Gas Phase Reactions of the Cyclic Ethylenehalonium Ions $(CH_2)_2X^+$ (X = Cl, Br) with Glycine[1]

Richard A. J. O'Hair,*,† Michael A. Freitas,† and Todd D. Williams‡

Department of Chemistry, Kansas State University, Manhattan, Kansas 66506-3701, and Mass Spectrometry Laboratory, University of Kansas, Lawrence, Kansas 66045

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The gas phase reactions of glycine with the cyclic ethylenehalonium ions $(CH_2)_2X^+$ (X = Cl, Br) **A** in the CI source of a tandem mass spectrometer reveal a rich chemistry. The mechanisms of these reactions were determined by analyzing the unimolecular fragmentation reactions of the product ions. The major products are consistent with alkylation by $(CH_2)_2X^+$ ions to form a $[M + C_2H_4X]^+$ adduct ion, in which addition to both nitrogen and oxygen occurs, with the former dominating. Independently generated $[H_2NCH_2CO_2CH_2CH_2X + H]^+$ ions undergo partial isomerization to form $[XCH_2CH_2NHCH_2CO_2H + H]^+$ ions, with isomerization being greatest when X = Br. This, together with the fact that $(CH_2)_2X^+$ fragment ions are also observed, is consistent with a neighboring-group mechanism whereby a $[(CH_2)_2X^+ (H_2NCH_2CO_2H)]$ ion−molecule complex is formed. The $[M + C_2H_4X]^+$ adduct ions also lose HX to form $[M + C_2H_3]^+$ ions, both in the source and under MS/MS conditions. Comparison of the MS/MS spectrum with that of an authentic sample indicates that the most likely structure of this $[M + C_2H_3]^+$ ion is that of $CH_3CH{=}NHCH_2CO_2H^+$. These experimental results are consistent with the *ab initio* calculated (at the MP2(FC)/6-31G*//HF/6-31G* level) relative stabilities of various isomeric $[M + C_2H_3]^+$ ions. For $(CH_2)_2Br^+$ an additional $[M + Br]^+$ ion is observed whose structure, based upon MS/MS studies, is consistent with attachment of Br^+ onto nitrogen and to a lesser extent onto oxygen. Finally, the structure of a $[M + CH_2{=}NH_2]^+$ ion, formed in the source reaction between the primary product ion $CH_2{=}NH_2^+$ and glycine, was also studied by MS/MS. This ion consists of two types of structures: ion dipole complexes and a covalent structure. The latter eliminates NH_3 to form a $[M + CH]^+$ ion of structure $CH_2{=}NHCH_2$-CO_2H^+.

Introduction

We recently demonstrated that tandem mass spectrometry MS/MS[2] can be used to determine the regioselectivity of gas phase alkylation reactions of glycine[3a] and the tautomeric 2-hydroxypyridine/2-pyridone system.[3b] For example, the dimethylchlorinium ion, $(CH_3)_2Cl^+$, undergoes a nonregioselective S_N2 reaction, with methylation occurring at both nitrogen (eq 1) and oxygen (eq 2). In contrast, the ambident electrophile $CH_3OCH_2^+$

$$H_2NCH_2CO_2H + (CH_3)_2Cl^+ \longrightarrow [CH_3NHCH_2CO_2H + H]^+ + CH_3Cl \quad (1)$$

$$H_2NCH_2CO_2H + (CH_3)_2Cl^+ \longrightarrow [H_2NCH_2CO_2CH_3 + H]^+ + CH_3Cl \quad (2)$$

$$H_2NCH_2CO_2H + CH_3OCH_2^+ \longrightarrow [CH_2{=}NHCH_2CO_2H]^+ + CH_3OH \quad (3)$$

reacts almost exclusively via a regiospecific pathway involving addition at nitrogen followed by elimination of CH_3OH to form a $[M + CH]^+$ ion with the structure $CH_2{=}NHCH_2CO_2H^+$ (eq 3). The latter reaction has a direct solution analog in the reaction of glycine with formaldehyde under acidic conditions.[4]

Our interest in these alkylation reactions stems from their role in the damage of two important classes of biological macromolecules: DNA and proteins.[5] In order to determine *intrinsic* reactivity, we have embarked on a program to examine the gas phase reactions of charged electrophiles with models and building blocks of proteins and DNA.[3] The gas phase reactions of cyclic ethylene halonium ions $(CH_2)_2X^+$ (X = Cl, Br) with small biological molecules are therefore attractive to us since they allow us to (i) probe the structure and reactivity of possible alkylated intermediates in the reactions of 1,2 dihaloalkanes with biomolecules[6] and (ii) make comparisons with the known isoelectronic carcinogens, the epoxides.[5f]

The gas phase chemistry of cyclic ethylene halonium ions $(CH_2)_2X^+$ (X = Cl, Br) has been studied both experimentally and theoretically.[7,8] High level *ab initio*

* Corresponding author. Phone: (913) 532-7497. Fax: (913) 532-6666. E-mail: rohair@KSU.KSU.EDU.
† Kansas State University.
‡ University of Kansas.
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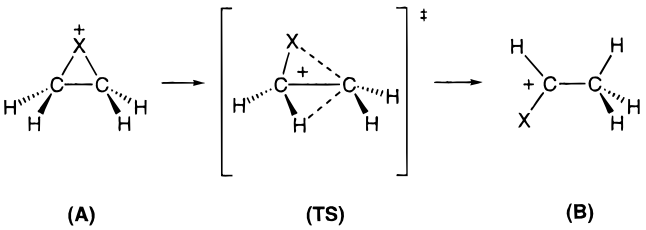
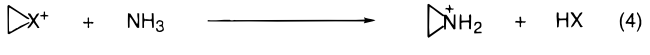
Scheme 1



(A) **(TS)** **(B)**

Relative energies (kcal mol^{-1})	(A)	(TS)	(B)
X=Cl	0.0	+27.8	-4.3
X=Br	0.0	+26.5	+2.7

calculations have been carried out on both $C_2H_4X^+$ potential energy surfaces.[7] The key findings for the isomerization of **A** to **B** are summarized in Scheme 1. An early ICR study by Beauchamp's group considered the formation and reactivity of both the acyclic 2-haloethyl cations CH_3CHX^+ **B** and cyclic ethylenehalonium ions $(CH_2)_2X^+$ **A** (X = Cl, Br).[8a] These ions were formed by electron impact on 1,1- and 1,2-dihaloethanes, respectively. An important finding was that the two isomeric ions were noninterconverting under the experimental conditions. Moreover, the reactions of the cyclic ethylenehalonium ions $(CH_2)_2X^+$ (X = Cl, Br) with a number of simple nucleophiles were investigated. A summary of the kinetics, thermodynamics, and proposed mechanism for the reaction of NH_3 with these cyclic ethylenehalonium ions is shown in eq 4. More recently, Nibbering et al. have studied the ion−molecule reactions of **A** and **B** with other species.[8b] Finally, the cyclic bromonium ion has been used as a CI reagent to distinguish between certain isomeric *E* and *Z* alkenes.[8c,d]



(4)

X = Cl: ΔH^o = -42.5 kcal mol^{-1} ; k = 5.0 x 10^{-10} cm^3 molecule^{-1} sec^{-1}

Br: ΔH^o = -31.2 kcal mol^{-1} ; k = 9.0 x 10^{-12} cm^3 molecule^{-1} sec^{-1}

Experimental Section

All experiments were performed on a Fisons/VG (Manchester, U.K.) Autospec-Q instrument of E1BE2qQ geometry (where E = electric sector, B = magnetic sector, q = RF only quadrupole, and Q = quadrupole). MS/MS experiments were performed in the unimolecular MIKES mode, in which the ion of interest was mass selected using E1B and the metastable fragments were determined by scanning E2. In addition, some collision-induced decomposition (CID) reactions were studied by mass selecting the ion of interest using E1BE2 and allowing these ions to undergo collisions with xenon in the RF only quadrupole. The xenon pressure was set to attenuate the precursor ion 50%, corresponding to a pressure of 2×10^{-4} mBarr indicated on a Penning gauge near the collision cell. The product ions were identified by scanning the final quadrupole from 20−200 amu in 5 s. The quadrupole analyzer resolution was 1 amu FWHM. Alkylated glycine ions were formed in the chemical ionization source using either 1,2-dichloroethane or 1,2-dibromoethane as the CI gas. The CI plasmas for both these reagents are very clean, giving intense *m*/*z* 63/65 ions for 1,2-dichloroethane and *m*/*z* 107/109 ions for 1,2-dibromoethane, consistent with the formulas $C_2H_4X^+$. Apart from the minor presence of the radical cations of XCH_2CH_2X, very few other ions are observed. Glycine was introduced through a heated direct insertion probe.

