Novel Cross-Linking Alkylating Agents, 1-(2-Chloroethyl)-3-methyl-3-acyltriazenes

Richard H. Smith, Jr.,[1] Andrew F. Mehl, Donald L. Shantz, Jr., Gwendolyn N. Chmurny,[2] and Christopher J. Michejda*

Laboratory of Chemical and Physical Carcinogenesis, BRI-Basic Research Program, NCI-Frederick Cancer Research Facility, Frederick, Maryland 21701

Received September 23, 1987

The preparation and hydrolytic decomposition of a series of novel cross-linking alkylating agents, 1-(2-chloroethyl)-3-methyl-3-acyltriazenes, is described. The synthesis of 3-carbethoxy-1-(2-chloroethyl)-3-methyltriazene, 3-acetyl-1-(2-chloroethyl)-3-methyltriazene, and 1-(2-chloroethyl)-3-methyl-3-(methylcarbamoyl)triazene has been accomplished through the use of a common intermediate, 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene, bearing a key protecting group on the 2-ethyl position. Following acylation, the blocking group was removed with tetra-*n*-butylammonium fluoride and the resulting alcohol was converted to the desired chloro substituent by reaction with carbon tetrachloride and triphenylphosphine. Kinetic studies on the proteolytic decomposition at neutral pH of the (2-chloroethyl)triazenes, the corresponding (2-hydroxyethyl)triazenes, and the analogous 1,3-dimethyl-3-acyltriazenes revealed that the reactions proceed by N_2–N_3 heterolysis. The rates of the reactions are dependent on the stabilities of the incipient alkyldiazonium ions and on the ability of the 3-acyl substituents to stabilize the adjacent negative charge.

Introduction

The chemistry of 1,3-dialkyltriazenes,[3] 1,3,3-trialkyltriazenes,[4,5] and 1,3-dialkyl-3-acyltriazenes[6] has been explored extensively in our laboratory. The alkyltriazenes are extremely sensitive to acid-catalyzed decomposition, which yields alkyldiazonium ions and the corresponding alkylamines as the primary products. These triazenes are potent, directly acting mutagens,[7] where presumably the alkyldiazonium ions alkylate the bacterial DNA. The mechanism of decomposition of the more stable 1,3-dialkyl-3-acyltriazenes is more complicated than that exhibited by the unacylated triazenes, but the primary products are still alkyldiazonium ions.[6] These compounds are potent biological alkylating agents, as evidenced by their mutagenic activity and the ability to alkylate DNA in vitro and in vivo (Smith, Brashears, and Michejda, in preparation). Experiments on a series of 1,3-dimethyl-3-acyltriazenes revealed that some of these compounds possess potent cytotoxic properties against a variety of human tumors implanted in nude mice (Smith, Paull, and Michejda, in preparation). Since methylating cytotoxic agents are usually limited in their activity to those tumors that are characterized by a deficiency in methylation repair,[8] we sought a set of triazenes that would have the ability to cause lethal cross-links in DNA. This study reports on the synthesis and chemical properties of 1-(2-chloroethyl)-3-methyl-3-acyltriazenes, which, by analogy with (2-chloroethyl)nitrosoureas,[9] would be expected to form cross-links in DNA.

Experimental Section

Safety Note. Triazenes are potent biological alkylating agents and as such should be considered to be toxic and potentially carcinogenic compounds. Efficient hoods and protective clothing should be used at all times in working with these substances. Alkyl azides are unstable and potentially explosive, and suitable precautions must be observed in the handling of these substances.

Materials. All chemicals were reagent grade (Aldrich Chem. Co., Milwaukee, WI) and were used without further purification. Buffers for kinetic measurements were prepared as described previously[5] using water distilled from $KMnO_4$. A Fisher Accumet digital pH meter and a Fisher (13-639270) high ionic strength combination electrode (calomel reference) were used in pH measurements. IR and UV spectra were obtained on a Perkin-Elmer Model 297 infrared spectrophotometer and a Hewlett-Packard Model 8450A double-beam diode array processor, respectively. NMR spectra were obtained on a Varian XL-200 spectrometer and chemical shifts (δ) are reported in parts per million downfield from tetramethylsilane (TMS). Exact mass measurements were determined on either a VG-Micromass, ZAB-2F (for FAB spectra), or a VG 70-250 (for EI spectra) mass spectrometer. Mass measurements were confirmed by peak matching.

2-Azidoethanol (1). 2-Chloroethanol (241.5 g, 3.0 mol) was added rapidly to a solution of sodium azide (234.5 g, 3.61 mol) in 800 mL of water at room temperature. The reaction mixture was stirred at 30 °C for 1 h and then at 70 °C for 24 h. The resulting red solution was cooled to room temperature, saturated with sodium sulfate, and extracted with 4 × 400 mL of methylene chloride. The combined organic layers were dried two times over anhydrous sodium sulfate and concentrated on a rotary evaporator at 25 °C to give 206 g (2.37 mol, 79.0%) of crude 2-azidoethanol.[10] Although this substance can be purified by reduced pressure distillation (77 °C, 24 mm), it was found that the undistilled material was of adequate purity for use in the next reaction. This was fortunate given the highly explosive nature of low molecular weight organic azides.[11]

