Mechanisms of Decomposition of (*Z*)-2,2,2-Trifluoro-1-arylethanediazoates in Aqueous Media

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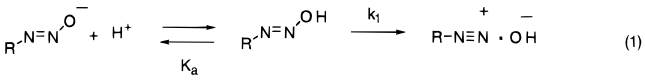
Abstract: A study of the kinetics of decay of three (*Z*)-2,2,2-trifluoro-1-arylethanediazoates at 25 °C in aqueous media, 4% 2-propanol by volume, ionic strength 1 M ($NaClO_4$) in the pH range 4−13, as well as the results of experiments to detect deuterium incorporation into products from solvent is reported. It is concluded in the case of the unsubstituted compound that the buffer-independent reaction involves rate-limiting heterolytic bond fission of the diazoic acid to yield a diazonium ion intermediate, and a similar mechanism is indicated for the other two compounds. General acid catalysis of the decay of the diazoic acids at pH < 7 is observed, and it is concluded that the reaction involves rate-limiting N−O bond cleavage of the diazoic acid that is concerted with protonation of the leaving hydroxide ion by the catalyst.

Introduction

We have been engaged in a detailed quantitative study of the chemistry of decomposition of alkanediazoates. These compounds are claimed to be reactive intermediates in the carcinogenic and cancer chemotherapeutic activity of a wide range of *N*-nitroso compounds.[1] Our studies have obtained evidence in a number of instances that diazonium ions are required as reactive intermediates and are formed by unassisted N−O bond cleavage in the rate-limiting step, as indicated in eq 1.[2−4] Most all of the data concern the reactions of



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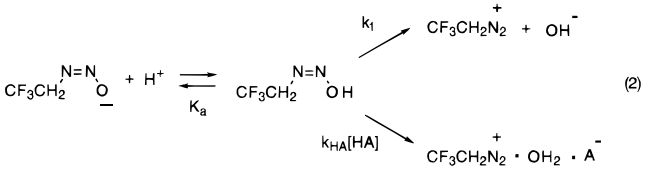
(*E*)-alkanediazoates. However, we recently reported[3] evidence requiring the intermediacy of a diazonium ion in the decay of a single primary (*Z*)-alkanediazoate that was 2600 times more reactive than its *E* isomer, and unique among all compounds studied, the *Z* isomer exhibited a general acid catalyzed mode of decomposition, as indicated in eq 2.



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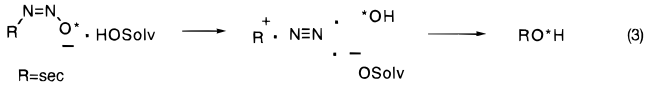
Others have investigated, by other approaches, the decomposition reactions of other alkanediazoates. The observation that an isotopically distinct terminal oxygen in *sec*-(Z)-alkanediazoates is incorporated into the product alcohols has been interpreted in terms of a concerted mechanism that bypasses the diazonium ion intermediate—the "ion-triplet" mechanism of eq 3.[5]



(3)

A similar mechanism starting from the diazoic acid, as in eq 4, has been proposed on the basis of effects of leaving group on product yields in nitrous acid mediated, compared to related, deaminations.[6]

(4)

Because of the substantially greater reactivity of the (*Z*)-diazoates compared to their *E* isomers, it has not been technically feasible for us to study directly the (Z)-diazoates for which these alternative mechanisms have been claimed.

We have recently carried out a study of the mechanism of decay of three (*Z*)-2,2,2-trifluoro-1-arylethanediazoates, and this is the subject of this report. In summary, we find evidence in the form of isotope incorporation from solvent that requires that a diazonium ion intermediate is formed from the decay of the diazoic acid in the case of the unsubstituted compound. General acid catalysis of the reaction occurs in the case of all compounds studied, and additional evidence is presented in support of the mechanism for this reaction being identical with that originally proposed in the case of the general acid catalyzed decay of the (*Z*)-trifluoroethanediazoic acid (eq 2). The absence of evidence that would *require*, in any case, the mechanisms of eqs 3 and 4 is emphasized.

