Table IV. Asymmetric Oxidative Cyclization of 1 Catalyzed by Complex 2 with t-BuOOH in Benzene

substrate, X	time,[b] h	cyclized products: yield,[c] %	product ratio 3/4	$[\alpha]_D$ of 3,[d] deg (c, CCl_4)	ee, %
1b, Me	70	67	58/42	+6.87 (7.56)	21
1c, 4-H	59	75	58/42	+4.48 (3.03)	18
1d, 4-Cl	151	81	76/24	+5.53 (7.96)	7.4

[a] The reaction conditions are shown in the text. [b] Reaction time required for >98% completion. [c] Determined by GLC using n-pentadecane as an internal standard. [d] Measured at 25-29 °C.

acetate (4.64 g, 13.8 mmol), palladium acetate (3.10 g, 13.8 mmol), and acetonitrile (35 mL) was stirred at room temperature for 1 h. To this mixture was added (-)-β-pinene (6 mL, 37.8 mmol), and stirring was continued for 1.5 h. After the resulting metallic palladium was filtered off, a small spatulaful of phenylmercuric acetate was added to the filtrate, and the mixture was left overnight at room temperature. Metallic palladium further precipitated was filtered again, and the filtrate was diluted with ether, washed with brine and 10% aqueous solution of $NaHCO_3$, and dried over $MgSO_4$. Removal of ether followed by column chromatography on Al_2O_3 with n-pentane as the eluent gave a yellow solution. From the solution [(3,2,10-η^3-pinene)PdCl]$_2$ (1.22 g, 32%) was precipitated as yellow crystals. After collection of the crystals, the filtrate was distilled at 82-85 °C (1.5 mmHg) to give a 7:8 mixture of 2-benzylidene-6,6-dimethylbicyclo[3.1.1]heptane (15) and 2-benzyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (16) (0.860 g, 29%). The spectral properties of 15 and 16 are in good agreement with the published data.[19]

The title complex 14 was then prepared from the above mixture according to the method of Trost et al.[20] To glacial acetic acid (80 mL) and acetic anhydride (3 mL) were added sodium acetate (4.80 g, 58 mmol), sodium chloride (3.36 g, 56 mmol), cupric acetate (3.68 g, 20 mmol), and then palladium chloride (0.80 g, 4.5 mmol) in that order. The mixture was heated at 95 °C for 3 h and cooled to 60 °C. The above mixture of 15 and 16 (0.850 g, 4.0 mmol) in glacial acetic acid (5 mL) was then added in one portion, and the solution was stirred at 60 °C for 24 h. The solution was cooled, filtered, poured into water, and extracted with benzene. The organic layer was washed with water, saturated aqueous solution of $NaHCO_3$ and brine and dried over $MgSO_4$. Removal of ether followed by column chromatography on SiO_2 with chloroform as the eluent gave yellow crystals. Recrystallization from chloroform-n-pentane gave the pure compound 14 (0.090 g, 6.3%): mp 181-183 °C dec; $[\alpha]^{27}_D$ +9.96° (c 1.00, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 1.22 (s, Me), 1.40 (s, Me) 2.10 (m, 2 H), 2.52 (br s, 1 H), 3.30 (m, 2 H), 3.78 (br s, 1 H, C_{10}-H), 7.21 (s, 5 H, Ph). Anal. Calcd for $C_{32}H_{38}Cl_2Pd_2$: C, 54.41; H, 5.42. Found: C, 54.15; H, 5.29.

Catalytic Cyclization of 2c (X = H) Using Complex 9 in the O_2-Cu(OAc)$_2$ System. The chloride complex 14 was converted into the acetate complex 9 by treatment with AgOAc. Thus, a mixture of the chloride complex 14 (0.080 g, 0.113 mmol as a dimer) and AgOAc (0.038 g, 0.226 mmol) in chloroform (5 mL) was stirred for 30 min in the dark. After the resulting AgCl was filtered off, the solution was passed through a short column of SiO_2. A yellow solution eluted with chloroform was concentrated in vacuo to leave a yellow oil of 9. According to the general procedure described above, the cyclization of 2c (0.335 g, 2.26 mmol) was performed by using this material as the catalyst and Cu(OAc)$_2$ (0.410 g, 2.26 mmol) in methanol (4.6 mL). After the reaction was complete in 34 h, usual workup followed by Kugelrohr distillation gave an 87:13 mixture of 3c and 4c (0.230 g, 70%). The optical rotation of purified 3c was $[\alpha]^{22}_D$ +0.64° (c 3.88, CCl_4), which corresponds to 2.5% ee.

