

The Roles of Hetero Atoms in Solvolytic Reactions. III.¹⁾ Some Evidence for Preference of Intramolecular Catalysis by Nitrogen in Hydrolysis of Tertiary Alkyl Esters

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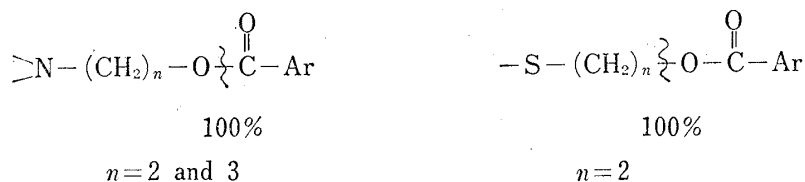
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p-Nitrobenzoates of tertiary alcohols substituted with methyl and phenyl groups on *N*-methyl-3- and 4-piperidinol were prepared from the reactions of the corresponding piperidinones with methyl lithium and phenyllithium followed by esterification.

In methanolysis, the cleavage modes between alkyl-oxygen and oxygen-acyl bonds were determined by proton magnetic resonance studies of products (Chart 3). That all of the tertiary piperidinol esters resulted in the mixed cleavage is specially interesting because tertiary alkyl ester usually undergoes hydrolysis in alkyl-oxygen cleavage.

Rates of solvolysis measured in 80% aqueous acetone (Table I) do not represent appreciable difference on the substituents. These evidence strongly supports the intervention of a solvent to the promotion of the oxygen-acyl cleavage.

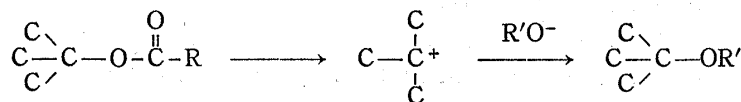
We have demonstrated that in ester hydrolysis, the nitrogen atom is effective to the cleavage of a oxygen-acyl bond,⁵⁾ whereas the sulfur atom promotes S_N1 reactions by strong S-participation to stabilize a carbonium ion.¹⁾ Such intramolecular catalysis by nitrogen, though a nucleophilic ability of nitrogen to an electron deficient center is also observable,^{5,6)} would be caused by an interaction with a solvent.



In addition to this catalysis, it is well known⁷⁾ that the esters of tertiary alcohols and/or alcohols which correspond to stabilized carbonium ion such as benzhydrols,⁸⁾ allyl alcohols⁹⁾

- 1) Paper II in this series: S. Ikegami, T. Asai, K. Tsuneoka, S. Matsumura, and S. Akaboshi, *Tetrahedron*, **30**, 2087 (1974).
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- 4) Location: 4-9-1, Anagawa, Chiba-shi, 280, Japan.
- 5) S. Ikegami, K. Uoji, and S. Akaboshi, *Tetrahedron*, **30**, 2077 (1974).
- 6) For reviews, see a) A. Streitwieser, Jr., "Solvolytic Displacement Reactions," McGraw-Hill Co., New York, N.Y. 1962, pp. 16-18, 103-120; b) B. Capon, *Quart. Revs.*, **18**, 45 (1964); c) E.S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co. Inc., New York, N.Y. 1959, Chapter 14.
- 7) a) C.K. Ingold, "Structure and Mechanism in Organic Chemistry," 2nd ed., Cornell University Press, Ithaca, N.Y. 1969, Chapter XV; b) Ref. 4c, Chapter 8 and 9.
- 8) a) J. Kenyon, S.M. Partridge, and H. Philips, *J. Chem. Soc.*, **1936**, 85; b) W.J. Hills, J. Kenyon, and H. Philips, *ibid.*, **1936**, 576; c) M.P. Balfe, M.A. Doughty, J. Kenyon, and R. Poplett, *ibid.*, **1942**, 605; d) M.P. Balfe, A.A. Evans, J. Kenyon, and N.N. Nandi, *ibid.*, **1946**, 803; e) M.P. Balfe, J. Kenyon, and R. Wicks, *ibid.*, **1946**, 807; f) H.C. Goering, E.G. Briody, and J.F. Levy, *J. Am. Chem. Soc.*, **85**, 3059 (1963); g) H.C. Goering and S. Chang, *Tetra hedron Letters*, **1965**, 3607.
- 9) a) J. Kenyon, S.M. Partridge, and H. Philips, *J. Chem. Soc.*, **1937**, 207; b) M.P. Balfe, W.J. Hills, J. Kenyon, H. Philips, and B.C. Platt, *ibid.*, **1942**, 556.

