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Mechanisms of Benzyl Group Transfer in the Decay of (*E*)-Arylmethanediazoates and Aryldiazomethanes in Aqueous Solutions

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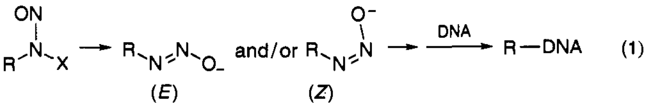
Abstract: Rate constants are reported for the buffer-independent decay of ten (*E*)-arylmethanediazoates in aqueous media at 25 °C, ionic strength 1 M ($NaClO_4$), 4% 2-propanol, in the region of pH 4−12. The rate constants are proportional to hydrogen ion concentration at high pH and become pH independent in the low-pH region. Varying concentrations of oxyanion, amine, and hydrazine buffers over the range 0.05−0.2 M increased the pseudo-first-order rate constant for decay of the diazoates by less than 10%. The azide−water selectivities, k_a/k_s, for partitioning of the benzyl groups in the decay of (*E*)-(3,5-bis(trifluoromethyl)phenyl)methanediazoate and the (3,5-bis-(trifluoromethyl)phenyl)diazomethane are determined to be 0.20 and 0.21 M^{-1}, respectively, in phosphate buffered water and 0.27 and 0.26 M^{-1}, respectively, in 20/80 DMSO−water. It is concluded that these two reactants decompose, in these media, via a common free diazonium ion intermediate that is formed in the case of the diazoate upon unassisted N−O bond cleavage of the diazoic acid. A common rate-limiting step is indicated for all the diazoates by the correlation line for the plot of log k_1, the pH independent rate constant, against σ that has a slope $\varrho = -1.23$. Product ratios for trapping of benzyl groups derived from other pairs of arylmethanediazoates and aryldiazomethanes with less electron withdrawing groups are different outside experimental error, indicating the importance of different nitrogen-separated ion pairs in these reactions. The (*E*)-(*p*-methoxy)phenyl)methane-^{16}O-diazoate decomposes in $^{16}O/^{18}O$ water to give alcohol that has an "excess" abundance of ^{16}O compared to solvent. Decomposition of the same compound in 50/50 trifluoroethanol−water with varying concentrations of azide indicates that azide ion appears to trap a limiting amount, ~80%, of the *p*-methoxybenzyl group. Quantitative analysis of the data indicates that 16% of the *p*-methoxybenzyl cation is trapped by solvent at the nitrogen-separated ion pair stage, in the absence of azide ion. There is a 9-fold enhancement of selectivity for trifluoroethanol at the ion pair stage that is ascribed to a proton switch initiated by the leaving hydroxide ion in the ion pair. The values of $k_a/k_s \sim 0.2$ M^{-1} and $k_T/k_H \sim$ 0.5−0.6 for the trifluoroethanol−water selectivity and $k_{ET}/k_T \sim 1$ for the ethanol−trifluoroethanol selectivity are independent of substituent in the decay of arylmethanediazoates (X = H and EWG) in water, water−trifluoroethanol (50/50), and water−trifluoroethanol−ethanol (50/40/10), respectively. It is concluded from this that the product-determining steps do not involve chemical bonding but rather rotational/translational reorientation of the nucleophiles in the first solvation sphere of the carbocation intermediates. It is concluded that the values of $k_H/k_T = 0.5−0.6$ indicate preferential solvation of the cation precursor by trifluoroethanol. It is shown that a preferential interaction for trifluoroethanol of <1 kcal/mol is required to generate the observed selectivities.

Introduction

The carcinogenicity, mutagenicity and cancer chemotherapeutic activity of compounds containing the *N*-alkyl-*N*-nitroso moiety is believed to be due to the formation upon decomposition of alkanediazoates that subsequently alkylate DNA (eq 1).[1]



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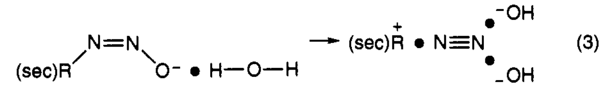
Recent reports have summarized evidence that the rate-limiting step for the decomposition at physiological pH of the (*E*)-methane-,[2] (*E*)-primary alkane-,[3] (*E*)-2-butane-,[4] and (*Z*)-trifluoroethanediazoates[3] involves N−O bond fission of the diazoic acid to yield diazonium ions as in eq 2.

$$R{-}N{=}N{-}O^- + H^+ \underset{K_a}{\rightleftharpoons} R{-}N{=}N{-}OH \xrightarrow{k_1} R{-}\overset{+}{N}{\equiv}N + {}^-OH \quad (2)$$

The generality of this mechanism remains in question. Moss concluded from a series of experiments, involving a combination of stereochemical and diazoate−oxygen scrambling experiments with secondary *syn*-alkanediazoates, that the results were best interpreted in terms of the rate-limiting formation of an ion triplet as in eq 3.[5] The dependence of the mechanism upon the structure of the putative carbocation was emphasized, with the



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[⊗] Abstract published in *Advance ACS Abstracts*, April 1, 1995.

[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, 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.; Ho, J.; Fishbein, J. C. *J. Am. Chem. Soc.* **1993,** *115,* 3016.

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

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mechanism of eq 3 intervening only in the case of systems capable of forming secondary and more stable cations.

The factors that control alkylating selectivity of alkanediazoates, diazonium ions, and carbocations are central to understanding the fundamental aspects of nitrosamine carcinogenesis. Though much-investigated they are not well-understood.[6-8] Some recent investigations of the selectivities of a range of aralkylating agents, some derived from *N*-nitrosoureas, for nucleophilic sites on some DNA bases have led to some important conclusions about factors affecting selectivity.[9-11] However, the basis for some observed selectivities, particularly those of aralkylating agents derived from nitrosoureas, remains obscure.

The present report is a detailed investigation of the effects of the structure of (*E*)-arylmethanediazoates and aryldiazomethanes on the mechanisms of decomposition and the factors that control the product-determining steps in benzyl group transfer in these reactions.

Experimental Section

Materials. Chemicals were generally purchased as ACS or analytical grade. Organic chemicals were further purified where necessary by recrystallization or distillation.

Sodium (*E*)-Arylmethanediazoates. All diazoates, except sodium (*E*)-(3,5-bis(trifluoromethyl)phenyl)methanediazoate, were synthesized by the method adapted from Thiel.[12] A typical procedure is described for sodium (*E*)-phenylmethanediazoate.

All procedures were carried out under an argon atmosphere and employed oven-dried glassware, Thus, 0.32 g (13.9 mM) of sodium was reacted with 10 mL of absolute ethanol. When the reaction was complete, 30 mL of dry diethyl ether and 1.71 g (13.9 mM) of benzylhydrazine were added followed by the dropwise addition of 3.26 mL (2.88 g, 27.8 mM) of *n*-butyl nitrite. White precipitation formed after 30 min and reaction was complete after 16 h. Diazoate was isolated by filtration, and the filtrate was washed with diethyl ether and dried and stored in a vacuum desiccator. The yield was not measured. ^{1}H NMR (DMSO-d_6) δ 7.22 (m, 5 H), 4.26 (s, 2 H). Anal. Calcd: C, 53.17; H, 4.46; N, 17.71. Found: C, 52.88; H, 4.41; N, 17.58.

Other diazoates synthesized by essentially the same procedure were the following. Sodium (*E*)-(4-(dimethylamino)phenyl)methanediazoate: ^{1}H NMR (DMSO-d_6) δ 7.03 (d, 2 H), 6.63 (d, 2 H), 4.52 (s, 2 H), 3.41 (s, 6 H). Anal. Calcd: C, 53.73; H, 6.01; N, 20.88. Found: C, 53.56; H, 6.05; N, 20.78. Sodium (*E*)-(4-methoxyphenyl)-methanediazoate: ^{1}H NMR (DMSO-d_6) δ 7.12 (d, 2 H), 6.81 (d, 2 H), 4.56 (s, 2 H), 3.70 (s, 3 H). Anal. Calcd: C, 51.07; H, 4.82; N, 14.89. Found: C, 50.97; H, 4.86; N, 14.86. Sodium (*E*)-(4-methylphenyl)-methanediazoate: ^{1}H NMR (DMSO-d_6) δ 7.07 (q, 4 H), 4.58 (s, 2 H), 2.24 (s, 3 H). Anal. Calcd: C, 55.81; H, 5.27; N, 16.27. Found: C, 54.89; H, 5.28; N, 16.01. Sodium (*E*)-(4-chlorophenyl)methanediazoate: ^{1}H NMR (DMSO-d_6) δ 7.26 (q, 4 H), 4.62 (s, 2 H). Anal. Calcd: C, 43.66; H, 3.14; N, 14.55. Found: C, 43.51; H, 3.21; N, 14.51. Sodium (*E*)-(4-(trifluoromethyl)phenyl)methanediazoate: ^{1}H NMR (DMSO-d_6) δ 7.62 (d, 2 H), 7.46 (d, 2 H), 4.73 (s, 2 H). Anal. Calcd: C, 42.49; H, 2.67; N, 12.39. Found: C, 41.77; H, 2.72; N, 12.51. Sodium (*E*)-(3,5-dichlorophenyl)methanediazoate: ^{1}H NMR (DMSO-d_6) δ 7.37 (s, 1 H), 7.25 (s, 2 H), 4.64 (s, 2 H). Anal. Calcd: C, 37.03; H, 2.22; N, 12.34. Found: C, 37.12; H, 2.23; N, 12.34. Sodium (*E*)-(pentafluorophenyl)methanediazoate: ^{1}H NMR (DMSO-d_6) δ 4.69 (s).

Sodium (3,5-bis(trifluoromethyl)phenyl)methanediazoate and sodium diphenylmethanediazoate were prepared analogously except that anhydrous ethanol was the solvent. After 15 h of reaction, diazoate was precipitated by adding 10 volumes of diethyl ether to the reaction solution. Sodium (3,5-bis(trifluoromethyl)phenyl)methanediazoate: ^{1}H NMR (DMSO-d_6) δ 7.88 (s, 3 H), 4.81 (s, 2 H). Anal. Calcd: C, 36.75; H, 1.71; N, 9.52. Found: C, 31.87; H, 2.41; N, 8.38. Sodium diphenylmethanediazoate: ^{1}H NMR (DMSO-d_6) δ 7.28 (m, 10 H), 5.88 (s, 1 H).

Benzylhydrazines. All benzylhydrazines, except 4-(dimethylamino)benzylhydrazine, were synthesized by a modified literature procedure.[13a] A typical procedure is described for 3,5-dichlorobenzylhydrazine. Yields were not optimized but hydrazines that were spectroscopically pure (^{1}H NMR) were obtained.

To 5 mL (159 mM) of anhydrous hydrazine maintained at 0 °C was added dropwise 3.0 g (15.3 mM) of 3,5-dichlorobenzyl chloride in 15 mL of dry methanol. After 2 h at room temperature the reaction was complete (^{1}H NMR). Methanol was removed by a rotavapor and the residue was extracted with 3 × 30 mL of diethyl ether. The diethyl ether was removed by a rotavapor and the residue distilled under reduced pressure. The fraction boiling at 120 °C (less than 1 mmHg) was collected, yielding 1.65 g (56%). ^{1}H NMR (DMSO-d_6) δ 7.39 (s, 1 H), 7.35 (s, 2 H), 3.73 (s, 2 H), 3.51 (b, 5 H).

