Alkaline Hydrolyses of Alkyl Nitrites and Related Carboxylic Esters

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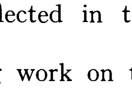
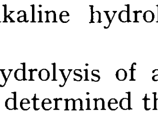
Alkaline hydrolysis of alkyl nitrites and related carboxylic esters was investigated. Marked differences between alkyl nitrites and the corresponding esters in hydrolysis are as follows. (1) Alkaline hydrolysis of alkyl nitrite is much slower than that of the corresponding ester. (2) However, acid hydrolysis of alkyl nitrite is markedly faster than that of the corresponding ester. (3) There is no concurrent oxygen exchange between the nitroso-oxygen of n-hexyl nitrite and hydroxide in alkaline hydrolysis at 45.0 and 55.1 °C. (4) The polar effect of substituents on the leaving alkoxide group in alkaline hydrolysis of alkyl nitrites is roughly two-fold larger than that for the esters, *i.e.* ρ° 1.46 for substituted benzyl nitrites, 0.994 for substituted benzyl benzoates, 0.764 for substituted benzyl acetates ρ^{*} 2.54 for alkyl nitrites, 1.26 for alkyl benzoates, 1.28 for alkyl acetates. (5) The steric requirements for alkaline hydrolysis of alkyl nitrites are less than those for the esters, *i.e.* Taft δ-values 1.03 for alkyl nitrites, 1.52 for alkyl benzoates, 1.50 for alkyl acetates. These differences are rationalized in terms of the two main differences of the electrophilic centres, (1) the greater electronegativity of nitrogen than of carbon, and (2) the presence of a lone pair on nitrogen but not on carbon.

THOUGH there are numerous studies of nucleophilic substitution on sp^2 hybridized carbon, only very few systematic investigations of nucleophilic substitution on sp^2 hybridized trivalent nitrogen are known.[1] Previously we reported one of the first quantitative investigations of nucleophilic substitution on sp^3 hybridized nitrogen in which the steric requirement around sp^3 nitrogen was found to be rather small compared with sp^3 carbon, while the nucleophilicity towards sp^3 nitrogen is nearly identical with that for sp^3 carbon.[2] As an extension of our general survey on substitution reactions on nitrogen we have looked into nucleophilic substitution on sp^2 hybridized trivalent nitrogen in comparison with that on sp^2 hybridized carbon, by examining the alkaline hydrolysis of alkyl nitrite as a model reaction since the hydrolysis of the analogous carboxylic esters has been investigated extensively.[3]

Alkyl nitrite (A) and alkyl formate (B) are isoelectronic. The nitrogen atom in alkyl nitrite retains a pair of unshared electrons, unlike the C–H σ bond in the carboxylic ester. The electronegativity of nitrogen is greater than that of carbon (Pauling electronegativity, 3.0 for nitrogen and 2.5 for carbon). Such differences may be reflected in the alkaline hydrolyses of the substrates.


(A)


(B)

Pioneering work on the hydrolysis of alkyl nitrites was carried out by Allen who determined the kinetics of hydrolyses of n-propyl and t-butyl nitrite and confirmed N–O bond fission for both alkaline and acid hydrolysis.[1b] Later, Kobayashi reported oxygen exchange between isoamyl nitrite and solvent water in

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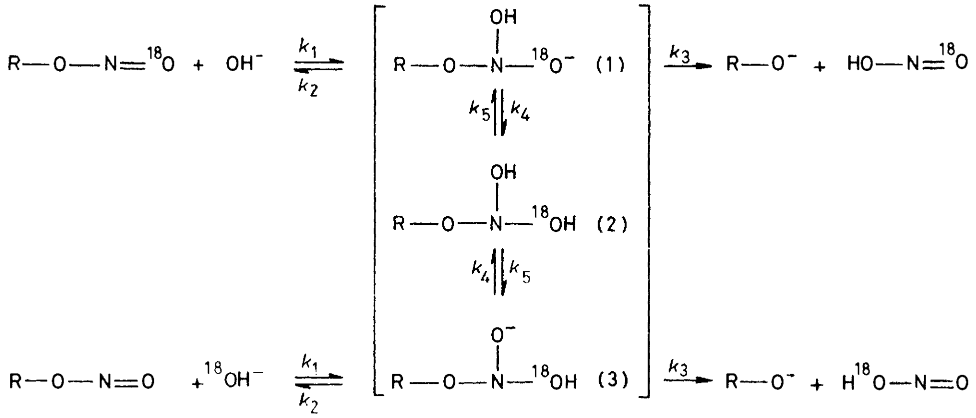
[1] (*a*) C. K. Ingold, 'Structure and Mechanism in Organic Chemistry,' Cornell University Press, Ithaca, 1967, 2nd edn., p. 618; (*b*) A. D. Allen, *J. Chem. Soc.*, 1954, 1968; (*c*) A. D. Allen and G. R. Schonbaum, *Canad. J. Chem.*, 1961, **39**, 940; (*d*) A. D. Allen and G. R. Schonbaum, *ibid.*, 1961, **39**, 947; (*e*) acid catalysed denitrosation has been investigated in detail, B. C. Challis and M. R. Osborne, *J.C.S. Chem. Comm.*, 1972, 518; C. N. Berry and B. C. Challis, *ibid.*, p. 627; B. C. Challis and M. R. Osborne, *J.C.S. Perkin II*, 1973, 1526; C. N. Berry and B. C. Challis, *ibid.*, 1974, 1638; B. C. Challis and S. P. Jones, *ibid.*, 1975, 153; T. D. B. Morgan and D. L. H. Williams, *ibid.*, 1972, 74; T. D. B. Morgan, D. L. H. Williams, and J. A. Wilson, *ibid.*, 1973, 437; D. L. H. Williams and J. A. Wilson, *ibid.*, 1974, 13; D. L. H. Williams, *J.C.S. Chem. Comm.*, 1974, 324; I. D. Biggs and D. L. H. Williams, *J.C.S. Perkin II*, 1975, 107; D. L. H. Williams, *ibid.*, p. 655; I. D. Biggs and D. L. H. Williams, *ibid.*, 1976, 601; 1977, 47; D. L. H. Williams *ibid.*, 1976, 1838.

