

## Thermodynamics of the Ionization of Some Thiols in Aqueous Solution

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Dissociation constants for a number of thiols have been determined by a spectrophotometric method and the corresponding heats of ionization have been determined calorimetrically. The following values were obtained for the ionization reactions in water at 25°C ( $pK_a$ -values corrected to zero ionic strength;  $\Delta H_i$ -values determined at the indicated ionic strengths,  $I$ ):

	$pK_a$	$\Delta H_i$ kcal/mole	$I$
$C_2H_5SH$	10.61	6.42	0.015
$(CH_3)_2CHSH$	10.86	5.38	0.010
$(CH_3)_3CSH$	11.22	5.30	0.01—0.1
$HOCH_2CH_2SH$	9.72	6.21	0.015
$CH_3CONHCH_2CH_2SH$	9.92	6.26	0.015
$^-OCOCH_2SH$	10.68	6.28	0.05
$^-OCOCH_2CH_2SH$	10.84	6.10	0.05
$^+NH_3CH_2CH_2SH$	8.23	7.43	0.01
$o^-OCOC_6H_4SH$	8.88	5.72	0.1
$p^-OCOC_6H_4SH$	5.80	—	—
$CH_3COSH$	3.62	0.56	0.015

Energy changes for processes in solution, in particular aqueous ionization processes, are discussed. Free energies, heats, and entropies for the thiol ionization processes investigated are discussed and are compared with corresponding values for analogous carboxylic acids and phenols.

The weakly acidic properties of thiols have been known for a long time and it is recognized that a great deal of their chemical properties in aqueous solution are intimately connected with formation of the thiolate ion,  $RS^-$ . Of special interest in this connection seem to be oxidation reactions (see, *e.g.*, Ref.<sup>1</sup>) and in particular several proposed biochemical reaction mechanisms.<sup>2,3</sup>

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Surprisingly enough no systematic study of dissociation constants has hitherto been undertaken for thiols in water and practically no heats (or entropies) of ionization are known. In this paper we report results from a thermodynamic study of the ionization processes in aqueous solution of a representative group of thiols. Dissociation constants have been determined by a spectrophotometric technique and heats of ionization have been determined calorimetrically.

### EXPERIMENTAL

*Materials.* The alkane thiols, EtSH, *i*-PrSH and *t*-BuSH (Fluka, *purum*) were purified by fractional distillation at atmospheric pressure through a 10-plate column until they were better than 99.9 % pure, as judged by VPC analysis (Pye Argon Chromatograph, Apiezone column).

Thioglycolic acid,  $\beta$ -mercaptopropionic acid and  $\beta$ -hydroxyethanethiol (Fluka, *purum*) were fractionally distilled at reduced pressure. Purities were 99.8–100 % as indicated by iodine titration.

$\beta$ -Aminoethanethiol (Fluka, *purum*) was purified by repeated sublimation at reduced pressure. The equivalent weight determined by iodine titration indicated the compound to be 99.8 % pure.

$\beta$ -Acetylaminoethanethiol was prepared from  $\beta$ -aminoethanethiol by acetylation in aqueous solution with acetic anhydride. The compound was fractionally distilled at *ca.* 1 mm Hg. Equivalent weights as determined by iodine titration in acetic acid were 0.3 % too low.

Thiolacetic acid was prepared from hydrogen sulfide and acetic anhydride.<sup>4</sup> The compound was repeatedly distilled at atmospheric pressure and at 100 mm Hg. Titration with standard alkali under nitrogen gave the theoretical equivalent weight.  $n_D^{25} = 1.4618$ ,  $d_4^{25} = 1.0627$ .

*o*- and *p*-Mercaptobenzoic acids were prepared and purified as described in Ref.<sup>5</sup>

"Cellosolve" (ethyleneglycolmonoethylether) used in the calorimetric control experiments was *purissimum* quality. It was fractionally distilled before use. When dissolved in water it showed a neutral reaction.

*Determination of dissociation constants.* Dissociation constants were determined spectrophotometrically according to the method recently described by Ernst and Menashi.<sup>6</sup> Use was made of the fact that the thiolate ion has a strong absorbance in the 250 m $\mu$  region where absorption by the undissociated thiol group is very low.

The spectrophotometric measurements were made using a Beckman DU spectrophotometer fitted with a thermostated ( $25.0 \pm 0.1^\circ\text{C}$ ) cell compartment.

pH measurements (used as a check on the calculated values) were performed with glass electrodes (Radiometer Type 202 B IP in the acid and neutral range, and Type B AH in the alkaline range) and a Radiometer pH meter 22. The pH meter was calibrated against standard buffer solutions ( $\pm 0.02$  pH units).

Water used in preparing the thiol solutions was glass distilled, freed from oxygen and carbon dioxide by boiling and stored under nitrogen.

Stock solutions of the thiols (0.05–0.3 g thiol/l of water) were prepared immediately before the measurements. Thiol concentrations were determined by iodine or alkali titration before and after the experiments (*t*-BuSH cannot be titrated). The titration values did not change during a series of measurements, except for EtSH. Here the concentrations were slightly lower after the experiments, and in this case it was assumed that this was due to an evaporation roughly linear with time. The small correction for the change in ethanethiol concentration during the experiment was applied.

In the spectrophotometric measurements the optical density at a suitable wavelength was determined at several pH values. The most suitable wavelength, which was equal or close to the absorption maximum for  $\text{RS}^-$ , was determined in a separate experiment. In all cases, even for the compounds with two ionizable groups, a wavelength could be chosen where the variation in optical density as a function of pH was solely due to the thiolate ion.

The spectrophotometric solutions were prepared immediately before the experiment by adding the calculated amount of thiol (*ca.* 1 ml) to the appropriate solution of sodium

hydroxide or hydrochloric acid which had been kept in a bath thermostated at 25.0°C. Hydrogen ion concentrations were calculated from the known amounts of reagents and were in all cases checked by pH measurements. For the experiments with compounds having  $pK_a$ -values between 5 and 9 the hydrogen ion concentration could not be accurately calculated and the measured pH-values were therefore used in the calculations.

Spectrophotometric readings were in all cases stable, indicating that no oxidation of the thiol occurred.

*Calorimetric experiments.* The calorimetric experiments were carried out in an isothermal-jacket glass calorimeter which has been described in detail elsewhere.<sup>7</sup> The heat equivalent of the calorimetric system was determined electrically by passing a known current for a given time (240–300 sec) through the heater. Calibrations were performed on the systems after the reaction had taken place. No significant correlation between the observed heat capacity values and the ampoule content and kind of calorimetric buffer was observed. During the course of the experiments three slightly different calorimetric set-ups were used, giving three sets of calibrations. Within each series mean values were used in calculation of the calorimetric results.