Other benzylhydrazines synthesized were the following. 4-Methoxybenzylhydrazine: bp 139 °C (5 mmHg); yield 54%; ^{1}H NMR (DMSO-d_6) δ 7.20 (d, 2 H), 6.68 (d, 2 H), 3.72 (s, 3 H), 3.65 (s, 2 H), 3.34 (b, 5 H). 4-Methylbenzylhydrazine: bp 108−111 °C (4 mmHg); yield 63%; ^{1}H NMR (DMSO-d_6) δ 7.18 (d, 2 H), 7.10 (d, 2 H), 3.67 (s, 2 H), 3.35 (b, 5 H), 2.26 (s, 3 H). Benzylhydrazine: bp 111−5 °C (15 mmHg); yield 37%; ^{1}H NMR (DMSO-d_6) δ 7.29 (m, 5 H), 3.72 (s, 2 H), 3.38 (b, 5 H). 4-Chlorobenzylhydrazine: bp 133−5 °C (5 mmHg); yield 33%; ^{1}H NMR (DMSO-d_6) δ 7.33 (s, 4 H), 3.71 (s, 2 H), 3.41 (b, 5 H). 4-(Trifluoromethyl)benzylhydrazine: bp 130 °C (7 mmHg); yield 40%; ^{1}H NMR (DMSO-d_6) δ 7.62 (t, 2 H), 7.57 (d, 2 H), 3.82 (s, 2 H), 3.51 (b, 5 H). 3,5-Bis(trifluoromethyl)benzylhydrazine: bp 69 °C (less than 1 mmHg); yield 83%; ^{1}H NMR (DMSO-d_6) δ 8.00 (s, 2 H), 7.92 (s, 1 H), 3.89 (s, 2 H), 3.51 (b, 5 H). Pentafluorobenzylhydrazine: bp 62 °C (less than 1 mmHg); yield 51%; ^{1}H NMR (DMSO-d_6) δ 3.82 (s, 2 H), 3.57 (b, 5 H).

4-(Dimethylamino)benzylhydrazine was synthesized as described in the literature:[13b] bp 167 °C (7 mmHg); yield 45%; ^{1}H NMR (DMSO-d_6) δ 7.12 (d, 2 H), 6.66 (d, 2 H), 3.62 (s, 2 H), 3.28 (b, 5 H), 2.83 (s, 6 H).

Aryldiazomethanes. These were synthesized using the method of Creary.[14] 3,5-Bis(trifluoromethyl)phenyldiazomethane: ^{1}H NMR (DMSO-d_6) δ 7.52 (s, 2 H), 7.49 (s, 1 H), 6.01 (s, 1 H); UV spectra (MeCN) 204 nm, 222 nm, 291 nm (max). 3-Chlorophenyldiazomethane: ^{1}H NMR (DMSO-d_6) δ 7.28 (5, 1 H), 7.00 (d, 2 H), 6.92 (d, 1 H), 5.76 (s, 1 H); UV spectra (MeCN) 226 nm, 284 nm (max). 4-Methylphenyldiazomethane: ^{1}H NMR (DMSO-d_6) δ 7.11 (d, 2 H), 6.86 (d, 2 H), 5.66 (s, 1 H), 2.24 (s, 3 H). UV spectra (MeCN) 280 nm (max). Phenyldiazomethane: ^{1}H NMR (DMSO-d_6) δ 7.28 (t, 2 H), 7.00 (q, 3 H), 5.69 (s, 1 H); UV spectra (MeCN) 222 nm, 280 nm (max).

Kinetics. The kinetics of decay of diazoates were monitored at 225, 230, or 235 nm, as previously described,[2-4] using an Applied Photophysics DXMV.17 stopped-flow spectrophotometer or Milton Roy 1001+ or 3000 spectrophotometers.

Products. Products were separated and quantified after 10-half-lives of decay using a Waters chromatography system with Axxiom data system and Waters Wisp-Ultra autoinjector attached. Separations were carried out using a 15 cm Waters C-18 μ-bondapak column in series with another 15 cm C-18 column (Column Resolution Inc., San Jose). Random checks entailing re-injection and quantitation of products after 15 and 20 halftimes of reactions indicated that the products were stable to the reaction conditions. Quantitation of the products was achieved by interpolation from standard curves, containing

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(6) Dipple, A. *Chemical Carcinogens* Politzer, P., Martin, J. F., Eds.; Elsevier: New York, 1988; p 32. Dipple, A.; Moschel, R. C. *Mutation and the Environment*; Wiley-Liss Inc.: New York, 1990; p 71.

(7) Church, K. M.; Gold, B. *Chem. Res. Tox.* **1988**, *1*, 269.

(8) Loechler, E. L. *Chem. Res. Tox.* **1994**, *7*, 277.

(9) Moschel, R. C.; Hudgins, W. R.; Dipple, A. *J. Org. Chem.* **1979**, *44*, 3324.

(10) Moschel, R. C.; Hudgins, W. R.; Dipple, A. *J. Org. Chem.* **1980**, *45*, 533.

(11) Moschel, R. C.; Hudgins, W. R.; Dipple, A. *J. Org. Chem.* **1986**, *51*, 4180.

(12) Thiele, J. *Chem. Ber.* **1908**, *41*, 2806.

(13) (a) Anderson, F. E.; Kaminsky, D.; Dubnick, B.; Klutchko, S. R.; Cetenko, W. A., Gylys, J.; Hart, J. A. *J. Med. Pharm. Chem.* **1962**, *5*, 221. (b) Hoffmann-LaRoche & Co., A-G., Brit. Patent 880,278; *Chem. Abs.* **1962**, *57*, 4592b.

(14) Creary, X. *J. Am. Chem. Soc.* **1980**, *102*, 1611.

at least three points, that were generated from products that were either commercially available or synthesized by literature methods.

"Excess ^{16}O Incorporation". Experiments were carried out to detect if the ^{16}O in the original diazoate returned to give the alcohol product in the course of decomposition in isotopically mixed $^{16}O/^{18}O$ water. The diazoate was allowed to decay for 10–15 half-lives in 1 mL of ~50/50 $H_2{}^{16}O/H_2{}^{18}O$ after which the reaction solution was extracted with 3 × 1.5 mL of freshly distilled ether. The ether layers were removed each time with a pasteur pipet, combined, and dried by passage through a pasteur pipet containing $MgSO_4$. The ether was evaporated off with a stream of argon and the sample, dissolved in anhydrous ethanol, was analyzed on a Hewlett Packard 5890 GC/MS. The exact ^{18}O composition of the water was determined by injecting 1 μL of phenylacetaldehyde and 0.2 mL of freshly distilled acetonitrile into the spent reaction mixture and allowing the exchange to proceed for at least 15 h. After this time the acetonitrile was mostly removed under a stream of argon, cloudiness indicating sufficient concentration, and the aldehyde was isolated by ether extraction as above.

Ratios of ^{16}O- and ^{18}O-containing products were the average of ratios from at least four analyses per compound.

Deuterium Incorporation. Diazoates were dissolved to a final concentration of 0.05 M in 5 mL of aqueous solutions in which the exchangeable hydrons were more than 99% enriched with deuterium. Decomposition was allowed to proceed for various times (see Results) after which the solution was extracted two times with 10 mL of ether. In the case of experiments employing diazabicyclo[2.2.2]octane (DABCO) buffers, the ether extract was extracted with 10 mL of 1 M HCl and then 2 × 10 mL of H_2O. The ether phase was dried by passage through a column of $MgSO_4$, evaporated under a stream of argon, reconstituted by addition of 200 μL of anhydrous ethanol, and analyzed by GC/MS. Additional experiments with the (*E*)-(3,5-dichlorophenyl)-methanediazoate were attempted in solutions containing 3 M NaOD (60 °C) but a colored precipitate formed within hours of initiation of the reaction and no extractable alcohol product was detected by GC/MS.

Results

Kinetics. For all the diazoates studied, the change in absorbance due to diazoate and diazoic acid decay that was observed at 225, 230, or 235 nm obeyed a single exponential process with semilogarithmic plots of the decay being linear for ≥5 half-lives. First-order rate constants, k_{obsd}, for the decay of substituted arylmethandiazoates were determined in the range of pH between 4 and 13 in various aqueous oxyanion and amine buffers at 25 °C, ionic strength 1 M ($NaClO_4$), 4% 2-propanol. With one exception, the effect of changing buffer concentration, which was typically varied at a given buffer ratio between 0.05 and 0.20 M, had a negligible effect of the value of k_{obsd}. The buffers used for each diazoate included acetic acid, biphosphate, primary and secondary amines, and hydrazine. In no case did the value of k_{obsd} at the highest concentrations of these buffers increase by more than 10% above the value of k_0, the buffer-independent rate constant derived by extrapolation of the plots of k_{obsd} against buffer concentration to the intercept. A total of 42 such experiments involved primary and secondary amines and hydrazine. In the case of borate buffers, particularly at high fractions of borate anion, the value of k_{obsd} decreased by as much as 50% as the buffer concentration changed from 0.05 to 0.20 M. This did not obviate an accurate extrapolation to a value of k_0 and the effect of borate buffer was not further investigated. Values of k_0 as a function of pH are plotted in Figure 1 for the ten diazoates studied.

Both the solvent deuterium isotope effects on k_0 and $k_0^{H_2O}/k_0^{D_2O}$ and activation parameters that characterize the pH-independent region in Figure 1 were determined in certain cases. The values are included in Table 1.

Products. The product alcohols formed in the decay of diazoates in aqueous 0.005 M NaOH were quantitated by HPLC and the yields, which are nearly quantitative, are summarized in Table 1.

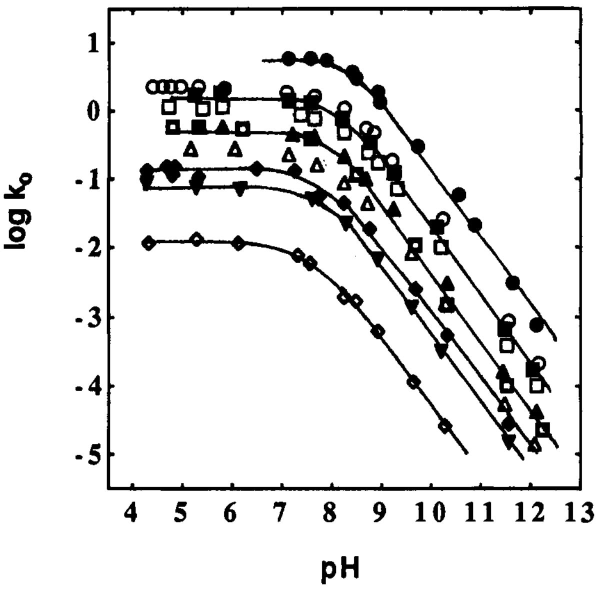


Figure 1. Plot of log k_0, the buffer-independent rate constant for decay of (*E*)-arylmethanediazoates in water, 4% 2-propanol, ionic strength 1 M ($NaClO_4$), 25 °C, against pH. Substituents are represented by symbols as follows: 4-$N(CH_3)_2$, ●; 4-OCH_3, ○; 4-CH_3, ■; 4-H, □; 4-Cl, ▲; 4-CF_3, △; 3,5-Cl_2, ◆; 3,5-$(CF_3)_2$, ▼; 2,3,4,5,6-F_5, ◇; diphenyl, □. Solid lines are fits to eq 4 using constants k_1 and K_a in Table 1. Some fits are omitted for clarity.

Partitioning of the substituted benzyl group during decomposition between pairs of solvent nucleophiles in mixed solvents was studied by carrying out the decomposition reactions either in 50%/50% trifluorethanol–water and quantitating the product ratio of alcohol–trifluoroethyl ether or in 50/40/10 water–trifluoroethanol–ethanol and quantitating the ether to alcohol ratios. The data are summarized in Table 2. Partitioining ratios for the reaction in solvent water between H_2O and azide ion, in aqueous solutions, are summarized in Table 3. For comparison, an analogous study was carried out on some benzyl chlorides and aryldiazomethanes and these data are also summarized in Tables 2 and 3. In the case of the reactions of the 3,5-bis-(trifluoromethyl)-substituted and unsubstituted benzyl chlorides with azide and solvent, the rate constant ratios were determined by the kinetics of decay in the absence and presence of azide ion using HPLC and the method of initial rates.

A detailed study of the partitioning of the *p*-methoxybenzyl group during decay of the diazoate and the chloride in 50%/50% trifluoroethanol–water with varying concentrations of azide ion was carried out. The fractions of trifluoroethyl ether, alcohol, and azide products determined in these experiments are plotted as a function of azide ion concentration in Figure 2. It is to be noted that analyses at all azide ion concentrations were carried out in duplicate and all data points are plotted in Figure 2.

