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Rate-Limiting Formation of Diazonium Ions in the Aqueous Decomposition of Primary Alkanediazoates‡

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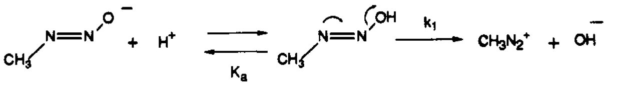
Abstract: Rate constants, k_0, for the buffer-independent decomposition of four primary (*E*)-alkanediazoates and one primary (*Z*)-alkanediazoate in aqueous media at 25 °C, ionic strength 1 M ($NaClO_4$) are reported. Between pH 4 and 12 the plot of log k_0 against pH is biphasic with a hydrogen ion-dependent reaction at the high-pH end changing to a pH-independent region at lower pH. The change in absorbance at 235 nm of the relatively stable (*E*)-trifluoroethanediazoate as a function of pH gives a good fit to a simple titration curve for a monofunctional acid with $pK_a = 7.00 \pm 0.04$ that is in good agreement with the kinetic pK_a determined from the pH–rate profile between pH 4 and 12. The plot of log k_1, the pH-independent rate constant, against σ^* for the primary (*E*)-alkanediazoates, and (*E*)-methane- and (*E*)-2-butanediazoates previously reported, yields a common line with a slope $\rho^* = -4.4$. Of the 1-butanol formed from the decomposition of (*E*)-1-butanediazoate in D_2O at $pH_{obs} = 10.50$, 6% contains deuterium, while, of the 1-butanol formed in the presence of 1 M NaOD in D_2O, 25% contains deuterium. A total of 96% of the iodotrifluoroethane formed upon decomposition of (*E*)-trifluoroethanediazoate in a D_2O solution that is 1 M in NaI contains at least a single deuterium atom. These data combined with small negative values of $\Delta S\#$, normal solvent deuterium isotope effects, and the decreases in k_1 of between 500- and 1000-fold on change of solvent to ethanol are consistent with a mechanism that involves the rate-limiting unassisted heterolytic bond fission of the diazoic acid to yield the diazonium ion. The decomposition of [^{16}O]-(*E*)-1-butanediazoate in water containing 47 ± 2% ^{18}O yields 1-butanol of which 49 ± 2% contains ^{18}O. This observation, in combination with the observed pH-dependent deuterium incorporation into 1-butanol during decomposition of (*E*)-1-butanediazoate, above, indicates that the 1-butanediazonium ion is a diffusionally equilibrated intermediate. The rate constant for the pH-independent decomposition of the (*Z*)-trifluoroethanediazoate is 2600 times greater than that for the corresponding (*E*) isomer. The decomposition of the (*Z*)-trifluoroethanediazoate, but not its (*E*) isomer, is catalyzed by buffer acids, and the catalysis by carboxylic acids is characterized by a Bronsted plot with a slope $\alpha = 0.41$. Catalysis by methoxylammonium ion is comparatively weak, the rate constant falling a log unit below the aforementioned Bronsted line. The solvent deuterium isotope effect for formic acid catalysis is $k_{HA}/k_{DA} = 3.1 \pm 0.2$. It is concluded that the mechanism for general acid catalysis of the decomposition of the (*Z*)-diazoic acid entails proton transfer to oxygen that is concerted with N-O bond heterolysis to yield the diazonium ion.

Introduction

Alkanediazoates are purported to be reactive intermediates that mediate the powerful DNA-alkylating activities of many compounds that contain the *N*-alkyl-*N*-nitroso functionality and are mutagenic, carcinogenic, and cancer chemotherapeutic agents.[1,2] A fundamental understanding of the aqueous chemistry of these reactive intermediates is therefore desirable. We recently reported the first quantitative analysis of the decomposition chemistry of an alkanediazoate—(*E*)-methanediazoate.[3,4] It was concluded that the mechanism involves the unassisted heterolytic N–O bond fission to yield the diazonium ion as in eq 1. A similar conclusion was reached about the mechanism of decomposition of (*E*)-2-butanediazoate.[5]



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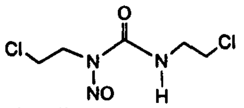
It is reasonable to presume that the same mechanism will be obtained for the simplest primary (*E*)-alkanediazoates. Some indirect investigations in which diazoic acids are reasonably posited as intermediates are not inconsistent with the mechanism of eq 1. The nitrous acid-catalyzed deamination of 1-butylamine in acetic acid gives yields of esters and alkenes that are identical to those derived from the decomposition of *N*-nitroso-*N*-butylacetamide and N^1-butyl-N^3-*p*-nitrophenyltriazene.[6] These results require a common diazonium ion intermediate. It was recently shown in a particularly elegant analysis that the nitrous acid-catalyzed deamination of a chiral 1-deuterio-1-butylamine in water occurs with 98% inversion, and the simplest interpretation of this result is that the diazonium ion intermediate, presumably formed from the diazoic acid, undergoes S_N2 substitution.[7] Whether these reactions involve exclusively the (*E*) or (*Z*) forms of the diazoic acids or a mixture of the two is uncertain.

The effect of substituents on the lifetimes and mechanism of decomposition of alkanediazoates has not been elucidated. Understanding these effects is particularly germane, as the alkanediazoates derived from the cancer chemotherapeutic agent bis(chloroethyl)nitrosourea, below, contains the chloroethane



moiety. Similarly, other (haloethyl)nitrosoureas that act in part

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‡ This paper is dedicated to the memory of Prof. Elena Peña, whose untimely passing we deeply regret.

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[1] Lawley, P. D. In *Chemical Carcinogens*; Searle, C. D.; Ed.; ACS Monograph 182; American Chemical Society: Washington, D.C., 1984.

[2] Lijinsky, W. *Chemistry and Biology of N-nitroso Compounds*; Cambridge University Press: Cambridge, U.K., 1992.

[3] Hovinen, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 366.

[4] Hovinen, J.; Finneman, J. I.; Satapathy, S. N.; Ho, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 10321.

[5] Finneman, J. I.; Ho, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1993**, *115*, 3016.

[6] Maskill, H.; Southam, R. M.; Whiting, M. C. *J. Chem. Soc., Chem. Commun.* **1965**, 496.

[7] Brosch, D.; Kirmse, W. *J. Org. Chem.* **1991**, *56*, 907.

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via diazoate intermediates have cancer chemotherapeutic activity[8] and the (*E*)-chloroethanediazoate has recently been shown to have antileukemic activity in vivo.[9] The possibility that the diazoic acid forms of these agents decompose by S_N2 substitution at the internal methylene adjacent to nitrogen has been suggested.[9] There is precedent for a change in mechanism as a function of substituent in the case of more stable (*E*)-arenediazoates in which compounds with electron-donating groups decompose according to the mechanism of eq 1 whereas for those with electron-withdrawing groups the rate-limiting step involves isomerization to the more reactive (*Z*) forms.[10]

The nature of possible differences in aqueous chemistry of isomeric (*E*)- and (*Z*)-diazoates has not been quantitatively addressed. It has been known for some time that the (*E*) forms are qualitatively more stable than the corresponding (*Z*) forms,[11,12] but the magnitude of the difference has yet to be established. Further it is not known whether there are differences in the mechanisms by which (*E*) and (*Z*) forms decompose and there is some evidence that might suggest that differences do exist. A mechanism involving the intermediacy of as short-lived primary carbocation was suggested in the basic hydrolysis of (*Z*)-1-propanediazoate[13] whereas the data summarized above[7] would suggest a primary diazonium ion that undergoes S_N2 substitution. Similarly, the mechanism of eq 2 was proposed to rationalize the

(2)

data from stereochemical and isotope-scrambling studies of the decomposition of secondary (*Z*)-alkanediazoates[14] while, as above, the mechanism of eq 1 was deduced in the case of (*E*)-2-butanediazoate. It has recently been reported that simple (*E*)-alkanediazoates are more mutagenic in bacteria[15] and more cytotoxic and mutagenic in mammalian cells than the corresponding (*Z*) compounds.[16] The (*E*)- and (*Z*)-(2′-chloroethyl)-thioethanediazoates differ in their DNA cross-linking activities,[9] and while the (*E*)-chloroethanediazoate is an antileukemic in vivo, the (*Z*) isomer is inactive.[9] The differences in reactivity and mechanism of decomposition of the isomers that may account for these observations are not understood.

We report here the first study of the effects of structure on the rates and mechanisms by which primary alkanediazoates decompose. It is concluded that even primary (*E*)-alkanediazoates with strong electron-withdrawing groups decompose with rate-limiting unassisted heterolytic bond fission to yield diazonium ions that in all cases are free intermediates. The first kinetic study of a pair of isomeric (*E*)- and (*Z*)-alkanediazoates is also summarized, and the quantitative and qualitative differences in reaction chemistry are determined.

Experimental Section

Materials. In general chemicals were purchased as the best available commercial grade and organic chemicals were further purified by distillation or recrystallization. Trifluoroethylhydrazine was purchased from Aldrich Chemical company as an aqueous solution, and the hydrazine was purified by extraction into ether which was then dried, and the hydrazine was subsequently purified by distillation. The compound (2-cyanoethyl)hydrazine was synthesized from the addition of hydrazine to acrylonitrile according to the procedure of Suminov.[17] Other hydrazines were synthesized by the reaction of a 10-fold excess of hydrazine with the required alkyl halide in refluxing ethanol. After removal of most of the solvent by rotary evaporation, the biphasic mixture was twice extracted with ether, the ether phases were combined and dried over $MgSO_4$, and the hydrazines were purified by distillation.

(*E*)-Alkanediazoates. These compounds were synthesized by the reaction of the appropriate hydrazine with 2 equiv of butyl nitrite and 1 equiv of sodium ethoxide in anhydrous ether after the original method of Thiele.[11] Subsequent to extensive washing with ether, the white precipitates were used without futher purification. Proton NMR in DMSO-d_6 indicated only signals (indicated below) expected for the diazoates. In all cases, ultraviolet spectra in ethanol exhibited the characteristic λ_{max} between 220 and 225 nm which disappeared, with resulting baseline absorbance from 210 to 300 nm, instantly upon the addition to the cuvette of a drop of aqueous acid. (*E*)-*n*-Butanediazoate. ^{1}H-NMR (DMSO-d_6) (ppm): 0.86 (3H, t), 1.36 (4H, m), 3.38 (2H, t). Anal. Obsd: C, 38.80; H, 7.22; N, 22.53. Calcd: C, 38.71; H, 7.31; N, 22.57. (*E*)-Methoxyethanediazoate. ^{1}H-NMR (DMSO-d_6) (ppm): 3.22 (3H, s), 3.38 (2H, t), 3.58 (2H, t). (*E*)-Cyanoethanediazoate. ^{1}H-NMR (DMSO-d_6) (ppm): 2.54 (2H, t), 3.62 (2H, t). (*E*)-Trifluoroethanediazoate. ^{1}H-NMR (DMSO-d_6) (ppm): 4.10 (2H, q). Anal. Obsd: C, 15.59; H, 1.44; N, 16.74. Calcd: C, 15.98; H, 1.34; N, 18.7.

syn-Trifluoroethanediazoate. This compound was synthesized by the method of Moss,[18] involving the potassium ethoxide-stimulated cleavage of *N*-nitroso-*N*-(trifluoroethyl)urethane. Subsequent to washing the precipitate with ether and drying under vacuum, the proton NMR indicated the presence of 6% potassium ethoxide on the basis of the integrations of the methylene resonances of the two compounds. (*Z*)-Trifluoroethanediazoate. ^{1}H-NMR (DMSO-d_6) (ppm): 3.70 (2H, q). Anal. for the mixture containing 6% potassium ethoxide. Obsd: C, 15.18; H, 1.32; N, 15.64. Calcd: C, 14.90; H, 1.36; N, 16.33.