generally take place the cleavage of an alkyl-oxygen bond. Thus, in order to assess the strength of nitrogen catalysis, it is of special interest to examine the hydrolysis of tertiary alkyl esters.



This report deals with the solvolysis of the cyclic systems (I, II) as related to the previous study.⁵⁾

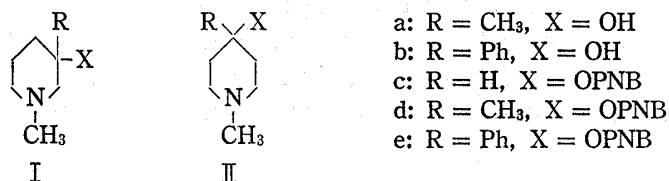


Chart 1

Result and Discussion

Cleavage Modes

Methyl and phenyl tertiary alcohols (Ia, Ib, IIa, IIb) were prepared from 1-methyl-3- and 4-piperidinones by treatment of an excess of freshly prepared methyllithium and phenyllithium. All alcohols were converted to *p*-nitrobenzoates in the usual manner (in tetrahydrofuran (THF)).

The cleavage ratios of these *p*-nitrobenzoates between alkyl-oxygen and oxygen-acyl bonds were determined by proton magnetic resonance (pmr) studies of methanolysis products (Chart 2) and they were substantiated by infinity titers in methanolysis. The results are illustrated in Chart 3 with the data of the secondary cases (Ic, IIc).

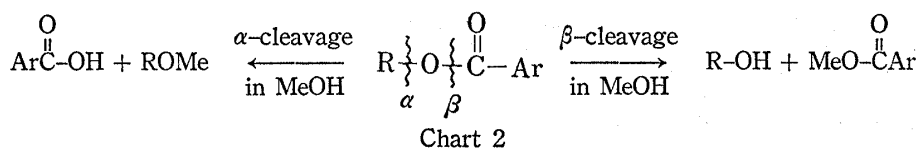


Chart 2

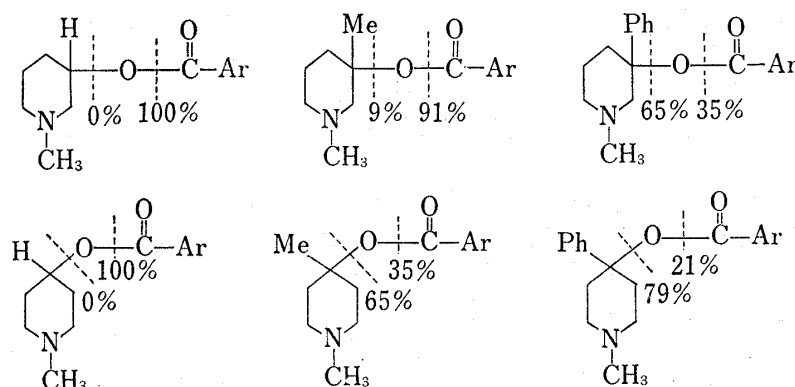


Chart 3

The effects of methyl and phenyl to the secondary esters were apparently observed on the cleavage modes. However, the difference of the effects between the substituents is unexpectedly small. The replacement of the methyl of Id by a phenyl group merely increases 9% of α -cleavage to 65%. Similarly, 65% of α -cleavage observed for IIId increases 79% by replacing the methyl by a phenyl group. As previously pointed out on the secondary case, nitrogen

effect between β - and γ -positions is not appreciably affective to intramolecular catalysis. In the hydrolysis of the tertiary systems, the same argument is also possible.