Experiments were carried out to determine the yield of ester in the acetic acid catalyzed decomposition of some aryldiazomethanes in 50/50 v/v trifluoroethanol–water mixtures containing 0.05 M acetic acid buffer (50% anion). The ratios of yields of ester to solvent-derived products are summarized in Table 4. Included are product ratios determined for the decay of some (*E*)-arylmethanediazoates under the same conditions.

Isotope Incorporation. Experiments were carried out to determine if the ^{16}O oxygen atom originally attached to the diazoate was incorporated into the product alcohol. For three diazoates decomposed in aqueous media containing ~50/50 $H_2{}^{16}O/H_2{}^{18}O$, the isotopic content of the product alcohols was compared to that of phenylacetaldehyde subsequent to the aldehyde oxygen equilibration with solvent. The data are summarized in Table 5.

Table 1. Table of Rate and Equilibrium Constants, Thermodynamic Parameters, Solvent Deuterium Isotope Effects and Alcohol Yield from the Decomposition of (*E*)-Arylmethanediazoates in Aqueous Media at 25 °C and Ionic Strength 1 M ($NaClO_4$)

substituent	k_1,[a,b] s^{-1}	pK_a[a,c]	$\Delta H^{\#}$[a,d] kcal/mol	$\Delta S^{\#}$[a,d] cal/(deg mol) (σ)	k_{H_2O}[e]/k_{D_2O} (σ)	alcohol yield,[f] %
4-$N(CH_3)_2$	6.9[g]	8.38				
4-OCH_3	2.2	8.23	15.9 (0.1)	−3.6 (0.1)	1.52 (0.02)	101
4-CH_3	1.7	8.13				98
H	1.1	8.16	16.0 (0.1)	−4.9 (0.2)		99
4-Cl	0.58	8.03				98
4-CF_3	0.28[g]	7.95				93
3,5-$(Cl)_2$	0.13	7.97	17.1 (0.1)	−5.8 (0.1)	1.75 (0.02)	99
2,3,4,5,6-$(F)_5$	0.012	7.63				
3,5-$(CF_3)_2$	0.081	7.86				82
diphenyl	0.60	7.83				

[a] Reaction solutions contained 4% by volume 2-propanol. [b] The limiting pH independent rate constant as in eq 4. Standard errors are ±5% unless otherwise noted. [c] Constant as in eq 4. [d] Measurements at 10 temperatures ranging between 5 and 50 °C in reaction medium buffered with 0.15 M acetate. The measured pH of these buffers at 25 °C ranged from pH 4.5 to 4.7. [e] The reaction media contained 4% by volume of the appropriate (OL)-2-propanol. Values are the mean and standard deviation of three runs, one each in acetate buffers containing 25, 50, or 75% acetic acid and the value of pH_{obs} in these experiments ranged from pH 4.28 to 5.45. [f] Reactions carried out in 0.005 M NaOH with substrate concentration ~0.0005 M (no 2-propanol). Yields are based on the mass of the starting material. [g] Standard error of ±15%.

Table 2. Water−Trifluoroethanol Selectivities (k_H/k_T) and Ethanol−Trifluoroethanol Selectivities (k_{ET}/k_T) for Benzyl Group Transfer in the Decomposition of (*E*)-Arylmethanediazoates, Aryldiazomethanes, and Substituted Benzyl Chlorides at 22 ± 1 °C[a]

	(E)-$ArCH_2N_2O^-$		$ArCHN_2$	$ArCH_2Cl$
substituent	k_H/k_T[b]	k_{ET}/k_T[c]	k_H/k_T[b,d]	k_H/k_T[b]
4-OMe	0.80 (0.74)[e]			1.5
4-Me			0.94	
4-H	0.48	0.95[f]	0.50	1.9
4-Cl	0.60	1.06[g]		2.4
3-Cl			0.58	
3,5-$(Cl)_2$	0.54[h]	0.95[i]		8.0
F_5	0.72			
3,5-$(CF_3)_2$	0.54		0.53	

[a] Values are averages of duplicate experiments that in all cases differed by less than 2% of the smaller value. Unitless values calculated from the ratios of product concentrations determined by HPLC divided by the ratios of the solvent mole fractions. [b] Reactions carried out in 50/50 v/v trifluoroethanol−water, ionic strength 0.50 M ($NaClO_4$). Value is unitless. [c] Solvent composition was 50/50/10 v/v/v water−trifluoroethanol−ethanol, ionic strength 0.50 M ($NaClO_4$). Value is unitless. [d] Contained 0.05 M acetate buffer, 50% anion. [e] As in footnote *b* except ionic strength was 1.0 M ($NaClO_4$). [f] The value $k_H/k_T = 0.49$ in this solution. [g] The value $k_H/k_T = 0.33$ in this solution. [h] Average of four determinations. [i] The value $k_H/k_T = 0.40$ in this solution.

Table 3. Values of k_a/k_s (M^{-1}), Azide Ion−Solvent Selectivities, for Benzyl Group Transfer in the Decomposition of (*E*)-Arylmethanediazoates, Aryldiazomethanes, and Substituted Benzyl Chlorides at 22 ± 1 °C

substituent	(*E*)-$ArCH_2N_2O^-$	$ArCHN_2$	$ArCH_2Cl$
4-CH_3O	30[a,b]		30[a,c]
4-H	0.24[d]	0.35[d]	1.2×10^3 [a,e]
3,5-$(Cl)_2$			1.2×10^4 [a,f]
3,5-$(CF_3)_2$	0.20[d]	0.21[d]	
	0.27[g]	0.26[g]	
	0.24[h]	0.59[h]	

[a] Solvent was 50/50 v/v water−trifluoroethanol. Ionic strength 1 M ($NaClO_4$). [b] Selectivity for the 84% of the ion that escapes to the free ion stage as described in the text. [c] From the inverse of the slope of the double reciprocal plot of 1/(fraction of azide product) against 1/[N_3^-] that contained four points. The standard error of the slope is 1% and the intercept value was 0.991 ± 0.004. [d] Solvent was H_2O containing 2 M NaN_3. [e] $k_s = 3.4 \times 10^{-7}$ s^{-1}. [f] $k_s = 4.1 \times 10^{-9}$ s^{-1}. [g] Solvent was 20/80 v/v dimethyl sulfoxide−water containing 2 M NaN_3. [h] Solvent was 20/80 v/v trifluoroethanol−water containing 2 M NaN_3.

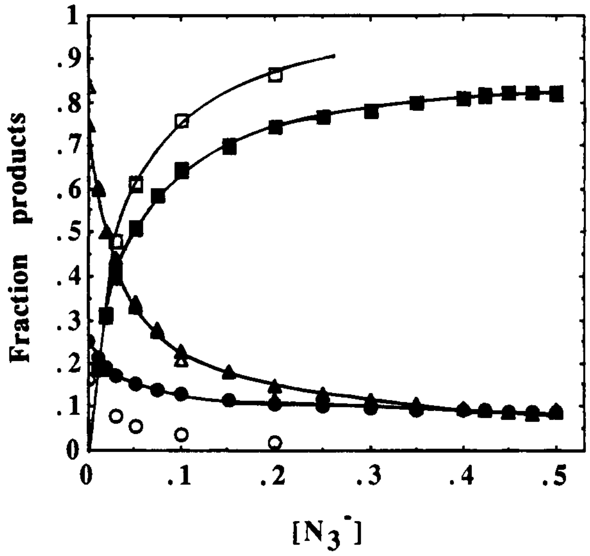


Figure 2. Product yields in the decomposition of (*E*)-(*p*-methoxyphenyl)methanediazoate (solid symbols) and *p*-methoxybenzyl chloride (open symbols) in 50/50 water−trifluoroethanol as a function of azide ion concentration (M), ionic strength 1 M ($NaClO_4$), 22 ± 1 °C. Products are represented as follows: azide adduct, squares; alcohol, triangles; trifluoroethyl ether, circles. Duplicate determinations at each azide ion concentration are plotted. The solid line for the fractional yield of azide adduct is based on eq 8 using values for the parameters $k_{sep}/k'_H = 14$, $k'_T/k'_H = 1.65$, and $k'_a/k_{sep} = 0.49$ and those for the free cation as in Table 6. Solid lines shown in Figure 2 for the yields for ether and alcohol are calculated from the known and derived rate constant ratios above and in Table 6 based on Scheme 3 (see text).

Table 4. Product Ratios, [Ester]/([Alcohol] + [Trifluoroethyl Ether]) for Benzyl Group Transfer in the Decomposition of Aryldiazomethanes and (*E*)-Arylmethanediazoates in 50/50 Water−Trifluoroethanol (0.05 M Acetate Buffer, 50% Anion)

	4-CH_3	4-H	3-Cl	3,5-$(CF_3)_2$
$ArCHN_2$	1.08	0.96	0.67	0.39
(*E*)-$ArCH_2N_2O^-$		0.01		0.11

Attempts were made to measure deuterium incorporation into products in the course of decomposition of the diazoates. Diazoates were decomposed in various D_2O solutions and the products were analyzed by mass spectrometry. The following experiments (diazoate, buffer and concentration, percent buffer base, number of half-lives of reaction) were carried out and the analysis in every case indicated that 1% or less of the product molecules had incorporated an atom of deuterium: (*E*)-(pentafluorophenyl)methanediazoate, DABCO 1 M, 90%, 6 $t_{1/2}$; (*E*)-(3,5-bis(trifluoromethyl)phenyl)methanediazoate, DABCO 1 M, 90% base, 23 $t_{1/2}$; (*E*)-(3,5-bis(trifluoromethyl)phenyl)-

Table 5. Summary of "Excess ^{16}O Incorporation" in the Decomposition of (*E*)-Arylmethane-^{16}O-diazoates in $H_2{}^{16}O/H_2{}^{18}O$[a]

substituent	experiment no.	mass ratio obsd	% ^{16}O in alcohol[b]	% ^{16}O in solvent[c]	% ^{16}O alcohol/% ^{16}O solvent
4-CH_3O−	1	138/140	62	48	1.29
	2	138/140	65	51	1.27
4-CH_3	1	122/124	54	48	1.13
3,5-$(CF_3)_2$	1	244/246	43	43	1.00
	2	244/246	44	43	1.02

[a] All reactions were 0.10 M carbonate buffer, ionic strength 1.1 M ($NaClO_4$). [b] Based on the sum of the ion counts for the two masses indicated in the previous column. [c] Based on the sum of the ion counts for the ^{16}O-containing and ^{18}O-containing phenylacetaldehydes after oxygen exchange with solvent.

methanediazoate, NaOD 0.1 M, 0.2 $t_{1/2}$; (*E*)-(4-(trifluoromethyl)phenyl)methanediazoate, NaOD 0.1 M, 1 $t_{1/2}$; (*E*)-(3,5-dichlorophenyl)methanediazoate, DABCO 1 M, 90% base, 21 $t_{1/2}$; (*E*)-(3,5-dichlorophenyl)methanediazoate, NaOD 0.10 M, 0.5 $t_{1/2}$; (*E*)-phenylmethanediazoate, NaOD 0.1 M, 7 $t_{1/2}$. The alcohol product of the decomposition of (*E*)-(3,5-(bis(trifluoromethyl)phenylmethanediazoate, in $D_2N(CH_2)_3ND_2$ buffer (3.0 M), 90% base, 5.5 $t_{1/2}$, indicated 3% deuterium incorporation.