Catalytic Cyclization of 1 Using t-BuOOH in Benzene. An anhydrous, 5.6 M solution of t-BuOOH in benzene was prepared by azeotropic drying of 80% t-BuOOH. Using this reagent (3.0 mmol), the cyclization of 1 (2.5 mmol) was carried out in benzene (4.8 mL) under otherwise the same conditions as above. In this case, n-pentadecane was used as an internal standard for GLC analyses. Results are summarized in Table IV.

(19) Mehta, G.; Singh, B. P. *Tetrahedron* **1974**, *30*, 2409.
(20) Trost, B. M.; Strege, P. E.; Weber, L.; Fullerton, T. J.; Dietsche, T. J. *J. Am. Chem. Soc.* **1978**, *100*, 3407.

Competitive Dehydration and Deamination of α,ω-Amino Alcohols and α,ω-Amino Acids in the Gas Phase

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Acid-catalyzed cyclization of straight chain α,ω-amino acids and α,ω-amino alcohols (chain lengths from C_2 to C_5) has been studied as a function of reaction conditions in the gas phase. Tandem mass spectrometry was used for product analysis. Competitive dehydration and deamination from the protonated amino alcohols and amino acids were found to depend on the reaction region (mass spectrometer ion source vs. mass spectrometer collision region) in two types of mass spectrometers. The ratio of deamination to dehydration for both types of compounds was found to show dramatic variation with varying chain length in the collision region of the mass spectrometer. No such effect was observed for reactions occurring in the ion source. These results can be rationalized with calculated thermochemical data on the assumption of thermodynamic control in the ion source and kinetic control in the collision region of the mass spectrometer.

Acid-catalyzed intramolecular cyclization of straight chain α,ω-amino alcohols can result in either dehydration or deamination.[2-5] When the reaction is examined in the chemical ionization source of a mass spectrometer,[6,7] that is under conditions where numerous collisions occur,[6-8] the

(1) Present address: Rohm and Hass Company, Spring House, PA 19477.

(2) Audier, H. E.; Milliet, A.; Perret, C.; Tabet, J. C.; Varenne, P. *Org. Mass Spectrom.* **1978**, *13*, 315.
(3) Longevialle, P.; Girard, J.; Rossi, J.; Tichy, M. *Org. Mass Spectrom.* **1979**, *14*, 414.

0022-3263/85/1950-1287$01.50/0

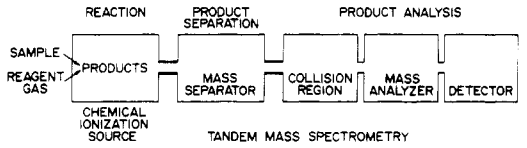


Figure 1. Schematic representation of the MS/MS experiment, emphasizing the formal analogy that exists between this method of carrying out reactions and analyzing their products with the corresponding aspects of solution chemistry. The *reactor* is a chemical ionization source, *separation* is achieved by mass analysis, and product *characterization* is by collisional dissociation and a second stage of mass analysis.

thermodynamically favored dehydration product is the major ion recorded in the mass spectrum.[2-5] By contrast, when the protonated amino alcohol is examined in the zero or single collision conditions of the collision region of a tandem mass spectrometer,[9-11] either deamination or dehydration is the dominant reaction channel depending upon the carbon chain length.[5] For example, the propane derivative displayed 90% dehydration upon undergoing a single activating collision with N_2 at 7000 eV translational energy. In contradistinction, the protonated butane δ-amino alcohol gave 90% deamination under the same conditions.[5] This dramatic difference in product distribution was rationalized through analysis of relevant thermochemical data and interpreted to be the result of thermodynamic control in the ion source and kinetic control in the collision region.