Typical source conditions for the 1,2-dichloroethane plasma were: source temperature = 250 °C; electron energy = 70 eV; emission current = 0.2 mA. The source pressure was 2×10^{-5} mBarr, as measured on the source ion gauge. For the 1,2-dibromoethane plasma two different source conditions were investigated:

(i) Pure 1,2-dibromoethane was used at: source temperature = 250 °C; electron energy = 70 eV; emission current = 1 mA. In order to achieve a source pressure of 3×10^{-5} mBarr (as measured on the source ion gauge) the CI reagent was heated to a temperature of 70 °C.

(ii) 1,2-Dibromoethane was diluted by passing an argon flow through the 1,2 dibromoethane reservoir headspace to the source. Argon and total CI gas flow valves were adjusted to provide an argon ion current (*m*/*z* 40) 60% of that for *m*/*z* 107 (derived from 1,2 dibromoethane). The source temperature = 250 °C; electron energy = 70 eV; emission current = 1.00 mA; source pressure = 2×10^{-5} mBarr.

Both dibromoethane plasmas (i) and (ii) gave very similar spectra. The advantage of using plasma (ii) is that it showed less of a tendency to "foul up" the CI source and produced less abundant "background" ions than (i).

All reagents were commercially available and were used without further purification. $H_2NCD_2CO_2H$ (98% D), $H_2{}^{15}NCH_2CO_2H$ (99% ^{15}N), and $BrCD_2CD_2Br$ (99% D) were obtained from Cambridge Isotope Laboratories. The esters of glycine and XCH_2CH_2OH were generated via two procedures: (i) Macroscale (gram quantities) of both esters were synthesized as their HCl salts via a reported literature procedure.[9a] The chloro ester HCl salt was recrystallized from methanol,[9a] the bromo ester HCl salt was recrystallized from ethanol.[9b] Both esters (HCl salts) gave ^1H NMR spectra similar to those reported in the literature.[9b] (ii) Microscale (milligram quantities) of the various glycine isotopomers of both esters were formed in situ by generating a 2 N alcoholic HCl solution using acetyl chloride and then adding this solution to the appropriate glycine isotopomer. This procedure is based upon that described by Knapp for methyl ester formation.[9c] Morpholinone was prepared from glycine and 2-chloroethanol via a literature procedure.[10a]

Morpholinone and the esters formed via both procedures were analyzed by isobutane chemical ionization: source temperature = 250 °C; electron energy = 70 eV; emission current = 0.75 mA; source pressure = 4×10^{-5} mBarr.

Computational Methods

Structures of ions and neutrals were optimized at the Hartree−Fock level using the GAMESS[11] program with the standard 6-31G* basis set.[12] All optimized structures were then subjected to frequency calculations with the same basis set, followed by a calculation of the correlated energy using the MP2(FC)/6-31G* level of theory (FC = frozen core). Energies are corrected for zero-point vibrations scaled by 0.9.[13] In each case, a set of possible rotamers was explored,[14] initially

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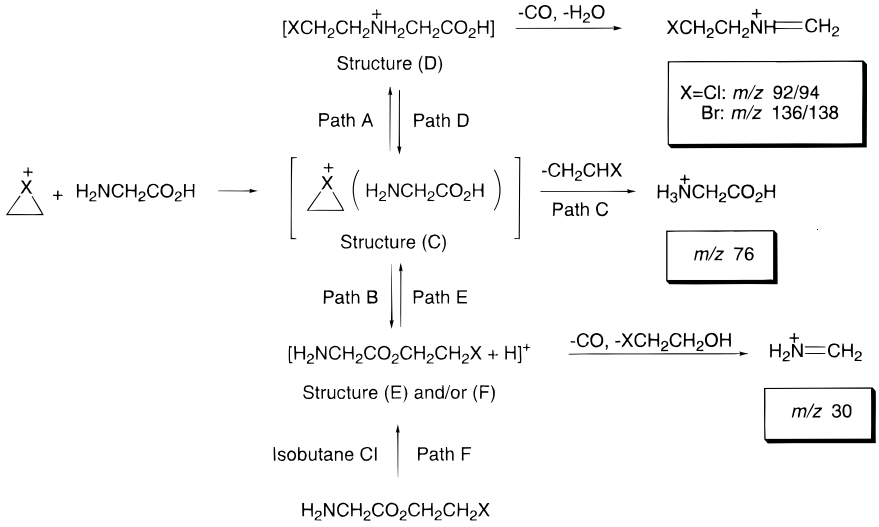
Scheme 2



at the AM1 level.[15] The AM1-optimized geometries were then resubmitted to HF/6-31G* optimizations.[14] Complete structural details and lists of vibrational frequencies for each HF/6-31G*-optimized structure can be found in the supporting information.

Results and Discussion

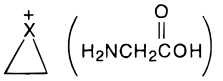
(A) CI MS Studies of the Gas Phase Reactions of $(CH_2)_2X^+$ (X=Cl and Br) with Glycine. The CI plasmas using either 1,2-dichloroethane or 1,2-dibromoethane as the CI gas give intense $(CH_2)_2X^+$ ions, with very few other ions present. This, together with the use of various isotopomers of glycine, makes assignment of the products formed upon introduction of glycine through the direct insertion probe relatively straightforward.

Reaction of glycine with the cyclic ethylenehalonium ions $(CH_2)_2X^+$ gives rise to the following: protonated glycine, $[M + H]^+$; the adducts $[M + C_2H_4X]^+$ together with their corresponding iminium ions $[M + C_2H_4X - CO - H_2O]^+$ and $CH_2{=}NH_2^+$ as well as minor peaks corresponding to $[M + C_2H_3]^+$ and $[M + C_2H_3 - CO - H_2O]^+$.[16] When X = Br, a $[M + Br]^+$ ion is also observed (eq 5). The assignment of this ion was confirmed by using

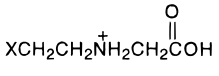
$$\triangleright Br^+ + H_2NCH_2CO_2H \longrightarrow [H_2NCH_2CO_2H + Br]^+ + C_2H_4 \quad (5)$$

a $BrCD_2CD_2Br$ CI plasma. Reaction 5 is directly analogous to the addition of nucleophiles to the sulfur atom of thiiranes, resulting in desulfurization.[17] Furthermore, transfer of X^+ in the gas phase has been observed for XNH_3^+ (X = Cl) and XCO^+ (X = Cl, Br).[18] A careful examination of the CI mass spectra reveals the formation of a number of secondary product ions. The most abundant is the $[2M + H]^+$ ion, while others correspond to ions with the formulas $[M + CH_2{=}NH_2]^+$ and $[M + CH]^+$.

