3, the integral areas of the 2-hydrogen of 3 and the methyl group of 4 were used as the substrate and product peaks, respectively.

Kinetics of Sulfonium Salt Dealkylation. Stock solutions of host (1.49 mM) and KSCN (0.426 M) were made in 10 mM deuterated cesium borate buffer at pD = 9. Stock solutions of the internal integration standard KHP (9.25 mM), 5-nitroquinoline (1.38 mM), and the sulfonium salts (3.8–6.8 mM) for HPLC studies were made by weighing each solid and dissolving it in 10.0 mL of HPLC borate buffer in a 10-mL volumetric flask. The reaction rates were monitored by integration of substrate and internal standard peak areas from an HPLC trace using a Waters Baseline 810 software package. Each kinetic run using ethylmethyl(*p*-nitrophenyl)sulfonium salt as a substrate was performed twice. Sample reaction mixtures for each kind of experiment (without and with a competitive inhibitor) follow. For host-catalyzed dealkylation of **12**, the reaction mixture consisted of 80 μL of sulfonium salt stock solution (3.80 mM), 30 μL of KHP stock solution, 120 μL of host stock solution, 30 μL of KSCN stock solution, and 240 μL of buffer. The uncatalyzed reaction used 120 μL of buffer instead of host stock solution. The reaction mixtures for the competitive inhibition study consisted of 70 μL of ethylmethyl(*p*-nitrophenyl)sulfonium stock solution, 30 μL of KSCN stock solution, 30 μL of KHP stock solution, 210 μL of 5-nitroquinoline stock solution, and 160 μL of host stock solution. For the uncatalyzed reaction, 160 μL of buffer was added instead of host solution.

For each experiment, the buffered pH = 9 solution of substrate, inhibitor (if any), internal standard, and host (for catalyzed reactions) was prepared without nucleophile in an Eppendorf tube and cooled to −5 °C in a salt–ice-water bath. The solution of nucleophile (chilled) was added, and the tube was shaken vigorously just prior to the first injection of sample. The tube was then placed in an oil bath maintained at 46 °C by a Thermo Watch. At each time point, the reaction mixture was cooled to −5 °C, and a 20-μL aliquot was removed and neutralized with 20 μL of pH = 7 phosphate buffer. The 40-μL sample was injected onto the column, and the reaction mixture was returned to the oil bath. A gradient elution was used to separate the reaction mixture components. Solvent A was H_2O, 0.1% TFA by volume; solvent B was acetonitrile, 0.1% TFA by volume. Elution was performed at 1.8 mL/min using a linear gradient from 20% to 100% solvent B from 0 to 10 min, maintained at 100% B from 10 to 12 min, brought back to 80% solvent A from 15 to 17 min, and washed from 17 to 35 min with 80% solvent A. Compounds were detected at 254 and 230 nm. Generally, KSCN eluted with the void volume, the KHP standard eluted at 3.3 min, the sulfonium salt eluted at 5.3 min, and the host eluted at 6.5 min. A calibration consisting of measured relative peak areas of five samples of various sulfonium salt concentrations and fixed KHP concentration was used to convert peak areas to concentrations.

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Mechanism of Decomposition of (*E*)-Methanediazoate in Aqueous Solutions[†,1]

Jari Hovinen, Jari I. Finneman, Surya N. Satapathy, Jian Ho, and James C. Fishbein*

Contribution from the Department of Chemistry, Wake Forest University, Winston-Salem, North Carolina 27109. *Received July 15, 1992*

Abstract: Rate constants for the decomposition of (*E*)-methanediazoate (**1**) at 25 °C, ionic strength 1 M ($NaClO_4$), are independent of the concentration of nucleophile in up to 0.25 M propylamine base, 0.5 M methoxyamine base, 0.20 M thiosulfate dianion, and 0.50 M azide ion. When the CH_3 group of **1** is transferred to benzoate ions, benzyl alcohol, and water upon decomposition in near neutral D_2O solutions, the isotopic integrity of the methyl group is maintained to the extent of 70–90%. The rate constant for the decomposition of protonated **1** in ethanol is 680 times slower than that in aqueous 4% ethanol under identical buffering and ionic strength conditions. Trapping of the methyl group derived from **1** by two pairs of nucleophiles gives the same ratios of methylated products as those determined from the decomposition of diazomethane. The solvent deuterium isotope effect for the decomposition of the protonated form of **1** is $k_{H_2O}/k_{D_2O} = 1.49 \pm 0.09$, and the activation parameters for its decomposition are $\Delta H^{\ddagger} = 69.6 \pm 1.5$ kJ/mol and $\Delta S^{\ddagger} = -4.5 \pm 9.5$ J/deg mol. It is concluded that **1** decomposes via equilibrium protonation on oxygen with subsequent rate-limiting cleavage of the O–N bond of the diazoic acid to yield the methanediazonium ion. This conclusion and measurements of the rate constants for decomposition of diazomethane under comparable conditions (25 °C, aqueous 5% acetonitrile, ionic strength 0.20 M) permit the first semiquantitative description of the decomposition of a simple alkanediazoate and associated intermediates in wholly or predominately aqueous media.

Introduction

Alkanediazoates are believed to be intermediates that are central to the DNA alkylating activity of a large class of *N*-alkyl-*N*-nitroso compounds that are carcinogens and/or cancer-chemotherapeutic agents.[2] Simple syn and anti alkanediazoates were synthesized separately nearly 100 years ago.[3] Alkanediazoates are generally unstable in aqueous solutions, decomposing with the evolution of nitrogen gas, though some of the anti forms are reportedly stable in cold water.[4] Some anti forms are known qualitatively to be more stable than the analogous syn forms.[4]

We recently reported the first rate constants for the decomposition of a simple alkanediazoate (**1**) in aqueous media at physiological pH.[5] On the basis of the pH–rate profile for the decomposition of **1** and the observed 92% yield of methanol, it was deduced that the mechanism of decomposition of **1** involves a rate-limiting reaction of the protonated diazoate D–H, as in eq 1. A minimal mechanism was presented in light of the well-known complexity of the mechanisms of decomposition of analogous arenediazoates.

There is a diversity of opinion about the mechanisms by which simple alkanediazoates decompose. Recent theoretical studies[6]

[†] This work is dedicated to Dr. W. P. Jencks on the occasion of his 65th birthday.

(1) Funded by National Institutes of Health under Grant CA52881. Partial support for J. Hovinen was kindly provided by the Finnish Academy of Sciences and the Foundation of Antti and Jenny Wihuri.