1-Azido-2-(*tert*-butyldimethylsiloxy)ethane (2). 2-Azidoethanol (1) (105 g, 1.21 mol), used as prepared, and *tert*-butylchlorodimethylsilane (200 g, 1.33 mol) were dissolved in 200 mL of dry *N,N*-dimethylformamide (DMF) and stirred under nitrogen. Over a period of 20 min, imidazole (204 g, 3.0 mol) was added

(1) Permanent address: Department of Chemistry, Western Maryland College, Westminster, MD 21157.
(2) Chemical Synthesis and Analysis Laboratory, Program Resources, Inc., NCI-FCRF, Frederick, MD 21701.
(3) Smith, R. H.; Denlinger, C. L.; Kupper, R.; Mehl, A. F.; Michejda, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 3726–3730.
(4) Sieh, D. H.; Wilbur, D. J.; Michejda, C. J. *J. Am. Chem. Soc.* **1980**, *102* 3883–3887.
(5) Smith, R. H., Jr.; Denlinger, C. L.; Kupper, R.; Koepke, S. R.; Michejda, C. J. *J. Am. Chem. Soc.* **1984**, *106*, 1056–1059.
(6) Smith, R. H., Jr.; Mehl, A. F.; Hicks, A.; Denlinger, C. L.; Kratz, L.; Andrews, A. W.; Michejda, C. J. *J. Org. Chem.* **1986**, *51*, 3751–3757.
(7) Sieh, D. H.; Andrews, A. W.; Michejda, C. J. *Mutat. Res.* **1980**, *73*, 227–235.
(8) Yarosh, D. B. *Mutat. Res.* **1985**, *145*, 1–16.
(9) Hemminki, K.; Ludlum, D. B. *JNCI, J. Natl. Cancer Inst.* **1984**, *73*, 1021–1028.
(10) This compound can be distilled under reduced pressure; however, it should be noted that there have been reports of explosions with this substance (Fagley, T. F.; Klein, E.; Albrecht, J. F. *J. Am. Chem. Soc.* **1953**, *75*, 3104–3106.
(11) Bretherick, L. *Handbook of Reactive Chemical Hazards*, 2nd ed.; Butterworths: Boston, MA, 1979; pp 308, 386.

0022-3263/88/1953-1467$01.50/0

portionwise with stirring. The temperature of the reaction rose to about 40 °C. The solution was stirred at 40 °C under nitrogen for 24 h. The reaction mixture was cooled to room temperature, poured into 1 L of water, and extracted with pentane (4 × 300 mL). The pentane layers were dried over anhydrous sodium sulfate, concentrated on a rotary evaporator at 25 °C, and distilled at reduced pressure through a 4-in. Vigreux column to give 230 g (1.14 mol, 94.7%) of 1-azido-2-(*tert*-butyldimethylsiloxy)ethane (**2**): bp 37–39 °C (0.02 mm); IR (CH_2Cl_2) 2940, 2860, 2120, 1115, 940, 840 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.09 (6 H, s), 0.92 (9 H, s), 3.27 (2 H, t, J = 5 Hz), 3.80 (2 H, t, J = 5 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ −5.54, 18.18, 25.77, 53.16, 62.59.

1-(2-(*tert*-Butyldimethylsiloxy)ethyl)-3-methyltriazene (3). A 1.4 M ether solution of methyllithium (468 mL, 0.656 mol) was added dropwise over a period of 1.5 h to a stirred solution of 1-azido-2-(*tert*-butyldimethylsiloxy)ethane (**2**) in anhydrous ether (200 mL) at −20 °C under nitrogen. On occasion, the reaction mixture during the addition turned into a gel, which was broken up by the addition of sufficient anhydrous ether and mechanical agitation before the addition of the methyllithium solution was continued. The resulting yellow solution was allowed to warm gradually to room temperature over 2 h. It was then cooled to 0 °C and hydrolyzed by careful addition of 100 mL of a 10% ammonium hydroxide solution containing 10% (w/v) ammonium chloride. The ether layer was separated and the aqueous layer was reextracted with pentane (300 mL). The ether and pentane layers were combined, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator at 25 °C. Distillation at reduced pressure through a 4-in. Vigreux column produced a small forefraction, bp 55 °C (0.02 mm). The Vigreux column was then replaced with a short-path distillation head and the distillation continued, yielding 54.2 g (0.419 mol, 70.4%) of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene (**3**): bp 54–56 °C (0.02 mm); IR (CH_2Cl_2) 3480, 2940, 2860, 1100, 840 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.08 (6 H, s), 0.89 (9 H, s), 1.58 (1 H, b), 3.23 (3 H, b), 3.59 (2 H, br t, $J \sim 5$ Hz), 3.83 (2 H, t, J = 5 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ −5.36, 18.30, 25.86 (30.89), 46.73, 47.91 (60.98), (61.95) 62.80.

