$HClO_4$. The solution was placed in a photochemical reactor (ca. 420-mL aliquots), purged with nitrogen for 30 min, and then irradiated under a continuous flow of nitrogen until HPLC analysis revealed the almost complete disappearance of **1**. The irradiated solution was concentrated under vacuum (at 30 °C) to a volume of ca. 5 mL and chromatographed on a reversed-phase silica gel column (Merck). The column was eluted initially with water and then with a mixture of water–acetonitrile (95/5 v/v). The fractions containing pure photoproduct (TLC, R_f = 0.5 in system A) were combined, concentrated under vacuum to a small volume, and passed through a Dowex (Cl^-) column to give, after lyophilization, 0.13 g of **3**, 85% yield: ^1H NMR (CD_3CN, TMS) δ 11.62 (s, 1, C5-NH), 9.95 (d, 2, C6-NH), 9.06 (m, 2, Py^+-αH), 8.67 (m, 1, Py^+-γH), 8.53 (s, 1, C2-H), 8.18 (m, 2, Py^+-βH), 7.98 (m, 1, CHO), 6.07 (dd, 1, C1′-H), 5.56 (m, 2, 2′-H and 3′-H), 4.28 (m, 3, 4′-H and 5′-H_2), 2.05 (s, 9, $3CH_3$); UV (H_2O, pH 6.0) nm (ϵ) 300 (sh, 2200), 235 (max, 15300), 215 (min, 9960); UV (H_2O, pH 10.0) 260 (max, 10700), 232 (min, 8600). Anal. Calcd for $C_{21}H_{24}N_5O_8Cl$: C, 49.4; H, 4.7; N, 13.7. Found: C, 48.9; H, 4.6; N, 13.4.

Preparation of 4. **1** (0.3 g, 0.61 mmol) was dissolved in a freshly prepared 1 mM aqueous solution of $NaHCO_3$ (3 L, pH $\simeq$7.8). The solution was deoxygenated and irradiated under conditions similar to those described for preparation of **3**. Irradiation was continued until 90% of **1** was reacted as revealed by HPLC analysis. A resulting suspension of water-insoluble photoproduct was filtered through a membrane filter (0.45 μm). The solid material was washed well with water and dried under vacuum over P_2O_5 to give **3**, 0.102 g, as a red powder (37% yield): UV (CH_3CN) nm (ϵ) 327 (max, 38400), 258 (min, 7000); UV ($CHCl_3$) 334 (max, 40600); FAB MS, m/z (rel intensity) 914 (0.3, M^+ + 2), 911 (0.3, M^+ - 1), 457 (13), 456 (45), 198 (100); EI MS (70 eV), m/z (rel intensity) 457 (10), 456 (8), 414 (4), 396 (3), 354 (1), 336 (1), 259 (5), 198 (82). Anal. Calcd for $C_{42}H_{44}N_{10}O_{14}$: C, 55.2; H, 4.8; N, 15.3. Found: C, 54.8; H, 4.8; N, 15.1.

Preparation of 6. **5** (0.1 g, 0.4 mmol) was dissolved in water (2 L) containing triethylamine (0.01 M) buffered to pH 9.0 with CH_3COOH. The solution was deoxygenated and irradiated as in the case of **3** to ca. 90% conversion of substrate. Centrifugation of the resulting suspension gave a red solid material, which was washed with water and dried under vacuum to give **6**, 0.054 g (64% yield) as a red powder: ^1H NMR ($CHCl_3$, TMS) δ 8.48 (s, 2, C2-H), 8.22 (b s, 4, Py-αH), 7.82 (s, 2, C8-H), 5.14 (m, 4, Py-βH), 3.84 (s, 6, N9-CH_3), 3.26 (s, 2, Py-γH); UV (CH_3CN) nm (ϵ) 327 (max, 37200), 257 (min, 4300); UV ($CHCl_3$) 336 (max, 40100), 264 (min, 6500); FAB MS, m/z (rel intensity) 425 (0.8, M^+ + 1), 424 (0.8, M^+), 423 (2.30 (M^+ - 1), 212 (100). Anal. Calcd for $C_{22}H_{20}N_{10}$: C, 62.2; H, 4.7; N, 33.0. Found: C, 61.7; H, 4.6; N, 32.7.

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Enthalpies of Solvation of Ions. Aliphatic Carboxylic Acids: Steric Hindrance to Solvation?

