A Strong Preference for a Salt-Bridge Structure in the Gas Phase: Reactions of Deprotonated Amino Acids with Borane

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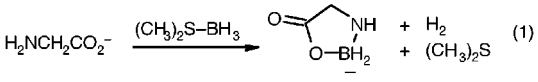
In recent years there has been a growing interest in the existence of salt-bridge-type structures in the gas phase, and they often have been implicated in the fragmentation pathways of peptides.[1−12] Although it appears that amino acids prefer conventional structures (rather than the zwitterions found in solution), there is evidence that metal salts of proline and arginine prefer to adopt salt-bridge structures in the gas phase (i.e., metal complexed to the amino acid zwitterion).[6,8,9,13] We have recently found that borane is a potentially useful reactant for characterizing gas-phase biomolecules,[14] and in the present communication, we report a remarkably large preference for a salt-bridge structure in the product from the reaction of borane with deprotonated glycine. In addition, we provide evidence for the formation of unusual boron heterocycles in reactions with other amino acids and in the collision-activated dissociation (CAD) of the reaction products.

Using a modified Finnigan LCQ quadrupole ion trap mass spectrometer,[15] the M-1 anion from glycine was allowed to react with the dimethyl sulfide complex of BH_3 (DMS−BH_3). A rapid reaction leads to several products, but an ion corresponding to the addition of BH_3 with loss of H_2 dominates (eq 1).



(1)

A logical product is a cyclic borohydride where the combination of a hydride from the boron and proton from the nitrogen leads to H_2 loss and collapse to a five-membered ring.[16,17] The identity of the hydrogens involved in the H_2 loss was confirmed in two labelleing experiments. Starting with $H_2NCD_2CO_2^-$, the reaction with the borane leads exclusively to H_2 loss. A sample spectrum

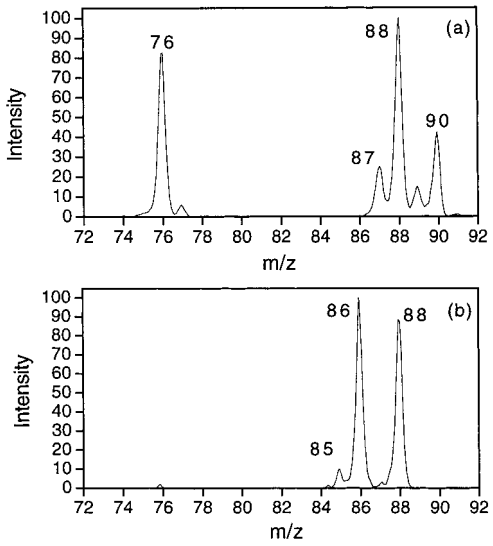
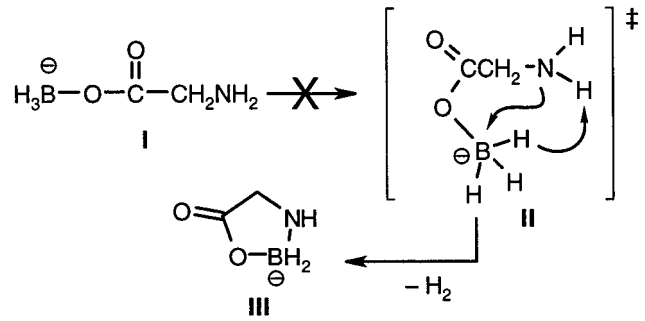


Figure 1. (a) Reaction of 2,2-dideuterioglycine (M-1) anion with BH_3-DMS. Reactant ion is at $m/z = 76$ and the products are at $m/z = 88$ ($+^{11}BH_3$ -H_2) and $m/z = 87$ ($+^{10}BH_3$ -H_2). Absence of an ion at $m/z = 86$ ($+^{10}BH_3$ -HD) confirms that only H_2 is lost. Ions at $m/z = 89$ and 90 are adducts. (b) CAD of $m/z = 88$. Ions at $m/z = 86$ and 85 correspond to loss of H_2 and HD, respectively.