1-(2-(*tert*-Butyldimethylsiloxy)ethyl)-3-carbethoxy-3-methyltriazene (4a). A solution of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene (**3**) (24.0 g, 0.11 mol) in anhydrous ether (70 mL) was added dropwise over 1.5 h to a stirred suspension of potassium hydride (~6 g, 0.15 mol) in anhydrous ether containing 50 mg (1.3×10^{-4} mol) of dicyclohexano-18-crown-6 ether at 25 °C under nitrogen. Stirring was continued for 30 min until hydrogen evolution had ceased. The reaction mixture was cooled to −30 °C and then ethyl chloroformate (13.1 g, 0.12 mol) in anhydrous ether (70 mL) was added dropwise with stirring over 2 h. The reaction was stirred and allowed to warm gradually to 0 °C over 30 min, at which time hydrolysis was accomplished by the careful addition of 250 mL of 10% ammonium hydroxide solution containing 10% (w/v) ammonium chloride. The ether layer was separated and the aqueous layer reextracted with pentane (100 mL). The ether and pentane layers were combined and dried twice over anhydrous sodium sulfate and concentrated on a rotary evaporator at 25 °C. Distillation of $^1/_{10}$ of the crude product at reduced pressure using a short-path distillation head gave 1.68 g (0.0645 mol, 58.6%, yield based on the fraction of total product distilled) of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-carbethoxy-3-methyltriazene (**4a**): bp 90–95 °C (0.07 mm); IR (CCl_4) 2960, 2940, 2860, 1725, 1160, 840 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.04 (6 H, s), 0.87 (9 H, s), 1.37 (3 H, t, J = 7 Hz), 3.24 (3 H, s), 3.92 (2 H, m), 4.94 (2 H, m), 4.38 (2 H, q, J = 7 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ −5.36, 14.45, 18.21, 25.89, 29.41, 61.20, 62.87, 63.87, 154.5. The crude product was determined to be sufficiently pure to be used directly in the next reaction.

3-Carbethoxy-2-(2-hydroxyethyl)-3-methyltriazene (5a). A 1.0 M tetrahydrofuran solution of tetra-*n*-butylammonium fluoride (140 mL, 0.14 mol) was added portionwise over 5 min with stirring to a solution of 1-(2-*tert*-butyldimethylsiloxy)-ethyl)-3-carbethoxy-3-methyltriazene (**4a**) (29.0 g, 0.133 mol) in tetrahydrofuran (20 mL). The reaction solution was heated to 35 °C and stirring continued for 30 min. The volume of the reaction was reduced by one-half on a rotary evaporator at 25 °C and the resultant solution chromatographed on a column of 300 g of silica gel 60 (EM, neutral, 70–230 mesh) packed in 1:1 pentane–ether. The column was eluted with 4 L of ether with about 20 psi head pressure of nitrogen. The first 200 mL of eluent contained a large amount of an oil assumed to be *tert*-butylfluorodimethylsilane. Later eluent fractions contained a mixture containing one major and several minor components, as shown by TLC on silica gel. These fractions were combined (18.6 g) and rechromatographed on a column of 200 g of silica gel 60 (EM Science, Darmstadt, FRG) packed in pentane and eluted sequentially with 500 mL each of pentane; 25%, 50%, and 75% ether in pentane, and finally with 2 L of ether. The first liter of ether eluent contained the desired product, 3-carbethoxy-1-(2-hydroxyethyl)-3-methyltriazene (**5a**), 4.58 g (0.026 mol, 19.5%). Attempts to further purify this substance by reduced pressure (0.002 mm) distillation generally failed as a result of thermal decomposition during distillation: IR (CH_2Cl_2) 3600, 3460, 2940, 1710, 1155, 990 cm^{-1}; UV (CH_3CN) λ_{max} 233 nm (log ϵ 4.14); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.36 (3 H, t, J = 7 Hz), 1.66 (1 H, b), 3.25 (3 H, s), 3.98 (4 H, s), 4.37 (2 H, q, J = 7 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.48,* 29.53, 61.02, 63.14, 63.38,* 154.4* (* = attached proton test, APT, indicated odd number of protons attached); exact mass calcd, m/z for $C_6H_{14}N_3O_3$ (M + 1 by FAB) 176.1035, found 176.1031.

3-Carbethoxy-1-(2-chloroethyl)-3-methyltriazene (6a). A solution of triphenylphosphine (2.83 g, 0.0108 mol) and 3-carbethoxy-1-(2-hydroxyethyl)-3-methyltriazene (**5a**) (1.89 g, 0.0108 mol) in 25 mL of carbon tetrachloride (dried over 3A molecular sieves) was refluxed overnight under nitrogen. The reaction mixture was cooled to room temperature and diluted with pentane (100 mL). After standing at 10 °C for 4 h, the reaction mixture was filtered through a pad of Celite to remove precipitated triphenylphosphine oxide. The filtrate was concentrated on a rotary evaporator at 22 °C, redissolved in a minimum amount of ether, and chromatographed on a column of 40 g of silica gel 60 packed in 1:10 ether–pentane and eluted with 200 mL each of 10%, 20% and 30% ether in pentane. The first 200 mL of eluent contained 1.4 g of a yellow oil, which on distillation at reduced pressure with a short-path distillation apparatus produced 1.22 g (0.00630 mol, 58.3%) of the desired compound, 3-carbethoxy-1-(2-chloroethyl)-3-methyltriazene (**6a**): bp 60–62 °C (0.003 mm); IR (CCl_4) 2990, 2970, 1730, 1155, 990 cm^{-1}; UV (CH_3CN) λ_{max} 233 nm (log ϵ 4.19); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.39 (OCH_2CH_3, t, J = 7 Hz), 3.28 (NCH_3, s), 3.88 ($ClCH_2$, t, J = 6 Hz), 4.12 (CH_2N, t, J = 6 Hz), 4.39 (OCH_2CH_3, q, J = 7 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 14.47 (OCH_2CH_3), 29.76 (NCH_3), 41.92 ($ClCH_2$), 62.50 (CH_2N), 63.17 (OCH_2CH_3), 154.27 (C=O); (^1H and ^{13}C NMR assignments made via ^{13}C-APT and 2D-heteronuclear correlated spectrum (2D-COSY) experiments); exact mass calcd, m/z for $C_6H_{12}N_3O_2Cl$ 193.0618, found 193.0629 (by EI).