[2] (*a*) F. Yamamoto and S. Oae, *Bull. Chem. Soc. Japan*, 1975, **48**, 77; (*b*) S. Oae and T. Sakurai, *ibid.*, 1976, **46**, 730.

[3] (*a*) S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237; (*b*) ref. 1*a*, p. 1128; (*c*) T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' W. A. Benjamin, New York, 1966, ch. 1; (*d*) W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969.

both alkaline (in DMSO–$D_2{}^{18}O$) and acid (in dioxan–$H_2{}^{18}O$) hydrolyses,[4] and explained the result by Bender's addition–elimination mechanism.[5] However in our experience of ^{18}O tracer experiments, we have frequently found that accurate results could only be obtained when the original organic compounds are labelled with ^{18}O but not when ^{18}O-enriched aqueous media such as ^{18}O-enriched acid or hydroxide are used as the only ^{18}O-labelled component. Therefore possible oxygen exchange in the alkaline hydrolysis of alkyl nitrite was re-examined using n-hexyl [^{18}O]nitrite.[6]



SCHEME 1 Addition–elimination mechanism

RESULTS

Attacking Site of Nucleophile.—N–O bond fission has been confirmed in the alkaline hydrolysis of 1-methylheptyl nitrite.[1b] However, there is a possibility that OH^- attacks the benzylic carbon of benzyl or β-phenethyl nitrite to give either benzyl alcohol or styrene in the alkaline hydrolysis, since nitrite, $^-O–N=O$, is a good leaving group and the benzylic position is quite reactive. However, alkaline hydrolysis of both nitrites gave benzyl and β-phenethyl alcohol in quantitative yield, thus eliminating the possibility of C–O bond fission. Further, benzyl nitrite was hydrolysed in ^{18}O-enriched alkaline water–dioxan. A negligibly small amount (1.5%) of original ^{18}O in $^{18}OH^-$–$H_2{}^{18}O$ was detected in the resulting benzyl alcohol, thus revealing that OH^- attacks nitrogen exclusively even in alkaline hydrolysis of both benzyl and β-phenethyl nitrite.

Kinetics.—Alkaline hydrolysis of both alkyl nitrites and benzoates was carried out in 61% dioxan–water. Since good second-order rate constants were obtained up to 50% completion of the reaction, there is no possibility that NO_2^-, generated by the reaction, competes with OH^- as the nucleophile during the reaction. The results are listed in Tables 1 and 2. The relative rates of alkaline hydrolysis of several alkyl nitrites, benzoates, acetates, and formates at 35.1 °C are summarized in Table 4. The rates of alkaline hydrolysis of alkyl nitrites in 61% dioxan–water are quite similar to those in 56% acetone–water. Therefore, the rates of hydrolysis in 61% dioxan–water are presumed to compare with those of acetates and formates in 56% acetone–water. Activation parameters for the reactions of both nitrites and esters are summarized in Table 6 together with those for related esters cited in the literature.

TABLE 1

Kinetics of alkaline hydrolyses of alkyl nitrites in 61% dioxan–water

Ester	$[OH^-]_0$/ M	$[Ester]_0$/ M	T/°C	10^4k_2/ l mol^{-1} s^{-1}
$PhCH_2ONO$	0.0993	0.0680	25.6	2.26 ± 0.08
	0.0893	0.0630	30.1	3.03 ± 0.06
	0.0873	0.0648	35.1	5.23 ± 0.11
	0.0915	0.0667	35.7	5.14 ± 0.08
	0.0863	0.0618	40.2	8.39 ± 0.20
	0.0872	0.0665	45.0	13.3 ± 0.30
	0.0884	0.0629	49.9	17.8 ± 0.30
p-$CH_3C_6H_4$-CH_2ONO	0.0845	0.0627	35.1	2.91 ± 0.04
p-$CH_3OC_6H_4$-CH_2ONO	0.0824	0.0591	35.1	2.76 ± 0.03
p-$ClC_6H_4CH_2ONO$	0.0825	0.0579	35.1	12.0 ± 0.40
m-$ClC_6H_4CH_2ONO$	0.0778	0.0555	35.1	14.8 ± 0.10
$PhCH_2CH_2ONO$	0.0870	0.0692	35.1	1.85 ± 0.01
	0.0771	0.0602	45.0	3.95 ± 0.03
	0.0795	0.0633	55.0	9.45 ± 0.18
n-C_4H_9ONO	0.0911	0.0560	35.1	0.562 ± 0.016
	0.0914	0.0566	54.5	3.14 ± 0.005
n-$C_6H_{11}ONO$	0.0903	0.0531	35.1	0.394 ± 0.007
	0.0911	0.0521	45.0	0.940 ± 0.03
	0.0916	0.0556	55.1	2.11 ± 0.04
$Ph(CH_3)CHONO$	0.0843	0.0684	35.1	1.19 ± 0.01
cyclo-C_5H_9ONO	0.0905	0.0570	35.1	0.254 ± 0.005
s-C_4H_9ONO	0.0909	0.0480	35.1	0.138 ± 0.004