The *N*-nitroso-*N*-(trifluoroethyl)urethane was synthesized by reaction of 5 g of *N*-(trifluoroethyl)urethane with 2 equiv of $NOBF_4$ and 1.0 equiv of 2,6-di-*tert*-butyl-4-methylpyridine in methylene chloride as described previously for the synthesis of *N*,*N*″-dimethyl-*N*′-nitro-*N*-nitrosoguanidine.[19] The reaction mixture was concentrated to a yellow slush which was then extracted with ~250 mL of pentane. The pentane containing the nitrosourethane was then concentrated, and the viscous yellow liquid was passed through a silica gel column that was eluted with 50% CH_2Cl_2/50% pentane. The leading yellow fraction was concentrated to a viscous yellow liquid which, exhibiting only the expected resonances in ^{1}H-NMR, was immediately used in the subsequent alkaline cleavage to give the diazoate. ^{1}H-NMR ($CDCl_3$) (ppm): 1.48 (3H, t), 4.38 (2H, q), 4.60 (2H, q).

The *N*-(trifluoroethyl)urethane was synthesized by the dropwise addition of 7 g of ethyl chloroformate to a stirred solution of 100 mL of ethyl ether containing 2.2 equiv of trifluoroethylamine. Considerable white precipitate formed as the ethyl chloroformate was introduced, and 10 min after the last drop of ethyl chloroformate was added, the precipitate was separated from the liquid by filtration and washed with ethyl ether. The solvent was stripped from combined filtrate and washings leaving the white solid product that was twice recrystallized in 10% CH_2Cl_2/90% pentane. ^{1}H-NMR ($CDCl_3$) 1.25 (3H, t), 4.18 (2H, q), 4.98 (1H, br), 3.80 (2H, m).

Trifluorodiazoethane. The synthesis was carried out according to a modification of the method of Gilman.[20] The product was collected by passing argon through the reaction solution containing trifluoroethylamine hydrochloride and sodium nitrite in the water at 0 °C, allowing gas and trifluorodiazoethane to exit through a trap containing acetonitrile maintained at −40 °C.

Kinetics. The kinetics of diazoate decay were typically monitored at 225 or 230 nm using either a Milton Roy 3000 diode array spectrophotometer or an Applied Photophysics DX.17MV stopped-flow spectrometer. The cuvettes, or observation cell and syringes in the case of the stopped-

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[8] Wheeler, G. P. *A Review of Studies of the Mechanisms of Action of Nitrosoureas*; ACS Symposium Series *30*; American Chemical Society: Washington, D.C., 1978.

[9] (a) Lown, J. W.; Koganty, R. R.; Bhat, U. G.; Sapse, A.-M.; Allen, E. B. *Drugs Exp. Clin. Res.* **1986**, *XII*, 463. (b) Sapse, A.-M.; Allen, E. B.; Lown, J. W. *J. Am. Chem. Soc.* **1988**, 110, 5671. (c) Lown, J. W.; Cauhan, S. M. S. *J. Org. Chem.* **1981**, *46*, 5309. (d) Lown, J. W.; Cauhan, S. M. S.; Koganty, R. R.; Sapse, A.-M. *J. Am. Chem. Soc.* **1984**, *106*, 6401. (e) Naghipur, A.; Ikonomou, M. G.; Kebarle, P.; Lown, J. W. *J. Am. Chem. Soc.* **1990**, *112*, 3178.

[10] Hegarty, A. F. In *The Chemistry of the Diazonium and Diazo Groups*; Patai, S., Ed.; J. Wiley & Sons, Ltd.: New York, 1978.

[11] Thiele, J. *Chem. Ber.* **1908**, *41*, 2806.

[12] Lown, J. W.; Chauhan, S. M. S.; Koganty, R. R.; Sapse, A.-M. *J. Am. Chem. Soc.* **1984**, *106*, 6401.

[13] Gold, B.; Deshpande, A.; Linder, W.; Hines, L. *J. Am. Chem. Soc.* **1984**, *106*, 2072.

[14] Moss, R. A. *Acc. Chem. Res.* **1974**, *7*, 421.

[15] Ukawa, S.; Tobita, C.; Mochizuki, M. *Mutat. Res.* **1988**, *203*, 391.

[16] Ukawa, S.; Mochizuki, M. *Mutat. Res.* **1991**, *252*, 114.

[17] Suminov, S. I.; Kost, A. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1963**, *33*, 2152.

[18] Moss, R. A. *J. Org. Chem.* **1966**, *31*, 1082.

[19] Galtress, C. L.; Morrow, P. R.; Nag, S.; Smalley, T. L.; Tschantz, M. F.; Vaughn, J. S.; Wichems, D. N.; Ziglar, S. K.; Fishbein, J. C. *J. Am. Chem. Soc.* **1992**, *114*, 1406.

[20] Gilman, H.; Jones, R. G. *J. Am. Chem. Soc.* **1943**, *65*, 1458.

flow, were thermostated by means of an attached water bath. Reaction solutions were made up to ionic strength 1 M ($NaClO_4$) and were 4% by volume 2-propanol. The 2-propanol was necessitated by the instability of the diazoates in purely aqueous media. Thus stock solutions of the diazoates were made up in 2-propanol, additionally containing 0.01 M NaOH. These solutions were then diluted into cuvettes containing aqueous buffers in the appropriate volumes to give a final 4% by volume of 2-propanol. In the case of the stopped-flow, the reactions were carried out by mixing 25 parts of the aqueous buffer with 1 part diazoate in 2-propanol solution using 2.5 and 0.1 mL syringes, respectively.

Product Analysis. Quantitation of product alcohols and acetaldehyde was carried out using a Hewlett-Packard model 5890A gas chromatograph equipped with a 5% Carbowax 20 M, 60/80 Carbopack B column (Supelco) and a flame ionization detector. Concentrations of products were calculated from the integrations by interpolation from standard curves that contained at least three points.

In the decomposition of (*E*)-1-butanediazoate, the alkene products were quantitated by NMR in the following way. In a parafilm-sealed 5-mm NMR tube, the diazoate was allowed to decompose in 1 mL of a D_2O solution under a 1-mL column of $CDCl_3$ that had been carefully layered over the D_2O and that contained a known concentration of the internal standard tert-butyl methyl ether. At the reaction end point the NMR tube was manually subjected to centrifugal force such that the organic layer descended to the bottom of the tube. Subsequently the NMR spectrum of the $CDCl_3$ layer was recorded and the integration units for the signals at 4.95 (dd) and 5.45 (m) ppm, for the 1-butene and 2-butenes, respectively, were used to calculate concentrations on the basis of the integration of the proton signals from the internal standard. Removal of the D_2O layer and analysis of its NMR spectrum indicated no detectable signals from the butenes.

Deuterium Isotope Incorporation. The extent of deuterium incorporation from D_2O into the α carbon during the course of decomposition of diazoates was determined for a number of products. Reaction mixes were generally made up containing D_2O, buffer salts, $NaClO_4$ for constant ionic strength (1 M), and diazoate, which ranged in concentration from 0.005 to 0.01 M. The workup varied, as described in the paragraphs below, depending on the product, and the variation was a function of either the particulars of the structures of the products or chromatographic behavior on the Hewlett-Packard 5890 GC/MS used to analyze deuterium incorporation. The method for calculating the extent of deuterium incorporation was the same as that described previously for pentafluorobenzoate methyl esters.[4] The ions monitored for each product are given in the footnotes of Table 2.

For the analysis of deuterium incorporation into 1-butanol during the decomposition of 1-butanediazoate, the reaction mixture was first extracted with 20 mL of chloroform and the chloroform fraction was then extracted three times with 20 mL each time of NaCl-saturated H_2O. Controls with authentic 1-butanol dissolved in D_2O indicated that this extractive workup yielded 1-butanol that was less than 4% deuteriated at the exchangeable site. The chloroform solution containing 1-butanol was dried on $MgSO_4$ and was reduced in volume under a stream of dry nitrogen. A 1–2 μL volume was injected into the GC/MS, the separation employing a Carbowax 20M, 30 m × 0.32 mm, capillary column (Ohio Valley capillaries).

Isolation of 1-iodo-2,2,2-trifluoroethane from decomposition of (*Z*)- and (*E*)-trifluoroethanediazoates involved extraction of the reaction mixture with 10 mL of isooctane. The product was concentrated by passing argon through the isooctane at room temperature and allowing the gas (and iodotrifluoroethane) to exit through a tube which vented into a stoppered test tube (with a venting needle inserted) that contained ~200 μL of isooctane maintained at −100 °C. The venting tube was immersed at the tip in the ~200 μL of isooctane.

The methyl mercaptoacetate anion adduct, (carboxymethyl)methyl, 2,2,2-trifluoroethyl sulfide, that was formed from trapping of the intermediates in the decomposition of trifluoroethanediazoates was isolated by ether extraction and concentration using a rotary evaporator as above. The trifluoroethanethiolate anion adduct, bis(2,2,2-trifluoroethyl) sulfide, formed with the same diazoates was isolated by extraction with isooctane and was further concentrated, as described above for the 1-iodo-2,2,2-trifluoroethane.

Excess ^{16}O Incorporation. The possibility of incorporation of the ^{16}O originally attached to the (*E*)-1-butanediazoate into the product 1-butanol was analyzed as follows. The decomposition of (*E*)-1-butanediazoate was carried out, at 25 °C, in 1 M sodium hydroxide solution which contained ~50% of $H_2{}^{18}O$. The reaction vial was well sealed under argon and kept more than 10 half-lives to assure that the diazoate was converted into the products quantitatively ($t_{1/2}$ = 1.2 h, [diazoate] = 0.055 M). At the end of the reaction, the internal standard, phenylacetaldehyde, was injected through the rubber stopper into the reaction solution and freshly dried (over CaH) acetonitrile was added, to solubilize the aldehyde, to give a solution that was 10% by volume acetonitrile. The reaction solution was shaken well and left stirring over 24 h. The products of the reaction (butanols) and phenylacetaldehyde were extracted into freshly distilled ether. Samples were analyzed by mass spectrometry on a Hewlett-Packard 5989A mass spectrometer with a Hewlett-Packard 5890 gas chromatograph attached. The isotopic abundance of ^{18}O in 1-butanol was deduced from the relative intensities of the protonated formaldehyde peaks (m = 31 for ^{16}O and 33 for ^{18}O) after correction for their relative abundances in authentic [^{16}O]-1-butanol. For the phenylacetaldehyde the relative amounts of ^{18}O and ^{16}O were calculated from the intensities of the M+ peaks. In all cases the relative intensities for a given sample were the mean of a minimum of quadruplicate analysis.