3-Acetyl-1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene (4b). A solution of 1-(2-(*tert*-butyldimethylsiloxy)-ethyl)-3-methyltriazene (**3**) (21.74 g, 0.10 mol) in ether (50 mL) was added dropwise over 1.5 h to a stirred suspension of potassium hydride (4.41 g, 0.11 mol) in anhydrous ether containing 50 mg (0.00013 mol) of dicyclohexano-18-crown-6 ether at room temperature under nitrogen. When hydrogen evolution had ceased, the reaction mixture was cooled to −10 °C and a solution of acetyl chloride (8.64 g, 0.11 mol) in ether (40 mL) was added dropwise over 2 h. The reaction mixture was allowed to warm to 0 °C over 1 h and hydrolyzed by the addition of 75 mL of 10% ammonium hydroxide containing 10% (w/v) of ammonium chloride. The ether layer was separated and the aqueous layer extracted with pentane (2 × 100 mL). The organic layers were combined, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator. The residue was distilled at reduced pressure through a 4-in. Vigreux distillation column to give, after a small forefraction, 15.7 g (0.0645 mol, 64.5%) of 3-acetyl-1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene (**4b**): bp 78–84 °C (0.08 mm); IR (CH_2Cl_2) 2960, 2950, 2860, 1685, 1150, 1105, 980, 840 cm^{-1}; ^1H NMR ($CDCl_3$, Me_4Si) δ 0.04 (6 H, s), 0.86 (9 H, s), 2.43 (3 H, s), 3.21 (3 H, s), 3.93 (2 H, t, J = 5 Hz), 4.00 (2 H, t, J = 5 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ −5.32, 18.20, 21.83, 25.75, 26.60, 61.00, 64.50, 173.2.

3-Acetyl-1-(2-hydroxyethyl)-3-methyltriazene (5b). A 1.0 M solution (68 mL) of tetra-*n*-butylammonium fluoride in tet-

rahydrofuran was added dropwise to a stirred solution of 3-acetyl-1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene (**4b**) in tetrahydrofuran at 0 °C. The reaction solution was allowed to warm gradually to room temperature over 1 h. The volume of the solution was reduced 50% with a rotary evaporator at 25 °C and the residue was chromatographed on a column of 200 g of silica gel 60 (EM, neutral, 70–230 mesh) packed in 3:1 ether–pentane. The column was eluted with 4 L of 4:1 ether–pentane. The final 3 L of solvent were concentrated on a rotary evaporator to give 6.75 g (0.0465 mol, 72.5%) of 3-acetyl-1-(2-hydroxyethyl)-3-methyltriazene (**5b**) as a colorless oil, which failed to distill satisfactorily at reduced pressure (0.002 mm): IR (CH_2Cl_2) 3600, 3470, 2940, 1680, 1140, 975 cm^{-1}; UV (CH_3CN) λ_{max} 237 (log ϵ 4.09); ^1H NMR ($CDCl_3$, Me_4Si) δ 2.09 (1 H, b), 2.44 (3 H, s), 3.22 (3 H, s), 3.96 (2 H, m), 4.04 (2 H, m); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.83 (CH_3), 26.80 (CH_3), 60.85 (CH_2), 64.00 (CH_2), 173.15 (C=O) [APT experiment allowed assignment of the number of attached protons]; exact mass calcd, m/z for $C_5H_{11}N_3O_2$ 145.0851, found 145.0848 (by EI).

3-Acetyl-1-(2-chloroethyl)-3-methyltriazene (6b). A solution of triphenylphosphine (5.89 g, 0.0225 mol) and 3-carbethoxy-1-(2-hydroxyethyl)-3-methyltriazene (**5b**) (2.9 g, 0.020 mol) in 50 mL of carbon tetrachloride (dried over 3A molecular sieves) was refluxed overnight under nitrogen. The reaction mixture was cooled to room temperature and diluted with pentane (250 mL). After standing at 10 °C overnight, the reaction mixture was filtered through a pad of Celite to remove precipitated triphenylphosphine oxide. The filtrate was concentrated on a rotary evaporator at 22 °C, and the residue (4.2 g) was dissolved in a minimum amount of ether and chromatographed on a column of 35 g of silica gel 60 packed in 10% ether in pentane and eluted with 600 mL of this same solvent mixture. Evaporation of the eluent on a rotary evaporator and vacuum transfer (40 °C/0.005 mm) of the residue gave 1.94 g (0.0119 mol, 59.6%) of 3-acetyl-1-(2-chloroethyl)-3-methyltriazene (**6b**): IR (CCl_4) 2970, 1710, 1515, 1145, 990 cm^{-1}; UV (CH_3CN) λ_{max} 238 nm (log ϵ 4.23); ^1H NMR ($CDCl_3$, Me_4Si) δ 2.45 (CH_3, s), 3.23 (NCH_3, s), 3.90 ($ClCH_2$, t, J = 5.5 Hz), 4.12 (CH_2N, t, J = 5.5 Hz); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 21.85 (CH_3), 26.92 (NCH_3), 41.78 ($ClCH_2$), 62.68 (CH_2N), 173.0 (C=O); exact mass calcd, m/z for $C_5H_{10}N_3OCl$ 163.0512, found 163.0506 (by EI).