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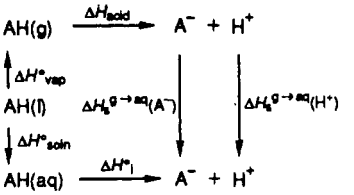
Abstract: By use of solution calorimetry, plus literature data such as enthalpies of vaporization and gas-phase acidities, a thermochemical cycle is used to evaluate the relative enthalpies of solvation of carboxylate anions from the gas phase into aqueous solution. It is found that the weaker solution-phase acidity of the larger carboxylic acids arises from a complex mixture of entropic and enthalpic effects on the solvation of the neutral acids and the anions. An increase in steric bulk results in an *increase* in the enthalpy of solvation of both the acids and anions, but the neutral acid is more sensitive to the steric effect than the anion is. Solvation enthalpy thus is the opposite predicted by the usual concept of "steric hindrance to solvation"; it is the entropy of solvation that makes the larger acids more weakly acidic in terms of free energy in aqueous solution.

The relationships that chemists have perceived between structure and reactivity were altered in the late 1960s with the advent of modern gas-phase ion/molecule chemistry. Many "well-known" structural trends, such as the nonmonotonic change in the basicities of the multiply methylated amines[1] and the decrease in acidity of the aliphatic alcohols with increasing alkyl group size,[2] were shown to be due in large part to the solvation of the species involved. In the gas phase, where only the intrinsic structure of the molecule controls the reactivity, different trends were found. Notably, in the work of Brauman and Blair,[2] the importance of polarizability as a controlling effect in alcohol acidities was shown. It was also postulated[2] that the reversal of acidities for the alcohols on going to the condensed phase was due to "steric hindrance to solvation" of the alkoxides. This concept is one widely used in organic chemistry[3] to explain how a change in alkyl group structure affects reactivity trends, generally by increasing the energy of an ionic species in solution more than of some neutral species in equilibrium with it.

Scheme I



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While the importance of polarizability in explaining gas-phase structure–reactivity trends has been demonstrated many times over,[4] "steric hindrance to solvation" has been more of a facile explanation than an experimentally defined interaction. We approach this problem by analyzing the enthalpies of solvation of ions from the gas phase into aqueous solution, $\Delta H_s^{g\rightarrow aq}$. Should steric hindrance to solvation be important, this could be evident as a reduction in the enthalpy of solvation. We limit ourselves in this work to aqueous solvent, with the intent of examining less structured ones later.

Ion solvation enthalpies can be obtained by use of the thermochemical cycle in Scheme I. This method was used by Aue and co-workers[5] to determine solvation enthalpies for alkylammonium ions. Similarly, Haberfeld and Rakshit[6] showed that the reversal in the acidities of the haloacetic acids (XCH_2CO_2H) on going from the gas phase (X = Br > Cl > F in acidity) to aqueous solution is due to the relatively greater solvation of the $FCH_2CO_2^-$ ion than for $BrCH_2CO_2^-$. It was argued[6] that the fluoro anion, being the most basic in the gas phase, is therefore the best hydrogen-bond acceptor in aqueous solution and is therefore better solvated compared to the less basic gas-phase anions. We use the same approach here to analyze the solvation of aliphatic carboxylic acids. In aqueous solution, the acidity of the aliphatic carboxylic acids decreases with increasing alkyl group size,[7] while in the gas phase the opposite is true.[8,9]

Experimental Section

Calorimetry. The solution calorimeter is similar in construction to the one described by Arnett and co-workers,[10] with the following exceptions. The 300-mL Dewar flask is stirred by a Transicoil PN1121-115 electric motor with internal tachometer. This is regulated for constant revolutions per minute (rpm) and is operated typically at 1000 rpm.

The temperature sensor is a Fenwall GA51M2 glass-encased thermistor. This was originally sealed with epoxy glue into the end of a 8-mm glass tube, with the glass thermistor tip projecting from the epoxy so as to be in direct contact with the solution. This direct contact was intended to reduce the thermal mass of the sensor and thus decrease the response time, but we now find that the same thermistor simply placed in a 5-mm NMR tube filled with silicone oil responds to the heater pulse at essentially the same rate as the thermistor did when in direct contact with the liquid.

The detection circuitry is a Wheatstone resistance bridge with the thermistor as one leg of the bridge. The other resistive elements are metal film resistors, adjusted to approximately balance the bridge at the operational temperature. The voltage across the bridge is fed to a Siliconix 7600 operational amplifier, set up as an inverting amplifier with a gain of 10, followed by another stage of amplification (LM356 op amp) with a gain of 10. The output voltage from this circuit, ca. 5 mV/mdeg change in the calorimeter temperature, with a high-frequency noise level of ca. 0.5 mV, is fed to a strip chart recorder. The heat of stirring results in a constantly rising base line on the recorder. To obtain a flat base line, a ramp voltage from an op amp integrator circuit is electronically summed with the output of the detection electronics; the output of this integrator circuit is adjusted manually until the base-line fall is just canceled out by the heat of stirring.