The present study uses a related set of compounds, α,ω-amino acids, to show that the amino alcohol data do not represent an isolated case in which there is a delicate balance in product distribution with molecular size in an homologous series. In addition, focus falls on differences in gas-phase ionic chemistry due to the reaction milieu, in particular the differences between examining mass spectral reactions in the ion source and in the field free region. The former experiment employs conventional MS scans, the latter uses the newer approach of tandem mass spectrometry (MS/MS). To enquire in more detail into both the amino alcohol and the amino acid systems, collisions occurring in the low-energy (eV) range[12-13] were used as well as those occurring at high (keV) energy.[14] Low-energy collisions cause effective collisional dissociation, but the energy transfer is strongly dependent upon the particular collision energy chosen. Detailed insights into ion structure and mechanism can be supplied through use of this method of collisional activation.[15] High-energy collisions sometimes access excited electronic states which then show different fragmentation behavior to that observed at low energy.[16] It was of interest to establish whether or not this occurred in these systems.

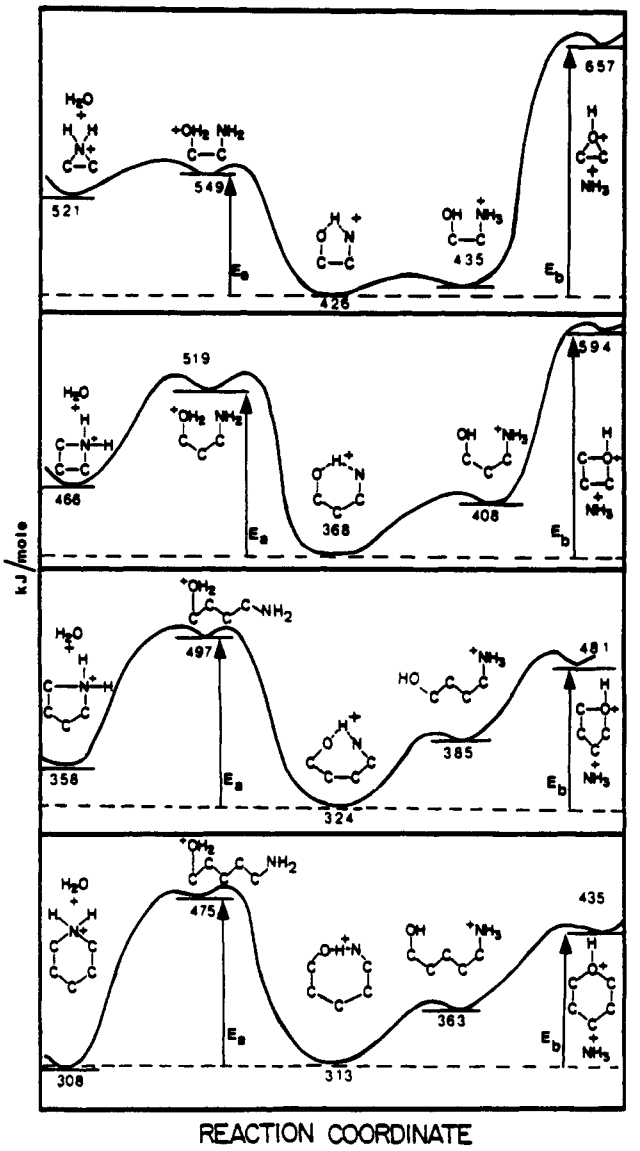


Figure 2. Summary of enthalpies associated with deamination and dehydration of protonated α,ω-amino alcohols.

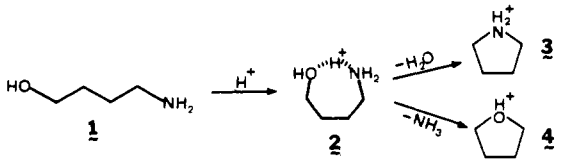
Results and Discussion

The experimental approach used to study the gas-phase acid-catalyzed cyclization of amino aicds and amino alcohols is shown schematically in Figure 1. In this experimental arrangement there are two possible reaction regions. The first is the chemical ionization source itself, where low-energy ion/molecule reactions occur under multiple collision conditions and from which products or unreacted (but ionized) reagents can be withdrawn. The second region is the collision region which is usually operated under conditions where relatively few collisions occur. These collisions are normally too energetic to allow association (ion/molecule) reactions; rather excitation followed by collision-induced dissociation occurs. This is achieved in the low (eV) range of collision energies by using quadrupole mass analysis or in the high-energy (keV) range with sector mass spectrometers. These reacitons may be used to identify products which are formed in the ion source as well as to follow the product distribution arising from the protonated molecule.