TABLE 2

Kinetics of alkaline hydrolyses of alkyl benzoates in 61% dioxan–water

Ester	$[OH^-]_0$/ M	$[Ester]_0$/ M	T/°C	10^4k_2/ l mol^{-1} s^{-1}
$PhCH_2OCOPh$	0.0178	0.0127	15.4	30.2 ± 0.2
	0.0175	0.0127	25.0	67.9 ± 1.2
	0.0179	0.0126	35.1	146 ± 3
$PhCH_2CH_2OCOPh$	0.0143	0.0117	35.1	78.5 ± 0.6
n-C_4H_9OCOPh	0.0183	0.0130	35.1	46.8 ± 0.3
$Ph(CH_3)CHOCOPh$	0.0163	0.0135	35.1	20.8 ± 0.8
cyclo-C_5H_9OCOPh	0.0161	0.0136	35.1	11.8 ± 0.4
s-C_4H_9OCOPh	0.0149	0.0124	35.1	7.77 ± 0.2
n-C_4H_9OCOPh	0.0152	0.0138	35.1	0.49 ± 0.005

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[4] M. Kobayashi, *Chem. Letters*, 1972, 37.

[5] (*a*) M. L. Bender, *J. Amer. Chem. Soc.*, 1951, **73**, 1926; (*b*) M. L. Bender, *ibid.*, 1953, **75**, 5986; (*c*) M. L. Bender and R. S. Dewey, *ibid.*, 1956, **78**, 317; (*d*) M. L. Bender, R. D. Ginger, and J. P. Unik, *ibid.*, 1958, **80**, 1044; (*e*) M. L. Bender and R. J. Thomas, *ibid.*, 1961, **83**, 4189; (*f*) M. L. Bender, H. Matsui, R. J. Thomas, and S. W. Tobey, *ibid.*, p. 4193; (*g*) M. L. Bender and H. d'A Heck, *ibid.*, 1967, **89**, 1211.

[6] Preliminary report, S. Oae, N. Asai, and K. Fujimori, *Tetrahedron Letters*, 1977, 2103.

TABLE 3

^{18}O Exchange experiments of nitroso oxygen with hydroxide oxygen in the alkaline hydrolysis of n-hexyl nitrite in 61% dioxan–water

Origin of dicyclohexyl-*N*-nitrosamine		^{18}O Content in dicyclohexyl-*N*-nitrosamine (atom %)[5]
t/min	Completion of hydrolysis (%)	
Control experiments [reaction (1)]		
0	0	1.334 [a]
0	0	1.338 [b]
Reaction at 45.0 °C	$[\mathrm{Nitrite}]_0$ 0.0584M, $[\mathrm{OH}^-]_0$ 0.0898M	
0	0	1.338
807	30 4	1.345
1 733	49.8	*c*
2 501	60.8	1.336
3 465	70.1	1.346
5 092	80.1	1.335
Reaction at 55.1 °C	$[\mathrm{Nitrite}]_0$ 0.0558M, $[\mathrm{OH}^-]_0$ 0.0910M	
0	0	1.342
346	29.6	1.330
730	49.5	1.347
1 041	60.3	1.342
1 452	71.5	1.344
2 103	80.6	1.333

[a] Time for reaction (1) is 23 days at room temperature. [b] Time for reaction (1) is 62 days at room temperature. [c] Not measured.

Oxygen Exchange Studies.—The alkaline hydrolysis of ^{18}O-labelled n-hexyl nitrite was carried out under the conditions of the kinetics studies. After partial reaction, unchanged n-hexyl nitrite was converted into crystalline dicyclohexyl-*N*-nitrosamine which was then subjected to routine ^{18}O analysis,[7] since n-hexyl nitrite is an unstable liquid and purification of a small amount of the nitrite is very difficult. As shown in Table 3, the results of a control experiment [reaction (1)] reveal that the nitroso-group of the nitrite is transferred into dicyclohexyl-*N*-nitrosamine without any loss of the original ^{18}O label in the nitrite. The results in Table 3 reveal that no oxygen

$$\mathrm{RON{=}O} + (\text{cyclo-}\mathrm{C_6H_{11}})_2\mathrm{NH} \longrightarrow \mathrm{ROH} + (\text{cyclo-}\mathrm{C_6H_{11}})_2\mathrm{N{-}N{=}O} \quad (1)$$

exchange took place between n-hexyl nitrite and OH^- during alkaline hydrolysis even up to 80% completion of the reaction at both 45.0 and 55.1 °C.

The discrepancy between our results and those of Kobayashi[4] is due mainly to the difference in reaction conditions. Kobayashi stirred, at room temperature, a two-phase mixture of isoamyl nitrite (17.0 g, 0.15M), DMSO (86 g), $Me_4N^+OH^-$ (*ca.* 3.5 g, 0.04M), and $D_2{}^{18}O$ (1.5 atom %; 9.2 g, 0.46M) for one week or a mixture of isoamyl nitrite (25.0 g, 0.214M), DMSO (40 ml), NaOH (8.0 g, 0.20M), and $H_2{}^{18}O$ (30 ml, 1.6M) for three months. Then the alkyl nitrite was recovered for ^{18}O analysis.[8] Given the amount of OH^- ion. *ca.* 0.3 mol. equiv. of isoamyl nitrite in the former case, the mixture should become acidic after OH^- has been consumed. Under acidic conditions, not only ^{18}O exchange between NO_2^- and $D_2{}^{18}O$ can take place[16] but also both hydrolysis and ester formation are considered to be reversible.[1b] In view of the very high concentration of the mixture which is separated in two phases and contains only 3 mol. equiv. of $D_2{}^{18}O$, the reaction would soon reach an equilibrium between isoamyl nitrite and the hydrolysed products after the mixture becomes acidic, and hence the ^{18}O label in water must be incorporated into the nitrite by the processes mentioned above. Even in the latter case, there is somewhat less OH^- than isoamyl nitrite. Since the mixture consists of two phases, one containing isoamyl nitrite as major component and the other OH^- and water as major components, there is the possibility that the organic layer becomes acidic and the ^{18}O label in the solvent may be incorporated into isoamyl nitrite by the mechanism described earlier, if the stirring is not adequate.

