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Determination of the Gas-Phase Basicity of Betaine and Related Compounds Using the Kinetic Method

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We report the gas-phase basicity (GB, negative of the free energy of protonation) of the zwitterionic compound betaine [(carboxymethyl)trimethyl ammonium hydroxide] (**1**), as 232.9 ± 0.8 kcal/mol[1] as measured by the kinetic method.[2] Comparison of this value with the gas-phase basicity of the conjugate base[3] of acetic acid (348.5 kcal/mol),[4] glycine (335.1 kcal/mol),[4] or *N*,*N*-dimethylglycine (337.1 kcal/mol, determined in this study) shows that the permanent charge increases the acid strength by ca. 100 kcal/mol, consistent with the expected magnitude of the attractive Coulombic interaction between the carboxylic anion and the quaternary ammonium cation in the zwitterion. The substitution of a hydrogen on acetic acid by a trimethylammonium group provides the largest substituent effect yet observed for a proton affinity (PA) or gas-phase basicity,[2,4,5] dwarfing the next largest difference of 28.5 kcal/mol between trifluoroacetate and acetate.[4,5] This measurement, together with a parallel study by Lee and Beauchamp,[6] also represents the first estimation of the gas-phase basicity of a zwitterionic compound. The results are also important in connection with the transfer of ionic compounds from the condensed phase to the vapor phase, a process which underlies desorption ionization techniques and hence many applications of mass spectrometry.

$(CH_3)_3N^+CH_2CO_2^-$
1 (betaine)

$(CH_3)_2NCH_2CO_2CH_3$
2 (*N*,*N*-dimethylglycine methyl ester)

The thermochemical properties of nonvolatile compounds can be estimated by the kinetic method.[2,7] The method relies on the isolation of an ion-bound complex which dissociates primarily through two competitive pathways as shown in the equation below:

$$B_1H^+ + B_2 \leftarrow [B_1HB_2^+] \rightarrow B_2H^+ + B_1$$

Thermochemical information may be obtained from the product ion spectrum using the relationship $\ln(I_1/I_2) = (\Delta[\Delta G])/RT_{\mathrm{eff}}$.[8] The kinetic method has been used to investigate the gas-phase thermochemistry of many compounds.[2]

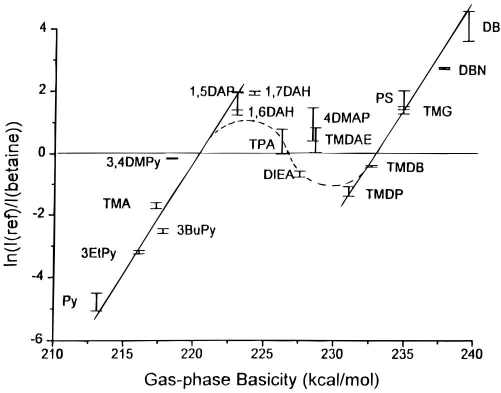

Figure 1. Kinetic method plot of the gas-phase basicity (GB) of reference compounds versus natural logarithm of the ratio of the protonated monomers as measured in the product ion spectrum. Values are averages and standard deviations from determinations made over a 3-week period. The points have been fitted to two correlation lines (see text for discussion), suggesting the presence of two species. The lower GB line has a correlation coefficient of 0.944 and an *x*-intercept of 220.2 kcal/mol while the line at higher GB has a correlation coefficient of 0.990 and an *x*-intercept of 232.9 kcal/mol. Reference compounds: Py, pyridine; 3EtPy, 3-ethylpyridine; 3BuPy, 3-butylpyridine; TMA, trimethylamine; 3,4DMPy, 3,4-dimethylpyridine; 1,5DAP, 1,5-diaminopentane; 1,6DAH, 1,6-diaminohexane; 1,7DAH, 1,7-diaminoheptane; TPA, tripropylamine; DIEA, *N*,*N*-diisopropylethylamine; 4DMAP, 4-(dimethylamino)pyridine; TMDAE, *N*,*N*,*N*′,*N*′-tetramethyl-1,4-diaminoethane; TMDB, *N*,*N*,*N*′,*N*′-tetramethyl-1,4-diaminobutane; TMDP, *N*,*N*,*N*′,*N*′-tetramethyl-1,3-diaminopropane; PS, Proton Sponge; TMG, 1,1,3,3-tetramethylguanidine; DBN, 1,5-diazabicyclo[4.3.0]non-5-ene; DBU, 1,7-diazabicyclo[5.4.0]undec-7-ene.

