Intramolecular Nucleophilic Participation. 11. Return as a Complication in *o*-Nitrobenzhydryl Bromide Solvolysis

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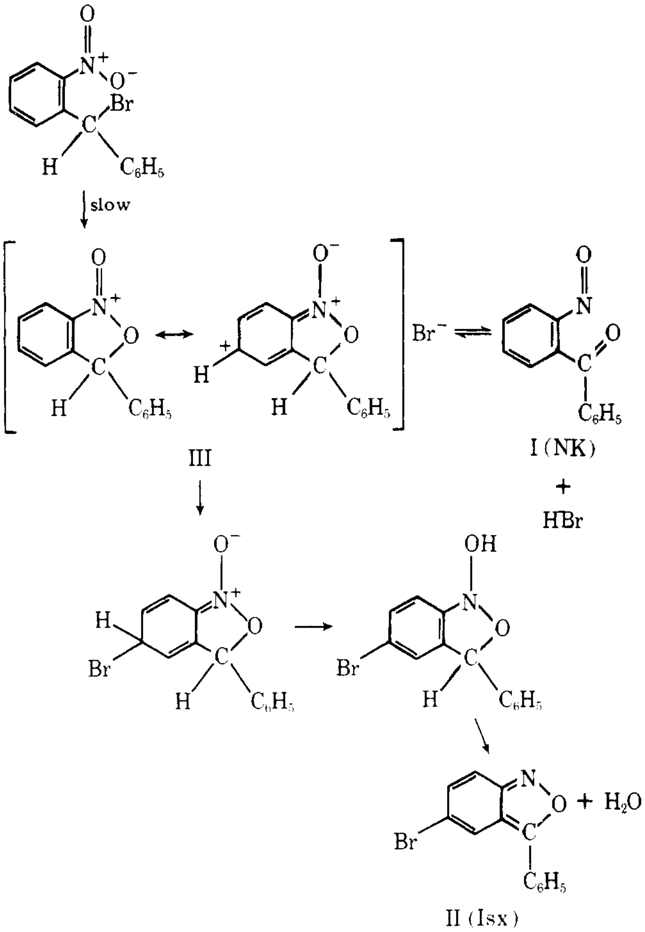
Rate studies of the solvolysis of *o*-nitrobenzhydryl bromide in 20–50 vol % of 2,2,2-trifluoroethanol–benzene mixtures in the presence and absence of 2,6-lutidine, hydrogen chloride, and lithium chloride have been conducted. The immediate reaction product is *o*-nitrosobenzophenone, which reacts further to form 5-bromo-3-phenyl-2,1-benzisoxazole if sufficient hydrogen bromide is present in the medium. In the presence of added chlorides anion exchange of the substrate accompanies solvolysis. When the trifluoroethanol (TFE) content of the medium is high, the extent of anion exchange is markedly reduced if 2,6-lutidine is included in the reaction mixture. In 50%, but not in 20%, TFE–benzene mixtures 2,6-lutidine significantly increases the solvolysis rate. Evidence is presented that trifluoroethoxide ion, generated from 2,6-lutidine, is responsible for the rate increase. A discussion of the solvolysis mechanism is presented in which it is proposed that the observed rate effect of added base results from interference with the return of cationic intermediates to starting materials.

A mechanism, similar to that suggested by Dickinson[1] in another context, has been proposed to describe the role of the nitro group as an internal nucleophile in the solvolysis of *o*-nitrobenzhydryl bromide.[2-4] The ion pair III, generated through rupture of the carbon–bromine bond, has been designated as the precursor of the two alternate reaction products, *o*-nitrosobenzophenone (I) and 5-bromo-3-phenyl-2,1-benzisoxazole. In media which are sufficiently basic to promote removal of a proton from III (90% aqueous acetone[2] and acetic acid containing sodium acetate[3]) the nitroso ketone (I) is the product. In acetic acid and 2,2,2-trifluoroethanol–benzene mixtures which contain hydrogen bromide the isoxazole (II) is the product (Scheme I),

In all solvent systems so far investigated *o*-nitrobenzhydryl bromide reacts significantly more rapidly than does its para isomer, at least in part in reflection of anchimeric assistance by the *o*-nitro group. The fact that the ortho–para reactivity ratio for the two isomers (k_o/k_p) increases as the medium becomes less polar and less nucleophilic may be a reflection of increased involvement of the ortho substituent as an internal nucleophile as the medium becomes less adapted to provide for stabilization of positive charge. In this connection it has been proposed alternately that the solvolysis of the ortho isomer is less subject than that of the para isomer to ion pair return to form starting material.