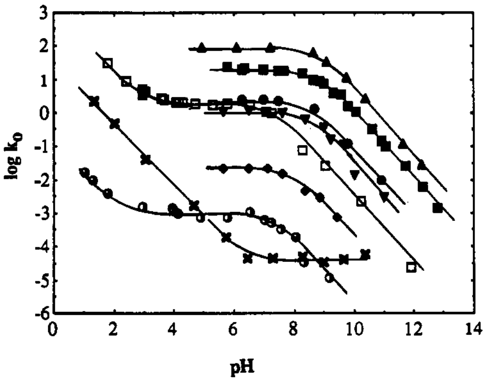

Figure 1. Values of log k_0, the buffer-independent rate constant for decomposition, against pH for alkanediazoates and 2,2,2-trifluorodiazoethane in aqueous solutions, 25 °C, ionic strength 1 M ($NaClO_4$), 4% 2-propanol. Compounds represented: (▲) (*E*)-2-butanediazoate (ref 5); (■) (*E*)-1-butanediazoate; (●) (*E*)-methanediazoate; (▼) (*E*)-2-methoxyethanediazoate; (□) (*Z*)-2,2,2-trifluoroethanediazoate; (◆) (*E*)-2-cyanoethanediazoate; (◐) (*E*)-2,2,2-trifluoroethanediazoate; , (×) 2,2,2-trifluorodiazoethane.

Results

Kinetics. The kinetics of decay of primary alkanediazoates, at 25 °C, ionic strength 1 M ($NaClO_4$), 4% 2-PrOH by volume, monitored at 225, 230 or 235 nm, were cleanly first-order for between 3 and 5 half-lives. Checks of the spectra between 215 and 300 nm at reaction end point gave essentially baseline spectra except in the case of the trifluoroethane diazoates as detailed below. The kinetics for the (*E*)-*n*-butane-, methoxyethane-, and cyanoethanediazoates were studied in the pH range between 5 and 13. In the presence of varying concentrations (0.02–0.3 M) of phosphate, biphosphate, cyanoethylamine, ethanolamine, butylamine, diethanolamine, hydrazine, and borate buffers, the first-order rate constants k_{obsd} typically increased by less than 10%, in a few cases as much as 15%, above the value of the buffer-independent rate constant, k_0, that was obtained by linear extrapolation to zero buffer concentration of plots of k_{obsd} against buffer. A total of 28 such experiments using the different amines above and hydrazine were carried out with the four primary (*E*)-alkanediazoates. The changes in the value of k_0 as a function of pH are plotted in Figure 1.

Observations during initial experiments with (*Z*)-trifluoroethanediazoate led us to first undertake an analysis of the kinetics of decomposition of 2,2,2-trifluorodiazoethane that simplified the analysis of the diazoate chemistry. The decay of absorbance of 2,2,2-trifluorodiazoethane was monitored at the λ_{max} of 217 nm and gave good first-order kinetics for between 3 and 5 half-lives under all conditions. The buffer-independent rate constants k_0 were obtained as indicated above and were plotted as a function of pH in Figure 1. With one exception the rate constants k_{obsd} increased by less than 15% with increasing buffer concentration up to a concentration of 0.2 M. Borate buffers stimulated the

Table 1. Kinetic Parameters for Decomposition of Primary Alkane Diazoates and Trifluorodiazoethane, 25 °C, H_2O, 4% 2-PrOH, $\mu = 1$ ($NaClO_4$)

compound	pK_a[a]	k_1[b] (s^{-1})	k_H[c] ($M^{-1}\ s^{-1}$)	$\Delta H^{\#}$[d] (kJ mol^{-1})	$\Delta S^{\#}$[e] (J $K^{-1}\ mol^{-1}$)	$k_0^{H_2O}/k_0^{D_2O}$	$k_0^{H_2O}/k_0^{EtOH}$
(*E*)-2-butanediazoate	8.83[f]	96[f]		60	−5 (7)		
(*E*)-1-butanediazoate	8.77	22		61	−16 (3)	1.3	810
(*E*)-methanediazoate	8.68	2.5		70[g]	−5[g] (9)	1.5[g]	680[g]
(*E*)-methoxyethanediazoate	8.45	1.2					
(*E*)-cyanoethanediazoate	7.96	0.023					
(*E*)-trifluoroethanediazoate	7.14	0.0008	0.16	88	−7 (10)	1.8	>500
(*Z*)-trifluoroethanediazoate	7.15	2.1	1800	57	−46 (1)	2.0	1872
trifluorodiazoethane		0.000 046[h]	60[h]				

[a] As in eq 5. [b] As in eq 5, except as noted. Standard error of ±10%. [c] As in eq 6, except as noted. Standard error of ±10%. [d] Parameter refers to k_1, the pH-independent reaction of the diazoic acid. Standard error of ±5%. [e] Parameter refers to k_1, the pH-independent reaction of the diazoic acid. Absolute value of the standard error is indicated in parentheses. [f] Previously reported in ref 5. [g] Previously reported in ref 4. The reaction solutions contained no 2-propanol. [h] See Results.

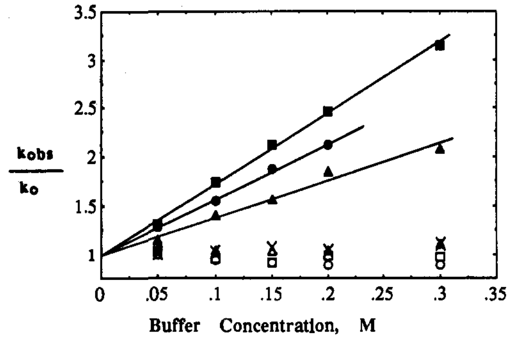

Figure 2. Plots of k_{obs}/k_0, the observed first-order rate constant divided by the extrapolated buffer-independent rate constant, as a function of buffer concentration for the decomposition of alkanediazoates in aqueous solutions, 25 °C, ionic strength 1 M ($NaClO_4$), 4% 2-propanol. Solid symbols are for (*Z*)-2,2,2-trifluoroethanediazoate, open symbols are for (*E*)-2,2,2-trifluoroethanediazoate, and ×'s for (*E*)-1-butanediazoate. Squares and ×'s are for experiments carried out in 20% acetate buffer, circles are for experiments in 50% acetate buffer, and triangles are for 20% cyanoacetate buffers.

rate of decomposition by as much as 50%, at a buffer concentration of 0.2 M, above the value of k_0. In dilute perchloric, acetic, formic, and boric acid buffers the absorbance between 205 and 280 nm after 10 half-lives of decomposition was less than 5% the initial absorbance at 217 nm. In the presence of dilute hydroxide, biphosphate, and ethylene diamine dication buffers, the decay of absorbance at 217 nm was accompanied by an increase in absorbance at higher wavelengths, λ_{max} = 254 nm, with an isosbestic point at 234 nm. No attempt was made to isolate the product with λ_{max} = 254 nm. The dependence on pH of the rate constant for buffer-independent decay of trifluorodiazoethane indicates a two-term rate law in this pH range including a heretofore unreported pH-independent term, k_1, and a proton-dependent term k_H that was previously reported.[21] Values for these constants are listed in Table 1.

As indicated above, the decomposition of (*E*)-trifluoroethanediazoate, monitored at 235 nm, exhibited good first-order kinetics for 3–4 half-lives of reaction, despite the fact that, under some conditions detailed below, other changes in the ultraviolet spectrum occurred on a comparable or longer time scale. In summary, the kinetics were likely well behaved at this selected wavelength (235 nm) in spite of the non-steady-state formation of 2,2,2-trifluorodiazoethane under some reaction conditions for two reasons. First, the absorbance maximum of 2,2,2-trifluorodiazoethane is sufficiently narrow compared to that of the diazoate that it is effectively transparent at this wavelength. Second, the wavelength monitored was sufficiently close to the isosbestic point for the decay of trifluorodiazoethane to the unidentified product with λ_{max} = 254, above, so as to obviate its interference over the period that the reaction was monitored. In perchloric, acetic, formic, and some boric acid buffers, the diazoate ultraviolet spectrum between 200 and 280 nm decayed cleanly to baseline. Between pH 6 and 8, with phosphate and ethylenediamine buffers, the spectral changes were complex. In 0.05 M biphosphate buffer, pH 7.1, the decrease in absorbance was accompanied by a transient increase in absorbance at lower wavelengths with a λ_{max} = 217 nm, identical with that of 2,2,2-trifluorodiazoethane, and an isosbestic point at 222 nm. The rate constant for the decay at 235 nm was within 5% of that determined, over the course of 2 half-lives, from the increase in absorbance at 217 nm. The maximum at 217 nm subsequently decayed, with a rate constant (=4.0 × 10^{-5} s^{-1}) that was within 15% of that observed in the pH-independent reaction of 2,2,2-trifluorodiazoethane. There was an accompanying increase in absorbance at 254 nm that itself decayed much more slowly. The end point and rate constant for this final decay were not analyzed.

The decay of (*Z*)-trifluoroethanediazoate between pH 2 and 12 was monitored at 225 adn 235 nm and was cleanly first-order to 5 half-lives of reaction. Analysis of by conventional spectrophotometer of the ultraviolet spectrum of the product was carried out immediately subsequent to decomposition of the diazoate in the stopped-flow spectrophotometer. The product exhibited a λ_{max} at 217 nm, identical to that observed for 2,2,2-trifluorodiazoethane, and when checked, decayed with a rate constant that was within 10% that expected on the basis of experiments carried out with authentic 2,2,2-trifluorodiazoethane.

Activation parameters and solvent deuterium isotope effects were determined for the buffer-independent rate constants for a number of the diazoates at a pH at which the rate constants are pH independent. The effect on the pH-independent rate constant of changing solvent from water to ethanol was also investigated in three cases. All the values are summarized in Table 1.