Proton-bound dimers of betaine (**1**) were generated from betaine and a variety of reference compounds, including substituted pyridines and amines, by ammonia desorption chemical ionization. Collision-induced dissociation of the mass-selected dimer ion was effected, and the abundance ratio of the resulting protonated monomers was measured.[9] The product ion spectrum of the proton-bound dimer of betaine with *N*,*N*,*N*′,*N*′-tetramethyl-1,2-diaminoethane (TMDAE) shows two products, of almost equal abundance, corresponding to the individual protonated monomers. This result suggests that betaine and TMDAE have similar gas-phase basicities. The results for a large set of dimers are plotted (Figure 1) as the natural logarithm of the ratio of the product ion abundances ($I_{\mathrm{ref}}/I_{\mathrm{betaine}}$) versus the known gas-phase basicity (GB) of the

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(1) All error estimates represent the standard deviations of the intercepts from linear regression analysis of the data in the plots of the natural logarithm of the relative abundance ratios versus GB of the reference bases. The individual data points are the averages of triplicate determinations from 2−4 different days.

(2) Cooks, R. G.; Patrick, J. S.; Kotiaho, T.; McLuckey, S. A. *Mass Spectrom. Rev.* **1995**, *13*, 287.

(3) The GB of the conjugate base of a carboxylic acid is thermochemically indistinguishable from the value ΔG_{acid} of the acid itself. This fact is utilized throughout this paper so that GB (values) can be discussed consistently.

(4) Lias, S. G.; Bartmess, J. E.; Liebman, J. F.; Holmes, J. L.; Levin, R. D.; Mallard, W. G. *J. Phys. Chem. Ref. Data* **1988**, *17* (S1), 1.

(5) Gal, F.; Maria, P.-C. *Prog. Phys. Org. Chem.* **1990**, *17*, 159.

(6) Complementary experiments have been reported by Beauchamp, J. L., presented at the 209th National Meeting of the American Chemical Society, Anaheim, CA, April 2−7, 1995. H.-N. Lee and J. L. Beauchamp, submitted for publication.

(7) Majumdar, T. K.; Clairet, F.; Tabet, J. C.; Cooks, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 2897.

(8) In this equation I_X ($X = 1, 2$) is the relative intensity of the product ion B_XH^+, R is the ideal gas constant, T_{eff} is the effective temperature of the excited cluster ion, and $\Delta(\Delta G)$ is the difference in the free energy of protonation (gas-phase basicity) between the two bases, B_X.

(9) All chemicals used were obtained from either Sigma Chemical (St. Louis, MO) or Aldrich (Milwaukee, WI) and used without further purification after dilution in methanol containing 1% hydrochloric acid. Betaine was obtained as its hydrochloride salt, and the reference compounds were obtained as either their free bases or the hydrochloride salts. *N*,*N*-Dimethylglycine methyl ester was prepared by reaction of *N*,*N*-dimethylglycine in methanolic hydrochloric acid (ca. 1 M) overnight at ambient temperature. Experiments were performed on a Finnigan TSQ700 (Finnigan MAT, San Jose, CA) using ammonia desorption chemical ionization (DCI) at 4−5 Torr of ammonia with the probe temperature being raised from ambient to 800 °C at 1000 °C/min. Mixed dimers were formed by applying to the probe a mixed sample from a single solution and also by separately depositing the two samples onto the probe. (Note also that results obtained by CI using pyridines in the vapor state were indistinguishable from those obtained using ammonia DCI and their hydrochloride salts.) The dimer of interest was mass-selected using Q1 and dissociated in Q2 by 6 eV collision with argon (0.3 m Torr), and the resulting product ions were analyzed by scanning Q3 across the mass range of interest in 0.5 s. All proton affinities and basicities are based on the scale of Lias et al.[4]

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Table 1. ΔG_{acid} and Natural Logarithm of Product Ion Abundance Ratios for CID of Proton-Bound Dimers of *N*,*N*-Dimethylglycine and Reference Amino Acids

ref compd	ΔG_{acid} (kcal/mol)[a]	$\ln(I_{\text{ref}}/I_{\text{dimethylglycine}})$
glycine	335.1	1.614 ± 0.029
alanine	334.6	2.377 ± 0.037
isoleucine	332.2	4.656 ± 0.114

[a] Values from ref 13. Note that $\Delta G_{\text{acid}} \equiv$ GB (conjugate base).

reference compound. The plot shows two parallel lines having *x*-intercepts of 220.4 and 232.9 kcal/mol. These intercepts represent the GB values of two compounds, both molecular weight 118, which are present in the CI plasma. This interpretation is justified by the fact that betaine and related compounds such as carnitine are known to undergo trans-methylation[10] during desorption ionization to produce the methyl ester by transfer of a methyl group from the quaternary ammonium salt. This process produces a second, isomeric species also capable of forming proton-bound cluster ions with reference compounds of appropriate basicity. The plot cannot be interpreted as a single, poorly correlated line since this would require an effective temperature in excess of 1400 K, which is inconsistent with previous studies on numerous compounds using the kinetic method under similar conditions.[2] The slopes of the individual, effectively parallel lines provide reasonable effective temperatures of 758 and 783 K.[11,12]

