

Gas-Phase Basicity of $(\text{CH}_3)_3\text{N}^+-\text{C}_6\text{H}_4-\text{COO}^-$ Zwitterions: A New Class of Organic Super Bases

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While it is well known that zwitterions and salt bridges commonly occur in solution, the effect of solvent on and the chemistry of these ionic forms of organic molecules in the gas phase are much less established. Whereas glycine is a zwitterion in solution within a range of pH, the neutral form of this amino acid is ~ 18 kcal/mol more stable in the absence of water.¹ Evidence for the existence of the zwitterionic form of gas-phase arginine in the presence of a charge has been recently reported,² as has the role of salt bridges in the structure and dissociation pathways of larger gas-phase biomolecules.³ The electric field produced by a nearby charge can dramatically affect the protonation energy of a carboxylate group in the gas phase. This effect was independently measured both by Cooks and Beauchamp and their co-workers,⁴ who reported the gas-phase basicity (GB) of the zwitterion betaine, $(\text{CH}_3)_3\text{N}^+\text{CH}_2\text{CO}_2^-$. The GB of betaine is 239.2 kcal/mol.⁵ The gas-phase acidity (GA) of glycine (which corresponds to the GB of $\text{H}_2\text{NCH}_2\text{CO}_2^-$) is 334.7 kcal/mol.⁶ The difference in protonation energy of the carboxylate group in betaine vs glycine (95.5 kcal/mol) is primarily due to the nearby positively charged quaternary nitrogen in betaine. The effect of charge on the energetics of zwitterion or ion-pair formation is reported elsewhere.⁷ Here, we show how the distance between the fixed positive charge and the carboxylate group in positional isomers of trimethylammonio benzoic acid affects the GB of these zwitterionic molecules.

Experiments were performed using a 2.7-T Fourier transform mass spectrometer with an external electrospray ionization source.⁸ Trimethylammonio benzoic acid (TMAB) was synthesized using the method of Hojo and co-workers,⁹ except that the end product was not recrystallized. Ions were formed by electrospray using aluminosilicate capillaries pulled to a ~ 5 μm o.d. and 50:50 $\text{CH}_3\text{OH}:\text{H}_2\text{O}$ solutions that were $\sim 10^{-4}$ M in TMAB and reference base. The GB of *o*-TMAB was measured with the

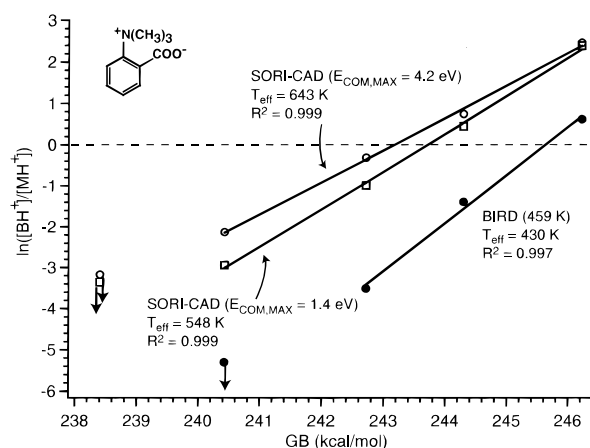


Figure 1. Kinetic method plots for the dissociation of $(\text{B}\cdot\text{TMAB} + \text{H})^+$ measured by BIRD at a vacuum chamber temperature of 459 K (\bullet) and by SORI-CAD with a maximum center of mass collision energy of 1.4 eV (\square) and 4.2 eV (\circ). Effective temperatures obtained from the slope of these data for each of the conditions are indicated. The reference bases used and their GB values are 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (GB = 246.2 kcal/mol), 1,5,7-triazabicyclo[4.4.0]dec-5-ene (GB = 244.3 kcal/mol), 1,8-diazabicyclo[5.4.0]undec-7-ene (GB = 242.7 kcal/mol), 1,5-diazabicyclo[4.3.0]non-5-ene (GB = 240.4 kcal/mol), and *N,N,N',N'*-tetramethylguanidine (GB = 238.4 kcal/mol). Arrows indicate upper limits to the measured ratio.

kinetic method of Cooks et al.,¹⁰ using several reference bases of kinetic and known GB. Kinetic plots for proton-bound dimers of *o*-TMAB and reference base, B, were obtained using both blackbody infrared radiative dissociation (BIRD) and sustained off-resonance irradiation collisional activated dissociation (SORI-CAD). With BIRD, ions are activated by absorption of blackbody photons generated by the heated vacuum chamber walls.⁸ With SORI-CAD, ions are activated via multiple low-energy collisions with nitrogen gas introduced into the vacuum chamber by a pulsed valve ($P[\text{N}_2] = 2 \times 10^{-6}$ Torr). The internal energy deposited into an ion with SORI-CAD can be readily varied and can be much higher than that deposited by BIRD.¹¹

Dissociation of proton-bound dimers consisting of a reference base and *o*-TMAB results in formation of BH^+ (reaction k_1) and/or *o*-TMABH⁺ (reaction k_2).



