

Thermodynamics of the Ionization of Some Thiazoles in Aqueous Solution

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Dissociation constants for a number of thiazoles have been determined at 25°C by potentiometric titration and the corresponding heats of ionization have been determined calorimetrically. Free energies, enthalpies, and entropies for the thiazole ionization processes are discussed.

In this paper, results are reported from a thermodynamical investigation of the protonization reactions for a number of thiazoles in aqueous solution. Heats of solution in water and in dilute hydrochloric acid have been determined calorimetrically and dissociation constants have been determined by a titrimetric technique. From the experimental results free energies, enthalpies, and entropies are calculated for the ionization of the thiazolium compounds.

EXPERIMENTAL

Materials. All compounds were prepared (see Refs. 1-3) and purified at Department of Organic Chemistry, University of Marseille. After a crude distillation the thiazoles were repeatedly distilled through 20-plate columns packed with pyrex or tantal rings, and the pure compounds stored in glass ampoules under nitrogen. Before the experiments, the purities were checked by gas chromatography and in all cases judged to be $\geq 99.5\%$. Water used in the preparation of the calorimetric liquids was glass distilled.

Calorimetric experiments. The calorimetric experiments were carried out in an isothermal-jacket glass calorimeter which has been described in detail elsewhere.⁴ The thiazole compounds were contained in sealed glass ampoules and the calorimeter was charged with 100 ml of liquid (water or 0.1 N HCl).

Electrical calibrations were performed on the systems before the reactions had taken place and covered closely the same temperature range as the solution experiments. The final temperature was in all experiments $25.00 \pm 0.05^\circ\text{C}$. In calculating the calorimetric results mean values from the calibration experiments, corrected for small variations in the heat capacity, were used.

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Table 1. Summary of results from titrimetric and calorimetric experiments. (Mean values).

Substance	pK_a	Heats of solution in				ΔH for the reaction $BH_{aq} + \rightarrow B_{aq} + H_{aq}$ kcal/mole
		100 ml of water		100 ml of 0.1 HCl		
		Amount of substance mmole	ΔH , kcal/mole	Amount of substance mmole	ΔH , kcal/mole	
Thiazole	2.55 ± 0.02	1.5	1.11 ± 0.01	1.5	3.02 ± 0.02	2.02 ± 0.03
2-Methyl thiazole	3.40 ± 0.02	3.5	1.91 ± 0.01	3.1	5.09 ± 0.03	3.21 ± 0.03
4-Methyl thiazole	3.16 ± 0.03	3.7	1.68 ± 0.02	3.4	4.64 ± 0.02	2.99 ± 0.03
5-Methyl thiazole	3.03 ± 0.02	3.4	1.32 ± 0.01	2.9	4.17 ± 0.01	2.88 ± 0.02
2,4-Dimethyl thiazole	3.98 ± 0.02	1.9	2.73 ± 0.02	1.5	6.94 ± 0.02	4.21 ± 0.03
2,5-Dimethyl thiazole	3.91 ± 0.02	1.2	2.25 ± 0.01	1.1	6.24 ± 0.04	3.99 ± 0.04
4,5-Dimethyl thiazole	3.73 ± 0.02	1.5	1.63 ± 0.04	1.3	5.58 ± 0.02	3.97 ± 0.05
2,4,5-Trimethyl thiazole	4.55 ± 0.03	0.7	2.75 ± 0.01	0.8	7.70 ± 0.02	4.95 ± 0.02
2- <i>t</i> -Butyl thiazole	3.00 ± 0.03	0.4	1.78 ± 0.05	0.9	5.45 ± 0.04	3.71 ± 0.06
4- <i>t</i> -Butyl thiazole	3.04 ± 0.03	0.7	1.61 ± 0.04	1.3	5.43 ± 0.05	3.86 ± 0.06

Units of measurements. 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.

