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Hydrolysis of Diazomethane—Kinetics and Mechanism[1]

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Abstract: The reaction between diazomethane and the hydronium ion was studied in a THF–water (60:40 v/v) mixture at 25 °C. When a large excess of diazoalkane was used, the kinetics were zero order in diazoalkane and first order in acid for the pH range $4 < \mathrm{pH} < 5.5$. The pH rose dramatically at the start of the reaction: the pH rise was measured by use of a novel continuous-flow system. Combination of the kinetic and pH data allowed estimation of the protonation rate as 4×10^8 $\mathrm{M^{-1}\,s^{-1}}$. Isotope-exchange studies showed that water deprotonates the methanediazonium ion less rapidly than it displaces nitrogen; however, the hydroxide ion reacts more rapidly as a base than as a nucleophile. The rates of nucleophilic attack of water and the hydroxide ion on the methanediazonium ion were estimated as $1.8\ \mathrm{s^{-1}}$ and $1 \times 10^4\ \mathrm{M^{-1}\,s^{-1}}$, respectively, in THF–water (60:40 v/v). The pK_a of the methanediazonium ion in this medium was ten.[2]

Introduction

A considerable effort has been deployed recently to identify the factors responsible for the rapidity of certain proton transfers.[3,4] Such analyses, necessarily involving a separation of thermodynamic driving force and purely kinetic reactivity terms, have been successfully applied to proton transfers to aliphatic diazo compounds.[5,6] The reactions of the most simple, unstabilized diazoalkane, diazomethane **1**, with strong acids such as the hydronium ion in solution eq 1, have however defied quantitative study,

$$\underset{\mathbf{1}}{\mathrm{CH_2N_2}} + \mathrm{H_3O^+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \underset{\mathbf{2}}{\mathrm{CH_3N_2{}^+}} + \mathrm{H_2O} \xrightarrow{k_2} \mathrm{CH_3OH_2{}^+} + \mathrm{N_2} \tag{1}$$

precisely because of their extreme rapidity. Indeed not only is the protonation step rapid but also particular conditions must be used to avoid the very rapid decomposition of the intermediate methanediazonium ion **2**. In the gas phase, ion cyclotron resonance experiments involving **2** provide the rate constants for deprotonation by nitrogen bases and approximate limits for the proton affinity of diazomethane;[7] in superacid media **2** can be observed,[8] but only below −100 °C. In more nucleophilic media, kinetic studies on the protonation of **1** have of necessity been limited to buffered weak-acid solutions, where the concentration of the intermediate **2** is low;[9] for similar reasons investigations of the methanolysis of diazobutane were restricted to basic solutions.[10] Earlier kinetic studies of the comparative reactivity of simple diazoalkanes toward phenols were carried out in apolar media where the nature of the rate-determining step is uncertain.[11,12]

In the present work we describe a novel approach to the problem, leading to the determination of the rate of protonation of diazomethane by the hydronium ion and also the rates of nucleophilic attack of water and the hydroxide ion on the methanediazonium ion.

Experimental Section

Materials. Deionized water was distilled from alkaline $\mathrm{KMnO_4}$. Deuterated water had an isotopic purity of 99.7%. Tetrahydrofuran (THF) was successively refluxed over and distilled from $\mathrm{CuCl_2}$, KOH, and sodium wire. Dioxane was refluxed with 2 N HCl for 8 h with a rapid passage of nitrogen; the aqueous layer was removed after the addition of KOH pellets, and the residue was refluxed over sodium metal before distillation. Concentrated $\mathrm{HClO_4}$ (70%) was the Fluka "puriss" product.

Diazomethane solutions in THF were prepared in fire-polished glassware equipped with rubber stoppers as follows: to a mixture of 3 mL of aqueous KOH (30%) and 8 mL of THF kept at 10 °C was added 0.40 g (3.88 mmol) of *N*-methyl-*N*-nitrosourea[13] in one batch. Nitrogen gas was passed vigorously through the THF layer, to remove the diazomethane formed, and then through another 30 mL of THF at 0 °C. The gas from this flask was passed through an aqueous acid trap. By renewing the contents of the reaction vessel once, we could prepare solutions of 10^{-1} M diazomethane in 10 min. Solutions in dioxane were similarly prepared. The concentration of diazomethane was determined by titration of a sample with benzoic acid.

[$^2\mathrm{H}_1$]Methan[^{2}H]ol ($\mathrm{CH_2DOD}$) was prepared by adding diazomethane in THF slowly to $\mathrm{D_2O}$ with pD 1.

[$^2\mathrm{H}_2$]Methanol ($\mathrm{CHD_2OH}$) was prepared by adding dideuteriodiazomethane[14] in THF slowly to water with pH 1.

4-Methoxy-1-butanol (**4**) was prepared according to the published procedure,[15] in 69% yield: bp 67–69 °C (16mmHg) [lit.[15] 63–64 °C (7mmHg)]; mass spectrum (CI), *m/e*(relative intensity) 105 (4%, M + 1), 87 (30%, M − 17), 73 (100%, M − 31).

***O*-Methyldioxanium Perchlorate**[16] (**6**). Diazomethane (0.1 M) in dioxane (50 mL) was treated with concentrated $\mathrm{HClO_4}$ (30 μL). The white precipitate so-formed was transferred in suspension by pipette to a flask of pentane (30 mL), and the pentane and excess dioxane were decanted. The precipitate was washed twice with pentane and dried by a stream of dry nitrogen. The residual solid was washed and dried twice in this manner to yield 30 mg of **6**: mp 72–74 °C;[16] NMR ($\mathrm{CF_3CO_2H}$) δ 4.36 (t, J = 4.3 Hz, 4 H, O-CH_2-), 4.73 (s, 3 H, $^+$O-CH_3), 5.05 (t, J = 4.3 Hz, 4 H, $^+$O-CH_2-).