The rate constant, k_{obsd}, for the decay of (*Z*)-trifluoroethanediazoate was markedly increased by increasing concentrations of carboxylic acid buffers. The amount of increase relative to the buffer-independent rate constant k_0 is indicated in Figure 2, which depicts plots of k_{obsd}/k_0 against buffer concentration. The contrasting behavior of the (*E*)-trifluoroethanediazoate isomer and an experiment with (*E*)-1-butanediazoate is also illustrated by Figure 2. The slopes, k_2, of plots of k_{obsd} against buffer concentration plotted against the percent acid form of the buffer gave intercept values at 100% buffer acid that represent the catalytic constants, k_{HA}, for buffer acid catalysis. In all cases, the value of k_2 at 0% acid form of the buffer was less than 10% of the value of k_2 at 100% acid form (k_{HA}). All of the data concerning buffer catalysis are summarized in supplementary tables. Experiments at 0.03 and 0.3 M acetic acid buffer (20% acetate) gave reaction-end-point absorbances at λ_{max} = 217 nm (indicative of 2,2,2-trifluorodiazoethane formation) that were equal within 10%. In an experiment to detect whether the general acid-catalyzed reaction was subject to stimulation by added nucleophiles, the values of k_{obsd} at four concentrations of NaBr up to 1 M were determined in reactions buffered by 0.3 M acetic acid buffer (20% AcO^-). The value of k_{obsd} at 1 M NaBr was

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(21) Dahn, H.; Lenoir, J. H. *Helv. Chim. Acta* **1979**, *62*, 2218.

less than 5% larger than the value of k_{obsd} in the absence of NaBr. More than 80% of the value of k_{obsd} was due to catalysis by the acetic acid buffer in these experiments.

The solvent deuterium isotope effect on the buffer-catalyzed reaction of (*Z*)-trifluoroethanediazoate was determined by dividing the value of k_2 determined in H_2O by that determined in D_2O for experiments at identical buffer ratios. An example of typical data is given in Figure 3. For four determinations in formic acid buffers the value of the isotope effect was $k_2^{H_2O}/k_2^{D_2O} = 3.1 \pm 0.2$. A single determination for acetic acid gave the value $k_2^{H_2O}/k_2^{D_2O} = 2.8$.

Products. The products of decay of a number of the diazoates were determined by a combination of gas chromatography (GC) and NMR techniques. Decomposition of (*E*)-1-butanediazoate in D_2O, 0.1 M NaOD gave 47% 1-butanol and 21% 2-butanol by GC and 17% 1-butene and 11% 2-butene by NMR (total yield = 96%). Decomposition products (and respective yields that were quantitated by GC) of (*E*)-2-methoxyethanediazoate that was decomposed in 0.2 M 50% dianion biphosphate buffer were 2-methoxyethanol (84%), acetaldehyde (17%), and methanol (16%) (total yield 100% or 101%). Decomposition of (*Z*)- and (*E*)-trifluoroethanediazoates in 0.3 M $HClO_4$ gave 86% and 94% yields of trifluoroethane, respectively, as quantitated by GC.

An indirect analysis was used to quantitate the product of (*E*)-trifluoroethanediazoate decomposition at neutral pH. Near neutral pH the spectroscopic evidence indicates that the (*E*)-trifluoroethanediazoate decomposes to trifluorodiazoethane that subsequently decomposes to an unidentified product with an ultraviolet spectrum that has a $\lambda_{maz} = 254$. Only a 15% yield of trifluoroethanol was detectable by GC, even after 10 half-lives for trifluorodiazoethane decomposition, in an experiment that was carried out at pH 5.3 in which the diazoate was decomposed in 0.05 M acetate buffer. In order to assess the yield of trifluorodiazoethane formed from (*E*)-trifluoroethanediazoate, the following experiment was carried out. The diazoate was allowed to decompose at pH 6.9, 0.02 M phosphate buffer for 5 half-lives and the reaction was then quenched with $HClO_4$ and analyzed for trifluoroethanol by GC. Trifluorodiazoethane quantitatively decomposes to trifluoroethanol in acidic media,[21] so detection of trifluoroethanol upon quench of the reaction with acid is evidence of trifluorodiazoethane. A less than quantitative yield of trifluoethanol is expected because during the incubation period some of the trifluorodiazoethane product decomposes to an unknown. The theoretical maximum amount of trifluoroethanol expected can be calculated for the kinetic scheme in eq 3, in which A is the diazoate, B is the diazo compound, and C is the unknown, using eq 4 and the relevant rate constants that were independently measured.[22] The calculated maximum yield of trifluoroethanol for reaction pH = 6.90 is 78% while the measured yield of trifluoroethanol was 69%, giving a normalized yield of 89% (=69%/78%).

$$A \xrightarrow{k_A} B \xrightarrow{k_B} C \qquad (3)$$

$$[B] = (k_A[A_0]/(k_B - k_A))(e^{-k_At} - e^{-k_Bt}) \qquad (4)$$

Isotope Incorporation. For three diazoates, experiments were carried out to determine the extent of α proton exchange during the course of decomposition. The analysis was performed by GC/MS generally after allowing for 8–10 half-lives of diazoate decomposition by trapping the alkyl group fragment with various nucleophiles. The results and conditions of the experiments are summarized in Table 2.

Experiments were carried out to detect the possibility of excess ^{16}O incorporation into 1-butanol that could arise due to internal return during the decomposition of (*E*)-[^{16}O]-1-butanediazoate in ^{18}O-containing water. The 1-butanol analyzed by mass spectrometry contained 47(±2)% ^{16}O compared to the internal standard phenylacetaldehyde that, after oxygen exchange with solvent, contained 49(±2)% ^{16}O (duplicate runs).

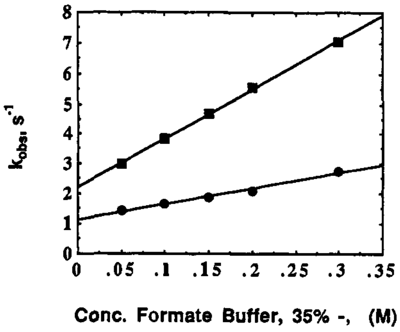

Figure 3. Plot of the change in k_{obsd}, for the decay of (*Z*)-trifluoroethanediazoate, as a function of buffer concentration in H_2O (squares) and D_2O (circles) in formate buffer (35% anion), 25 °C, ionic strength 1 M ($NaClO_4$), 4% (OL)-2-propanol.

Discussion

Rate Laws. Rate constants for the decay of primary alkanediazoates were generally determined in the range of pH 4–10, and within this range the rate law for disappearance of total diazoate (diazoate plus diazoic acid) is indicated in eq 5. This

$$k_0 = k_1/(1 + K_a/[H^+]) \qquad (5)$$

rate law is qualitatively identical with that observed in the case of (*E*)-methanediazoate investigated earlier. Good fits to the rate law of eq 5, solid lines in Figure 1, are obtained using the parameters summarized in Table 1 (see below regarding trifluoroethanediazoates). As deduced previously for the methyl compound, the constant K_a is taken as the ionization constant for the diazoic acid. Support for this interpretation in the present case is found from independent spectroscopic evidence. At pH 9.3 the ultraviolet spectrum of the (*E*)-trifluoroethanediazoate exhibits the characteristic λ_{max} = 224 nm while at pH 5.2 the ultraviolet spectrum shows no relative maximum between 210 and 300 nm with the absorbance increasing gently as a function of wavelength from 280 to 210 nm. The spectrum at low pH is inconsistent with the spectrum expected for protonation on nitrogen to give the (trifluoroethyl)nitrosamine which would exhibit a λ_{max} near 230 nm, as observed for the stable dialkylnitrosamines. The change in diazoate absorbance at 235 nm was monitored as a function of pH and exhibited an inflection at pH 7.00 ± 0.04. This spectrometric pK_a is in good agreement with the value assigned on the basis of the kinetic analysis (Table 1). A good linear relationship exists between the kinetic pK_a values and the electron-withdrawing abilities of the substituents (σ_I) in the case of the primary (*E*)-alkane- and (*E*)-methanediazoic acids: p$K_a = -3.39\sigma_I + 8.68$ ($r^2 = 0.993$).

In the cases of the trifluoroethanediazoates, additional experiments in more acidic media indicated the existence of a buffer-independent acid-catalyzed reaction of the diazoic acid which becomes dominant below pH 4. The more general rate law of eq 6, written in terms of total diazoate and diazoic acid

$$k_0 = (k_1 + k_H[H^+])/(1 + K_a/[H^+]) \qquad (6)$$

concentration, is therefore indicated with the rate constants k_1 and k_H representing the uncatalyzed and acid-catalyzed rate constants, respectively, for the decomposition of the diazoic acids. The solid lines in Figure 1 for the trifluoroethanediazoates are fits to the data using the values for the constants that are indicated in Table 1. The observation of the buffer-independent acid-catalyzed reaction k_H was incidental to an investigation of the

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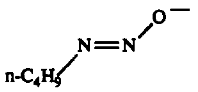
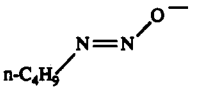
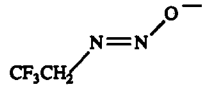
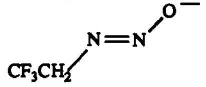
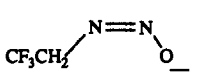
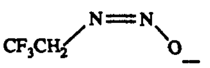
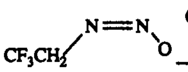
(22) Cappellos, C.; Bielski, B. H. T. *Kinetic Systems*; Wiley-Interscience: New York, 1972; p 48.

Table 2. Deuterium Isotope Incorporation Resulting from Diazoate Decomposition in Deuterium Oxide Solutions

	Reaction[a]		Product Deuterium Content[b] (SD) % $P\text{-}H_2$	%P-HD	%$P\text{-}D_2$
1)[c]		$\xrightarrow[D_2O]{}$ $CH_3CH_2CH_2CL_2OH$	94 (1)	6 (1)	0
2)		$\xrightarrow[D_2O]{\text{1M NaOD}}$ $CH_3CH_2CH_2CL_2OH$	75 (1)	24 (1)	1 (1)
3)[d]		$\xrightarrow[D_2O]{\text{NaI}}$ CF_3CL_2I	0	5	95
4)[e]		$\xrightarrow[D_2O]{\text{NaI}}$ CF_3CL_2I	1 (1)	3 (0)	96 (1)
5)[e]		$\xrightarrow[D_2O]{\text{NaI}}$ CF_3CL_2I	3 (2)	5 (2)	92 (4)
6)[f]		$\xrightarrow[D_2O]{CF_3CH_2S^-}$ $CF_3CH_2SCL_2CF_3$	18 (2)	55 (2)	28 (3)
7)[g]		$\xrightarrow[D2O]{CH_3OC(O)CH_2S^-}$ $CH_3OC(O)CH_2SCL_2CF_3$	48 (1)	37 (0)	15 (1)

[a] Reactions carried out at room temperature. [b] Results are given as a percentage of the total signal corrected according to the signal distribution observed for authentic $P\text{-}H_2$ standard. Total correction for each signal was no more than 5% of the observed value. [c] Reaction carried out in 0.05 M phosphate buffer, pH_{obs} = 10.50. Data is the average of three experiments, two analyses per experiment. Ion analyzed was CL_2OH^+. [d] Reaction carried out in 0.02 M $DClO_4$. Data is the average of four analyses from a single experiment. Ion analyzed was $CF_3CL_2I^+$. [e] Reaction carried out in 0.1 M biphosphate buffer, 80% dianion, pH_{obs} = 7.22. Data is the average of four analyses from a single experiment. Ion analyzed was $CF_3CL_2I^+$. [f] Data are the average of duplicates, four analyses per experiment. Ion analyzed was $CF_3CL_2SCH_2^+$. [g] Reaction was carried out in methylmercaptoacetate buffer, pH_{obs} = 8.36. Data is the average of three analyses from a single experiment. Ion analyzed was $CF_3CL_2SCH_2^+$.

buffer-catalyzed decomposition of the (*Z*)-trifluoroethanediazoate that is discussed below. A complete investigation of the buffer-independent decomposition of the diazoic acids that is catalyzed by the proton is presently being undertaken and will be reported elsewhere.