Linear Free Energy Relationships.—All kinetic data for the reactions of substituted benzyl nitrites in Table 1, substituted benzyl benzoates reported by Bender,[5] and substituted benzyl acetates reported by Tommila[9] can be correlated better with σ^0 [10] than with Hammett σ values as shown in Table 6. In order to separate the polar and steric effects of alkaline hydrolysis of the alkyl nitrites and

TABLE 4

Relative rates of alkaline hydrolyses at 35.1 °C

Alkyl group in ester	$k_2^{\mathrm{rel.}}$ [a]
Nitrites (in 61% dioxan–water)	
$PhCH_2$	1.00
$PhCH_2CH_2$	0.354
$PhCHCH_3$	0.228
$\mathrm{Pr^n}$ [b]	0.139
$\mathrm{Pr^n}$ [c]	420
$\mathrm{Bu^n}$	0.107
cyclo-C_5H_9	0.048 9
$\mathrm{Bu^s}$	0.0264
$\mathrm{Bu^t}$ [b]	0.002 62
$\mathrm{Bu^t}$ [c]	994
Benzoates (in 61% dioxan–water)	
$PhCH_2$	27.9
$PhCH_2CH_2$	15.0
$PhCHCH_3$	3.97
$\mathrm{Bu^n}$	8.95
cyclo-C_5H_9	2.26
$\mathrm{Bu^s}$	1.49
$\mathrm{Bu^t}$	0.0945
Benzoates (in 56% acetone–water)	
$PhCH_2$ [d]	25.8
$PhCH_2CH_2$ [d]	13.9
$\mathrm{Bu^n}$ [d]	8.31
cyclo-C_5H_9 [d]	1.98
$\mathrm{Bu^s}$ [d]	1.12
$\mathrm{Bu^t}$ [d]	0.0662
Acetates (in 56% acetone–water)	
$PhCH_2$ [d]	346
$PhCH_2CH_2$ [d]	206
$\mathrm{Bu^n}$ [e]	8.39
$\mathrm{Bu^s}$ [e]	13.1
$\mathrm{Bu^t}$ [e]	1.13
Formates	
$PhCH_2$ [d]	99 200 (in 56% acetone–water)
$\mathrm{Pr^n}$ [f]	78 700 (in water)
$\mathrm{Bu^n}$ [f]	70 700 (in water)
$\mathrm{Pr^i}$ [f]	32 700 (in water)

[a] k_2 for $PhCH_2ONO$ in 61% dioxan–water is 5.23×10^{-4} l mol^{-1} s^{-1}. [b] Ref. 1*b*. [c] Acid hydrolysis at 0°.[16] [d] Ref. 9. [e] R. W. A. Jones and D. R. Thomas, *J. Chem. Soc.* (*B*), 1966, 661. [f] J. Barthel and G. Bäder, *Z. Phys. Chem.*, 1966, **48**, 114.

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[7] S. Oae, T. Kitao, and Y. Kitaoka, *J. Amer. Chem. Soc.*, 1962, **84**, 3362.

[8] M. Kobayashi, personal communication.

[9] (*a*) E. Tommila, *Ann. Acad. Sci. Fennicae*, 1942, **A59**, 3 (*Chem. Abs.*, 1944, **38**, 6173); (*b*) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1938, 1801.

[10] Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, 1965, **86**, 875.

TABLE 5

Activation parameters for alkaline hydrolyses of alkyl nitrites and carboxylic esters

Substrate	Solvent	$\Delta H^‡$/ kcal mol^{-1} [a]	$\Delta S^‡$/ cal mol^{-1} K^{-1} [a]	γ [b]	Ref.
$PhCH_2ONO$	61% Dioxan–H_2O	16.5	−20.1	0.9968	
$PhCH_2CH_2ONO$	61% Dioxan–H_2O	15.8	−24.3	0.9985	
n-$C_6H_{11}ONO$	61% Dioxan–H_2O	16.3	−26.0	0.999 96	
n-C_3H_7ONO	60% Dioxan–H_2O	16.3	−24.6	0.9999	*c*
t-C_4H_9ONO	60% Dioxan–H_2O	18.7	−24.8	0.9986	*c*
$PhCH_2OCOPh$	61% Dioxan–H_2O	13.5	−23.1	0.9999	
$PhCH_2OCOPh$	56% Acetone–H_2O	14.74	−19.3		*d*
$PhCH_2OCOCH_3$	56% Acetone–H_2O	11.8	−24.4		*d*
$PhCH_2OCOH$	56% Acetone–H_2O	10.97	−15.1		*d*
n-C_4H_9OCOH	H_2O	8.72	−23.1	0.9997	*e*

[a] At 35.1 °C. [b] Correlation coefficient. [c] Ref. 1*b*. [d] Ref. 9. [e] J. Barthel and G. Bäder, *Z. Phys. Chem.*, 1966, **48**, 114.

carboxylic esters, Taft's equation (2) [11] was applied to the data in Tables 1 and 2 and kinetic data for carboxylic esters cited in the literature. The ρ* and δ values computed by using the least squares method are given in Table 7.

$$\log k_{\mathrm{rel}} = \rho^*\sigma^* + \delta E_{\mathrm{s}} \qquad (2)$$

Plots of log k_{rel} − $\rho^*\sigma^*$ against E_{s} values give straight lines except for α-methylbenzyl esters which were, therefore, omitted in the above computation (Figures 1 and 2). Since both ρ* and δ values for the benzoates obtained from the reactions in the different solvent systems are quite similar, the data for alkyl nitrites in Table 7 can be directly compared with those for alkyl acetates.