Scheme 1



is shown in Figure 1a. Conversely, $D_2NCH_2CO_2^-$ reacts with BH_3 to give a product corresponding to HD loss.

Our first thought was that the BH_3 would add to the carboxylate and then using the exothermicity of the initial addition, expel a hydride ion (H^-) which would deprotonate the amine eventually leading to ring closure (Scheme 1). To gain a better understanding of the mechanism, we have completed ab initio calculations on this reaction at the MP2/6-31+G(d,p)//MP2/6-31+G(d) level.[18] The data are summarized in Table 1. The addition at the carboxylate with loss of DMS is only exothermic by about 17 kcal/mol which is not nearly enough energy to fuel the H_2 expulsion process. The transition state, **II**, is over 40 kcal/mol

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(17) The product could also be an acyclic salt bridge, $^-H_2B{=}NH^+CH_2CO_2^-$. This structure is related (i.e., isoelectronic on the N-terminal side) to one suggested as a product in a recent study of the reactions of XCH_2^+ ions with neutral glycine, $H_2C{=}NH^+CH_2CO_2H$. In that study, the acyclic form was preferred, but in the present case, the cyclic form is favored by about 5 kcal/mol, and the cyclization barrier is relatively low. O'Hair, R. A. J.; Freitas, M. A.; Gronert, S.; Schmidt, J. A. R.; Williams, T. D. *J. Org. Chem.* **1995**, *60*, 1990.
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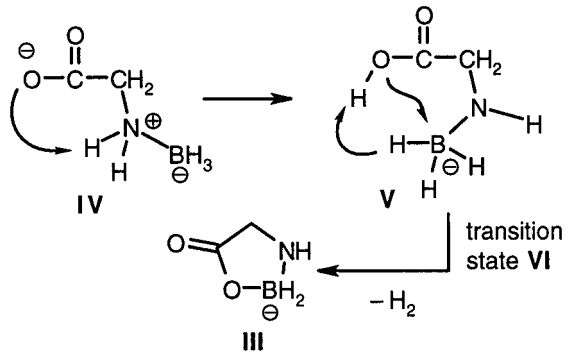
Table 1. Computed Energies of Species in the Reaction of Deprotonated Glycine with DMS−BH_3[a]

species	MP2	ZPE[b]	rel. MP2[c]
I	−309.66927	0.10662	−16.8
II	−309.56737	0.09717	41.7
III	−308.51719	0.08565	−17.8
IV	−309.68420	0.10796	−25.4
V	−309.65549	0.10543	−8.9
VI	−309.63541	0.09992	0.6
VII	−307.32759	0.06298	3.9
VIII	−307.31715	0.06164	9.7

[a] Calculations at the MP2/6-31+G(d,p)//MP2/6−31+G(d) level. [b] Zero-point energies (ZPE) calculated at the HF/6−31+G(d) level and scaled by 0.9135.[19] [c] Energies relative to the separated reactants.

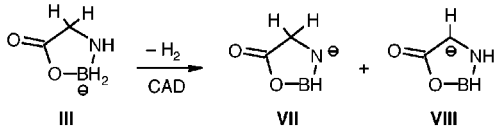
Scheme 2



less stable than the reactants; therefore, clearly another pathway must be active.