Experimental Section

Materials. All chemicals for synthesis were used as purchased. Chemicals for kinetic and analytical work were purchased as reagent grade or better. Water was glass distilled.

Synthesis of (*Z*)-Diazoates. These were generated from the potassium ethoxide stimulated cleavage of the parent nitrosourethanes

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(1) Lawley, P. D. In *Chemical Carcinogens*; Searle, C. D., Ed.; ACS Monograph 182; American Chemical Society; Washington, DC, 1984. Lijinsky, W. *Chemistry and Biology of N-nitroso Compounds*; Cambridge University Press: Cambridge, U.K., 1992.

(2) Hovinen, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 366. Hovinen, J.; Finneman, J. I.; Satapathy, S. N.; Ho, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 10321.

(3) Ho, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1994**, *116*, 6611.

(4) Finneman, J. I.; Fishbein, J. C. *J. Am. Chem. Soc.* **1995**, *117*, 4228.

(5) Moss, R. A. *Acc. Chem. Res.* **1974**, *7*, 421.

(6) Southam, R. M.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1982**, 597.

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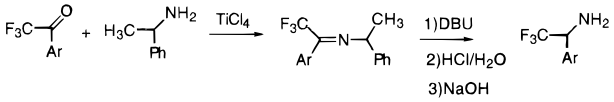
according to the procedure of Moss.[7] The diazoates were contaminated in every case with <10% potassium ethoxide according to ^{1}H-NMR. The solid diazoates were unstable even under high vacuum in a desiccator so that all experiments were performed on the compounds within a few hours of their synthesis. Potassium (*Z*)-2,2,2-trifluoro-1-phenylethanediazoate: ^{1}H-NMR (DMSO-d_6) δ 7.23 (m, 5H), 5.91 (q, 1H). Potassium (*Z*)-2,2,2-trifluoro-1-(4-methylphenyl)ethanediazoate: ^{1}H-NMR (DMSO-d_6) δ 7.13 (d, 2H), 7.00 (d, 2H), 5.90 (q, 1H), 2.22 (s, 3H). Potassium (*Z*)-2,2,2-trifluoro-1-(4-methoxyphenyl)ethanediazoates: ^{1}H-NMR (DMSO-d_6) δ 7.16 (d, 2H), 6.78 (d, 2H), 5.93 (q, 1H), 3.69 (s, 3H).

Ethyl-*N*-nitroso-*N*-((1-aryl)-2,2,2-trifluoroethyl)urethanes. These were synthesized from the parent urethanes using 2 equiv of $NOBF_4$ and 1 equiv of 2,6-di-*tert*-butyl-4-methylpyridine, as described previously.[3] After 30 min to 2 h of reaction, most of the solvent was evaporated off and the reaction was quenched with pentane. The resulting slurry was filtered, and the eluant was collected and combined with pentane washings. Pentane was evaporated by means of an argon stream, and the residue was dissolved in a minimum of 1/1 pentane/dichloromethane and chromatographed on silica using an eluant of identical composition. The first yellow band was collected, and the product was obtained as a yellow oil after the solvent was removed by means of an argon stream. The yields were typically ~60−40%.

Urethanes. These were made from the reaction of 2,2,2-trifluoro-1-arylethanamines with ethyl chloroformate analogous to the method described previously.[3]

2,2,2-Trifluoro-1-arylethanamines. These were generated via the reactions in the scheme below. This method gave adequate yields of the final desired product, whereas the more direct hydrogenolysis of precursor oximes[8] failed to give yields greater than 5% in our hands.



2,2,2-Trifluoro-1-arylethanones. These were synthesized by literature methods.[9] 1-Phenyl-2,2,2-trifluoroacetaldehyde: bp 69−73 °C (43 Torr) (lit.[9] 54−56 °C (12 Torr)); ^{1}H-NMR ($CDCl_3$) δ 8.08 (d, 2H), 7.73 (m, 1H), 7.56 (t, 2H). 1-(4-Methylphenyl)-2,2,2-trifluoroacetaldehyde: bp 65−66 °C (13 Torr) (lit.[10] 69 °C (13 Torr)); ^{1}H-NMR ($CDCl_3$) δ 7.98 (d, 2H), 7.35 (d, 2H), 2.47 (s, 3H). 1-(4-Methoxyphenyl)-2,2,2-trifluoroacetaldehyde: bp 87 °C (7 Torr) (lit.[11] bp 98−99 °C (17 Torr)); ^{1}H-NMR ($CDCl_3$) δ 8.06 (d, 2H), 7.02 (d, 2H), 3.92 (s, 3H).