TABLE 6

Polar substituent effects on alkaline hydrolyses of benzyl nitrites and benzyl carboxylates

Substrate	Solvent	T/°C	ρ°
$XC_6H_4CH_2{-}ONO$	61% Dioxan–water	35.1	1.46 (γ 0.991)
$XC_6H_4CH_2{-}O\overset{\overset{\displaystyle O}{\|}}{C}{-}Ph$	61% Dioxan–water	35.1	0.994 (γ 0.9998) [a]
$XC_6H_4CH_2{-}O\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3$	56% Acetone–water	25.0	0.746 (γ 0.997) [b]

[a] Ref. 5. [b] Ref. 9.

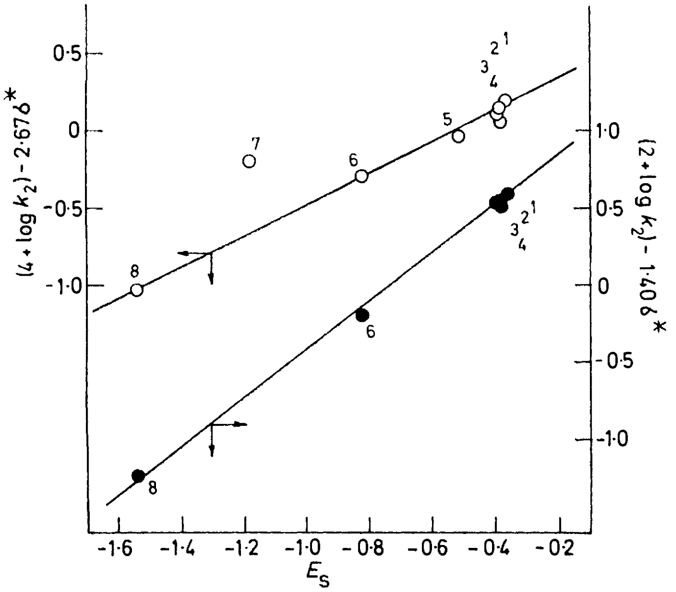

FIGURE 1 Plots of (log k_2 − $\rho^*\sigma^*$) for alkaline hydrolysis of alkyl nitrites in 61% dioxan–water and acetates in 56% acetone–water against Taft's E_{s} values: 1, Pr$^{\mathrm{n}}$; 2, $PhCH_2$; 3, Bu$^{\mathrm{n}}$; 4, $PhCH_2CH_2$; 5, cyclo-C_5H_9; 6, Bu$^{\mathrm{s}}$; 7, $PhCH(CH_3)$; 8, Bu$^{\mathrm{t}}$. ○, Alkyl nitrite in 61% dioxan–water; ●, acetate in 56% acetone–water

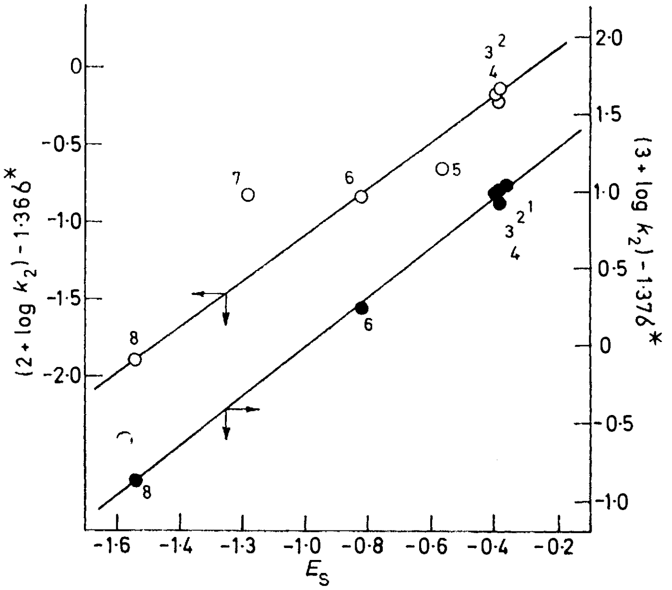

FIGURE 2 Plots of (log k_2 − $\rho^*\sigma^*$) of alkaline hydrolyses of benzoates in 61% dioxan–water and 56% acetone–water against Taft's E_{s} values (for key see Figure 1): ○, in 61% dioxan–water; ●, in 56% acetone–water

TABLE 7

Polar and steric effects on alkaline hydrolyses of nitrites and related carboxylates

Substrate	Solvent	T/°C	ρ *	δ	γ
R–O–N=O	61% Dioxan–water	35.1	2.67	0.979	0.9988
$R{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}Ph$	61% Dioxan–water	35.1	1.36	1.50	0.9994
	56% Acetone–water [a]	25.0	1.37	1.61	0.9991
$R{-}O{-}\overset{\overset{\displaystyle O}{\|}}{C}{-}CH_3$	56% Acetone–water [a]	24.7	1.47	1.45	0.9991

[a] Ref. 9.

