chloride; (8) washed with CH₂Cl₂ (three times for 2 min); (9) Boc-amino acid (two-fold excess) in CH₂Cl₂ was added and mixed for 10 min; Boc-Arg(NO₂) and Boc-N^{im}-benzylhistidine were dissolved in DMF and both these amino acids were used in threefold excess; (10) added DCI (twofold excess) in CH₂Cl₂ and mixed for 2.5 hr; (11) washed with DMF (three times for 3 min); (12) steps 9 and 10 repeated using 1:1 DMF–CH₂Cl₂ as the solvent; (13) washed with DMF (three times for 3 min); (14) washed with a 1:2 mixture of methanol–chloroform (three times for 2 min).

Aspartylarginylvalyltyrosylisoleucylhistidine. Boc-N-methyl-phenylalanine polymer ester (5.75 g, 3.25 mmol of N-methylphenyl-alanine) was placed in the reaction vessel and the Boc group removed at each cycle with 50% trifluoroacetic acid in CH₂Cl₂. Boc-amino acids coupled successively were: proline, N^{im}-benzylhistidine, iso-leucine, O-benzyltyrosine, valine, nitroarginine, and β-benzyl-aspartic acid. At the end, the polymer, after washing once with CF₃COOH, was suspended in freshly distilled CF₃COOH and a slow stream of HBr (prewashed through a gas washer containing 10% resorcinol in acetic acid) was passed through the suspension for 35 min. The mixture was filtered and washed twice with CF₃-COOH and the combined filtrates were evaporated to dryness. The oily residue was triturated with dry ether and the powdery mass filtered, washed twice with dry ether, and dried in vacuo over P₂O₅ and KOH pellets. The crude product (3.00 g) was hydroge-nated over palladium black (2 g) in a mixture of methanol–acetic acid–water (5:1:1) under 2 atm of H₂ for 36 hr to give 2.62 g of the crude, unblocked peptide. The product was dissolved in deionized water, a small amount of insoluble material removed by filtration, and the solution passed through a column of anion exchange resin IRA-410 (acetate form) (column dimensions: 2 × 75 cm). The product was eluted with additional water and the aqueous eluant indicating absorption at 280 mμ was pooled and lyophilized. Silica gel tlc (BAW) of the product showed one major component and two minor components.

A portion of the lyophilized powder (600 mg) was dissolved in a minimum volume of 0.01 N acetic acid and the solution subjected to purification on a column of CM cellulose (4 × 75 cm) by the procedure reported by Khairallah, et al.[19] The major com-ponent yielded 0.417 g of amorphous powder: loss of water at 100°, 4.84%; [α]²³D −4.5° (c 1, AcOH); tlc (cellulose) R_f 0.21 (BAW), R_f 0.26 (BAWP), R_f 0.50 (PAW); PC R_f 0.10 (BAW), R_f 0.43 (BA-WP), E(Glu) 1.07. Amino acid ratios found were: Asp 0.92; Arg 1.00; Val 1.10; Tyr 0.80; Ile 1.11; His 1.03; Pro 0.00.

(19) P. A. Khairallah, I. H. Page, F. M. Bumpus, and R. R. Smeby, Science, 138, 523 (1962).

Anal. Calcd for C₃₆H₅₃N₁₁O₉·H₂O·2CH₃COOH: C, 52.09; H, 6.80; N, 16.72. Found: C, 51.90; H, 6.67; N, 16.79.