Imines. These were prepared by methods analogous to literature procedures. In a typical procedure, to 20 g (0.11 mol) of 1-(4-methylphenyl)-2,2,2-trifluoroacetaldehyde and 40 g (0.33 mol) of 1-phenylethylamine in 400 mL of dry toluene was added 55 mL of a 1 M solution of $TiCl_4$ in toluene. Precipitation occurred immediately, and subsequent to 30 min stirring at room temperature, the solution was filtered, the solid discarded, and the filtrate evaporated to a residue that was purified by distillation under reduced pressure. *N*-(1-Phenylethyl)-1-phenyl-2,2,2-trifluoroethanimine: bp 119−120 °C (4 Torr) (lit.[12] bp 99−101 °C (0.5 Torr)); ^{1}H-NMR ($CDCl_3$) δ 7.28 (m, 10H), 4.54 (q, 1H), 1.45 (d, 3H). *N*-(1-Phenylethyl)-1-(4-methylphenyl)-2,2,2-trifluoroethanimine: ^{1}H-NMR ($CDCl_3$) δ 7.30 (m, 9H), 4.57 (q, 1H), 2.41 (s, 3H), 1.44 (d, 3H). *N*-(1-Phenylethyl)-1-(4-methoxyphenyl)-2,2,2-trifluoroethanimine: bp 142 °C (2 Torr), ^{1}H-NMR ($CDCl_3$) δ 7.31 (m, 5H), 7.14 (d, 2H), 6.97 (d, 2H) 4.61 (q, 1H), 3.86 (s, 3H), 1.45 (d, 3H).

Tautomerization and Hydrolysis. The imines were tautomerized by heating, by means of an oil bath, at 120 °C for 24 h using 5 mol % 1,8-diazabicyclo[5.4.0]undec-7-ene as a catalyst.[13] ^{1}H-NMR analysis of the crude reaction indicated that the tautomerization was complete under these conditions in all cases. The product imines were subsequently hydrolyzed in aqueous 2 M HCl, and acetophenone was removed by extracting this reaction mix with diethyl ether. The amines were subsequently isolated by basifying the aqueous acid solution using concentrated aqueous NaOH and extracting with diethyl ether. The final products were purified by distillation under reduced pressure. 1-Phenyl-2,2,2-trifluoroethylamine: bp 84 °C (19 Torr) (lit.[8] bp 35 °C (0.3 Torr)); ^{1}H-NMR ($CDCl_3$) δ 7.40 (m, 5H), 4.38 (q, 1H), 1.76 (b, 2H). 1-(4-Methylphenyl)-2,2,2-trifluoroethylamine: bp 92−93 °C (18 Torr); ^{1}H-NMR ($CDCl_3$) δ 7.32 (d, 2H), 7.19 (d, 2H), 4.36 (q, 1H), 2.36 (s, 3H), 1.73 (b, 2H). 1-(4-Methoxyphenyl)-2,2,2-trifluoroethylamine: bp 78 80 °C (3 Torr); ^{1}H-NMR ($CDCl_3$) δ 7.36 (d, 2H), 6.91 (d, 2H), 4.36 (q, 1H), 3.82 (s, 3H), 1.73 (b, 2H).

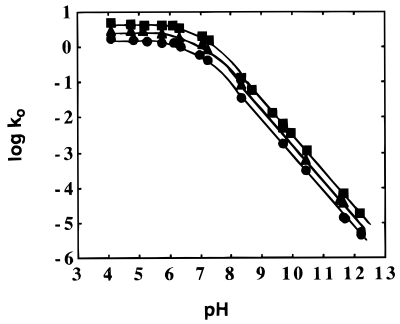


Figure 1. Plot of log k_o, the buffer-independent rate constant for decay of (*Z*)-2,2,2-trifluoro-1-arylethanediazoates at 25 °C in aqueous media, 4% 2-propanol by volume, ionic strength 1 M ($NaClO_4$), against pH. Points are defined as follows: ●, unsubstituted; ▲, 4-CH_3; ■, 4-CH_3O.

