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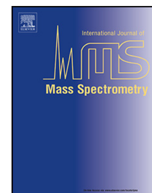

Gas-phase acid-base properties of 1-aminocycloalkane-1-carboxylic acids from the extended kinetic method

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Dedicated to Professor Veronica Bierbaum on the occasion of her 65th birthday and in recognition of her outstanding contributions to gas-phase ion chemistry and for many years of valued friendship

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ABSTRACT

The gas-phase proton affinities (PA) and gas-phase acidities (GA) for the non-protein amino acids 1-aminocyclopropane-1-carboxylic acid (**1**), 1-amino-1-cyclobutane-carboxylic acid (**2**), cycloleucine (**3**) and 1-amino-1-cyclohexane (**4**) have been determined using the extended kinetic method in ESI-tandem mass spectrometers. These non-protein amino acids are found in a variety of foods and can compete with other aliphatic amino acids in a variety of biochemical processes. We find a positive trend in proton affinity with an increasing ring size for the four amino acids. Experimental proton affinities of 896 ± 8.0, 913 ± 8.0, 931 ± 8.0, and 933 ± 8.0 were determined for **1**–**4**, respectively. Hybrid density functional theory calculations at the B3LYP/6-311++G(d,p)//B3LYP/6-31+G(d) level of theory give predictions for the proton affinities of **1**–**4** that are in excellent agreement with the measured values and support the positive trend. In contrast, we find that the gas-phase acidities (ΔH_{acid}) for **1**–**4** are the same within error. Acidities of 1425 ± 8 kJ/mol, 1424 ± 8 kJ/mol, 1428 ± 10 kJ/mol, and 1423 ± 8 kJ/mol were determined for **1**–**4**. Theoretical predictions for the acidities for **1**–**4** are in excellent agreement with the measured acidities and support the conclusion that there is no trend with changing ring size.

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1. Introduction

Aliphatic amino acids are vitally important to the structure and function of proteins. Proteins fold, in part, in order to segregate the hydrophobic amino acid residues on the inside of the protein away from water. In addition to their role in protein conformation and chemistry, the amino acids are important biological species in their own right. Amino acids serve a variety of functions as neurotransmitters, as intermediates in biochemical pathways, and as building blocks for other biochemical species. An amino acid's behavior in biological systems depends in part on their fundamental chemical properties, including their intrinsic acid/base properties [1]. Solution pK_a values for all of the common protein amino acids (PAA) are readily available [1], as are the intrinsic gas-phase proton affinities (PA) [2–24] and gas-phase acidities (GA, ΔH_{acid}) [19,22,23,25–30].

We have been using the extended kinetic method to measure gas-phase proton affinities and gas-phase acidities for a class of compounds known as "non-protein amino acids" (NPAA) [9,10,12,29,31]. NPAAs are not coded for by RNA, but are found throughout nature as secondary products of plant and fungi metabolism [32]. Many NPAAs are similar in structure to one or more of the PAAs and can compete with them in a variety of biological processes, including being mis-incorporated into proteins [33–39]. In addition to their biological relevance, NPAAs serve as useful model compounds for studying the interplay between amino acid structure and thermochemical properties.

We are especially interested in homologous series of amino acids in which the side-chain length is varied systematically. To date we have measured the PA[9] and GA[29] of proline and its 4- and 6-membered ring analogs, the PA[10] and GA[29] of lysine, and its lower homologs, ornithine, 2,4-diaminobutanoic acid, and 2,3-diaminoproanoic acid, the PA and GA of longer homologs of serine and cysteine [40], and the PA of oxy-analogs of arginine and ornithine [12]. For most of these systems, we find a direct correlation between PA and the number of carbon atoms in the side chain. This is due in part to inductive effects and added polarizability of the additional carbon atoms, but also on differences in intramolecular hydrogen bonding ability in side chains containing heteroatoms. In contrast to the PA results, we have

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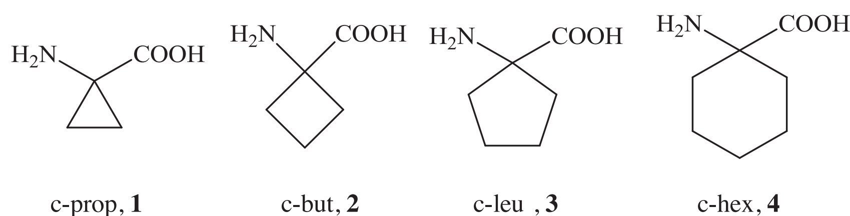

Scheme 1. 1-Aminocycloalkane-1-carboxylic acids.

found that the acidity of these amino acids is in general nearly independent of the number of carbon atoms in the side chain, regardless of the degree of intramolecular hydrogen bonding.

In this manuscript, we extend our studies of NPAAs to those containing cyclic aliphatic side chains, 1-aminocyclopropane-1-carboxylic acid (c-prop, **1**), 1-aminocyclobutane-1-carboxylic acid (c-but, **2**), 1-aminocyclopentane-1-carboxylic acid (c-leu, **3**) and 1-aminocyclohexane-1-carboxylic acid (c-hex, **4**) (Scheme 1).

Amino acid **1** is commonly found in fruits such as apples, pear and cranberries [33]. It is an ethylene precursor [41], which leads to ripening in fruits, and is also a general inhibitor of valine and binds to the *N*-methyl-D-aspartate (NMDA) receptor as a glutamate antagonist [33,42]. Amino acids **1** and **2** have also been shown to bind to the NMDA receptor at the glycine binding site as agonists, activating ligand-gated ion channels [43]. In contrast, **3** is an NMDA glycine antagonist [43]. All four of these species have been shown to stabilize β-helices in model peptides, with **4** allowing the most conformational flexibility [44–46]. We present here the first experimental study of the PA and GA of these species as well as supporting hybrid density functional theory calculations.