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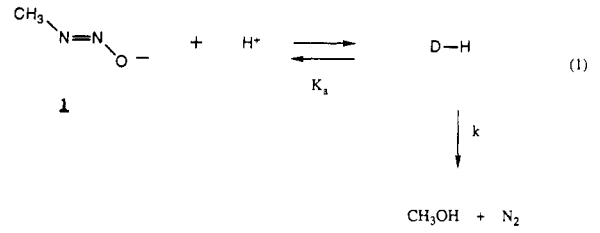

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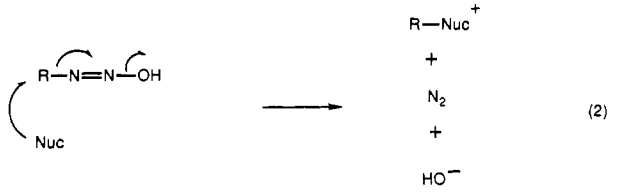
have indicated that the mechanism of decomposition of simple diazoates like **1** could involve an S_N2-type attack on the diazoic acid, as in eq 2 (Nuc = nucleophile), but this has been considered



(2)

unlikely by others.[7,8] In heterogeneous partly aqueous basic media and in protic nonaqueous media, the decomposition products of some syn diazoates include diazoalkanes, and a base-catalyzed elimination mechanism, as in eq 3, has been suggested (B = base).[9]

(3)

Recent theoretical calculations on **1** and its syn analogue have been interpreted as indicating that a mechanism such as that of eq 3 is feasible in aqueous media.[10] Probably the most widely held opinion is that the mechanism for compound **1** involves decomposition of the diazoic acid to a diazonium ion that acts as the ultimate alkylating agent.[11] The nature of the rate-limiting step for this process is unclear. It could involve either rate-limiting isomerization to the more reactive syn form, in analogy with the chemistry of certain arenediazoates,[12] or direct formation of the diazonium ion by N–O bond fission.

We report here experimental evidence that rules out the mechanisms of eqs 2 and 3 as the dominant mechanisms for decomposition of **1** in the physiological pH region. It is further concluded that the rate-limiting step for decomposition of **1** involves unassisted N–O bond fission of the diazoic acid. This conclusion affords the first semiquantitative description of methyl group transfer from a diazoate to water.

Experimental Section

Organic chemicals were purified by distillation or recrystallization prior to use. Inorganic chemicals were the best available commercial grade and were used without further purification. Water was distilled in glass; ethanol for kinetics runs was distilled from sodium. The (*E*)-methanediazoate was prepared as previously reported.[5]

Kinetics. Except where indicated, most kinetic runs were carried out using an Applied Photophysics DX17MV stopped-flow spectrophotometer thermostated by a circulating water bath. In these cases, rate constants were obtained from the first-order decay of the diazoate or diazomethane using at least 4 half-lives of data. All data points collected by the instrument were used in the determination of the rate constant in the case of the diazoate. In the case of diazomethane, a mixing schlieren (see methods below), typically of magnitude less than 2% of the total absorbance change, interfered with the first millisecond of the reaction. This time period was not included in the rate constant determination for reactions with rate constants greater than 30 s^{-1}. All reactions otherwise exhibited good first-order kinetics of decomposition.

(*E*)-Methanediazoate. Typically, 1 part aqueous solution containing diazoate and 0.05 or 0.1 M NaOH was mixed with 20 or 25 parts reaction buffer that contained adequate $HClO_4$ to neutralize the excess base. Upon mixing, the diazoate concentration ranged from 0.05 to 0.3 mM, and after the decomposition reaction, the absorbance decrease was monitored at 225, 230, or 235 nm.[5] For reactions in ethanol, the diazoate was sufficiently stable that the diazoate could be dissolved in neutral ethanol. In these cases, the ethanolic diazoate solution was used within 1 h of preparation. Some kinetics runs were carried out in deuterium oxide solutions containing 0.09 M NaOD, and rate constants were determined from the first-order decay of the methyl proton signal monitored by ^1H NMR.[5] The reaction solutions in these cases contained 0.005–0.01 M diazoate and 0.002 M *tert*-butyl alcohol as an internal standard. The disappearance of the diazoate was monitored by integration of the signal from the diazoate methyl protons at various times and correction of the observed value for any changes due to variations in instrument tuning using the integration value of the signal from the protons of the internal standard *tert*-butyl alcohol. The rate constants were obtained from the single exponential decay of the diazoate protons, monitored for more than 2 half-lives.

Diazomethane. Diazomethane was generated in a commercially available unit (Aldrich Chemical) by the decomposition of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) in aqueous base. Gaseous diazomethane diffusing from the generator, in which 0.05 g of MNNG had been decomposed, was collected over a period of 30 min in 3 mL of magnetically-stirred, dry acetonitrile (cooled at −30 °C). Subsequently, the generator was opened and the yellow acetonitrile solution was diluted with an additional 10–25 mL of dry acetonitrile. Aliquots of this solution were removed by syringe and used for kinetic runs.

The first-order rate constants k_{obs} for decay of diazomethane were determined by injecting 1 part of the acetonitrile solution containing diazomethane with 20 parts aqueous buffer into the observation cell of the stopped flow and observing the disappearence of absorbance at 235 nm. The rate constant k_{obs} was obtained from the first-order decay process that was monitored for between 4 and 10 half-lives. Values of k_{obs} at different pHs and buffer concentrations were measured using sodium hydroxide solutions and borate, phosphate, ethanolamine, diethanolamine, and morpholine buffers. The rate constant k_0, the buffer-independent rate constant for decomposition of diazomethane, was obtained by extrapolating the linear buffer dilution plots of k_{obs} against buffer concentration to the y intercept.

Products. Experiments were carried out in which the (*E*)-methanediazoate or diazomethane was decomposed in the presence of anionic nucleophiles in order to compare the ratios of alkylated nucleophiles formed from the two alkylating agents. For most of the diazoate reactions, reactions in phosphate buffer (trapping by benzoate ions) were carried out in the stopped flow, whereas the slow reaction in 0.01 M NaOH (trapping by anions of 2-mercaptoethanol and phenol) was carried out by dissolving the diazoate directly into the reaction solution and allowing it to react for 100 min. A similar procedure was used in one set of experiments in which trapping by iodide ion in D_2O solutions containing 0.002 M NaOD was monitored. These latter runs were allowed to react for 10 min. For reactions with diazomethane, the gas was allowed to diffuse into the stirred, thermostated reaction mixture over the course of 30 min (reactions in phosphate buffer) or 100 min (reactions in 0.01 M NaOH). Quantitation of the final concentrations of alkylated nucleophiles was based on interpolation using 3-point standard curves and was carried out by gas chromatography using a Hewlett-Packard 5890A instrument with flame-ionization detection and a 5% Carbowax 20M, 60/80 Carbopack B column (Supelco). Checks for product stability by incubation for twice the stated reaction time prior to analysis indicated no measurable decomposition in any case.

The extent of deuterium incorporation into the methyl group of the (*E*)-methanediazoate that was decomposed in buffered D_2O solutions was determined by decomposing the diazoate in the stopped flow, collecting the sample, and extracting the products into $CHCl_3$. With benzoate anion nucleophiles, the protium content of the reaction solutions was less than 0.5%. In the case of experiments with benzyl alcohol as the nu-

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cleophile, the protium content of the reaction solution was 0.9% due to the fact that the solutions were 1 M in benzyl alcohol that contained an exchangeable proton.