That there is some validity to this proposal is apparent in the results of a comparative study of the solvolysis rates of the *o*- and *p*-nitro- and *o*- and *p*-bromobenzhydryl bromides in 2,2,2-trifluoroethanol–benzene mixtures, a solvent system of low nucleophilicity.[4] The slopes (*m* values) of plots of the logarithms of the solvolysis rate constants vs. Grunwald–Winstein[5] *Y* values of the solvent mixtures are substantially more than unity when the substrates are the *o*- and *p*-bromo- and *p*-nitrobenzhydryl bromides. The *m* value for *o*-nitrobenzhydryl bromide, on the other hand, is substantially less than unity. Reactions with *m* values substantially larger than unity supposedly are strongly subject to ion pair return.[6] It is presumed that once the nitro group of *o*-nitrobenzhydryl bromide is locked to the exocyclic carbon through formation of intermediate III, it is not easily dislodged through displacement by bromide ion. The present investigation, which has been concerned with the influences of 2,6-lutidine, lithium chloride, hydrogen bromide, and hydrogen chloride on the rate of reaction of *o*-nitrobenzhydryl bromide in 2,2,2-trifluoroethanol–benzene mixtures, provides further information on return as a complication in the solvolytic process.

Scheme I



Experimental Section

Materials. Analytical reagent grade benzene (Mallinckrodt Chemical Co.), 99+% 2,2,2-trifluoroethanol (Aldrich Chemical Co.), and 96% 2,6-lutidine (Aldrich Chemical Co.) were used without further purification. Lithium bromide (Matheson Coleman and Bell 99.0% anhydrous reagent powder) was dried at 150 °C before use. Lithium chloride (G. Fredrick Smith anhydrous reagent) was used without further purification. Analytical reagent lithium chloride (Mallinckrodt Chemical Co.) was dried at 120 °C before use.

2,6-Lutidinium bromide was prepared by bubbling hydrogen bromide (Matheson Gas Co.) into 5 mL of 2,6-lutidine dissolved in 100 mL of benzene for 2 min. The solid precipitate was collected by filtration and recrystallized using isopropyl alcohol.

o-Nitrobenzhydryl bromide was prepared by the photoinduced reaction of *o*-nitrodiphenylmethane with *N*-bromosuccinimide in the presence of benzoyl peroxide with some modification of the procedure[2] described previously. Reaction was initiated through irradiation

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of the reactant mixture with a 275-W sunlamp through the Pyrex glass wall of a round-bottom flask. The lamp was placed at a distance of 1 in. from the flask, and the temperature of the reaction mixture was held at 15–20 °C. Removal of carbon tetrachloride from the product mixture was carried out at reduced pressure below 30 °C to avoid tar formation which occurs at higher temperatures.

Rates of Solvolysis of *o*-Nitrobenzhydryl Bromide. Rate runs were conducted spectrophotometrically using a Beckman DU-2 spectrophotometer equipped with a temperature controlled sample compartment. Rate samples were prepared by mixing appropriate quantities of stock solutions in the 1-cm absorption cells (total volume 3.0 mL). Benzene was used as the solvent in preparing 2,6-lutidine stock solution, and 2,2,2-trifluoroethanol was used to prepare the stock solutions of the lithium salts, 2,6-lutidinium bromide, hydrogen bromide, and hydrogen chloride (Matheson Gas Co.). The hydrogen halide contents of the stock solutions were determined through titration with standard sodium hydroxide solutions using bromthymol blue indicator. The 1-cm absorption cells containing the rate samples except for the substrate (2.9 mL) were placed in the temperature-controlled sample compartment of a Beckman DU-2 spectrophotometer and allowed to equilibrate to the compartment temperature (25.0 °C). Reactions were initiated through transfer to the absorption cell of 0.10 mL of a stock solution of the substrate (the benzhydryl halide or nitroso ketone in benzene, previously adjusted to a temperature of 25.0 °C). The cell was shaken and timing was started when it was returned to the cell compartment. The blank cells contained only the solvent mixtures in the same proportions as in the rate samples. Formation of product, either *o*-nitrosobenzophenone or 5-bromo-3-phenyl-2,1-benzisoxazole, was monitored by observing the change in absorption of the reaction mixtures at the appropriate wavelengths. In those cases in which the isoxazole was the product, measurements were made at a wavelength in the region of 355–382.5 nm, in which a characteristic absorption maximum of that compound in the various solvents is located (ϵ_{max} 14 000). In those runs in which the nitroso ketone was the product, its formation was monitored either at the wavelength of its visible absorption maximum, 737 nm (ϵ_{max} 40), or at a wavelength on its absorption shoulder, 310 nm (ϵ 6100). The starting bromide does not absorb significantly in the 355–382.5-nm region as compared to the isoxazole, nor does it display absorption in the visible region where the nitroso ketone absorbs. At 310 nm both the starting bromide (ϵ 1880) and the isoxazole (ϵ 2400) absorb in addition to the nitroso ketone.