1-(2-(*tert*-Butyldimethylsiloxy)ethyl)-3-methyl-3-(methylcarbamoyl)triazene (4c). Methyl isocyanate (5.99 g, 0.105 mol) was added dropwise to a stirred solution of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyltriazene (**3**) (21.74 g, 0.10 mol) in pentane (75 mL), under nitrogen, and at a rate to maintain a gentle reflux. Following this addition, the reaction mixture was stirred at 30 °C for 30 min and then concentrated on a rotary evaporator at 25 °C to yield 27.17 g (0.0990 mol, 99.0%) of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyl-3-(methylcarbamoyl)triazene as a colorless oil: ^1H NMR ($CDCl_3$, Me_4Si) δ 0.01 (6 H, s), 0.84 (9 H, s), 2.92 (3 H, d, J = 5 Hz), 3.22 (3 H, s), 3.82 (2 H, t, J = 5 Hz), 3.97 (2 H, t, J = 5 Hz), 6.35 (1 H, b); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ −5.35, 18.25, 25.79, 26.86, 27.53, 61.12, 63.97, 155.64.

1-(2-Hydroxyethyl)-3-methyl-3-(methylcarbamoyl)triazene (5c). A 1.0 M solution (100 mL) of tetra-*n*-butylammonium fluoride in tetrahydrofuran was added dropwise to a stirred solution of 1-(2-(*tert*-butyldimethylsiloxy)ethyl)-3-methyl-3-(methylcarbamoyl)triazene (27.0 g, 0.095 mol) in 25 mL of tetrahydrofuran at −10 °C. The reaction solution was allowed to warm gradually to 10 °C over 1 h. The volume of the solution was then reduced 50% in a rotary evaporator at 25 °C and the resultant solution chromatographed on a column of 250 g of silica gel 60 (EM, neutral, 70–230 mesh) packed in ether. The column was eluted with 5 L of ether. The final 3 L of eluent were concentrated in a rotary evaporator and the residue (6.7 g) was recrystallized from methylene chloride–ether to give 4.24 g of 1-(2-hydroxyethyl)-3-methyl-3-(methylcarbamoyl)triazene (**5c**) (0.0265 mol, 27.8%): mp 72–74 °C; IR (CH_2Cl_2) 3600, 3450, 2955, 1690, 1510, 1190, 1050 cm^{-1}; UV (CH_3CN) λ_{max} 245 nm (log ϵ 4.04); ^1H NMR ($CDCl_3$, Me_4Si) δ 1.78 (1 H, t, J = 6 Hz), 2.94 (3 H, d, J = 5 Hz), 3.26 (3 H, s), 3.97 (2 H, t, J = 5 Hz), 4.02 (2 H, m-A_2B_2X), 6.34 (1 H, b); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 26.86, 27.60, 60.72, 63.72, 155.54; exact mass calcd, m/z for $C_5H_{12}N_4O_2$ 160.0960, found 160.0967 (by EI).

1-(2-Chloroethyl)-3-methyl-3-(methylcarbamoyl)triazene (6c). A solution of triphenylphosphine (6.22 g, 0.0237 mol) and 3-carbethoxy-1-(2-hydroxyethyl)-3-methyltriazene (**5c**) (3.8 g, 0.0237 mol) in 60 mL of carbon tetrachloride (dried over 3A molecular sieves) was refluxed overnight under nitrogen. The reaction mixture was cooled to room temperature and diluted with pentane (220 mL). After standing at 10 °C overnight, the reaction mixture was filtered through a pad of Celite to remove precipitated triphenylphosphine oxide. The filtrate was concentrated on a rotary evaporator at 22 °C, redissolved in a minimum amount of ether, and chromatographed on a column of 35 g of silica gel 60 packed in 10% ether in pentane and eluted with 350 mL each of 10%, 20%, 30%, 40%, and 50% ether in pentane. Concentration of the final 1 L of eluent on a rotary evaporator and recrystallization of the residue from ether–pentane gave 2.38 g of 1-(2-chloroethyl)-3-methyl-3-(methylcarbamoyl)triazene (**6c**) (0.0133 mol, 56.2%): mp 48.5–49.5–49.5 °C; IR (CCl_4) 3460, 3400 (weak), 2970, 2910, 1705, 1500, 1190, 1070, 1050 cm^{-1}; UV (CH_3CN λ_{max} 245.5 nm (log ϵ 4.05); ^1H NMR ($CDCl_3$, Me_4Si) δ 2.95 ($NHCH_3$, d, J = 5 Hz), 3.26 (NCH_3, s), 3.86 (CH_2Cl, t, J = 6 Hz), 4.05 (CH_2N, t, J = 6 Hz), 6.37 (NH, b); proton-decoupled ^{13}C NMR ($CDCl_3$, Me_4Si) δ 26.87 ($NHCh_3$), 27.70 (NCH_3), 41.97 (CH_2Cl), 62.43 (CH_2N), 155.2 (C=O); (^1H and ^{13}H NMR assignments made via ^{13}C-APT and 2D-COSY spectra); exact mass calcd, m/z for $C_5H_{11}N_4OCl$ 178.0621, found 178.0598 (by EI).