Formation of cyclo-(Pro-MePhe-) during the Synthesis of Prolyl-N-methylphenylalanine Polymer Ester. From Boc-N-methylphenyl-alanyl polymer ester (3 g, containing 1.86 mmol of Boc-MePhe) the corresponding hydrochloride salt of prolyl-N-methylphenylalanine polymer ester was synthesized by the general procedure. The free amino group was liberated by treatment with 30 ml of 10% Et₃N in DMF (two times for 6 min). The polymer was washed with DMF and the effluent combined with the Et₃N wash. The polymer on hydrolysis at this stage showed very little proline or N-methylphenylalanine (Table Ia). The combined filtrates were evaporated to dryness on a rotary evaporator, the residue dissolved in water (15 ml), the pH adjusted to 3.5 with 1 N HCl under ice-cold conditions, and the aqueous solution extracted with AcOEt (six 10-ml portions). The organic phase was washed with H₂O (three 10-ml portions) and saturated NaCl solution (two 10-ml portions), dried (Na₂SO₄), and evaporated to give 250 mg of crude product. Crystallization from a small volume of AcOEt yielded cyclo-(Pro-MePhe-): mp 137° (softens at 132°); tlc (silica gel) R_f 0.68 (BAW), R_f 0.77 (BAWP), R_f 0.70 (BPW); amino acid ratios found were Pro 1.01, MePhe 1.00; ir (KBr) 2960, 2907, 1660, 1640 (d), 1453, 1395, 1294 cm⁻¹.

Anal. Calcd for C₁₅H₁₈N₂O₂: C, 69.72; H, 7.02; N, 10.85. Found: C, 69.96; H, 6.96; N, 10.86.

Similarly, filtrates obtained during the neutralization of the hy-drochloride salts of alanyl-N-methylphenylalanyl polymer, alanyl-prolyl polymer and prolylprolyl polymer were evaporated in vacuo. Hydrolysis of the residue in each case gave an equal ratio of the corresponding acids in the expected range.

Boc-N^{im}-benzylhistidine Polymer Ester. Hydroxymethyl poly-mer (2 g) prepared according to the procedure reported by Stewart and Young[12] was washed with DMF and treated with a solution of Boc-N^{im}-benzylhistidine (1.726 g, 5 mmol) in DMF (30 ml). The mixture was stirred for 10 min followed by treatment with a solu-tion of DCI (1.03 g; 5 mmol) in CH₂Cl₂ (5 ml). The mixture was percolated with N₂ for 4 hr, filtered, and washed with DMF. The polymer was again treated with Boc-N^{im}-benzylhistidine (0.863 g) and DCI (0.5 g) as above, and the mixture stirred overnight under N₂. The polymer was filtered, washed with DMF, MeOH, AcOH, CHCl₃, and EtOH, and dried over P₂O₅ and KOH pellets. Weight increase (0.444 g) and amino acid analysis of the hydrolysate indi-cated that 0.5 mmol of N^{im}-benzylhistidine was esterified per gram of the polymer.

Communications to the Editor

A Complete Thermodynamic Analysis of the "Anomalous Order" of Amine Basicities in Solution[1,2]

Sir:

It has been recognized for many years[3-5] that the basicity order of simple aliphatic amines in aqueous solution at 25° (NH₃ < primary < secondary > tertiary) cannot be explained by any single cumulative substit-uent factor such as the inductive effect. The source of the peculiar inverted order has merited the attention

of a number of able chemists.[6-9] It is not idiosyncratic to any alkyl series (such as the methylamines) nor is it limited to aqueous solution or 25°.

The availability of accurate gas-phase basicities,[10] when combined with appropriate thermodynamic properties for solution of the amines from the gas phase to water,[11] now makes it possible to separate all thermodynamic properties for the ionization into internal (gas phase) terms and those for solvation. Previous estimates of relative gas-phase basicities

(1) Taken in part from the thesis of F. M. J., III, University of Pitts-burgh, 1971.
(2) Supported by grants from the National Science Foundation (GP-6550-X) and the Office of Saline Water.
(3) G. Bredig, Z. Phys. Chem., 13, 191 (1894).
(4) N. F. Hall and M. R. Sprinkle, J. Amer. Chem. Soc., 54, 3469 (1932).
(5) H. S. Harned and B. B. Owen, ibid., 52, 5079 (1930); 50, 3157 (1928).

