 1×10^{-3} M concentration and in the presence of five times equimolar amounts of MeOH, in both cases using 20 mm thickness of NaCl cell and in 20 times expansion of 1755–1700 cm-1 region to usual measurement. Under this condition the instrument is able to resolute 0·16 cm-1 difference. Wave

Table 6. Results of the preparation of amino bromide hydrobromides

X = Br, HBr salt	Yield, %	m.p., °C	Formula	Analysis — Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1b	49	164·5–165	$C_6H_{13}NBr_2$	27·82	5·06	5·41	28·12	5·25	5·45
2b	68	144–145·5[a]	$C_6H_{13}NBr_2$				27·64	5·09	5·47
3b	74	155–156	$C_6H_{13}NBr_2$				27·87	5·09	5·55
1a	80	131 (dec)	$C_5H_{11}NBr_2$	24·51	4·53	5·72	24·57	4·63	5·68
2a	52	194 (dec)[b]							
3a	64	108 (dec)	$C_5H_{11}NBr_2$				24·45	4·57	5·67

[a] The literature[36] reports m.p. 132°. [b] The literature[35] reports m.p. 192–193° (dec).

Table 7. Results of the preparation of amino alcohol *p*-nitrobenzoate hydrochlorides

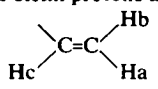
Compd HCl salt	Recrystn solv.	m.p., °C	Yield, %	Formula	Analysis — Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
1b (X = OPNB)	i-PrOH–EtOH	199–199·5	72	$C_{13}H_{16}N_2O_4 \cdot HCl \cdot 1/2H_2O$	50·41	5·86	9·04	50·55	5·67	8·98
2b (X = OPNB)	i-PrOH	211–212[a]	82	$C_{13}H_{16}N_2O_4 \cdot HCl \cdot 1/2H_2O$				50·81	6·00	9·11
3b (X = OPNB)	EtOH	221–222	92	$C_{13}H_{16}N_2O_4 \cdot HCl$	51·92	5·70	9·32	52·00	5·71	9·25
4 (X = OPNB)	EtOH	175·5–176	91	$C_{11}H_{14}N_2O_4 \cdot HCl \cdot 1/2H_2O$	46·57	5·68	9·87	46·74	5·54	9·89
5 (X = OPNB)		146–147[b]	95	$C_{12}H_{16}N_2O_4$	49·92	5·93	9·70	49·56	5·93	9·66

[a] M.p. of the free base, 97–98°. T. Ishii (*J. Pharm. Soc. Japan* (Japanese), 71, 1097 (1951)) reports m.p. 100–101° for the free base. [b] M.p. of the free base, 49°.

numbers of C=O stretching bands were corrected on the basis of the absorption of vapor (1768·17 cm-1). The results are shown in Table 4.

Analysis of solvolysis products

(a) *Methanolysis products of amino halides.* The methanolysis solns sealed in ampoules were allowed to remain in a constant temp bath for at least 10 times half-lives and directly analysed by GLPC using N-methyl-2-pyrrolidinemethanol as an internal standard for quantitative analysis. Yields were quantitative for all cases. All peaks were trapped using a slight big column packed with the same bases as that for analysis, and then PMR and mass spectra were measured for structural characterisation. N-Methyl-1,2,5,6-tetrahydropyridine, which was produced from **1b** (X = Cl) and **2b** (X = Cl), was characterised by spectral comparison (PMR and mass) with an authentic sample. The structural confirmation of the methoxy compounds, **1b** (X = OMe), **3b** (X = OMe) and N-methyl-N-methoxymethyl-3-butenylamine, was obtained spectroscopically: **1b** (X = OMe); PMR: 2·27 s (NCH_3), 3·36 s (OCH_3). Mass, *m/e* (%): 129 (5·3, M^+), 114 (3·0, M^+-CH_3), 99 (8·0, M^+-OCH_2), 58 (37, $C_3H_8N^+$), 44 (100, $C_2H_6N^+$) base peak. **3b** (X = OMe); PMR: 2·41 (NCH_3), 3·36 s (OCH_3). Mass, *m/e* (%): 129 (3·0, M^+), 114 (1·5, M^+-CH_3), 98 (4·5, M^+-OCH_3), 84 (100, M^+-CH_2OCH_3) base peak. N-methyl-N-methoxymethyl-3-butenylamine; PMR: 2·43 s (NCH_3), 3·80 s (OCH_3), 4·60 s (NCH_2O), pattern of typical monosubstituted terminal olefin protons at 5·01 (Ha), 5·05 (Hb), and 5·80 (HC)



J_{ac} = 9 Hz, J_{bc} = 18 Hz. Mass, *m/e* (%): 98 (12, M^+-OCH_3), 44 (100, $C_2H_6N^+$) base peak.

Two or three products from **1a**~**3a** (X = Br) were observed on GLPC, but only major component was trapped and characterised to be 1-azabicyclo[3.1.0]hexane, the mass spectrum of which showed the same pattern as that previously reported by Gassman and Fentiman.[43] The PMR spectrum can be interpreted in consistency with the azabicyclic structure.