In the reaction of *o*-nitrobenzhydryl bromide (followed at 310 nm) in solvents initially containing neither 2,6-lutidine nor hydrogen bromide, the nitroso ketone was formed initially and followed later by isoxazole as the hydrogen bromide content of the mixture increased. For these runs the infinity absorbances, A_∞ (to be expected if nitroso ketone were formed quantitatively), were obtained by duplicating the rate runs but with the inclusion of a sufficient quantity of 2,6-lutidine to prevent accumulation of hydrogen bromide. At an initial substrate concentration of 8.45×10^{-5} M, the absorbance (due to nitroso ketone) of a reaction mixture which initially contained neither 2,6-lutidine nor hydrogen bromide reached a maximum value of 95% of the final absorbance of a duplicate run with 2,6-lutidine present. The maximum was reached after 5 half-lives of reaction. A number of rate mixtures of varied initial substrate concentration were subjected to spectrophotometric measurement at both 310 and 355 nm; isoxazole was not formed to a significant extent during the initial 50% of the reactions. Solvolysis rate constants (later reported) for conversion of starting bromide to nitroso ketone were calculated using data collected during that phase of reaction. The constants, k_{obsd}, as defined by eq 1, were obtained from the slopes of the linear plots of ln ($A_\infty - A_t$) values[3] vs. time, where A_t is the absorbance at time t.

$$\frac{-d[RBr]}{dt} = \frac{d(NK)}{dt} \text{ or } \frac{d(Isx)}{dt} = k_{obsd}[RBr] \qquad (1)$$

For the solvolysis reactions of *o*-nitrobenzhydryl bromide in the presence of chloride ions (LiCl or HCl), rate constants were evaluated essentially as described above except for the replacement of [RBr] in eq 1 with [RX], where [RX] = [RBr] + [RCl]. This treatment is based upon the assumption that the molar absorbtivity of *o*-nitrobenzhydryl chloride at 310 nm and in the region of 355–370 nm does not significantly differ from that of *o*-nitrobenzhydryl bromide and the additional assumption that the absorbtivity of 5-chloro-3-phenyl-2,1-benzisoxazole at 355 nm is comparable to that of its bromine-containing analogue. The monitored reaction product in runs with HCl in the medium was isoxazole and that with lithium chloride in the medium was nitroso ketone.

Rate Studies of the Reaction of *o*-Nitrosobenzophenone with Hydrogen Bromide. Rate runs were conducted spectrophotometrically by the general procedure described above for the solvolysis reactions of *o*-nitrobenzhydryl bromide in which the isoxazole was the product. Isoxazole formation in the reactions of *o*-nitrosobenzophenone with hydrogen bromide was monitored by observing the change in absorption of the reaction mixtures at a wavelength in the region of 370–382.5 nm. Hydrogen bromide concentrations were in sufficient excess of the initial concentrations of nitroso ketone that the individual reactions were pseudo-first-order. Pseudo-first-order rate constants, k_p, for the reactions (see eq 2) were calculated from the slopes of plots of ln ($A_\infty - A_t$) values vs. time.

$$\frac{-d[NK]}{dt} = \frac{d[Isx]}{dt} = k_p[NK] \qquad (2)$$

Results

The Effects of 2,6-Lutidine on Reaction Rate. In 2,2,2-trifluoroethanol (TFE)–benzene mixtures containing sufficient 2,6-lutidine to prevent accumulation of hydrogen bromide in the medium, *o*-nitrobenzhydryl bromide reacts to form *o*-nitrosobenzophenone (I or NK). Even when 2,6-lutidine is not included in the reaction mixtures, the product of reaction at the low initial substrate concentrations of the rate studies (<10^{-4} M) is the nitroso ketone. Only in later phases of the reaction in base free and initially acid free medium does slow formation of 5-bromo-3-phenyl-2,1-benzisoxazole (II or Isx) occur through reaction of the nitrosoketone with cogenerated hydrogen bromide. If hydrogen bromide is initially present in the medium at a concentration of 10^{-2} M or higher, the isoxazole is the only detectable product.

In Table I first-order solvolysis rate constants, k_{obsd} (see eq 1), for reactions of *o*-nitrobenzhydryl bromide in 20–50% TFE–benzene mixtures in the presence and absence of 2,6-lutidine are summarized. Rate constants for reaction in 20 and 50% TFE–benzene mixtures initially containing hydrogen bromide rather than 2,6-lutidine are also presented. For both solvent mixtures rate constants for reaction in the initial presence of hydrogen bromide are closely comparable to those for solvolysis in the absence of added hydrogen bromide or 2,6-lutidine (cf. runs 20-1, -7, -8, and -9 and runs 50-1, -2, -9, -10, and -11). The k_{obsd} values are considered to be reproducible within ±5%.