The calibration heater is a 56-Ω carbon resistor placed in a 5-mm-diameter glass tube. The tube is sealed at the bottom and filled with silicone oil to improve heat transfer. A 12.05-V dc pulse, either 0.313 or 3.32 s long (time regulated by a 555 timer chip circuit), is used to calibrate the thermistor both before and after an injection of sample.

Liquid samples are injected into the calorimeter with a Hamilton 50- or 25-μL syringe; the amount delivered is determined by weighing the syringe before and after delivery. Solid samples are injected with a 5-mL disposable syringe, modified by cutting the tip off and sealing it with a Teflon disk that pops out on depressing the plunger. The weighed solid sample is placed in a small well in this disk. Typically, 20–50 mg of sample is injected into 300 mL of water, resulting in solution concentrations of 0.6–4 mM.

The accuracy of the calorimeter was tested by measuring the enthalpies of solution or reaction for a number of compounds, as given in Table I. The worst case of deviation from the literature values was 0.3 kcal/mol, and the average was 0.1 kcal/mol. For the runs with NaOH/water, the solution was 0.01 M in base, assuring at least a 2-fold excess of base in all cases. For the weakest acids, the smaller range of sample was used to give a larger base/acid ratio. The temperature of the solution was 24 ± 1 °C (ambient) in a temperature-regulated room.

All experiments were done with use of water purified by a MilliQ apparatus. Carboxylic acids were obtained commercially. The enthalpy of fusion for pivalic acid was determined by differential scanning calorimetry[11] to be 0.5 kcal/mol. The pivalic acid sample was purified by sublimation.

The measured enthalpies of solution of the carboxylic acids were not corrected for ionization. Due to the weak acidities involved (pK_as 3.5–5.0) and the small values of $\Delta H°_i$, this would be a negligible correction.

For pivalic acid, with the standard slotted stirrer[10] used at 1000 rpm, dissolution of the acid was visibly slow. A wide-bladed stirrer resulted in increased heat of stirring and in complete visible dissolution of the acid.

Table I. Comparison of Measured Enthalpies of Solution and Ionization with Literature Values

compd	$\Delta H°_s$-(H_2O)	$\Delta H°_s$-(HO^-/H_2O)[a]	$\Delta H°_i$[b]	$\Delta H°_i$[c]	dev
malononitrile	1.4 ± 0.2	1.7 ± 0.1	13.6 ± 0.3	13.4	0.2
nitromethane	0.7 ± 0.04	−6.7 ± 0.1	5.9 ± 0.1	5.9	0.0
1-nitropropane	−0.2 ± 0.01	−10.8 ± 0.2	2.7 ± 0.2	2.6	0.1
acetic acid	−0.4 ± 0.05	−13.9 ± 0.2	−0.2 ± 0.2	−0.1	−0.1
2,4-pentanedione	0.4 ± 0.2	−10.5 ± 0.2	2.4 ± 0.4	2.4	0.0
phenol	2.6 ± 0.1	−5.8 ± 0.1	4.9 ± 0.2	4.8	0.1
o-cresol	0.0 ± 0.1	−7.4 ± 0.2	5.9 ± 0.3	5.7	0.2
m-cresol	0.4 ± 0.1	−7.1 ± 0.4	5.8 ± 0.5	5.5	0.3
p-cresol	0.7 ± 0.2	−7.0 ± 0.3	5.6 ± 0.5	5.5	0.1
KCl	4.2 ± 0.02			4.2[d]	0.0

[a] Enthalpy of solution into 0.01 M aqueous NaOH, this work. [b] $\Delta H°_i$ = 13.3 kcal/mol + $\Delta H°_s(H_2O)$ − $\Delta H°_s(HO^-/H_2O)$, where 13.3 kcal/mol is the enthalpy of autoprotolysis of water: $2H_2O \rightarrow H_3O^+ + HO^-$.[7] [c] Literature values, from ref 7. [d] Enthalpy of solution. Wagman, D. D.; Evans, W. H.; Parker, V. B.; Schumm, R. H.; Halow, R.; Bailey, S. M.; Churney, K. L.; Nuttall, R. L. *J. Phys. Chem. Ref. Data, Suppl.* **1982**, *11* (1).