Discussion

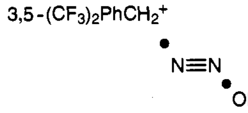
The kinetic studies presented here indicate that the rate-limiting step for decomposition of (*E*)-arylmethanediazoates involves unimolecular decomposition of the diazoic acid. The plots of log k_0, the rate constant for the buffer-independent decay, against pH, in the range of pH from 4 to 10, are qualitatively similar to those observed for all alkanediazoates studied to date.[2-4] In Figure 1, the change from a pH-dependent to a pH-independent reaction with decreasing pH is consistent with the diazoic acid being the reactive form. The data in Figure 1 are well fit by the rate law of eq 4

$$k_0 = k_1/(1 + K_a/[H^+]) \tag{4}$$

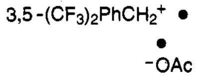
for which K_a is the dissociation constant for the diazoic acid and k_1 is the rate constant for the rate-limiting step using the values for the constants K_a and k_1 indicated in Table 1. The unassisted nature of the decomposition of the diazoic acid is indicated by the absence of a significant increase in the observed rate constant for decomposition, k_{obsd}, with increasing concentrations of buffers including good to quite strong nucleophiles (see Results).

The proton dependence in eq 4 rules out the pH-independent mechanism of eq 3 in the physiological pH range—even for the (*E*)-(*p*-(dimethylamino)phenyl)methanediazoate that could form an extremely stable carbocation directly by the mechanism of eq 3.

Rate-Limiting Formation of Diazonium Ions. A common free diazonium ion intermediate for the decomposition of (3,5-bis(trifluoromethyl)phenyl)methanediazoate and (3,5-bis(trifluoromethyl)phenyl)diazomethane is indicated by the azide−solvent selectivities, in Table 3, that are identical within experimental error for reactions in phosphate-buffered water and phosphate-buffered 20/80 DMSO−water. The lifetime of the (3,5-bis(trifluoromethyl)phenyl)methyl cation is sufficiently shortlived that it cannot be a free intermediate in either reaction.[15] Formation of the carbocation from the diazohydroxide either in a concerted mechanism or via a stepwise reaction in which the diazonium ion decomposes to the carbocation faster than it can diffuse away from the hydroxide ion would generate the nitrogen separated ion pair **a** while the acetic acid catalyzed decomposition of the (3,5-bis(trifluoromethyl)phenyl)diazomethane would involve the intermediate **b**. Evidence suggests that different azide−solvent trapping ratios should be observed if **a** and **b** are involved in the product-determining steps. Shortlived carbocations either in ion pairs with different gegenions or in different ion−molecule pairs exhibit measurably different selectivities.[18] Thus the azide−water selectivities, k_a/k_H, that are the same within experimental error for the (3,5-bis(trifluoromethyl)phenyl methanediazoic acid and the (3,5-bis(trifluoromethyl)phenyl)diazomethane decomposition reactions in water and 20/80 DMSO−H_2O indicate a common free intermediate which, given that the carbocation is too short lived to be a free intermediate, must be the (3,5-bis(trifluoromethyl)phenyl)methane diazonium ion. The different values of k_a/k_H for the reaction of (*E*)-phenylmethanediazoate and phenyldiazomethane rule out a common free intermediate for these substrates and provide a positive control for the claim that differences between the two 3,5-bis(trifluoromethyl) compounds ought to be observed if the diazonium ion were not a common free intermediate in product formation in that case.



a



b

The correlation of Figure 3 suggests that rate-limiting formation of a diazonium ion from the diazoic acid, as in eq 2, is a mechanism that is common to all the substituted phenylmethanediazoic acids. The line (log $k_1 = -1.23\sigma + 0.05$, $r^2 = 0.998$) includes all phenylmethanediazoic acids except the pentafluoro compound. An alternative plot (not shown) of log k_1 against corresponding substituted benzylammonium ion pK_a that includes the data for the (pentafluorophenyl)methanediazoate also gives a good linear correlation, log $k_1 = 1.25(pK_a(RNH_3^+)) - 11.77$, $r^2 = 0.990$. The slope of the plot of Figure 3 indicates that the substituents experience a large net increase in positive charge in going from the ground to the transition state. The sensitivity to substituents of the diazoic acid decomposition is somewhat greater than that observed in the equilibrium protonation of benzylamines for which $\varrho = -1.07$ for the plot of $-pK_a$ against σ.[20] A similar enhanced sensitivity to substituents was observed in the diazonium ion-forming

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(15) The rate constant for the reaction of the 1-(*p*-nitrophenyl)ethyl cation with solvent in 50/50 trifluoroethanol−water has been estimated by extrapolation to be $k_s \sim 10^{13}\ s^{-1}$.[16] The greater electron-withdrawing power of the 3,5-bis(trifluoromethyl) substituents ($\sigma = 0.92$ compared to $\sigma = 0.78$ for *p*-NO_2)[17] and absence of the α-methyl group in the benzylic system suggest that the rate constant for its capture by solvent will be larger still.

(16) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361.

(17) Hine, J. *Structural Effects on Equilibria in Organic Chemistry*; R. E. Kreiger: New York, 1981.

(18) (a) Thus the ratios of solvent versus leaving group capture of the 4-octyl cation vary by a factor of 2.5 for various deaminative reactions of 4-octylamine derivatives in acetic acid. Maskill, H.; Southam, R. M.; Whiting, M. C. *J. Chem. Soc., Chem. Commun.* **1965**, 496. (b) The capture of the 1-(4-methylphenyl)ethyl cation by solvent and added nucleophiles has been estimated to occur to the extent of ~30% at the ion pair stage while the remaining 2/3 to the capture occurs at the free cation stage in 50/50 trifluoroethanol−H_2O.[19] Despite the fact that only ~30% of the cation is trapped at the ion pair stage, different leaving groups yield measurably different trapping ratios for various pairs of nucleophiles.[19]

(19) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373.

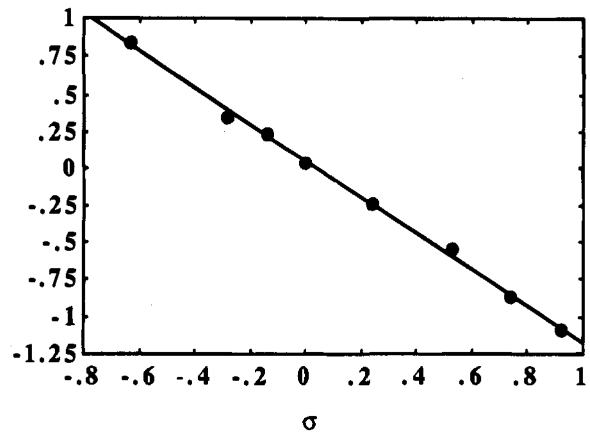


Figure 3. Plot of log k_1, the pH-independent rate constant for decay of (*E*)-arylmethanediazoates in water, ionic strength 1 M, 25 °C, against Hammett σ.

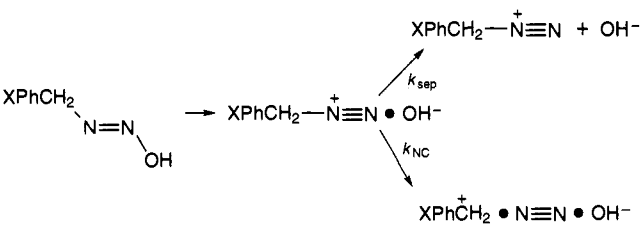
decomposition of aralkyltriazenes.[21] This enhanced sensitivity can be rationalized by the larger amount of charge born by the carbon fragment in the diazonium ion compared to the benzylammonium ion.[22]

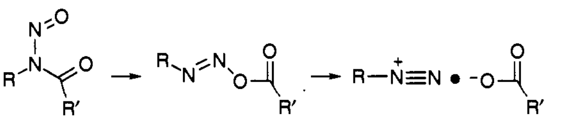
The structure–reactivity relations based on kinetic results indicate that there is no detectable carbocation character in the transition state for substituted phenylmethanediazoic acid decomposition and this is consistent with rate-limiting formation of the diazonium ions. There are no significant positive deviations in the plot of log k_1 against σ (Figure 3) for powerfully electron-donating substituents such as *p*-MeO- and *p*-$(CH_3)_2N$- that would indicate the onset or existence of a coupled concerted formation of the carbocation. Corollary to this, a plot of log k_1 against σ^+ gives a line fitted to the points for the meta-substituted compounds from which the points for the *p*-methoxy and *p*-(dimethylamino) substituents deviate negatively by 0.7 and 1.3 log units, respectively. Similarly, the value of the rate constant k_1 for the (pentafluorophenyl)methanediazoic acid is some 7-fold smaller than that for the (3,5-bis(trifluoromethyl)phenyl)methanediazoic acid. This is again consistent with negligible resonance interaction of substituents because the pentafluorophenyl substituent is inductively more electron withdrawing than the 3,5-bis(trifluoromethyl)phenyl substituent while the former is more effective at stabilizing a developing carbocation by resonance in the solvolysis of arylethyl tosylates.[23] Finally, substitution for a hydrogen of a benzene ring in changing from phenylmethanediazoate to diphenylmethanediazoate depresses the rate constant for decomposition of the diazoic acid by about a factor of 2. By comparison, the rate constant for solvolysis in ethanol of 1,1-diphenylethyl chloride is 9 × 10^4 greater than that for 1-phenylethyl chloride.[24]

The values of $\Delta S\#$ that are near zero and the normal solvent deuterium isotope effects are consistent with the unimolecular mechanism of eq 2 in which there is some solvent electrostriction about the developing hydroxide ion.[2]

Benzylic diazonium ions are claimed to be intermediates in some related systems. These include the decay of diazoesters that are formed in the unimolecular decomposition of *N*-nitrosamides in polar, polar-protic and nonpolar organic media (eq 5)[25,26] and the acid catalyzed decomposition of aralkyltriazenes (eq 6).[21] By contrast, the decomposition of benzylazoxytosylate is claimed to proceed by a fully concerted reaction on the basis of intermediate values of ϱ for substituents in both the benzylic and arylsulfonate moieties.[27]

Scheme 1





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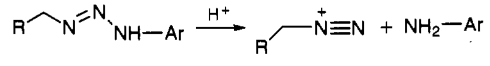

(6)

Nitrogen-Separated Ion Pairs. (a) Qualitative Analysis. The conclusion that in the most polar media the (3,5-bis(trifluoromethyl)phenyl)methane diazonium ion is a free intermediate can be formalized in the reaction in Scheme 1, in which $k_{sep} > k_{NC}$. However, a number of results indicate that, starting from diazoates or aryldiazomethanes, either a change in medium or a change to less electron withdrawing substituents even in the most polar media yields diazonium ions that are not diffusionally equilibrated, so that $k_{sep} \leq k_{NC}$[28a] (Scheme 1).

1. Table 3 indicates that in 20/80 trifluoroethanol–water there are detectable differences between the (3,5-bis(trifluoromethyl)phenyl)methanediazoate and the (3,5-bis(trifluoromethyl)phenyl)diazomethane decomposition reactions in the azide–solvent trapping ratios. Similarly the data in Table 4 indicate that in 50/50 trifluoroethanol–water the acetic acid catalyzed decomposition of (3,5-bis(trifluoromethyl)phenyl)diazomethane gives a substantially larger fraction of acetate ester product than in the case of the diazoate. These results are inconsistent with a common free diazonium ion intermediate in the decomposition of the (3,5-bis(trifluoromethyl)phenyl(methanediazoate and (3,5-bis(trifluoromethyl)phenyl)diazomethane in these media. The larger yield of the acetate ester in the case of the decomposition of the (3,5-bis(trifluoromethyl)phenyl)diazomethane in 50/50 trifluorethanol–water is consistent with the fact that the rate-limiting step for hydrolysis is strongly general acid catalyzed,[29] and presumably the diazonium ion conjugate acid decomposes to a significant degree while still in close vicinity to the acetate conjugate base to yield ester product.

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(20) Blackwell, L. F.; Fischer, A.; Miller, I. J.; Topsom, R. D.; Vaughan, J. *J. Chem. Soc.* **1964**, 3588.

(21) 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.

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

(23) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513. Allen, A. D.; Kwong-Chip, U. J. M.; Mistry, J.; Sawyer, J. F.; Tidwell, T. T. *J. Org. Chem.* **1987**, *52*, 4164.