For reactions in 50% TFE–benzene in which 2,6-lutidine is initially present in the medium k_{obsd} values increase with increasing base concentration of the medium up to a maximum value over four times that for reaction in the absence of 2,6-lutidine (cf. runs 50-1 to 50-8). Similar results have been obtained for reactions in 40 and 30% TFE–benzene, though as the benzene content of the medium increases the k_{obsd} value becomes decreasingly sensitive to 2,6-lutidine (cf. runs 40-1 to 40-9 and 30-1 to 30-6). In all three solvent systems (30, 40, and 50% TFE–benzene mixtures) k_{obsd} values for runs at $[RBr]_i < 10^{-4}$ M appear to reach a maximum when the 2,6-lutidine content of the medium is of the order of 10^{-2} M. At relatively high 2,6-lutidine concentrations k_{obsd} values are somewhat depressed from their maximum values (see runs 30-6, 40-9, and 50-8), presumably because of an unfavorable influence of significant quantities of base on the ionizing power of the media. When the medium content of TFE is reduced to 20%, k_{obsd} values for reaction in the presence of 2,6-lutidine are closely similar to those for reaction in base-free media or in solutions initially containing hydrogen bromide (cf. runs 20-1 to 20-9).

An explanation for the rate enhancement accompanying *increases in the lutidine concentration* of the medium will be developed subsequently. The explanation is based on the premise that the solvolysis of *o*-nitrobenzhydryl bromide is complicated by return. Presumably the base, which serves effectively to extract a proton from a reaction intermediate (a species related to III) to form nitroso ketone (I), interferes with the return of that intermediate to starting material. The

Table I. Rate Constants for Solvolysis of *o*-Nitrobenzhydryl Bromide in 2,2,2-Trifluoroethanol (TFE)–Benzene Mixtures at 25.0 °C

run	10^4[RBr]$_i$, M	10^4[2,6-Lut]$_i$,[a] M	10^4[HBr]$_i$, M	product[b]	$10^3 k_{obsd}$, s^{-1}
		Reactions in 20 vol % TFE			
20-1	0.572			NK	1.09[c]
20-2	0.572	33.0		NK	1.04
20-3	0.572	330		NK	1.18
20-4	174	430		NK	1.05
20-5	87	430		NK	1.03
20-6	174	860		NK	1.02
20-7	0.494		160	Isx	1.28
20-8	0.494		310	Isx	1.08
20-9	0.247		160	Isx	1.14
20-10	0.554	200		NK	1.31[d]
20-11	0.554			NK	1.56[d,c]
		Reactions in 30 vol % TFE			
30-1	0.286			NK	1.71[c]
30-2	0.572			NK	1.71[c]
30-3	0.572	5.73		NK	1.94[c]
30-4	0.572	28.7		NK	2.68[c]
30-5	0.572	287		NK	3.86
30-6	0.572	2870		NK	3.41
		Reactions in 40 vol % TFE			
40-1	0.286			NK	2.52[c]
40-2	0.572			NK	2.39[c]
40-3	0.286	4.87		NK	6.06[c]
40-4	0.572	4.87		NK	5.77[c]
40-5	0.286	24.4		NK	8.03[c]
40-6	0.572	24.4		NK	7.88[c]
40-7	0.286	244		NK	9.50
40-8	0.572	244		NK	9.08
40-9	0.572	2440		NK	8.13
		Reactions in 50 vol % TFE			
50-1	0.242			NK	3.02[c]
50-2	0.845			NK	3.02[c]
50-3	0.572	4.0		NK	11.2[c]
50-4	0.572	20		NK	12.9
50-5	0.670	40		NK	14.0
50-6	0.572	200		NK	13.9
50-7	0.670	400		NK	14.3
50-8	0.670	4000		NK	10.4
50-9	3.0		2900	Isx	3.13[e]
50-10	0.480		410	Isx	2.72
50-11	0.480		200	Isx	2.94
50-12	0.670	40		NK	4.55[f]
50-13	0.670	400		NK	6.47[g]
50-14	0.572	200		NK	4.29[h]
50-15	0.554	200		NK	11.4[d]
50-16	0.554	200		NK	10.8[i]
50-17	0.572	200		NK	9.09[i]
50-18	0.554			NK	3.92[d,c]
50-19	0.554			NK	3.52[i,c]
50-20	0.572	200		NK	14.6[j]

[a] Initial 2,6-lutidine concentration. [b] *o*-Nitrosobenzophenone is NK; 5-bromo-3-phenyl-2,1-benzisoxazole is Isx. [c] Initial rate constants; k_{obsd} decreased somewhat toward the end of the run as NK was converted to Isx. [d] Medium contained lithium bromide (197×10^{-4} M). [e] From ref 4. [f] Medium contained lutidinium bromide (38×10^{-4} M). [g] Medium contained lutidinium bromide (380×10^{-4} M). [h] Medium contained lutidinium bromide (675×10^{-4} M). [i] Medium contained lithium bromide (493×10^{-4} M). [j] Medium contained lithium perchlorate (414×10^{-4} M).

extent of return should then decrease with increasing concentration of the base in the medium. When the concentration of 2,6-lutidine reaches 10^{-2} M (in 30, 40, and 50% TFE), the extent of return apparently is negligible.