Results

Aqueous enthalpies of ionization are taken from a standard compilation.[7] Gas-phase enthalpies of acidity are from a recent work covering a large number of such acids in a single overlapping scale.[9] The standard-state symbol is not included for any thermochemical values involving gas-phase ions, since these cannot be directly related to the standard state of 1 atm.[8] Obtaining enthalpies of vaporization for carboxylic acids is not straightforward because of the partial dimerization of the vapor.[12] Enthalpies of vaporization are taken from calorimetric work covering a number of the acids of interest.[12,13] For those not available this way, $\Delta H°_{vap}$ has been calculated from the correlation of the observed $\Delta H°_{vap}$ vs boiling point for aliphatic carboxylic acids and then corrected for the dimerization of carboxylic acids in the gas phase.[14] It should be noted that the correction for dimerization in ref 12 is inconsistently applied; on the basis of data in ref 14, all carboxylic acids should have approximately the same fraction of dimer present in the gas phase at room temperature, yet the fraction used in ref 12 varies from 8 to 47% in

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Table II. Enthalpies Pertinent to Scheme I, for RCO_2H

R	pK_a[a]	ΔH_{acid}[b]	$\Delta H°_{vap}$[c]	$\Delta H°_{soln}(AH)$[d]	$\Delta H°_i$[e]
Me	4.76	348.5 [0.0]	12.2	−0.41	−0.10
Et	4.87	347.4 [−1.1]	14.0	−0.56	−0.14
n-Pr	4.82	346.5 [−2.0]	16.7	−0.56	−0.69
i-Bu	4.78	345.5 [−3.0]	17.5[f]	−0.75	−1.15
i-Pr	4.85	346.0 [−2.5]	15.4	−0.68	−0.75
n-Bu	4.84	346.2 [−2.3]	19.3[f]	−0.63	−0.70
H	3.75	345.3 [−3.2]	11.4	−0.15	−0.04
t-Bu	5.03	344.6 [−3.9]	17.1[f,g]	+0.32	−0.70
$MeOCH_2$	3.57	342.3 [−6.2]	21.3[f]	−1.60	−0.95
FCH_2[h]	2.59	338.6	19.64	+3.01	−1.67
$ClCH_2$[h]	2.86	336.0	18.51	+3.76	−1.14
$BrCH_2$[h]	2.90	335.2	18.40	+3.47	−1.00
F_2CH[h]	1.34	330.8	15.80	−1.68	−1.99
Cl_2CH[h]	1.36	328.9	14.04	−1.71	−2.04

[a] Reference 7. [b] Reference 8 and 9, kilocalories per mole. Values in square brackets are relative to the value listed as 0.0. [c] Reference 12, corrected with data from ref 14 as noted in the text, kilocalories per mole. [d] This work, kilocalories per mole. [e] Reference 7, kilocalories per mole. [f] From the bp vs $\Delta H°_{vap}$ correlation in ref 12, plus the dimerization correction from ref 14. [g] $\Delta H°_{vap}$(pivalic acid) was calculated by adding the enthalpy of fusion (0.5 kcal/mol, this work) to the literature enthalpy of vaporization. [h] From reference 6.

an irregular fashion. We have thus used the calorimetric vaporization data from ref 12 but the dimerization data from ref 14, with a constant 44% dimerization for all RCO_2H.[15]

These data are presented in Table II. Data for the haloacetic acids from ref 6 are also included for purposes of comparison. The enthalpy of solvation of the neutral acid AH is calculated with eq 1, while the enthalpy of solvation of the ions $A^- + H^+$ is obtained from eq 2.

$$\Delta H°_s{}^{g\to aq}(AH) = -\Delta H°_{vap}(AH) + \Delta H°_{soln}(AH) \quad (1)$$

$$\Delta H_s{}^{g\to aq}(A^- + H^+) = -\Delta H_{acid}(AH) - \Delta H°_{vap}(AH) + \Delta H°_{soln}(AH) + \Delta H°_i(AH) \quad (2)$$

To obtain the single-ion enthalpy of solvation of A^- requires the enthalpy of solvation of the proton. This has been the object of much dispute; we adopt a value of −271.6 kcal/mol here. This is derived from Randles' value for the electrochemically determined solvation enthalpy of the potassium ion, with the later correction for surface potential by Trasatti and further adjustments by Klots.[16] Using the Randles–Trasatti–Klots (RTK) value, we calculate $\Delta H_s{}^{g\to aq}(A^-)$ as the enthalpy of solvation of $A^- + H^+$ from eq 2 minus the RTK value for $\Delta H_s{}^{g\to aq}(H^+)$ of −271.6 kcal/mol. While future work may result in a better absolute anchor value for single-ion solvation enthalpies, whatever value is adopted does not affect the conclusions in this work concerning the *relative* solvation of the A^- ions. We nevertheless present the data as single-ion solvation enthalpies for comparison to other data and to obtain a feeling for the size of the enthalpies involved, relative to the same quantity for the neutral carboxylic acids. These data are given in Table III.