(6) H. C. Brown, H. Bartholomay, Jr., and M. D. Taylor, ibid., 66, 435 (1944).
(7) F. E. Condon, ibid., 87, 4481, 4485, 4494 (1965).
(8) R. G. Pearson and D. C. Vogelsong, ibid., 80, 1038 (1958).
(9) A. F. Trotman-Dickenson, J. Chem. Soc., 1293 (1949).
(10) M. T. Bowers, D. H. Aue, H. M. Webb, and R. T. McIver, Jr., J. Amer. Chem. Soc., 93, 4314 (1971).
(11) F. M. Jones, III and E. M. Arnett, Progr. Phys. Org. Chem., in press.

Table I. Thermodynamic Properties (Relative to Ammonia) for Ionization and Solvation of Amines and Their Conjugate Ions at 25°[a]

Amine	$\delta_R \Delta G_i°$ (g)[b]	$\delta_R \Delta G_i°$ (w)	$\delta_R \Delta G_s°$ (B)	$\delta_R \Delta G_s°$ (BH+)	$\delta_R \Delta H_i°$ (g)[c]	$\delta_R \Delta H_i°$ (w)	$\delta_R \Delta H_s°$ (B)	$\delta_R \Delta H_s°$ (BH+)	δ_R (TΔS_i°) (g)[d]	δ_R (TΔS_i°) (w)	δ_R (TΔS_s°) (B)	δ_R (TΔS_s°) (BH+)
NH₃	0	0	0	0	0	0	0	0	0	0	0	0
MeNH₂	9.5	1.92	−0.27	7.3	9.3	0.70	−2.57	6.0	−0.2	−1.22	−2.30	−1.3
Me₂NH	15.8	2.09	0.00	13.7	15.4	−0.45	−4.72	11.2	−0.4	−2.54	−4.72	−2.6
Me₃N	20.4	0.75	1.07	20.7	19.6	−3.67	−4.67	18.6	−0.8	−4.42	−5.76	−2.1
EtNH₂	12.0	1.96	−0.21	9.8	11.8	1.23	−4.51	6.1	−0.2	−0.73	−4.31	−3.8
Et₂NH	20.6	2.42	0.22	18.4	20.2	0.25	−6.77	13.1	−0.4	−2.17	−6.99	−5.2
Et₃N	27.1	2.01	1.26	26.4	26.3	−2.17	−8.22	20.3	−0.8	−4.17	−9.48	−6.1
i-PrNH₂	14.4	1.94	(−0.06)[e]	(12.4)	14.2	1.48	−4.83	7.9	−0.2	−0.46	(−4.77)	(−4.5)
t-BuNH₂	16.5	1.96	(0.03)	(14.5)	16.3	1.87	−5.56	8.8	−0.2	−0.09	(−5.58)	(−5.7)
◇NH	18.3[f]	2.79	(0.80)	(16.3)	17.9	0.03	−5.72	12.2	−0.4	−2.76	(−6.52)	(−4.2)
▭NH	20.1[f]	2.81	1.20	18.5	19.7	0.32	−6.65	12.7	−0.4	−2.49	−7.85	−5.8
⬠NH	21.4[f]	2.56	1.56	20.4	21.0	0.17	−7.09	13.7	−0.4	−2.39	−8.67	−6.7
NH₃ (ref value)	ΔG_i°, 198.4[g]	12.62	−2.408	−77.1[g]	Proton affinity, 207	12.49	−8.54	−83.8	8.60	−0.127	−6.14	−6.7

[a] All values in kcal/mol. All values except those cited under footnotes b–d and those in parentheses are taken from ref 1 and 11. They were derived from a variety of literature sources, with suitable corrections, or were measured by F. M. J., III. For ionization, BH⁺ + NH₃ ⇌ B + NH₄⁺; for solution, ΔP_s(B or BH⁺) − ΔP_s(NH₃ or NH₄⁺). [b] Values in this column and that under c have standard errors of ±0.1–0.2 kcal/mol; all others have errors <±0.1 kcal/mol. [c] Determined from $\delta_R \Delta H_i°$(g) = $\delta_R \Delta G_i°$(g) + δ_R(TΔS_i°)(g). [d] Formal entropy difference derived from symmetry factors after S. Benson.[14] [e] Values in parentheses are estimated from measured values for closely related compounds by Barclay–Butler correlations of ΔH° vs. ΔS° for which all correlation coefficients were >0.99. [f] From ref 10. [g] We are grateful to Professor D. M. Aue for helpful suggestions regarding the derivation of these data.