The deuterium content in the methylated products in these experiments was analyzed by mass spectrometry on a Hewlett-Packard 5989A mass spectrometer with a Hewlett-Packard 5890 gas chromatograph attached. In the case of the pentafluorobenzoate methyl esters, the relative abundance of the mono-, di-, and undeuterated species was calculated from the M = 227, 228, and 226 signals after subtracting from the higher mass signals the amount of these signals expected on the basis of an authentic spectrum of benzoate methyl esters. The amount of correction based on this empirical approach was in good agreement with the amount expected on the basis of ^{13}C and ^{18}O natural abundance.[13] No signal of mass expected for the CD_3 ester (M = 229) was observed. Relative abundance of any of the three species was calculated by dividing the intensity of the signal attributed to a species, e.g., CH_2D ester, by the sum of intensities ascribed to esters of all isotopic contents.

In the case of the benzyl methyl ether, the mass spectrum of an authentic sample of the CH_3 compound shows approximately equal intensity signals for the M^+ and M^{-1} masses; the intensity of the latter was presumably due to the relatively stable nature of the α-methoxybenzyl cation formed on H• fragmentation. An analysis of relative isotopic abundance in the product derived from the reaction in D_2O was carried out by assuming that the fragmentation was independent of the isotopic composition of the methyl group—in other words, that the secondary isotope effect on loss of H• from the benzylic carbon is ~1.

The percent abundance of the [$^1H_3$]methyl ether can be calculated alternatively, as follows, without assumption about the magnitude of the secondary isotope effect on H• loss, and this gives agreement within 5% with the number derived by the method above. From the observed intensity of the M = 121 signal (M^{-1} for $PhCO_2CH_3$), the intensity of signals at 122, 123, and 124 that are due to the methyl ether can be calculated on the basis of the empirically determined relative intensities observed with the authentic methyl ether. The sum of these intensities, plus that at M = 121, divided by the total intensities at M = 121, 122, 123, and 124, gives the percent abundance of [$^1H_3$]methyl ether.

In the case of the benzoate methyl ester, a control spectrum with authentic [$^1H_3$]methyl ester showed an M^{-1} signal that was 7.3% of the M^+. The signal due to the [$^1H_3$]methyl ester was calculated by correcting for the fragmentation, independent of isotopic content. As the M^+ = 136 (CH_3 ester) was predominant, the correction of the observed intensity of the CH_3 ester amounted to less than 3%. Because the isotopic selectivity of the cleavage was uncertain and the signal intensity for the deuterated esters was small, calculation of the exact percentages of each of the deuterated esters was not attempted.

A single experiment was carried out to analyze the deuterium content of methanol formed in the decomposition of the diazoate in phosphate-buffered D_2O. The reaction was carried out on the stopped flow. The isotopic content of the methanol product was analyzed by ^1H NMR (500 MHz).

Deuterium incorporation during the decomposition of diazomethane was assayed by trapping with benzoate anion, extracting the reaction mixture, and analyzing the methanebenzoate by mass spectrometry. The percent of monodeuterated material was calculated by correcting for the fragmentation of the di- and trideuterated material (above). Due to the predominance of the monodeuterated material in experiments at pD = 7.2, this correction amounted to a change in signal intensity of the monodeuterated species by 3% or less. For experiments at pD > 10, di- and trideuterated products predominate, and the calculation of the monodeuterated material incurs a large uncertainty due to the uncertainty of the isotopic effect on fragmentation. Thus, for the percent of monodeuterated product, only ranges are reported that were determined by assuming a fragmentation by loss of H• or D• of intensity equal to between 0 and 7.3% of the parent peak, the upper limit established by the fragmentation observed by authentic methyl ester.

Results

First-order rate constants k_{obs} for the decomposition of (*E*)-methanediazoate at 25 °C were measured under a range of experimental conditions and are summarized in Table I. Where directly comparable (i.e., ionic strength 1 M ($NaClO_4$) in H_2O (experiments 6 through 10) or 0.09 M NaOD in D_2O (first entry, experiment 3)), the values of k_{obs} are in good agreement with those reported previously.[5]

Experiments 1–4 (Table I) indicate that the rate constants for decomposition of the diazoate are increased by less than 10% in the presence of good to strong neutral or anionic nucleophiles including 0.50 M azide ion and 0.2 M thiosulfate dianion. Experiment 5 (Table I) indicates that there is a less than 25% increase in k_{obs} for the decomposition of the diazoate in the presence of 0.5 M NaI.

Experiments 6–10 (Table I) were carried out to assess the solvent deuterium isotope effect on the decomposition of the diazoate. The reaction pH in all five experiments is in the region in which the decomposition reaction is independent of pH and buffer concentration.[5] The mean and standard deviation for the five experiments is k_{H_2O}/k_{D_2O} = 1.49 ± 0.09.

The effect on reaction rate of changing the medium from water to ethanol is addressed in experiment 11 (Table I). The first entry is a control run in aqueous 4% ethanol at ionic strength 0.15 M ($NaClO_4$) and shows that the value of k_{obs} decreases by 25% from the value of 2.6 s^{-1} found in water at ionic strength 1 M ($NaClO_4$). The subsequent two entries (experiment 11, Table I) are for determinations of k_{obs} in ethanol at ionic strength 0.15 M ($NaClO_4$) and at the same acetate buffer ratio as for the reaction in aqueous 4% ethanol and indicate that the reaction is similarly independent of buffer concentration. The final two entries (experiment 11, Table I) indicate that the value of k_{obs} does not vary with pH at this region of pH in ethanol.

For the (*E*)-methanediazoate, the effect on k_{obs} of changing the temperature at a value of pH at which the reaction is pH