We estimate the uncertainty in $\Delta H°_s{}^{g\to aq}(AH)$ as ±0.6 kcal/mol and that in $\Delta H_s{}^{g\to aq}(A^- + H^+)$ as ±0.9 kcal/mol. These arise from the relative uncertainties in the gas-phase acidities of ±0.2 kcal/mol,[9] in the enthalpy of solution of ±0.1 kcal/mol, in the enthalpy of ionization of ±0.1 kcal/mol, and in the enthalpy of vaporization of ±0.5 kcal/mol. The last is probably the least certain link in the thermochemical cycle, although the observed correlation of boiling point with $\Delta H°_{vap}$ provides some assurance that the data are reasonable.

(15) Data from ref 12 are incorrectly cited in ref 23, a standard compilation of enthalpies of formation and vaporization. For *i*-$PrCO_2H$, the $\Delta H°_{vap}$ from ref 12 is cited without a correction for dimerization; for *n*-$PrCO_2H$, the corrected one is cited; and for $EtCO_2H$, a more complicated thermochemical cycle is used that differs from the value in ref 12 by 3 kcal/mol.

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Table III. Gas-Phase to Aqueous Solution Enthalpies of RCO_2H and RCO_2^-[a]

R	$\Delta H°_s{}^{g\to aq}$ (AH)[b]	$\Delta H°_s{}^{g\to aq}$ ($A^- + H^+$)	$\Delta H°_s{}^{g\to aq}$ (A^-)[b]	$\Delta H°_s{}^{g\to aq}$ (A^-)[c]
Me	−12.7 [0.0]	−361.3	−89.7 [0.0]	−77.0 [0.0]
Et	−14.6 [−1.9]	−362.1	−90.5 [−0.8]	−75.9 [1.1]
n-Pr	−17.4 [−4.7]	−364.5	−92.9 [−3.2]	−75.1 [1.5]
i-Bu	−18.2 [−5.5]	−364.9	−93.3 [−3.6]	−75.1 [1.9]
i-Pr	−16.1 [−3.4]	−362.8	−91.2 [−1.5]	−75.1 [1.9]
n-Bu	−19.9 [−7.2]	−366.8	−95.2 [−5.4]	−75.3 [1.8]
H	−11.5 [1.2]	−356.9	−85.3 [4.4]	−73.8 [3.2]
t-Bu	−17.4 [−4.7]	−362.0	−90.4 [−0.7]	−73.0 [4.0]
$MeOCH_2$	−22.9 [−10.2]	−366.1	−94.5 [−4.8]	−71.6 [5.4]
FCH_2[c]	−16.6 [−3.9]	−356.9	−85.3 [4.4]	−68.7 [8.3]
$ClCH_2$[c]	−14.8 [−2.0]	−351.9	−80.3 [9.4]	−65.5 [11.4]
$BrCH_2$[c]	−14.9 [−2.2]	−351.1	−79.5 [10.2]	−64.6 [12.4]
F_2CH[c]	−17.5 [−4.8]	−350.3	−78.7 [11.0]	−61.2 [15.8]
Cl_2CH[c]	−15.8 [−3.0]	−346.7	−75.1 [14.6]	−59.3 [17.6]

[a] Kilocalories per mole. [b] Value in square brackets is $\delta\Delta H_s{}^{g\to aq}$, relative to the value for $MeCO_2H$. [c] Reference 6.

Table IV. Solvation Enthalpies for RCO_2H and RCO_2^- by Size of R[a]

R–CO_2H	pK_a	ΔH_{acid}	$\Delta H°_s{}^{g\to aq}$ (AH)[b]	$\Delta H_s{}^{g\to aq}$ (A^-)[b]	$\Delta H_s{}^{g\to aq}$ (A^-)[c]
Series 1: G_3CCO_2H, G = H or Me					
Me	4.75	348.5	−12.7 [0.0]	−89.7 [0.0]	−77.0 [0.0]
Et	4.87	347.4	−14.6 [−1.9]	−90.5 [−0.8]	−75.9 [1.1]
i-Pr	4.84	346.0	−16.1 [−3.4]	−91.2 [−1.5]	−75.1 [1.9]
t-Bu	5.03	344.6	−17.4 [−4.7]	−90.4 [−0.7]	−73.0 [4.0]
Series 2: $H(CH_2)_nCO_2H$, *n* = 0–4					
H	3.75	345.3	−11.5 [1.2]	−85.3 [4.4]	−73.8 [3.2]
Me	4.75	348.5	−12.7 [0.0]	−89.7 [0.0]	−77.0 [0.0]
Et	4.87	347.4	−14.6 [−1.9]	−90.5 [−0.8]	−75.9 [1.1]
n-Pr	4.81	346.5	−17.4 [−4.7]	−92.9 [−3.2]	−75.5 [1.5]
n-Bu	4.82	346.2	−19.9 [−7.2]	−95.2 [−5.4]	−75.3 [1.8]
Series 3: $G_3CCH_2CO_2H$, G = H or Me					
Et	4.87	347.4	−14.6 [0.0]	−90.5 [0.0]	−75.9 [0.0]
n-Pr	4.81	346.5	−17.4 [−2.8]	−92.9 [−2.4]	−75.5 [0.4]
i-Bu	4.77	345.5	−18.2 [−3.6]	−93.3 [−2.8]	−75.1 [0.8]