followed the inductive effect order[12] proving that the inverted order in solution is due to solvation. Now, a complete dissection of the data allows separation of solvation effects on the ionization reaction into those due to structural changes in the amines (B) and those assignable to their ions (BH⁺).

The fundamental equations for combining the data are derived from the following cycle where P represents any thermodynamic property (G°, H°, S°), g and w represent gas phase and water medium, and subscripts i and s represent ionization and solution processes, respectively, and

gas phase   BH⁺(g) →¹ H⁺(g) + B(g)

            ²↓   ³↓   ⁴↓

aqueous solution   BH⁺(w) →⁵ H⁺(w) + B(w)
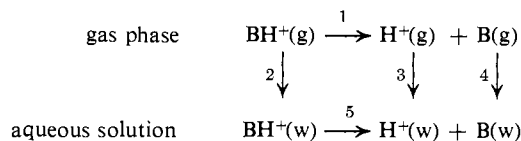
from which

$$BH⁺(g) \longrightarrow H⁺(g) + B(g) \qquad \Delta P_i(g) \qquad (1)$$

$$BH⁺(g) \longrightarrow BH⁺(w) \qquad \Delta P_s(BH⁺) \qquad (2)$$

$$H⁺(g) \longrightarrow H⁺(w) \qquad \Delta P_s(H⁺) \qquad (3)$$

$$B(g) \longrightarrow B(w) \qquad \Delta P_s(B) \qquad (4)$$

$$BH⁺(w) \longrightarrow B(w) + H⁺(w) \qquad \Delta P_i(w) \qquad (5)$$

$$\Delta P_i(g) = \Delta P_i(w) - \Delta P_s(B) - $$
$$\Delta P_s(H⁺) + \Delta P_s(BH⁺) \qquad (6)$$

An identical equation could be derived for any other base B′ and the difference between them would show the effect of structural change which we represent by a structural operator δ_R.[13] Ammonia is the reference compound, for which $\delta_R \Delta P = 0$. The term for the proton will subtract out leaving

$$\delta_R \Delta P_s(BH⁺) = \delta_R \Delta P_i(g) + \delta_R \Delta P_s(B) - \delta_R \Delta P_i(w) \qquad (7)$$

for determining the structural effect on the relative solvation of each ammonium ion from the gas phase to water. There is no direct way of determining $\delta_R \Delta P_s$(BH⁺) experimentally. In the dissection presented in Table I the measured gas-phase property is the relative free energy of ionization $\delta_R \Delta G_i°$(g) which is determined by ion cyclotron spectrometry using a trapped ion cell.[10] Enthalpy differences, $\delta_R \Delta H_i°$(g), are derived by assuming that the only entropy contribution to $\delta_R \Delta S_i°$(g) is from differences in symmetry numbers.[14]

Although we expect to discuss these results in detail elsewhere, several points are worth noting.

(a) The effect of substituting alkyl groups for hydrogens on ammonia has a large effect on $\Delta G_i°$(g) and $\Delta H_i°$(g) which is almost entirely neutralized by large and opposite effects on the free energy and enthalpy of solvation of the corresponding ions. This is in conformity with the qualitative theory of Trotman-Dickenson,[9] as also is the fact that the free energies of solution of the amines are almost constant except for a slight base strengthening contribution for amines of higher carbon number.