(b) *Hydrolysis and methanolysis products of p-nitrobenzoates.* Analysis of methanolysis products were carried out in the same manner as previously described and only alcohols having no change in the skeltons were obtained quantitatively, accompanying by methyl *p*-nitrobenzoate. This fact represents the occurrence of the cleavage of a O–CO bond in methanolysis. In the analysis of hydrolysis products the soln (80% aqueous acetone) in sealed ampoules were allowed to remain in a constant temp bath for ten half-lives, treated with excess K_2CO_3 to remove *p*-nitrobenzoic acid and water, and analysed by GLPC. There was obtained quantitatively alcohols having no skeletal change in all cases.

Gas chromatographical analysis of the products

A standard column of 8–10 feet × 1/8″ glass spiral tubing was employed with a flow rate of 20–30 ml/min of N_2 as a carrier gas in Varian gas chromatograph Model 1440 (single column, FID). The column was packed with 10% by weight of polyethylene glycol 6000 supported on acid-washed 60–80 mesh chromosorb W. Trapping was done using the same instrument employed with a column of 6 feet × 1/4″ packed with the same base. Analysis and trapping of methanolysis products of **1a** and **3a** (X = Br) were carried out using a column of 10 feet × 1/8″ packed with 80–100 mesh chromosorb 103. Conditions and retention times are as follows: at 80°, 8·5 min (**3b** (X = OMe)), 12·5 min (**1b** (X = OMe)), 4·0 min (N-methyl-1,2,5,6-tetrahydropyridine); at 60°, 8·5 min (N-methyl-N-methoxymethyl-3-butenylamine) and at 130°, 37 min (1-azabicyclo[3.1.0]hexane).

Acknowledgement—We wish to express our gratitude to Professor C. F. Hammer, Georgetown University, for the information of his unpublished observations and to Dr. S. Saito, Tokyo Research Laboratory, Tanabe Seiyaku Co., Ltd, for microanalyses. We are grateful to Dr. T. Iwakura for programming the calculations of rates and physical parameters and to members of the computer room of the institute for arranging the computation. We also thank Mr. M. Uoji for spectral measurements.

REFERENCES

[1a] T. C. Bruice and S. J. Benkovic, *Bioorganic Mechanisms* Vol. 1, Chapter 1, W. A. Benjamin Inc., New York, N.Y. (1966); [b] W. P. Jencks, *Catalysis in Chemistry and Enzymology* Chapters 2, 3 and 10. McGraw-Hill Book Co., New York, N.Y. (1969); [c] A. J. Kirby and A. R. Fersht, *Progress in Bioorganic Chemistry* (Edited by E. T. Keisen and F. J. Kezdy) p. 53. Wiley-Interscience, New York, N.Y. (1971)

[2a] A. Streitwieser, Jr., *Solvolytic Displacement Reactions* pp. 16–18, 103–120. McGraw-Hill Co., New York, N.Y. (1962); [b] B. Capon, *Quart. Revs.* **18**, 45 (1964); [c] E. S. Gould, *Mechanism and Structure in Organic Chemistry* Chapter 14. Henry Holt and Co. Inc., New York, N.Y. (1959)

[3] G. Solomon, *Helv. Chim. Acta.* **16**, 1361 (1933)

[4a] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* 2nd Ed., Chapter XV. Cornell University Press, Ithaca, N.Y. (1969); [b] Ref 2c, Chapters 8 and 9

[5] S. Ikegami, T. Asai, K. Tsuneoka, S. Matsumura and S. Akaboshi, *Tetrahedron* **30**, 2087 (1974)

[6] K. Tsuneoka and S. Ikegami, Manuscript in preparation

[7a] C. F. Hammer, S. R. Heller and J. H. Craig, *Tetrahedron* **28**, 239 (1972); [b] C. F. Hammer and S. R. Heller, *Chem. Comm.* 919 (1966)

[8a] N. J. Leonard, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.) **17**, 243 (1956); [b] N. J. Leonard, T. W. Milligan and T. L. Brown, *J. Am. Chem. Soc.* **82**, 4075 (1960)

[9] L. A. Paquette and L. D. Wise, *Ibid.* **89**, 6659 (1967)

[10] A. Padwa and A. Battisti, *Ibid.* **94**, 521 (1972)

[11] L. A. Paquette and R. W. Begland, *Ibid.* **87**, 3784 (1965)

[12] *Synthetic Methods of Organic Compounds* **13**, 11 (Japanese), Ed. by the Commission of the Society of Synthetic Organic Chemistry (1961)

[13] R. E. Lyle, R. E. Adel and G. C. Lyle, *J. Org. Chem.* **24**, 342 (1959)

[14] F. F. Blicke and C.-J. Lu, *J. Am. Chem. Soc.* **77**, 29 (1955)

[15] C.-H. Kao, *J. Chem. Eng. China*, **15**, 80 (1948); *C.A.* **44**, 3993*e* (1949)

[16] P. Karrer, P. Portmann and M. Suter, *Helv. Chim. Acta* **31**, 1617 (1948)