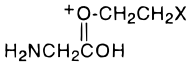
How are these products formed and what are their structures? A possible scheme for the reaction between $(CH_2)_2X^+$ and glycine, which accounts for some of these CI products, is shown in Scheme 2.[19] Initially, an ion−molecule complex **C** is formed, which can subsequently react to form the covalent adducts **D**−**F** (paths A and B) or via proton transfer (path C). On the basis of our previous studies on the $[M + CH_3]^+$ ions of glycine, we expect the order of the relative stabilities of these adducts to be **D** > **E** > **F**.[3a] Unlike our previous studies on the methylation of glycine (eqs 1 and 2) where the leaving group (CH_3Cl) carries away part of the energy of the reaction, thereby preventing isomerization of the different $[M + CH_3]^+$ adducts, the adducts formed via paths A and B in Scheme 2 should have sufficient energy to dissociate back to the ion−molecule complex **C** (via paths D and E), thereby offering a mechanism to isomerize the adducts. One way to test this hypothesis is to independently synthesize the proposed adducts (e.g., path F) and see if they isomerize.



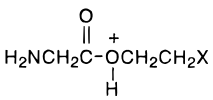
(C)



(D)



(E)



(F)

In order to answer these questions, the unimolecular fragmentation reactions of some of the source-generated CI product ions were studied in a series of MIKES experiments and are discussed in detail below (sections B and C).

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(19) A reviewer has suggested an alternative loss of HCO_2H from structure D in Scheme 2 rather than the shown combined losses of the elements of CO and H_2O. We cannot exclude this possibility since the neutral products are not analyzed in our experiments. For further discussions of these two alternative losses of [C, H_2, O_2] from protonated amino acids see: (a) Yalcin, T.; Khouw, C.; Csizmadia, I. G.; Peterson, M. R.; Harrison, A. G. *J. Am. Soc. Mass Spectrom.* **1995**, *6*, 1165. (b) Meot-Ner, M.; Field, F. H. *J. Am. Chem. Soc.* **1973**, *95*, 7207.

Table 1. MS/MS Spectra of the $[M + CH_2CH_2Cl]^+$ Ions of Glycine

precursor ion, *m/z*	unimolecular MIKE spectra [*m/z* (loss) abundance]
$[H_2NCH_2CO_2H + C_2H_4Cl]^+$, 138[a,b]	120 (H_2O) 13; 110 (CO) 32; 102 (HCl) 4; 92 (CH_2O_2) 100; 76 (C_2H_3Cl) 0.3; 74 (CHClO) 0.8; 63 ($C_2H_5NO_2$) 1.3; 56 (CH_3ClO_2) 0.6; 42 ($C_2H_5ClO_2$) 0.4; 30 ($C_3H_5ClO_2$) 2.6
$[H_2{}^{15}NCH_2CO_2H + C_2H_4Cl]^+$, 139[a,b]	121 (H_2O) 5; 111 (CO) 25; 103 (HCl) 2.5; 93 (CH_2O_2) 100; 77 (C_2H_3Cl) 0.8; 75 (CHClO) 2.5; 63 ($C_2H_5{}^{15}NO_2$) 1.9; 57 (CH_3ClO_2) 1.6; 43 ($C_2H_5ClO_2$) 1.3; 31 ($C_3H_5ClO_2$) 3.2
$[H_2NCD_2CO_2H + C_2H_4Cl]^+$, 140[a,b]	122 (H_2O) 2; 112 (CO) 28; 104 (HCl) 1.7; 94 (CH_2O_2) 100; 78 (C_2H_3Cl) 0.7; 76 (CHClO) 0.5; 63 ($C_2H_3D_2NO_2$) 0.9; 58 (CH_3ClO_2) 0.6; 44 ($C_2H_5ClO_2$) 0.2; 32 ($C_3H_5ClO_2$) 2.3
$[H_2NCH_2CO_2CH_2CH_2Cl + H]^+$, 138[b,c]	110 (CO) 100; 102 (HCl) 6; 92 (CH_2O_2) 0.8; 76 (C_2H_3Cl) 0.3; 74 (CHClO) 2; 63 ($C_2H_5NO_2$) 4; 49 ($C_3H_7NO_2$) 0.6; 42 ($C_2H_5ClO_2$) 0.8; 30 ($C_3H_5ClO_2$) 10
$[H_2NCH_2CO_2CH_2CH_2Cl + H]^+$, 138[b,d]	110 (CO) 100; 102 (HCl) 29; 92 (CH_2O_2) 1.9; 76 (C_2H_3Cl) 1.0; 74 (CHClO) 6.7; 63 ($C_2H_5NO_2$) 16; 49 ($C_3H_7NO_2$) 1.9; 42 ($C_2H_5ClO_2$) 2.2; 30 ($C_3H_5ClO_2$) 12
$[H_2{}^{15}NCH_2CO_2CH_2CH_2Cl + H]^+$, 139[b,d]	111 (CO) 100; 103 (HCl) 31; 92 (CH_2O_2) 1.9; 77 (C_2H_3Cl) 1.9; 75 (CHClO) 8.7; 63 ($C_2H_5{}^{15}NO_2$) 23; 49 ($C_3H_7{}^{15}NO_2$) 3.2; 42 ($C_2H_5ClO_2$) 3.9; 30 ($C_3H_5ClO_2$) 22
$[H_2NCD_2CO_2CH_2CH_2Cl + H]^+$, 140[b,d]	112 (CO) 100; 104 (HCl) 34; 94 (CH_2O_2) 2.2; 78 (C_2H_3Cl) 1.5; 75 (CHClO) 5.5; 63 ($C_2H_3D_2NO_2$) 65; 49 ($C_3H_5D_2NO_2$) 3.3; 44 ($C_2H_5ClO_2$) 4.8; 32 ($C_3H_5ClO_2$) 70

[a] Formed in the $ClCH_2CH_2Cl$ CI plasma reaction of glycine. [b] ^{35}Cl isotope was mass selected. [c] Isobutane CI analysis of the recrystallized HCl salt of the ester. [d] Isobutane CI analysis of an aliquot of the in situ generated ester.