***O*-Methyltetrahydrofuranium perchlorate**[16] (**3**) was prepared as described for **6**. NMR ($\mathrm{CF_3CO_2H}$): δ 2.58 (m, 4 H, CH$_2$-CH_2-CH$_2$), 4.62 (s, 3 $^+$O—CH_3), $^+$O-CH_3), 4.97 (m, 4 H, $^+$O-CH_2).

***O*-Methyltetrahydropyranium perchlorate**[16] (**5**) was prepared as described for **6**. NMR ($\mathrm{CF_3CO_2H}$): δ 2.15 (m, 6 H), 4.70 (s, 3 H, $^+$O-CH_3), 4.93 (t, J = 5.2 Hz, 4 H, $^+$O-CH_2).

Apparatus and Techniques. Kinetic experiments were carried out on a Durrum D-110 stopped-flow spectrophotometer linked to a Datalab DL 90 transient recorder, Textronix 604 storage monitor, and Facit tape perforator. The data were analyzed on an IBM 7040 computer. The diazomethane hydrolyses were observed at 237 nm (log ϵ = 3.56). The bromocresol green anion was monitored at 625 nm (log ϵ = 4.66).

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[1] Presented in part at the 4th IUPAC Symposium on Physical Organic Chemistry, York, 1978. Preliminary communication: McGarrity, J. F.; Smyth, T. *J. Chem. Soc., Chem. Commun.* **1977**, 347–348.

[2] Acidities in this medium are expressed on the molar scale, and the activity of water is taken as unity.

[3] *Symp. Faraday Soc.* **1975**, *No. 10*, 60–99.

[4] Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354–360.

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[10] Kirmse, W.; Rinkler, H. A. *Justus Liebigs Ann. Chem.* **1967**, *707*, 57–65.

[11] Adamson, D.; Kenner, J. *J. Chem. Soc.* **1937**, 1551–1556.

[12] McGarrity, J. F. In "The Chemistry of the Diazonium and Diazo Groups"; S. Patai Ed., Wiley: Chichester, **1978**; pp 179–230.

[13] This was preferred to other diazomethane precursors, despite its toxicity, as it gave more reproducible yields in our procedure.

[14] Gassman, P. G.; Greenlee, W. J. *Org. Synth.* **1973**, *53*, 38–43.

[15] Palomaa, M. H.; Janson, R. *Chem. Ber.* **1931**, *64*, 1607–1610.

[16] These salts were handled without problems in the dry state at room temperature; however, *they exploded violently when being heated* and should be treated cautiously.

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Table I. Zero-Order Kinetic Data for Hydrolysis of 1 in THF–H_2O (60:40 v/v) at 25 °C

$10^5[H_2O^+]_{init}$,[a] M	13.80	11.48	11.22	10.71	9.12	7.08	6.02	5.62	4.26	3.39	2.69
$10^5 k_{obsd}$,[a] M^{-1} s^{-1}	27.9[c]	24.0[c]	30.1[c]	27.3[c]	17.9	14.5	15.1	12.9	11.6	7.14	8.44

[a] Determined from pH measurement on mixed solution. [b] Each value is the mean of at least three runs, error = ±5%. [c] No delay allowed between mixing and observation.

The reactions were initiated by mixing equal volumes of the pure organic cosolvent containing the diazo compound with a mixture of cosolvent–H_2O (20:80 v/v, 0.2 M $NaClO_4$) containing the appropriate concentration of $HClO_4$ (maximum 2 × 10^{-4} M) to give the reaction medium of cosolvent–H_2O (60:40 v/v $HClO_4$, 0.1 M $NaClO_4$).[17] The spectrophotometer was thermostated at 25 ± 0.5 °C; however, the mixing of two different solvent systems inevitably produced a temperature rise in the observation chamber. When dioxane and THF were cosolvents, the changes were +0.5 and +3.0 °C, respectively. The duration of these changes was conveniently monitored by following the anomalous absorbance increase (maximum value +0.02 unit), caused at all wavelengths by the thermal gradient across the observation chamber.[18] In the THF solutions this absorbance diminished to $^1/_6$ of the maximum value after 3 s, so for the less rapid reactions a delay of 3 s was applied before observation. For the most rapid reactions where this was impossible, no systematic temperature effect could be noticed. An upper limit of 10^{-3} M was imposed on the diazomethane concentration, as otherwise passage through the mixing jet caused boiling off and distortion of the light signal by the bubbles. Similarly for acid concentrations greater than 10^{-4} M, nitrogen evolution was too rapid and gave similar distortion.

The hydrolyses in basic aqueous solution were followed on a Pye Unicam SP 1800, thermostated by circulation of water directly around the sample cuvettes. Reactions were initiated by mixing rapidly 30 μL of 0.1 M CH_2N_2 solution in dioxane with the aqueous solution, by means of a perforated Teflon plunger.[19]