Water used in preparation of the calorimetric liquids was deionized, freed from dissolved gases by boiling, and was cooled and stored under nitrogen. To the water was added calculated amounts of carbonate free sodium hydroxide solution and a suitable excess of thiol. This buffer solution was prepared in a 1 l separatory funnel fitted with gas inlet and outlet tubes at the top and connected by a glass joint to a pipette, in such a way that funnel and pipette could be flushed with purified hydrogen before and during the mixing procedures.

While being flushed with hydrogen the calorimeter was charged with the appropriate buffer solution from the pipette. The sealed glass ampoule contained about 1 mmole of dilute hydrochloric acid (1.690 mmole HCl per g of solution). The calorimeter reached thermal equilibrium 1 min after breaking the ampoule, and initial and final thermistor resistance values were evaluated graphically.

Time-temperature slopes in the fore and after periods of the calorimetric runs were normal, which indicated that slow side reactions (*e.g.* oxidation of the thiol) were absent.

Calorimetric buffer solutions were in no case stored for longer period of time than one day and were never exposed to air.

The  $pK_a$ -values for carboxylic and thiol groups of *p*-mercaptobenzoic acid are close (*ca.* 5 and 5.80, respectively). This fact, together with the very low solubility of the undissociated compound made it impossible to determine accurately the  $\Delta H_i$ -value for the SH-group by the direct calorimetric method.

*Calorimetric "control" experiments.* A consequence of the high  $pK_a$ -values of the thiols is that a correction must be applied to account for the reaction of hydrochloric acid with the hydroxyl ions present in the buffer solution. This correction is quite large in the case of *i*-PrSH and *t*-BuSH. In the latter case there is the further difficulty that the thiol concentration, which has to be known accurately to enable calculation of the correction, cannot be determined by titration.

In order to check the reliability of the corrections we applied, a set of experiments was carried out in which *i*-PrSH and *t*-BuSH were allowed to dissolve in 0.1 M NaOH and in water. Reactions were slow and reproducible results were not obtained presumably due to the low solubility in water and the high volatility of the thiols.

However a solution of the thiol in "cellosolve" mixed instantaneously and values for these heats of solution together with the appropriate corrections enabled the calculation of heats of ionization of the thiols.

*Units of measurement.* The results of the calorimetric experiments are expressed in terms of the defined calorie, equal to 4.1840 abs. joules, and refer to the isothermal process at 25°C.

## RESULTS

*Determination of dissociation constants.* Results from the spectrophotometric measurements are given in Tables 1a–1k. The following symbols have been used

$D$  = measured optical density  
 $D_0$  = optical density of uncharged species  
 $D_1$  = » » » singly charged species  
 $D_2$  = » » » doubly charged species  
 $I$  = ionic strength

$f_1$  and  $f_2$  are the activity coefficients for singly and doubly charged species, respectively.

$K_1$  and  $K_2$  are the thermodynamic dissociation constants for the first and second ionization step, respectively.

In calculation of the dissociation constants eqns. 1–4 and the appropriate form of eqn. 5 (given in connection with each table) was applied (*cf.* Ref.<sup>6</sup>).

$$K_1 = \frac{[H^+]f_1^2[A^-]}{[HA]} \quad (\text{Monobasic acid}) \quad (1a)$$

$$K_1 = \frac{[H^+]f_1^2[HA^-]}{[H_2A]} \quad (\text{Dibasic acid}) \quad (1b)$$

$$K_2 = \frac{[H^+]f_2[A^{2-}]}{[HA^-]} \quad (2)$$

$$f_1^2 [H^+][OH^-] = K_w \quad (3)$$

$$-\log f_z = 0.5 z^2 \left[ \frac{\sqrt{I}}{1 + \sqrt{I}} \right] - 0.3I \quad (4)$$

The ionic product for water,  $K_w$ , was taken as  $1.008 \times 10^{-14}$  (Ref.<sup>8</sup>). The activity coefficient for the doubly charged ion  $^+NH_3CH_2CH_2S^-$  was taken as unity (*cf.* Ref.<sup>9</sup>).  $D_0$ ,  $D_1$  and  $D_2$  were measured directly, or, where that was not possible, calculated from eqn. (5) by means of a series of successive approximations. Eqn. (5) was solved graphically and  $K$  was obtained from the slope of a straight line. The equation for the line was evaluated by means of the method of least squares.

Within experimental error (0.05 pH units) measured pH-values always agreed with those calculated from eqns. 1–5.

For each compound two independent series of measurements were carried out. Uncertainties given in the tables include estimates of possible systematic errors.

*Determination of heats of ionization.* In order to arrive at the enthalpy change accompanying the ionization reaction (the quantity measured calorimetrically refers to the reverse reaction!) the following corrections must be applied.

1. The heat of dilution of HCl contained in the ampoule. This correction has been obtained from blank experiments in connection with another investigation<sup>5</sup> and amounts to  $\Delta H = -0.525 \pm 0.002$  kcal/mole of HCl.

2. For the experiments performed in the high pH-range the neutralization reaction between  $H^+$  and  $OH^-$  must be considered. The amounts neutralized were calculated from the known concentrations of RSH and NaOH and from the measured  $pK_a$ -values. Activity coefficients were calculated from eqn. (4). The heat of ionization for water was taken to be 13.50 kcal/mole.<sup>10</sup>

Table 1. Dissociation constants.

Table 1a.

$\text{CH}_3\text{CH}_2\text{SH}$

$$\lambda = 240 \text{ m}\mu. \frac{1}{D-D_0} = \frac{K_w}{[\text{OH}^-] \cdot K_a (D_1 - D_0)} + \frac{1}{D_1 - D_0} \quad (5a)$$

Total conc. of RSH moles/l	$D_0$	$[\text{Na}^+]$ moles/l $\times 10^3$	$D$	$[\text{OH}^-]$ moles/l $\times 10^3$	$D_1$	$K_a$
$0.687 \times 10^{-4}$	0	0.236	0.124	0.212	0.358	$2.49 \times 10^{-11}$
		0.425	0.173	0.392		
		1.181	0.267	1.130		
		2.362	0.297	2.305		
		3.543	0.330	3.480		
		9.448	0.344	9.382		
$1.037 \times 10^{-4}$	0	0.461	0.278	0.410	0.562	$2.38 \times 10^{-11}$
		1.317	0.412	1.242		
		2.635	0.466	2.550		
		3.952	0.513	3.858		
		13.173	0.564	13.070		

Mean  $K_a = (2.44 \pm 0.06) \times 10^{-11}$   
 $\text{p}K_a = 10.61 \pm 0.01$

Table 1b.