Table 2. MS/MS Spectra of the $[M + CH_2CH_2Br]^+$ Ions of Glycine

precursor ion, *m/z*	unimolecular MIKE spectra [*m/z* (loss) abundance]
$[H_2NCH_2CO_2H + C_2H_4Br]^+$, 182[a,c]	164 (H_2O) 0.7; 154 (CO) 8; 136 (CH_2O_2) 100; 107 ($C_2H_5NO_2$) 5.7; 102 (HBr) 1.1; 93 ($C_3H_7NO_2$) 0.6; 79 ($C_4H_9NO_2$) 0.3; 74 (CHBrO) 0.7; 58 (C_2H_5BrO) 0.3; 56 (CH_3BrO_2) 0.4; 42 ($C_2H_5BrO_2$) 0.3; 30 ($C_3H_5BrO_2$) 0.6
$[H_2{}^{15}NCH_2CO_2H + C_2H_4Br]^+$, 183[a,c]	165 (H_2O) 0.7; 155 (CO) 7; 137 (CH_2O_2) 100; 107 ($C_2H_5{}^{15}NO_2$) 3.8; 103 (HBr) 0.7; 93 ($C_3H_7{}^{15}NO_2$) 0.5; 79 ($C_4H_9{}^{15}NO_2$) 0.2; 75 (CHBrO) 0.5; 59 (C_2H_5BrO) 0.1; 57 (CH_3BrO_2) 0.2; 43 ($C_2H_5BrO_2$) 0.1; 31 ($C_3H_5BrO_2$) 0.4
$[H_2NCD_2CO_2H + C_2H_4Br]^+$, 184[b,c]	166 (H_2O) 1.0; 156 (CO) 8; 138 (CH_2O_2) 100; 107 ($C_2H_3D_2NO_2$) 2.2; 104 (HBr) 0.2; 93 ($C_3H_5D_2NO_2$) 0.2; 79 ($C_4H_7D_2NO_2$) 0.3; 76 (CHBrO) 0.2; 60 (C_2H_5BrO) 0.1*; 58 (CH_3BrO_2) 0.1*; 44 ($C_2H_5BrO_2$) 0.2; 32 ($C_3H_5BrO_2$) 0.3
$[H_2NCH_2CO_2CH_2CH_2Br + H]^+$, 182[c,d]	154 (CO) 100; 136 (CH_2O_2) 53; 107 ($C_2H_5NO_2$) 15; 102 (HBr) 3; 93 ($C_3H_7NO_2$) 2.1; 79 ($C_4H_9NO_2$) 0.8; 74 (CHBrO) 1.3; 58 (C_2H_5BrO) 0.2*; 56 (CH_3BrO_2) 0.2*; 42 ($C_2H_5BrO_2$) 0.4; 30 ($C_3H_5BrO_2$) 3
$[H_2NCH_2CO_2CH_2CH_2Br + H]^+$, 182[c,e]	154 (CO) 100; 136 (CH_2O_2) 87; 107 ($C_2H_5NO_2$) 72; 102 (HBr) 15; 93 ($C_3H_7NO_2$) 9.3; 79 ($C_4H_9NO_2$) 3.6; 74 (CHBrO) 6.5; 58 (C_2H_5BrO) 1.3*; 56 (CH_3BrO_2) 1.3*; 42 ($C_2H_5BrO_2$) 2.0; 30 ($C_3H_5BrO_2$) 6.1
$[H_2{}^{15}NCH_2CO_2CH_2CH_2Br + H]^+$, 183[c,e]	155 (CO) 100; 137 (CH_2O_2) 93; 107 ($C_2H_5{}^{15}NO_2$) 80; 103 (HBr) 15; 93 ($C_3H_7{}^{15}NO_2$) 9.5; 79 ($C_4H_9{}^{15}NO_2$) 3.6; 75 (CHBrO) 6.2; 59 (C_2H_5BrO) 0.8*; 57 (CH_3BrO_2) 0.8*; 43 ($C_2H_5BrO_2$) 1.8; 31 ($C_3H_5BrO_2$) 9.5
$[H_2NCD_2CO_2CH_2CH_2Br + H]^+$, 184[c,e]	156 (CO) 100; 138 (CH_2O_2) 85; 107 ($C_2H_3D_2NO_2$) 71; 104 (HBr) 15; 93 ($C_3H_5D_2NO_2$) 9.2; 79 ($C_4H_7D_2NO_2$) 3.6; 76 (CHBrO) 3.4; 60 (C_2H_5BrO) 0.3*; 58 (CH_3BrO_2) 0.3*; 44 ($C_2H_5BrO_2$) 1.9; 32 ($C_3H_5BrO_2$) 9.5

[a] Formed in the $BrCH_2CH_2Br$ CI plasma 1. [b] Formed in the $BrCH_2CH_2Br$ CI plasma 2. [c] ^{79}Br isotope was mass selected. [d] Isobutane CI analysis of the recrystallized HCl salt of the ester. [e] Isobutane CI analysis of an aliquot of the in situ generated ester. *peak is broad and poorly resolved.

(B) MS/MS Studies of the $[M + C_2H_4X]^+$, $[M + C_2H_3]^+$, and $[M + Br]^+$ Product Ions. (i) Structure of the $[M + C_2H_4X]^+$ Ions. The MIKE spectra of the $[M + C_2H_4Cl]^+$ ions are listed in Table 1. The base peak in the MIKE spectrum of $[M + C_2H_4Cl]^+$ is due to the formation of an iminium ion $CH_2{=}NHC_2H_4Cl^+$ via loss of the elements of CO and H_2O. The next largest peak is due to loss of CO. Another iminium ion ($CH_2{=}NH_2^+$), formed via the loss of CO and $ClCH_2CH_2OH$, is weak by comparison. The losses of H_2O, HCl, HCl + CO, and HCl + CO + H_2O and the formation of $H_3NCH_2CO_2H^+$, $[H_4,C_2,N]^+$, $C_2H_4Cl^+$, and CH_2Cl^+ ions represent minor channels in comparison. The latter ion is a fragment of $C_2H_4Cl^+$.[20] A similar series of fragment ions are observed for the MIKE spectra of the $[M + C_2H_4Br]^+$ ions (Table 2). In addition, a minor channel involving the formation of Br^+ is observed. The loss of mass 28 could correspond to either a loss of CO or C_2H_4. Since these two losses cannot be distinguished under the low resolution of the daughter ions for the MS/MS conditions used, the related $[M + C_2D_4Br]^+$ ions were formed in a $BrCD_2CD_2Br$ CI plasma. The MS/MS spectrum (CID in the RF only quadrupole) of the ^{15}N glycine $[M + C_2D_4Br]^+$ ion (*m/z* 187) is shown in Figure 1. Both losses of CO (to form an ion at *m/z* 159) and C_2D_4 (to form an ion at *m/z* 155) are observed. The latter result confirms that the $[M + Br]^+$ ions are formed via eq 5.

Results from the isotopically labeled experiments using $H_2NCD_2CO_2H$ and $H_2{}^{15}NCH_2CO_2H$ confirm the assignments described above and indicate that the two iminium ions are formed from at least two different $[M + C_2H_4X]^+$ precursor ions, in direct analogy to our previous results on the methylation of glycine.[3a] The formation of $CH_2{=}NHC_2H_4X^+$ is indicative of alkylation on nitrogen to form an ion of structure **D**, while the formation of $CH_2{=}NH_2^+$ is indicative of alkylation on oxygen to form an ion(s) of structure **E** and/or **F**. The ratio of the $CH_2{=}NHC_2H_4X^+$ to $CH_2{=}NH_2^+$ ions is approximately 38:1 when X = Cl and 166:1 when X = Br.[21]

In contrast to our previous studies on the methylation of glycine, there is a possibility that the $[M + C_2H_4X]^+$ adduct ions can undergo the isomerization reactions shown in Scheme 2. To investigate this possibility, the fragmentation reactions of the $[M + H]^+$ ion of the glycine esters ($H_2NCH_2CO_2CH_2CH_2X$) were investigated (see Table 1 for X = Cl and Table 2 for X = Br).[22] Under unimolecular MIKE conditions, these $[M + H]^+$ ions undergo similar losses to the $[M + C_2H_4X]^+$ ions described above. Particularly noteworthy is the observation of both $C_2H_4X^+$ and $H_3NCH_2CO_2H^+$ ions. For X = Cl, the ratio of the $CH_2{=}NHC_2H_4Cl^+$ to $CH_2{=}NH_2^+$ ions is

(20) Monstrey, J.; Van de Sande, C. C.; Levsen, K.; Heimbach, H.; Borchers, F., *J. Chem. Soc., Chem. Commun.* **1978**, 796.

(21) We recognize that these ratios should only be used in a qualitative sense since they are likely to depend on the internal energy content of the source-generated ions (see ref 2).

(22) We were unable to examine the fragmentation reactions of the $[M + H]^+$ ions of the β-halo-*N*-ethylglycine species ($XCH_2CH_2NHCH_2CO_2H$ where X = Cl, Br) since there is no reported procedure for their synthesis in the literature.