pH measurements were made with a Philips CA 14/20 combined glass electrode connected to a Radiometer PH 25b meter; the system was calibrated with aqueous standards and then with known concentrations of acid in the mixed solvents. Continuous-flow pH experiments were carried out with an Ingold (Zurich) microcapillary glass electrode, type 138-UL (with active surface of diameter 1mm, length 20mm), together with an Ingold 308-K19 standard calomel reference electrode, installed as illustrated in Figure S-1. The voltage difference, measured on a Metrohm E 512 pH meter, was recorded against time on a Varian G-2000 strip chart recorder. The system was calibrated with 9 different acid solutions, 10^{-1}–10^{-5} M in THF–H_2O (60:40 v/v, μ = 0.1). As required by the Nernst equation for the glass electrode, the slope of the linear voltage–pH plot was 59 mV $(pH)^{-1}$. This calibration was extrapolated to the pH region 5–13. In flow experiments a flow rate of 0.5 mL s^{-1} was employed, and typically 5 s sufficed for a stable reading to be attained. The pH so-measured corresponded to that of the reaction solution 0.5 s after mixing (the time taken to reach the center of the capillary electrode). The pK_a of bromocresol green in THF–water (60:40 v/v) was determined from the UV absorptions of the acidic and basic forms at different acid concentrations. GLC analyses were performed on a Hewlett-Packard 5710 instrument with a flame-ionization detector. Packed-glass columns (0.64-cm diameter, 113-cm length) were used. For methanol, SE-30 (20% on chromosorb WAW 60/80), N_2 carrier gas at 20 mL min^{-1}, temperature 60 °C: CH_3OH at 1.4 min; THF at 3.0 min; dioxane at 5.3 min. For 4, column Silar 5CP (3% on chromosorb WAW 60/80), N_2 carrier gas at 20 mL min^{-1}, temperature 80 °C for 2 min and then 8 °C min^{-1} to 110 °C: THF at 0.6 min; 4 at 4.0 min. For the quantitative product analyses, solutions 0.1 M in diazomethane were hydrolyzed and 2 μL samples were injected directly onto the columns; the detector had been previously calibrated with authentic samples of each product.

The MS measurements were performed on a Hewlett-Packard 5980 A instrument coupled to a Hewlett-Packard 5710 GLC. Chemical ionization spectra were measured with CH_4 as reactant gas, source pressure 1 mm and ionization energy 200 eV. For each sample five GLC/MS injections were made. For each injection the three mass units of interest were repetitively scanned at 20 amu s^{-1}, and the three spectra corresponding to the summit of the product GLC peak were retained. Each hydrolysis was performed twice. The EI spectra of methanol were run at 70 eV. The peaks examined were *m/e* 36 ($CD_3OD^{+\cdot}$ from CD_3OD), 35 ($CHD_2OD^{+\cdot}$ from CHD_2OD), and 34 ($CH_2DOD^{+\cdot}$ from CH_2DOD, $CD_2{=}OD^+$ from $CD_3OD^{+\cdot} - D\cdot$ and from $CHD_2OD^{+\cdot} - H\cdot$). The extent of fragmentation from the molecular ions of CD_3OD, CH_2DOD, and CHD_2OH was measured directly from the spectra of authentic samples.

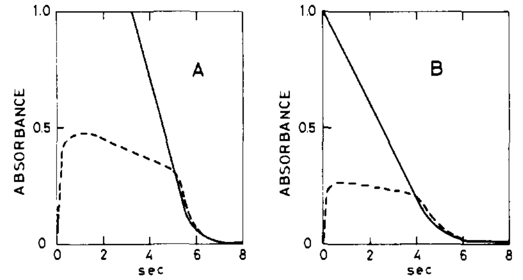

Figure 1. Absorbance–time profiles for hydrolyses of 1 in THF–H_2O (60:40 v/v) at 25 °C in the presence of BCG indicator, followed at 237 nm (—) and 625 nm (---): (A) CH_2N_2 = 4 × 10^{-4} M, $[H_3O^+]_{init}$ = 3.6 × 10^{-5} M, [BCG] = 5.6 × 10^{-6} M; (B) $[CH_2N_2]$ = 1.4 × 10^{-4} M, $[H_3O^+]_{init}$ = 1.4 × 10^{-5} M, [BCG] = 2.8 × 10^{-6} M.

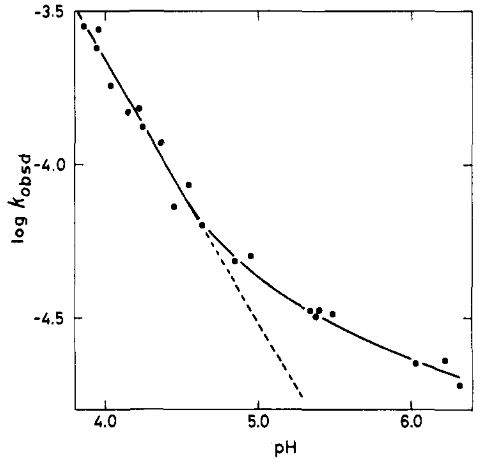

Figure 2. log $[H_3O^+]_{init}$–log k_{obsd} (zero-order) plot for acid-catalyzed hydrolysis of 1 in THF–H_2O (60:40 v/v) at 25 °C.

Results and Discussion

Hydrolysis in Acidic Solution. Kinetics. No absorbance could be detected after the dead time of our instrument (≈5 ms), when a solution of CH_2N_2 (10^{-4} M) was mixed with another 10^{-4} M in hydronium ion. Thus under these conditions the reaction is complete after 5 ms. In all other experiments described here *the diazomethane was initially in excess by at least tenfold over acid.* Under these conditions the observed decays were *zero order in diazomethane* (Figure 1).

The slopes of these decays in THF–H_2O, k_{obsd}, gave a linear correlation with the initial hydronium ion concentrations $[H_3O^+]_{init}$ of slope 2.1 ± 0.1 s^{-1} (Table I).

However with acid concentrations lower than 10^{-5} M the decays were zero order for less than 4 half lives. Furthermore the log k_{obsd}–log $[H_3O^+]_{init}$ plot was linear, with slope equal to 1, only for acid concentrations between 10^{-4} and 10^{-5} M (Figure 2), so it appears that the overall mechanism changes when less acidic solutions are employed.

The observed zero-order kinetics imply that the rate-determining step is not the protonation of diazomethane and that the concentration of an intermediate, shown below to be the diazonium ion 2, remains constant throughout the hydrolysis. With reference to eq 1, the condition $k_1 \gg k_{-1}$ and the stoichiometric excess of diazomethane ensure that effectively all the hydronium ions initally

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(17) The most obvious means of generating the reaction medium is by mixing CH_2N_2 in cosolvent–H_2O (60:40 v/v, 0.1 N NaOH (lifetime ca. 1 h)), with cosolvent–H_2O (60:40 v/v of varying acidities). This proved to be impractical as the diazomethane had almost completely reacted during the neutralization process before observation.