It is obvious¹⁰⁾ that in solvolysis of a non-resonance-stabilized system, a methyl substituent makes the transition state more stable (5–6 kcal. mole⁻¹) than that of the corresponding secondary system. Similarly, the effect of replacing a methyl by a phenyl substituent at the tertiary position corresponds to 4–5 kcal. mole⁻¹. However, these effects become far smaller in a resonance-stabilized species. Consequently, the effects of methyl and phenyl substituents highly stabilize a transition state on displacement reactions and therefore, generally result in alkyl-oxygen cleavage; 1-methyl- and 1-phenylcyclohexyl esters undergo solvolysis *via* S_N1 process. Furthermore, if a system involves a nitrogen atom at the β -position, its rate of solvolysis would much increase by β -N-participation. Even though the present systems are advantageous to proceed *via* S_N1 process, that oxygen-acyl fission was still observed for the esters (Id, Ie, IID, IIE) must reveal the intramolecular catalysis by nitrogen to promote the β -cleavage.

Rates of Solvolysis

Rates of solvolysis for the *p*-nitrobenzoates (Id, Ie, IID, IIE) were measured in 80% aqueous acetone (Table I). The rate data shown in Table I apparently consist of two components

TABLE I. Rates of Solvolysis of 3- and 4-Substituted 3- and 4-Piperidinyl *p*-Nitrobenzoates in 80% Aqueous Acetone^{a)}

Compound	First-order rate constant $k \times 10^{-6} \text{ sec}^{-1}$				ΔH^\ddagger kcal mole ⁻¹	ΔS^\ddagger e.u.
	125°	100°	75°	50		
Id		37.1	7.99	1.36 ^{b)}	15.2	-39.0
Ie		190.0 ^{c)}	14.0	0.687 ^{b)}	26.3	-5.5
IId	104 ^{d)}	9.19		0.0235 ^{b)}	28.0	-7.1
IIE			71.7 ^{e)}	4.09	25.0	-6.1

a) computer calculated rates using a least-squares program (TOSBAC 3400)

b) rate extrapolated from the rates at higher temperatures

c) $k_1 = 7.12 \times 10^{-4} \text{ sec}^{-1}$ (in MeOH)

d) $k_1 = 1.41 \times 10^{-4} \text{ sec}^{-1}$ (in MeOH)

e) $k_1 = 1.10 \times 10^{-4} \text{ sec}^{-1}$ (in MeOH)

which are mixed rate observed for the different cleavages. Hence, estimating each component would make the modes of nitrogen effects more clear. On the basis of the cleavage ratios as shown in Chart 3, each fraction of the rates, k_α (rate for α -cleavage) and k_β (rate for β -cleavage), was calculated according to a correlation equation, $k_{\text{obs}} = Fk_\alpha + k_\beta$, where F is a molar fraction. These calculated rates are summarized in Table II along with kinetic data for the secondary compounds (Ic, IIc).

The rate ratio, $k_{\text{PB}}/k_{\text{Me}}$, of S_N1 mechanism in the compound II may be an expected value since similar ratios are obtained in cyclohexyl (190),¹¹⁾ tetrahydro-3-pyranyl (250),¹¹⁾ and tetrahydro-4-thiopyranyl (167)¹¹⁾ derivatives. In the case of the system I, it was resulted to be unusually small value when compared with S-containing similar system (37),¹⁾ probably making possible to consider strong nucleophilic participation by nitrogen of the β -position.

On the other hand, the effect by intramolecular catalysis of nitrogen to facilitate β -cleavage appeared with complication. Methyl substituent does not have appreciable influence to their rates. However, the effect of replacing the methyl by a phenyl substituent caused the rate of Id to decrease by a factor of 0.19, whereas that of IId to increase by a factor of 105.