Table I. Rate Constants for the Decomposition of (*E*)-Methanediazoate at 25 °C

exp no.	buffer base, % base	concn, M	medium[a]	addend concn, M	pH	k_{obs}, s^{-1}
1	propylamine,[b] 50	0.020	H_2O	none	11.07	0.0122
		0.050			11.09	0.0112
		0.100			11.09	0.0111
		0.25			11.09	0.0104
		0.50			11.09	0.0126
2	methoxyamine,[b] 50	0.80	H_2O	none	4.86	2.4
		0.160			4.86	2.5
		0.24			4.86	2.6
		0.32			4.84	2.5
		1.00			5.01	2.5
3	OD^-[c]		D_2O	NaN_3		
		0.090		0		0.000 048
		0.090		0.100		0.000 044
		0.090		0.20		0.000 046
		0.090		0.50		0.000 044
4	OD^-[c]		D_2O	$Na_2S_2O_3$		
		0.090		0.050		0.000 049
		0.090		0.100		0.000 048
		0.090		0.150		0.000 046
		0.090		0.20		0.000 042
5	OD^-[c]		D_2O	NaI		
		0.090		0.10		0.000 052
		0.090		0.10		0.000 055
		0.090		0.20		0.000 059
		0.090		0.20		0.000 062
		0.090		0.50		0.000 059
		0.090		0.50		0.000 052
		0.090		0.50		0.000 059
6	MES,[b,d] 50	0.080	H_2O	none	6.53	2.6
		0.080	D_2O	none	6.83[e]	1.57
7	MES,[b,d] 10	0.160	H_2O	none	5.51	2.6
		0.160	D_2O	none	5.90[e]	1.82
8	acetate,[b] 90	0.160	H_2O	none	5.72	2.4
		0.160	D_2O	none	5.79[e]	1.63
9	acetate,[b] 50	0.160	H_2O	none	4.61	2.5
		0.160	D_2O	none	4.76[e]	1.70
10	phosphate dianion,[b] 50	0.160	H_2O	none	6.33	2.5
		0.160	D_2O	none	6.44[e]	1.74
11	acetate,[b] 50	0.100	H_2O[f]	none	4.25	2.1
	acetate, 50	0.052	ethanol[f]	none		0.0032
		0.104				0.0028
	acetate, 8	0.065	ethanol[f]	none		0.0031
		0.130				0.0031

[a] Ionic strength 1 M ($NaClO_4$) unless noted. [b] Rate constants measured by spectrophotometry. [c] Rate constants measured by monitoring ^1H NMR signal of the diazoate methyl signal. [d] MES = morpholinoethanesulfonate anion. [e] Uncorrected. [f] Ionic strength 0.15 M ($NaClO_4$).

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Table II. Product Ratios for Trapping by Pairs of Nucleophiles of Alkylating Equivalents Generated from (*E*)-Methanediazoate and Diazomethane[a]

		product ratios			
methyl donor	expt no.	methylbenzoate:[b,c] methylpentafluorobenzoate	mean (SD)	(methylthio)ethanol:[c,d] phenyl methyl ether	mean (SD)
(*E*)-methyldiazoate	1	2.10	2.08 (0.01)	42	38 (4)
	2	2.07		37	
	3	2.07		34	
diazomethane	1	2.20	2.10 (0.11)	39	36 (3)
	2	2.12		35	
	3	1.97		33	

[a] Reactions at 25 °C, ionic strength 1 M ($NaClO_4$). [b] Reactions were buffered with 0.025 M each of phosphate monoanion and dianion, and nucleophiles were benzoate and pentafluorobenzoate anion at concentrations of ~0.10 M each. [c] Product ratios are observed product ratios divided by exact ratio of concentrations of nucleophiles in each experiment, as determined gravimetrically. [d] Reaction medium contained 0.010 M NaOH and ~0.10 M each of sodium phenoxide and sodium 2-mercaptoethanol anions.

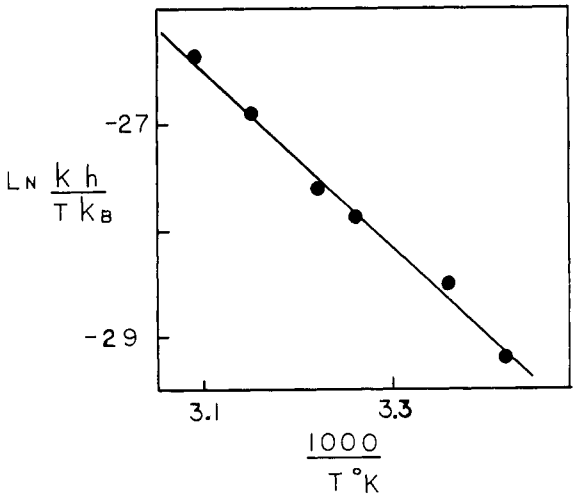

Figure 1. Eyring plot for the decomposition of (*E*)-methanediazoate (**1**) in aqueous solutions, ionic strength 1 M ($NaClO_4$).

independent was investigated over a 30 °C range (19.0–50.3 °C) in water, ionic strength 1 M ($NaClO_4$), 0.026 M biphosphate buffer (30% phosphate dianion). The resulting Eyring plot[14] is presented in Figure 1 and yields $\Delta S^{\ddagger} = -4.5 \pm 9.5$ J/deg mol and $\Delta H^{\ddagger} = 69.6$ kJ/mol.

Evidence for the existence of *N*-nitrosomethylamine as the protonated form of the diazoate was sought by monitoring the decay of the diazoate at 350 nm at a pH at which the reaction was pH independent. An average change in absorbance over 10 half-lives of reaction of 0.005 ± 0.001 AU was observed for 13 trials at pH 6.66 (H_2O, 25 °C, ionic strength 1 M, 0.010 M morpholinoethanesulfonate buffer) at an initial diazoate concentration of 6.4×10^{-3} M.

A comparison of the nucleophilic selectivities of the alkylating intermediate in the decomposition of (*E*)-methanediazoate and diazomethane was made by allowing the two compounds, in parallel runs, to decompose in the presence of two added nucleophiles. Two sets of such experiments—one involving competition between benzoate anion and pentafluorobenzoate anion and the other involving the anions of phenol and 2-mercaptoethanol—were carried out. The ratios of methylated products obtained were quantitated, and the results are presented in Table II.

The trapping of the methyl group by iodide ion, compared to the trapping by D_2O, was determined for the decomposition of the diazoate in D_2O at 0.50 M NaI, 0.002 M NaOD. In duplicate determinations, methyl iodide accounted for 80.5 ± 1% of the product.

Incorporation of deuterium from solvent D_2O during the decomposition of the (*E*)-($^1H_3$)-methanediazoate was assayed by trapping the methyl group by benzoate anion, pentafluorobenzoate anion, or benzyl alcohol, isolating the products, and analyzing the deuterium content by mass spectrometry. The results of these experiments carried out in D_2O at 25 °C, ionic strength 1 M ($NaClO_4$), 0.05 M phosphate buffer, are summarized in Table III. In the case of the benzyl methyl ether, the calculation of the percent of each isotopically labeled species that appears in Table III is based on the assumption that the extent of fragmentation of the M^+ ion in the mass spectrometer is insensitive to the isotopic content of the methyl group (see Experimental Section). A second method of calculation that is independent of this assumption (see Experimental Section) gives an average value of $CH_3\% = 81 \pm 1$, in good agreement with the value of 79% reported in Table III. In none of the experiments analyzed by mass spectrometry was a signal for the trideuteriomethyl group seen, and an upper limit on the percent yield of this product is 0.3% based on the minimum signal integrated by the instrument in these experiments.