[a] Data from Tables II and III; all enthalpies in kilocalories per mole. [b] Values in square brackets are relative to the value listed as 0.0.

Discussion

In Table IV, the data are presented in three different series that begin with the acids with smaller alkyl groups and progress to the larger alkyl groups in a regular pattern for each series. In all three series, the *neutral* acids show a consistent trend of increasingly exothermic enthalpies of solvation as the alkyl group becomes larger. The data in Table II indicate that this is mostly due to an increase in the enthalpy of vaporization with increasing size. This trend of the larger acids being better solvated would tend to weaken acidity as steric bulk of the R group increases.

For the carboxylate *anions* in series 1, where the increases in alkyl group size is most proximate to the reactive site, there is an increase in the enthalpy of solvation for R = Me to Et to *i*-Pr and then a decrease in solvation on going to R = *t*-Bu. This small decrease in $\Delta H_s{}^{g\to aq}(A^-)$ from R = *i*-Pr to R = *t*-Bu is evidence for steric hindrance to solvation, but the uncertainty of the data (±0.9 kcal/mol, as indicated previously) is such that this cannot be taken as definitive. For the anions in series 2 and 3, where the change in alkyl group bulk is more distant from the carboxylate site, increased alkyl group bulk consistently results in a more exothermic solvation process for the anions.

In all three series, however, it is the neutral acid that consistently has the larger increase in exothermicity of solvation for a given increase in alkyl group bulk, compared to the anion. This results in the *smaller* RCO_2H being stronger acids ($\Delta H°$) in aqueous solution. When combined with the stronger gas-phase acidity for the *larger* carboxylic acids, the result is a close balance of the enthalpy of acidity in aqueous solution, where the larger acids have slightly more exothermic values.

Table V. Entropies of Solvation for RCO_2H in Aqueous Solution

R	ΔS_{acid}[a]	$\Delta S°_{vap}$[b]	$\Delta S°_{soln}$[b]	$\Delta S°_{ic}$	$\Delta S_s^{g\to aq}(AH)$[d,e]	$\Delta S_s^{g\to aq}(A^-)$[e,f]
H	23.5	25.5	−1.1	−17.3	−26.6 [4.2]	−36.5 [9.0]
Me	23.5	27.1	−3.7	−22.1	−30.8 [0.0]	−45.5 [0.0]
Et	23.5	27.8	−6.6	−22.8	−34.4 [−3.6]	−49.8 [−4.3]
n-Pr	23.5	27.0	−9.2	−24.4	−36.2 [−5.4]	−53.2 [−7.7]

[a] Reference 9. [b] See text. [c] Reference 7. [d] From the entropic analogue of eq 1. [e] Values in square brackets are relative to the value for $MeCO_2H$. [f] From the entropic analogue of eq 2.

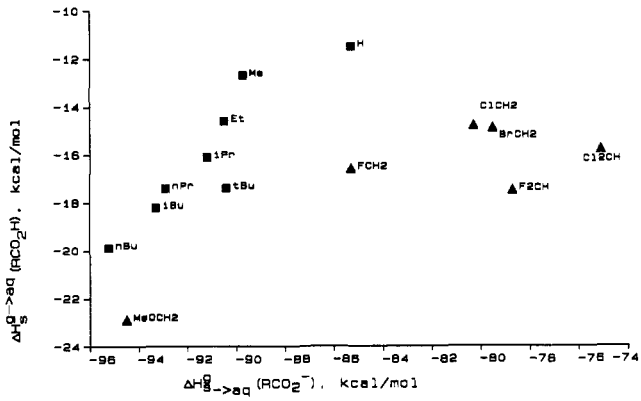

Figure 1. Single-ion solvation enthalpies of carboxylic acids vs carboxylate anions.

