The Base-Promoted Dehydrohalogenation of 1-(2-Chloroethyl)-3-alkyl-3-acyltriazenes

David W. Farnsworth,*,‡ Brunon Pruski,‡,[1] and Richard H. Smith, Jr.*,†,‡

Department of Chemistry, Western Maryland College, Westminster, Maryland 21157, and Molecular Aspects of Drug Design Section, ABL-Basic Research Program, NCI-Frederick Cancer Research and Development Center, Frederick, Maryland 21702-1201

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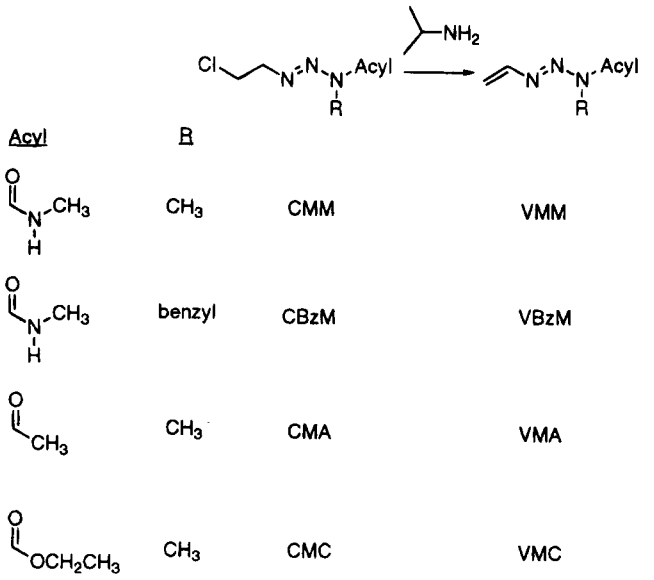
We report on an unusual instance of alkylamine-promoted dehydrohalogenation of 1-(2-chloroethyl)-3-alkyl-3-acyltriazenes. Some time ago, we published a general method for the preparation of 1-(2-chloroethyl)-3-methyl-3-acyltriazenes.[2] The hydrolytic decomposition of these compounds is complex, following different mechanisms and giving different products in acidic, neutral, and basic buffers.[3,4] In alkaline aqueous solution, 1-(2-chloroethyl)-3-methyl-3-(*N*-methylcarbamoyl)triazene (CMM) undergoes dehydrohalogenation leading to the formation of 1-vinyl-3-methyl-3-(*N*-methylcarbamoyl)-triazene (VMM). Subsequent work has revealed that relatively weak bases like alkylamines are sufficient to bring about this reaction. Furthermore, dehydrohalogenation promoted by amines is a relatively general reaction of 1-(2-chloroethyl)-3-methyl-3-acyltriazenes.

As a typical example, CMM was cleanly converted to VMM simply by being stirred in an excess of anhydrous isopropylamine at room temperature for 48 h. The isolated yield after column chromatographic purification, using ether–pentane eluent, was 78%. Tests revealed that the reaction occurs in the presence of a variety of different amines. The efficiency of conversion follows the order isopropylamine > *n*-propylamine ≫ diethylamine > pyrrolidine (conversion was not observed for either triethylamine or pyridine). The structure of the acyltriazene was also varied to determine the generality of this reaction. 1-(2-Chloroethyl)-3-benzyl-3-(*N*-methylcarbamoyl)triazene (CBzM) is converted to 1-vinyl-3-benzyl-3-(*N*-methylcarbamoyl)triazene (VBzM) under the same conditions (Scheme 1). Similar reactions with other 1-(2-chloroethyl)-3-methyl-3-acyltriazenes led to somewhat more complex product mixtures. 1-(2-Chloroethyl)-3-methyl-3-acetyltriazene (CMA) yielded a mixture of 1-vinyl-3-methyl-3-acetyltriazene (VMA) and 1-vinyl-3-methyltriazene (VMT) upon being stirred in isopropylamine for 12 h. 1-(2-Chloroethyl)-3-methyl-3-carbethoxytriazene (CMC) gave a mixture of 1-vinyl-3-methyl-3-carbethoxytriazene (VMC) and 1-vinyl-3-methyltriazene (VMT) over the same reaction time with isopropylamine. In light of the general lack of stability of simple 1,3-dialkyltriazenes, it appears likely that VMT results from subsequent deacylation of VMC, rather than by the reverse sequence of reactions, deacylation followed by dehydrohalogenation. Product mixtures were determined by isolation (in the case of CMM) or by ^{1}H NMR analysis of a CD_2Cl_2 solution of the residue obtained by reduced pressure evaporation of the isopropylamine reaction solution.