(*E*)-Alkanediazoates. A number of experimental observations rule out certain mechanisms for the hydrogen ion-independent reaction (k_1, eqs 5 and 6) of the (*E*)-alkanediazoates, and it is concluded that the correct mechanism involves rate-limiting formation of the diazonium ion from the (*E*)-diazoic acid, as in eq 1.

The deuterium isotope incorporation studies summarized in Table 2 rule out both an elimination mechanism that would require diazoalkane intermediates and S_N2 mechanisms involving attack on the diazoic acid for certain of the diazoates. Such mechanisms have been suggested previously.[9,23] Entry 1 (Table 2) rules out the possibility that decomposition of 1-butanediazoate occurs via elimination, with abstraction of an α proton and loss of hydroxide ion, to give diazobutane. Such a mechanism requires every product molecule to contain at least a single deuterium atom in contrast to the observation that 94% of the 1-butanol contains two protons. The observation that 25% of the 1-butanol that is formed from the decomposition of (*E*)-1-butanediazoate under basic conditions (entry 2, Table 2) contains at least a single deuterium atom requires that the product cannot be formed exclusively by an S_N2 reaction of the diazoic acid because such a mechanism requires that [α-$^1H_2$]-1-butanol is the exclusive product. Better evidence that the S_N2 mechanism can account for an insignificant fraction of diazoate decomposition is found in the 99% yield of dideuteriated trifluoroethyl iodide formed in the decomposition of the (*E*)-trifluoroethanediazoate in D_2O in the presence of sodium iodide (Table 2, entries 3 and 4). The absence of an S_N2 mechanism for the reaction of the highly nucleophilic iodide ion means that weaker nucleophiles must also react by an alternative mechanism. Consistent with this conclusion is the failure, in 28 experiments, to observe increases of more than 10% in k_{obsd} (for decomposition of the diazoates) with increasing buffer concentration up to 0.2 M of various nucleophilic amine buffers including hydrazine (see Results).

A common mechanism of decomposition for all the (*E*)-alkanediazoates studied is indicated by the correlation line in the plot in Figure 4 of log k_1 against σ^* about which the points are randomly distributed. The plot includes the data for the (*E*)-methane- and (*E*)-2-butanediazoates, for which compounds the mechanism of decomposition involves rate-limiting formation of the diazonium ion as in eq 1.[3-5] The slope of the plot has a value of $\rho^* \sim -4.4$ (log $k_1 = -4.38\sigma^* + 0.78$ ($r^2 = 0.977$)) that indicates that there is a substantial amount of positive charge development in going from the ground state to the transition state. Similar or slightly smaller values of ρ^* are observed for the effect of substituents attached to the "remaining group" on the rate constants for acid-catalyzed hydrolysis of acetals and ketals.[24]

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(23) Loew, G.; Poulsen, M. T.; Spangler, D.; Kirkjian, E. *Int. J. Quantum Chem., Quantum Biol. Symp.* **1983**, *10*, 201. Thomas, C.; Reynolds, C. A. *Int. J. Quantum Chem.* **1986**, *XXX*, 751. Hart, H.; Brewbaker, J. L. *J. Am. Chem. Soc.* **1969**, *91*, 716. Fiering, A. E.; Ciabattoni, J. *J. Org. Chem.* **1972**, *37*, 3784. Reynolds, C. A.; Thomson, C. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1927.

(24) Cordes, E. H. *Prog. Phys. Org. Chem.* **1967**, *4*, 1.

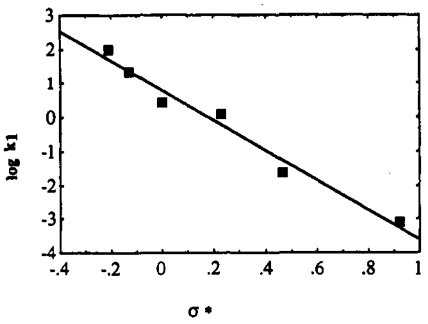

Figure 4. Plot of the log of the pH-independent rate constant for decomposition of diazoic acids as a function of σ^*. Reaction conditions as in Table 1.

Alternatively a plot of log k_1 against pK_a of the corresponding primary ammonium ions (not shown) for four of the primary (*E*)-alkanediazoates, excluding the point for (*E*)-methanediazoate, gives a line of slope = 0.87, indicating that the sensitivity of the rate constants for diazoic acid decomposition is similar to that for the equilibrium protonation of the analogous primary amines.

The absolute values of the pH-independent rate constants, their dependence upon substituent and solvent, and the solvent deuterium isotope effects rule out rate-limiting isomerization processes. The rate constants for pH-independent decomposition of all the (*E*)-alkanediazoic acids studied here, except the trifluoroethane compound, are too fast to represent the type of rate-limiting (*E*) to (*Z*) isomerization process observed in the case of some (*E*)-arenediazoic acids. The rate constant for isomerization of the (*E*)-*p*-nitrobenzenediazoic acid[25] of 0.005 s^{-1} represents an upper limit for the value expected for isomerization of (*E*)-alkanediazoic acids because the transition state for isomerization is stabilized by resonance interaction with the benzene ring and the *p*-nitro group.[26] The large negative value of ρ^* observed in the correlation of Figure 4 is also inconsistent with this mechanisn of isomerization in which the transition state, with substantial negative charge located on the nitrogen nearest to the benzene ring, would be stabilized by electron-withdrawing substituents. Similarly, isomerizations involving inversion at a nitrogen with a double bond are characterized by substituent effects that are distinctly different from those observed for the present reaction. In the case of symmetrically substituted azobenzenes there is no correlation of rate constant with substituent,[27] while the rate constants for inversion of imines[28] and azines[29] increase with increasing electron withdrawal by substituents attached to either the carbon or the noninverting nitrogen, respectively. The large decrease in k_1 of 500- to 1000-fold that is observed when the solvent is changed from water to ethanol in the present case (Table 1) is in contrast to the solvent effects observed on isomerizations involving inversion at nitrogen which are small and in the opposite direction with respect to solvent polarity. The rate constant for isomerization of azobenzene[30] *increases* 6-fold in changing from water to heptane while that for 4-amino-4′-(diethylamino)azobenzene[31] *increases* less than 8- and 3-fold as the solvent is changed from 2-propanol or DMSO, respectively, to benzene. Finally, the solvent deuterium isotope effect for the rate-limiting isomerization of (*E*)-*p*-nitrobenzenediazoic acid to the (*Z*) form is the inverse,[25] $k_H/k_D = 0.93$, opposite the normal solvent deuterium isotope effects observed in the present reaction (Table 1).

None of the experimental results are inconsistent with the mechanism of eq 1, in which the rate-limiting step involves unassisted N–O bond fission to yield the diazonium ion. The unassisted nature of the bond cleavage is deduced from the lack of substantial catalysis of the decomposition by a variety of oxygen and nitrogen acid buffers in experiments where the buffer concentration was varied up to 0.3 M. As pointed out previously for the methyl compound,[4] the solvent deuterium isotope effects, solvent effects, and small values of $\Delta S^{\#}$ (Table 1), measured under conditions in which the reaction is pH independent, are all consistent with the mechanism of eq 1. The deactivating effects of electron-withdrawing groups (above and Figure 4) are also consistent with the rate-limiting formation of a diazonium ion. The slope of 0.87 of the plot of log k_1 against pK_a of the analogously substituted primary ammonium ion indicates that in the rate-limiting N–O bond fission (k_1, eq 1) the substituents experience a change in charge of $\sim$+0.9 in going from the ground-state diazoic acid to the transition state. This indicates substantial progress toward formation of a diazonium ion in the transition state. A more quantitative analysis of the position of the transition state along the reaction coordinate is not possible because the substituent effect on the equilibrium formation of the diazonium ion is unknown. Heterolytic bond cleavage yielding diazonium ions is a rate-limiting step that is common to a number of systems including the following: decay of trialkyltriazenium ions;[32] acid-catalyzed and uncatalyzed decomposition of aralkyltriazenes;[33] acyltriazenes[34] and acyltriazenium ions;[34] (*Z*)-arenediazoic acids and ethers;[26,35] (*E*)-arenediazo ethers;[36] and (*E*)-arenediazoic acids with electron-donating groups in the benzene ring.[26] In the case of (*E*)-arenediazo ethers,[37] and possibly certain dialkyltriazenium ions,[38] the observation of general acid catalysis raises the possibility that formation of the diazonium ion could be assisted by proton donation from solvent. Such a mechanism has been discounted in the case of aralkyltriazenes[33] but may be operative in the case of the (*Z*)-trifluoroethanediazoate, as discussed in a later section. Although not rate limiting, diazonium ion formation via N–O bond cleavage has been claimed in the nitrous acid-catalyzed deamination of primary amines[6] and in nitrosamide and related deamination reactions in nonpolar solvents.[39]

Diazonium Ions. The results of the product deuterium incorporation studies are qualitatively consistent with the intermediacy of diazonium ions on the basis of what is known from similar experiments in the literature on diazoalkane decomposition. The difference in the extent of deuterium incorporation at low and high pH in the case of the decomposition of 1-butanediazoate parallels Kirmse's observation in the methanolysis of 1-diazobutane.[40] In deuteriated methanol the percent of methyl butyl ether containing only a single deuterium atom decreases from 75% in neutral media to 23% at 0.89 M CH_3ONa, the balance being dideuteriated material. In this reaction, incorporation of a single deuterium is required to form the diazonium ion while more extensive exchange is due to the

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(25) Lewis, E. S.; Hanson, M. P. *J. Am. Chem. Soc.* **1967**, *89*, 6268.

(26) Levin, C. M. *J. Am. Chem. Soc.* **1975**, *97*, 5649.

(27) Talaty, E. R.; Fargo, J. C. *Chem. Commun.* **1967**, 65.

(28) Curtin, D. Y.; Hauser, J. W. *J. Am. Chem. Soc.* **1961**, *83*, 3474.

(29) Howell, J. M.; Kirschenbaum, L. J. *J. Am. Chem. Soc.* **1976**, *98*, 877.

(30) Halperin, J.; Brady, G. W.; Winkler, C. A. *Can. J. Res.* **1950**, *28B*, 140.

(31) Wildes, P. D.; Pacifici, J. G.; Irick, G.; Whitten, D. G. *J. Am. Chem. Soc.* **1971**, *93*, 2004.

(32) Sieh, D. H.; Michejda, C. J. *J. Am. Chem. Soc.* **1981**, *103*, 442. Smith, R. H.; Denlinger, C. L.; Kupper, R.; Koepke, S. R.; Michejda, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 1056.