DISCUSSION

The characteristic features of the data summarized in Tables 1—7 are as follows. (1) Rates of alkaline hydrolysis of alkyl nitrites are much smaller than those of the corresponding carboxylic esters, especially

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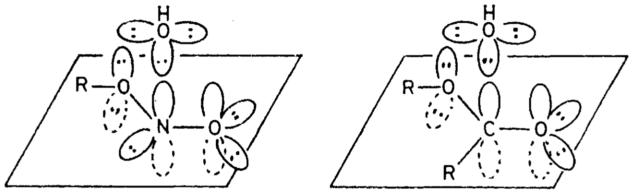
[11] R. W. Taft, jun., 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, Chapman and Hall, London, 1956, p. 556.

formates (Table 4). (2) However, rates of acid hydrolysis of alkyl nitrites are much larger than those of the carboxylic esters (Table 4). (3) There is no noticeable oxygen exchange between n-hexyl nitrite and OH$^-$ during alkaline hydrolysis of n-hexyl nitrite, whereas oxygen exchange was observed in the reaction of the benzoates in the same solvent system.[5] (4) The polar substituent effects of alkoxide groups in the alkaline hydrolysis of alkyl nitrites are about twice those of the carboxylic esters (ρ^0 and ρ^*; Tables 6 and 7). (5) Taft's δ values for alkaline hydrolysis of the alkyl nitrites are smaller than those for the corresponding carboxylic esters (Table 7). (6) Activation entropies for alkaline hydrolysis of the alkyl nitrites are somewhat greater than those of the carboxylic esters (Table 5).

Since the lone pair is considered to be less bulky than any alkyl group, steric hindrance in the transition state of the reaction of the alkyl nitrite must be smaller than that of the corresponding carboxylic ester. Actually, Taft δ values for the reaction of the alkyl nitrites are substantially smaller than those for the carboxylic esters. This is in keeping with our previous observation that the introduction of a methyl group at the α-position of pyridine retards nucleophilic substitution on sp^3 hybridized carbon but, however, accelerates nucleophilic substitution on sp^3 nitrogen.[2a] Hence, the reaction of the alkyl nitrite should be sterically more favoured than that of the ester. When the rate of reaction of the nitrite is compared with that of the formate which is sterically similar, the reaction of the formate is *ca.* 10^5 faster than that of the corresponding nitrite. Therefore, either the electronegativity difference between carbon and nitrogen and/or the presence of the lone pair on nitrogen should be responsible for this difference in the rates. The data in Table 5 show that the difference in rates between the alkyl nitrites and the carboxylic esters depends mainly on the activation enthalpy.

Recently, the interaction between nucleophiles and electrophiles has been expressed successfully by the combination of two terms, an electrostatic and an orbital interaction term.[12] Sometimes one of these dominates over the other. One case is the 'charge controlled reaction' in which an electrostatic term plays a major role, since a large energy gap separates the highest occupied orbital of a nucleophile from the lowest unoccupied orbital of an electrophile.[12b] The other case is the 'orbital controlled reaction' which takes place when the highest occupied orbital of a nucleophile and the lowest unoccupied orbital of the electrophile are nearly degenerate.[12b] The carbonyl group of the carboxylic ester is highly polarized because of the big electronegativity difference between C and O. Therefore, the ester is an electrophile hard enough for a charge controlled reaction.[12b] On the other hand, the nitroso-group is less polarized than carbonyl because of the smaller electronegativity difference between N and O. Thus an alkyl nitrite is considered to be a relatively poor electrophile for a charge controlled reaction compared with a carboxylic ester. In other words the ester is a harder substrate than alkyl nitrite for nucleophilic substitution. Since OH$^-$ is a typical hard nucleophile which favours the charge controlled reaction,[12b] the rate of alkaline hydrolysis of the ester should be greater than that of the nitrite.

On the other hand the transition states of the reaction for both alkyl nitrite and ester can be illustrated as in Scheme 2 in which OH$^-$ attacks the nitroso-nitrogen or carbonyl carbon in a direction perpendicular to the trigonal plane for maximal overlap of the lone pair of OH$^-$ and the π^*-orbital of the nitroso or carbonyl group, respectively. The lone pair on nitrogen is considered to be repulsed by the lone pair on OH$^-$ thus destabilizing the transition state of the reaction of alkyl nitrite. There is no such lone pair–lone pair interaction in the reaction of the ester. Thus the repulsive effect of lone pairs should also be responsible for the smaller rate of the alkaline hydrolysis for the nitrite, as well as the electronegativity.



(4) (5)

SCHEME 2 Transition state of reaction

The lack of noticeable oxygen exchange between n-hexyl nitrite and OH$^-$ during hydrolysis, and the clearly observable oxygen exchange between alkyl carboxylates and OH$^-$ for alkaline hydrolysis under the same conditions, can be rationalized in terms of the repulsive effect of the lone pair in the transition state. The following three possible explanations are conceivable for the lack of oxygen exchange in the hydrolysis of the alkyl nitrite. (1) Although the life time of the intermediate (1) is long enough for ^{18}O to be equilibrated by the process (1) $\rightleftarrows$ (2) $\rightleftarrows$ (3), the partitioning of the tetrahedral addition intermediate may be highly favoured for the products ($k_2 \ll k_3, k_4$). (2) Both forward reaction from the intermediate (1) to the hydrolysed products and backward reaction from the intermediate (1) to the starting materials are *much faster* than the proton transfer process from (1) to (2) (k_2, $k_3 \gg k_4$). (3) The reaction is somewhat concerted. Possibility (1) is ruled out in view of the fact that the polar substituent effect on the leaving group is larger for the alkyl nitrite than for the ester. The intermediate (1), if formed, is expected to be very unstable because of the repulsion between the lone pair on the nitrogen atom and seven lone pairs on the vicinal O