Kinetic Measurements. Rates of triazene decomposition in aqueous solution were followed spectrophotometrically with a Hewlett-Packard Model 8450A diode array spectrophotometer. The reaction solutions were contained in thermostated 1-cm cells, the temperature being held constant to within ±0.1 °C. The disappearance of each triazene was followed by monitoring the change in absorbance at its respective λ_{max} (recorded in relevant synthesis section). A typical kinetic run involved charging the reaction cuvette with buffer (1.341 mL) and initiating the reaction by adding 9 μL of a 4.5×10^{-3} M solution of the triazene in acetonitrile, the final triazene concentration being 3.0×10^{-5} M. The reference cuvette contained 1.341 mL of buffer and 9 μL of acetonitrile. A minimum of 100 absorbance vs. time points were measured over 3.5 half-lives. The first-order rate constants were calculated from these data by means of a computer program employing the Guggenheim approximation least-squares method.[12]

Results and Discussion

The synthesis of simple 1,3-dialkyltriazenes and their acylated derivatives can be accomplished in a relatively straightforward manner by the reaction of alkyl azides with alkyllithiums or Grignard reagents.[13] This route was not applicable to the functionalized triazenes. It is not possible to prepare organometallic reagents containing a heteroatom on the β-carbon because of immediate elimination (the Boord reaction).[14] Similarly, attempts to add organometallic reagents to 2-haloethyl azides resulted in an elimination reaction, presumably because metal–halogen interchange is more rapid than the addition to the azide moiety. Interestingly, the reaction of 2-chloroethyl azide[15] with methyllithium did produce a low yield (3.2%) of 1-(2-hydroxyethyl)-3-methyltriazene. The actual yield of this compound may have been somewhat higher, but it proved to be very unstable under hydrolytic workup conditions.

In order to prepare these triazenes, we adopted a less direct approach. The reaction of 2-azidoethanol (**1**)[10] prepared by the reaction of 2-chloroethanol with sodium azide, with *tert*-butyldimethylsilyl chloride (TBDMS-Cl) catalyzed by immidazole,[16] resulted in the smooth formation of 1-azido-2-(*tert*-butyldimethylsiloxy)ethanol (**2**).

(12) Guggenheim, E. A. *Philos. Mag.* **1926**, *2*, 538.
(13) Smith, R. H., Jr.; Michejda, C. J. *Synthesis* **1983**, 476–477.
(14) March, J. *Advanced Organic Chemistry*, 3rd ed.; John Wiley and Sons: New York, 1985; p 925.
(15) Wiley, R. H.; Moffat, J. *J. Org. Chem.* **1957**, *22*, 995–996.
(16) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190–6191.

Table I. Comparative Rates of Proteolytic Decomposition of 3-Acyltriazenes[a] at 70 °C in pH 7.5, 0.10 M Lysine Buffer[b]

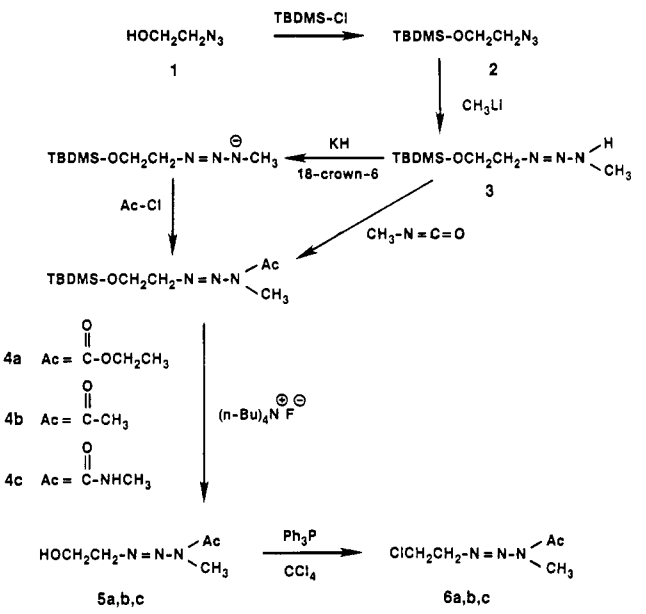
substr	$10^4 k_{obsd}$, s^{-1}	$t_{1/2}$ (min)
7a	21.9 ± 0.04	5.26
5a	16.7 ± 0.04	6.90
6a	1.75 ± 0.01	66.1
7b	5.16 ± 0.06	22.4
5b	3.62 ± 0.04	31.9
6b	0.341 ± 0.006	338
7c	2.52 ± 0.02	45.9
5c	1.52 ± 0.002	75.9
6c	0.174 ± 0.002	664

[a] The initial concentration of the substrates was 3.0×10^{-5} M. The first-order rate plots were linear over the observation period. [b] Ionic strength was 0.25 M, maintained with $NaClO_4$.