Deuterium Incorporation into Product Alcohols. These experiments were carried out by decomposition of the diazoates (~0.005 M), either with conventional or stopped-flow conditions as appropriate (5 mL reaction volumes). Products were isolated by extraction with 2 × 10 mL ether, and the ether phase was treated with 1 × 10 mL of 0.2 M $DClO_4$ in D_2O. The ether phase was then washed with 3 × 10 mL of NaCl-saturated H_2O and concentrated, and the isotopic analysis of the product alcohols was carried out by GC−MS.

Product analysis by ^{1}H-NMR was carried out subsequent to the decay, upon addition of 1 equiv of $DClO_4$, of (*Z*)-2,2,2-trifluoro-1-(4-methylphenyl)ethanediazoate in 0.05 M NaOD in D_2O/20% CD_3CN by volume and containing *tert*-butyl methyl ether as an internal standard.

Kinetics. The instrumentation and general procedures followed were the same as those previously described.[4]

Results

The decay of (*Z*)-2,2,2-trifluoro-1-(4-methylphenyl)ethanediazoate in 0.05 M NaOD in predominantly aqueous media (20% CD_3CN by volume) gave a 95% yield of 2,2,2-trifluoro-1-(4-methylphenyl)ethanol.

The decay of the (*Z*)-2,2,2-trifluoro-1-arylethanediazoates in aqueous media, 4% 2-propanol by volume, ionic strength 1 M ($NaClO_4$) at 25 °C, exhibited good first-order behavior for more than four half-lives of reaction. Values of the rate constants, k_o, for the buffer-independent rate constant for decomposition were determined as the intercepts of plots of k_{obsd} against buffer concentration. The standard error in the values was typically less than ±5%. Plots of log k_o as a function of pH are presented in Figure 1.

Activation parameters for the decay of (*Z*)-2,2,2-trifluoro-1-(4-methylphenyl)ethanediazoate were determined, at pH = 5.51 (pH measured at 25 °C), to be $\Delta H^{\#} = 14.9$ (±0.1) kcal mol^{-1} and $\Delta S^{\#} = -6.9$ (±0.3) cal deg^{-1} mol^{-1}. These experiments were carried out between 5 and 50 °C (13 temperatures) in 0.05 M morpholinoethanesulfonate buffer (20% acid) in which it was separately determined that the contribution to the reaction rate constant due to buffer catalysis was less than 5% of k_{obsd} at 25 and 50 °C.

(7) Moss, R. A. *J. Org. Chem.* **1966**, *31*, 1082.
(8) Wang, Y.; Mosher, H. S. *Tetrahedron Lett.* **1991**, *32*, 987.
(9) Diderich, G. *Helv. Chim. Acta* **1972**, *55*, 2103.
(10) Stewart, R.; Van der Linden, R. *Can. J. Chem.* **1960**, *38*, 399.
(11) Hatanaka, Y.; Hashimoto, M.; Kurihara, H.; Nakayama, H.; Kanaoka, Y. *J. Org. Chem.* **1994**, *59*, 383.
(12) Pirkle, W. H.; Hauske, J. R. *J. Org. Chem.* **1977**, *42*, 2436.
(13) Kukar, V. P.; Soloshonok, V. A.; Galushko, S. V.; Rozhenko, A. B. *Dokl. Akad. Nauk. SSSR* **1990**, *310*, 886.