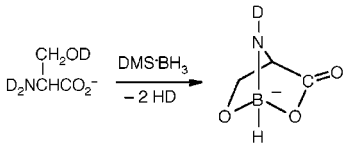
As an alternative, the BH_3 could add to the N-terminus to give a salt-bridge structure, **IV** (Scheme 2). A virtually barrierless, but endothermic proton transfer from nitrogen to the carboxylate (**V**) sets the system up for expulsion of H_2 and collapse to **III**.[20] *The surprising outcome is that salt-bridge **IV** is nearly 9 kcal/mol more stable than the conventional structure, **I**.*[21] This happens despite the fact that borane makes much more stable complexes with carboxylates than amines. For example, the computed complexation energy of borane with acetate is 11 kcal/mol greater than it is with methylamine. Obviously, the favorable electrostatic interaction of the N−B dipole with the carboxylate anion is providing enough stabilization to reverse the normal borane selectivity (carboxylate over amine). This is reasonable, and simple point charge models suggest that the salt-bridge structure could provide electrostatic stabilizations from 25 to 45 kcal/mol (depending on how the charge loci are defined). From **IV**, proton transfer from N to O gives another conventional isomer of the anion, **V**. Again, the conventional structure is much less stable than the salt-bridge, and **IV** is preferred over **V** by over 15 kcal/mol. These calculations indicate that the carboxylate in **IV** (PA = 321.6 kcal/mol) is *less basic* than the amine in **V** (PA = 338.2 kcal/mol). *This is an unusual example of an anionic site (carboxylate of **IV**) having a lower proton affinity than a neutral site (amine of **V**) in the gas phase.* It is a result of two factors. First, Squires and co-workers[22] have shown that borane complexation to neutral sites in a molecule can greatly reduce the proton affinity of a nearby anion. For example, the proton affinity of $CH_3SCH_2^-$ is reduced by about 20 kcal/mol when the sulfur is complexed to borane. However, in this case, the conventional isomer of the anion (i.e., $CH_3SCH_2BH_3^-$) was predicted to be considerably more stable than the salt-bridge structure. In addition, Cooks[23] and Williams[24] have independently shown that the nearby positive charge in a somewhat related species, betaine ($(CH_3)_3N^+$-$CH_2CO_2^-$), greatly reduces the proton affinity of the carboxylate. Second, the presence of the formal negative charge on the adjacent boron will greatly enhance the proton affinity of the amine.

Scheme 3



From **V**, loss of H_2 occurs through transition state **VI** to give **III** in a process that is overall exothermic by about 18 kcal/mol.[25] The H_2 expulsion barrier (0.6 kcal/mol) is near the energy of the reactants, which is consistent with the fact that the reaction produces a mixture of adducts and H_2 expulsion products. Collision-activated dissociation experiments on **III** led to the loss of an additional H_2 molecule (Scheme 3). CAD on the deuterium-labeled substrates (either on C or N) led to the loss of a mixture of H_2 and HD, indicating that two products were formed (Figure 1b). The experiments suggest that formation of **VII** is preferred, and the calculations indicate that it is the more stable product.[26]

In addition, we have studied the reactions of the conjugate bases of other, common amino acids with the borane complex. When the side chain of the amino acid has a nucleophilic group, it is also involved in the reactions with the boron. For example when deprotonated serine reacts with borane, two molecules of H_2 are readily lost. If the exchangeable protons are replaced with deuterium, two HD molecules are lost in the reaction (no evidence of H_2 loss). These results suggest the formation of a novel bicyclic borohydride (eq 2). Details of these studies will be presented elsewhere.



In summary, the reaction of deprotonated glycine with borane in the gas phase leads to a salt-bridge structure that is significantly more stable than the possible conventional isomers. In addition, we have found that borane gives extensive reactivity and a range of novel products in its reactions with amino acids. We are currently studying the reactions of boron compounds with peptide derivatives, and the results of that work will be reported soon.[27]

Acknowledgment. We thank the NIH-RIMI program (P20 RR11805) and NSF-RUI program (CHE-9974506) for generous support. S.G. thanks Dr. R. A. J. O'Hair for helpful suggestions regarding this work and the manuscript.

Supporting Information Available: A figure showing the computed geometries of the intermediates and transition states (**I**−**VIII**) (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) The acyclic form of the ion (ref 17) is formed initially from transition state **VI**, but the cyclization barrier is well below the entrance channel

(26) In the *N*,*N*-dideutero system, formation of **VII** is also favored but to a lesser extent due to the reversal of isotope effects. Transition states were not found in the calculations, and it appears that a two-step path involving H^- expulsion followed by proton abstraction is operative.

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