2. Experimental

Experiments were performed in either a Thermo TSQ Quantum Discovery triple quadrupole instrument or a Thermo LCQ-DECA ion trap instrument. Full experimental details have been presented elsewhere [9,29]. For proton affinity studies, dilute solutions (ca. 1–5×10^{-4} M) of an amino acid and one of a series of reference bases in slightly acidified (1% HOAc) 50:50 methanol:water are directly infused (flow rates 5–15 μl/min) into the electrospray ionization source of the TSQ or LCQ. Electrospray and ion focusing conditions were varied to maximize the ion count for the proton-bound heterodimer $[A-H^+-B_i]^+$. For triple quadrupole studies, the proton-bound dimer ions are isolated in Q1 at a resolution of 0.7 Da and are allowed to pass into the RF-only collision cell (Q2). The isolated ions are allowed to undergo collision-induced dissociation with argon gas maintained at a pressure of 0.3 mTorr. Product ion spectra are recorded at collision energies between 0 and 30 V (lab). For ion trap studies, the proton-bound dimer ions are isolated at $q_z = 0.250$ with an isolation width set as large as possible while still maintaining isolation to avoid RF heat of the ions during isolation. CID is performed with the background helium gas serving as the target gas with activation amplitudes ranging from 0 to 100%. In both the instruments, the ion intensities of each primary product and any secondary products are recorded and are used in an extended kinetic method (KM) analysis to give PAs and protonation entropies. Secondary product ion intensities are added to the corresponding primary product intensities before undergoing KM analysis. Experiments are repeated on at least three days and are averaged to give the final ratios $\ln[B_iH^+/AH^+]$ for use in the KM workup. For gas-phase acidity studies, the method remains the same except that slightly basic (10% NH_4OH) 80:20 methanol:water solutions are used to form proton-bound dimer ions of the form $[A^- - H^+ - B_i^-]^-$. Solution concentrations are also increased to ca. 1×10^{-3} M in order to produce sufficient proton-bound heterodimer ion intensity.

Enthalpy (PA, ΔH_{acid}) and entropy contributions (ΔS_{prot}, ΔS_{deprot}) are obtained from the extended kinetic method that has been described in detail elsewhere [47–49]. The relevant equations governing an EKM analysis for PA is given in Eq. (1), where $I_{[BiH+]}$ and $I_{[AH+]}$ are the

$$\ln\left(\frac{I_{BiH+}}{I_{AH^+}}\right) \approx \frac{\Delta H_{Bi}-\Delta H_{avg}}{RT_{eff}} - \frac{\Delta H_{A}-\Delta H_{avg}}{RT_{eff}} + \frac{\Delta S_{Bi}}{R} - \frac{\Delta S_{A}}{R} \quad (1)$$

intensities of the protonated reference base and protonated amino acid products, PA_{Bi} is the proton affinity of the *i*th reference base, and PA_{avg} is the average proton affinity of the set of *i* reference bases. This method requires a plot of the final ratios $\ln(I_{[BiH+]}/I_{[AH+]})$ versus $PA_{Bi}-PA_{avg}$. In the traditional method of EKM data analysis the experiment is repeated at *n* different collision energies and a separate line is added to plot 1 for each energy. A second plot (plot 2) is then generated of the negative intercepts of the lines from plot 1 versus their slopes from which the ion affinity and entropy contribution is obtained. In our analysis, traditional plots 1 and 2 are generated for each system in order to gauge the quality of the EKM data and to aid in choosing reference compounds. However, we only use the ion affinity and entropy contributions as input for further analysis using the ODR method.

The orthogonal distance regression (ODR) method as implemented in the ODR-pack program of Ervin and co-workers is used to extract proton affinities/gas-phase acidities and protonation/deprotonation entropies from the data [50]. In this method all intensity ratios of *m* reference compounds at *n* collision energies are analyzed simultaneously. A total of *n* lines are generated and forced to cross at a single isothermal point, which gives the proton affinity/acidity and protonation/deprotonation entropy for the amino acid in question. This method gives a more realistic estimation of the errors in the derived quantities by using Monte Carlo simulations to determine isothermal points from randomly perturbed intensity ratios. For these studies, we used a window of ±8 kJ/mol in the reference acidity/basicity values and a window of ±0.05 for the ln(ratio) values. Proton affinity/acidity values and protonation/deprotonation entropies are reported with error bars corresponding to ±one standard deviation, as determined from the Monte Carlo simulations, except when the simulations generated an uncertainty lower than the 8 kJ/mol uncertainty in the reference compounds. In these cases, we adopt ±8 kJ/mol as the uncertainty in our derived enthalpies and entropies. The ODR workup also generates effective temperature values for each activation energy. All kinetic method plots shown in this manuscript are generated using the ODR-derived effective temperatures rather than using the traditional best-fit method. For gas-phase acidity studies, the analysis is identical except that the ratios $\ln(I_{[ref-H]^-}/I_{[AA-H]^-})$ are plotted versus $GA_{Ai}-GA_{avg}$ to make plot 1.

Predictions for proton affinities and ΔH_{acid} for all amino acids studies were also obtained from hybrid density functional theory calculations using the B3LYP functional combinations [51,52]. All molecular orbital and density functional theory calculations were

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