Table 1. Summary of Rate and Equilibrium Constants for the Uncatalyzed and General Acid Catalyzed Decomposition of (*Z*)-2,2,2-Trifluoro-1-arylethanediazoates in Aqueous Solutions, 25 °C, Ionic Strength 1 M ($NaClO_4$), 4% 2-Propanol by Volume

		substituent	
constant	unsubstituted	4-CH_3	4-CH_3O
k_1[a]	1.64	2.8	4.7
pK_a	6.71	6.85	6.85
k_{CNAc}[b,c]	193	350	380
k_{MeOAc}[b,d]	108	171	220
k_{Ac}[b,e]	32	58	72
k_{Cac}[b,f]	12	16.5	19
k_{NH_3OH}[b,g]	7.1		

[a] Units of s^{-1}. [b] Units of $M^{-1}\ s^{-1}$. [c] Rate constant for catalysis by cyanoacetic acid. [d] Rate constant for catalysis by methoxyacetic acid. [e] Rate constant for catalysis by acetic acid. [f] Rate constant for catalysis by cacodylic acid. [g] Rate constant for catalysis by hydroxylammonium ion.

Plots of k_{obsd} against buffer concentration indicated catalysis by buffers in the lower range of pH studied. Values of k_{obsd} that were greater, by between 50% and 400%, than the extrapolated intercept, k_o, were measured at the highest buffer concentrations of 0.2 M (total buffer). Such plots were linear and the slopes were taken as values of k_2, the apparent second-order rate constant for catalysis. The active form of the buffer was the acid, as indicated by linear plots of the values of k_2 against "percent buffer acid" which exhibited non-zero values at "100% acid", k_{HA}, and values at "0% acid" that were not different from zero within the limits of the standard errors. The values of k_{HA}, the second-order rate constants for apparent general acid catalysis by cyanoacetic, methoxyacetic, acetic, and cacodylic acids and hydroxylammonium ion are listed in Table 1 as k_{CNAc}, k_{MeOAc}, k_{Ac}, k_{Cac}, and k_{NH_3OH}, respectively.

There was no detectable stimulation of the decay of diazoates by buffers with pK_a values greater than 7. In the cases of amines such as ethylenediamine free base, morpholine, and ethanolamine, there was a reproducible decrease in k_{obsd} with increasing buffer concentration. At 0.2 M buffer, typically the highest buffer concentration used, the value of k_{obsd} was 5−10% smaller than the value of k_o obtained by extrapolation to the *y* intercept of the plot of k_{obsd} against buffer concentration.

Incorporation of deuterium into the α-carbon atom of the product alcohols was detected by GC−MS analysis after washing from the products all exchangeable deuterium. The results are summarized in Table 2. Control runs indicate that the $(M + 1)^+/M^+$ ratio of signals in authentic alcohol that was subjected to the same work-up conditions is not appreciably different than predicted on the basis of "natural abundance". In all cases the experimental runs indicate deuterium incorporation from solvent into the α-carbon because the $(M + 1)^+/M^+$ mass ratio is different from the controls outside the reported standard deviations. The percent of the product containing an atom of deuterium varies from a low of 3% for the runs in acetic acid buffer, to between 12 and 50% for the reactions in more basic media.

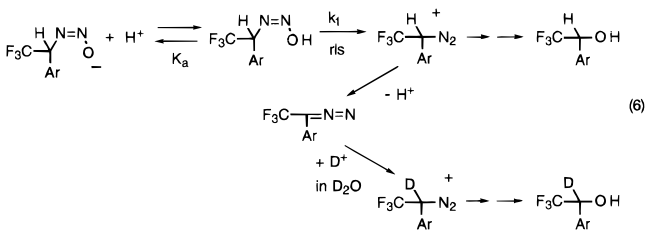
Discussion

Mechanism of the Buffer-Independent Reaction. The decreasing value of log k_o with increasing pH illustrated in Figure 1 at pH > 7 rules out the pH-independent "ion-triplet" mechanism of eq 3 for the decay of the (*Z*)-2,2,2-trifluoro-1-arylethanediazoates. The biphasic dependence on pH in the range between pH 4 and 13 is qualitatively similar to what has been observed in the case of all other (*E*)- and (*Z*)-alkanediazoates studied to date[2−4,14] and is consistent with the rate-limiting decay of the diazoic acid. The rate law for this mechanism is as written in eq 5, and good fits to the

$$k_o = k_1/(1 + K_a/[H+]) \qquad (5)$$

experimental data in Figure 1 are indicated by the solid lines that were generated using values for the parameters k_1 and pK_a that are summarized in Table 1.