The Effects of 2,6-Lutidinium Bromide on Reaction Rate. That the most effective base in the medium is 2,2,2-trifluoroethoxide ion, rather than 2,6-lutidine itself, is suggested by the results of rate runs in 50% TFE–benzene mixtures in which both 2,6-lutidine and 2,6-lutidinium bromide were included in the reaction mixtures (cf. 50-5, -6, -7, and 50-12, -13, -14). Values of k_{obsd} for reactions in such mixtures are substantially less than those for reaction in the presence of lutidine alone. When lithium bromide is substituted for lutidinium bromide, k_{obsd} values, though somewhat less than those for reactions in the absence of lithium bromide, are much less affected (cf. runs 50-15, -16, -17).

Presumably in 2,2,2-trifluoroethanol solution 2,6-lutidine reacts to form trifluoroethoxide ion (eq 3).[7,8]

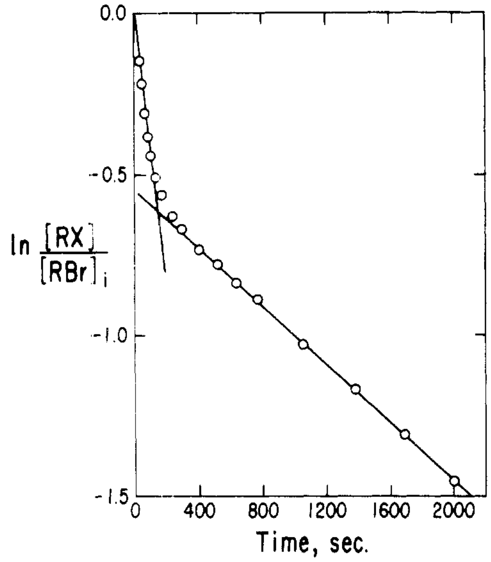
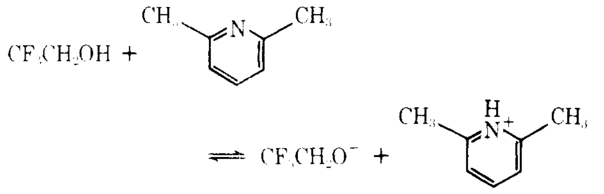


Figure 1. The solvolysis of *o*-nitrobenzhydryl bromide ($[RBr]_i$ = 5.54 × 10^{-5} M) at 25 °C in 50% TFE–benzene containing 3.67 × 10^{-2} M lithium chloride but no 2,6-lutidine.



(3)

The concentration of trifluoroethoxide in the medium is then governed by the ratio of 2,6-lutidine and 2,6-lutidinium ion in the medium, though this is at best a semiquantitative relationship since the complication of ion pairing is likely significant in a medium such as 50% TFE–benzene. The results of rate studies cited above do, however, indicate that k_{obsd} values are far more sensitive to the ratio of 2,6-lutidine to lutidinium bromide concentration than to the ratio of lutidine to lithium bromide concentration.

Solvolysis in the Presence of LiCl and HCl. As an independent means of testing the validity of the conclusion that return is a rate-complicating feature of *o*-nitrobenzhydryl bromide solvolysis, a kinetic investigation has been made of the extent to which anion exchange takes place when solvolysis occurs in the presence of lithium chloride or hydrogen chloride. The rate runs, conducted as described in detail in the Experimental Section, were intepreted through examination of plots of ln ($[RX]/[RBr]_i$) vs. time, where [RX] = [RBr] + [RCl] and $[RBr]_i$ = [RBr] at initiation of reaction. The reaction mixtures contained substrate at initial concentrations of $<10^{-4}$ M and lithium or hydrogen chloride at concentrations $>10^{-2}$ M. In Figure 1 a plot of data obtained in a typical run is presented in which a pronounced reduction in slope as the reaction progresses is apparent. The plots for such runs were in general a composite of two lines of different slopes, k_i and k_f, for initial and final phases of reaction, respectively. The change in slope is considered to be reflective of anion exchange resulting in the conversion of the substrate RBr to RCl. Values of k_i represent rate constants for solvolysis of RBr in the medium. Beyond the break point in the plots, the conversion of unreacted substrate to *o*-nitrobenzhydryl chloride (RCl) is considered to be complete; k_f values then represent the solvolysis rate constants for RCl. A rough approximation of the extent of anion exchange occurring in the runs was made by extrapolating the lines pertaining to the later phases of the reaction (slope k_f) to the ordinate axes. The antinaperian logarithms of the intercepts times 100 were recorded as representative of the percentages of anion exchange of initial substrate occurring during solvolysis.