10) a) H.C. Brown, *Chem. in Brit.*, 1966, 199. b) H.C. Brown, "Boranes in Organic Chemistry," Part III, Cornell University Press, Ithaca, N.Y. 1972.

11) K. Tsuneoka and S. Ikegami, Manuscript in preparation.

TABLE II. Rates Calculated to Alkyl-oxygen and Oxygen-carbonyl Cleavages^{a)}

Compound	R	$k_{\text{obs}}^b)$	$k \times 10^{-6} \text{ sec}^{-1}$		Rate ratio			
			$k_{\alpha}^c)$	$k_{\beta}^d)$	k_{α}	k_{β}	k_{α}	k_{β}
Ic	H	0.253 ^{e)}	—	0.253				
Id	Me	1.36	0.12	1.24				
Ie	Ph	0.687	0.447	0.240	3.7	0.19	—	4.9
IIc	H	0.0302 ^{e)}	—	0.0302				
IID	Me	0.0235	0.0153	0.0082			—	0.27
IIE	Ph	4.09	3.23	0.86	210	105		

a) Rates, k_{α} and k_{β} , were calculated on the basis of cleavage ratios (Chart 3) determined by pmr spectra of methanolysis products ($k_{\text{obs}} = Fk_{\alpha} + k_{\beta}$), b) rate at 50° (cf. Table 1), c) rate calculated to alkyl-oxygen fission, d) rate calculated to oxygen-carbonyl fission, e) ref. 5

It would be expected that the amount of nucleophilic participation varies with the stabilities of carbonium ion of the reaction center and of intermediary ion, while in intramolecular catalysis, the intervention of a solvent is so effective to rate, that the effect of a substituent is not only minimized factor, but also variable factor. Recently, Bruice and Mautner¹²⁾ have pointed out that the mechanism in weakly basic hydrolysis of N,N-dimethylaminoethyl benzoate and related compounds is best explained by intramolecular general base-catalyzed solvent attack. On the other hand, we have previously proposed the initial solvation in nearly neutral medium which may be driving force to promote the β -cleavage with an enhanced rate.⁵⁾ The present evidence strongly suggests that the effect of a solvent is an important key to facilitate hydrolysis of ester. Finally it would be emphasized that esters of amino alcohols having C₂ and C₃ units between amino and hydroxy groups involve the cleavage of a oxygen-acyl bond in solvolytic reactions as far as systems do not give extremely stabilized carbonium ion and the cleavage ratio depends upon the stability of an ion at the reaction center.¹³⁾

Experimental¹⁴⁾

1,3-Dimethyl-3-piperidinol (Ia)—Under N₂ atmosphere, to an ethereal solution of MeLi prepared freshly from 12 g (85 mmoles) of MeI and 1.3 g (0.19 atom) of lithium wire (Merck Co.) in 80 ml of anhyd. (C₂H₅)₂O, a solution of 4.4 g (39 mmoles) of N-methyl-3-piperidinone in (C₂H₅)₂O was added dropwise at 0–5°. After the reaction mixture was stirred at room temperature for 20 hr, H₂O (15 ml) was added under cooling and the ethereal layer was separated, dried and evaporated under atmospheric pressure. The resulting oil was distilled *in vacuo* to give 3.5 g (69.5% yield) of colorless oil, bp 64–66°/14 mmHg.

1,4-Dimethyl-4-piperidinol (IIa)—The reaction of N-methyl-4-piperidinone with MeLi was carried out in the similar procedure to the synthesis of Ia. There was obtained colorless oil of bp 80–87°/19 mmHg, which solidified on standing, mp 63–64°, in 24% yield. Lit.¹⁵⁾ reports bp 93–100°/37 mmHg or mp 64.5–69.5° for IIa.

1-Methyl-3-phenyl-3-piperidinol (Ib)—Phenyllithium was prepared from bromobenzene and lithium wire. The procedure was the same as used for the preparation of Ia. Colorless oil of bp 112–114°/4 mmHg was obtained in 82% yield. Lit.¹⁶⁾ reports bp 106–108°/0.4 mmHg for Ib and mp 134–136° for its hydrochloride.