Table III. Isotopic Composition of the Methyl Group Derived from (*E*)-Methanediazoate Decomposed in D_2O in the Presence of Nucleophiles at 25 °C, Ionic Strength 1 M ($NaClO_4$)

		percentage isotopic composition of the methyl group (standard deviation)[a]		
nucleophile	product	H_3	H_2D	HD_2
benzoate	(L_3)-methylbenzoate[b]	75 (1)	nd[c]	nd[c]
pentafluoro-benzoate	(L_3)-methylpenta-fluorobenzoate[b]	71 (1)	25 (1)	3.0 (0.1)
benzyl alcohol	(L_3)-methylbenzyl ether[d]	79 (1)	14 (1)	7 (3)
D_2O	(L_3)-methanol[e]	89	11	

[a] Except for the determination of the isotopic content of methanol, the values are mean values for duplicate samples, values for each of which were the mean of four analyses by mass spectrometry. No signal was observed for the trideuterated species (D_3) in any experiment. Analysis of the methanol sample is based on a single determination by ^1H NMR. [b] Reaction conditions were 0.050 M phosphate, pH_{obs} = 6.80. [c] Not determined, see methods. [d] Reaction conditions were 0.050 M phosphate, pH_{obs} = 6.94. [e] Analysis of deuterium content was by ^1H NMR, no signal for CHD_2 was observed. Reaction conditions were 0.050 M phosphate buffer, pH_{obs} = 6.06.

Deuterium incorporation into the product in ethanol from the decomposition of (*E*)-[$^1H_3$]methanediazoate in D_2O was measured by ^1H NMR. The singlet for CH_3OD (3.25 ppm) is well separated from the triplet signal for CH_2DOD (3.23 ppm), so the relative amounts of these species could be accurately quantitated on a 500-MHz instrument. No signal for the CHD_2OD species was observed. The percent of the total signal for each of the two methanol species observed is reported in Table III.

Rate constants for the decomposition of diazomethane were measured at 25 °C, ionic strength 0.2 M ($NaClO_4$), in aqueous solutions containing 5% by volume acetonitrile. The buffer-independent rate constants k_0 are plotted as a function of pH in Figure 2 (circles). The values of k_0 are taken from the intercepts of buffer dilution plots. The plots of k_{obs} against buffer concentration were linear with increases in k_{obs} of less than 10% with 2- to 3-fold increases in buffer concentration up to 0.05 M for

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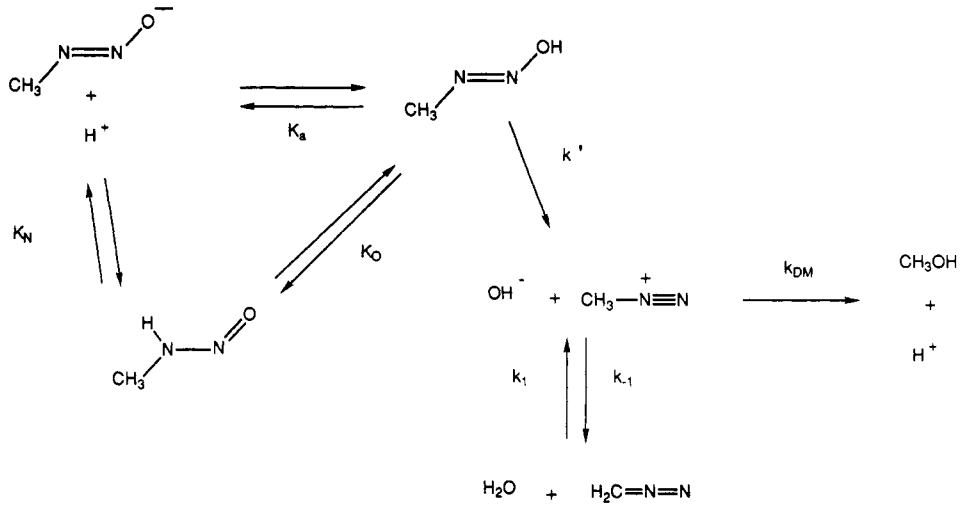
Scheme I



experiments at pH > 10.4. The value of k_0 in these experiments is estimated to be accurate to a few percent. Below pH = 10.4, in experiments with borate and secondary amine buffers, the value of k_{obs} increased markedly, but still linearly, with buffer concentration. The largest effect observed was at pH = 9.03, where the value of k_{obs} increased 9-fold at 0.20 M borate buffer above the intercept value. As a consequence of the relatively large effect of buffer concentration in these experiments, the standard error in k_0 in these experiments is 10%.

The catalysis of decomposition of diazomethane by diethanolamine and morpholine buffers was investigated in further detail. Observed second-order rate constants for buffer catalysis k_{BH} were taken as the slopes of plots of k_{obs} against total buffer concentration. For both buffers, the value of k_{BH} increased with increasing proportion of the acid form of the buffers. Plots of k_{BH} against percent buffer acid gave intercept values at 100% acid of 7420 and 10 000 M^{-1} s^{-1} for diethanolamine and morpholine cations respectively (three points per plot, intercept values ±5%). The values of the intercepts at 0% acid form were 0 ± 300 M^{-1} s^{-1} in both cases.

The effect of D_2O on the kinetics of decomposition of diazomethane in diethanolamine buffers was investigated. Plots of k_{obs} against buffer concentration were determined at identical buffer ratios in H_2O and D_2O for three different buffer ratios (pH range 9.06–8.39, pD range 9.31–8.67). Two examples are illustrated in Figure 3. The value of the slope in H_2O divided by that in D_2O for a given buffer ratio gave the isotope effect k_{BH}/k_{BD} = 6.5 ± 0.4. The values of the intercepts of such plots yielded the isotope effect on the pH-independent decomposition (see Discussion) of diazomethane as k_{H_2O}/k_{D_2O} = 8.2 ± 1.5.

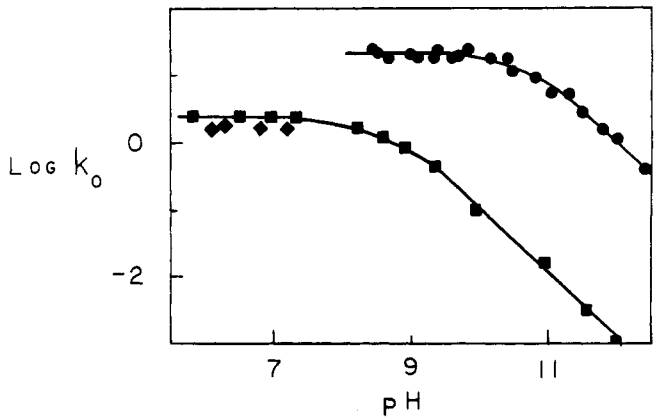


Figure 2. Plot of log k_0 against pH for the decomposition of diazomethane (●) in aqueous 5% acetonitrile, ionic strength 0.2 M ($NaClO_4$) and (*E*)-methanediazoate (■, ref 5, ◆ in D_2O) in aqueous solution, ionic strength 1 M ($NaClO_4$).