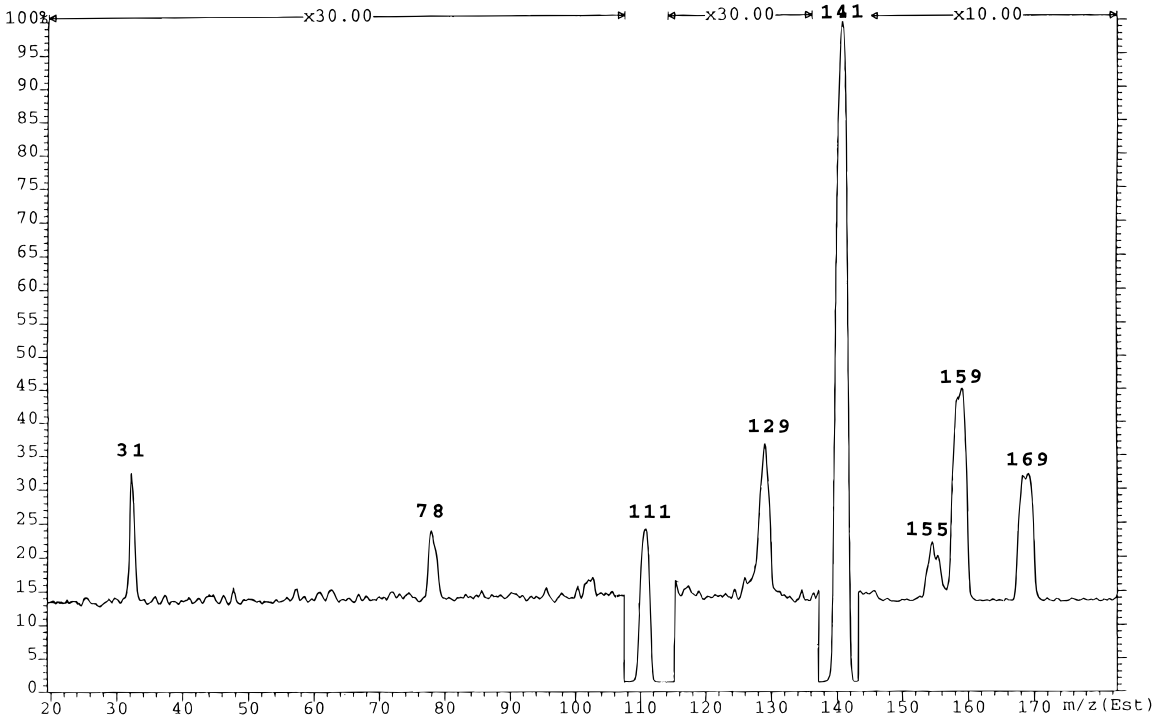


Figure 1. CID spectrum of the $[M + CD_2CD_2Br]^+$ ion of the ^{15}N isotopomer of glycine.

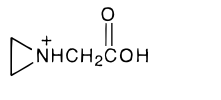
Table 3. MS/MS Spectra of the $[M + C_2H_3]^+$ Ions of Glycine

precursor ion, *m/z*	unimolecular MIKE spectra [*m/z* (loss) abundance]
$[H_2NCH_2CO_2H + C_2H_3]^+$, 102[a]	84 (H_2O) 53; 74 (CO) 100; 56 (CH_2O_2) 67; 45 (C_3H_7N) 0.4; 42 ($C_2H_4O_2$) 3; 30 ($C_3H_4O_2$) 17; 28 ($C_3H_6O_2$) 1.9
$[H_2{}^{15}NCH_2CO_2H + C_2H_3]^+$, 103[a]	85 (H_2O) 76; 75 (CO) 100; 57 (CH_2O_2) 68; 45 ($C_3H_7{}^{15}N$) 1.2; 43 ($C_2H_4O_2$) 2; 31 ($C_3H_4O_2$) 23; 29 ($C_3H_6O_2$) 1.2
$[H_2NCD_2CO_2H + C_2H_3]^+$, 104[a]	86 (H_2O) 29; 76 (CO) 100; 58 (CH_2O_2) 94; 45 ($C_3H_5D_2N$) 3.4; 44 ($C_2H_4O_2$) 6; 32 ($C_3H_4O_2$) 15; 30 ($C_3H_6O_2$) 2.1
$[H_2NCH_2CO_2H + C_2H_3]^+$, 102[b]	84 (H_2O) 30; 74 (CO) 36; 56 (CH_2O_2) 100; 45 (C_3H_7N) 6; 42 ($C_2H_4O_2$) 9; 30 ($C_3H_4O_2$) 4; 28 ($C_3H_6O_2$) 7
$[H_2{}^{15}NCH_2CO_2H + C_2H_3]^+$, 103[b]	85 (H_2O) 43; 75 (CO) 74; 57 (CH_2O_2) 100; 45 ($C_3H_7{}^{15}N$) 4; 43 ($C_2H_4O_2$) 4; 31 ($C_3H_4O_2$) 4; 29 ($C_3H_6O_2$) 3
$[H_2NCD_2CO_2H + C_2H_3]^+$, 104[c]	86 (H_2O) 48; 76 (CO) 100; 58 (CH_2O_2) 56; 45 ($C_3H_5D_2N$) 2; 44 ($C_2H_4O_2$) 3; 32 ($C_3H_4O_2$) 5; 30 ($C_3H_6O_2$) 4
$[CH_3CH{=}NHCH_2CO_2H]^+$, 102[d]	84 (H_2O) 53; 74 (CO) 20; 56 (CH_2O_2) 100; 45 (C_3H_7N) 8; 42 ($C_2H_4O_2$) 13; 30 ($C_3H_4O_2$) 3; 28 ($C_3H_6O_2$) 8
$[CH_3CH{=}{}^{15}NHCH_2CO_2H]^+$, 103[d]	85 (H_2O) 84; 75 (CO) 36; 57 (CH_2O_2) 100; 45 ($C_3H_7{}^{15}N$) 21; 43 ($C_2H_4O_2$) 16; 31 ($C_3H_4O_2$) 5; 29 ($C_3H_6O_2$) 9
$[CH_3CH{=}NHCD_2CO_2H]^+$, 104[d]	86 (H_2O) 95; 76 (CO) 36; 58 (CH_2O_2) 100; 45 ($C_3H_5D_2N$) 11; 44 ($C_2H_4O_2$) 14; 32 ($C_3H_4O_2$) 3; 30 ($C_3H_6O_2$) 3
protonated 2-morpholinone, 102[e]	84 (H_2O) 28; 74 (CO) 30; 56 (CH_2O_2) 100; 45 (C_3H_7N) 3.5; 42 ($C_2H_4O_2$) 6; 30 ($C_3H_4O_2$) 3; 28 ($C_3H_6O_2$) 4

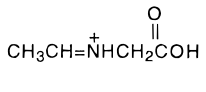
[a] Formed in the $ClCH_2CH_2Cl$ CI plasma. [b] Formed in the $BrCH_2CH_2Br$ CI plasma 1. [c] Formed in the $BrCH_2CH_2Br$ CI plasma 2. [d] Isobutane CI analysis of an aliquot of the acid catalysed condensed phase reaction of glycine and acetaldehyde. [e] Isobutane CI analysis of 2-morpholinone.

approximately 1:8.[21] In contrast, when X = Br, the ratio of the $CH_2{=}NHC_2H_4Br^+$ to $CH_2{=}NH_2^+$ ions is approximately 16:1.[21] These observations are readily explained by the neighboring-group-initiated isomerization mechanism shown in Scheme 2, which results in the formation of the ion−molecule complex **C**.[23] Furthermore, this isomerization is greatest when X = Br, consistent with the greater effectiveness of Br as a neighboring group.[24]

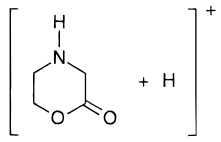
(ii) Structure of the $[M + C_2H_3]^+$ Ions. The MIKE spectra of source-generated $[M + C_2H_3]^+$ ions are listed in Table 3. A number of different structures are possible for the $[M + C_2H_3]^+$ ions, including structures **G**−**J**. In order to establish the structure of these ions, we have (i) assessed the thermodynamics for the formation of structures **G**−**J** from glycine and the cyclic ethylenechlorinium ion through the use of *ab initio* calculations and (ii) independently generated $[M + C_2H_3]^+$ ions via protonation of the neutral precursors to structures **H** and **I** and studied their MS/MS spectra (Table 3).[25,26]



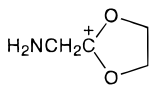
(G)



(H)



(I)



(J)

The most stable conformations for each of the ions are shown in Figure 2, while the energetics associated with

(23) For an excellent review of ion−molecule complexes (sometimes called ion−neutral complexes) in the gas phase (including their role in isomerization reactions) see: Bowen, R. D. *Acc. Chem. Res.* **1991**, *24*, 364.

(24) (a) March, J. *Advanced Organic Chemistry*, 4th ed.; Wiley: New York, 1992; pp 308−312. (b) Angelini, G.; Speranza, M. *J. Am. Chem. Soc.* **1981**, *103*, 3792.