$(\text{CH}_3)_2\text{CHSH}$

$\lambda = 240 \text{ m}\mu. \text{ Eqn. (5a).}$

Total conc. of RSH moles/l	$D_0$	$[\text{Na}^+]$ moles/l $\times 10^3$	$D$	$[\text{OH}^-]$ moles/l $\times 10^3$	$D_1$	$K_a$
$1.343 \times 10^{-4}$	0	0.142	0.100	0.120	0.629	$1.54 \times 10^{-11}$
		0.189	0.122	0.163		
		0.378	0.211	0.333		
		0.614	0.265	0.558		
		0.945	0.350	0.870		
		1.217	0.416	1.128		
		2.318	0.528	2.206		
		4.552	0.591	4.426		
$0.938 \times 10^{-4}$	0	0.378	0.174	0.350	0.579	$1.22 \times 10^{-11}$
		0.564	0.219	0.529		
		0.844	0.293	0.797		
		1.123	0.333	1.069		
		1.447	0.356	1.390		

Mean  $K_a = (1.38 \pm 0.09) \times 10^{-11}$   
 $\text{p}K_a = 10.86 \pm 0.03$

Table 1c.

(CH<sub>3</sub>)<sub>3</sub>CSH

$\lambda = 245 \text{ m}\mu$ . Eqn. (5a).

Total conc. of RSH moles/l	$D_0$	[Na <sup>+</sup> ] moles/l $\times 10^3$	$D$	[OH <sup>-</sup> ] moles/l $\times 10^3$	$D_1$	$K_a$
$1.169 \times 10^{-4}$	0	1.387	0.195	1.340	0.480	$5.30 \times 10^{-12}$
		2.290	0.267	2.225		
		4.735	0.352	4.650		
		9.444	0.397	9.348		
		23.539	0.441	23.432		
		47.056	0.443	46.949		
$1.473 \times 10^{-4}$	0	1.387	0.346	1.319	0.766	$6.76 \times 10^{-12}$
		2.290	0.457	2.200		
		4.735	0.587	4.623		
		9.444	0.675	9.315		
		23.539	0.710	23.403		
		47.056	0.712	46.919		

$$\text{Mean } K_a = (6.03 \pm 0.70) \pm 10^{-12}$$

$$\text{p}K_a = 11.22 \pm 0.05$$

Table 1d.

HOCH<sub>2</sub>CH<sub>2</sub>SH

$\lambda = 235 \text{ m}\mu$ . Eqn. (5a).

Total conc. of RSH moles/l	$D_0$	[Na <sup>+</sup> ] moles/l $\times 10^3$	$D$	[OH <sup>-</sup> ] moles/l $\times 10^3$	$D_1$	$K_a$
$1.459 \times 10^{-4}$	0	0.142	0.437	0.062	0.795	$1.98 \times 10^{-10}$
		0.236	0.571	0.132		
		0.472	0.699	0.344		
		2.362	0.772	2.221		
		9.448	0.792	9.303		
$1.162 \times 10^{-4}$	0	0.142	0.353	0.075	0.617	$1.81 \times 10^{-10}$
		0.236	0.457	0.150		
		0.472	0.559	0.367		
		9.448	0.587	9.337		

$$\text{Mean } K_a = (1.90 \pm 0.09) \times 10^{-10}$$

$$\text{p}K_a = 9.72 \pm 0.02$$

Table 1e.

CH <sub>3</sub> CONHCH <sub>2</sub> CH <sub>2</sub> SH						
$\lambda = 235 \text{ m}\mu$ . Eqn. (5a).						
Total conc. of RSH moles/l	$D_0$	[Na <sup>+</sup> ] moles/l $\times 10^4$	$D$	[OH <sup>-</sup> ] moles/l $\times 10^4$	$D_1$	$K_a$
$1.515 \times 10^{-4}$	0	1.008	0.329	0.482	0.949	$1.17 \times 10^{-10}$
		1.260	0.403	0.616		
		1.512	0.462	0.774		
		2.520	0.632	1.511		
		8.820	0.790	7.560		
$1.501 \times 10^{-2}$	0	1.008	0.346	0.466	0.958	$1.25 \times 10^{-10}$
		1.260	0.409	0.619		
		1.512	0.479	0.761		
		2.520	0.655	1.493		
		8.820	0.810	7.550		

$$\text{Mean } K_a = (1.21 \pm 0.05) \times 10^{-10}$$

$$\text{p}K_a = 9.92 \pm 0.02$$

Table 1f.

-OCOCH <sub>2</sub> SH							
$\lambda = 245 \text{ m}\mu$ . $\frac{1}{D-D_1} = \frac{f_2 \cdot K_w}{f_1^2 [\text{OH}^-] \cdot K_a (D_2 - D_1)} + \frac{1}{D_2 - D_1}$ (5b)							
Total conc. of RSH moles/l	$D_1$	[Na <sup>+</sup> ] moles/l $\times 10^3$	$D$	[OH <sup>-</sup> ] moles/l $\times 10^3$	$f_2/f_1^2$	$D_2$	$K_a$
$1.728 \times 10^{-4}$	0.052	0.374	0.224	0.160	0.955	0.787	$1.87 \times 10^{-11}$
		0.559	0.347	0.317	0.946		
		0.791	0.416	0.532	0.937		
		1.158	0.527	0.873	0.925		
		1.614	0.567	1.320	0.917		
$1.797 \times 10^{-4}$	0.054	0.374	0.249	0.148	0.955	0.810	$2.30 \times 10^{-11}$
		0.559	0.389	0.300	0.945		
		0.791	0.461	0.514	0.937		
		1.158	0.567	0.857	0.924		
		1.614	0.622	1.300	0.917		

$$\text{Mean } K_a = (2.09 \pm 0.20) \times 10^{-11}$$

$$\text{p}K_a = 10.68 \pm 0.04$$

Table 1g.

-OCOCH<sub>2</sub>CH<sub>2</sub>SH

$\lambda = 240 \text{ m}\mu$ . Eqn. (5b).

Total conc. of RSH moles/l	$D_1$	[Na <sup>+</sup> ] moles/l $\times 10^3$	$D$	[OH <sup>-</sup> ] moles/l $\times 10^3$	$f_2/f_1^2$	$D_2$	$K_a$
$1.376 \times 10^{-4}$	0.010	0.377	0.200	0.208	0.955	0.849	$1.44 \times 10^{-11}$
		0.478	0.286	0.295	0.951		
		0.628	0.342	0.436	0.944		
		0.817	0.441	0.609	0.937		
		1.257	0.542	1.032	0.923		
		12.570	0.689	12.320	0.800		
$1.460 \times 10^{-4}$	0.012	0.377	0.217	0.198	0.956	0.921	$1.47 \times 10^{-11}$
		0.440	0.271	0.252	0.953		
		0.628	0.386	0.422	0.944		
		0.754	0.438	0.540	0.939		
		1.257	0.576	1.020	0.923		
		12.570	0.795	12.300	0.799		

Mean  $K_a = (1.46 \pm 0.06) \times 10^{-11}$   
 $pK_a = 10.84 \pm 0.02$

Table 1h.