(24) Brown, H. C.; Rei, M. *J. Am. Chem. Soc.* **1964**, *86*, 5008.

(25) White, E. H.; Field, K. W. *J. Am. Chem. Soc.* **1975**, *97*, 2148.

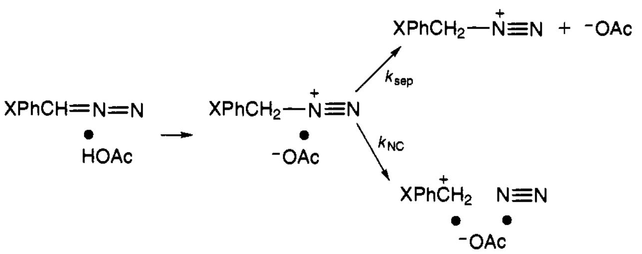
(26) White, E. H.; Field, K. W.; Hendrickson, W. H.; Dzadzic, P.; Roswell, D. F.; Paik, S.; Mullen, P. W. *J. Am. Chem. Soc.* **1992**, *114*, 8023 and references within.

(27) Gordon, I. M.; Maskill, H. *J. Chem. Soc., Chem. Commun.* **1989**, 1358.

(28) (a) We reserve more detailed discussion of the possible mechanisms of substitution for a later section. However, it is not ruled out for compounds with the most strongly electron withdrawing substituents that, in a fraction of the cases, the k_{NC} step, Schemes 1 and 2, may in fact involve bypass of the carbocation in an uncoupled concerted process that gives products directly. (b) Note here that there is no evidence for the existence of coupled concerted reaction of acetate ion with the diazonium ion. In the present case the decrease in the ratio of ester to solvent-derived products with increase in electron-withdrawing strength of substituents is opposite what is expected for the onset of coupled concerted processes.

(29) Finneman, J. I.; Fishbein, J. C. *J. Org. Chem.* **1994**, *59*, 6251.

Scheme 2



2. A difference in the fraction ester product formed from phenyldiazomethane compared to phenylmethanediazoate in acetate-buffered 50/50 trifluoroethanol−water is also evident in Table 4. The difference in product yields persists in a more polar medium (water, ionic strength 1 M) as indicated in Table 3 by the measurably different azide-to-water selectivities for the decomposition of the phenylmethanediazoic acid compard to phenyldiazomethane. The absence, in water, of a free intermediate in the case of the phenylmethyldiazonium ion contrasts with the case of the (3,5-bis(trifluoromethyl)phenyl)methane diazonium ion, discussed above, and must be due to the larger rate constant for formation of the more stable carbocation in the case of the phenylmethane diazonium ion, $k_{NC} \geq k_{sep}$ (Scheme 1).

A minimum of about half of the phenylmethane diazonium ion must decompose to the carbocation before it diffuses away from the acetate ion in the acetic acid catalyzed decomposition of phenyldiazomethane in 50/50 trifluoroethanol−water. This minimum is established by the data in Table 4 which indicate that phenyl acetate accounts for ~49% of the products. It is highly likely that a significantly larger fraction of the diazonium ion decomposes before diffusional separation because at least one or two solvent molecules should have some access to the cation that is likely sufficiently reactive that it should be unselective, in bonding, between acetate and solvent (see below).

3. The observation that the (*E*)-(*p*-methoxyphenyl)methanediazoate decomposes in $^{16}O/^{18}O$ labeled water to give 28% return of the ^{16}O originally attached to the diazoate (Table 5) suggests that much if not all of the diazonium ion must decompose faster than diffusion away of the hydroxide ion because return seems an inherently inefficient process.

In the acetic acid catalyzed hydrolysis of aryldiazomethanes, the decreased yields of ester with increasing electron-withdrawing strength of the substituents (Table 4) indicate the substituent dependence of the competition between diazonium ion dissociation and diffusional separation of the diazonium ion from the acetate ion. As detailed in a later section, for the substituent H and electron withdrawing groups (EWG), the selectivities for reactions of nucleophiles with the resulting cations are independent of substituent. Thus the substituent-dependent selectivity observed here must reflect the substituent effect on the partitioning between diazonium ion decomposition and the diffusion apart of the initially formed ion pair, k_{NC} and k_{sep}, respectively, Scheme 2.[28b] As k_{sep} is likely substituent independent, the dependence of ester yield is due to the change in k_{NC} with changing substituent. A plot of log (yield of ester product/yield of solvent products) against σ for the substituents X = H, 3-Cl, 3,5-$(CF_3)_2$ has a slope $\varrho = -0.43$ ($r^2 = 0.999$) for the substituent dependence of k_{NC}. Such a small value of ϱ may reflect the early transition state that might be expected for this process but also may reflect the large degree of cationic character in the carbon fragment of the diazonium ion that has recently been suggested by the ab initio calculations of the Glaser group.[22]

Rate constants for the diffusional separation of ion pairs are thought to be in the range of $10^{10}-10^{11}$ s^{-1} in mainly aqueous media.[30] Thus the conclusion that k_{sep} and k_{NC} are competitive for X = H to 3,5-$(CF_3)_2$ in the reaction in Scheme 2 indicates that $k_{NC} \sim 10^{10}-10^{11}$ s^{-1} as well.

(b) Altered Selectivity of a Nitrogen-Separated Ion Pair. Quantitative Analysis. The above analysis indicates that the nitrogen-separated ion pair is an intermediate that is central to the alkylating activity of most (*E*)-arylmethanediazoates and a similar conclusion has been reached by other investigators in the case of secondary (*Z*)-alkanediazoates.[31] It is therefore of importance to investigate this intermediate in a quantitative way in order to establish some basis for thinking about the chemistry and dynamics of these types of species. While in general the analysis would be complicated by the existence of both ion-paired and free carbocations we have chosen a system for which the behavior of the free cation is quantitatively well-understood—the (*E*)-(*p*-methoxyphenyl)methanediazoate. The reactivity with solvent and azide ion of the diffusionally equilibrated *p*-methoxybenzyl cation in 50/50 water−trifluoroethanol has recently been investigated.[32] Azide ion reacts with this cation at the diffusion-controlled limit of $\sim 5 \times 10^9$ M^{-1} s^{-1} so that this reaction can be used as a clock for accurate estimates of other processes. In the case of the (*E*)-(*p*-methoxyphenyl)methanediazoate, the observation, summarized in Table 5, that the ^{16}O originally attached to the diazoate is in part retained in the product alcohol in the decomposition in $^{16}O/^{18}O$ water suggested that the nitrogen-separated ion pair would be at least partly involved in the product-determining steps for the decomposition in 50/50 water−trifluoroethanol.

The changes, as a function of azide ion concentration, in the fractions of products quantitated in the decomposition of the (*E*)-(*p*-methoxyphenyl)methanediazoate in 50/50 trifluoroethanol−water that are depicted in Figure 2 indicate two important results. First, the yield of azide adduct appears to nearly level off at higher azide ion concentrations well below a quantitative yield. The small proportion of reaction, ~20%, that is not readily trapped as azide adduct is likely due to products formed at the stage of the nitrogen-separated ion pair. The preponderant product-determining reaction pathway (~80%, Figure 2, data for azide adduct) has a much greater susceptibility to azide ion trapping consistent with the intermediacy of the *p*-methoxybenzyl cation that has been shown to have significant azide−solvent selectivity of $k_a/k_s \sim 30$ M^{-1}. Second, there is a change in the ratio of ether to alcohol products with changing azide ion concentration. The ether−alcohol ratio is ~1/3 at very low azide ion concentration and ~1/1 at azide ion concentrations of ~0.5 M. The relative increase in the proportion of trifluoroethyl ether compared to alcohol product at high azide ion concentration indicates that the nitrogen-separated ion pair gives a larger proportion of ether compared to the overall reaction.

A quantitative description of the system is afforded by Scheme 3 in which azide ion trapping occurs at both the ion pair and free carbocation stage.[33] The change in the trifluoroethyl ether−alcohol ratio that is observed in Figure 4 is described according to Scheme 3 by eq 7, where F_T/F_{OH} is the ratio of the fraction of ether to fraction of alcohol products, *a*

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(30) (a) The association constants estimated for random encounter complexes are model dependent but are on the order of 0.1 M^{-1}.[30b] Rate constants for diffusion-limited reactions like thermodynamically favorable proton transfers or capture of unstable carbocations are in the range 10^9-10^{10} M^{-1} s^{-1},[30c] so the rate constants for diffusional separation must be on the order of $10^{10}-10^{11}$ s^{-1}. See k_{sep}, Table 6. (b) Hand, E. S.; Jencks, W. P. *J. Am. Chem. Soc.* **1975**, *97*, 6221 and references within. (c) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 1.

(31) Moss, R. A.; Reger, D. W.; Emery, E. M. *J. Am. Chem. Soc.* **1970**, *92*, 1366. Moss, R. A.; Fritz, A. W.; Emery, E. M. *J. Org. Chem.* **1971**, *36*, 3881. Moss, R. A.; Lane, S. M. *J. Am. Chem. Soc.* **1967**, *89*, 5655.

(32) Aymes, T. L.; Richard, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 9507.

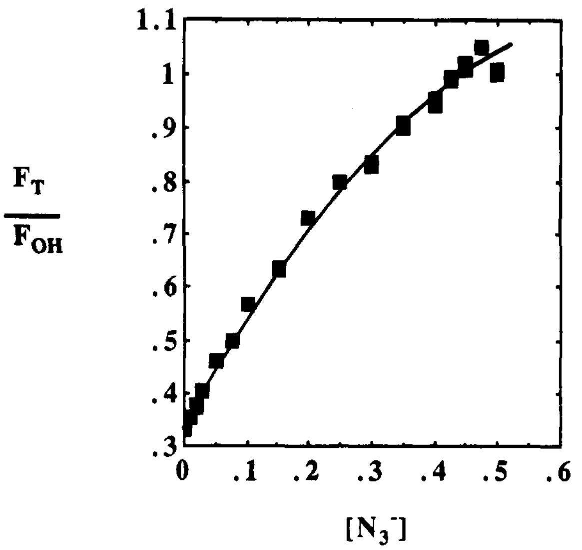
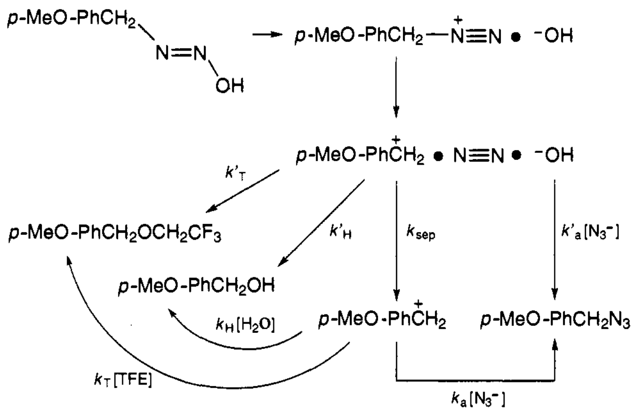


Figure 4. Plot of the ratio of the fraction of ether product divided by the fraction of alcohol product, F_T/F_{OH}, as a function of azide ion concentration (M) in the decay of (*E*)-(*p*-methoxyphenyl)methanediazoate in 50/50 trifluoroethanol–water, ionic strength 1 M ($NaClO_4$), 22 ± 1 °C. Duplicate determinations at each azide ion concentration are plotted. The solid line is the fit of the data to eq 7 (based on Scheme 3) using values of the parameters $k_{sep}/k'_H = 14$ and $k'_T/k'_H = 1.65$ and those for the free cation as in Table 6 (see text).