Discussion

Overview. As deduced below, the experimental evidence is consistent with the mechanism of Scheme I for the decomposition of the (*E*)-methanediazoate (**1**), with k' being the rate-limiting step. All of the rate and equilibrium constants and rate constant ratios for which values have been measured or limits can be assigned are presented in Scheme I. The values are summarized in Table IV. The upper limit for the equilibrium constant K_O is based on experiments in which ultraviolet spectroscopic evidence of the *N*-nitroso group was sought (see Results). Less than 1.5% of the total protonated diazoate was in the form of the nitrosamine at pH = 6.66 (where protonated **1** predominates). This calculation is based on the upper limit of absorption at 350 nm at time zero of reaction and the assumption that the extinction coefficient at 350 nm for the *N*-nitrosomethylamine is the same as that measured for the stable *N*-nitrosodimethylamine (ϵ_{350} = 50 in water).[15] From the observed kinetic pK_a of 8.63 for the decomposition of the diazoate[5] and the upper limit for K_O, the upper limit of pK_N < 6.81 is calculated. This value is not inconsistent with our previous estimated limit (pK_N < 6.43), which was based on the pK_a of methanenitramide of 6.43 and the recognition that the nitroso group is a comparatively better electron-accepting group than the nitro group.[16] Values in Table IV relevent to the reactions of methanediazonium ion and diazomethane are discussed in more detail below.

Three experimental results are consistent with the assignment of k' (Scheme I) as the rate-limiting step. The experiments described were carried out in the pH region where the decomposition reaction was pH independent—where the diazoic acid is predominant—and therefore measure effects on the k' step alone. First, the solvent deuterium isotope effect on pH-independent decomposition is k_{H_2O}/k_{D_2O} = 1.49 ± 0.09. A value of k_{H_2O}/k_{D_2O} > 1 for the k' step is expected because of the fractionation factor (ϕ) for the lyoxide ion product of ϕ = 0.434.[17] The large fractionation factor for the lyoxide ion is mainly due to the differences in zero-point energy between the solvating water molecules in H_2O and D_2O,[17] and the observed isotope effect is, therefore, largely due to the development of hydrogen bonds between the penultimate lyoxide ion and solvent molecules in the transition state. The contribution to the observed effect that is due to loss of the proton bound to the diazoic acid in the transition state is likely to be negligible, because the measured fractionation factors for protons attached to weak oxygen acids are all close to ϕ = 1.[18]

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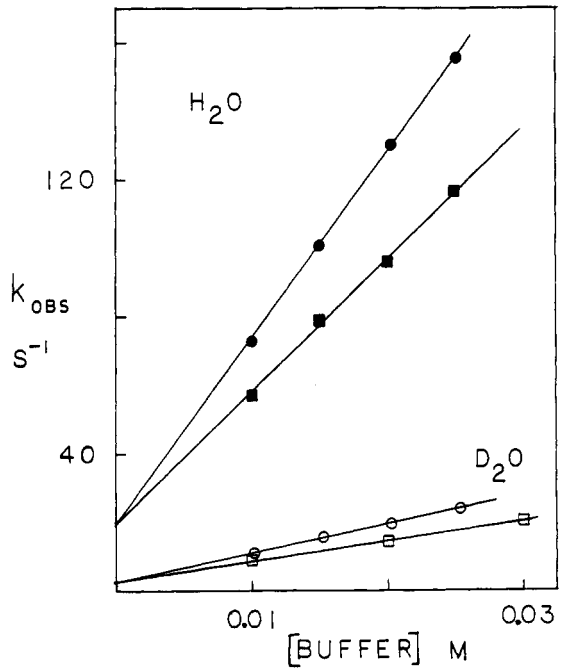

Figure 3. Plots of k_{obs} against buffer concentration for the decomposition diazomethane in H_2O (closed symbols) and D_2O (open symbols) in the presence of diethanolamine buffers (50% cation (squares) and 70% cation (circles)) at 25 °C, ionic strength 0.2 M ($NaClO_4$).

Table IV. Summary of Rate and Equilibrium Constants Determined for Decomposition of (*E*)-Methanediazoate and Associated Intermediates in Aqueous Solutions at 25 °C[a]

constant	value
K_a	2.32×10^{-9} M[b]
k'	2.6 s^{-1} [b]
K_O	<0.015[b]
K_N	$>1.55 \times 10^{-7}$ M[b]
k_1	22 ± 2 s^{-1} [c,d]
k_{-1}/k_{DM}	1130 ± 100 M^{-1} [c,e]

[a] Consult Scheme I for the relevant rate and equilibrium processes to which the constants refer. [b] Ionic strength 1 M, $NaClO_4$. [c] Ionic strength 0.2 M, 5% acetonitrile by volume. [d] The rate constant for protonation of diazomethane by H_2O. [e] The rate constant k_{-1} is for proton transfer between methanediazonium ion and hydroxide ion. The rate constant k_{DM} is for reaction of methanediazonium ion with H_2O.

Second, the small observed value of $\Delta S^{\ddagger} = -4.5 \pm 9.5$ J/deg mol for the pH-independent reaction is consistent with k' being rate limiting. Values of $\Delta S^{\ddagger} < 0$ are known for reactions that are cleanly S_N1 and in which the anionic leaving groups are substantially less basic than the hydroxide ion leaving group of the present reaction.[19-21] The value of $\Delta S^{\ddagger}$ for the present reaction that is at most slightly positive is mutually consistent with solvent electrostiction about the hydroxide ion leaving group that is indicated by the solvent deuterium isotope effect.

Third, the large decrease by a factor of ~680 in the rate constant for the pH-independent decomposition reaction that occurs as the solvent is changed from aqueous 4% ethanol to 100% ethanol is consistent with the assignment of k' as the rate-limiting step. It was previously reported that there is a large solvent effect on the decomposition of the diazoate anion **1**,[22] the diazoate being stable for 12 h in CD_3OD but unstable in water. At least some part of this effect is undoubtedly due to the less favorable equilibrium constant for protonation of **1** in methanol compared to H_2O. The present experimental results indicate a large solvent effect on decomposition of the diazoic acid. The decrease in rate constant with decreasing dielectric constant is expected for the proposed mechanism because k' involves ion pair formation from a neutral reactant (Scheme I).

Alternatives. There is no evidence of a significant contribution to the decomposition of the (*E*)-methanediazoate by an S_N2 mechanism such as that illustrated in eq 2. In D_2O with 0.5 M NaI, the yield of methyl iodide formed from the decomposition of **1** is 80%. For this amount of product to be formed by an S_N2 reaction, a 400% increase in the rate constant for decomposition of **1** is required. In contrast, there is at most a 25% increase in k_{obs} at 0.50 M NaI.

The absence of a significant S_N2 component for the decomposition of **1** in the presence of other nucleophiles is further attested to by experiments 1–4, summarized in Table I. There is no significant change in the value of k_{obs} for the decomposition of **1** with increasing concentrations of good to quite strong nucleophiles (up to 0.5 M in the case of azide ion). Alkylation of these and weaker nucleophiles must therefore occur by a mechanism that involves capture of the methyl group subsequent to a rate-limiting step that does not involve a molecule of nucleophile.