Scheme II

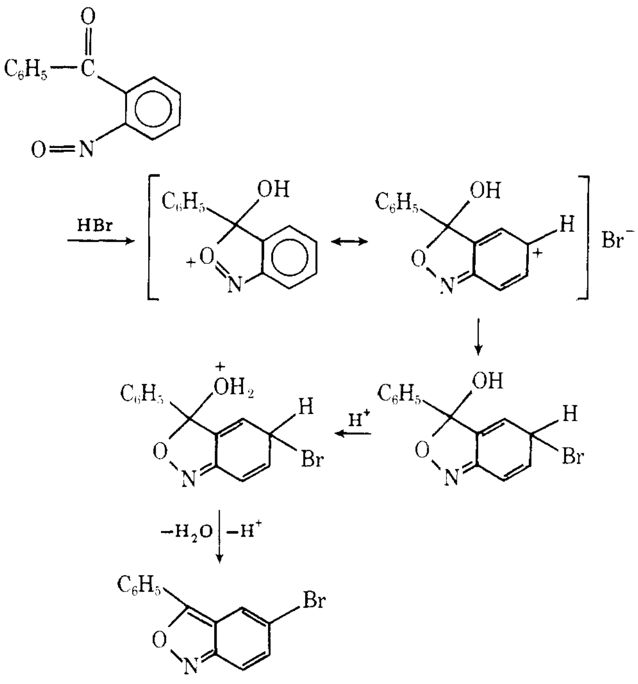


Table II presents a listing of values of k_i, k_f, and the percentages of anion exchange accompanying reaction in 20 and 50% TFE–benzene in the presence of lithium chloride or hydrogen chloride. The rate constants, k_i, are generally similar to those (k_{obsd}) reported in Table I for reactions conducted without added 2,6-lutidine, hydrogen bromide, or salts. The k_f values, relating to that phase of reaction in which *o*-nitrobenzhydryl chloride undergoes solvolysis, show much the same trends with changes in reaction conditions as do k_i values. As is the case for k_i, k_f for reaction in 50% TFE, but not in 20% TFE, increases substantially when 2,6-lutidine is included in the medium.

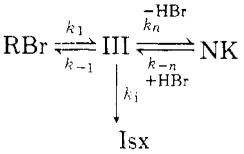
In 20% TFE–benzene the percentage of anion exchange in the reacting halide is of the order of 35% for lithium chloride and 28% for hydrogen chloride. A twofold change in hydrogen chloride concentration did not appreciably alter the percentage of anion exchange. The percentage of exchange drops to about 22 when 2,6-lutidine (200 × 10^{-4} M) is present in the medium. In 50% TFE–benzene the observed exchange is not sensitive to the change in the source of chloride (HCl or LiCl) and is of the order of 55% in the absence of 2,6-lutidine. It drops to low levels (a trace to 10%) when the base is present in the reaction mixture, a noteworthy observation in view of the earlier conclusion that in 50% TFE–benzene 2,6-lutidine reduces the complication of return in *o*-nitrobenzhydryl bromide solvolysis. It is presumed that the observed exchange (RBr → RCl) accompanying solvolysis proceeds by attack of chloride on solvent-separated ion pairs ($R^+||Br^-$) or free cation (R^+) and return of the exchanged intermediates to form *o*-nitrobenzhydryl chloride. In view of Goering's[9] observations concerning the effect of azide on the solvolysis of carbonyl labeled para-substituted *p*-nitrobenzhydryl benzoates it is considered unlikely that intimate ion pairs (R^+Br^-) generated from benzhydryl substrates undergo halide exchange reactions. The relative insensitivity of the observed percentages of halide exchange accompanying solvolysis to changes in LiCl and HCl concentrations, when they are in large excess of substrate concentration, is rather surprising. It may reflect a relatively low degree of dissociation of the inorganic chlorides in the TFE–benzene mixtures.

Table II. Rate Constants for Solvolysis of *o*-Nitrobenzhydryl Bromide in the Presence of HCl and LiCl (TFE–Benzene Mixtures, 25.0 °C)

$10^4[\mathrm{RBr}]_i$, M	$10^4[\mathrm{HCl}]_i$, M	$10^4[\mathrm{LiCl}]_i$, M	10^3k_i,[a] s^{-1}	10^3k_f,[b] s^{-1}	% exchange[c]
		Reactions in 20% TFE			
0.554		147[d]	1.18	0.119	35
0.554		147	1.17	0.123	34
0.554	380		1.11	0.106	27
0.554	760		1.24	0.108	28
0.554		147	1.50[e]	0.133	22
0.554		147	1.38[e]	0.136	21
		Reactions in 50% TFE			
0.554		147	3.93	0.515	55
0.554		367	3.86	0.444	58
0.369	950		2.80	0.377	54
0.369	1800		3.50	0.369	57
0.554		147	12.4[e]	[f]	trace
0.554		367	11.7[e]	1.07	10

[a] Values of k_{obsd} in initial phases of solvolysis. [b] Values of k_{obsd} in final phases of solvolysis. [c] Estimated percentage of the starting amount of RBr which is converted to RCl during the course of solvolysis. [d] At LiCl concentrations as high as 0.05 M the solvent mixture separates into two phases. [e] Medium contained 2,6-lutidine (200 × 10^{-4} M). [f] Insufficient exchange occurred to permit evaluation of k_f.