Scheme 3



$= k_{sep}/k'_H$, $b = k'_T/k'_H$, $C_1 = (k_H[H_2O]/k_T[TFE]) + 1$, $C_2 =$

$$F_T/F_{OH} = \frac{\dfrac{a}{C_1 + F_1[N_3^-]} + b}{\dfrac{a}{C_2 + F_2[N_3^-]} + 1} \tag{7}$$

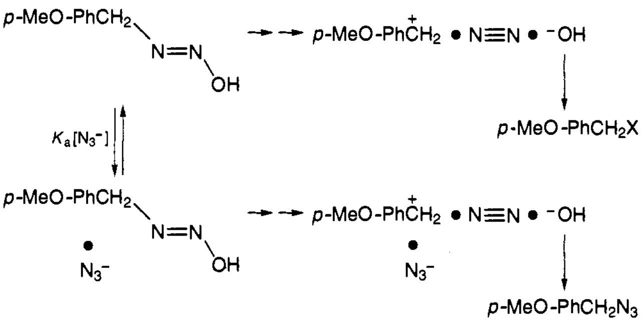
$(k_T[TFE]/k_H[H_2O]) + 1$, $F_1 = k_a/k_T[TFE]$, and $F_2 = k_a/k_H[H_2O]$. The terms indicated by upper case parameters are characteristic of the free carbocation, and values for these terms were directly measured in an earlier study of azide ion trapping in solvolysis of *p*-methoxybenzyl chloride by Aymes and Richard.[32] For self-consistency we have repeated the analysis and have obtained similar results that are summarized in Table 6. A nonlinear least-squares fit of the data in Figure 2 to eq 7 gives the solid line in Figure 4 and values for the variables $a = k_{sep}/k'_H = 14 \pm 1$ and $b = k'_T/k'_H = 1.65 \pm 0.04$. These rate constant ratios and those determined for reactions of the free cation from the reactions of *p*-methoxybenzyl chloride can be used in combination with the expression for the fractional yield of azide adduct, F_{az}, as a function of azide ion concentration, in eq 8, to yield the final unknown ratio, k'_a/k_{sep}. In eq 8, the terms in upper

Table 6. Experimental and Derived Values of Rate Constants and Rate Constant Ratios for Scheme 3

k_a/k_s	$30^{a,b}$ $(1)^c$	$\log k_{sep}$	$10.24^{j,k}$ $(0.24)^l$
k_T/k_H	$0.19^{b,d}$ $(0.02)^c$	$\log k'_H$	$9.09^{j,k}$ $(0.24)^l$
k_{sep}/k'_H	$14^{d,e}$ $(1)^c$	$\log k'_T$	$9.25^{j,k}$ $(0.25)^l$
k'_T/k'_H	$1.65^{d,e}$ $(0.04)^c$	$\log k_H[H_2O]$	8.15^k $(0.05)^c$
k'_a/k_{sep}	$0.49^{a,f,g} - 0.20^{a,h,i}$ $(0.03)^c-(0.02)^c$	$\log k_T[TFE]$	7.42^k $(0.04)^c$

[a] Units of M^{-1}. [b] Based on the observed product ratios for the decomposition of *p*-methoxybenzyl chloride. The term k_s represents the sum $k_s = k_T[CF_3CH_2OH] + k_H[H2O]$. [c] Standard error. [d] Unitless. [e] From the fit of the data in Figure 4 to eq 7, see text. [f] Limit assuming the model of Scheme 3. [g] From the fit of the data in Figure 2 to eq 8. [h] Limit from the model of Scheme 4. [i] From the fit of the data in Figure 2, according to eq 9. [j] The mean value based $k'_a = 5 \times 10^9$ M^{-1} s^{-1} and the two limiting values of k'_a/k_{sep}. [k] Values have units of s^{-1}. [l] From the range in k'_a/k_{sep}.

Scheme 4



$$F_{az} = \left[\frac{1}{d[N_3^-] + C_3}\right]\left[\frac{1}{1 + \dfrac{1}{C_4[N_3^-]}}\right] + \left[\frac{1}{1 + \dfrac{C_3}{d[N_3^-]}}\right] \tag{8}$$

case are known rate constant ratios: $C_3 = (k'_T + k'_H + k_{sep})/k_{sep}$ and $C_4 = (k_a/(k_H[H_2O] + k_T[TFE]))$. The unknown *d* is $d =$ k'_a/k_{sep}. A value of $k'_a/k_{sep} = 0.49 \pm 0.03$ is obtained from the nonlinear least-squares fit of the data for the fractional yield of azide adduct versus azide ion concentration in Figure 2. The fit is shown as the solid line for the azide adduct data. Other solid lines shown in Figure 2 for the yields of ether and alcohol are calculated from the known and derived rate constant ratios above and their coincidence with the experimental data attests to internal consistency of the model.

The possibility that some of the azide ion trapping of the ion pair could occur through a preassociation mechanism yields a somewhat smaller value of $k'_a/k_{sep} = 0.20 \pm 0.02$. Some of the azide adduct could be formed if azide ion associates with the diazoic acid prior to formation of the diazonium ion as in Scheme 4, lower path. A value for the random association constant of $K_a = 0.3$ M^{-1} in this partly organic medium is

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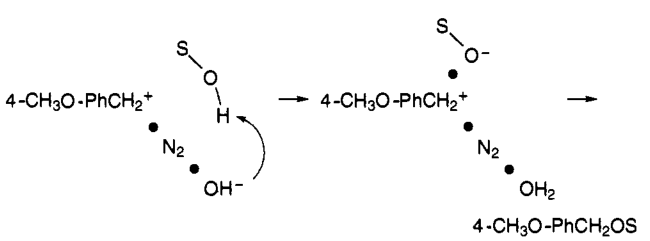
(33) A simpler model involving azide ion trapping of the free carbocation only can be shown to be inconsistent with the changes in yields of alcohol and trifluoroethyl ether products with increasing azide ion concentration. The inconsistency arises from the fact that a comparison of the ratio of trifluoroethyl ether to alcohol from the *p*-methoxybenzyl chloride compared to that from the (*p*-methoxyphenyl)methanediazoate requires that the ion pair, which yields 11% of the total products in such a model in the latter reaction, gives almost exclusively (93%) trifluoromethyl ether product. This constrains, based on the k_a/k_s trapping ratio (=26.6 ± 0.3) derived from the appropriate treatment, the yield of trifluoroethyl ether to be greater, by ~30%, and the yield of alcohol to be less, by ~30%, than observed at the highest azide ion concentrations. This difference is outside the experimental errors of the determinations that are in the range of ±1% (see the duplicates in Figure 2).

Scheme 5



presumed.[16] The value of k'_a/k_{sep} is then obtained using eq 9, where F_{N_3} is the function for the fractional yield of azide adduct as expressed in eq 8. It should be noted that the inclusion of the preassociation pathway does not alter the values of C_1-C_4 and the rate constant ratios contained therein.

$$F_{az} = \frac{1}{1 + \frac{1}{K_a[N_3^-]}} + \left[1 - \frac{1}{1 + \frac{1}{K_a[N_3^-]}}\right] F_{N3} \quad (9)$$

Table 6 summarizes the values of rate constant ratios obtained by the above analyses. Also included in Table 6 are the absolute values or ranges for the various rate constants that are obtained by taking a value for $k_a = k'_a = 5 \times 10^9\ M^{-1}\ s^{-1}$ for azide ion trapping of the cation and ion pair.[34]

The rate constant ratios and rate constants in Table 6 allow quantitation of some important observations. In the absence of azide ion, 84% ($=100\% k_{sep}/(k_{sep} + k'_H + k'_T)$) of the cation escapes the ion pair to form the free ion, and the remaining 16% is captured at the ion pair stage. A larger percentage of the ion pair separates to free ions in trifluoroethanol–water compared to water. In water, a minimum of 30% of the cation is captured at the ion pair stage based on the "excess ^{16}O incorporation" observed in the decomposition in $^{16}O/^{18}O$ water (Table 5). This may be due to enhanced diffusional separation in trifluoroethanol–water, possibly due to thermodynamically favorable proton transfer between hydroxide ion and the surrounding alcohol molecules.

Formation of the trifluoroethyl ether is favored over alcohol in the ion pair, $k'_T/k'_H = 1.65$, and this represents a 9-fold enhancement of ether formation compared to the reaction of the free carbocation ($k_T/k_H = 0.19$). Enhanced trifluoroethyl ether formation must be due to a proton switch reaction in the ion pair, as indicated in Scheme 5, that is favored when SOH is trifluoroethanol compared to when SOH is water due to the greater thermodynamic driving force for formation of trifluoroethoxide compared to hydroxide.[35] While ether is preferentially formed in the ion pair in Scheme 5, the rate of formation of alcohol must be enhanced relative to that for reaction of the cation with water (k_H) in order to be competitive with ether formation and diffusional separation (note values for k_H and k'_H in Table 6). The formation of alcohol in the ion pair may in part occur through a mechanism involving proton transfer as above but nitrogen extrusion and reaction of the cation with the original hydroxide ion leaving group also likely occurs. Again, the latter process has precedent in the decomposition in water by the excess ^{16}O incorporation into product alcohol formed in $^{16}O/^{18}O$ labeled water.

The proton switch mechanism represents a process by which the selectivity of the cationic intermediate can be substantially altered from that observed for the free cation. The importance of this mechanism is constrained by certain criteria. First, such a mechanism can only obtain when the proton transfer from the acidic site to hydroxide ion is thermodynamically favorable, otherwise there will be no enhanced reactivity relative to solvent water. Second, the cation must be sufficiently selective between the conjugate base, resulting from protonation of hydroxide ion, and solvent molecules. A decrease in selectivity of the cation and the consequent increase in reactivity of the cation that occurs upon the addition of electron-withdrawing groups to the benzene ring will minimize the importance of the proton switch mechanism. As the cation becomes so unstable that it reacts with solvent upon encounter, the proton switch process will become unimportant because it is a relatively slow process and because enhancement of nucleophilicity by formation of the conjugate base does not enhance selectivity. Third, the capture of the cation by the conjugate base, trifluoroethoxide in Scheme 5, must be encounter controlled or nearly so, otherwise diffusional separation will predominate without enhanced capture compared to the free ion. There is evidence that supports the notion that this criterion is met in the present case. The rate-limiting step for capture of the more stable 1-(4-methoxyphenyl)ethyl cation by trifluoroethoxide ion appears to involve extrusion of a hydrogen-bonded solvent molecule from the solvent-separated ion pair so that the intimate ion pair yields ether faster than diffusional separation.[19] A similar fate must obtain in the present case with the less stable 4-methoxybenzyl cation in the intimate ion pair subsequent to proton transfer.

It is thus likely that the rate-limiting step for ether formation in the ion pair is the proton-transfer step. The analysis summarized in Table 6 indicates that the ether formation at the ion pair stage occurs with a rate constant on the order of $10^9\ s^{-1}$. The small magnitude of the rate constant for thermodynamically favorable proton transfer is not unreasonable in light of what has been measured previously for some thermodynamically favorable proton switches that occur through intervening water molecules.[36] The small value of the rate constant for ether formation may thus indicate the involvement of thermoneutral proton transfers through bridging water molecules and also the entropically unfavorable nature of the switch that must circumnavigate the intervening nitrogen molecule.

In the main (84%), the (*E*)-(*p*-methoxyphenyl)methanediazoate reacts via a relatively stable carbocation with appreciable selectivity as indicated by the value of $k_a/k_s = 30\ M^{-1}$. This finding is in accord with the study of Moschel and co-workers.[11] They demonstrated the high selectivity for N^2 of guanosine of the (*p*-methoxyphenyl)methylating intermediate derived from hydrolysis of the nitrosourea and ascribed this activity to the relatively stable, selective, resonance-stabilized carbocation.

Selectivity in Benzyl Group Transfer for X = H and EWG. (a) Absence of Coupled Concerted Reactions. In general, we expected that the changes in selectivity in substitution reactions of benzyl derivatives would follow the pattern well-documented in the substitution reactions of 1-phenethyl derivatives.[37] For the phenethyl derivatives, good to strong electron-donating groups generate relatively long-lived stable cations with appreciable selectivity. Destabilization of the cation results in short-lived cations that react with reduced selectivity at the ion pair stage, while further destabilization results in increasing selectivity for strong nucleophiles that reflects the onset of a coupled concerted S_N2 reaction for these nucleophiles. Moschel et al. rationalized the change in product yields and

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(34) McClelland and co-workers have recently verified by direct methods that such a value is valid for the diffusion-limited trapping of reactive carbocations by azide ion. McClelland, R. A.; Kanagasabapathy, V. M.; Banait, N. S.; Steenken, S. *J. Am. Chem. Soc.* **1991**, *113*, 1009.