(18) Miller, M. L.; Gorden, G. *Anal. Chem.* **1976**, *48*, 778–779.

(19) We are indebted to Professor C. A. Bunton for suggesting this technique.

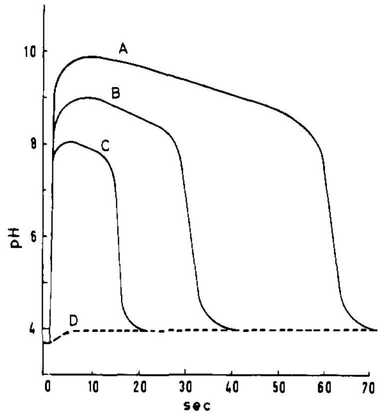

Figure 3. pH-time profiles during the hydrolysis of 1 in THF-H_2O (60:40 v/v) at 25 °C, standard electrode experiments: $[H_3O^+]_{init} = 2 \times 10^{-4}$ M, $[CH_2N_2] = 3.0 \times 10^{-2}$ M (A), 1.4×10^{-2} M (B), 6.3×10^{-3} M (C), 0 M (D).

present are converted into intermediate **2**. The rate-determining step is thus the hydrolysis of **2**, regenerating the hydronium ion which is immediately consumed by reaction with more diazomethane. Hence

$$k_{obsd} = k_2[CH_3N_2^+] = k_2[H_3O^+]_{init} \quad (2)$$

where $k_2 = 2.1$ s^{-1}, and

$$[H_3O^+]_{hyd} \ll [H_3O^+]_{init} \quad (3)$$

where $[H_3O^+]_{hyd}$ is the concentration of the hydronium ion during hydrolysis. Such a kinetic situation, resulting from the excess of substrate, has previously been encountered with the protonation of diphenyldiazomethane in aprotic solvents[20] and is especially familiar to enzyme kineticists. With our system we were able to verify this interpretation by checking the change in pH of the solution during hydrolysis.

pH Measurements. In Figure 3 the pH-time profiles for reactions of different concentrations of diazomethane in THF, with acid in THF-H_2O (20:80 v/v), illustrate that the pH rises abruptly after mixing, before returning to its (new) equilibrium value. The height and duration of the pH "jump" depend on the initial concentration of the diazomethane employed. This phenomenon was also investigated under the conditions of the kinetic runs, by adding bromocresol green (BCG) indicator to the hydrolysis solution and following the evolution of the BCG anion (the pK_a of BCG is 8.06 ± 0.01 in THF-H_2O (60:40 v/v, 0.1 M $NaClO_4$)). The profiles obtained (Figure 1) confirm that the lifetime of the BCG anion, indicating the pH jump, corresponds well to the duration of the zero-order decay.

A further consequence of the proposed scheme is open to verification: if the rate of regeneration of the hydronium ion equals its rate of consumption, then

$$k_1[CH_2N_2][H_3O^+]_{hyd} = k_2[CH_3N_2^+] = k_2[H_3O^+]_{init} \quad (4)$$

Precise measurements of $[H_3O^+]_{hyd}$ using conventional glass electrodes proved to be impossible as either the response was too slow or the low-resistance glass of rapid-response electrodes became rapidly poisoned by the cosolvent. This dilemma was avoided by the use of a continuous-flow pH measurement. The reaction medium, mixed in the stopped-flow mixing chamber, was flowed through a microcapillary glass electrode for a time sufficient to allow the latter to attain a stable value. Determinations were made only for the start of the reaction, before nitrogen evolution perturbed the measurement. In this way values of $[H_3O^+]_{hyd}$ could be determined for a tenfold variation in $[H_3O^+]_{init}$ and $[CH_2N_2]$—the latter being corrected for reaction occurring during the 0.5 s before the electrode center is reached. The resultant values (Table II) obeyed eq 4 extremely well ($r = 0.999$), with $k_1 = (2.0 \pm 0.1) \times 10^8$ M^{-1} s^{-1}.

Table II. Dependence of $[H_3O^+]_{hyd}$ on $[CH_2N_2]$ and $[H_3O^+]_{init}$ during the Hydrolysis of 1 in THF-H_2O (60:40 v/v) at 25 °C

$[CH_2N_2]$,[a] M	$[H_3O^+]_{init}$, M	$[H_3O^+]_{hyd}$, M	$10^8 k_1$,[b] M^{-1} s^{-1}
1.6×10^{-1}	7.1×10^{-4}	4.5×10^{-11} [c]	2.0
2.9×10^{-1}	5.3×10^{-4}	1.8×10^{-11} [c]	2.1
7.5×10^{-2}	4.9×10^{-4}	6.9×10^{-11} [c]	2.0
1.6×10^{-2}	3.8×10^{-4}	2.3×10^{-10} [c]	2.2
3.1×10^{-2}	3.5×10^{-4}	1.2×10^{-10} [c]	1.9
4.7×10^{-2}	3.5×10^{-4}	8.1×10^{-11} [c]	1.9
4.8×10^{-2}	2.3×10^{-4}	4.9×10^{-11} [c]	2.0
2.9×10^{-2}	1.9×10^{-4}	6.6×10^{-11} [c]	2.1
1.6×10^{-2}	1.6×10^{-4}	1.0×10^{-10} [c]	2.0
1.3×10^{-2}	7.0×10^{-5}	5.7×10^{-11} [c]	2.0
6.4×10^{-4}	8.0×10^{-5}	6.0×10^{-10} [d]	4.4
2.4×10^{-4}	6.3×10^{-5}	1.3×10^{-9} [d]	4.2
1.5×10^{-4}	4.3×10^{-5}	1.4×10^{-9} [d]	4.3
1.2×10^{-4}	3.9×10^{-5}	1.7×10^{-9} [d]	4.0
3.8×10^{-4}	3.6×10^{-5}	5.0×10^{-10} [d]	4.0

[a] Initial concentration minus that of the diazomethane already reacted before the measurement of $[H_3O^+]_{hyd}$ is made (0.5 and 0.3 s for electrode and indicator methods, respectively). [b] Calculated according to eq 4. [c] Continuous-flow electrode measurements. [d] Stopped-flow indicator measurements.