The Source of Isoxazole as a Reaction Product. Clearly the observation of halide exchange coupled with the effect of 2,6-lutidine on the *o*-nitrobenzhydryl bromide reaction rate calls for modification of the solvolysis mechanism discussed in the introduction. A modified form of that mechanism,

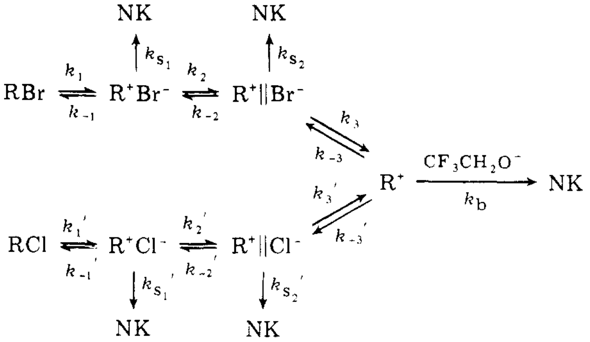


does not, however, readily accomodate experimental observations concerning the rate at which the nitroso ketone (NK) is converted to isoxazole (Isx) in the presence of hydrogen bromide. It has been found that at 25 °C at initial nitroso ketone concentrations of 0.2–0.4 × 10^{-5} M and hydrogen bromide concentrations of 400–600 × 10^{-4} M (cf. the reaction conditions of Table I), conversion to isoxazole is immeasurably fast both in 20 and 50% TFE–benzene. If the conversion of NK to Isx by hydrogen bromide proceeded by way of III, as shown just above, a substantial portion of III should return to *o*-nitrobenzhydryl bromide during that reaction.

To illustrate it can be recalled that roughly 55% of reaction intermediates formed during the solvolysis of *o*-nitrobenzhydryl bromide in 50% TFE containing HCl generate RCl. If this figure is used as an estimate of the extent to which return to starting material occurs during RBr solvolysis in 50% TFE–benzene containing HBr (and assuming that in reactions in the presence of HBr, $k_i \gg k_n$), it follows that $k_{-1}/(k_{-1} + k_i) = 0.55$ and $k_{-1}/k_i = 1.2$. Thus substantial amounts of RBr should build up in the medium during HBr induced conversion of NK to Isx. The results summarized in Table I indicate that conversion of RBr to Isx in the presence of HBr proceeds at an easily measurable rate.

It is concluded, therefore, that in all reactions in TFE–benzene, whether conducted in the presence of 2,6-lutidine, in the absence of base or acid, *or* in the presence of HBr, NK is the immediate product. In the presence of sufficient HBr it converts at a very fast rate to Isx by a process not involving a common intermediate (such as III).

Scheme III



Pseudo-first-order rate constants, k_p, for conversion of nitroso ketone to isoxazole (eq 2) have been determined for the reaction at 25 °C in 50% TFE–benzene solutions of very low hydrogen bromide concentration. Under the condition that $[\mathrm{NK}]_i = 0.222 \times 10^{-4}$ M and $[\mathrm{HBr}]_i = 1.7 \times 10^{-4}$ M, k_p is $3.00 \times 10^{-3}\ s^{-1}$; at $[\mathrm{NK}]_i = 0.443 \times 10^{-4}$ M and $[\mathrm{HBr}]_i = 3.4 \times 10^{-4}$ M, k_p is $13.9 \times 10^{-3}\ s^{-1}$. It appears that the reaction is higher than first order in hydrogen bromide and likely second order. This observation, coupled with the conclusion that intermediates in the reaction are structurally different from those in the solvolysis of *o*-nitrobenzhydryl bromide, is consistent with a reaction path for conversion of nitroso ketone to isoxazole like that shown in Scheme II.

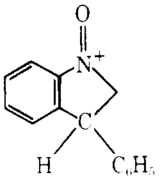
As touched on in earlier discussion the combined results of pertinent rate runs summarized in Tables I and II are viewed as indicative that external return as a complication in *o*-nitrobenzhydryl bromide solvolysis is sharply reduced when 2,6-lutidine is included in the reaction mixtures. This is accounted for in terms of the pathway (subject to later refinement)

$$\mathrm{RBr} \rightleftharpoons \mathrm{Int} \xrightarrow{k_s + k_b[\mathrm{B}]} \mathrm{NK} \xrightarrow[\text{fast}]{\mathrm{HBr}} \mathrm{Isx}$$

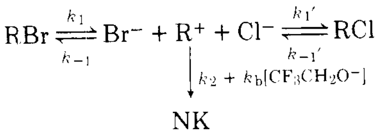
in which the base, B, attacks a reaction intermediate (Int) in competition with the process by which the intermediate returns to starting material. The constant k_s is introduced in the above reaction scheme in recognition of the fact that nitroso ketone is the immediate reaction product even when base (2,6-lutidine and/or $CF_3CH_2O^-$) is not present in the reaction mixture.