(b) However, as Everett[15] suggested, hydrophobic interactions of alkyl groups produce large changes in the enthalpy and entropy of solution of the free amines which almost exactly compensate.[16] Furthermore, thanks to the water structure breaking effect of the charge on nitrogen, the entropy of solvation of the ammonium ions is almost constant within the methyl

(12) J. I. Brauman, J. M. Riveros, and L. K. Blair, J. Amer. Chem. Soc., 93, 3914 (1971); S. B. Munson, ibid., 87, 2332 (1965).

(13) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions," Wiley, New York, N. Y., 1963.

(14) S. W. Benson, J. Amer. Chem. Soc., 80, 5151 (1958). The validity of this assumption is supported by recent measurements by P. Kebarle which were graciously communicated to us privately: P. Kebarle, ibid., in press.

(15) M. C. Cox, D. H. Everett, D. A. Landsman, and R. J. Munn, J. Chem. Soc. B, 1373 (1968).

(16) E. M. Arnett and D. R. McKelvey, "Solvent-Solute Interactions," J. F. Coetzee and C. D. Ritchie, Ed., Marcel Dekker, New York, N. Y., 1969.

series. However, the corresponding term $\delta_R(T\Delta S^\circ)_S(B)$ for the free bases is very sensitive to the size and number of alkyl groups and dominates the structural effect on entropy of ionization in solution, $\delta_R(T\Delta S^\circ)_i(w)$. Thus, contrary to Trotman-Dickenson's proposal, the decreasing entropy of ionization in going down the series NH₃, primary, secondary, tertiary, is caused primarily by an overwhelmingly large decreasing entropy of solution of the amines rather than to an increasing entropy of solution for their ions.

(c) The heats of solution of the amines become increasingly exothermic, as the carbon content is increased, and are apparently much more dependent on hydrophobic structure-making effects[15-17] than on hydrogen bonding to or from the amino group.[7] Hydrophobic effects assert themselves less strongly in the corresponding $\delta_R\Delta H_s^\circ(BH^+)$ for the primary ions. However, the same increasingly endothermic progression of NH₃ (0) < primary (~9) < secondary (~15) < tertiary (~21) is found for the methyl and ethyl series. The decreasing increments $9 > 7 = 7$ kcal/mol are of the correct magnitude to be attributed to hydrogen bonding.[8,18] Some contribution from Born charging energy due to changing ion size must be involved, but the effect of changing alkyl groups within a primary, secondary, or tertiary series is so small compared to differences between series that we feel safe in attributing the effect primarily to hydrogen bonding.

(d) Finally, we note that a complete analysis of these ionization data still does not lead to a simple interpretation of the anomalous order. Most of the contributing thermodynamic properties change in a reasonable and orderly way. The inverted order of aqueous base strength arises from slight differences in the rate of change of the thermodynamic properties in response to progressive alkyl substitution.

(17) C. V. Krishnan and H. L. Friedman, *J. Phys. Chem.*, **75**, 3598 (1971).

(18) E. M. Arnett, L. Joris, E. Mitchell, T. S. S. R. Murty, T. M. Gorrie, and P. v. R. Schleyer, *J. Amer. Chem. Soc.*, **92**, 2365 (1970).

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have described new equilibrium techniques for determining accurate quantitative relative gas-phase basicities of amines.[2,3] Gas-phase basicities of alkylamines determined by these techniques are reported here and correlated with ionization potentials to provide quantitative relative hydrogen affinities. These data provide a basis for detailed quantitative interpretation of the factors governing basicity of alkylamines in the gas phase and in solution.

We define the gas-phase basicity (GB) of B as the negative of the free energy (ΔG°) for reaction 1, while the proton affinity (PA) is the negative of the enthalpy (ΔH°) for reaction 1. The hydrogen affinity (HA)

$$B + H^+ \rightleftharpoons BH^+ \tag{1}$$

$$B\cdot^+ + H\cdot \rightleftharpoons BH^+ \tag{2}$$
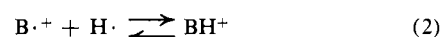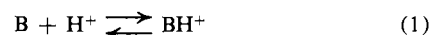
$$PA(B) = -IP(B) + HA(B\cdot^+) + IP(H\cdot) \tag{3}$$

of $B\cdot^+$ is the negative enthalpy for reaction 2 and is equivalent to the bond dissociation energy of BH^+. From these definitions eq 3 readily follows. From our PA's and from known adiabatic IP's,[4] accurate relative hydrogen affinities can be calculated for the first time (Table I).