<sup>+</sup>NH<sub>3</sub>CH<sub>2</sub>CH<sub>2</sub>SH

$\lambda = 235 \text{ m}\mu$   $\frac{1}{D-D_1} = \frac{[\text{H}^+]}{K_a(D_2-D_1)} + \frac{1}{D_2-D_1}$  (5c)

Total conc. of RSH moles/l	$D_1$	pH measured	$I$ moles/l $\times 10^4$	$f_1$	$D$	$D_2$	$K_a$
$1.686 \times 10^{-4}$	0.015	7.87	1.478	0.986	0.302	0.913	$6.48 \times 10^{-9}$
		8.10	1.466	0.986	0.420		
		8.33	1.448	0.986	0.536		
		8.51	1.373	0.987	0.622		
		8.80	1.325	0.987	0.722		
$1.886 \times 10^{-4}$	0.017	7.97	1.602	0.986	0.322	0.931	$5.47 \times 10^{-9}$
		8.20	1.569	0.986	0.443		
		8.47	1.567	0.986	0.576		
		8.68	1.559	0.986	0.669		
		8.99	1.555	0.986	0.791		

Mean  $K_a = (5.93 \pm 0.70) \times 10^{-9}$   
 $pK_a = 8.23 \pm 0.05$



Table 1i.

$\text{CH}_3\text{COSH}$

$$\lambda = 245 \text{ m}\mu. \frac{1}{D_1 - D} = \frac{K_a}{[\text{H}^+] \cdot f_1^2 (D_1 - D_0)} + \frac{1}{D_1 - D_0} \quad (5d)$$

Total conc. of RSH moles/l	$D_1$	[Cl <sup>-</sup> ] moles/l $\times 10^4$	$D$	[H <sup>+</sup> ] moles/l $\times 10^4$	$f_1^2$	$D_0$	$K_a$
$0.825 \times 10^{-4}$	0.762	0.472	0.587	1.049	0.976	0.180	$2.50 \times 10^{-4}$
		0.945	0.559	1.481	0.972		
		1.889	0.483	2.319	0.966		
		3.306	0.430	3.660	0.958		
		9.445	0.280	9.587	0.933		
$0.771 \times 10^{-4}$	0.714	0.496	0.545	1.028	0.976	0.166	$2.32 \times 10^{-4}$
		0.991	0.508	1.472	0.972		
		3.469	0.400	3.798	0.958		
		9.912	0.234	10.006	0.931		

Mean  $K_a = (2.41 \pm 0.10) \times 10^{-4}$   
 $\text{p}K_a = 3.62 \pm 0.02$

Table 1j.

$o\text{-}^-\text{OCOC}_6\text{H}_4\text{SH}$

$$\lambda = 270 \text{ m}\mu. \frac{1}{D_2 - D} = \frac{K_a}{f_2[\text{H}^+](D_2 - D_1)} + \frac{1}{D_2 - D_1} \quad (5e)$$

Total conc. of RSH moles/l	$D_2$	pH measured	$I$ moles/l $\times 10^4$	$f_1/f_2$	$D$	$D_1$	$K_a$
$0.708 \times 10^{-4}$	0.812	7.74	0.887	1.048	0.212	0.212	$1.33 \times 10^{-9}$
		7.98	1.150	1.049	0.316		
		8.61	1.409	1.051	0.419		
		8.79	1.633	1.052	0.489		
		9.11	1.901	1.056	0.598		
$0.724 \times 10^{-4}$	0.830	7.40	0.934	1.048	0.263	0.268	$1.30 \times 10^{-9}$
		7.85	1.149	1.049	0.325		
		8.46	1.413	1.051	0.430		
		8.65	1.620	1.052	0.485		
		9.06	1.908	1.056	0.610		

Mean  $K_a = (1.32 \pm 0.12) \times 10^{-9}$   
 $\text{p}K_a = 8.88 \pm 0.04$

Table 1k.

<i>p</i> -OCOC <sub>6</sub> H <sub>4</sub> SH							
$\lambda = 305 \text{ m}\mu$ . Eqn. (5e).							
Total conc. of RSH moles/l	$D_2$	pH measured	$I$ moles/l $\times 10^6$	$f_1/f_2$	$D$	$D_1$	$K_a$
$0.391 \times 10^{-4}$	0.709	5.25	4.521	1.023	0.193	0	$1.69 \times 10^{-6}$
		5.62	5.311	1.025	0.280		
		5.75	6.263	1.027	0.335		
		5.90	7.665	1.030	0.419		
$0.586 \times 10^{-4}$	1.050	5.44	5.899	1.026	0.405	0.177	$1.45 \times 10^{-6}$
		5.69	6.564	1.028	0.562		
		5.84	7.864	1.031	0.594		
		5.95	9.324	1.033	0.693		
		6.11	10.549	1.040	0.750		

$$\text{Mean } K_a = (1.57 \pm 0.12) \times 10^{-6}$$

$$\text{p}K_a = 5.80 \pm 0.04$$

3. In the experiments carried out at  $\text{pH} < 7$  (thiolacetic acid) part of the added acid did not react. This amount was calculated and subtracted from the total amount of added HCl.

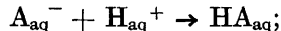
The experimental results are summarized in Table 2. The following symbols have been used:

$\log R_i/R_f$  is the expression proportional to the corrected temperature change;

$\varepsilon$  is the heat capacity expressed in cal/units of  $\log R_i/R_f$ ;

$q_{\text{exp}}$  is the experimentally determined heat effect;

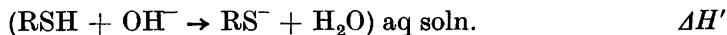
$q_{\text{corr}}$  is the heat effect referring to the reversed ionization investigated:



$\Delta H_i$  is the heat of ionization which is equal to  $q_{\text{corr}}$ /mmole of HCl (corr.).

Uncertainties given in Table 2 are standard deviation of the mean.

*Results from calorimetric "control" experiments.* Results from the "control" experiments on *i*-PrSH and *t*-BuSH will not be reported in detail. The ampoule liquid was a solution of thiol in cellosolve; ca. 1 mmole RSH/g liquid. The difference between the heat of solution of this liquid in 0.1 M NaOH and in water, respectively, is the enthalpy change for the reaction



As the ampoule content was only 0.5 ml and the calorimetric vessel contained 100 ml liquid or water, the cellosolve present in the final solution is judged not to interfere significantly with the  $\Delta H'$  value.