(25) The MS/MS spectra of ions of structures **G** and **J** were not studied since there are no literature syntheses of the neutral precursors to **G** or **J**.

(26) We were very concerned about "memory effects" in our CI source. Thus, the experiments involving the $[M + C_2H_3]^+$ ions formed via four different methods were studied on four different days. The CI source was cleaned between each of these different runs. The MIKE spectra of the $[M + C_2H_3]^+$ ions formed via the reactions between glycine and the $BrCH_2CH_2Br$ plasma were studied on two different occasions (separated by about 6 months) and gave reproducible results.

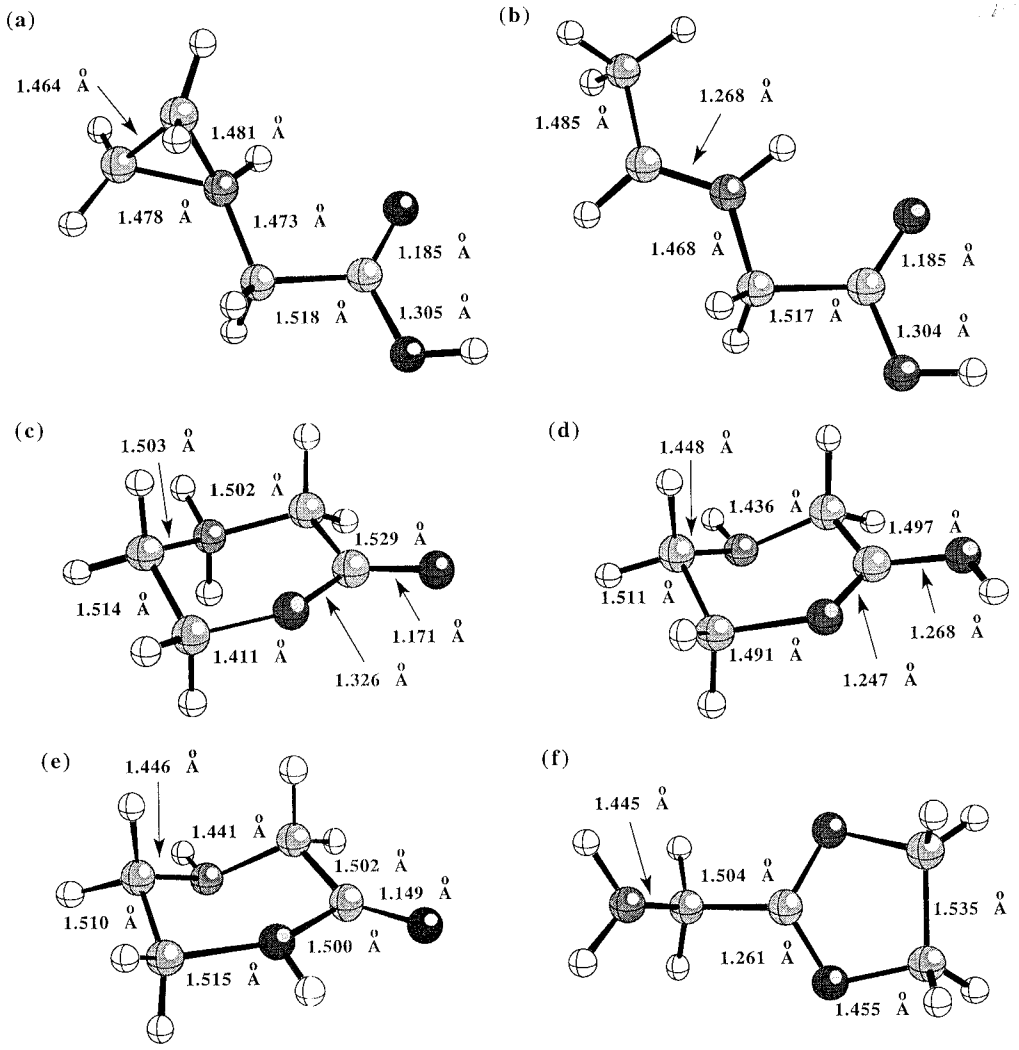


Figure 2. HF/6-31G*-optimized structures of (a) aziridinium ion **G**; (b) immonium ion **H**; (c) N-protonated morpholinone **I-N**; (d) CO-protonated morpholinone **I-CO**; (e) O-protonated morpholinone **I-O**; (f) **J**.

Table 4. Energies Associated with the Formation of $[M + C_2H_3]^+$ Ions in the Reaction of $H_2NCH_2CO_2H$ and Cyclic $CH_2CH_2Cl^+$

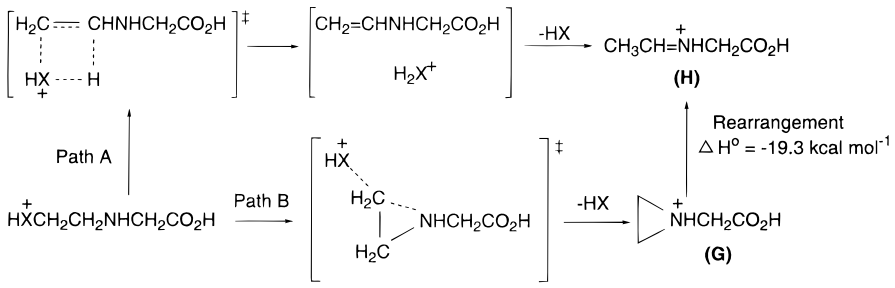
	energies[a] (Hartrees)		
species	HF/6-31G*	MP2(FC)/ 6-31G*	ZPE[b]
cyclic $(CH_2)_2Cl^+$	−537.212 00	−537.590 43	0.053 60
cyclic $(CH_2)_2NH_2^+$	−133.407 95	−133.820 30	0.082 03
NH_3	−56.184 36	−56.353 71	0.033 30
HCl	−460.059 98	−460.192 24	0.006 53
$H_2NCH_2CO_2H$[c]	−282.831 10	−283.599 56	0.078 00
G, $(CH_2)_2NHCH_2CO_2H^+$[d]	−360.060 80	−361.075 25	0.124 52
H, $CH_3CH{=}NHCH_2CO_2H^+$[e]	−360.097 02	−361.103 68	0.122 15
I-N, N-protonated 2-morpholinone[f]	−360.063 41	−361.078 62	0.127 52
I-CO, CO-protonated 2-morpholinone[g]	−360.060 82	−361.065 17	0.125 47
I-O, O-protonated 2-morpholinone[h]	−360.020 39	−361.035 18	0.123 94
J[i]	−360.059 65	−361.061 73	0.124 81

[a] All calculations were carried out on the HF/6-31G* optimized geometries. [b] Scaled by 0.9. [c] From ref 3. [d] See Figure 2a for geometry. [e] See Figure 2b for geometry. [f] See Figure 2c for geometry. [g] See Figure 2d for geometry. [h] See Figure 2e for geometry. [i] See Figure 2f for geometry.

their formation are listed in Table 4. For **I**, protonation at all three sites was considered. A total of 5, 9, 1, 4, 2, and 2 unique conformations were found for the species **G**, **H**, N-protonated **I-N**, CO-protonated **I-CO**, O-protonated **I-O**, and **J** at the HF/6-31G* level of theory (Appendices 2 and 3, supporting information). To establish the reliability of these calculations for predicting energetics, we have also calculated the structures and energies of the reactants and products of eq 4. The MP2/6-31G*//HF/6-31G* level of theory (Table 4) predicts that this reaction is 41.9 kcal mol^{-1} exothermic, in good agreement with the experimental value of −42.5 kcal mol^{-1}.[8a] At the MP2/6-31G*//HF/6-31G* level of theory, the order of stabilities for the various $[M + C_2H_3]^+$ ions is **H** > **I-N** > **G** > **I-CO** > **J** > **I-O**. Furthermore, formation of each of these $[M + C_2H_3]^+$ ions from glycine + cyclic $(CH_2)_2Cl^+$ is predicted to be thermodynamically viable.