The observation that deuterium is incorporated into the α-carbon of the product alcohol in the decay of (*Z*)-2,2,2-trifluoro-1-phenylethanediazoate (Table 2) requires the intermediacy of a diazonium ion, as in eq 6, that can undergo hydron



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exchange that is competitive with hydrolysis. A mechanism exclusively involving direct formation of the carbocation from the diazoic acid, as in eq 4, is ruled out because it does not provide the opportunity for the observed deuterium incorporation into the product alcohol. The fact that deuterium incorporation is not quantitative is inconsistent with decomposition of the diazoic acid to diazoalkane by an elimination mechanism that has been proposed elsewhere.[15]

The possibility of a mechanism involving some nucleophilic assistance to decay of the diazoic acid is ruled out by the failure of nucleophilic amine buffers to stimulate the decay of the diazoates.[16]

A common mechanism for all three of the 2,2,2-trifluoro-1-arylethanediazoates, involving rate-limiting N−O bond cleavage to yield the diazonium ion (eq 6), is suggested by the good correlation of log k_1 against σ (not shown), $\log k_1 = -1.64\sigma + 0.22$ ($r^2 = 0.9998$). The negative value of ρ is indicative of

Table 2. Deuterium Isotope Incorporation into 2,2,2-Trifluoro-1-(phenylethyl)alcohol from Solvent in the Decay of (*Z*)-2,2,2-Trifluoro-1-phenylethanediazoate in D_2O Containing 4% 2-Propanol-(OD) by Volume

	signal at mass = 177/signal at mass = 176[a]	
conditions	control[b] (σ)	expt (σ)
1.0 M NaOD[c]	0.119[d] (0.002)	1.09[e] (0.01)
0.10 M NaOD[c]	0.109[f] 0.001)	0.194 (0.006)
1.0 M 1,3-propanediamine buffer, 95% free base[c,g]	0.109[f] (0.001)	0.251 (0.005)
0.60 M acetate buffer, 75% acid form[h,i]	0.109[f] (0.001)	0.1355 (0.0003)

[a] Mean and standard deviation of quadruplicate analyses of each sample. [b] 2,2,2-Trifluoro-1-(phenylethyl)alcohol subjected to reaction conditions noted. [c] Reaction run at 22 ± 2 °C. [d] Signal at mass = 178 was 6.23% of that at mass = 177. [e] Signal at mass = 178 was 9.36% of that at mass = 177. [f] Control run at 0.10 M NaOD; analyzed on the same day for the last three experiments listed in the Table. [g] Observed value of pD = 11.90. Reaction worked up after 7 days. [h] Reaction was carried out by mixing in the stopped-flow and collecting and working up the eluant from succesive reactions. Ionic strength kept constant at 1 M with $NaClO_4$. Reaction temperature was 25 °C. [i] Under these conditions 65% of the reaction occurs via the acetic acid catalyzed pathway.

(14) Finneman, J. I.; Ho, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 3016.

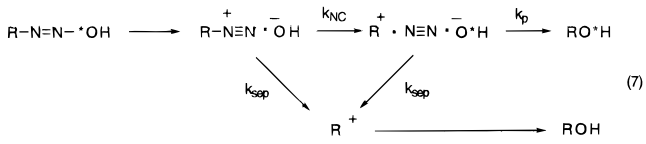
(15) Hart, H.; Brewbaker, J. L. *J. Am. Chem. Soc.* **1969**, *91*, 716. Fiering, A. E.; Ciabattoni, J. *J. Org. Chem.* **1972**, *37*, 3784.

(16) See discussion of this possibility and refs in ref 2.

substantial positive charge formation in the rate-limiting step. As noted previously in the case of the decay of (*E*)-arylmethanediazoic acids,[4] the magnitude of ρ in the present case is not inconsistent with what might be expected for the rate-limiting formation of diazonium ions. Values of ρ of between -1.2 and -2.2 have also recently been reported for general acid catalysis in the hydrolysis of aryldiazomethanes.[17]

Absence of Evidence Requiring Alternative Mechanisms. The controversy between the stepwise, eqs 1, 2, and 6, and concerted, eqs 3 and 4, mechanisms of decomposition is one of long-standing.[14] Our series of investigations has detailed a number of specific instances in which it is possible to obtain evidence that *requires* the intermediacy of diazonium ions.[2−4] More than this, we have been able to *rule out* the "ion-triplet" mechanism of eq 3, on the basis of kinetic results, in the case of every compound we have studied. It has not been possible to study the kinetics of decay, and thus provide a direct test of the "ion-triplet" mechanism, of the (*Z*)-diazoates for which the "ion-triplet" mechanism was originally proposed.