In calculating  $\Delta H'$  the following corrections were applied:

1. From separate experiments it was found that the heat of solution of cellosolve is slightly more exothermic in 0.1 M NaOH than in pure water ( $\Delta H = -48.55$  and  $-47.90$  cal/g, respectively). The heat of solution of the ampoule liquid in NaOH solution was corrected to allow for this.

Table 2. Heats of ionization.

calorimetric liquid	Ampoule content, mmole HCl	$\log R_1/R_2 \times 10^4$	$q_{\text{exp}}$ cal	$q_{\text{corr}}$ cal	mmole of HCl (corr)	$\Delta H_1$ kcal/mole
.41 mmole $\text{C}_2\text{H}_5\text{SH}$	1.0968	8219	7.713	6.951	1.0833	6.42
.58 mmole NaOH	0.8844	6594	6.188	5.566	0.8731	6.38
05.0 ml liquid	1.1268	8419	7.900	7.118	1.1131	6.39
= 9384	1.2165	9071	8.512	7.670	1.2019	6.38
tarting pH = 10.17	1.1872	9001	8.447	7.625	1.1729	6.50
	0.8478	6390	5.996	5.398	0.8368	6.45
	1.1415	8566	8.038	7.245	1.1276	6.43
					Mean	$6.42 \pm 0.01$
.15 mmole of $(\text{CH}_3)_2\text{CHSH}$	0.8642	6038	5.550	4.388	0.8121	5.40
.00 mmole NaOH	0.8656	6061	5.571	4.403	0.8131	5.42
00.0 ml liquid	0.8849	6062	5.572	4.389	0.8320	5.28
= 9194	0.9079	6290	5.781	4.571	0.8540	5.35
tarting pH = 10.71	0.8884	6244	5.739	4.549	0.8352	5.45
					Mean	$5.38 \pm 0.03$
.54 mmole $(\text{CH}_3)_3\text{CSH}$	0.6001	5630	5.283	2.048	0.3840	5.33
.35 mmole NaOH	0.6022	5649	5.301	2.065	0.3861	5.35
05.0 ml liquid	0.6382	5866	5.505	2.115	0.4121	5.13
= 9384	0.7538	6971	6.542	2.748	0.5024	5.47
tarting pH = 11.45					Mean	$5.32 \pm 0.09$
.86 mmole $\text{HOCH}_2\text{CH}_2\text{SH}$	1.1526	8345	7.831	7.198	1.1510	6.25
.58 mmole NaOH	1.1451	8313	7.801	7.172	1.1435	6.27
05.0 ml liquid	1.0559	7550	7.085	6.505	1.0544	6.17
= 9384	0.8919	6392	5.998	5.507	0.8906	6.18
tarting pH = 9.23	1.1785	8455	7.934	7.287	1.1769	6.19
	1.0495	7549	7.084	6.508	1.0480	6.21
					Mean	$6.21 \pm 0.02$
.88 mmole $\text{CH}_3\text{CONHCH}_2\text{CH}_2\text{SH}$	1.0604	7515	7.052	6.428	1.0558	6.09
.58 mmole NaOH	1.1328	8203	7.698	7.033	1.1280	6.23
05.0 ml liquid	1.1322	8241	7.733	7.068	1.1274	6.27
= 9384	1.0649	7878	7.393	6.767	1.0603	6.38
tarting pH = 9.69	1.1225	8078	7.580	6.920	1.1177	6.19
	1.0883	8096	7.597	6.957	1.0837	6.42
	1.1358	8259	7.750	7.083	1.1310	6.26
	0.8403	6066	5.692	5.194	0.8364	6.21
					Mean	$6.26 \pm 0.04$
.99 mmole $\text{HOCOCH}_2\text{SH}$	1.0615	7950	7.460	6.499	1.0320	6.30
.64 mmole NaOH	1.0888	8132	7.631	6.650	1.0588	6.28
05.0 ml liquid	1.1645	8729	8.191	7.151	1.1331	6.31
= 9384	1.0312	7696	7.222	6.285	1.0023	6.27
tarting pH = 10.45	0.8865	6608	6.201	5.377	0.8603	6.25
					Mean	$6.28 \pm 0.01$

Calorimetric liquid	Ampoule content, mmole HCl	$\log R_i/R_f \times 10^4$	$q_{\text{exp}}$ ' cal	$q_{\text{corr}}$ ' cal	mmole of HCl (corr)	$\Delta H_i$ kcal/mole
3.18 mmole HOCOCH <sub>2</sub> CH <sub>2</sub> SH	1.0408	7642	7.171	6.204	1.0101	6.14
4.64 mmole NaOH	1.0514	7678	7.205	6.232	1.0206	6.11
105.0 ml liquid	0.9045	6682	6.270	5.415	0.8766	6.18
$\epsilon = 9384$	1.0412	7533	7.069	6.102	1.0105	6.04
Starting pH = 10.46	1.0342	7497	7.035	6.075	1.0037	6.05
					Mean	6.10 ± 0.03
2.49 mmole NH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> SH	0.9875	8496	7.815	7.292	0.9875	7.38
1.16 mmole HCl	0.9578	8267	7.604	7.096	0.9578	7.41
99.6 ml liquid	0.9047	7834	7.206	6.727	0.9047	7.44
$\epsilon = 9198$	0.8953	7767	7.144	6.670	0.8953	7.45
Starting pH = 8.24 (measured)	0.9017	7835	7.207	6.729	0.9017	7.46
					Mean	7.43 ± 0.01
4.01 mmole CH <sub>3</sub> COSH	0.7848	887	0.832	0.416	0.7199	0.58
1.58 mmole NaOH	1.0975	1103	1.035	0.453	0.9745	0.46
Starting pH = 3.40	1.0956	1302	1.222	0.641	0.9750	0.66
2.32 mmole of CH <sub>3</sub> COSH						
1.58 mmole of NaOH	1.0703	1193	1.120	0.553	0.9911	0.56
Starting pH = 3.90	1.0215	1103	1.035	0.494	0.9510	0.52
105 ml liquid						
$\epsilon = 9384$					Mean	0.56 ± 0.03
0.99 mmole <i>o</i> - <sup>-</sup> OCOC <sub>6</sub> H <sub>4</sub> SH	0.7250	5113	4.764	3.879	0.6879	5.64
2.20 mmole NaOH	0.7629	5295	4.933	4.028	0.7258	5.55
8 mmole NaCl <sup>a</sup>	0.7722	5476	5.102	4.192	0.7351	5.70
Starting pH (measured) = 10.45	0.7367	5273	4.913	4.022	0.6996	5.75
99.6 ml liquid	0.7580	5590	5.208	4.305	0.7209	5.97
$\epsilon = 9317$					Mean	5.72 ± 0.07

<sup>a</sup> These measurements were made in connection with another study,<sup>5</sup> where the ionic strength was maintained at 0.1.