In the chemical ionization source, ionization occurs when the sample is reacted with a reagent ion of choice, in this case a Brønsted acid. The bifunctional compounds under

(4) Longevialle, P.; Milne, G. W. A.; Fales, H. M. *J. Am. Chem. Soc.* **1973**, *95*, 6666.
(5) Davis, D. V.; Cooks, R. G. *Org. Mass Spectrom.* **1981**, *16*, 176.
(6) Munson, M. S. B.; Field, F. H. *J. Am. Chem. Soc.* **1966**, *88*, 2621.
(7) Harrison, A. G. "Chemical Ionization Mass Spectrometry"; CRC Press: Boca Raton, FL, 1983.
(8) Richter, W. J.; Schwarz, H. *Angew Chem., Int. Ed. Engl.* **1978**, *17* 424.
(9) McLafferty, F. W., Ed. "Tandem Mass Spectrometry"; John Wiley and Sons, Inc.: New York, 1983; Chapter 6.
(10) Cooks, R. G.; Glish, G. L. *Chem. Eng. News* **1981**, *59*, 40.
(11) Yost, R. A.; Fetterolf, D. D. *Mass Spectrom. Rev.* **1983**, *2*, 1.
(12) Yost, R. A.; Enke, C. G.; McGilvery, D. C.; Smith, D.; Morrison, J. D. *Int. J. Mass Spectrom. Ion Phys.* **1979**, *30*, 127.
(13) Dawson, P. H.; Douglas, D. J. *Int. J. Mass Spectrom. Ion Phys.* **1983**, *47*, 121.
(14) Levsen, K.; Schwarz, H. *Mass Spectrom. Rev.* **1983**, *2*, 77.
(15) Hunt, D. F.; Shabanowitz, J.; Giordani, A. B. *Anal. Chem.* **1980**, *52*, 386.
(16) McLuckey, S. A.; Cooks, R. G. *Int. J. Mass Spectrom. Ion Phys.* **1984**, *56*, 223.

Scheme I[a]



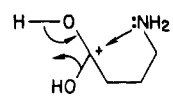
[a] The major reactions open to protonated 4-aminobutanol (1) are dehydration and deamination to generate the protonated cyclic amine 3 and the protonated cyclic ether 4.

study each contain two sites at which protonation could occur.[17] Other bifunctional molecules, such as α,ω-diamines[18] and α,ω-diethers,[19] have been shown to have anomalously high proton affinities due to the formation of a stable intramolecular proton-bound species. Such a species has been shown to occur in α,ω-amino alcohols[20] and should likewise form in α,ω-amino acids.[21]

When energized, the intramolecular proton-bound species may undergo ring contraction accompanied either by deamination or by dehydration as illustrated in Scheme I for protonated 4-aminobutanol. Estimates of the enthalpies of intermediates and products for processes of the type shown in Scheme I were made by using the method of Benson[22] in combination with known proton affinity data. Details of the procedure appear in the Appendix. The thermochemistry itself is shown in Figure 2 for the amino alcohols and in Figure 3 for the amino acids. An examination of the relative stabilities of the various intermediates and products in the competitive elimination reactions suggests that it might be possible to favor one product over the other simply by varying the reaction conditions. In the case of protonated 4-aminobutanol, for example, under thermodynamic control such as might be encountered in the chemical ionization source of a mass spectrometer, the thermodynamically more stable dehydration product should be formed. Under kinetic control, such as obtains in the collision region of the mass spectrometer, the kinetically more stable deamination product should predominate.

On the basis of the data on Figures 2 and 3, one predicts water loss to be the thermodynamically preferred reaction for all of the protonated amino alcohols and amino acids studied. However, under kinetic control the lower energy pathway corresponds to loss of ammonia for the four and five carbon compounds and loss of water for the two and three carbon compounds. This is based on a comparison of the activation energies (labeled E_a and E_b in Figures 2 and 3) for each of the reactions.