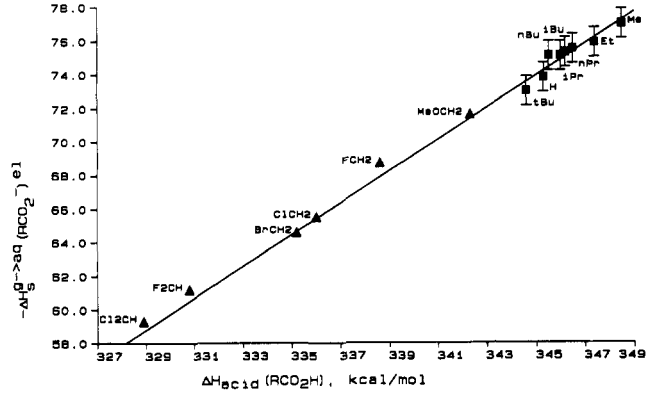

Figure 2. Enthalpy of electrostatic solvation for RCO_2^- vs ΔH_{acid} (RCO_2H). Relative uncertainties in ΔH_{acid} are ±0.1 kcal/mol. The line is the least-squares fit to aliphatic carboxylic acids (■).

The gas-phase acidity of the aliphatic carboxylic acids is also not a good criterion for predicting the solvation enthalpies of the acids or their conjugate anions. For the aliphatic carboxylate anions in this work, ΔH_{acid} (gas phase) versus $\Delta H_s^{g\to aq}(RCO_2^-)$ gives a scatter plot, with correlation coefficient $r = 0.053$. In contrast, carboxylic acids with good polar/inductive electron-acceptor groups, such as the haloacetic acids, show a regular trend ($r = 0.927$) of *decreasing* solvation with decreasing gas-phase basicity of the carboxylate anion,[6] as might be expected. For the neutral form, there is a weak correlation ($r = -0.35$) of $\Delta H_s^{g\to aq}(RCO_2H)$ with $\Delta H_{acid}(RCO_2H)$, with the more acidic acids being better solvated but with R = H and *t*-Bu less solvated than expected. Figure 1 shows the solvation energies of the neutral acids and their anions plotted against each other. It reveals a general parallel trend of increasing solvation for both the neutral acid and the anion as the size of the alkyl group is varied ($r = 0.91$). This indicates that some factor in solvation is operating for both the neutral and anion. In contrast, the haloacetic acids vary little in neutral solvation enthalpy, but a great deal in anion solvation enthalpy.

To further examine these data, we adopt the analysis of Aue and co-workers, which they used to examine the solvation energetics of alkylamines and their conjugate acids, the ammonium ions.[6] It was argued by these workers that the solvation of the ion can be divided into a general solvation term, primarily due to cavity making plus van der Waals interactions, and an electrostatic term, arising from the charge of the ion. The ion's general solvation was taken as approximately equal to the solvation of the corresponding neutral amine. This results in

$$\Delta H_s^{g\to aq}(\text{ion}) = \text{general solvation term} + \text{electrostatic term}$$

$$\simeq \Delta H_s^{g\to aq}(\text{neutral}) + \Delta H_s^{g\to aq}(\text{ion})^{el} \quad (3)$$

The electrostatic term, $\Delta H_s^{g\to aq}(\text{ion})^{el}$, is thus calculated as the difference of the enthalpy of solvation of the ion and of the neutral species. These data for our RCO_2H species are presented in the final columns in Tables III and IV. It can be seen that all carboxylate anions with alkyl groups larger than methyl are *less* solvated than acetate in terms of $\Delta H_s^{g\to aq}(A^-)^{el}$. Hydrogen as a smaller substituent also results in decreased electrostatic solvation. Within the experimental uncertainty of this derived electrostatic term, nothing can be said about any trend within the groups from ethyl to isobutyl, however. Figure 2 reveals that reduced electrostatic solvation closely follows weaker gas-phase anion proton affinity ($r = 0.944$), as might be expected for hydrogen-bonding interactions with the solvent. Any effect due to the difference in size of the *tert*-butyl group and of hydrogen is effectively subtracted out of the electrostatic term, as indicated by the fit of both of these points to the line in Figure 2. The scatter correlation mentioned previously for the total solvation enthalpies vs anion proton affinity now has become an excellent correlation, when the nonelectrostatic term is removed. This implies that the analysis is correctly separating steric and electrostatic effects. As shown in Figure 2, the haloacetic acids and methoxyacetic acid also fit the correlation for the aliphatic acids, within the experimental uncertainty.