The same information may be gleaned from the results of the indicator experiments in Table II; $[H_3O^+]_{hyd}$ was determined from the maximum absorbance of the BCG anion, normally 0.3 s after mixing. The value of k_1 obtained, $(4.2 \pm 0.2) \times 10^8$ M^{-1} s^{-1}, is greater than that derived from the electrode experiments. The latter is probably the less accurate value as the pH of the flowing solution certainly changes along the electrode and complicates the measurement. One should however note the significance of the electrode experiment, as it allows us to test eq 4 over a variety of acid and substrate concentrations; such variations under kinetic conditions are much more restricted technically (see Experimental Section). We feel that the two experiments are complementary, and we are satisfied with the agreement between their results.

Nucleophilic Attack on the Methanediazonium Ion. In the foregoing analysis, no discussion was made on the nature of the intermediate which hydrolyzes with a rate constant of 2.1 s^{-1} to yield the hydronium ion. Several alternatives to the methanediazonium ion may be imagined. The methyl cation is an unlikely candidate, as its enthalpy of formation in the gas phase is 49 kcal mol^{-1} greater than that of the diazonium ion.[21] Certainly the corresponding difference will be less in aqueous solution, as the completely unstabilized methyl cation should benefit more from solvation.[22] However the diazonium ion can also be expected to have a considerably negative solvation enthalpy, by analogy with that of CH_3CO^+, where a value of −16 kcal mol^{-1} was found in fluorosulfuric acid.[24] Consequently the difference in solvation enthalpies is unlikely to compensate for the large gas-phase difference.

Methyl perchlorate can be excluded as a possibility as its solvolysis rate[25] of 1.76×10^{-3} s^{-1} is much lower than that of the intermediate.

The most acceptable alternative would be the oxonium ion resulting from nucleophilic attack of the THF on the methanediazonium ion. Fortunately this can be tested, as *O*-methyltetrahydrofuranium ions formed in situ give predominantly ring-opened solvolyses products in ethanol and acetic acid.[26] The methyl oxonium ions derived from THF, tetrahydropyran, and

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(20) Bethell, D.; Callister, J. D. *J. Chem. Soc.* **1963**, 3808-3819.

(21) Foster, M. S.; Williamson, A. D.; Beauchamp, J. L. *Int. J. Mass. Spectrom. Ion Phys.* **1974**, *15*, 429-436.

(22) The enthalpy of solvation of the methyl cation should however be much less than those measured for onium ions, e.g., H_3O^+ where hydrogen bond interactions predominate.[23]

(23) Taft, R. W.; Wolf, J. F.; Beauchamp, J. L.; Scorrano, G.; Arnett, E. M. *J. Am. Chem. Soc.* **1977**, *99*, 5964-5972.

(24) Staley, R. H.; Wieting, R. D.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1977**, *99*, 5964-5972.

(25) Koskikallio, J. *Acta Chem. Scand.* **1969**, *23*, 1477-1489.

(26) Allred, E. L.; Winstein, S. *J. Am. Chem. Soc.* **1967**, *89*, 3991-3997.

Scheme I

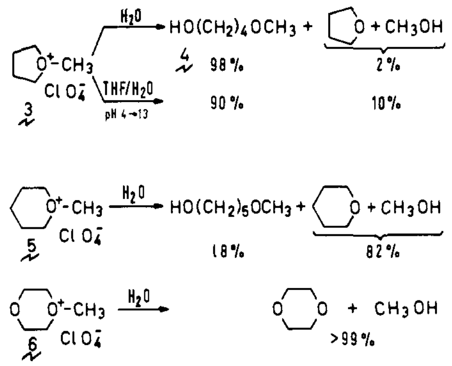

Table III. Variation of Product Composition with Acidity for the Hydrolysis of 1 in THF-H_2O (60:40 v/v) at 25 °C

pH	4.0	8.0	9.0	11.0	13.0
yield[a] of CH_3OH	88%	88%	88%	94%	97%
yield[a] of 4	12%	12%	12%	6%	3%

[a] Measured by GLC.

dioxane were prepared and isolated as their perchlorates by treating diazomethane in the appropriate solvent with concentrated (70%) perchloric acid. The simplicity of this method of preparation of these hygroscopic and explosive[16] compounds counterbalances the poor yields. The distribution of hydrolysis products in water was similar to that observed by Winstein for reaction in ethanol and in acetic acid (Scheme I).

The yield of 4-methoxy-1-butanol (**4**) from the hydrolysis of *O*-methyltetrahydrofuranium perchlorate (**3**) was reduced to 90% when the solvent was changed to THF-water (60:40 v/v). However in this solvent the product ratio was independent of pH for the range of our experiments. The lesser extent of ring opening in the hydrolysis of *O*-methyltetrahydropyranium perchlorate (**5**) relative to that found for **3** is a consequence of the difference in ring size of the cyclic ions.[27] However it is remarkable that *O*-methyldioxanium perchlorate (**6**) gave no ring opening; calibration experiments showed that under our analytical conditions less than 1% ring-opened product could be detected. Therefore THF was preferred to dioxane as cosolvent in the kinetic experiments, as with the former we can monitor the fate of the methanediazonium ion.

The variation of diazomethane hydrolysis products with pH in THF-water (60:40 v/v) is presented in Table III.