Table I. Gas-Phase Basicities (GB) and Derived Thermodynamic Data for Alkylamines[a]

Amine	GB[a]	PA[b]	IP[d]	HA
Ammonia	[198 ± 3]	[207 ± 3][c]	234.1	127 ± 3
Methylamine	[209.8][a]	[218.4][a]	206.8	111.6
Ethylamine	212.5	221.1	204.3	111.8
n-Propylamine	213.7	222.3	202.5	111.2
n-Butylamine	214.3	222.8	200.9	110.1
Isobutylamine	214.6	223.2	200.6	110.2
Isopropylamine	214.7	223.3	201.1	110.8
sec-Butylamine	215.8	224.4	200.6	111.4
tert-Butylamine	216.8	225.4	199.2	111.0
Dimethylamine	216.6	224.9	190.0	101.3
Diethylamine	221.8	230.1	184.7	101.2
Di-n-propylamine	223.6	231.9	180.8	99.1
Di-n-butylamine	224.4	232.7	177.3	96.4
Diisopropylamine	226.0	234.3	178.3	99.0
Trimethylamine	221.3	229.1	180.3	95.8
Triethylamine	228.0	235.8	173.0	95.3
Tri-n-propylamine	230.3	238.2	166.7	91.3

[a] All values in kcal/mol. GB's were measured relative to methylamine (209.8 kcal/mol). Multiple overlap of ΔG°'s established errors in relative GB's at 0.2 kcal/mol (see ref 3). [b] PA's calculated from GB's by correction for symmetry and the entropy of H⁺ [A. P. Altshuller, *J. Amer. Chem. Soc.*, **77**, 3480 (1955)]. [c] A plot of PA *vs.* IP (Figure 1) was used to approximate ΔPA for NH₃ and CH₃NH₂. Absolute PA of NH₃ taken as 207 ± 3 kcal/mol [M. A. Haney and J. L. Franklin, *J. Chem. Phys.*, **50**, 2029 (1969)]. [d] Reference 4.

Basicities of amines in solution have presented difficulties in interpretation for many years.[5] Munson

(2) Both high pressure and trapped ion techniques provide equilibrium constants for proton-transfer reactions (ref 3).

(3) M. T. Bowers, D. H. Aue, H. M. Webb, and R. T. McIver, *J. Amer. Chem. Soc.*, **93**, 4314 (1971).

(4) K. Watanabe, T. Nakayama, and J. R. Mottl, *J. Quant. Spectrosc. Radiat. Transfer*, **2**, 369 (1962).

(5) (a) E. J. King, "Acid Base Equilibria," Pergamon Press, New York, N. Y., 1965, pp 141 ff; (b) J. Clark and D. D. Perrin, *Quart. Rev., Chem. Soc.*, **18**, 295 (1964); (c) J. J. Christensen, R. M. Izatt, D. P. Wrathall, and L. D. Hansen, *J. Chem. Soc. A*, 1212 (1969); (d) A. G. Evans and S. D. Hamann, *Trans. Faraday Soc.*, **47**, 34 (1951); (e) A. F. Trotman-Dickenson, *J. Chem. Soc.*, 1293 (1949); (f) R. G. Pearson and D. C. Vogelsang, *J. Amer. Chem. Soc.*, **80**, 1038 (1958).

Quantitative Relative Gas-Phase Basicities of Alkylamines. Correlation with Solution Basicity[1]

Sir:

While many relative gas-phase basicities have been established in recent years, the inherently qualitative nature of these data make a precise evaluation of the factors governing gas-phase basicity impossible. We