Why do the enthalpies of solvation of these species show the trend that they do? The simple concept of steric hindrance to solvation, as commonly taught in undergraduate[17] and graduate[3] texts, does not agree with the experimental observation that the larger species, both neutral and ionic, are consistently *better* solvated enthalpically. The nature of the thermodynamics of solvation of nonpolar species in water must be examined. It has been shown that alkanes have a zero or slightly negative enthalpy of solution in water at room temperature; their low solubility is due to a negative entropy of solvation (pure liquid to aqueous solution).[18] This implies that dissolution of the alkane must result in a net ordering of the solvent, due to the nature of cavity formation, relative to the pure solvent.[18] A reasonable visualization of this is that there is some disorder in bulk water, due to the large free volume present. Cavity formation results in a more ordered volume of solvent around the surface of the cavity.[18] This is true at room temperature, although at higher temperatures enthalpy disfavors solvation as well.[19] To properly analyze the behavior seen here, the complete entropic cycle corresponding to Scheme I must be examined also. The entropy of gas-phase proton transfer, ΔS_{acid}, is essentially the same for all these acids.[20] The entropy of aqueous acidity becomes increasingly negative with larger R groups.[7] Entropies of vaporization can be obtained from vapor pressure vs temperature data,[21] corrected for the partial dimer-

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ization of the acids in the gas phase.[14] Entropies of solution come from vapor pressure vs composition data for aqueous solutions.[22] The last appear to be the limiting factor at present; values were found in the literature only for R = H, Me, Et, and *n*-Pr. An entropy of solvation for the proton of 30.9 eu is used.[16] These data are summarized in Table V.

For the entropies, increasing alkyl chain length results in more ordered solvation for both the acid and the conjugate base, but now the increment for each homologation is larger for the anion than the neutral. This disfavors the bulkier anions, resulting in the larger acid being less acidic for entropic reasons. If the analogous separation, based on eq 3, of the anions' solvation entropies into electrostatic and neutral terms is done, the electrostatic entropies of solvation shown in Table V are obtained. We estimate the relative uncertainty in $\Delta S_s^{g\rightarrow aq}(A^-)^{el}$ as at least 4 eu, so nothing definite can be said about the apparent trend observed.

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Conclusions

It has been found that the enthalpy of acidity of aliphatic carboxylic acids becomes stronger with an increase in substituent bulk in RCO_2H, in both gas-phase and aqueous solution. The reasons for this are completely different in the two phases, however. As noted,[2] polarizability is the controlling force in the gas phase, while relative solvation energies appear to be the major factor in solution. Larger alkyl groups result in increased solvation enthalpies both for the acid and for the anion. The relatively greater solvation enthalpy of most of the neutral aliphatic carboxylic acids with increasing steric bulk, compared to the effect in the corresponding anions, when added to the gas-phase acidity favoring the larger acid, results in a close balance for the enthalpy of acidity in solution. It is the entropic effect of the anion resulting in a more ordered solution with increasing substituent bulk, relative to the neutral acid, that actually makes the larger carboxylic acids weaker in aqueous solution. Chemical intuition, in the form of the concept of steric hindrance to solvation,[3,17] reflects not an enthalpic process but an ergonic one.

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One-Electron Oxidation of 9-Methylanthracene and 9-[(Trimethylsilyl)methyl]anthracene: Reversal of Radical-Cation Selectivity by the Trimethylsilyl Group

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Abstract: Oxidation of 9-methylanthracene by pyridine/iodine proceeds mainly through nucleophilic attack on the intermediate anthracene radical cation rather than deprotonation. Replacement of a methyl proton by trimethylsilyl completely reverses the regiochemistry.

One-electron oxidation of hydrocarbons produces startling effects on reactivity that have only recently been recognized. Among these are activation toward electrocyclic[1] reactions, enhanced electrophilicity, and increased acidity.[2] Pharmacologically, such behavior is dramatically illustrated by the metabolic activation of certain methylated polycyclic aromatic hydrocarbons (PAH's) to form potent carcinogens[3] in which radical cations are mechanistically implicated.[4] However, it is not yet clear whether carcinogenicity of PAH's is coherent with the properties of their radical cations. Nevertheless, their metabolic activation follows reactivity patterns, i.e., deprotonation leading ultimately to formation of benzylic nucleic acid residues[5] and epoxidation leading to similar adducts, which are consistent with the duality of alkylaromatic radical cations as both strong acids and strong electrophiles. Activation and covalent binding of chemical carcinogens either via their radical cations or, more probably, through oxidation to strong electrophiles capable of alkylating macromolecular cellular nucleophiles is one of the triggering processes in carcinogenesis. Therefore, it is clear that a thorough understanding of the variables associated with deprotonation of alkylated PAH radical cations is necessary for the elucidation of the oxidative mechanisms in general and PAH carcinogenesis in particular.

We have been interested in elucidating oxidative mechanisms operating in PAH metabolism. Our investigations have been focused on studies on the role of solvent, stereoelectronics, and other effects that mimic changes in metabolic pathways using noncarcinogenic anthracene derivatives. For example, we reported

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