The increase in the yield of methanol with increase in pH indicates that the hydroxide ion reacts with **2** as a nucleophile, in competition with THF and water. The most noticeable feature of these results is that in acid solution, **4** is formed in only 12% yield. *Therefore the fraction of diazomethane that solvolyzes via 3 is at most 15%.*

A further plausible alternative intermediate species would be methylene diazenium ion **7**. This species may not necessarily be on a product-forming pathway (no formaldehyde-derived products were obtained), but it could complicate the kinetic analysis if present in a substantial equilibrium concentration.

$$CH_2N_2 + H_3O^+ \rightleftarrows \underset{\mathbf{7}}{H_2C{=}N^+{=}N{-}H} + H_2O \qquad (5)$$

Indeed we have found that **7** can be observed as a minor product, along with **2**, under conditions of kinetically controlled protonation of diazomethane in fluorosulfuric acid-sulfuryl chlorofluoride at low temperature.[7] When the acidity of the solution is decreased however by increasing the concentration of fluorosulfate anion, **7** is seen to be completely transformed into **2**,[28] confirming that it is the thermodynamically less stable product under these conditions. In water, which is a better hydrogen bond acceptor than the superacid system, the diazenium species should be better solvated. However it has been shown[23] that the difference in solvational ability of water and fluorosulfuric acid is minor for onium ions stabilized by charge delocalization, as it is for **7**. Hence we conclude that **7** will be the less stable isomer under our hydrolysis conditions. As protonation on nitrogen should also be reversible in the much less acidic aqueous medium, **7** should not accumulate as a kinetically controlled intermediate.

Table IV. Variation of Product Deuterium Incorporation with Acidity for the Hydrolysis of 1 in THF-D_2O (60:40 v/v) at 25 °C

pD	3.0	6.0	7.0	8.0	10.0	13.9
CD_3OD		33%[a]	36%	37%	50%	100%
CHD_2OD		33%	32%	33%	28%	
CH_2DOD	100%	33%	32%	30%	22%	
$CD_3O(CH_2)_4OD$		31%	37%	36%	49%	100%
$CHD_2O(CH_2)_4OD$		35%	33%	33%	29%	
$CH_2DO(CH_2)_4OD$	100%	34%	30%	31%	22%	

[a] Yields of isotopically substituted products expressed as percentages of the total yield of each product.

By a process of elimination we can identify the intermediate, of which the first-order solvolysis rate in our medium is 2.1 s^{-1} as methanediazonium ion **2**. As the relative rates of reaction of **2** with water and THF can be calculated from the product ratio 5.6:1 and the molarities of the two solvents are 22.2 and 4.9 M, respectively, we evaluate the second-order rate constant for nucleophilic attack of each in THF-water (60:40 v/v) as $k_2(H_2O) = 8.0 \times 10^{-2}\ M^{-1}\ s^{-1}$ and $k_2(THF) = 4.3 \times 10^{-2}\ M^{-1}\ s^{-1}$.

The small difference in rate constants for attack of the two nucleophiles on the methanediazonium ion indicates little selectivity on the part of the latter.

Deprotonation of the Methanediazonium Ion. The significance of the reverse deprotonation step in eq 1 was tested by monitoring the deuterium incorporation in both products of the solvolysis in THF-D_2O mixtures. The isotope ratio was measured by mass spectrometry after GLC separation. Chemical Ionization (CI) was used for **4** to reduce fragmentation, with its possible associated isotope effects. Two fragmentations involving loss of water and methanol molecules from the M + 1 ion did occur readily, forming presumably the cyclic oxonium ions, but both mother and labeled daughter peaks had the same isotope ratio. The electron impact (EI) spectra of partially deuterated methanol (for which methane CI is inappropriate) were complex as methanol radical cation readily loses a carbon-bound hydrogen atom.[29] The fragmentations of a series of deuterated methanols were determined; from these data and the relative intensities of the MS peaks at *m/e* 36, 35, and 34 in the solvolysis-derived methanol, the extent of deuterium incorporation can be calculated.

The results for each product (Table IV) show that in acidic solution protonation is irreversible but becomes reversible as the pH increases. The exchange experiment in acidic solution was carried out at an initial acidity (pD 3) higher than that employed for the kinetic experiments. When solutions of initial pD 4 and diazomethane concentration of 0.1 M are employed, the solution becomes sufficiently basic during hydrolysis that significant exchange is observed. For the same reason the preparation of authentic [$^2H_1$]methan[^2H]ol is carried out at initial pD 1. In the hydrolysis of neutral and basic solutions, the hydronium ion catalyzed reaction is no longer predominent (see below), and the pD change during reaction is less important.

So we can write with reference to eq 1, $k_2 > k_{-1}$, and furthermore conclude

$$K_a(2) = k_{-1}/k_1 < k_2/k_1 \qquad (6)$$

Hence we estimate a lower limit of 8.2 for the pK_a of the methanediazonium ion in THF-H_2O (60:40 v/v).

Hydrolysis in Basic Solution. For values of pH >5 the hydrolysis rate is greater than that attributable to protonation by H_3O^+ alone, so protonation by water is kinetically significant. The

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Table V. First-Order Kinetic Data for Hydrolysis of 1 in THF-H_2O (60:40 v/v) at 25 °C

pH	$[OH^-]$,[a] M	k_{obsd},[b] s^{-1}
9.20	2.2×10^{-7}	2.2×10^{-1}
9.35	3.1×10^{-7}	2.1×10^{-1}
9.90	1.1×10^{-6}	1.7×10^{-1}
10.41	3.5×10^{-6}	1.4×10^{-1}
10.55	4.9×10^{-6}	1.3×10^{-1}
10.77	8.1×10^{-6}	1.2×10^{-1}
10.80	8.7×10^{-6}	1.2×10^{-1}
11.27	2.6×10^{-5}	9.5×10^{-2}
11.35	3.1×10^{-5}	9.1×10^{-2}
11.39	3.4×10^{-5}	8.9×10^{-2}
11.49	4.3×10^{-5}	7.4×10^{-2}
11.53	4.7×10^{-5}	6.5×10^{-2}
11.82	9.1×10^{-5}	3.8×10^{-2}
11.96	1.3×10^{-4}	3.2×10^{-2}
12.17	2.0×10^{-4}	2.3×10^{-2}

[a] Calculated by assuming $pK_W = 15.86$ in THF-H_2O (60:40 v/v 57.2:42.8 w/w).[33] [b] Each value is the mean of at least three runs, error = ±5%.

isotope-exchange results in nonacidic solution indicate that deprotonation by OH^- occurs. It may be argued that this exchange takes place via the diazomethane conjugate base. However the pK_a of water in our reaction medium is 15.86.[30] So exchange at pH 8 occurs in neutral solution in which it is improbable that diazomethane would be deprotonated.