(33) Jones, C. C.; Kelly, M. A.; Sinnott, M. L.; Smith, P. J. *Chem. Commun.* **1980**, *322*. Jones, C. C.; Kelly, M. A.; Sinnott, M. L.; Smith, P. J.; Tzotos, G. T. *J. Chem. Soc., Perkin Trans. 2* **1982**, 1655.

(34) Smith, R. H.; Wladkowski, B. D.; Herling, J. A.; Pfaltzgraff, T. D.; Pruski, B.; Klose, J.; Michejda, C. J. *Org. Chem.* **1992**, *57*, 654.

(35) Anderson, C. S.; Broxton, T. J. *J. Org. Chem.* **1980**, *45*, 2454. Broxton, T. J.; Mcleish, M. J. *J. Org. Chem.* **1982**, 47, 3675.

(36) Broxton, T. J.; Roper, D. L. *J. Org. Chem.* **1976**, *41*, 2157. Broxton, T. J. *Aust. J. Chem.* **1978**, *31*, 1519.

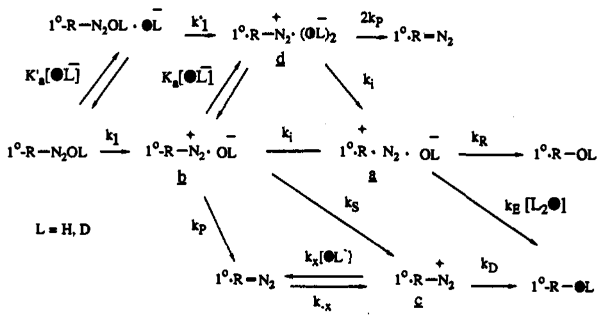
(37) Stray, A. C.; Broxton, T. J. *J. Org. Chem.* **1980**, *45*, 2409. Stray, A. C.; Broxton, T. J. *Aust. J. Chem.* **1982**, *35*, 961.

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

(39) White, E. H.; Ryan, T.; Field, K. W. *J. Am. Chem. Soc.* **1974**, *94*, 1360. White, E. H.; Field, K. W. *J. Am. Chem. Soc.* **1975**, *97*, 2148. White, E. H.; Field, K. W.; Hendrickson, W. H.; Dzadzic, P.; Roswell, D. F.; Paik, S.; Mullen, P. W. *J. Am. Chem. Soc.* **1992**, *114*, 8023 and references within.

(40) Kirmse, W.; Rinkler, H. A. *Leibigs Ann. Chem.* **1967**, *707*, 57.

Scheme 1



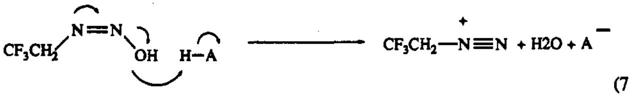
competition between methanolysis and proton abstraction, the latter reaction being more strongly accelerated at higher methoxide ion concentrations. The observation that the iodotrifluoroethane formed from the decomposition of (*E*)-trifluoroethanediazoate in D_2O (1 M NaI) is nearly completely dideuteriated is consistent with the intermediacy of the trifluoroethanediazonium ion that is known to undergo hydron exchange more rapidly than dediazoniation.[20,21,41]

It can be shown that the primary diazonium ions formed from the (*E*)-diazoates in the present study are diffusionally equilibrated intermediates, in contrast to what has been concluded in the basic hydrolysis of (*Z*)-1-propanediazoate. Gold observed[13] in the decomposition of [^{16}O]-(*Z*)-1-propanediazoate in mixed $H_2{}^{16}O/H_2{}^{18}O$ that the $^{16}O/^{18}O$ ratio in the product 1-propanol was equal to that in the solvent in neutral aqueous media but significantly greater than that of the solvent in ~1 M hydroxide ion. It was thus concluded that the diazonium ion (**b**, formed via k_1, Scheme 1) was sufficiently long-lived to separate from hydroxide ion in the initially formed ion pair ($k_S > k_i$) in neutral media but that in basic media the reaction pathway involved the nitrogen-separated ion pair **a** ($k_i > k_S$, Scheme 1) that collapsed to give 1-propanol with "excess" ^{16}O ($k_R \sim k_E$, Scheme 1, ● = oxygen from bulk solvent while O = oxygen from original diazoate). The possible explanations for the hydroxide ion dependence of the ^{16}O incorporation that was in excess of the solvent composition were, admittedly,[13] not compelling. We have carried out similar experiments in duplicate with the [^{16}O]-(*E*)-1-butanediazoate in mixed $H_2{}^{16}O/H_2{}^{18}O$ at 1 M NaOH and found that the ^{16}O content of the product 1-butanol was identical within experimental error with the ^{16}O composition of the solvent. This result requires either a diazonium ion that is sufficiently long-lived to diffuse away from the hydroxide ion in 1 M NaOH ($k_S \gg k_i$, Scheme 1) or a nitrogen-separated ion pair, **a** in Scheme 1, that is sufficiently short-lived that it is captured by solvent before the original ^{16}O on the hydroxide ion leaving group can diffuse back and capture the cation ($k_i > k_S$, $k_E \gg k_R$, Scheme 1).

The latter mechanism involving the nitrogen-separated ion pair, **a** ($k_i \gg k_S$, Scheme 1), can be ruled out because such a mechanism predicts little in the way of deuteroxide ion-stimulated deuterium incorporation into product 1-butanol, in contrast with what is observed. The amount of deuterium incorporation during decomposition of (*E*)-1-butanediazoate in D_2O increases 4–5-fold from 6% at pD ~ 10.5 to 25% at 1 M NaOD (entries 1 and 2 in Table 2). The incompatibility of the mechanism involving the nitrogen-separated ion pair, **a** (Scheme 1), with this observation can be illustrated using Scheme 1. If this mechanism were operative ($k_i \gg k_S$), then the incorporation of deuterium from D_2O into 6% of the product 1-butanol at pD = 10.5 indicates that proton abstraction by the deuteroxide ion leaving group in the ion pair **b** (k_P, Scheme 1) is much slower than the formation of the carbocation to give **a** (k_i, Scheme 1). The 6% deuterium incorporation sets a value of $k_i/k_P \sim 17$ as a lower limit, assuming all the deuterium incorporation is due to the k_P process ($0.06 = k_P/(k_P + k_i)$). In the limiting case of very high deuteroxide ion concentrations where all of the reaction occurs through intermediate **d** (either via K_a or K'_a), the amount of deuterium incorporation would be less than double that observed at pH = 10.5. The fraction of deuterium incorporation in this case can be calculated as ~11% ($=2k_P/(2k_P + k_i)$) using the value $k_i/k_P = 17$. The maximum deuterium incorporation expected at 1 M deuteroxide ion is, however, considerably smaller than this because random association constants K_a and K'_a in aqueous solutions are typically on the order of 0.2 M^{-1} or less.[42a] At most (assuming the K'_a path and $K'_a = 0.2\ M^{-1}$),[42b] ~20% of the reaction would occur through intermediate **d** at [OD^-] = 1 M and this would then predict no more than a 20% increase in the extent of deuterium incorporation at 1 M deuteroxide ion compared to pD = 10.5, *in contrast with the more than 400% increase observed.*

The lack of excess ^{16}O incorporation and the deuteroxide ion-dependent deuterium incorporation are best accommodated by the mechanism involving a free butanediazonium ion intermediate **c** ($k_S \gg k_i$) which undergoes lyoxide ion-catalyzed proton transfer, $k_x[OL^-]$, that is competitive with hydrolysis, k_D, at high pL, as has been observed by Kirmse in the methanolysis of 1-diazobutane.[40] For primary diazonium ions with electron-withdrawing groups attached, the value of the rate constant k_i must be smaller than that for the 1-butanediazonium ion so that such diazonium ions must be diffusionally equilibrated as well. The inconsistency in the experiments with (*Z*)-1-propanediazoate[13] in which there is apparently substantial excess ^{16}O incorporation—that presumably requires the intermediacy of **a** (Scheme 1)—that is concurrent with hydroxide ion-stimulated diazoalkane formation remains unresolved. We are currently investigating this aspect of the chemistry of primary (*Z*)-alkanediazoates.

Z vs E. The decomposition of the (*Z*)-trifluoroethanediazoic acid, but not the (*E*) isomer, exhibits general acid catalysis, and the mechanism for this reaction likely involves concerted assistance to diazonium ion formation as in eq 7, with subsequent rapid proton



(7)

loss to give trifluorodiazoethane. The product of the general acid-catalyzed reaction was confirmed by spectroscopic and kinetic analysis to be trifluorodiazoethane (see Results). The Bronsted plot for general acid catalysis by carboxylic acid buffers is illustrated in Figure 5. The value of the slope $\alpha = 0.41$ that is intermediate between limiting values of 1 and 0, for proton transfer between electronegative atoms, indicates a concerted mechanism in which the proton is "in flight" in the rate-limiting transition state. The solvent deuterium isotope effect on formic acid catalysis of $k_{HA}/k_{DA} = 3.1 \pm 0.2$ is consistent with this conclusion. The fact that the catalytic constant for methoxylammonium ion lies one log unit below the line containing the carboxylic acids in Figure 5 is consistent with the stabilizing electrostatic interaction between the penultimate carboxylate anion and the diazonium cation in the transition state for carboxylic acid catalysis that does not exist in the transition state for ammonium ion catalysis according to the mechanism of eq 7.

The fact that methoxylammonium ion is a weaker catalyst than a carboxylic acid of identical pK_a is inconsistent with a mechanism involving specific acid catalysis followed by nucleo-

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(41) Loehr, D. T.; Armistead, D.; Roy, J.; Dorn, H. C. *J. Fluorine Chem.* **1988**, *39*, 283.

(42) (a) Association constants for formation of hydrogen-bonding complexes between ammonium ions and phenolate ions have typical values of $K_{AB} \sim 0.2\ M^{-1}$ or less when statistically corrected for the number of hydrogens on the ammonium ions.[43] The values of equilibrium constants, K_a, for random association complexes are presumably smaller than this. (b) The K_a pathway predicts a smaller fraction because **b** and **d** are unlikely to be in rapid equilibrium given the probable magnitude of the rate constants k_i and k_P required for this mechanism which requires that the diffusional separation step k_S is negligibly small in comparison to k_i and k_P.

(43) Stahl, N.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4196.