2. A small amount of the thiol was not neutralized. This amount was calculated and subtracted from the total amount of RSH added.

From measurements of heats of solution of 1.690 M HCl in water and in 0.100 M NaOH the heat of ionization of water, appropriate to the experimental conditions, was calculated to be  $13.47 \pm 0.03$  kcal/mole. From this figure and the  $\Delta H'$ -values, the heats of ionization for *i*-PrSH and *t*-BuSH were calculated to be  $+ 5.54 \pm 0.20$  and  $+ 5.28 \pm 0.15$  kcal/mole. These values are in good agreement with those arrived at in the main experiments.

Table 3 summarizes the values arrived at in this work for the heats of ionization at the indicated ionic strengths. For *i*-PrSH the control experiments have been neglected as they are considered less reliable than the main experiments. For *t*-BuSH the mean value for main and control experiments, respectively, has been given. Uncertainties given include estimates of possible systematic errors.

Table 3. Heats of ionization for thiols at 25°C.

Thiol	Ionic strength	$\Delta H_i$ kcal/mole
$C_2H_5SH$	0.015	$6.42 \pm 0.02$
$(CH_3)_3CHSH$	0.010	$5.38 \pm 0.05$
$(CH_3)_2CSH$	0.01—0.1	$5.30 \pm 0.15$
$HOCH_2CH_2SH$	0.015	$6.21 \pm 0.03$
$CH_3CONHCH_2CH_2SH$	0.015	$6.26 \pm 0.04$
$^-OCOCH_2SH$	0.05	$6.28 \pm 0.03$
$^-OCOCH_2CH_2SH$	0.06	$6.10 \pm 0.04$
$^+NH_3CH_2CH_2SH$	0.01	$7.43 \pm 0.02$
$o^-OCOC_6H_4SH$	0.1	$5.72 \pm 0.08$
$CH_3COSH$	0.015	$0.56 \pm 0.04$

Earlier determinations of  $pK_a$  and  $\Delta H_i$  of thiols. Schwarzenbach and co-workers have made a systematic study of the acid strength of thiophenols, and aromatic and aliphatic dimercaptans in water-ethanol mixtures at 20°C.<sup>11-13</sup>

More recently Franzen<sup>1</sup> determined  $pK_a$  for a number of N-substituted aminothiols in water-ethanol mixtures at 18°C.

There has been no systematic investigation of the acid strength for thiols in water but  $pK_a$  values have been reported for all compounds investigated in this work with the exception of *p*-mercaptobenzoic acid and *i*-PrSH. Table 4 shows a summary of earlier data and a comparison with results from the present work.

As pointed out by Benesch and Benesch<sup>3</sup> it was long believed that  $\Delta H_i$  for thiols was negligible. The first  $\Delta H_i$  value published seems to be that of

Table 4.  $pK_a$  for thiols in water. Comparison between earlier investigations and the present work.

Compound	Method	Ref.	Temp. °C	$pK_a$	Present work $pK_a$ at 25°C
$C_2H_5SH$	<i>a</i>	14	20	10.64	10.61
$(CH_3)_3SH$	<i>a</i>	14	20	11.14	11.22
$^-OCOCH_2SH$	<i>b</i>	15	<i>ca.</i> 20	10.67	
	<i>c</i>	3	25	10.32	10.84
$^-OCOCH_2CH_2SH$	<i>b</i>	15	<i>ca.</i> 20	10.54	10.68
$^+NH_3CH_2CH_2SH$	<i>c</i>	3	25	8.35	8.23
$HOCH_2CH_2SH$	<i>a</i>	16	25	9.5	9.72
$CH_3CONHCH_2CH_2SH$ *	<i>a</i>	17	not given	9.2	9.92
$CH_3COSH$	<i>d</i>	19	25	3.33	3.62
$o^-OCOC_6H_4SH$	<i>a</i>	20	25	8.40	8.88

*a.* Potentiometric titration.

*b.* Mixing of calculated amounts of  $RS^-$  and NaOH. pH measured colorimetrically.

*c.* Spectrophotometric.

*d.* Conductimetric.

\* This compound has a special interest as it can be looked upon as a model for coenzyme A.  $pK_a$  for the thiol group of CoA has been reported to be 9.6.<sup>18</sup>

Benesch and Benesch for thioglycolic acid. By determining  $pK_a$  at 25 and 37°C they obtained the value of  $\Delta H_i = 6.9$  kcal/mole. Bearing in mind the uncertainty inherent in this indirect method of evaluating  $\Delta H_i$ , the value is in fair agreement with the directly obtained calorimetric value at 25°C, 6.28 kcal/mole.

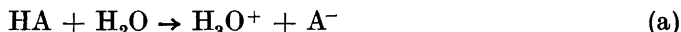
Wadsö<sup>21</sup> found (calorimetrically)  $\Delta H_i$  for  $\beta$ -acetylaminoethanethiol to be 6.5 kcal/mole at high ionic strength and the present work gives the value 6.26 kcal/mole at low ionic strength.

#### DISCUSSION

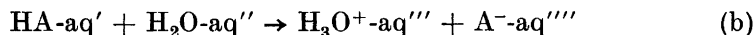
When attempts are made to correlate energy changes for chemical processes in solution with changes in molecular structure it is essential to consider both (A) structural changes in the reacting molecules and (B) changes in interactions between reacting molecules and the surrounding medium. In the literature it is frequently found that due consideration is not given to factors associated with (B) and correlations between molecular structure and energy changes are often solely interpreted in terms of inductive, steric and resonance effects supposedly operating in the reacting molecules. The apparent success of this type of approach draws a veil over the gross oversimplification which has to be made of the energetic picture, for many types of reaction in solution, not the least being the acid dissociation process.

In order to facilitate a more thorough discussion of energy changes for chemical reactions in solution the effects of (A) and (B) are usually treated separately. Although useful, such a separation should in the general case be considered as only a formal treatment as obviously the effects associated with (A) are influenced by effects connected with (B). (Effects associated with (A) cannot be identified with those prevailing in the ideal gaseous state. This is for instance demonstrated by changes in spectral properties caused by changes in the medium.) With a medium like water where there is good reason to believe some ordering of structure it seems likely that in the neighbourhood of the solute molecules the properties of the medium itself is a function of the solute.<sup>22</sup> It seems, therefore, most correct to look upon reacting species in aqueous solutions as forming some sort of a "complex" with the medium.