(35) White proposed a qualitatively similar mechanism to explain the formation of 3,5-dinitrobenzoate ester in the decomposition of *N*-(*sec*-butyl)-*N*-nitrosobenzamide in dioxane with added 3,5-dinitrobenzoic acid. White, E. H. *J. Am. Chem. Soc.* **1955**, *77*, 6011.

(36) Grunwald, E.; Chang, K. C.; Skipper, P. L.; Anderson, V. K. *J. Phys. Chem.* **1976**, *80*, 1425.

(37) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1982**, *104*, 4689. Ta-Shma, R.; Rappoport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 6082.

selectivity in the reaction of substituted benzyl chlorides and bromides with various nucleophilic sites on guanine according to this pattern.[11]

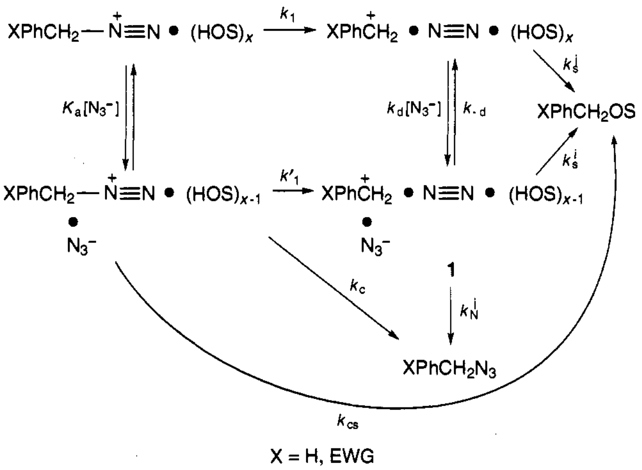
We have confirmed that there is an increase in the selectivity of substitution reactions of benzyl chlorides with increasing electron-withdrawing ability of the substituents that is reflective of the onset of a coupled concerted reaction. The data in Table 3 demonstrate that there are large increases in k_a/k_s, the azide−solvent selectivity, in changing from the *p*-methoxybenzyl chloride, which reacts via a free carbocation intermediate, to 3,5-bis(trifluoromethyl)benzyl chloride. Likewise there is a smaller but significant change in the water−trifluoroethanol selectivity, k_H/k_T (Table 2), that reflects the greater nucleophilicity of water compared to trifluoroethanol that is expected in a coupled concerted process.

In strong contrast to what is observed in the case of selectivities of benzyl chlorides, a similar analysis of selectivity in the decay of (*E*)-arylmethanediazoates or aryldiazomethanes gives no evidence of an increase in the value of either k_a/k_s (Table 3) or k_H/k_T (Table 2) in changing from the unsubstituted to the 3,5-bis(trifluoromethyl)phenyl compounds or the ethanol−trifluoroethanol selectivity (k_{ET}/k_T) (Table 2) in changing from the unsubstituted compound to (3,5-dichlorophenyl methanediazoate.

The small and similar values of k_a/k_s for arylmethanediazoates and aryldiazomethanes (X = H and EWG) reflect the absence of a coupled concerted mechanism of substitution.[38] These results compared with those of the aryl chlorides underscore the importance of the leaving group in determining whether a coupled concerted reaction that can result in increased selectivity will be observed. It is likely that the benzyl and (3,5-bis(trifluoromethyl)phenyl methane cations have no appreciable lifetime in the presence of a properly oriented azide ion[16,19,37] so that the azide ion products are at least to some extent formed by concerted mechanisms (see below); however, the onset of a concerted reaction that can result in a significant increase in selectivity requires interaction (coupling) between nucleophile and leaving group, the strength of which is in part determined by the nature of the leaving group.[39] In the substitution reactions of arylmethyldiazonium ions (X = H, EWG) there is insufficient coupling between N_2 and the powerful nucleophile azide ion to manifest increased selectivity through a coupled concerted reaction. It is conceivable that a coupled concerted reaction could occur with the addition of electron-withdrawing groups more powerful than 3,5-$(CF_3)_2$ or with nucleophiles that are stronger and more polarizable than the azide ion.

(b) Product-Determining Steps for Reactions of Benzyl Cations (X = H and EWG). The benzylic carbocations (X = H and EWG) formed from diazonium ion dissociation are short-lived. An estimated rate constant[40], k_g, of 5×10^{11} s^{-1} for the reaction of the benzyl cation with solvent is larger than that for the rotational reorientation of a water molecule in a dipole vector in bulk water (10^{11} s^{-1})[43] so that the benzyl cation likely reacts with the first nucleophile with which there is sufficient orbital overlap.

Scheme 6



The short lifetimes of the carbocations generated from arylmethanediazonium ions (X = H and EWG) mean that substitution by added nucleophiles that are at least as nucleophilic as solvent occurs by a preassociation mechanism, as illustrated for azide ion in the lower paths in Scheme 6, K_a, k'_1 or K_a, k_c. The preassociation mechanism is enforced by the fact that the rate constant for cation capture by such nucleophiles, k^i_N, is greater than that for diffusional separation, k_{-d}.[44] The absence, as discussed above, of any nucleophilic assistance indicates that $k_1 \sim k'_1 \sim k_c$.

The absence of a significant change in selectivity with increasing electron-withdrawing power of the substituents indicates that the rate-controlling barriers for the k^i_s and k^i_N steps in Scheme 6 are not chemical in nature. As indicated above in the case of the benzyl cation there is likely a small chemical barrier to capture by solvent, $k_s \sim 5 \times 10^{11}$ s^{-1}, while there is likely no chemical barrier for capture by azide ion in the encounter complex. With the addition of electron-withdrawing groups to the benzene ring an increase in k_s is predicted. For the 3,5-bis(trifluoromethyl)benzyl cation the rate constant k_s is probably on the order of a vibration, $\geq 10^{13}$ s^{-1}—that is, there is probably no chemical barrier to capture of this cation by a solvent molecule.[45] If the formation of products from intermediate **1** (Scheme 6) via k^i_s and k^i_N were determined by the height of chemical barriers for bond formation, then a significant decrease in the k_a/k_s (azide−solvent) ratio is predicted in going from the unsubstituted to the (3,5-bis(trifluoromethyl)phenyl) methanediazoate. This is because in the case of the cation from the latter compound, a few solvent molecules should compete equally well with the azide ion in **1** whereas in the case of the benzyl compound the hypothetical chemical barrier for reaction with solvent prevents effective competition by solvent for the cation in **1**. In contrast to this prediction, Table 3 shows that there is less than a 20% decrease in the value of k_a/k_s in changing from the unsubstituted to the (3,5-bis(trifluoromethyl)phenyl methanediazoate.[46]

Similarly, the absence of a *change* in both the k_H/k_T values (Table 2), in going from the unsubstituted compound to the (3,5-

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[38] Jencks, W. P. *Chem. Soc. Rev.* **1981**, 345.

[39] Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383.

[40] The rate constant for reaction of the 1-phenylethyl cation with solvent in 50/50 trifluoroethanol−water has been estimated to be $\sim 10^{11}$ s^{-1} by short extrapolation of a plot of log k_s against σ^+ that was determined by the azide ion trapping method.[16] The rate constant for the reaction with the benzyl cation is probably about a factor of 5 larger than this on the basis of the 5-fold difference in the rate constants for solvent capture of the (4-methoxyphenyl)ethyl and 4-methoxybenzyl cations which have also been determined by the azide ion trapping method.[16,32] A rate constant of $k_s \sim 4 \times 10^{11}$ s^{-1} for reaction of the benzyl cation with solvent in 50/50 trifluoroethanol−water was recently estimated.[32] A lower limit of $k_s \sim 1 \times 10^{11}$ s^{-1} in the same solvent can be estimated from $k_s = 5.6 \times 10^9$ s^{-1} recently determined for the 4-methylbenzyl cation[41] and $\varrho^+ = -4.0$ for the dependence on substituent of k_s for 1-arylethyl cations.[19] Benzylic carbocations with electron-withdrawing groups must be more reactive than this. Qualitative evidence that the benzyl cation is highly unselective is found in the concerted decomposition of benzyl azoxy tosylate in which 55% of the cation is trapped by solvent while 45% is apparently trapped by the nitrous oxide molecule in the nitrous oxide separated ion pair.[42]

[41] Thibblin, A. *J. Org. Chem.* **1993**, *58*, 7427.

[42] Maskill, H.; Jencks, W. P. *J. Chem. Soc., Chem. Commun.* **1984**, 944. Maskill, H.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 2062.

[43] Kaatze, U. *J. Chem. Eng. Data* **1989**, *34*, 371.

[44] Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161.

[45] The rate constant k_s for the more stable (1-(4-nitrophenyl)ethyl cation was estimated to be $k_s \sim 10^{13}$ s^{-1} by Richard and Jencks.[16]

bis(trifluoromethyl)phenyl methanediazoate, and the k_{ET}/k_T values (Table 2), in going from the unsubstituted compound to (3,5-dichlorophenyl)methanediazoate, indicates an absence of chemical barriers in the product-determining steps for the reaction of these cations with solvent and other nucleophiles.

It is concluded that the barriers to product formation from 1, Scheme 6, are likely physical—involving irreversible rotational or translational reorientation that is followed by bond formation. This conclusion is further buttressed by the studies of White,[26] Moss,[47] and Tidwell.[23] In these studies there is considerable evidence, in the observations of leaving group return and the stereochemistry of substitution, that the *more stable* 1-phenylethyl cation in nitrogen-separated, and other, ion pairs in polar media forms products with rate constants that are competitive with rotational and translational diffusion.

When there is no chemical barrier to product formation between a "properly" oriented nucleophile and the cation, product formation from **1** (Scheme 6) will occur by an uncoupled concerted reaction in which rotational/translational reorientation leads directly to products with no intervening potential well.[38] In some fraction of such cases, when the nascent cation and nucleophile are "properly" oriented, reactions will bypass the intermediate **1**, Scheme 6, by the uncoupled concerted, k_c or k_{cs}, pathways. This likely occurs to some extent in the reactions of azide ion (X = H and EWG) and perhaps in the reactions of solvent and acetate with the most reactive cations. But the k_c and k_{cs} pathways are likely entropically disfavored relative to the reaction through **1** because of the requirement for "proper" orientation of the nucleophile prior to the k_c of k_{cs} steps. This additional entropic barrier that disfavors k_c and k_{cs} relative to k'_1 is corollary to the uncoupled nature of these substitution reactions.

The conclusion that nucleophilicity is an unimportant determinant in the selectivity of substitution reactions of arylmethanediazonium ions (X = H and EWG) probably also applies to reactions that yield simple secondary alkyldiazonium ions. Such diazonium ions, which are formed in the decay of sec-alkanediazoic acids, are short-lived and dissociate to nitrogen-separated ion pairs faster than diffusion away of the hydroxide ion as indicated by the extensive stereochemical/isotope incorporation experiments of Moss.[5] The rate constant for reaction of a secondary carbocation with solvent water has been estimated be $\sim 2 \times 10^{11}\ s^{-1}$.[48]

Preferential Solvation. The values of $k_H/k_T \sim 0.5-0.6$ for arylmethanediazoates and aryldiazomethanes (X = H and EWG) can be explained by preferential solvation that favors association of trifluoroethanol with the carbocation precursors. The preference for formation of trifluoroethyl ether compared to alcohol is not due to the hydroxide ion assisted proton switch indicated for the (*p*-methoxyphenyl)methanediazoate. The greater avidity of the more basic ethanol compared to water, $k_{ET}/k_T \sim 1$ (Table 2), the fact that the rate constants for such processes are too slow (vide supra, k'_T, k'_H in Table 6) to be competitive with cation capture, and the fact that there is a similar preference for trifluoroethyl ether formation in the acetic acid catalyzed hydrolysis of the corresponding aryldiazomethanes militate against this possibility.