The GB of *o*-TMAB is obtained from the x -intercept of a plot of the natural log of the branching ratio, $\ln(k_1/k_2)$, vs GB of the reference base (Figure 1). The GB of *o*-TMAB obtained from the BIRD data at 459 K is 245.6 kcal/mol.¹² Values of 243.7 and 243.2 kcal/mol are obtained for the SORI-CAD data obtained with maximum center-of-mass collision energies of 1.4 and 4.2 eV, respectively.¹³ An “effective” temperature can be obtained from the slope of these data.¹⁰ The effective temperature obtained from the BIRD data is 430 K. This value is slightly lower than the actual temperature of the vacuum chamber walls, consistent with the high-energy tail of the ion internal energy distribution

(10) Cooks, R. G.; Patrick, J. S.; Kotiaho, T.; McLuckey, S. A. *Mass Spectrom. Rev.* **1994**, *13*, 287–339.

(11) Schnier, P. D.; Jurchen, J. C.; Williams, E. R. *J. Phys. Chem. B* **1999**, *103*, 737–745.

(12) The calculated GB of the isomer methyl dimethylammonio benzoate is 227.8 kcal/mol. Based on the large difference in GB, we rule this compound out as a possible contaminant.

(13) The maximum center of mass collision energy for the various protonated dimers in a data set was fixed by changing the maximum laboratory frame collision energy.

(1) (a) Jensen, J. H.; Gordon, M. S. *J. Am. Chem. Soc.* **1991**, *113*, 7917–7924. (b) Jensen, F. *J. Am. Chem. Soc.* **1992**, *114*, 9533–9537. (c) Jensen, J. H.; Gordon, M. S. *J. Am. Chem. Soc.* **1995**, *117*, 8159–8170.

(2) (a) Price, W. D.; Jockusch, R. A.; Williams, E. R. *J. Am. Chem. Soc.* **1997**, *119*, 11988–11989. (b) Wyttenbach, T.; Witt, M.; Bowers, M. T. *Int. J. Mass Spectrom.* **1999**, *183*, 243–252. (c) Jockusch, R. A.; Price, W. D.; Williams, E. R. *J. Phys. Chem. A* **1999**, *103*, 9266–9274.

(3) (a) Schnier, P. D.; Price, W. D.; Jockusch, R. A.; Williams, E. R. *J. Am. Chem. Soc.* **1996**, *118*, 7178–7189. (b) Jockusch, R. A.; Schnier, P. D.; Price, W. D.; Strittmatter, E. F.; Demirev, P. A.; Williams, E. R. *Anal. Chem.* **1997**, *69*, 1119–1126. (c) Deery, M. J.; Summerfield, S. G.; Buzy, A.; Jennings, K. R. *J. Am. Soc. Mass Spectrom.* **1997**, *8*, 253–261. (d) Summerfield, S. G.; Whiting, A.; Gaskell, S. J. *Int. J. Mass Spectrom. Ion Processes* **1997**, *162*, 149–161.

(4) (a) Patrick, J. S.; Yang, S. S.; Cooks, R. G. *J. Am. Chem. Soc.* **1996**, *118*, 231–232. (b) From 4a: Beauchamp, J. L. Presented at the 209th National Meeting of the American Chemical Society, Anaheim, CA, April 2–7, 1995.

(5) Price, W. D.; Jockusch, R. A.; Williams, E. R. *J. Am. Chem. Soc.* **1998**, *120*, 3474–3484.

(6) Hunter, E. P.; Lias, S. G. In *NIST Chemistry Webbook, NIST Standard Reference Database Number 69*; Mallard, W. G., Lindstrom, P. J., Eds.; National Institute of Standards and Technology: Gaithersburg, MD, March 1998.

(7) Strittmatter, E. F.; Wong, R. L.; Williams, E. R. *J. Am. Chem. Soc.*, submitted.

(8) Price, W. D.; Schnier, P. D.; Williams, E. R. *Anal. Chem.* **1996**, *68*, 859–866.

(9) Hojo, M.; Utaka, M.; Yoshida, Z. *Tetrahedron* **1971**, *27*, 4255–4262.

Table 1. Gas-Phase Basicities (in kcal/mol) of *o*-, *m*-, and *p*-Trimethylammoniumbenzoate and Betaine

	exptl	B3LYP (6-311++G**)		LMP2 (cc-pVTZ(-f)++)
		460 K	298 K	298 K
betaine	239.2 ^a	237.0	240.0	242.7
<i>o</i> -(CH ₃) ₃ N ⁺ PhCOO ⁻	245.6	245.5	248.4	250.7
<i>m</i> -(CH ₃) ₃ N ⁺ PhCOO ⁻			264.1	266.4
<i>p</i> -(CH ₃) ₃ N ⁺ PhCOO ⁻			267.5	269.9

^a From ref 5.

being somewhat depleted relative to that of a true Boltzmann.⁵ For SORI-CAD low and high collision energy data, the effective temperature is 548 and 643 K, respectively. The branching ratio for the protonated dimer of *o*-TMAB and one of the bases (1,5,7-triazabicyclo[4.4.0]dec-5-ene) inverts with ion internal energy. This indicates that the dissociation entropies for the two reaction channels differ. Using a modified version of the kinetic method,¹⁴ a difference in transition-state entropy for formation of BH⁺ vs TMABH⁺ of roughly 6 cal mol⁻¹ K⁻¹ is obtained; i.e., dissociation via the ion-zwitterion channel occurs via a “looser” transition state, as was reported earlier for dissociation of protonated dimers of betaine and reference base.⁵ Due to its lower temperature, the GB of *o*-TMAB measured by BIRD should be closer to the true GB at 298 K than the values obtained by SORI-CAD.