12) P.Y. Bruice and H.G. Mautner, *J. Am. Chem. Soc.*, **95**, 1582 (1973). Also see other references cited herein.

13) A study along this implication will be published.

14) Melting points are corrected. Boiling points are uncorrected. Pmr spectrum was taken by a Varian 100 Mc (HA-100) spectrometer with tetramethylsilane (TMS) as an internal standard.

15) R.D. Arcy, C.A. Grob, T. Kaffenberger, and V. Krasnobajew, *Helv. Chim. Acta*, **49**, 185 (1966).

16) S.M. McElvain and J.F. Voza, *J. Am. Chem. Soc.*, **71**, 896 (1949).

1-Methyl-4-phenyl-4-piperidinol (IIb)—This compound was synthesized from the reaction of N-methyl-4-piperidinone with freshly prepared PhLi on the same procedure as adapted for the synthesis of Ia. There was obtained pale yellow needles of mp 110—113° by recrystallization from acetone in 44.5% yield. Lit.¹⁷⁾ reports bp 123—128°/0.5 mmHg or mp 114—115°.

Procedure for the Preparation of *p*-Nitrobenzoates (Id, Ie, IID, IIe)—To a solution of 10 mmoles of tertiary alcohol dissolved in 6 ml of anhyd. THF, was added a solution of 10 mmoles of *p*-nitrobenzoyl chloride dissolved in THF (6 ml) under ice-cooling. The mixture was continuously stirred for 15—20 hr at room temperature. A solid which came out was assembled by filtration and recrystallized from iso-PrOH for Id and IID or EtOH for Ie and IIe to yield pure ester hydrochloride. The results and elemental analyses are summarized in Table III.

TABLE III. Physical Constants and Elemental Analyses of Tertiary Alcohol *p*-Nitrobenzoates

Compound	Yield (%)	mp (°C)	Formula	Analysis					
				Calcd.			Found		
				C	H	N	C	H	N
Id	44	199.0—199.5 ^{a)}	C ₁₄ H ₁₈ N ₂ O ₂				53.28	6.28	8.63
IID	68	220.0—220.5 ^{b)}	C ₁₄ H ₁₈ N ₂ O ₂	53.42	6.08	8.90	53.36	6.26	8.80
Ie	46	205.0—205.5 ^{c)}	C ₁₉ H ₂₀ N ₂ O ₂				60.31	5.80	7.29
IIe	90	190.5—191.0 ^{d)}	C ₁₉ H ₂₀ N ₂ O ₂	60.56	5.62	7.43	60.23	5.90	7.19

a) mp 71—72° (free base) b) mp 138—140° (free base) c) mp 86—87° (free base) d) mp 140—142° (free base)

Rate Measurements—The procedures for kinetic measurements were similar to those used for the related compounds previously reported.⁵⁾ Rate constants were determined by least-squares linear regression analysis to first-order rate expression using a TOSBAC 3400 computer. Physical parameters, enthalpy and entropy of activation, were calculated on the basis of Eyring's absolute rate equation.

Determination of Cleavage Ratios—A solution for methanolysis sealed in an ampoule was allowed to remain in a constant temperature bath for more than 10 times half-lives. After evaporating the solvent, a residue was dissolved in DMSO-*d*₆ and pmr spectrum was taken. Careful and repeating integrations to aromatic protons (8—9 ppm), which are contained in *p*-nitrobenzoic acid and its methyl ester, and methyl signal (3.93 ppm) of the ester was carried out. Careful comparison of an average of each integration gave the cleavage ratios as illustrated in Chart 3. The other method for determination such as direct comparison of methyl signals yielded an ambiguous result because of accompanying easy evaporation of product. Alternatively, ratios determined through infinity titers for kinetic measurements in MeOH were quite similar to those obtained by pmr measurements.

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17) S.M. McElvain and J.C. Safranski, Jr., *J. Am. Chem. Soc.*, **72**, 3134 (1950).