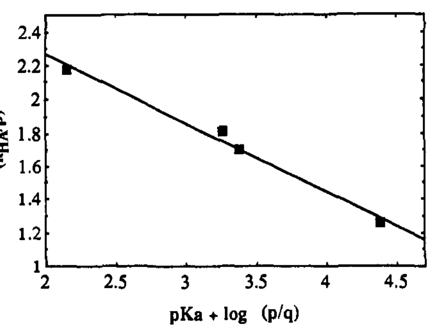
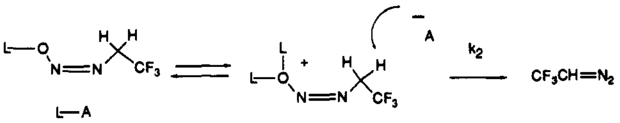


Figure 5. Statistically corrected Bronsted plot for the general acid catalyzed decomposition of (*Z*)-2,2,2-trifluoroethanediazoate by carboxylic acid buffers. The slope of the line is 0.41.

philic displacement on the diazoic acid at either the nitrogen bonded to oxygen or the methylene carbon. Analogous mechanisms have been considered previously in the oxy acid-catalyzed decomposition of dialkyltriazenes.[38] If such mechanisms were operative in the present case, the methoxylammonium ion, with the more powerfully nucleophilic conjugate base methoxylamine, would be a superior catalyst compared to a carboxylic acid of similar pK_a—in contrast to what is observed. The absence of such mechanisms is similarly indicated by an experiment in which the rate constant k_{obsd} increased by less than 5% with increasing amounts of bromide ion up to 1 M at a concentration of buffer at which 80% of the observed reaction was buffer catalyzed.

An alternative mechanism involving specific acid–general base catalyzed elimination as in eq 8 can be ruled out because the



(8)

upper limit for the solvent deuterium isotope effect expected for such a mechanism, $k_{HA}/k_{DA} < 2.51$ (derived below), is inconsistent with the experimentally obtained value of $k_{HA}/k_{DA} = 3.1 \pm 0.2$ for formic acid catalysis. The solvent deuterium isotope effect on the mechanism of eq 8 is due solely to secondary effects at exchangeable sites. The expected effect can then be deduced on the basis of fractionation factor theory.[44] The expression for the solvent deuterium isotope effect is presented in eq 9, where ϕ_{OH},

$$k_{HA}/k_{DA} = \phi_{OH}\phi_{HA}(1/\phi_{A^-})(1/\phi_{OH^+})^2 k_2^H/k_2^D \qquad (9)$$

ϕ_{HA}, ϕ_{A^-}, ϕ_{OH^+}, and k_2^H/k_2^D represent the fractionation factors for the OH group, the carboxylic acid, its anion, and the oxonium ion and the isotope effect on k_2 (eq 8), respectively. Suitable values for ϕ_{OH}, ϕ_{HA}, ϕ_{A^-}, and ϕ_{OH^+} are the fractionation factors for solvent water ($\phi = 1$),[44] acetic acid ($\phi = 0.96$),[45] acetate ion ($\phi = 0.89$),[45] and the lyonium ion ($\phi = 0.69$),[44] respectively. The value of k_2^H/k_2^D is unknown, but some consideration allows an upper limit of $k_2^H/k_2^D < 1.11$ to be deduced.[46] Thus an upper limit on the value of k_{HA}/k_{DA} for the mechanism of eq 8 can be calculated, from eq 9, as $k_{HA}/k_{DA} < 2.51$.

The reason for the observation of general acid catalysis in the case of the (*Z*) compound but not the (*E*) compound is uncertain, but some possible explanations can be ruled out. Concerted general acid catalysis would be enforced[57] in the case of the (*Z*) compound if the protonated (*Z*)-diazoic acid were too unstable to exist. Catalysis would not be observed in the corresponding (*E*) compound if the less reactive protonated (*E*)-diazoic acid had a substantial lifetime. However, this explanation is undermined by the fact that (*E*)-diazoic acids ((*E*)-2-butane-, (*E*)-1-butane-, and (*E*)-methanediazoic acid) that are as, or more, reactive as the (*Z*)-trifluoroethanediazoic acid exhibit no detectable general acid catalysis. It also seems unlikely that general acid catalysis of the (*E*) isomer becomes unobservable[57] because the difference in reactivity between the (*E*)- and (*Z*)-trifluoroethanediazoates manifests a shift in the transition state for general acid catalysis. Catalysis becomes difficult to observe as α approaches a value of 0.9–1.[57] In the present case catalysis would be difficult to observe if, in changing from the (*Z*) to the (*E*) form, the change in reactivity brings about a change in transition state structure that results in a much larger amount of proton transfer and consequently a larger value of Bronsted α. Indeed, inspection of a two-dimenstional reaction coordinate diagram[58] for the general acid catalyzed decomposition of the (*Z*)-trifluoroethanediazoic acid in which the transition state contains a reasonable diagonal component indicates that the change to the less reactive (*E*) compound should increase the value of Bronsted α. However the value of α is unlikely to change from a value of 0.4 to 0.9, in which case general acid catalysis would be hard to observe, given the small change in reactivity of 4.6 kcal/mol. In

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(44) Kresge, A. J.; More O'Ferrall, R. A.; Powell, M. F. In *Isotopes in Organic Chemistry*; Buncel, E., Ed.; Elsevier: Amsterdam, The Netherlands, 1987; Vol. 7.

(45) Gold, V.; Lowe, B. M. *J. Chem. Soc. A* **1968**, 1923.

(46) The value of k_2^H/k_2^D, and thus k_{HA}/k_{DA}, would be maximal, for a highly asymetric transition state in which there is essentially complete proton transfer with minimal N–O bond cleavage. Such a transition state would then resemble a carbanion that is hydrogen bonded with the conjugate carboxylic acid. The value of k_2^H/k_2^D could be appreciably greater than 1 if there were a transfer fractionation factor for such a carbanionic transition state that was less than unity. The expression for k_2^H/k_2^D could then be represented as the ratio of the fractionation factor for loss of carboxylate anion in going to the transition state divided by the transfer fractionation factor, ϕ_{C^-}, for formation of the carbanion, thus $k_2^H/k_2^D = \phi_{A^-}/\phi_{C^-}$. A value of ϕ_{C^-} for cyanide ion has been calculated $\phi_{CN^-} = 0.84$.[47] Others can be calculated[48] from equilibrium isotope effects on carbon acid ionizations or from solvent deuterium isotope effects on the rate constants for carbon acid hydron exchange in reactions where the transition state is quite late or known to involve diffusional separation of the catalyst conjugate acid–carbanion pair. For nine such values, it is concluded that $\phi_{C^-} > 0.8$ represents the lower limit. Thus $k_2^H/k_2^D = \phi_{A^-}/\phi_{C^-} < 0.89/0.80 < 1.11$. It should be noted that the values calculated from isotope effects on ionization equilibria represent true lower limits because they may contain a contribution due to the difference in the strength of hydrogen bonds to the carbanions by HOH compared to DOD where as in the present case the transition state contains the same $A\text{–}H\cdot C^-$ interaction in both H_2O and D_2O.

(47) Reenstra, W. W.; Abeles, R. H.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 1016.

(48) The lower limit for ϕ_{C^-} can be calculated directly, from the isotope effects on equilibrium ionization of some carbon acids, using $\phi_{OH^+} = 0.69$ for the hydronium ion. The values of $\phi_{C^-} = 0.80$, 0.90, and 0.81 for 2-acetylcyclohexanone,[49] methylacetylacetone,[49] and *tert*-butylmalononitrile,[50] respectively. Values of ϕ_{C^-} can be estimated from solvent isotope effects on proton-transfer reactions of carbon acids in which the transition state is very late with respect to proton transfer or in which the rate-limiting step in proton abstraction involves diffusion apart of the carbanion from the conjugate acid. The values of $\phi_{C^-} = 0.81$, 0.81, and 0.80 are calculated from k_{H_2O}/k_{D_2O} for the triethylamine-catalyzed detritiation of 1,4-dicyano-2-butene,[49] the lyoxide ion-catalyzed tritium incorporation into chloroform,[51] and the acetate ion-catalyzed detritiation of *tert*-butylmalononitrile,[52] respectively, using the values for fractionation factors for lyoxide ion, acetate ion, and acetic acid as indicated in refs 44 and 45. The late transition states for these reactions are indicated by the large values of Bronsted $\beta = 0.98$,[49] 1.12,[53] and 0.98,[54] respectively. Values of ϕ_{C^-} between 1 and 0.87 and of $\phi_{C^-} = 0.84$ can be calculated for the anion of thiamine on the basis of the solvent isotope effects for tritium abstraction by water and acetate, respectively, again using other fractionation factor values as in ref 44 and 45 and a difference in viscosity between H_2O and D_2O of 22%.[55] The rate-limiting step in these reactions has recently been shown to involve diffusion apart of the thiamine anion from the conjugate acids lyonium ion and acetic acids.[56]

(49) Walters, E. A.; Long, F. A. *J. Am. Chem. Soc.* **1969**, *91*, 3733.

(50) Hibbert, F.; Long, F. A. *J. Am. Chem. Soc.* **1971**, *93*, 2836.

(51) Kresge, A. J.; Lin, A. C. *J. Am. Chem. Soc.* **1975**, *97*, 6257.

(52) Hojatti, M.; Kresge, A. J.; Wang, W.-H. *J. Am. Chem. Soc.* **1987**, *109*, 4028.

(53) Lin, A. C.; Chiang, Y.; Dahlberg, D. B.; Kresge, A. J. *J. Am. Chem. Soc.* **1983**, *105*, 5380.

(54) Hibbert, F.; Long, F. A.; Walters, E. A. *J. Am. Chem. Soc.* **1971**, *93*, 2829.

(55) Millero, F. J.; Dexter,R.; Hoff, E. *J. Chem. Eng. Data* **1971**, *16*, 85.

(56) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 674.

(57) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425.

(58) Lowry, T. H.; Richardson, K. S. *Mechanisms and Theory in Organic Chemistry*, 3rd ed.; Harper and Row: New York, 1987.

addition, as above, a similar or greater change in reactivity within the series of (*E*)-diazoic acids does not manifest the onset of catalysis.

The present study is in contrast to the decomposition of areneazo ethers[38] and aralkyltriazenes,[33] for which the (*E*) compounds exhibit measurable general acid catalysis via a mechanism analogous to that of eq 7 while catalysis has not been reported for the (*Z*)-areneazo ethers and the (*Z*)-triazenes have not been isolated. The effects of structure on the general acid catalyzed decomposition of (*Z*)-diazoic acids are currently under investigation.

The results provide the first quantitative analysis of the difference in reactivity between identically substituted (*Z*)- and (*E*)-alkanediazoates. The trifluoroethanediazoates have identical rate laws for the buffer-independent process with the ratios of the pH-independent and hydrogen ion-dependent reaction constants of the diazoic acids being $k_1^{\mathrm{syn}}/k_1^{\mathrm{anti}} = 2600$ and $k_{\mathrm{H}}^{\mathrm{syn}}/k_{\mathrm{H}}^{\mathrm{anti}} = 11\,000$, respectively. Reactivity differences between (*E*) and (*Z*) isomers of as much as $\sim 10^8$ are known or can be calculated from the data in the literature.[59] The differences are often ascribed to the antiperiplanar arrangement of the lone pair on nitrogen and the scissile bond. While a substantial stereoelectronic effect is required in the cases where an especially large rate constant ratio is observed, there are substantial differences in the ground-state energies of the isomers[65] that may substantially contribute to the observed differences in rate constants, particularly in the case of reactions with product-like transition states.