GB values of *o*-, *m*-, and *p*-TMAB were calculated using both hybrid density functional and local MP2 theory at both 298 and 460 K (Table 1).¹⁵ The calculated GB of *o*-TMAB at 460 K is in excellent agreement with the experimentally measured values. The GB values of *m*- and *p*-TMAB are much higher and are outside the range that we are able to measure experimentally due to a lack of readily ionizable reference bases. The excellent agreement between experiment and theory for *o*-TMAB, however, suggests that the calculated values for the meta and para isomers should be reasonably accurate. Dissociation of protonated dimers of *p*-TMAB and 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene results in formation of only protonated *p*-TMAB, consistent with its much higher GB. It should be noted that the most basic organic molecule listed in the NIST database is 7-isopropyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (ITBD), with a GB of 248.4 kcal/mol.⁶ The GB values of both *m*- and *p*-TMAB are significantly greater than that of ITBD. Thus, both of these zwitterionic organic molecules are more basic than the current organic “super bases” used as reference compounds.

(14) (a) Cheng, X.; Wu, Z.; Fenselau, C. *J. Am. Chem. Soc.* **1993**, *115*, 4844–4848. (b) Cerda, B. A.; Wesdemiotis, C. *J. Am. Chem. Soc.* **1996**, *118*, 11884–11892.

(15) Local MP2 and density functional calculations were performed in Jaguar v3.5 (Portland, OR). The GB was calculated from the sum of electronic, zero point, and internal energy and entropy differences between the protonated and neutral TMAB plus a proton. Electronic energy was calculated at both the local MP2 (cc-pVTZ(-f)++//6-31G** basis) level and the B3LYP (6-311++G**//6-311G** basis) level. All other energy and entropy differences were determined from frequencies calculated at the RHF 6-31G* level. To account for the anharmonicity in the vibrational modes, these frequencies were scaled by 0.899.

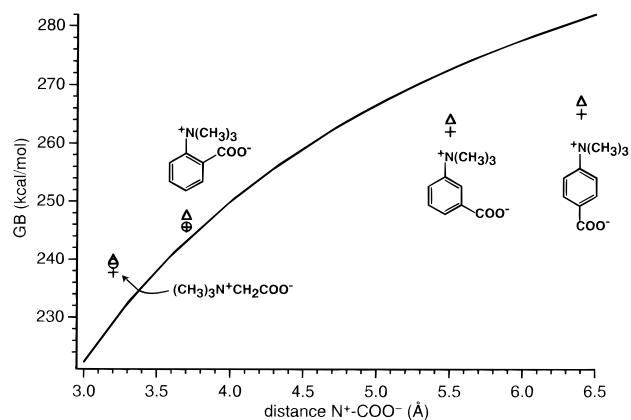


Figure 2. Plot of experimental (O), B3LYP (+), and local MP2 (Δ) GB of Me₃N⁺-X-COO⁻ (X= CH₂ or phenyl) versus the distance between the N and the midpoint of the two oxygens in COO⁻. The solid line is obtained by subtracting a point-charge Coulomb interaction at the distance indicated from the GB of benzoate.

It is clear that the proximity of the charged (CH₃)₃N⁺ group to the COO⁻ group has a significant effect on the GB of these isomers, i.e., the protonation free energy of the carboxylate group. As a reference, the GB of benzoate is 333.0 kcal/mol⁶ (a measure of the protonation free energy or GB of an aromatic COO⁻ group in the absence of a positive charge). To estimate the effect of the Coulomb interaction, a point-charge Coulomb energy was calculated from the coordinates of the quaternary nitrogen (*q*₁ = +1) and the midpoint of the two carboxylate oxygen atoms (*q*₂ = -1). These values, subtracted from the GB of benzoate (solid line), along with the calculated and measured GB values for the three TMAB isomers and betaine are shown in Figure 2. This extremely simplistic model provides a rough estimate of the GB of these zwitterions but overpredicts the effects of the Coulomb interaction as a function of distance. This could be due, in part, to inductive effects in the aromatic ring not taken into account with this model.

These results are particularly significant in that they demonstrate that the GB of a molecule can be easily varied by changing the distance between a fixed charge group and the protonation site. These results suggest that the GB of zwitterionic molecules can be easily adjusted between 248.4 and 284.1 kcal/mol, a range within which there are no organic reference bases currently available. This could provide a strategy to bridge the gap between gas-phase acidity (GB of anion) and basicity scales for organic molecules.

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