Conclusions

In the ensuing discussion of the mechanism of *o*-nitrobenzhydryl bromide solvolysis possible intermediates are identified as intimate or tight ion pairs,[10] R^+Br^-, solvent separated ion pairs, $R^+||Br^-$, and free cations, R^+, where R^+ is



A mechanism (see below) simplistically patterned after that proposed by Hughes, Ingold, and co-workers[11] for S_N1 type solvolyses which are subject to common ion rate depression does not suffice to explain the results of the present study.



$$\begin{tikzcd}
RBr \arrow[r, shift left, "k_1"] & Br^- + R^+ + Cl^- \arrow[l, shift left, "k_{-1}"] \arrow[d, "k_2 + k_b[CF_3CH_2O^-]"] \arrow[r, shift left, "k_1'"] & RCl \arrow[l, shift left, "k_{-1}'"] \\
 & NK &
\end{tikzcd}$$

In particular it does not account for the absence of common ion rate depression during solvolysis in the absence of 2,6-lutidine, even though anion exchange does occur.

An expanded form of this mechanism (Scheme III), which includes intimate and solvent separated ion pairs on the reaction coordinate, adapts reasonably well to the explanation of the gross experimental results. It is proposed that only when 2,6-lutidine is present in the medium is the cation (R^+) the direct precursor of NK, presumably formed by removal of a proton from R^+ by attack of trifluoroethoxide ion. The possibility that $CF_3CH_2O^-$ may also attack ion pairs which are precursors to R^+ cannot be totally excluded on the basis of evidence at hand. In the absence of added base NK formation is shown as occurring through direct collapse of solvent separated and intimate ion pairs with the loss of HBr. All steps leading to the formation of reaction product are shown as reversible with halide exchange occurring through solvent separated ion pairs or free cations. It is presumed that the more dissociated the intermediate, the more readily it will undergo halide exchange.

This mechanism accounts for the reduction in anion exchange by trifluoroethoxide ion in 50% TFE, exchange which is presumed to occur largely by way of the cation (R^+). It is in accord with the observation of mild common ion rate depression in reactions conducted in 50% TFE containing 2,6-lutidine and added LiBr as well as with the lack of evidence for common ion rate depression in reactions conducted in the absence of 2,6-lutidine and in the presence of LiBr or HBr.

As noted earlier anion exchange accompanying solvolysis in 2,6-lutidine free medium containing HCl or LiCl is significantly less for reaction in 20% TFE than in 50% TFE. This is explained on the presumption that the extent of dissociation and lifetime of ionic intermediates decrease, with a corresponding decrease in anion exchange, as the benzene content of the medium increases. In the presence of the base, however, anion exchange occurs much more extensively during solvolysis in 20% TFE than in 50% TFE. Presumably decreasing the trifluoroethanol content of the medium results in a decrease in trifluoroethoxide ion content of the medium with a corresponding reduction in the rate of attack on R^+ by $CF_3CH_2O^-$ relative to the rate of conversion of R^+ to RCl.

Somewhat puzzling is the fact that while k_{obsd} values for reaction in 20% TFE (unlike those for reaction in 50% TFE) are insensitive to the 2,6-lutidine concentration of the medium, the extent of anion exchange accompanying solvolysis is significantly larger in base free medium than when 2,6-lutidine is present. An explanation is proposed which hinges on the assumption that the base (trifluoroethoxide ion) has two effects on rates of individual steps of the overall reaction which counterbalance each other. This is akin to an explanation, given previously,[12] of the observation that the rate of hydrolysis of benzhydryl bromide in 80% aqueous acetone is somewhat depressed when sodium hydroxide is added to the medium; presumably the lyate ion interacts with the solvent and reduces its effectiveness as a proton source in the solvation shell required for ionization of the substrate. The presence of trifluoroethoxide ion is presumed to result in some reduction in the values of k_1, k_2, and k_3 (see the expanded reaction mechanism proposed above), the rate constants for processes in which dissociation of starting material occurs. On the other hand when trifluoroethoxide ion concentration is increased, $k_b[CF_3CH_2O^-]$ increases relative to $k_3[Br^-]$ (and also relative to $k_3[Cl^-]$) and return from the cation $[R^+]$ is reduced. In 50% TFE the reduction in return from the cation when trifluoroethoxide ion is present has far more influence on k_{obsd} than the opposing effect of the base on the rates of ionization of RBr and ion pair intermediates. As the medium is progressively altered from 50 to 20% TFE these opposing effects of the base on k_{obsd} values increasingly offset each other. In 50% TFE the concentrations of trifluoroethoxide ion, as generated from 2,6-lutidine, and of trifluoroethanol itself are high enough that the predominant influence of the base on k_{obsd} is reflected in $k_b[CF_3CH_2O^-]$.

Registry No.—*o*-Nitrobenzhydryl bromide, 1022-05-5; *o*-nitrodiphenylmethane, 5840-40-4; *N*-bromosuccinimide, 128-08-5; *o*-nitrosobenzophenone, 6502-35-8; 5-bromo-3-phenyl-2,1-benzisoxazole, 885-34-7; hydrogen bromide, 10035-10-6; 2,6-lutidine, 108-48-5; 2,2,2-trifluoroethanol, 75-89-8; 2,6-lutidinium bromide, 24994-61-4; lithium chloride, 7447-41-8; hydrogen chloride, 7647-01-0.

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