Conclusive proof that diazomethane is not a required intermediate in the decomposition of **1** is found in the data summarized in Table III. An elimination mechanism (eq 3) followed by decomposition of the diazomethane would require that the methyl group transfer that occurs upon decomposition of **1** in D_2O result in the incorporation of at least one deuterium atom from the solvent into the methyl group. In contrast, the data (Table III) indicate that when **1** is decomposed in D_2O (pD_{obs} = 6.7–6.9), between 70 and 90% of the methyl group of **1** is transferred to weak nucleophiles without exchange of the methyl protons with deuterium from the medium. The absence of buffer catalysis of the decomposition of **1**, as indicated experiments 1 and 2 in Table I and those reported previously,[5] is evidence against the possibility that a mechanism such as that of eq 3 contributes to the observed 10–30% incorporation of deuterium in products of the decomposition of **1**.

Rate-limiting isomerization of the anti-*N*-nitrosomethylamine to the syn form and subsequent hydrolysis of the syn-diazoic acid can also be ruled out. The rate constant for the pH-independent decomposition of protonated **1** is 2.6 s^{-1} ($t_{1/2}$ = 0.27 s). The half-life for the uncatalyzed isomerization of *N*-nitrosodimethylamine in aqueous solutions is 2 h at 37 °C, pH = 7.4.[23,24] The rate constant for *N*-nitrosomethylamine isomerization must be similar, or slightly smaller, on the basis of what is known of the effects of increases in steric bulk of substituents on nitrogen upon the rate constants for isomerization of amides.[25] Isomerization of *N*-nitrosomethylamine is, therefore, not a kinetically competent process to be rate limiting for the decomposition of the protonated form of **1**.

Similarly, the possibility that the rate-limiting step involves isomerization of the anti-diazoic acid to the syn form is unlikely. The diazoic acid should isomerize less readily than the nitrosamine form (discussed above), because the diazoic acid contains a formal N–N double bond. Evidence that is quantitatively consistent with the deduction that this isomerization is too slow to be rate limiting is found in the values of the rate constants for isomerization of anti-arenediazoic acids that contain electron-withdrawing substituents. These rate constants are smaller by factors of 10–1000 than the value of 2.6 s^{-1} for the pH-independent decomposition reaction of (*E*)-methanediazoate.[12] The rate constant for isom-

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Table V. Percent Deuterium Incorporation in the Methyl Group of Methyl Benzoate upon Decomposition of Diazomethane in D_2O in the Presence of Benzoic Acid Anion, 25 °C, Ionic Strength 1 M ($NaClO_4$)

	conditions		
	0.050 M phosphate, pD = 6.60[a]	0.050 M phosphate, pD = 10.52[b]	0.050 M phosphate, pD = 11.29[b]
% $PhCO_2CH_2D$	76	19–25	16–23
% ($PhCO_2CHD_2$ + $PhCO_2CD_3$)	24	81–75	84–77

[a] Average of duplicates, error is 2%. [b] See methods for calculation of range.

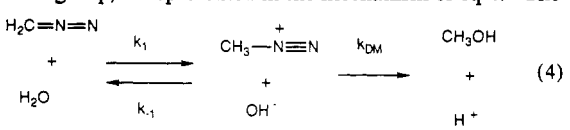
erization of the anti-methyldiazoic acid is expected to be substantially smaller than that for the anti-arenediazoic acids (above), because both the benzene ring and electron-withdrawing groups in the latter compounds stabilize the transition state for isomerization.[26]

Methanediazonium Ion and Diazomethane. The observation that deuterium is incorporated into between 30 and 10% of the products upon decomposition of **1** in D_2O solutions can be accounted for by the intermediacy of the methanediazonium ion, which can undergo deuterium exchange that is somewhat competitive with nucleophilic attack. The data in Table V affirm that diazomethane undergoes comparable exchange with deuterium from solvent under comparable conditions (0.050 M phosphate, pD = 6.60). While all products contain at least one deuterium atom due to the required protonation to give the reactive methanediazonium ion, the data in Table V indicate that 25% of the methylating equivalents incorporate at least one additional deuterium atom by proton exchange. Qualitatively similar observations, under conditions roughly comparable to those studied here, have been made previously.[27,28]

There is evidence that the decomposition of **1** and diazomethane occur via a common intermediate—presumably the methanediazonium ion. Table II summarizes the ratios of products formed from the decomposition of **1** and diazomethane in the presence of pairs of methyl group trapping agents. The fact that the ratios of products for pairs of trapping agents are independent, within experimental error, of the source of the methyl group is consistent with a common intermediate. The fact that the ratios involving trapping by the powerfully nucleophilic thiolate ion are the same for diazomethane and **1** further attest to the absence of a reaction of **1** by a mechanism such as that shown in eq 2 that is not accessible in the decomposition of diazomethane.

The pioneering work of McGarrity and Smyth[27] on the hydrolysis of diazomethane in aqueous 60% tetrahydrofuran yielded a pK_a value of 10 ± 0.3 for the methanediazonium ion and a rate constant of 1.8 s^{-1} for the decomposition of methanediazonium ion to give methanol. The value of this rate constant is close to the value of 2.6 s^{-1} that was determined for the decomposition of the protonated form of **1**, leading us to wonder at the similarity. The limited data reported by McGarrity and Smyth for the decomposition of diazomethane in wholly aqueous alkaline media[27] suggested a substantially different pK_a value and/or hydrolysis rate constant than that determined in aqueous 60% tetrahydrofuran. We therefore undertook a study of the decomposition of diazomethane in more aqueous media that we consider negligibly different (5% acetonitrile, ionic strength 0.2 M with $NaClO_4$) from the medium in which the decomposition of **1** has been studied (1 M ionic strength with $NaClO_4$).

Rate constants k_0 for the buffer–independent decomposition of diazomethane are plotted as a function of pH in Figure 2 (circles) along with those previously reported for **1** (squares). The data for diazomethane in Figure 2 are consistent with a change in rate-limiting step, as represented in the mechanism of eq 4. The



(4)

rate constant k_1, protonation of diazomethane by H_2O, is rate limiting in the pH-independent region, while capture of the methanediazonium ion by water (not hydroxide ion), with a rate constant k_{DM}, is rate limiting in the pH-dependent region. Equation 4 is identical with the mechanisms deduced for the hydrolysis of diazomethane in alkaline 60% THF–water,[27] alkaline water (1 M ionic strength),[27] and 80% DMSO/20% H_2O.[29]