The hydrolysis in basic solution involves the protonation equilibrium given in eq 7, and the observed rate constant will be

$$CH_2N_2 + H_2O \underset{k_{-3}}{\overset{k_3}{\rightleftharpoons}} CH_3N_2^+ + OH^- \xrightarrow{k_4} CH_3OH + N_2 \quad (7)$$

given in eq 8 with k_2 as the rate constant for the nucleophilic attack

$$k_{obsd} = \frac{k_3(k_2 + k_4[OH^-])}{k_2 + (k_{-3} + k_4)[OH^-]} \quad (8)$$

of the solvent on **2**. This mechanism is consistent with Kreevoy's results for buffered basic media[9] and is analogous to that proposed by Kirmse for the solvolysis of diazobutane in basic methanol.[10]

The hydrolyses in aqueous THF at pH >9 are kinetically *first order* in diazomethane, in accord with the above scheme, where now the protonation equilibrium no longer produces a high concentration of **2**. However the observed rate constants tabulated in Table V are not of integral order in $[OH^-]$. Indeed a plot of log k_{obsd} against pH curves sharply at pH 11. In the pH region 11.4–12.2 there is a linear relation between k_{obsd} and $1/[OH^-]$ ($r = 0.999$), with slope $(2.67 \pm 0.07) \times 10^{-6}$ M s^{-1} and intercept $(9.7 \pm 1.3) \times 10^{-3}$ M s^{-1}. So in this region $k_{-3}[OH^-] > k_2$ and

$$k_{obsd} = \frac{k_3(k_2 + k_4[OH^-])}{(k_{-3} + k_4)[OH^-]} \quad (9)$$

Hence $k_3k_2/(k_{-3} + k_4) = 2.7 \times 10^{-6}$ M s^{-1} and $k_3k_4/(k_{-3} + k_4) = 9.7 \times 10^{-3}$ s^{-1}, so $k_4/k_2 = (3.6 \pm 0.6) \times 10^3$ M^{-1}, and as k_2 is known to be 2.1 s^{-1}, $k_4 = (7.6 \pm 1.2) \times 10^3$ M^{-1} s^{-1}.

Furthermore as isotope-exchange results for this region show that deprotonation is much more rapid than nucleophilic substitution, $k_{-3}[OH^-] > k_2 \geq k_4[OH^-]$, expression 9 can be further simplified to $k_3k_2/k_{-3} = 2.7 \times 10^{-6}$ M s^{-1}. Hence $k_3/k_{-3} = K_b(CH_3N_2^+) = 1.3 \times 10^{-6}$ M, and the pK_a of the methanediazonium ion in this medium is 10.0 ± 0.3.

A similar treatment is applicable to the results obtained from hydrolysis in pure water by conventional UV spectroscopy. In these experiments with $[OH^-]$ varying between 0.1 and 0.4 M, the reactions were cleanly first order, and the derived first-order rate constants were proportional to $[OH^-]^{-1}$ ($r = 0.998$), with slope of $(3.45 \pm 0.06) \times 10^{-2}$ M s^{-1} and intercept of $(1.90 \pm 0.76) \times 10^{-2}$ s^{-1} (Figure 4).

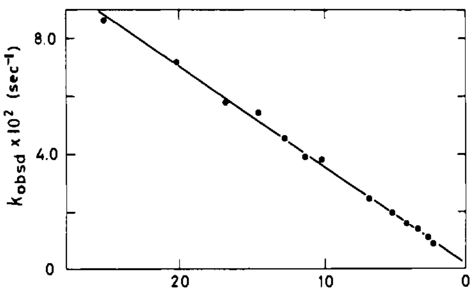

Figure 4. Plot of k_{obsd}(first order)–$[OH^-]^{-1}$ for hydrolyses of 1 in H_2O at 25 °C, μ = 0.5 M ($NaClO_4$).

Here we note that whereas the intercept, which contains rate constants involving hydroxide ion in the numerator and denominator, is roughly the same in pure water as in THF–water, the ratio $k_4/k_2 = (5.5 \pm 1.3) \times 10^{-1}$ M^{-1} in water is much smaller than the value found in THF–water. The unimportance of the $k_4[OH^-]$ terms in eq 9 for the experiments in water is apparent from the plot of log k_{obsd} against pH, which has a slope (−0.94) nearly equal to −1.

Therefore the hydroxide ion is a much more reactive nucleophile toward **2**, relative to water, in THF–water than in pure water. The increased reaction rate of hydroxide ion in the mixed solvent is a normal consequence of the diminished solvent polarity (and solvating power for small charged species), accelerating the reaction involving neutralization of charge.