The equation for an acid dissociation process



should then read



Eqn. (b) thus stresses the view that the immediate surroundings of the reacting compounds form an integral part of the chemical reaction system.

Empirical relationships between certain structural factors and acid strength have often been simply explained in terms of polar, steric or resonance effects. As a typical example can be mentioned the explanation still frequently offered for the observation that positive electrical charges or other strongly electron attracting groups will increase the acid strength of carboxylic acids: The effect of the electron attracting group (propagated along the carbon chain)

will result in a weakening of the O—H bond, thus facilitating the dissociation process. Interpretations of this sort (being very much in line with current discussions concerning substituent effects on kinetic data for reactions in solution) do not take into account all the factors influencing the dissociation process and are furthermore often in disagreement with observed thermodynamic data.<sup>10</sup> Polar effects supposedly resulting in weakening of a chemical bond are expected to mainly affect the enthalpy part of the free energy change (see *e.g.* Ref.<sup>23</sup>) but for substituted carboxylic acids of different strength the heats of ionization are nearly constant<sup>24</sup> and the differences in free energy change are essentially accounted for by differences in the entropy term.

Splitting up the free energy change into an enthalpy term and an entropy term can thus remove a misconception but does not usually make the energetics of the ionization process look any simpler. Even if the  $\Delta H_i$  and  $\Delta S_i$  terms thermodynamically are less complex than the  $\Delta G_i$  value it must be remembered that they are still gross effects each representing a relatively small quantity made up of differences between sometimes large numbers. Hepler's<sup>25</sup> formal separation of these terms into an internal and an external (solvent-solute) effect, however, seems promising as an attempt to simplify the picture.

When considering relationships between energy and structure it must be born in mind that several of the structural effect will influence both the

Table 5. Thermodynamics of ionization for thiols, carboxylic acids and phenols at 25°C.

Compound	X = SH			X = COOH <sup>a</sup>		
	$\Delta G_i$	$\Delta H_i$	$\Delta S_i$	$\Delta G_i$	$\Delta H_i$	$\Delta S_i$
C <sub>2</sub> H <sub>5</sub> X	14.48	6.42	-27.0	6.66	-0.08	-22.6
(CH <sub>3</sub> ) <sub>2</sub> CHX	14.82	5.38	-31.7	6.63	-1.01	-25.6
(CH <sub>3</sub> ) <sub>3</sub> CX	15.31	5.30	-33.5	6.87	-0.72	-25.5
HOCH <sub>2</sub> CH <sub>2</sub> X	13.26	6.21	-23.7			
CH <sub>3</sub> CONHCH <sub>2</sub> CH <sub>2</sub> X	13.54	6.26	-24.4	6.06 <sup>b</sup>	0.26 <sup>b</sup>	-19.5 <sup>b</sup>
<sup>-</sup> OCOCH <sub>2</sub> X	14.58	6.28	-27.8	7.78	-1.14	-29.9
<sup>-</sup> OCOCH <sub>2</sub> CH <sub>2</sub> X	14.79	6.10	-29.2	7.70	0.04	-25.7
+NH <sub>3</sub> CH <sub>2</sub> CH <sub>2</sub> X	11.23	7.43	-12.7	4.85	1.18	-12.3
CH <sub>3</sub> COX	4.94	0.56	-14.7	3.40 <sup>c</sup>	2.44 <sup>d</sup>	-3.3
				X = OH <sup>e</sup>		
				$\Delta G_i^*$	$\Delta H_i^*$	$\Delta S_i^*$
<i>o</i> - <sup>-</sup> OCOC <sub>6</sub> H <sub>4</sub> XH	12.12	5.72	-21.5	17.9	10.5	-24.8
<i>p</i> - <sup>-</sup> OCOC <sub>6</sub> H <sub>4</sub> XH	7.92			12.6	3.4	-30.8

a. Data taken from the compilation in Ref.<sup>24</sup> unless otherwise stated.

b. Ref.<sup>26</sup>

c. Ref.<sup>27</sup>

d. Derived from pK<sub>a</sub> determinations<sup>27</sup> at 25 and 37°C.

e. Ref.<sup>31</sup>

\* Note added in proof: A presumably more reliable set of data has recently been determined for the second ionization of salicylic acid (Ernst, Z. L., Irving, R. J. and Menachi, *J. Trans. Faraday Soc.* 60 (1964) 56:

$$\Delta G_i = 18.54 \text{ kcal/mole, } \Delta H_i = 8.51 \text{ kcal/mole and } \Delta S_i = -33.6 \text{ e. u.}$$

enthalpy and the entropy term: Differences in potential energy (*e.g.* bond energies, resonance energies, strain energies) are accounted for by the  $\Delta H_i$  term and probability differences by the  $T\Delta S_i$  term whereas changes in kinetic energy will affect both terms. (Changes in the interaction between solutes and medium will obviously affect both terms.) It is in fact frequently noted that it is easier to correlate  $\Delta G_i$  values with structural parameters than to correlate  $\Delta H_i$  or  $\Delta S_i$  values with changes in structure.<sup>23</sup> This *apparent* simplicity of the  $\Delta G_i$  term seems to be explained by the fact that the  $\Delta H_i$  and  $T\Delta S_i$  terms often largely compensate each other.<sup>23</sup>

Relationships between structural and energetic effects in aqueous ionization processes must be largely hypothetical as long as we do not know all contributions to the above mentioned gross effects. It is therefore believed that minor energy quantities (of the order of a few tenths of a kcal) should not seriously be considered at the present time. A cautious discussion, however, is judged to be useful; mainly because it will serve the purpose of systematizing our empirical knowledge. It is with these aspects in mind that the following discussion of energy changes is carried out.

In Table 5 are summarized free energies,  $\Delta G_i$  ( $\Delta G_i = -RT \ln K_a$ ), the calorimetrically determined enthalpy values,  $\Delta H_i$ , and the derived ionization entropies,  $\Delta S_i$  ( $\Delta G_i = \Delta H_i - T\Delta S_i$ ). As a comparison the corresponding values for carboxylic acids and phenols of analogous structures are also given. Inspection of Table 5 shows that free energies of ionization of the thiols are about 7 kcal/mole higher than for the corresponding carboxylic acids. This difference is made up by an essentially constant difference in the enthalpy term whereas entropy changes in general are similar. As with carboxylic acids,<sup>24</sup> therefore, differences in the strength of thiols can largely be traced back to differences in the entropy term. A marked exception to this rule is provided by the values for thiolacetic acid.