Several additional results are consistent with the assignment of k_1 (eq 4) as the rate-limiting step in the pH-independent reaction. First, the pH-independent decomposition is characterized by the large solvent deuterium isotope effect of k_{H_2O}/k_{D_2O} = 8.2 ± 1.5 (3 determinations), which is indicative of a primary isotope effect expected for a reaction involving proton transfer to carbon. The secondary isotope effect due to formation of the lyoxide ion in the k_1 step cannot explain more than a factor of ~2.5 of the difference in rate constants between H_2O and D_2O.[18] Second, the pH-independent decomposition of diazomethane is general acid catalyzed, as indicated by the fact that the stimulation of decomposition by ammonium ions occurs with a large solvent deuterium isotope effect on catalysis of k_{BH}/k_{BD} = 6.5 ± 0.4 (three determinations). Such a large effect is, again, indicative of a primary isotope effect, as is expected for rate-limiting proton transfer. Third, the deuterium incorporation studies mentioned above (Table V) rule out rapidly reversible formation of methanediazonium ion in the pH region where diazomethane decomposition is pH independent. The change in rate-limiting step to reversible formation of methanediazonium ion at higher pH is presumably responsible for the higher deuterium incorporation in methyl benzoate at higher pD (Table V). Similar observations were made by McGarrity and Smyth regarding the extent of deuterium incorporation into methanol product in 60% THF–D_2O with 100% trideuterated methanol observed at pD = 13.[27]

The general expression for the disappearence of diazomethane is given in eq 5, and the value of k_1 = 22 ± 2 s^{-1} can be obtained

$$k_{obs} = k_1/((k_{-1}[OH^-]/k_{DM}) + 1) \quad (5)$$

$$1/k_{obs} = (k_{-1}/k_{DM}k_1)[OH^-] + 1/k_1 \quad (6)$$

from the reciprocal of the intercept of the plot of $1/k_{obs}$ against $[OH^-]$ using the data in Figure 2 for the decomposition of diazomethane according to eq 6. On the basis of the slope and intercept of the plot, the value of the ratio k_{-1}/k_{DM} is 1130 ± 100 M^{-1}.

These data indicate that the rate-limiting step for the transfer of the methyl group from (*E*)-methanediazoate to water and stronger nucleophiles in weakly buffered media of physiological pH is the formation of the diazonium ion from the diazoic acid (k', Scheme I). A value of pK_a for the methanediazonium ion would yield the values of the rate constants k_{-1} and k_{DM}, but extrapolation of the value in 60% THF–H_2O[27] to a value for predominantly aqueous media is sufficiently uncertain that the derived quantities would have considerable inaccuracy.

A reviewer's comment prompts the speculation that the (*E*)-methanediazoate is unlikely to be the intermediate that gives rise to diazomethane in the synthetically useful alkaline decompositions of nitrosoureas, nitrosoguanidines, and related compounds.[30,31] These procedures generally produce diazomethane instantaneously upon contact of the nitroso compounds with

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aqueous and alcoholic solutions that are typically ~5 M or 40% in KOH. The half-life for decomposition of (*E*)-methanediazoate according to the mechanism of Scheme I under these conditions would likely be several to many hours at least. Unlikely alternative mechanisms for diazomethane generation are the onset of a new mechanism for decomposition of the (*E*)-methanediazoate in strongly basic aqueous solution or mechanisms for decomposition of the nitroso compounds that do not involve diazoates. It seems most likely that the diazomethane is formed from the intermediacy of the considerably more reactive (*Z*)-methanediazoate that instantly decomposes the diazomethane in alcoholic and basic aqueous media.[4,9,32]

Summary. This study establishes a semiquantitative picture of methyl group transfer in aqueous solution from one of the two simplest alkanediazoates to the product methanol. The decomposition chemistry of higher homologues of both **1** and its syn isomer is known to involve more complexity, likely including the intermediacy of carbocations.[4,33,34] We are currently investigating these and other aspects of diazoate chemistry.

Acknowledgment. We wish to thank Prof. Tina Aymes at the Department of Chemistry, University of Kentucky, for quantitating the amount of deuterium incorporation into methanol by 500 MHz ^{1}H NMR (Table III) and Prof. N. Ganapathisubramanian at the Department of Chemistry, Wake Forest University, for helpful discussions. We are particularly grateful to Prof. A. J. Kresge, University of Toronto, who pointed out an inconsistency in our initial interpretations concerning diazomethane hydrolysis that stimulated further investigation.

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Enolates of α-Allenyl Ketones: Formation and Aldol Reactions of Cumulenolates

Nicos A. Petasis* and Kurt A. Teets

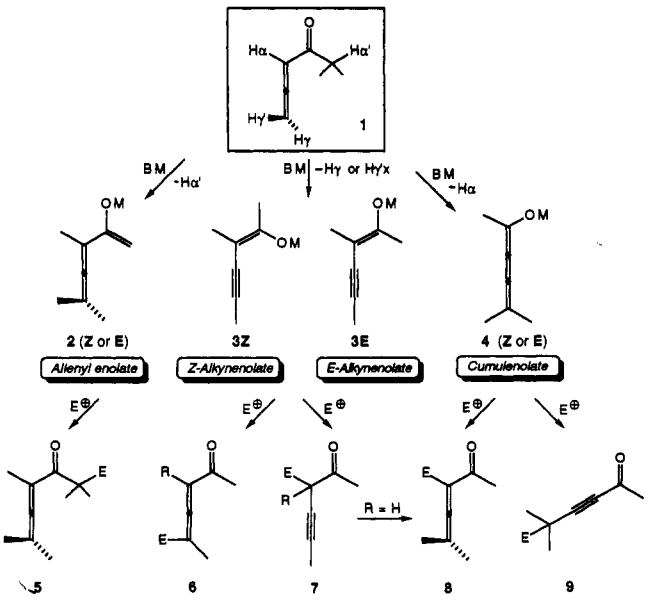
Contribution from the Department of Chemistry, University of Southern California, Los Angeles, California 90089-0744. *Received July 29, 1992*

Abstract: Enolization of α-allenyl ketones under kinetic conditions, followed by reactions with aldehydes and ketones, affords aldol products that suggest the intermediacy of cumulenolates, formed via the abstraction of a vinylic α-hydrogen. The origin for this marked difference with α-alkenyl ketones is attributed to the enhanced acidity of allenic hydrogens, to the predominance of the s-trans conformation, and to lithium complexation with both the carbonyl and the allene moieties. The relative stability of these enolates was examined with the use of semiempirical (MNDO) calculations which indicated that the lowest energy isomers are the (*Z*)-alkynolates. Both experimental and computational evidence suggest that the kinetic intermediate is the cumulenolate, while the thermodynamic enolate is the (*Z*)-alkynenolate.

Introduction

The α-allenyl ketone (α-allenic ketone, α-oxoallene) moiety is characterized by unique chemical reactivity resulting from the mutual activation of two of the most versatile functional groups in organic chemistry.[1] Although they are not common in target molecules, α-allenyl ketones do exist in nature[2] and have been used effectively in suicide enzyme inhibitors.[3] Despite the development of many synthetic routes to α-allenyl ketones,[1,4] their rich reactivity has not been fully exploited. Among the processes that have been studied[1] are their reactions with nucleophiles,[5] dienophiles,[6] and oxidizing agents,[7] as well as their thermal[8] and Lewis acid-catalyzed isomerizations.[9] During the exploration of a new synthetic strategy for the synthesis of eight-membered rings,[10] we had an

Scheme I



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