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[12] (*a*) K. Fukui and H. Fujimoto, *Bull. Chem. Soc. Japan*, 1968, **41**, 1989; H. Fujimoto, S. Yamabe, and K. Fukui, *Tetrahedron Letters*, 1971, 439,443; K. Fukui, *Accounts Chem. Res.*, 1971, **4**, 57; (*b*) G. Klopman, *J. Amer. Chem. Soc.*, 1968, **90**, 223; 'Chemical Reactivity and Reaction Paths,' Wiley, New York, 1974; (*c*) R. F. Hudson, *Angew. Chem. Internat. Edn.*, 1973, **12**, 36.

atoms. Therefore the life-time of intermediate (1) should be too short for proton transfer to give (2) which is presumed to be the important process for oxygen exchange as in the case of alkyl benzoates [possibility (2)].[5e,g] However, if the partial dissociation between RO and N=O takes place at the transition state (4) [possibility (3)], such an unfavourable lone pair–lone pair repulsion should be reduced. Although it is difficult to rule out possibility (2), the following observations suggest that possibility (3) is more plausible. Namely, the observation that the polar substituent effects on the leaving alkoxide group (ρ^0,ρ^*) are about twice as large for the alkaline hydrolysis of alkyl nitrites than for the esters seems to support this partial dissociation of the leaving group in the transition state. The activation entropy for alkaline hydrolysis of benzyl nitrite is 3 cal mol^{-1} K^{-1} larger than that of benzyl benzoate in 61% dioxan–water (Table 3). If the difference of activation entropy, 3.8 cal mol^{-1} K^{-1}, between the reaction in 61% dioxan–water and that in 56% acetone–water for benzyl benzoate can be applied to estimate the activation entropies of the reaction of benzyl acetate and formate in 61% dioxan–water from the data of the reaction in 56% acetone–water, the activation entropy for the reaction of benzyl nitrite becomes nearly identical to or larger than those of the corresponding formate and acetate, respectively. The ester is expected to be more solvated in the ground state by water than the nitrite because of the greater polarization of the carbonyl than the nitroso-group. In fact, solubility of the former in water is greater than that of the latter. Therefore, if alkaline hydrolysis of the alkyl nitrite proceeds *via* an addition–elimination mechanism similar to that of the ester, the entropy difference between the ground state and the addition intermediate must be greater for the nitrite than for the ester, while the entropy of activation for the alkyl nitrite should be smaller than that for the ester, since tetrahedral addition intermediates of both esters must equally be solvated rather strongly with water, eventually decreasing the entropy factor to nearly the same extent. However, this was not found to be the case. Thus the reaction is best explained in terms of the concerted mechanism [possibility (3)] since the partial dissociation of the leaving group compensates for the decrease of entropy in the transition state.

Edwards explained the immeasurably slow reaction of OH^- with hydrogen peroxide in terms of the lone pair repulsion between the nucleophile and the substrate.[13] The reaction of β-phenethyl nitrite with piperidine which has no lone pair being repulsed by the lone pair of nitrogen in the alkyl nitrite is 19 times faster than that of alkaline hydrolysis of the same compound in the same solvent. On the other hand, the reaction of β-phenethyl benzoate with piperidine is at least 10^2 times slower than its alkaline hydrolysis.[14] Consequently, the reaction of β-phenethyl nitrite with piperidine is much faster than that of the benzoate. The markedly higher rate of acid catalysed hydrolysis seems also to be explained in terms of a decrease of lone pair–lone pair interaction in the transition state for acid catalysed hydrolysis in which the nucleophile is neutral water and one of the oxygens of the alkyl nitrite is protonated.

EXPERIMENTAL

Solvents and Reagents.—Dioxan was purified by the method described[15] and stored in a refrigerator with argon. A sodium hydroxide solution of 61% dioxan–water was prepared by diluting sodium hydroxide solution (200 g) which was prepared with special reagent grade NaOH washed with water before use so that the total volume becomes 500 ml. The carbonate free distilled water was used for all experiments. The alkaline solution was titrated with standard 0.05N-HCl solution. Alkyl nitrites were prepared by the reaction of the corresponding alcohols and $NaNO_2$ in the presence of H_2SO_4 and distilled *in vacuo* before use.

Product Analyses.—Benzyl nitrite solution (20 ml) in 61% dioxan–water ([nitrite]$_0$ 0.0556M, [OH^-]$_0$ 0.1125M) was placed in a Pyrex tube connected to a vacuum line, evacuated under cooling with a dry ice–acetone bath, degassed by a freeze–thaw cycle, evacuated, and sealed. The tubes were placed in a thermostatted bath at 35.1 °C for 16 days. They were then opened and tetralin (135 mg) was added as the standard for analysis by g.l.c. on a 1 m stainless steel column packed with 10% SE-30 on 60—80 mesh Celite. The gas chromatograph of the sample solution, which was recorded with a Hitachi 023 instrument, gave only one peak of benzyl alcohol (yield 99.5%).

Product analysis in the alkaline hydrolysis of β-phenethyl nitrite was carried out in the manner described above and β-phenethyl alcohol (98.7%) was found to be the only product.