Rate of Nucleophilic Substitution of Nitrogen in the Methanediazonium Ion. It is to be expected that **2** be an extremely powerful methylating agent. However direct comparison of its solvolysis rate constant in THF–water (60:40 v/v) with those of similarly reactive species is difficult, as their reactions with hydroxylic solvents are too rapid to be followed conventionally at 25 °C. Trimethyloxonium ion **8** is the most reactive substrate previously studied and has a methanolysis rate constant of 3.02×10^{-3} s^{-1} at −23.4 °C—the highest temperature at which the reaction could be followed.[31] Preliminary studies of the hydrolysis of **8** under way in our laboratories with the use of a new rapid injection NMR technique[32] indicate a rate constant of $(3.34 \pm 0.05) \times 10^{-2}$ s^{-1} (in water-nitromethane (94:6 v/v)).[33] Therefore **2** is indeed the more reactive methylation agent by a factor of 60. This moderate difference in reactivity may appear surprising in view of the commonly accepted thermodynamic drive in favor of nitrogen expulsion from diazonium compounds. However it should be noted that according to ab initio 4-31G calculations[35] the large N≡N binding energy of molecular nitrogen is already present in the methanediazonium ion, so the enthalpy change on nitrogen loss may not be especially important. A large positive entropy of activation would be expected for nitrogen loss if it were unimolecular. The conclusion, based on theoretical grounds above that the substitution is bimolecular, is confirmed by the importance of the hydroxide ion as a nucleophile in the hydrolyses in basic aqueous THF. So the entropy of activation for the hydrolysis of **2** should be similar to that for **8**, and it is reasonable that the reactivities be similar.

Acidity of the Methanediazonium Ion. The acidity of **2** in THF–water is similar to that of nitromethane in water (pK_a = 10.2) and considerably greater than that of acetonitrile (pK_a = 25). In the gas phase **2** is a much stronger acid than nitromethane or acetonitrile, as the enthalpies of deprotonation (the entropy changes for reactions 10–12) will be minor in comparison.[37] The

$$CH_3N_2^+ \rightarrow CH_2N_2 + H^+ \quad \Delta H° = 213.5 \text{ kcal}^{21} \quad (10)$$

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$$CH_3NO_2 \rightarrow CH_2NO_2^- + H^+ \quad \Delta H^\circ = 357.0\ \text{kcal}^{36} \qquad (11)$$

$$CH_3CN \rightarrow CH_2CN^- + H^+ \quad \Delta H^\circ = 373.5\ \text{kcal}^{36} \qquad (12)$$

dramatic attenuation of the gas-phase acidity difference is entirely normal, as the enthalpies of solution of small charged species are much more negative than those of neutrals. So transfer to aqueous solution will favor the dissociated states in reactions 11 and 12 where both the proton and anion will be strongly solvated. For reaction 10 the stabilization will be less as the enthalpy of solvation of the proton will be to some extent offset by that of the diazonium ion.

Rate of Protonation of Diazomethane by the Hydronium Ion. The rate of protonation of diazomethane by the hydronium ion of $4 \times 10^8\ M^{-1}\ s^{-1}$ is extremely high for a formally neutral carbon base. A number of factors are responsible for this surprising reactivity. First, the reaction is strongly exoenergetic, as judged by the difference in pK_a's of the acidic species involved. This in itself is not however a sufficient cause, as even more basic substrates, e.g., nitronate and enolate anions, are protonated much less rapidly.

The localization of negative charge on the site of protonation, minor in the above two cases, is of great importance.[4] Although a number of resonance forms involving charge separation may be written for diazomethane and the dipole moment indicates slightly greater charge density on N,[38] evidence from infrared[39] and ^1H NMR[40] spectroscopy indicates that considerable negative charge is localized on the carbon atom (^{13}C NMR evidence has been shown to be less reliable in this respect[41]). So little further energy expenditure is necessary to localize all the negative charge on carbon prior to proton transfer.[5,6] Furthermore indirect evidence exists that the diazomethane carbon is a good hydrogen bond acceptor.[42] Hence the energy necessary to desolvate the acid species may be partially compensated by hydrogen bond formation to diazomethane before proton transfer.[4]

Both these factors should diminish the W^r term in the Marcus formalism for the energetics of proton transfer—i.e., that part of the activation free energy which is independent of the thermodynamic driving force. Accordingly the observed rate constant is close to the diffusion-controlled limit.

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Supplementary Material Available: Figure S-1, diagram of the installation for continuous-flow pH measurement with the use of a microcapillary glass electrode (1 page). Ordering information is given on any current masthead page.

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Transient Fluorine-Proton Overhauser Effects in (4-(Trifluoromethyl)benzenesulfonyl)-α-chymotrypsin

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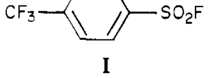
Abstract: Transient $^{19}F\{^1H\}$ nuclear Overhauser effects have been used to explore the protein environment of the trifluoromethyl group of the modified enzyme mentioned in the title. Computational results for a small model spin system which has dynamic properties appropriate for a protein the size of chymotrypsin are presented; these suggest that the NOE experiments should indicate the chemical shifts of those protons of the protein closest to the CF_3 group. It is shown that the data obtained are consistent with the structural model for the immediate environment of the CF_3 group that was proposed earlier (*J. Am. Chem. Soc.* **1979**, *101*, 7698).

The proteolytic enzyme α-chymotrypsin is inactivated by treatment with *p*-(trifluoromethyl)benzenesulfonyl fluoride (I).[1]



I

The reaction places a trifluoromethyl reporter group at the active center of the protein which can then be examined by fluorine magnetic resonance spectroscopy. Previous work has been aimed at defining the nature of the environment surrounding the CF_3 group in the protein derivative and has shown that there are interactions between protons of the enzyme structure and the fluorine nuclei, probably at internuclear distances defined by the van der Waals contact distances of hydrogen and fluorine.[2,3] Equilibrium $^{19}F\{^1H\}$ Overhauser effects, in which the modified protein was irradiated at a particular frequency in the proton spectrum until a steady state in the nuclear spin populations was reached, aided in the deduction of a crude model for the structure in the locale of the trifluoromethyl.[3]

In large molecules, cross-relaxation effects become important with the result that nuclear spins of the same type in such molecules rapidly acquire the same temperature.[4] An important

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