Despite this, it needs to be recognized that, in contrast to evidence that has been obtained that *requires* the intermediacy of diazonium ions in certain specific cases of (*E*)- and (*Z*)-diazoic acids, *none of the evidence so far adduced by other investigations* ***requires*** *decomposition by the concerted mechanisms of eq 3 or 4*. The experimental results that were rationalized on the basis of the "ion-triplet" mechanism involved oxygen isotope incorporation from the diazoate oxygen, in competition with solvent-derived oxygen, into the product of secondary (*Z*)-diazoate decomposition (eq 3).[5,18] In a recent comprehensive review these same results have been rationalized by the alternative concerted mechanism (eq 4).[19] The notion that there is an *established* mechanistic dichotomy is not supported by experimental fact. All experimental results interpreted in terms of the concerted mechansisms of eqs 3 and 4 are equally well accomodated by the diazonium ion mechanism in which the short-lived diazonium ion decomposes to a reactive carbocation before diffusional separation from the oxyanion leaving group as in eq 7, where k_{NC}, $k_p \geq k_{sep}$.[20]



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However, objectively, it is not possible to *rule out* the mechanisms of eq 3 and 4 for some or all of the substrates for which they are invoked; but, to reiterate, no evidence *requires* them and they are ruled out in some other instances.

Beyond this, it is an *ad hominem* presumption that there "ought" to be a concerted mechanism in the case of the more reactive *Z* compounds, while the analogous *E* compounds might decompose via diazonium ions.[19] There is no experimental evidence nor clearly enunciated logic upon which to base such speculation. Known differences in reactivity between *E* and *Z* isomers may be ascribable to inherent instability, relative to the *E* form, of the *Z* form or, additionally, to the antiperiplanar arrangement of the lone pair of electrons on nitrogen and the N−O bond of the diazoic acid in the *Z* form.[21] Recourse to a difference in mechanism is not required by the differences in stabilities of the *E* and *Z* forms.

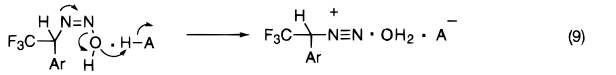
Application of the tautological notion of Jencks[22]—that the concerted mechanisms will be enforced when the hypothetical diazonium ion that is *initially formed*[23] from N−O bond cleavage is too unstable to exist for a single molecular vibration—presages the existence of mechanisms that bypass the diazonium ion intermediate. We have so far obtained no evidence that is suggestive of concerted mechanisms in which N−O and C−N bond cleavages, yielding the carbocation directly, are simultaneous, so-called "coupled-concerted" [22] mechanisms. The evidence[4,14] in fact is inconsistent with such a mechanism. However, evidence against an "uncoupled-concerted" mechanism[22]—in which the reaction coordinate is dominated by N−O bond cleavage while carbocation character due to C−N bond cleavage is not established—is more difficult to obtain. And so, in cases where there is not direct experimental evidence of diazonium ion involvement, there is a possibility of the incursion of uncoupled concerted mechanisms—but certainly no evidence that *requires* it.