The MS/MS spectra of the $[M + C_2H_3]^+$ ions formed via the reaction of cyclic ethylenehalonium ions are very similar to the $[M + H]^+$ ions formed via protonation of the neutral precursors to **H** and **I**. The most reasonable explanation to account for these facts is that the structure of this $[M + C_2H_3]^+$ ion is that of $CH_3CH{=}NHCH_2CO_2H^+$ and that the independently formed **I** ions undergo rearrangement to **H** ions.[26] Firstly, $CH_3CH{=}NHCH_2X\text{-}CO_2H^+$ undergoes a series of fragmentation reactions similar to those of its lower homologue, $CH_2{=}NHCH_2X\text{-}CO_2H^+$, an ion whose fragmentation reaction mechanisms were previously discussed in detail.[3a] Secondly, although there are several possible mechanisms for the formation

Scheme 3



of this $CH_3CH{=}NHCH_2CO_2H^+$ ion in the reaction of glycine with the cyclic ethylenehalonium ions, it is clear that at some stage migration of a hydrogen atom occurs. On the basis of Nibbering's related mechanisms for the loss of water from protonated β-haloethanols, either of the two mechanisms outlined in Scheme 3 seems most likely.[27,28] Path A involves a concerted 1,2-elimination of H_2X^+, resulting in the formation of an ion−molecule complex between H_2X^+ and the enamine $CH_2{=}CHNHCH_2XCO_2H$, which then undergoes proton transfer with concomitant loss of HX to form the observed product. A neighboring-group-initiated mechanism operates in path B, resulting in the formation of the intermediate aziridinium ion **G**, which subsequently undergoes rearrangement to form the more stable iminium ion **H**. We prefer path B, since such a mechanism is consistent with (i) that proposed by Berman et al. for the analogous reaction (eq 4) and (ii) experimental and *ab initio* studies of the parent $C_2H_6N^+$ system, which has been shown to undergo rearrangement.[8a,29] Finally, the independently generated **I** ions could isomerize via **G** to **H**, as shown in Scheme 4. It should be noted that the *ab initio* calculations predict that there is a favorable thermodynamic driving force for each of the steps: **I-O** → **G**; **I-CO** → **G**, and **G** → **H**.

(iii) Structure of the [M + Br]$^+$ Ions. The MIKE spectra of source-generated $[M + Br]^+$ ions are listed in Table 5. These ions fragment to form Br^+. They also lose H_2O, CO, the combined elements of H_2O and CO, and the combined elements of HOBr and CO. The last two fragmentations correspond to the formation of the iminium ions $CH_2{=}NHBr^+$ and $CH_2{=}NH_2^+$ and are consistent with initial attachment of Br^+ onto both nitrogen and to a lesser extent oxygen.[3a]

(C) MS/MS Studies of the [M + $CH_2{=}NH_2$]$^+$ and [M + CH]$^+$ Product Ions. We were interested in probing the structure of the $[M + CH_2{=}NH_2]^+$ product ion, since iminium ions are potential alkylation agents.[30] A number of structures are possible, including the proton bound dimer **K** and the covalent adduct **L**.[31] Structure **K** should dissociate to $CH_2{=}NH_2^+$ and $[H_3NCH_2CO_2H]^+$. According to Cook's kinetic method,[32] the relative ratio

Scheme 4

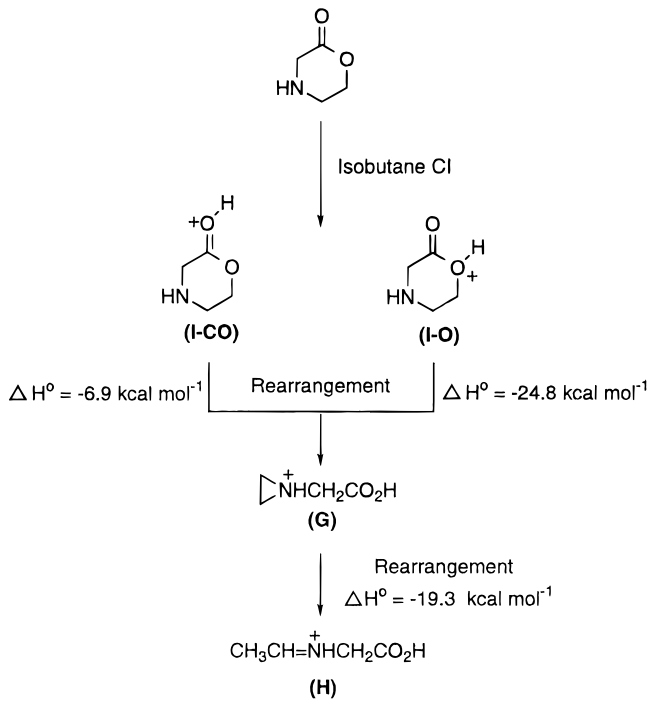


Table 5. MS/MS Spectra of the [M + Br]$^+$ Ions of Glycine Formed in the $BrCH_2CH_2Br$ CI Plasma

precursor ion, *m/z*	unimolecular MIKE spectra [*m/z* (loss) abundance]
$[H_2NCH_2CO_2H + Br]^+$, 154[b]	136 (H_2O) 22; 126 (CO) 100; 108 (CH_2O_2) 80; 79 ($C_2H_5NO_2$) 8; 30 (CHO_2Br) 4
$[H_2{}^{15}NCH_2CO_2H + Br]^+$, 155[b]	137 (H_2O) 14; 127 (CO) 100; 109 (CH_2O_2) 83; 79 ($C_2H_5{}^{15}NO_2$) 12; 31 (CHO_2Br) 5
$[H_2NCD_2CO_2H + Br]^+$, 156[b]	138 (H_2O) 42; 128 (CO) 100; 110 (CH_2O_2) 72; 79 ($C_2H_3D_2NO_2$) 48; 32 (CHO_2Br) 4

of these two product ions should be related to the relative proton affinities (PAs) of $CH_2{=}NH$ (PA = 204.1 kcal mol^{-1})[33] and $H_2NCH_2CO_2H$ (PA = 211.6 kcal mol^{-1}).[34] The spectrum shown in Figure 3 reveals three fragmentation channels for the $[M + CH_2{=}NH_2]^+$ ion of glycine: loss of H_3N, loss of $CH_2{=}NH$, and loss of $H_2NCH_2CO_2H$. These losses were confirmed by the labeling experiments listed in Table 6. The losses of $CH_2{=}NH$ and $H_2NCH_2CO_2H$ are entirely consistent with the proton bound dimer **K** and with the relative PAs of $CH_2{=}NH$ and H_2NCH_2-CO_2H. The other reaction channel suggests the formation of a covalent structure **L**, which decomposes via loss

(27) Heck, A. J. R.; de Koning, L. J.; Nibbering, N. M. M. *Org. Mass Spectrom.* **1993**, *28*, 245.

(28) We cannot totally rule out the possibility that the cyclic ethylene halonium ions undergo partial rearrangement to form $CH_3CH{=}X^+$ ions which then react with glycine to form the $CH_3CH{=}NHCH_2CO_2H^+$ ions.

(29) See: Barone, V.; Lelj, F.; Grande, P.; Russo, N.; Toscano, M. *Chem. Phys. Lett.* **1987**, *133*, 548 and references therein.

(30) Olah, G. A.; Donovan, D. J.; Keefer, L. K. *J. Nat. Cancer. Inst.* **1975**, *54*, 465.