Scheme 1



In aqueous alkaline buffers, the decomposition of CMA and CMC, unlike that of CMM, does not lead to dehydrohalogenation. Instead, these compounds undergo deacylation, followed by ring closure, to form 1-methyltriazoline. This difference is probably a reflection of the relative ease by which the acyl group of CMA and CMC undergoes nucleophilic attack by hydroxide ion. These data further support the supposition that dehydrohalogenation precedes deacylation in the reaction of these compounds in amine solvents, where 1-methyltriazoline is not observed as a product.

The rate of conversion of 1-(2-chloroethyl)-3-methyl-3-acyltriazenes to their vinyl analogs was determined by monitoring the appearance of the UV chromophore of the products. Unfortunately, end absorbance by the solvent prevented monitoring of the disappearance of the starting triazenes. The λ_{max} of the vinyl derivative of each 3-acyltriazene occurs at a longer wavelength (~+32 nm) than that of the respective 2-chloroethyl starting material, thus making kinetic measurements relatively easy. The k_{obs} for each compound tested is reported in Table 1. For CMM and CBzM, these rate constants reflect the rate of dehydrohalogenation. In the case of CMA and CMC, however, significant conversion of the initial dehydrohalogenation product, VMA and VMC, respectively, to VMT occurs during the course of the kinetic experiments. Thus, for CMA and CMC, the measured k_{obs} is a composite reflecting two consecutive pseudo first order rate constants. Despite this complicating feature, the apparent overall rate of reaction directly parallels the electron-withdrawing ability of the 3-acyl groups (carbethoxy > acetyl > methylcarbamoyl)[5] and 3-alkyl (benzyl > methyl), as would be expected for a reaction in which a

† Western Maryland College.
‡ NCI-Frederick Cancer Research and Development Center.

(1) Brunon Pruski on leave from Adam Mickiewicz University, Poznan, Poland.

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(5) As measured by the magnitude of their respective σ^I values: Charton, M. *J. Org. Chem.* **1964**, *29*, 1222–1227.

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Table 1. Rate Constants (k_{obs}) for Product Appearance ($\times 10^5$ s^{-1}) in Isopropylamine at 25 °C[a]

compd	k_{obs}
CMM	1.10
CBzM	2.58
CMA	8.84
CMC	10.20

[a] Initial triazene concentration = 3×10^{-5} M.

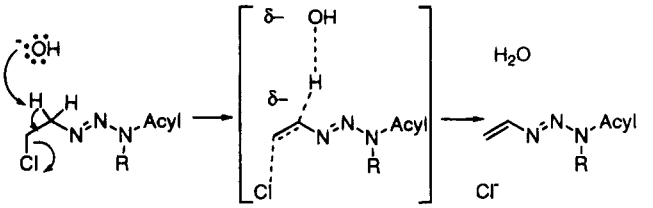
negative charge is developed in the transition state of the rate-determining step.

Additional experiments were performed to probe the mechanistic details of the dehydrohalogenation reaction. Because solvent isotope effects in amine solvents are less well-defined, we chose to perform the majority of our experiments in aqueous buffers. Kinetic measurements were made for the dehydrohalogenation of CMM using OD^- in D_2O and OH^- in H_2O as the respective bases. Rates obtained in aqueous 0.10 M lysine buffer at 70 °C gave k_{H_2O} of $4.45 \pm 0.13 \times 10^{-4}$ s^{-1} and k_{D_2O} of $1.07 \pm 0.03 \times 10^{-3}$ s^{-1}, while rates obtained in aqueous 0.10 M phosphate buffer gave k_{H_2O} of $6.115 \pm 0.082 \times 10^{-4}$ s^{-1} and k_{D_2O} of $1.140 \pm 0.014 \times 10^{-3}$ s^{-1}. The solvent isotope effect, k_{H_2O}/k_{D_2O}, was found to be 0.42 in lysine buffer and 0.54 in phosphate buffer. These experiments were performed in buffers of pH (or pD)[6] of 12.00 at 70 °C. Because these determinations were made at 70 °C, it was deemed prudent to assume that the solvent isotope effect was not significantly affected by elevated temperature. A similar experiment in the same phosphate buffer at 50 °C resulted in essentially the same value (given the standard error associated with each k value) for k_{H_2O}/k_{D_2O}, 0.51, with $k_{H_2O} = 5.854 \pm 0.11 \times 10^{-5}$ s^{-1} and $k_{D_2O} = 1.148 \pm 0.004 \times 10^{-4}$ s^{-1}. The results of these experiments are consistent with a mechanism in which a proton is transferred from the substrate to the base during the rate-determining step of the reaction.[7]

Experiments were also performed to test for deuterium incorporation into the starting material. ^1H NMR analysis of a reaction of CMM in D_2O at pH 12.0 after approximately half of the starting material had been consumed showed no deuterium incorporation at C_1 of the 2-chloroethyl group. Under the conditions of the NMR experiment, as little as 2% deuterium incorporation would have been detected. Thus, in aqueous buffers, proton transfer from the substrate to the base is not reversible.