While the mechanism for the pH-independent reaction of the (*E*)-diazoic acids, k_1^E, is now clearly understood (vide supra), it must be emphasized that the mechanism of the pH-independent decomposition of the (*Z*)-diazoic acid, k_1^Z, is less certain. The product deuterium incorporation studies indicate that neither an S_N2 mechanism nor an elimination reaction is operative. Entry 5 in Table 2 indicates that 97% of the iodotrifluoroethane contains at least a single deuterium, so that an S_N2 reaction with the diazoic acid and iodide ion is ruled out. Entry 7 in Table 2 indicates that the diazoalkane is not a required intermediate, as would be expected in the case of an elimination reaction, because 48% of the product thioether contains the two protons attached to the reactant diazoate. The two likely mechanisms for the pH-independent decomposition of the (*Z*)-diazoic acid are the unassisted N–O bond cleavage to give the diazonium ion as in eq 1 (identical with the mechanism for primary (*E*)-diazoic acids) and N–O cleavage that is assisted by proton donation from a water molecule to the departing OH^- group (analogous to the mechanism deduced for the general acid catalyzed reaction in the form of eq 10, as discussed further below). This uncertainty in the mechanism for the k_0^Z reaction means that the k_0^Z/k_0^E ratio of 2600 represents an upper limit for the difference in reactivity with respect to the mechanism involving unassisted formation of the diazonium ion (eq 1). There is a similar uncertainty about the values of k_0^Z/k_0^E for the reactions of arenediazo ethers[38] and arenediazoic acids,[69] for which general acid catalysis of decomposition of the (*E*) forms has been observed.

The mechanism for the buffer-independent–pH-independent decomposition of the (*Z*)-trifluoroethanediazoate may be identical to that for the observed general acid catalysis, as written in eq 10. The larger negative value of $\Delta S\# = -46$ J/(deg mol) is substantially different from the values observed for the (*E*) compounds, which decompose by unassisted mechanisms (eq 1) and is consistent with greater entropic demand of the transition state for eq 10 compared to eq 1. The point for the catalysis by water lies 1.5 log units above the Bronsted line extrapolated from the points for the carboxylic acid catalysts (Figure 5), and given the long extrapolation, this deviation is not significant enough to give weight to either the mechanism of eq 10 or that of eq 1. The mechanism of eq 10 does not necessarily violate Jencks's rule[70] that requires proton transfer to become thermodynamically favorable in the course of the reaction. This is because the hydroxide ion that is adjacent to the diazonium ion in the alternative stepwise reaction (as in eq 1) may be significantly more basic compared to a hydroxide ion in bulk solution. Compared to bulk solution the hydroxide ion adjacent to the diazonium ion is solvated by one less water molecule. The hydrogen-bonding interaction of a solvating water molecule adjacent to the hydroxide ion has been estimated to be stabilizing by between 2 and 7 kcal/mol on the basis of the change in solvent isotope effect on lyoxide ion-catalyzed detritiation of substituted thiamines[71] and of the change in pK_a of H_2O in going from solvent water to solvent DMSO,[72] respectively. The extent to which this loss of stabilization is counterbalanced by favorable electrostatic interactions between the hydroxide and diazonium ions is unclear because according to the recent theoretical calculations of Glaser and co-workers[73] the positive charge in the diazonium ion is diffuse and lies mainly in the carbon skeleton.

$$CF_3CH_2\overset{+}{N_2}\cdot HOH\cdot \overset{-}{O}H \qquad (10)$$

Biological Importance. The present study establishes that in general simple (*E*)-alkanediazoates decompose with rate-limiting N–O bond heterolysis that is unassisted and that yields diazonium ions that are diffusionally equilibrated intermediates. There is no evidence to indicate the intervention of concurrent S_N2 displacements on the diazoic acid even in the presence of quite

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[59] Values of k_Z/k_E of as much as 6×10^7 have been deduced in the case of nitrilium ion-forming eliminations of C-substituted imines.[60] A lower limit of $k_Z/k_E > 4500$ can be calculated from the known rate constant for decomposition of the (*E*)-nitrolic acid and a lower limit for the (*Z*) isomer based on the observation that it is a steady-state intermediate in the decay of the (*Z*)-ester to the nitrile oxide.[61] A ratio of $k_Z/k_E = 10^5$ was determined for the diazonium ion-forming decomposition of *p*-nitrobenzenediazo ethers,[37] and similar numbers can be calculated from the available data for other substituted benzenediazo ethers.[35,37] Values of $k_Z/k_E \sim 4 \times 10^6$ and 5×10^6 can be calculated for the diazonium ion-forming decomposition of benzene- and toluenediazoates, respectively. This is based on the reported rate constants for diazonium ion formation from the (*E*)-diazoate, on the analogous rate constant for the (*Z*) compound calculated from the rate constant for (*Z*)-diazoic acid formation from the reaction of hydroxide ion and the diazonium ion, and on equilibrium constants for diazoate formation from the diazonium ions.[25,62,63] The pK_a for the (*Z*) compounds was calculated on the basis of the observation that the (*Z*)-arenediazoic acids are one long unit less acidic than the corresponding (*E*) forms[64] and the reported pK_a values.[25]

(60) Hegarty, A. F.; Mullane, M. *Chem. Commun.* **1984**, 229. Hegarty, A. F.; Mullane, M. *J. Chem. Soc., Perkin Trans. 2* **1986**, 995.

(61) Egar, C.; Clery, M.; Hegarty, A. F.; Welch, A. J. *J. Chem. Soc., Perkin Trans 2* **1991**, 249.

(62) Lewis, E. S.; Suhr, H. *Chem. Ber.* **1958**, *91*, 2350.

(63) Ritchie, C. D.; Wright, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 6574.

(64) Sterba, V. In *The Chemistry of the Diazonium and Diazo Groups, Part 1*; Patai, S., Ed.; J. Wiley and Sons: New York, 1978.

(65) The (*E*)-*p*-nitrobenzenediazoate is 2.8 kcal/mol more stable than the (*Z*) isomer on the basis of the rate constants reported for the forward and reverse isomerization processes.[66] A difference of ~4 kcal/mol for the 4-nitrobenzenediazomethyl ethers can be calculated from the forward and reverse rate constants measured for diazonium ion formation by the (*E*) and (*Z*) isomers and the ratio $k_Z/k_E = 10^5$ known for the rate constants for diazonium ion formation from the ethers in the case of the analogous ethyl ethers.[36,37,67] Note also that the difference in energy of (*E*)- and (*Z*)-triazenes has been calculated to be as much as 6.5 ± 1 kcal/mol[68] while for simple azines (excluding fluorinated species) the differences are ~6 kcal/mol in favor of the (*E*) forms.[29]

(66) Goodman, P. D.; Kemp, T. J.; Pinot de Moira, P. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1221.

(67) Ritchie, C. D.; Virtanen, P. O. I. *J. Am. Chem. Soc.* **1972**, *94*, 1589.

(68) Nguyen, M. T.; Kanefi, J.; Hoesch, L.; Drieding, A. S. *Helv. Chim. Acta* **1984**, *67*, 1918. Nguyen, M. T.; Hoesch, L. *Helv. Chim. Acta* **1986**, *69*, 1627. Schmiedekamp, A.; Smith, R. H.; Michejda, C. J. *J. Org. Chem.* **1988**, *53*, 3433.

(69) Machackova, O. Sterba, V. *Collect. Czech. Chem. Commun.* **1972**, *37*, 3313.

(70) Jencks, W. P. *J. Am. Chem. Soc.* **1972**, *94*, 4731.

(71) Washabaugh, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 683.

(72) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 7251.

(73) Glaser, R.; Choy, G. S.-C.; Hall, M. K. *J. Am. Chem. Soc.* **1991**, *113*, 1109.

powerful nucleophiles such as iodide ion, hydrazine, and primary amines. Such an S_N2 mechanism is thus highly unlikely in the reactions of primary (*E*)-alkanediazoic acids with comparatively very weakly nucleophilic sites on DNA, in contrast to what has been posited.[9]

The observation that, in the case of the trifluoroethanediazoic acids, the (*Z*) isomer is more reactive than the (*E*) isomer by a factor of 2600 has some important implications with regard to conclusions that can be reached from some studies about the differences in the biological activities of the (*E*) compared to (*Z*) compounds. The conclusion that the (*E*)-2-haloethanediazoates are the "key" electrophiles[9a] for the cancer chemotherapeutic activities of the precursor *N*-(2-haloethyl)-*N*-nitrosoureas appears premature. The conclusion was based in large part on the fact that the (*E*)-2-chloroethanediazoate, but not the (*Z*) form, has antileukemic activity in vivo and DNA cross-linking activity in vitro. Assuming the (*E*) and (*Z*) isomers have a difference in reactivity that is similar to that observed in the case of the trifluoroethanediazoates, the half-life of the (*Z*)-2-chloroethanediazoate extrapolated from the plot of Figure 4 is on the order of 1 ms. Thus, much of the (*Z*) form would be inactivated in the dosing time in in vivo experiments and the mixing time in in vitro experiments, presumably prior to its dissemination to target tissues and sites, respectively. Both (*E*)- and (*Z*)-2-haloethanediazoates are sufficiently long-lived to alkylate DNA subsequent to their delivery to the target cells in the form of the relatively longer lived parent *N*-nitrosoureas. An alternative mechanism for DNA cross-linking by (haloethyl)nitrosoureas has been considered[74] and criticized.[75]

A similar caveat must be considered in rationalizing the observations that some (*Z*)-diazoates are less mutagenic in bacteria[15] and less mutagenic and cytotoxic in mammalian cells.[16] It is essential in interpreting the data to take account of the reactivity difference between the isomers, as indicated above. The half-lives at physiological pH of the more reactive primary (*Z*)-diazoates studied (methane-, ethane-, propane-, and butanediazoates)[15,16] are likely in the millisecond to microsecond time range assuming the (*Z*)/(*E*) reactivity ratio is roughly similar to what is observed in the present study for the trifluoroethanediazoates. These short lifetimes suggest that a considerably larger fraction of the (*Z*)-diazoate is subject to destruction within the mixing time of the experiment. Whether there are other differences in the decomposition chemistry between the (*E*) and (*Z*) isomers that manifest a difference in biological activity is yet to be determined.

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Supplementary Material Available: Tables of rate constants and experimental conditions for the decomposition of various alkanediazoates, and figures showing change in absorbance vs time, UV absorbance spectra, and second order rate constant vs percent acid form of the buffer (31 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[74] Buckley, N. *J. Am. Chem. Soc.* **1987**, *109*, 7918. Buckley, N.; Brent, T. P. *J. Am. Chem. Soc.* **1988**, *110*, 7520.

[75] Wurdeman, R. L.; Church, K. M.; Gold, B. *J. Am. Chem. Soc.* **1989**, *111*, 6408. Bleasdale, C.; Golding, B. T.; McGinnis, J.; Muller, S.; Watson, W. P. *J. Chem. Soc., Chem. Commun.* **1991**, 1726.