Carboxylic acids are known to first protonate on the carbonyl oxygen with hydroxy protonation being a minor process.[17] Fragmentation involving a forbidden 1,3 H shift, loss of water, and formation of an acylium ion is accompanied by a large release of kinetic energy which is seen as a very broad metastable peak.[17a] This mechanism is unlikely for the amino acids studied here since the metastable peaks for the fragmentation of these compounds are narrow and do not show the large kinetic energy releases seen in fragmentation of the carboxylic acids. In addition, calculated enthalpies for the hydroxy protonated amino acids were so much higher than those of the carbonyl protonated structures and the nitrogen protonated structures that water loss would not have been predicted for *any* of the amino acids if this structure were important. A mechanism which seems reasonable involves loss of water through participation of the nitrogen lone pair of electrons ("nucleophilic" attack on the carboxy carbon) as shown below.



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This proposal was confirmed with the use of tandem mass spectrometry to compare the daughter spectra of the protonated products with those of authentic protonated cyclic compounds. This is best illustrated with a specific example, such as 4-aminobutyric acid (4-ABA). When protonated, 4-ABA has a mass-to-charge ratio of 104^+. The product formed through dehydration of 4-ABA would thus have a mass-to-charge ratio of 86^+. This ion was mass selected, passed into the collision region of the mass spectrometer, and collisionally dissociated to form a daughter spectrum. This spectrum (4-ABA + H^+ - H_2O) was then compared to the daughter spectrum of the proposed product, a protonated lactam. This procedure was followed for both the deamination and dehydration products of the protonated amino alcohols (C_2–C_5) and the protonated amino acids (C_4 and C_5).[23] Typical data are

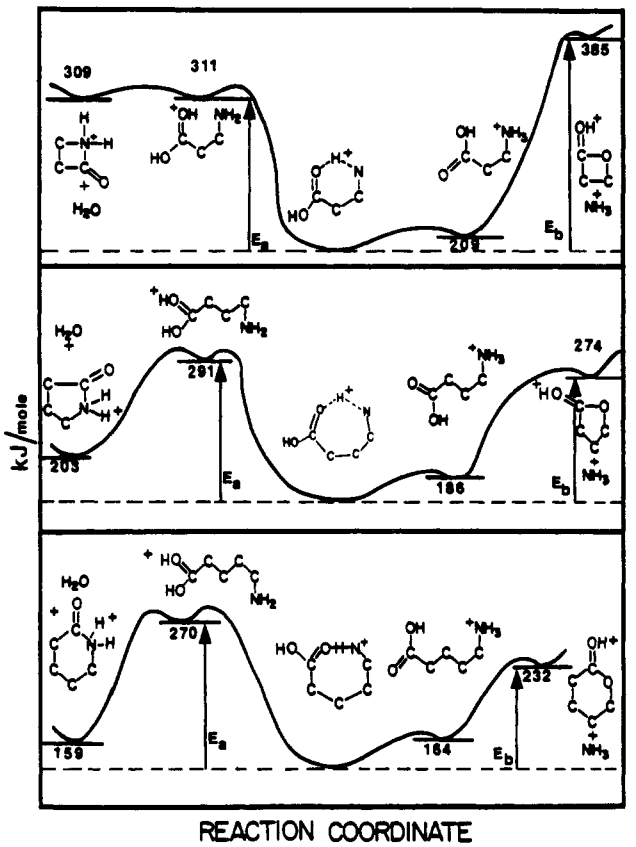

Figure 3. Summary of enthalpies associated with deamination and dehydration of protonated α,ω-amino acids.

(17) Even though the amino acids each contain 3 heteroatoms, protonation at the hydroxy oxygen has been shown to be a minor process: (a) Middlemiss, N. E.; Harrison, A. G. *Can. J. Chem.* **1979**, *57*, 2827. (b) Benoit, F. M.; Harrison, A. G.; Lossing, F. P. *Org. Mass Spectrom.* **1977**, *12*, 78.

(18) Yamdagni, R.; Kebarle, P. *J. Am. Chem. Soc.* **1973**, *95*, 3504.

(19) Morton, T. L.; Beauchamp, J. L. *J. Am. Chem. Soc.* **1972**, *94*, 3671.