^{18}O Tracer Studies on Attacking Site.—Sodium hydroxide (special reagent grade) was washed twice with water and dried *in vacuo* and used to prepare a 0.119N solution in 61% dioxan–$H_2{}^{18}O$. In order to determine the ^{18}O content of $^{18}OH^-$ in the solution, benzonitrile (1 g) was heated with ^{18}O-enriched alkaline dioxan–water solution (5 ml) in a sealed tube at 50° for one week. The mixture was cooled and benzamide which crystallized was collected, washed with water, dried, recrystallized thrice from $CHCl_3$, and subjected to routine ^{18}O analysis (1.145 excess atom %).

A 0.073M solution (10 ml) of benzyl nitrite in 0.118N-$Na^{18}OH$ solution in 61% dioxan–^{18}O-enriched water was introduced into a Pyrex glass tube, degassed, evacuated, sealed, and heated at 35.1 °C for 18 days. Then the mixture was diluted with water (10 ml) and extracted thrice with ether. The ether extracts were combined, washed with water, dried ($MgSO_4$), filtered, and solvent was evaporated to give an oily residue. The crude benzyl alcohol obtained was allowed to react with phenyl isocyanate (0.91 g) at room temperature for two days. Crystals of benzyl *N*-phenylcarbamate obtained from the mixture was recrystallized thrice from benzene–hexane, m.p. 77—78 °C, and subjected to ^{18}O analysis (0.009 excess atom %).

Synthesis of n-Hexyl [^{18}O]*Nitrite.*—To a solution of n-hexyl alcohol (25 g, 0.243 mol) and concentrated H_2SO_4

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[13] J. O. Edwards, ' Inorganic Reaction Mechanism,' Benjamin, New York, 1964, p. 78.

[14] S. Oae, N. Asai, and K. Fujimori, unpublished data.

[15] L. F. Fieser, ' Experiments in Organic Chemistry,' Heath, Boston, 1957, 3rd edn., p. 285.

(13.1 g, 0.134 mol) in ether (75 ml) was added dropwise a solution of $NaN^{18}O_2$ (18.5 g, 0.268 mol) in $H_2{}^{18}O$ (1.5 atom %, 60 ml), which was prepared as described by Amber,[16] with vigorous stirring at 0°. After addition, the mixture was stirred for 1 h, then neutralized with aqueous $NaHCO_3$ solution and extracted with ether. The organic layer was separated, washed with dilute aqueous solution of $NaHCO_3$, dried ($MgSO_4$), and the solvent was evaporated under vacuum. The residue was twice distilled through a Vigreux column under reduced pressure, b.p. 46.5 °C at 32 mmHg (yield 40%, 12.8 g).

Control Experiment [*Reaction* (1)].—A mixture of n-hexyl [^{18}O]nitrite (150 mg) and dicyclohexylamine (400 mg) was allowed to stand for 23 or 62 days at room temperature under argon. Crystals of dicyclohexyl-*N*-nitrosamine were collected, washed with pentane, and recrystallized five times from pentane to give the pure compound, m.p. 107.5—108 °C, which was subjected to ^{18}O analysis in order to estimate the ^{18}O content in the nitroso-group. The results are given in Tables 2 and 3.

^{18}O *Exchange between n-Hexyl Nitrite and* OH^-.—A solution of n-hexyl [^{18}O]nitrite in 61% dioxan–water was introduced in Pyrex heart-shaped flasks which were connected to a vacuum line, degassed, evacuated, and sealed under cooling with liquid N_2. The flasks were placed in a thermostatted bath at 45.0 ± 0.1° or 55.0 ± 0.1°, taken up from time to time, and cooled rapidly with dry ice–acetone to stop the reaction. The mixture was then diluted with the same amount of water. To the mixture dicyclohexylamine (214 g) was added and extracted with pentane. The extracts were combined and washed five times with an aqueous solution of $NaHCO_3$, dried ($MgSO_4$), filtered, and pentane was evaporated through a fractionating column. The oily residue was left for 24 days at room temperature under argon. Crystals of dicyclohexyl-*N*-nitrosamine were then collected, recrystallized from pentane, and subjected to ^{18}O analysis (Table 3).

Determination of ^{18}O *Content*.—^{18}O Analysis was carried out by the method developed by Rittenberg–Ponticorvo.[17] A sample (20 mg) was pyrolysed with purified $HgCl_2$ and $Hg(CN)_2$ (total 300 mg) in an evacuated, sealed silica tube at 550 °C for 12 h. The CO_2 formed was purified by distillation under vacuum and the peaks, *m/e* 44 and 46 corresponding to $C^{16}O_2$ and $C^{16}O^{18}O$, respectively, were measured on a Hitachi RMU-6MG mass spectrometer (error ±0.005 atom %).

Kinetic Studies.—The solution for a typical kinetic run was prepared by weighing a desired amount of an alkyl nitrite into a volumetric flask (100 ml) into which was added an NaOH solution of 61% dioxan–water so that the final concentration of OH^- was *ca.* 1.4 times that of the alkyl nitrite. Portions (5 ml) were pipetted into Pyrex glass tubes, degassed, and sealed as described for product analysis. These tubes were placed in a thermostatted bath and after 5 min one was taken up and subjected to sudden cooling (*t* 0). The mixture was transferred to a conical flask (100 ml) containing CCl_4 (30 ml). The remaining alkali was titrated with a standard solution of hydrochloric acid using neutral red–Bromothymol Blue (9 : 2) as an indicator.[1b] Kinetic measurements of the reaction of the benzoate were carried as for the alkyl nitrite.

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[16] M. Amber, M. Halman, and S. Pinchas, *J. Chem. Soc.*, 1960, 1242.

[17] D. Rittenberg and L. Ponticorvo, *J. Appl. Radio Isotopes*, 1956, **1**, 208.