Mechanism of General Acid Catalysis. In the case of all three (*Z*)-2,2,2-trifluoro-1-arylethanediazoic acids studied here, the decomposition is catalyzed by buffer acids. The general rate law must be as in eq 8. General acid catalysis was

$$k_{obsd} = (k_1 + k_{HA}[HA])/(1 + K_a/[H^+]) \qquad (8)$$

previously observed in the case of the single other (*Z*)-alkanediazoaic acid studied, and catalysis has not been observed in the case of any (*E*)-alkanediazoic acid studied.[3]

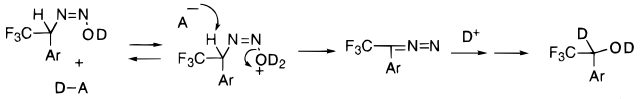
None of the data are inconsistent with the mechanism previously deduced for the general acid catalyzed decay of (*Z*)-trifluoroethanediazoic acid[3] that is illustrated in eq 9. The values



(9)

of Bronsted α for this reaction for the present substrates are $\alpha = 0.31 \pm 0.03$, 0.33 ± 0.02, and 0.33 ± 0.04 for the unsubstituted, 4-CH_3, and 4-CH_3O compounds, respectively. These values are slightly smaller than what was previously observed, $\alpha = 0.41$, for catalysis of the decay of the (*Z*)-trifluoroethanediazoic acid by carboxylic acids.

The absence of complete deuterium incorporation into products from solvent in the general acid catalyzed reaction rules out a mechanism involving specific acid catalyzed−general base catalyzed elimination as written, for the solvent D_2O, in eq 10.



(10)

Such a mechanism requires that the product alcohol formed from general acid catalysis contain 100% deuterium in the α-carbon atom when the decomposition is carried out in D_2O (eq 10). The data in Table 2 include an experiment in 0.6 M acetic acid buffer in which it has been independently shown that 65% of the observed reaction occurs by the general acid catalyzed pathway. Under such conditions, the product alcohol should contain a minimum of 65% D at the α-carbon if the mechanism of eq 10 is operative. Only 3% D is detected in the product. This is consistent with the high lability of the diazonium ion relative to the rate of its proton abstraction in this media, in

(17) Finneman, J. I.; Fishbein, J. C. *J. Org. Chem.* **1994**, *59*, 6251.
(18) Gold, B.; Deshpande, A.; Linder, W.; Hines, L. *J. Am. Chem. Soc.* **1984**, *106*, 6401.
(19) Zollinger, H. *Diazo Chemistry II*; VCH Publishers: New York, 1995.
(20) This can be seen in the detailed analysis of benzyl group transfer in the decay of (E)-arylmethanediazoates and aryldiazomethanes (ref 4).
(21) This has been discussed in more detail with relevent references in ref 3.
(22) Jencks, W. P. *Chem. Soc. Rev.* **1981**, 345.
(23) Our caveat and emphasis.

contrast to the more competitive proton exchange in more basic media (vide supra). Similar evidence could not be obtained in the general acid catalyzed decay of (*Z*)-trifluoroethanediazoic acid because the diazonium ion formed in that case is in hydronic equilibrium with the diazoalkane relative to its hydrolytic decay. In the case of (*Z*)-trifluoroethanediazoic acid the mechanism of eq 10 was ruled out on the basis of solvent deuterium isotope effects.[3]

The relatively weak catalytic activity of the hydroxylammonium ion compared to oxygen acids of similar acidity in the decay of (*Z*)-2,2,2-trifluoro-1-phenylethanediazoic acid rules out a mechanism involving equilibrium protonation of the diazoic acid followed by nucleophilic displacement by the conjugate base of the catalyst. A mechanism of this type has been proposed in the case of the oxygen acid-stimulated decomposition of certain alkyltriazenes.[24] In the present case, the point for hydroxylammonium ion lies 0.5 log units below the line established by oxygen acids on the statistically corrected Bronsted plot for catalysis. Yet hydroxylamine free base is, by any measure of intrinisic nucleophilicity, a superior nucleophile compared to the anions of cacodylic or acetic acid. Thus, if the rate-limiting step involves nucleophilic attack, hydroxylamine would be the most active "catalyst". The weaker activity of the hydroxylammonium ion compared to the oxygen acids is likely due to a favorable electrostatic interaction in the transition state for the reaction of oxygen acids.[3]

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Supporting Information Available: Tables giving experimental conditions and rate constants the three (*Z*)-ethanediazoates (11 pages). See any current masthead page for ordering and Internet access instructions.

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(24) Smith, R. H.; Denlinger, C. L.; Kupper, R.; Mehl, A. F.; Michejda, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 3726.