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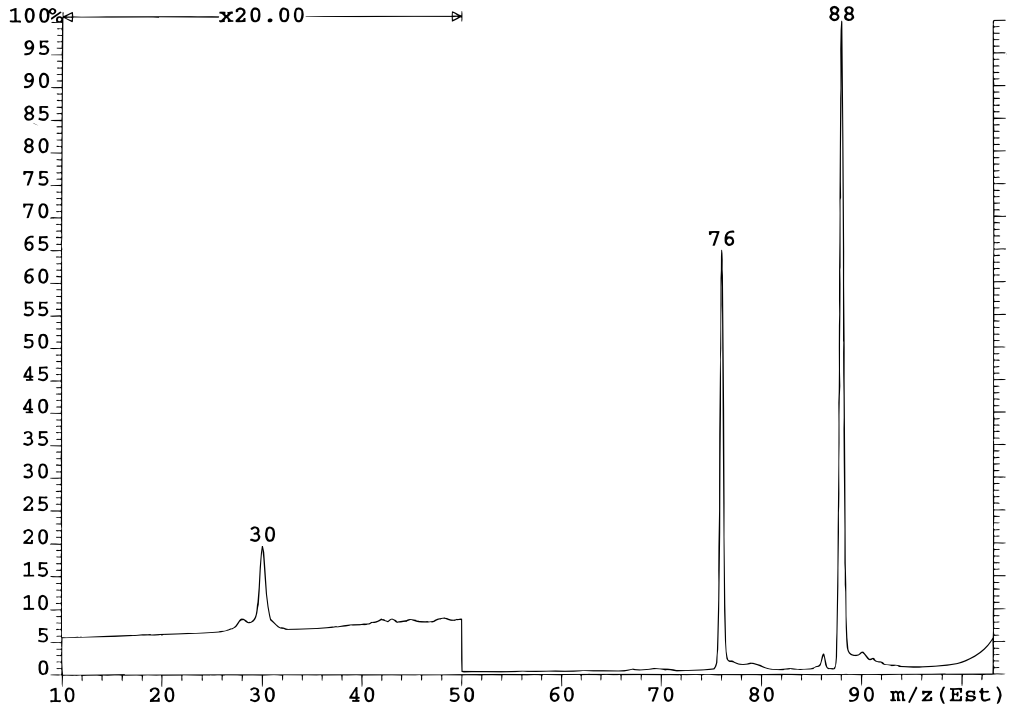
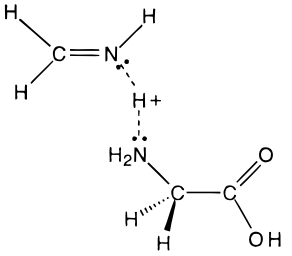
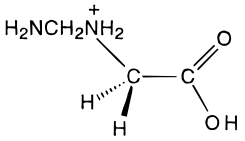


Figure 3. Unimolecular MIKE spectrum of the $[M + CH_2{=}NH_2]^+$ ion of glycine formed in the $ClCH_2CH_2Cl$ CI plasma.

of NH_3 to form an iminium ion, in direct analogy to eq 3.[3a] This was confirmed by performing MS/MS studies on this $[M + CH]^+$ product ion generated in the source (Table 6). The same product ions were observed for this $[M + CH]^+$ as observed previously for authentic $CH_2{=}NHCH_2CO_2H^+$,[3a] thereby confirming the structural assignment. Interestingly, this is an example of a small but growing number of cases where noncovalent and covalent adducts of the same reactants may coexist or form alternatively, depending on the conditions.[35,36]



(K)



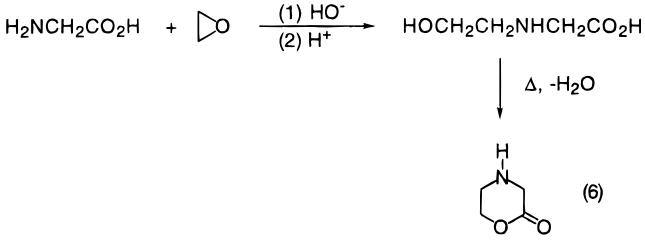
(L)

How do our gas phase studies compare with solution? Although cyclic ethylenehalonium ions have been observed in solution, their reactions with amino acids have not been studied.[37] Analogous reactions between the isoelectronic epoxides and amino acids in solution have, however, been shown to form *N*-(2-hydroxyalkyl)amino acids under basic conditions, which subsequently undergo dehydration reactions (eq 6).[10] Furthermore, a related Br^+ transfer from *N*-bromosuccinimide to the nitrogen atom of glycine (cf. eq 5) has recently been reported.[38]

Table 6. MS/MS Spectra of the $[M + CH_2{=}NH_2]^+$ and $[M + CH]^+$ Ions of Glycine

precursor ion, *m/z*	unimolecular MIKE spectra [*m/z* (loss) abundance]
$[H_2{}^{15}NCH_2CO_2H + CH_2{=}{}^{15}NH_2]^+$ 107[a]	89 ($H_3{}^{15}N$) 100; 77 ($CH_3{}^{15}N$) 72; 31 ($C_2H_5{}^{15}NO_2$) 0.6
$[H_2NCD_2CO_2H + CD_2{=}NH_2]^+$, 109[a]	92 (H_3N) 91; 78 (CHD_2N) 100; 32 ($C_2H_5NO_2$) 2.4
$[H_2NCH_2CO_2H + CH_2{=}NH_2]^+$, 105[b]	88 (H_3N) 100; 76 (CH_3N) 74; 30 ($C_2H_5NO_2$) 1.6
$[H_2NCH_2CO_2H + CH]^+$, 88[b]	70 (H_2O) 100; 60 (CO) 3.8; 44 (CO_2) 15; 42 (CH_2O_2) 2.2; 28 ($C_2H_4O_2$) 0.3
$[H_2{}^{15}NCH_2CO_2H + CH]^+$, 89[b]	71 (H_2O) 100; 61 (CO) 1.1; 45 (CO_2) 2.3; 43 (CH_2O_2) 1.0; 29 ($C_2H_4O_2$) 0.2
$[H_2NCD_2CO_2H + CD_2NH_2 - NH_3]^+$, 92[b]	74 (H_2O) 7; 64 (CO) 42; 48 (CO_2) 1.0; 46 (CH_2O_2) 100; 30 ($C_2H_2D_2O_2$) 0.8

[a] Formed in the $ClCH_2CH_2Cl$ CI plasma. [b] Formed in the $BrCH_2CH_2Br$ CI plasma.



(6)

Conclusions

From this and our previous study,[3a] certain trends are emerging in the gas phase electrophilic modification of glycine: (i) the most nucleophilic site is nitrogen, although attack by the electrophile onto oxygen occurs for

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CH_3^+ (using the $(CH_3)_2Cl^+$ reagent ion), the cyclic ethylenehalonium ions ($(CH_2)_2X^+$ where X = Br and Cl) and Br^+ (using the $(CH_2)_2Br^+$ reagent ion); (ii) isomerization between N-alkylated and O-alkylated products does not occur when the exothermicity of the original addition reaction is dissipated by a leaving group (e.g., methylation by $(CH_3)_2Cl^+$); (iii) isomerization between N-alkylated and O-alkylated products can occur when the exothermicity of the original addition reaction is not dissipated by a leaving group (e.g., alkylation by the cyclic ethylenehalonium ions); (iv) structurally similar electrophiles can give the same ionic product (e.g., the ions $CH_2{=}X^+$, where X = OCH_3 and NH_2, both give the imminium ion $CH_2{=}NHCH_2CO_2H^+$ via addition at nitrogen followed by elimination of HX). Our results once again emphasize the importance of using isotopically labeled glycine in conjunction with tandem mass spectrometry to establish the modes of reactivity in rather complex CI plasmas where even secondary reactions can be observed. Preliminary results on the gas phase reaction of NO^+ with glycine reveal a novel additional channel involving abstraction of a hydride ion from the CH_2 group. These and other reactions of a range of electrophiles with various biomolecules will be reported in due course.

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Supporting Information Available: Listing of source CI mass spectra (Appendix 1) and optimized geometries in the form of Cartesian coordinates and vibrational frequencies of all structures at the HF/6-31G* level (Appendix 2) together with their energies (Appendix 3) (37 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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