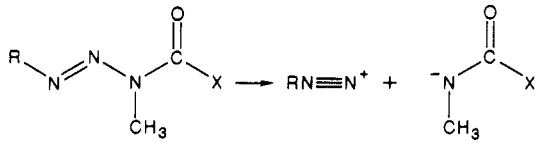
This compound is relatively stable and can be distilled under reduced pressure. The crude product, however, can be used in the next step, without distillation. The protected azide was then reacted with methyllithium in diethyl ether solution, using the reverse addition technique (methyllithium added to the azide) in order to minimize the possible reaction of the organometallic reagent with the protecting group. The resulting product, 1-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-methyltriazene (**3**) was isolated in 70% yield, after distillation. Acylation of the protected triazene was accomplished by the methods developed for the preparation of other triazenes.[13] Compound **3** in diethyl ether was converted to its anion by reaction with a slight excess of potassium hydride, catalyzed by 18-crown-6 ether. This solution was treated with ethyl chloroformate to give 1-[2-(*tert*-butyldimethylsiloxy)ethyl]-3-carbethoxy-3-methyltriazene (**4a**) or with acetyl chloride to yield the acetyl derivative **4b**. Use of the anion avoids the side production of hydrochloric acid which would catalyze decomposition of both the starting and product triazenes. Conversion of **3** to the methylcarbamoyl derivative **4c** did not require the intermediacy of the anion of **3** in keeping with our earlier finding[6] that dialkyltriazenes react cleanly with methyl isocyanate. All three acylation reactions proceeded in a highly regioselective manner, resulting in acylation of the less sterically hindered nitrogen of triazene **3**. Trace amounts of the more hindered isomer, indicated by ^1H NMR to be present in some of the crude product mixtures, were apparently lost during isolation. The deprotection of the siloxytriazenes was accomplished with tetra-*n*-butylammonium fluoride in tetrahydrofuran solution. This was the most troublesome step in the synthesis since it was necessary to use column chromatography to free the 3-acyl-1-(2-hydroxyethyl)-3-methyltriazenes **5a,b,c** from *tert*-butylfluorodimethylsilane and tetra-*n*-butylammonium hydroxide. Significant amounts of the triazenes were lost during chromatography. Triazenes **5a,b,c** were then converted smoothly to the chloroethyl derivatives **6a,b,c** by reaction with carbon tetrachloride and triphenylphosphine.[17] These reactions are summarized in Scheme I.

It was interesting to compare the kinetics of the proteolytic decomposition of the new acyltriazenes with the data previously obtained on the analogous 3-acyl-1,3-dimethyltriazenes.[6] Table I presents the first-order rate constants for the decomposition of the 3-carbethoxy-, 3-acetyl-, and 3-(methylcarbamoyl) derivatives of 1,3-dimethyltriazene (**7a,b,c**), 1-(2-hydroxyethyl)-3-methyltriazene (**5a,b,c**), and 1-(2-chloroethyl)-3-methyltriazene (**6a,b,c**) in a lysine buffer at pH 7.5. The acyl group has

Scheme I



a very similar effect for all three triazene types: carbethoxy derivatives decompose faster than acetyl derivatives, which decompose faster than methylcarbamoyl derivatives. On the basis of our earlier studies on 3-acyl-1,3-dimethyltriazenes,[6] the reactions at pH 7.5 are in the uncatalyzed domain and proceed according to the following mechanism:



Thus, the order of the acyl group effect mirrors the ability of the acyl group to stabilize the negative charge.[6] The difference in reactivity between the 1-methyl-, 1-(2-hydroxyethyl)-, and 1-(2-chloroethyl)triazenes should be a reflection of the stability of the incipient alkyldiazonium ion in the transition state of the dissociation. This, in fact, appears to be the case since the logarithms of the rates of decomposition for a given acyl substituent gave linear correlations with σ^* values for H, $HOCH_2$, and $ClCH_2$ substituents (0.490, 0.550, and 1.050, respectively[18]). These correlations were derived from the rearranged Taft equation:[18]

$$\log k_{obsd} = \log k_0 + \sigma^*\rho^*$$

The ordinate intercepts gave an estimate of the rate constants (k_0) of 3-acyl-1-ethyl-3-methyltriazene, since σ^* for CH_3 is defined as zero. The rate constants for these unknown triazenes were calculated to be 2.04×10^{-2} s^{-1}, 5.25×10^{-3} s^{-1}, and 2.18×10^{-3} s^{-1}, for the 3-carbethoxy-, 3-acetyl-, and 3-(methylcarbamoyl)triazenes, respectively. The ρ^* values for all three acyl groups were very close to −2.0, which suggests that the degree of N_2–N_3 bond breakage in the transition state in not particularly sensitive to the nature of the acyl substituent.

Finally, preliminary data from the P388 murine leukemia screen for antitumor agents, obtained under the auspices of the Division of Cancer Treatment, National Cancer Institute, Bethesda, MD, indicated that triazenes **6a,b,c** possess considerable activity. Triazene **6c** has been

(17) Hooz, J.; Gilani, S. S. H. *Can. J. Chem.* **1968**, *46*, 86–87.

(18) Wiberg, K. B. *Physical Organic Chemistry*, John Wiley and Sons: New York, 1964; pp 413–415.

selected for additional testing against selected human tumors implanted in nude mice. The biological data resulting from these studies will be reported in a separate publication.

Acknowledgment. This research was supported by the National Cancer Institute, DHHS, under contract No. N01-74101 with Bionetics Research, Inc. Partial support was also derived from NIH Grant No. F33-CA-07613, National Science Foundation Grant No. CHE-8521385, and the donors of the Petroleum Research Fund, administered by the American Chemical Society. We thank Dr. Climaco J. Metral and Mr. John Roman for exact mass determinations. The contents of this publication do not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial product, or organizations imply endorsement by the U.S. Government.