[17] It was found that the cleavage of tetrahydrofurfuryl acetate with HBr gave a mixture of two kinds of dibromo acetate in rough ratio of 1:1. We failed to separate both compounds by distillation even using a Spinning Band Column. *cf* M. Soulal, Brit. Pat., No. 820,503 (1959)

[18] B. Cohen, E. R. van Artsdalen and J. Harris, *J. Am. Chem. Soc.* **70**, 281 (1948); **74**, 1875, 1878 (1952)

[19] P. D. Bartlett, J. W. Davis, S. D. Ross and C. G. Swain, *Ibid.* **69**, 2971, 2977 (1947); **71**, 1415 (1949)

[20] R. C. Fuson and C. L. Zirkle, *Ibid.* **70**, 2726 (1948)

[21]E. G. Brain, F. P. Doyle and M. D. Mehta, *J. Chem. Soc.* 633 (1961)
[22a]H. Biel, L. G. Abood, W. K. Hoya, H. A. Leiser, P. A. Nuhfer and E. F. Kluchesky, *J. Org. Chem.* **26**, 4096 (1961); [b]J. H. Biel, W. K. Hoya and H. A. Leiser, *J. Am. Chem. Soc.* **81**, 2527 (1959)
[23]R. Paul and S. Tcheliticheff, *Bull. Soc. Chim. Fr.* 736 (1958)
[24]R. H. Reitsema, *J. Am. Chem. Soc.* **71**, 2041 (1949)
[25]R. D'Arcy, C. A. Grob, T. Kaffenberger and V. Krasnobajew, *Helv. Chem. Acta*, **49**, 185 (1966)
[26]Kupchan and his co-workers have observed strong nitrogen effect in hydrolysis of Veratrum alkaloid and the related heterocyclic compounds; [a]S. M. Kupchan, S. P. Eriksen and Y.-T. Shen, *J. Am. Chem. Soc.* **85**, 350 (1963); [b]S. M. Kupchan, S. P. Eriksen and M. Friedman, *Ibid.* **88**, 343 (1966); [c]S. M. Kupchan, S. P. Eriksen and Y.-T. S. Liang, *Ibid.* **88**, 347 (1966); [d]S. M. Kupchan, J. H. Block and A. C. Isenberg, *Ibid.* **89**, 1189 (1967)
[27a]A. Ågren, U. Hedsten and B. Jonsson, *Acta Chem. Scand.* **15**, 1532 (1961); [b]E. Schätzle, M. Rottenberg and M. Thürkauf, *Helv. Chim. Acta* **42**, 1708 (1959); [c]B. Hansen, *Acta Chem. Scand.* **12**, 324 (1958); **16**, 1927 (1962); [d]A. Hussian and P. Schurman, *J. Pharm. Sci.* **58**, 687 (1969)
[28]In recent report Bruice and Mautner have emphasized the mechanism of intramolecular general base-catalized solvent attack in weakly basic hydrolysis of N,N-dimethylaminoethyl benzoate and thionebenzoate, (P. Y. Bruice and H. G. Mautner, *J. Am. Chem. Soc.* **95**, 1582 (1973))
[29]An investigation along this implication is now in progress
[30a]E. K. Thornton and E. R. Thornton, *Isotope Effects in Chemical Reactions* (Edited by C. J. Collins and N. S. Bowman) ACS Monograph 167, pp. 213–285, Van Nostrand Reinhold Co., New York, N.Y. (1971); [b]E. R. Thornton, *Ann. Rev. Phys. Chem.* **17**, 349 (1966)
[31]See the literatures cited in 30*a*
[32]W. G. Craig, L. Hakka, P. M. Laughton and R. E. Robertson, *Can. J. Chem.* **41**, 2118 (1963)
[33]*cf* See L. J. Bellamy, *Advances in Infrared Group Frequencies* Chapter 5, Methuen and Co., Ltd, England (1968)
[34]J. Klosa and G. Delmar, *J. Prakt. Chem.* **16**, 71 (1962)
[35]E. Adlerona, V. Seidlona and M. Protina, *Cesk. Farm.* **12**, 122 (1963); *C. A.* **59**, 8702*a* (1963)
[36]E. Testa and G. Maffii, Brit. Pat. No. 929,657 (1963)
[37]E. S. Schipper, W. R. Boehme, M. L. Graeme, E. Siegmund and E. Chinery, *J. Med. Pharm. Chem.* **4**, 79 (1961)
[38]R. H. Hall and G. F. Wright, *J. Am. Chem. Soc.* **73**, 2213 (1951)
[39]W. Marckwald and O. Frobenius, *Chem. Ber.* **34**, 3544 (1901)
[40]K. Bowden and P. N. Green, *J. Chem. Soc.* 1164 (1952)
[41]G. Bondesson and R. Dahlbom, *Acta Chem. Scand.* **20**, 2370 (1966)
[42]L. F. Fieser, *Experiments in Organic Chemistry* 3rd Ed., pp. 281, 289. D. C. Heath and Co., Boston, Mass (1955)
[43]P. G. Gassman and A. Fentiman, *J. Org. Chem.* **32**, 2388 (1967)