The effect of preferential solvation is manifest because the barriers for capture of the cation by solvent are sufficiently small such that the product distribution reflects the solvent distribution in the first solvation shell of the reactant. To the extent that this solvation shell is different in composition from the bulk solvent due to specific attractive or repulsive forces between the reactant and a specific solvent component, this difference will be reflected in the product ratio.

The magnitude of the preferential interaction of trifluoroethanol compared to water that is required for the observed product ratios of $k_H/k_T = 0.5-0.6$ is approximately 1 kcal/mol.[49] This can be calculated from the change in equilibrium constant for association of trifluoroethanol and water with the reactant that is required for the observed values of k_H/k_T based on a model that assumes that the unselective cation is surrounded by five or two solvent molecules.[49]

Preferential solvation by trifluoroethanol compared to water has been previously invoked to explain enhanced selectivity of trifluoroethanol in the solvolyses of benzylazoxytosylate[42] and 1-(4-methylphenyl)ethyl derivatives[19] in 50/50 v/v trifluoroethanol−water.

Good experimental evidence for preferential solvation of solutes by the organic components, including alcohols, of mixed aqueous solvents is found in the change in ultraviolet[51] and ^{13}C-NMR[52] spectra of "reporter" betaines as a function of solvent

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[46] The same logic applies if it is assumed that both the phenyl- and (3,5-bis(trifluoromethyl)phenyl)methane azide adducts are formed solely by the uncoupled concerted, k_c, path. In the absence of a chemical barrier for the reaction of the (3,5-bis(trifluoromethyl)phenyl)methane cation with solvent, complex **2** would react with azide and solvent molecules with equal propensity, $k_c \sim k_{cs}$, so that there should be a measurable decrease in the yield of azide, and thus k_a/k_H, in going from the phenyl to the (3,5-bis(trifluoromethyl)phenyl)methanediazoate.

[47] Moss, R. A.; Landon, M. J. *J. Am. Chem. Soc.* **1970**, *92*, 5755.

[48] Chiang, Y.; Kresge, A. J. *J. Am. Chem. Soc.* **1985**, *107*, 6363.

[49] In the absence of preferential solvation the reactant will associate with the two solvent species in a purely statistical manner, and if the product selectivity reflects only the statistical probability of the occupation of sites which can react with the carbocation then the observed selectivities can be calculated. To illustrate, a model with five solvation sites is initially assumed. If $C^+ \cdot H_xT_y$ is the cation which upon formation from the diazoic acid, $D{\cdot}H_xT_y$ is surrounded by *x* water molecules and *y* equally reactive trifluoroethanol molecules, where H and T represent water and trifluoroethanol, respectively, then the fraction $X_{H_xT_y}$ of the reaction that occurs through this form can be calculated according to eq 10.

$$X_{H_xT_y} = [N!/(n_H!n_T!)]P_H^{n_H}P_T^{n_T} \qquad (10)$$

Equation 10 describes the fraction of each species according to the simple random walk for occupation of the five solvent sites assuming no cooperativity, where *N* is the total number of sites, n_H and n_T are the number of sites for a given species that are occupied by water and trifluoroethanol, respectively, and P_H and P_T are the probabilities of occupation of a single site by water and trifluoroethanol, respectively.[50] In the absence of solvent sorting P_H and P_T can be taken as the mole fraction of each solvent component and in 50/50 v/v $H_2O-CF_3CH_2OH$ $P_H \sim 0.8$ and $P_T \sim 0.2$. The fractions of alcohol and ether product from each of the five forms of the solvated cation can be calculated by multiplying the fractional occupancy of water or trifluoroethanol in a specific form of $C^+ \cdot H_xT_y$ by the value of $X_{H_xT_y}$ for that form. Summing the product fractions from each species and normalizing, as in Table 2, for the solvent mole fractions yields the value k_H/k_T. For the constraints above, the calculated value of k_H/k_T is $k_H/k_T = 1$. As discussed above, in 50/50 trifluoroethanol−water, product determination occurs to a substantial degree at the nitrogen-separated ion pair stage so the solvation sphere of the cation is reflective of that of the initial diazoic acid. The assumption that all 5 solvated diazoic acid species, $D \cdot H_xT_y$, are equally capable of reacting to form the respective cations is unlikely to be valid. Enrichment of the primary solvation shell by organic molecules should deactivate the diazoic acid with respect to ionization. An upper limit of $k_H/k_T = 1.2$ is calculated if it is assumed that when three of the five sites are occupied by trifluoroethanol that the diazoic acid is unreactive. The effect of preferential solvation on the populations of the various solvated species and the product ratios may be introduced by decreasing the value of P_H and increasing the value of P_T (eq 10) thus reflecting a greater probability for association of trifluoroethanol with the diazoic acids than is predicted solely on the basis of its mole fraction. The strength of the affinity for trifluoroethanol is determined from the difference in equilibrium constants for association of water and trifluoroethanol between the cases without preferential solvation and with the extent of preferential solvation required by the observed product ratios. The value of a 0.85 kcal/mol preference for trifluoroethanol is the largest value required and is calculated based on the model involving 5 solvating molecules, $P_H = P_T = 0.5$, and the conservative assumption that only the solvated diazoic acid species $D{\cdot}H_5T_0$, $D{\cdot}H_4T_1$, and $D{\cdot}H_3T_2$ are competent to form cations. Models with two solvating molecules give similar results.

[50] Reif, F. *Fundamentals of Statistical and Thermal Physics*; McGraw-Hill: New York, 1965; p 7.

[51] Dawber, J. G.; Ward, J.; Williams, R. A. *J. Chem. Soc., Faraday Trans. 1* **1988**, *84*, 713. Haak, J. R.; Engberts, J. B. F. N. *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 307.

composition and the change, as a function of solvent composition, in paramagnetic line broadening of the solvent signals caused by ionic inorganic complexes.[53] Infrared spectroscopic evidence consistent with the heterogeneity of acetonitrile–water mixtures has recently been summarized.[54]

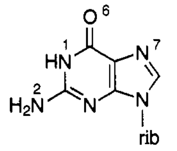
Compared to the present study, larger values[19] of k_H/k_T were observed in the solvolysis of (3-bromo- and 3-methoxy-1-phenyl)ethyl chlorides and (4-nitro-1-phenethyl)tosylates and this must indicate some additional factor or factors that cause(s) apparent enhancement in the reactivity of water in these systems and that mitigates the preferential solvation by trifluoroethanol that likely exists based on the present investigation. The difference in the k_H/k_T values may lie in preferential solvation of the anionic leaving groups by water and the difference between the two reactions in the proximity of the leaving groups to the reactive cationic sites.[55]

An additional factor may be the apparent diminished reactivity of alcohols with moderate to strong electron-withdrawing groups, including trifluoroethanol, in the solvolysis of the substituted 1-phenylethyl derivatives[19] above. In the case of trifluoroethanol the diminished activity was ascribed specifically to the unproductive orientation of solvating trifluoroethanol molecules due to the unique orientation of the dipole moment of this particular alcohol. Such effects do not appear to predominate in the product-determining steps for the decay of (*E*)-arylmethanediazoic acids for which $k_{ET}/k_T \sim 1$ for X = H, 4-Cl, and 3,5-Cl_2.

Biological Relevance. The present work establishes that for (*E*)-arylmethanediazoates, with X = H and EWG, nucleophilic character appears to be unimportant in the selectivity of benzyl group transfer. The observation that in mixed trifluoroethanol–water solutions the product ratios are dominated by preferential solvation by trifluoroethanol underscores the unimportance of nucleophilicity in this benzyl group transfer reaction. In the absence of nucleophilicity as an important consideration, the major determinant in selectivity appears to be the equilibrium constant K_a, e.g. Scheme 4, for association of a nucleophile (addend or solvent) with the diazoic acid or the diazonium ion. The magnitude of this association constant will be governed by the numerous small interactions that govern association constants in aqueous solutions.

It seems likely that similar considerations govern the selectivity of substitution reactions of secondary alkanediazoates that decompose through similarly short-lived cations (vide supra).

The conclusion that nucleophilic character is unimportant in selectivity in these reactions contrasts with a recent analysis that concludes that the increase in the ratio of O^6/N^2 aralkylation of guanosine by diazonium ions ($O^6/N^2 \sim 1$) derived from nitrosoureas compared to the O^6/N^2 ratio observed in reactions of benzyl chlorides and bromides ($O^6/N^2 < 1$) is due to enhanced reactivity of the "harder" oxygen nucleophile with the "harder" aralkylating agent from the nitrosoureas.[11] The observed selectivity of $O^6/N^2 \sim 1$ is what is to be expected if the product-determining step involves only rotational and translational reorientation that is independent of nucleophilicity and if there is little difference between the association constant K_a for O^6 compared to N^2. The absence[11] of a measurable change in the O^6/N^2 ratio as the substituent on the benzene ring is changed from H to NO_2 is similarly most consistent with the unimportance of "hard–hard" interactions that should change in changing substituent from H to NO_2.[56]



guanosine

In the reaction of guanine with the (*p*-methoxyphenyl)-methanediazoate presumably derived from the nitrosourea,[11] there is no evidence that the proton-switch mechanism observed in the present study markedly affects the product yields. The proton-switch mechanism could in theory enhance the reactivity of the O^6 or N^1 of guanine by abstraction of the ^{1}N-H proton. The proton switch mechanism is potentially of greater significance in reactions in the interstices of DNA where the diffusional separation of the hyroxide ion would be retarded and its basicity enhanced. It could in part account for the enhanced O^6-alkylating ability of secondary compared to primary alkanediazoates derived from nitrosoureas in the reactions with DNA.[57]

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Supplementary Material Available: List of experimental conditions and rate constants for the decay of (*E*)-arylmethanediazoates, double reciprocal plot of $1/\mathcal{F}_{az})$ against concentration of azide ion for the decay of *p*-methoxybenzyl chloride in trifluoroethanol–water, plot of log k_1 against ammonium ion pK_a for the decay of (*E*)-arylmethanediazoates, Eyring plots for the decay of (*E*)-(*p*-methoxy)phenylmethanediazoate, (*E*)-phenylmethanediazoate, and (*E*)-(3,5-dichloro)-phenylmethanediazoate (27 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(52) Dawber, J. G.; Williams, R. A. *J. Chem. Soc., Faraday Trans. 1* **1986**, *82*, 3097.

(53) Sastri, J. S.; Henwood, R. W.; Behrendt, S.; Langford, C. H. *J. Am. Chem. Soc.* **1972**, *94*, 753. Langford, C. H.; White, J. F. *Can. J. Chem.* **1967**, *45*, 3049. Behrendt, S.; Langford, C. H.; Frankel, L. S. *J. Am. Chem. Soc.* **1969**, *91*, 2236. Sastri, V. S.; Langford, C. H. *J. Phys. Chem.* **1970**, *74*, 3945.

(54) Jamroz, D.; Stangret, J.; Lindgren, J. *J. Am. Chem. Soc.* **1993**, *115*, 6165.

(55) This effect has been invoked in the observation of "retentive solvolyses". References 47 and the following: McManus, S. P.; Zutaut, S.E. *Tetrahedron Lett.* **1984**, *25*, 2859. Bone, J. A.; Pritt, J. R.; Whiting, M. C. *J. Chem. Soc., Perkin Trans. 2* **1975**, 1447.

(56) The definite preference for exocyclic sites O^6 and N^2 compared to the endocyclic N^7, $O^6/N^7 \sim 3-5$, in the study[11] is not so large as to require invocation of various elements of nucleophilicity for explanation. A combination of steric and statistical and other effects could conspire to generate such fairly small differences in selectivity.

(57) Saffhill, R. *Carcinogenesis* **1984**, *5*, 621.