Photoinduced Electron Transfer to a Carbenium Ion[1]

H. Al-Ekabi, H. Kawata,[2] and P. de Mayo*

Photochemistry Unit, Department of Chemistry, University of Western Ontatio, London, Ontario, Canada, N6A 5B7

Received August 14, 1987

Irradiation ($\lambda > 430$ nm) of the cation obtained by protonation of 1,1-di-*p*-anisylethylene (1) in the presence of excess 1 in benzene–trifluoroacetic acid solution results in electron transfer from the neutral ethylene and the formation of the corresponding radical and radical cation. These have been identified by the aid of flash photolysis and quenching experiments with an electron donor and by the nature of the final products. The radical cation was also prepared, for comparison, by using 9,10-dicyanoanthracene as the electron acceptor. The quantum yields of the photoproducts, derived from both radical and radical cation, are very low ($\sim 10^{-3}$), which suggests the occurrence of an efficient back-electron-transfer process between radical and radical cation to regenerate 1 and the ground-state cation.

Introduction

As part of our work on semiconductor mediated organic reactions we had occasion to study the reactions of 1,1-di-*p*-anisylethylene (1) in the presence of two pure samples of CdS.[3] A difference in behavior between them was observed in that while both samples gave the dimeric products **10–13**, believed to be derived from the radical cation $\mathbf{1}^{\bullet+}$, one sample gave, in addition, a substance believed to be **6**. A further difference found was that the CdS sample which produced **6** gave, in a "dark" reaction, another dimeric product identified as **3** and known to be formed[4] by simple acid catalysis from **1**. The other sample of CdS underwent no "dark" reaction whatsoever. From these observations we were led to suspect that **6** arose by the combined action of acid and light on **1**—despite the fact that washing the CdS did not remove its "acid" properties—and one possibility that presented itself was that **6** was generated by the action of light on the cation derived from **1**, i.e., **2**.

The photochemistry of carbenium ions has been largely restricted to that of those derived from unsaturated carbonyl compounds and to instances of valence tautomerism or geometrical isomerism.[5,6] There have been, also, a few reports of the photochemical reduction of cations where the products isolated are complex, and where the source of the "reducing" electron is unknown.[7,8] More relevant to the present study is the work of Barton, Haynes, and their co-workers who showed that simple Lewis acids efficiently catalyze the insertion of triplet oxygen into conjugated dienes to yield cyclic peroxides.[9] A model for this reaction was proposed involving the formation of a diene cation radical. A consequence of this model was that oxygenation of substrates other than dienes should have been possible, provided that the reaction of the cation radical with oxygen (or superoxide) were thermodynamically favored. Diphenylethylene and its derivatives were exam-

Table I. Quantum Yields of Photoproducts

		quantum yield ($\times 10^3$)[e]			
[acid],[a] M	C_A/C_0[b]	10	11	6	7
0	(1.0)				
0.13[c]	0.99	0.34	2.9	0.25	0.12
0.52[c,d]	0.95	0.45	2.4	0.22	0.15
1.03[c]	0.68	0.85	1.7	0.16	0.41
1.62[c]	0.36	0.90	1.0	0.05	0.70
2.34[c]	0.16	0.63	0.6	~0	0.57

[a] Trifluoroacetic acid. [b] The ratio of the concentration of olefin (C_A) to initial concentration of olefin (C_0; 4.2×10^{-2} M) was calculated from UV spectra. [c] The quantum yields, at these acid concentrations, were determined on a PTI "Quantacount" equipped with a 150-W xenon lamp: 3 h irradation at 480 nm. [d] Solution was irradiated at 480 nm, determined on JASCO spectroirradiator, calibrated with thermopile and potassium ferrioxalate (at 360 nm). [e] Error, ±15%.

(1) Publication No. 394 from the Photochemistry Unit, University of Western Ontario.
(2) On leave from College of Humanities and Social Sciences, Iwate University, Japan.
(3) Al-Ekabi, H.; de Mayo, P. *J. Org. Chem.* **1987**, *52*, 4756.
(4) (a) Evans, A. G.; Jones, N.; Jones, P. M. S.; Thomas, J. H. *J. Chem. Soc.* **1956**, 2757. (b) Tadros, W.; Sakla, A. B.; Abdou, S. E. *Ibid.* **1972**, 2839.
(5) Childs, R. F. *Rev. Chem. Intermed.* **1980**, *3*, 285.
(6) Cabell-Whiting, P. W.; Hogeveen, H. *Adv. Phys. Org. Chem.* **1973**, *10*, 129.
(7) (a) Van Tamelen, E. E.; Cole, P. M. *J. Am. Chem. Soc.* **1971**, *93*, 6158. (b) Owen, E. D.; Allen, D. M. *J. Chem. Soc., Chem Commun.* **1973**, 95.
(8) Van Tamelen, E. E.; Greelaw, R. H.; Schumacher, H. *J. Am. Chem. Soc.* **1971**, *93*, 6151.
(9) Barton, D. H. R.; Haynes, R. K.; Leclerc, G.; Magnus, P. D.; Menzies, I. D. *J. Chem. Soc., Perkin Trans.* **1975**, 2055.

0022-3263/88/1953-1471$01.50/0