(20) Meot-Ner, M.; Hamlet, P.; Hunter, E. P.; Field, F. H. *J. Am. Chem. Soc.* **1980**, *102*, 6393.

(21) While the intramolecular proton bound species is not the most stable form for the 2-carbon compounds 2-aminoethanol (see ref 20) and glycine, proton exchange between the terminal functional groups is possible. Glycine: Meot-Ner, M.; Hunter, E. P.; Field, F. H. *J. Am. Chem. Soc.* **1979**, *101*, 686.

(22) Benson, S. W. "Thermochemical Kinetics", 2nd ed.; John Wiley and Sons: New York, 1976.

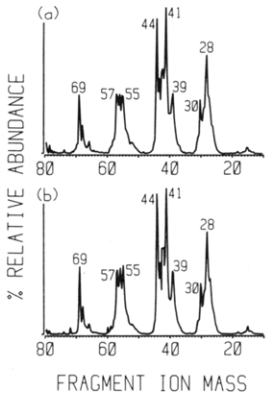

Figure 4. Comparative MS/MS spectra for the acid-catalyzed dehydration of 4-aminobutyric acid (4-ABA). Daughter ion spectra of (a) $[M + H - 18]^+$ from the reaction substrate and (b) $[M + H]^+$ from γ-butyrolactam.

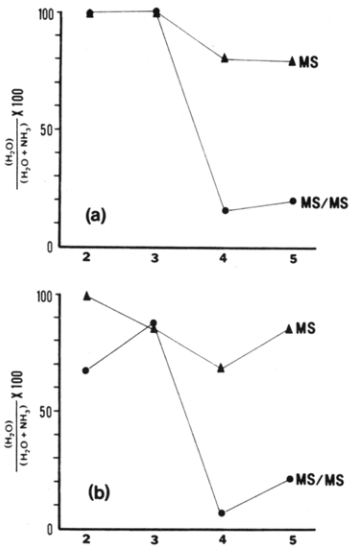

Figure 5. Competitive dehydration and deamination of protonated (a) amino acids and (b) amino alcohols studied in the ion source (▲, MS) and at 10 eV in the collision region (●, MS/MS) of a triple quadrope mass spectrometer.

shown in Figure 4 for 4-ABA.

We turn now to the behavior of the protonated amino acids and amino alcohols themselves. Results obtained with a triple quadrupole mass spectrometer are summarized in Figure 5 and are in agreement with expectation based on Figures 2 and 3. Reactions occurring in the ion source, as sampled in a normal CI mass spectrum, lead to predominant water loss for all of the compounds studied—the expected result. Collisional activation, which occurs at low collision energy in this tandem mass spectrometer, results in predominant loss of ammonia for the 4 and 5 carbon compounds and predominant loss of water for the 2 and 3 carbon compounds. This indicates that the ionic population present in the collision region is not under equilibrium control, but rather that reactions are being studied under kinetic control.

The results of the kilovolt energy experiments are shown in Figure 6. Water loss again predominates in the ion source of this spectrometer for all compounds indicating

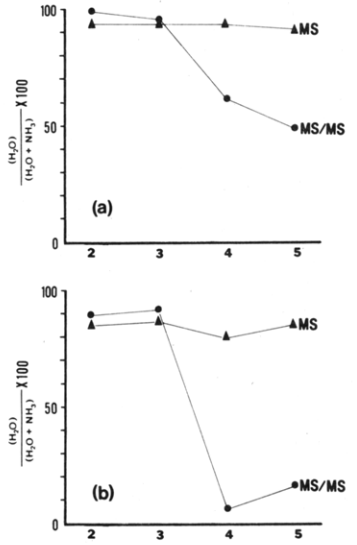

Figure 6. Competitive dehydration and deamination of protonated (a) amino acids and (b) amino alcohols studied in the ion source (▲, MS) and at 7000 eV in the collision region (●, MS/MS) of a reverse geometry (MIKES) mass spectrometer.