To test the hypothesis of the formation of isomeric compounds, the GB of the proposed trans-methylation product, *N*,*N*-dimethylglycine methyl ester (**2**), was estimated using the kinetic method and some of the reference bases used in the above study. This experiment yielded an estimated GB of 219.4 ± 0.5 kcal/mol with a linear regression correlation coefficient (*r*) of 0.996. This value agrees, within experimental error, with the value of 220.2 kcal/mol obtained for the less basic component in the betaine study (above). In addition, none of the ions corresponding to the proposed methyl cation bound dimers were observed in the product spectra, suggesting that methyl cation-transfer and isomerization do not occur for *N*,*N*-dimethylglycine methyl ester.

The GB of the conjugate base of *N*,*N*-dimethylglycine (which differs from betaine only in the absence of the third methyl group and the associated positive charge on the α-amino group) was determined using the kinetic method with glycine, alanine, and isoleucine serving as reference compounds (Table 1). Linear regression analysis of the data ($r = 0.999$) provides a value for GB of the *N*,*N*-dimethylglycine of 337.1 kcal/mol, slightly higher than the value of 334.4 kcal/mol reported for sarcosine (*N*-methylglycine).[13] As a control on the accuracy of these experimental results, the difference in GB of the conjugate bases of isoleucine and glycine was measured. The difference in gas-phase basicity between these two compounds was found to be 3.2 kcal/mol, in good agreement with the value of 3.2 kcal/mol reported previously.[7] These results support the interpretation of the data in Figure 1 as providing values for the gas-phase basicity of betaine and *N*,*N*-dimethylglycine methyl ester of 232.9 ± 0.9 and 220.4 ± 0.5 kcal/mol, respectively. Using the value of 6.9 kcal/mol for $T\Delta S$ previously assigned to amino acids[13] yields PA values for betaine and *N*,*N*-dimethylglycine methyl ester of 239.8 and 226.3 kcal/mol, respectively. Similarly, the PA of the conjugate base of *N*,*N*-dimethylglycine is estmated as 344.0 kcal/mol.

The Coulombic origin of the substituent effect in betaine is evident from the differences of 102−116 kcal/mol between its gas-phase basicity and that of the conjugate bases of related acids (glycine, *N*,*N*-dimethylglycine, and acetic acid). These differences are comparable to the value of 98 kcal/mol expected for Coulombic stabilization of a single positive charge separated from a single negative charge by 3.4 Å.[14] Only minor contributions to these differences may result from uncertainty in the separation of the charges and inductive effects resulting from methyl substitution at the amino group. Previous estimates of substituent effects on proton affinities and gas-phase basicities have ranged from <1 to ca. 30 kcal/mol;[4,5] thus the effect of more than 100 kcal/mol for the quaternary amino group is enormous by comparison. The value of 239.8 kcal/mol estimated above for the PA of betaine is consistent with the value of 242 kcal/mol estimated by Beauchamp and co-workers[6] in an FT-ICR and with their value of 243 estimated by AM1 calculations.

These results, with those of Beauchamp et al.,[6] represent the first determinations of the gas-phase basicity of a zwitterionic compound. In contrast to the gas-phase data, the basicities of betaine and acetate differ by only 1 kcal/mol in water and 9 kcal/mol in DMSO.[15] The contrast between the condensed and gas phases confirms the substantial effect of solvent in the stabilization of charges in the zwitterion.

An unexpected result of this kinetic method study is that the gas-phase properties of isomeric compounds have been estimated in a reaction mixture (i.e., the desorption ionization plasma). It is also noteworthy that the reference compounds employed in this study included some compounds whose high GB values are due to simultaneous binding to the proton by two spatially separate groups (e.g., the α,ω-diamines) and others which did not. The method is sufficiently rugged to allow such a range of reference compounds. Note that in estimating the gas-phase basicity of betaine it has been necessary to assume that there are no significant reverse activation energies for the competitive dissociations. It is expected that in the case of betaine the ion−dipole-promoted reverse reaction will proceed without an activation barrier.

The study of the ion chemistry and thermochemistry of zwitterions has relevance to a fundamental understanding of the process involved in the ionization of biological compounds and the behavior and stability of their ions in the gas phase. This information in turn should find practical application in the increasing number of studies in which polyfunctional compounds are ionized and characterized as the gas-phase ions.

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Supporting Information Available: Product ion spectra of the proton-bound dimers of betaine with pyridine and TMDAE (4 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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