The mechanism which is most consistent with all of the above observations is an E1cB-like E2 elimination, a single-step process in which proton abstraction by the base slightly precedes the loss of chloride ion in the transition state (Scheme 2). The electron-withdrawing ability of the triazeno moiety (and groups attached to it) presumably enhances the stability of the adjacent partial negative charge created by the nonsymmetrical breakage of the C–H and C–Cl bonds. Although a number of subtly different E1cB mechanisms[8] might also be considered, none of these is consistent with all of the observed data. Thus, we favor the following mechanistic scheme for the dehydrohalogenation of 1-(2-chloroethyl)-3-alkyl-3-(*N*-methylcarbamoyl)triazenes in alkaline aqueous buffers.

Scheme 2



Although secondary isotope effects were not measured for the title reaction in alkylamine solvents, it seems likely that this reaction also follows an E1cB-like E2 elimination mechanism with the alkylamine serving to abstract the proton. In support of this contention, we did observe that the dehydrohalogenation of CMM in 1:1 (v/v) isopropylamine–D_2O shows the same lack of deuterium incorporation into the starting material (isolated after approximately one half-life) as was observed in the analogous reaction in NaOD–D_2O.

In the case of CMM reacting with certain amines, *n*-propylamine and pyrrolidine, displacement of chloride by the amine competes with elimination. Stirring VMM in the presence of either amine does not lead to the formation of the substitution product, thus ruling out the possibility of an elimination followed by addition pathway.

The salient feature of the above reported dehydrohalogenation reaction is the fact that it occurs rapidly in the presence of relatively weak bases, alkylamines. We attribute this unusual behavior primarily to the activating effects of the adjacent triazeno moiety. In the presence of the stronger base, NaOH, dehydrohalogenation follows an E1cB-like E2 elimination mechanism. It appears likely that the amine-promoted reaction proceeds by a similar mechanism.

Experimental Section

Safety Note. Alkyltriazenes are potent biological alkylating agents, mutagens, and carcinogens. Great care should be exercised in all experimental procedures to minimize exposure. Efficient hoods and protective clothing, especially gloves, should be used at all times.

Materials. All chemicals were reagent grade and were used as purchased without further purification. The preparation of the triazenes used in this study has been previously published.[1,2,9] Buffers for kinetic measurements and product analyses were prepared as previously described[10] with water distilled from $KMnO_4$. The pH measurements were obtained using a high ionic strength combination electrode (calomel reference). UV spectra were recorded on a double-beam diode-array processor spectrophotometer. NMR spectra were obtained on a Varian XL-200 spectrometer. Exact mass measurements were determined on a VG 70-250 (for EI spectra) mass spectrometer. The purity of all new compounds obtained in this work was judged to be >95% by ^1H NMR spectral determinations (spectra available as supporting information).

General Dehydrohalogenation Procedure for CMM. The general reaction involved 60 mg (0.336 mmol) of 1-(2-chloroethyl)-3-methyl-3-(*N*-methylcarbamoyl)triazene and 6 mL of the particular amine (i.e., 5.6×10^{-2} M in triazene). The reaction solution was stirred for 24–48 h at 25 °C, with several studied for up to 144 h. Following the disappearance of all triazene, as determined by NMR and/or by TLC, excess amine

(6) For pOH = pOD, the equation $pOD = pOH_{nominal} + 0.4$ was used in accord with Glasoe, P. K.; Long, F. A. *J. Phys. Chem.* **1960**, *64*, 188–190.

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was removed by reduced pressure evaporation at specific time points until reaction completion. NMR spectra of the residue were then obtained on the residue dissolved in CD_2Cl_2. Characterization of the dehydrohalogenation product, 1-vinyl-3-methyl-3-(*N*-methylcarbamoyl)triazene [VMM], was obtained by comparison and spiking of NMR samples with authentic material. Several amines gave substitution as well as dehydrohalogenation products in ratios (substitution:dehydrohalogenation) of 25:75 (propylamine) and 93:7 (pyrrolidine). Pure samples of substitution products were isolated as described below.