The effect of strongly polar groups is here illustrated by the results for thiols carrying a formal charge. When  $C_2H_5SH$  is compared with  $^-O-CCH_2SH$

and  $^-OC-(CH_2)_2SH$  a very small decrease in ionization enthalpy is found,

0.14 and 0.32 kcal/mole, respectively. A positively charged ammonium group in the  $\beta$ -position will have a slightly more pronounced (and *vice versa* for the corresponding carboxylic acids) effect on  $\Delta H_i$ , which is increased by about 1 kcal/mole. Strongly polar effects thus exert only small or moderate influences on the ionization enthalpy for thiols, as has also been found to be the case for carboxylic acids. A more important consideration in the acid strength of both types of acids is the marked effect of polar groups on the ionization entropy. It has long been known that for carboxylic acids the presence of strongly electron attracting groups such as ammonium in the molecule very markedly decreases the ionization entropy and thus increases the acid strength.  $-\Delta S_i$  is for instance 10 e.u. lower for  $\beta$ -alanine than for propionic acid. Here, a similar difference (14 e.u.) is found between the analogous pair ethanethiol and

\* Ionic strength 0.01–0.05 except for *o*-mercaptobenzoic acid where it is 0.1; *cf.* Table 2.

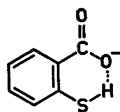


$\beta$ -aminoethanethiol. (The first dissociation step is confined almost entirely to the thiol group.<sup>3</sup>)

If a negative charge is close to the ionizable hydrogen the ionization entropy is decreased both for carboxylic acids and for thiols but for both acids the effect is moderate compared with the influence of a positive charge (propionic acid and ethanethiol taken as standards). When EtSH is substituted in the  $\beta$ -position with the moderately polar groups OH and  $\text{NHCOCH}_3$  there is no significant effect on the  $\Delta H_i$  value but the  $-\Delta S_i$  value is markedly lowered. A parallel effect is observed for the analogous pair propionic acid and N-acetyl- $\beta$ -alanine (as well as for other N-acetylated aminoacids<sup>26</sup>). This effect has been explained on the basis of a preferred orientation of the water molecules (prior to the ionization reaction) caused by hydrogen bonding between the hydrophilic groups and water.<sup>26</sup>

The presence of charged groups is supposed to orient the water molecules giving them an increased order *i.e.* decreasing the entropy.<sup>28-30</sup> The large  $-\Delta S_i$  value observed for acids carrying a negative charge has been explained as due to the fact that the "orientation power" is proportional to the square of the charge.<sup>29</sup> This "electrostriction theory" is further strengthened by the very low  $-\Delta S_i$  values observed for ammonium compounds (see, *e.g.*, Ref.<sup>30</sup>, p. 452) where no new charges are formed in the dissociation process. One would expect, however, that the  $-\Delta S_i$  value for  $\beta$ -mercaptopropionic acid should be lower than for thioglycollic acid; actually it is found to be slightly higher.

The thiol group in *o*-mercaptobenzoic acid has a low  $-\Delta S_i$  value contrary to what could be expected from electrostatic influences on the solvent by the negative ion in ortho position. This low value could possibly be explained by an internal hydrogen bond formation in the monoanion



analogous to what has been suggested for corresponding phenol<sup>31</sup>; *cf.*, Ref.<sup>32</sup>

The increased branching of the carbon chain in the series EtSH, *i*-PrSH and *t*-BuSH is accompanied by a decrease in heat of ionization and an increase in  $-\Delta S_i$  values. The difference in the entropy term will dominate which makes the thiols weaker acids with increased branching. The similar decrease in acid strength on going from acetic acid to trimethylacetic acid has been explained as an inductive effect from the electron donating alkyl groups together with decreased solvation of the carboxylate ion due to steric hindrance.<sup>30</sup> Neither of the above explanations seems convincing for either of the two groups of acids for the following reasons: (a) it is unlikely that a relative decrease in solvation would show up as an increase in the  $-\Delta S_i$  value; (b) strongly electron repelling ionic groups in thioglycollate and  $\beta$ -mercaptopropionate are shown to have only a small influence on  $-\Delta S_i$  for the thiols and it is therefore not believed that the relatively weak inductive effects from the methyl groups significantly will effect  $\Delta S_i$  values. A more likely explanation is given by King and King<sup>26</sup> who suggest that the increasing  $-\Delta S_i$  values accompanying

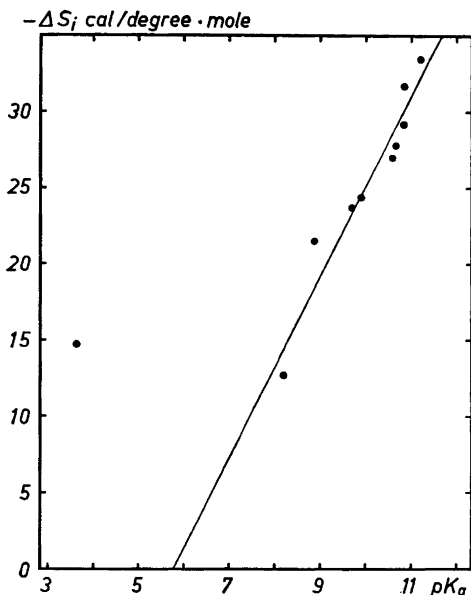


Fig. 1. Plot of  $-\Delta S_i$  versus  $pK_a$  for some thiols in aqueous solution.

branching of the carbon chain in carboxylic acids, is due to a solvent orientation effect in the disordered region<sup>22</sup> outside the inner hydration shell of the acid anion.

Similar to what has been found for carboxylic acids<sup>24</sup> and phenols<sup>34</sup> there exists also for thiols (thiolacetic acid is an exception) a linear relationship between  $pK_a$  (or  $\Delta G_i$ ) and  $\Delta S_i$ . In Fig. 1  $\Delta S_i$  has been plotted versus  $pK_a$  and the equation

$$\Delta S_i = -5.92 pK + 34.1 \quad (6)$$

has been calculated by the method of least squares. This relationship reflects the fact that the differences in acid strength of thiols are largely made up of differences in the entropy term and that  $\Delta H_i$  for the thiols is essentially constant. Therefore, compounds like thiolacetic acid with "abnormal"  $\Delta H_i$  values will not follow eqn. (6). For *p*-mercaptobenzoic acid the  $pK_a$ -value for the SH group was measured ( $pK_a = 5.80$ ) but it was not possible to determine its  $\Delta H_i$ -value. If *p*-mercaptobenzoic acid has a "normal"  $\Delta H_i$ -value its  $-\Delta S_i$ -value will, according to eqn. (6), be close to zero. However, as  $-\Delta S_i$ -values for neutral and negatively charged thiols are characterized by being in the order of 20–30 e.u., a value around zero seems very unlikely. On this basis therefore it is postulated that  $\Delta H_i$  for *p*-mercaptobenzoic acid will be low; in the order of  $-1$  to  $+1$  kcal/mole.

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