that equilibrium is substantially achieved. The previously published kilovolt energy results for the amino alcohols are almost identical with the low collision energy results (compare Figure 5b to Figure 6b). However, the amino acid results show some variation between the two types of experiments. In particular, for the four and five carbon amino acids, water loss occurs to a greater extent in the high-energy collision experiment than in the low-energy collision experiment, although it still does not dominate to the extent that it does under equilibrium conditions. This small anomaly suggests that the internal energies of the ions excited in the high-energy collision may be much greater than that of the ions generated at low energy.[24] Given highly excited ions there is a tendency under conditions of kinetic control toward control of reaction rates by their frequency factors or entropies of activation which are here very similar.[25] This should lead to the observed result of similar extents of deamination and dehydration. This argument is supported by the observation of ions due to *further* fragmentation of the dehydration and deamination products in significant abundance in the experiments done at high but not at low energy. Furthermore, the thermochemistry of Figure 3 suggests that such an increase in internal energy, as we move from the low energy to the high energy experiment, might be expected to have a greater effect on the butyric derivative than on the valeric derivative (compare $[E_b - E_a]$ for butyric vs. valeric), as is observed. There is no indication, in the comparison of high- and low-energy behavior, of anything but ground-state reactions in both experiments.

Experimental Section

The gas-phase reactions described in this paper were performed on two mass spectrometers: (1) a reversed geometry sector instrument of the MIKES (mass-analyzed ion kinetic energy) type[26] and (2) a Finnigan triple quadrupole mass spectrometer.[27]

(23) Standards for product confirmation for the reactions of protonated β-alanine were not available to us and cyclic products were assumed based on analogy with the other reactions. Since cyclic products from protonated glycine (an α-amino acid) are not feasible, the only reasonable fragmentation pathway for glycine involves water loss to form an acylium ion followed by loss of CO: Tsang, C. W.; Harrison, A. G. *J. Am. Chem. Soc.* **1976**, *98*, 1301.

(24) This is not always the case: Kenttämaa, H. I.; Cooks, R. G. *Int. J. Mass Spectrom. Ion Processes*, in press.

(25) The strong dependence of the reaction pathway on internal energy may be compared to the strong dependence of the isotope effect on internal energy (i.e., at high internal energies $i = k_H/k_D = 1$). With increasing internal energy the number of states of the two activated complexes become comparable as do their reaction rates: Levsen, K. "Fundamental Aspects of Organic Mass Spectrometry"; Verlag Chemie: Weinheim, New York, 1978; Chapter 3.

(26) Beynon, J. H.; Cooks, R. G.; Amy, J. W.; Baitinger, W. E.; Ridley, T. Y. *Anal. Chem.* **1973**, *45*, 1023A.

Isobutane was used as the chemical ionization (protonating) agent unless otherwise noted. All compounds were obtained commercially and were used without further purification.

Typical operating conditions for the MIKES instrument include a source pressure of 200 mtorr, an ion kinetic energy (collision energy) of 7000 eV, and a source temperature of 420 K. Air was used as the collision gas at a pressure of 2×10^{-5} torr which corresponds to single collision conditions. (Some of the high-energy experiments were repeated on a similar instrument [VG-Analytical Ltd ZAB-2F] and the results were in agreement with the MIKES results.)

Typical operating conditions for the Finnigan triple quadrupole instrument include a source pressure of 450 mtorr, a collision energy of 10eV, and a source temperature of 420 K. Argon was used as the collision target at a pressure of 0.2 mtorr which corresponds to single collision conditions. A series of experiments was performed on selected compounds in which the operating conditions for the triple quadrupole were varied over the ranges shown below; these changes did not cause the domiant reaction pathway to become a minor pathway (or vice versa) in any case.

collision energy	5–25 eV
collision pressure	0.2–2.0 mtorr
source temperature	360–440 K
source pressure	200–900 mtorr

Acknowledgment. We thank the National Science Foundation (CHE-8114410A3) for support. We thank Dr. Joseph Campana (Naval Research Laboratory, Washington, DC) for access to the ZAB spectrometer.