(a) Reaction with *n*-propylamine required 44–48 h. Excess amine was removed and the crude oil taken up in 2 × 10 mL of pentane. This was washed several times with water and dried over anhydrous sodium sulfate and excess solvent removed by rotary evaporation. The crude oil was purified by flash column chromatography using silica gel eluted with anhydrous diethyl ether to yield 12.6 mg (18.6%) of pure 1-[2-(*n*-propylamino)ethyl]-3-methyl-3-(*N*-methylcarbamoyl)triazene (PrMM), a slightly yellowish oil: λ_{max} 247 nm (ϵ = 9923): ^{1}H NMR (CD_2Cl_2, Me_4Si) δ 0.99 (3H, t, J = 7.43 Hz), 1.84 (2H, sextet, J = 7.62 Hz), 2.88 (3H, d, J = 4.8 Hz), 2.95 (2H, multiplet), 3.23 (3H, s), 3.34 (2H, t, J = 6.32 Hz), 4.18 (2H, t, J = 6.28 Hz), 4.73 (1H, bd s), 6.77 (1H, bd s); ^{13}C NMR (CD_2Cl_2, Me_4Si) δ 11.40, 19.85, 27.16, 27.36, 28.21, 46.40, 57.43, 155.56; MS *m/z* (relative intensity) 201 (M+, 7.2), 130 (10.1), 114 (12.4), 101 (7.7), 88 (36.2), 84 (11.3), 73 (40), 72 (100), 70 (14.4), 69 (64.1), 58 (73.8), 57 (19.2), 56 (77.5). Exact mass for M^+ ($C_8H_{19}N_5O$) 201.1591, found 201.1590 (by EI).

(b) Reaction with pyrrolidine required only 24 h, with no change in products or ratios over the next 24 h. The cleanup and purification procedure was as described above for (a) to yield 48.3 mg (67.4%) of pure 1-(2-pyrrolidinylethyl)-3-methyl-3-(*N*-methylcarbamoyl)triazene [PMM] which crystallized upon standing: λ_{max} 247 nm (ϵ = 7957); ^{1}H NMR (CD_2Cl_2, Me_4Si) δ 1.74 (4H, quintet, J = 3.4 Hz), 2.51 (4H, multiplet), 2.84 (2H, t, J = 6.74 Hz), 2.88 (3H, d, J = 4.88 Hz), 3.18 (3H, s), 3.87 (2H, t, J = 6.78 Hz), 6.32 (1H, bd); ^{13}C NMR (CD_2Cl_2, Me_4Si) δ 23.74, 27.23, 28.12, 42.49, 55.07, 57.89, 155.8; MS *m/z* (relative intensity) 213 (M^+, 1.2), 126 (2.2), 98 (1.6), 85 (10.1), 84 (100.0), 70 (2.7), 56 (5.4), 42 (11.6). Exact mass for M^+ ($C_9H_{19}N_5O$) 213.1589, found 213.1594 (by EI).

Product Studies. The products of dehydrohalogenation of the 1-(2-chloroethyl)-3-alkyl[aryl]-3-acyltriazenes (CMM, CBzM, CMA, and CMC) in isopropylamine were determined from reaction mixtures in which the initial triazene concentration was 5.6×10^{-2} M. Excess amine was removed by reduced pressure evaporation. NMR spectra were obtained in CD_2Cl_2 solution, and structure assignments were made by comparison and spiking with authentic samples.

Kinetic Studies. Rates of product appearance, used because of solvent absorbance overlap with starting material absorbance, in isopropylamine were followed spectrophotometrically at the appropriate λ_{max}. Reaction solutions were contained in thermostated 1 cm cells with the temperature held constant to within ±0.1 °C. In a typical kinetic run, the reaction cuvette was charged with 1.341 mL of isopropylamine, and the reaction was initiated by the addition of 9 μL of a 4.5×10^{-3} M solution of the triazene in acetonitrile; the final triazene concetration was 3.0×10^{-5} M. A minimum of 100 absorbance vs time readings was obtained over 3.5 half-lives. The first order rate constants were calculated from these data by means of a computer program based on the Guggenheim approximation least-squares method.[11]

Solvent isotope studies, k_{H_2O}/k_{D_2O}, were performed in 0.1 M lysine (ionic strength = 0.25 M maintained with added $NaClO_4$) and 0.1 M phosphate (ionic strength = 0.40 M with no added salt) buffers.

Deuterium Incorporation. Deuterium incorporation studies were performed in a 0.1 M NaOD solution (initial triazene concentration of 5×10^{-2} M), as well as in a 1:1 (v/v) isopropylamine–D_2O solution (initial triazene concentration of 8×10^{-2} M). ^{1}H NMR spectra were obtained after approximately one half-life, either directly on the reaction mixture (NaOD) or after reduced pressure solvent removal (isopropylamine). Deuterium incorporation was assayed by integration of the C_1 and C_2 methylene signals of the 2-chloroethyl moiety.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra for PrMM and PMM (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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