Appendix

Estimates of ΔH values were made through use of eq 1 where $[M + H]^+$ represents the protonated molecule, $-PA_M$ = negative of the proton affinity (PA) of species M, $\Delta H_f(M)$ represents the heat of formation of neutral M (calculated by using the method of group additivity, ref 22), and $\Delta H_f([H]^+) = 1530$ kJ/mol.[28]

$$\Delta H_f([M + H]^+) = -PA_M + \Delta H_f(M) + \Delta H_f[(H]^+) \quad (1)$$

Calculations for open chain, protonated forms were completed by using monofunctional proton affinity values without correction for substituent effects of the second functional group (for a precedent, see ref 21). Monofunctional PA values for the linear and cyclic amines, the alcohols, the acids, and the cyclic ethers were available from ref 29 with the exception of the PA of 5-aminopentanol which was estimated from ref 30. The PA's of the lactones and lactams of Figure 3 were not available and had to be estimated. The PA's of the lactones were estimated based on PA values for linear esters[29] in conjunction with the PA's of appropriate cyclic ketones and ethers,[29] and the PA's of the lactams were estimated by using PA values of amides[29] in conjuction with values for *N*-methyl lactams.[31] PA values for the amino alcohols (cyclic, protonated form) were available from ref 20. PA values for the chelated amino acids were not available and no attempt was made to estimate these values.

Registry No. 1, 13325-10-5; $HO(CH_2)_2NH_2$, 141-43-5; $HO(CH_2)_3NH_2$, 156-87-6; $HO(CH_2)_5NH_2$, 2508-29-4; $H_2N(CH_2)_2CO_2H$, 107-95-9; $H_2N(CH_2)_3CO_2H$, 56-12-2; $H_2N(CH_2)_4CO_2H$, 660-88-8; $H_2NCH_2CO_2H$, 56-40-6.

(27) Slayback, J. R. B.; Story, M. S. *Ind. Res. Dev.* **1981**, February, 129.

(28) Rosenstock, H. M.; Draxl, K.; Steiner, B. W.; Herron, J. T. "Energetics of Gaseous Ions"; American Chemical Society and American Institute of Physics: Washington, DC, 1977.

(29) Hartman, K. N.; Lias, S.; Ausloos, P.; Rosenstock, H. M.; Schroyer, S. S.; Schmidt, C.; Martinsen, D.; Milne, G. W. A. "A Compendium of Gas Phase Basicity and Proton Affinity Measurements"; NBS Publication, NBSIR 79-1777, 1979.

(30) Benoit, F. M.; Harrison, A. G. *J. Am. Chem. Soc.* **1977**, *99*, 3980.

(31) Bowers, M. T., Ed. "Gas Phase Ion Chemistry"; Academic Press: New York, 1979; Vol. 2.

Scope, Limitations, and Mechanism of the Homoconjugate Electrophilic Addition of Hydrogen Halides

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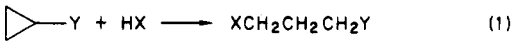
Hydrogen halides (HCl, HBr, HI) add by a homoconjugate 1,5 mechanism to cyclopropanes carrying certain electron-withdrawing substituents. When the substituent is $COCH_3$, COC_6H_5, CO_2H, or CN, the reaction gives the 1,3-disubstituted propane in high yield. Addition of DCl gives a product with deuterium only in the position α to the substituent. The order of rates is not in agreement with a mechanism whereby the cyclopropane ring is protonated initially, since the rate of such a process should be slowed by electron-withdrawing groups. The ketones, however, react much more rapidly than benzylcyclopropane, a model for the direct protonation mechanism. The homoconjugate mechanism involves rapid protonation of the side chain, followed by nucleophilic attack on the cyclopropane ring. The reaction is limited to substrates that can be protonated on the side chain to produce an intermediate with charge ajacent to the cyclopropane ring. This charge must be able to be transmitted by resonance to the unsubstituted ring positions in order to facilitate the nucleophilic step.

The addition of the elements of hydrogen halide (HX, X = Cl, Br, I) to cyclopropane bearing an electron-withdrawing group Y has been known for a century[2] (eq 1).



(1)

Because the mechanistic effects of the group Y have not been fully explored, we have carried out and report herein a survey of this reaction. Two general mechanisms have received support in the literature.[3] Initial protonation of

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(2) Perkin, W. H., Jr. *J. Chem. Soc.* **1885**, *47*, 801–855. Marshall, T. R.; Perkin, W. H., Jr. *Ibid.* **1891**, *59*, 853–894.

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