Determination of dissociation constants. Dissociation constants were determined by potentiometric titration according to the technique described by Metzger and Carrega.²

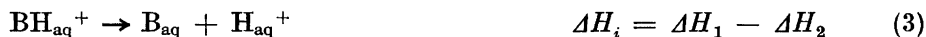
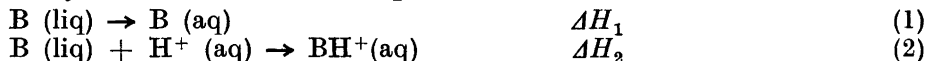
In the experiments a Radiometer pH meter TTT 1 C was used. The equipment was standardized by means of NBS standard samples (potassium biphthalate and potassium hydrogen tartrate).

RESULTS AND DISCUSSION

The experimental results are summarized in Table 1. Each calorimetric value is the mean of 4–6 experiments. Results from pK_a determinations were obtained from two separate titration curves. For each curve, pK_a values were calculated at three different pH values. Uncertainties given are the random errors * to which have been added estimates of possible systematic errors.

In Table 2 are summarized derived values for the standard free energies, enthalpies, and entropies of ionization. The standard free energy changes were calculated from the determined pK_a values using the expression $\Delta G^\circ = 2.303 RT pK_a$.

In order to arrive at the enthalpy change for the ionization of the thiazolium compounds, heats of solution of the thiazole bases (B) in water and in dilute hydrochloric acid were compared:



The thiazoles investigated are all very weak bases and some of them are significantly dissociated even in 0.1 N HCl. From the final pH of the hydrochloric acid solutions the amount of non-protonated base was calculated and corrected for in order to arrive at the enthalpy value ΔH_2 .

The derived ionization enthalpies (eqn. 3) refer to ionic strength 0.1, but it can be expected that the heat of dilution of the thiazolium salt does not markedly differ from that of the hydrochloric acid formed at the reaction. It is therefore assumed that $\Delta H_i = \Delta H_i^\circ$ (Table 2).

When an energy change for a chemical process in solution is discussed it is necessary to consider contributions both from the reacting molecules and from changes in interaction between solute and solvents. Further, for a solvent like water the solvent structure will certainly undergo local changes as the result of the ionization process (see, *e.g.*, Refs. 5,6). An apparently simple aqueous ionization reaction is therefore in fact a complex process and any discussion of its energetics must, at the present time, be merely of a descriptive nature.

From a first inspection of the data given in Table 2 it can be noted that ΔG_i° and ΔH_i° are of similar magnitude and thus the ΔS_i° values are small. This is in general agreement⁷ with other ionization reactions which can be written as



* $\sqrt{\Sigma \delta^2 / n(n-1)}$ for $n \geq 5$ and $\Sigma d/n$ for $n = 4$

Table 2. Thermodynamics of the aqueous ionization for some thiazolium ions, $\text{BH}_{\text{aq}}^+ + \text{H}_2\text{O}_{\text{aq}} \rightarrow \text{B}_{\text{aq}} + \text{H}_3\text{O}_{\text{aq}}^+$, at 25°C.

Substance	ΔG° kcal/mole	ΔH° kcal/mole	ΔS° e.u.
Thiazole	3.48	2.02	-4.9
2-Methyl thiazole	4.64	3.21	-4.8
4-Methyl thiazole	4.31	2.99	-4.4
5-Methyl thiazole	4.13	2.88	-4.2
2,4-Dimethyl thiazole	5.43	4.21	-4.1
2,5-Dimethyl thiazole	5.34	3.99	-4.5
4,5-Dimethyl thiazole	5.15	3.97	-4.0
2,4,5-Trimethyl thiazole	6.24	4.95	-4.3
2- <i>t</i> -Butyl thiazole	4.09	3.71	-1.3
4- <i>t</i> -Butyl thiazole	4.15	3.86	-1.0

In such proton transfer reactions there is no net formation of ions and thus there will only be minor contributions to the ΔS_i° values from a change in the compression of the solvent molecules. From Table 2 may be further noted that the $-\Delta S_i^\circ$ values are very similar for thiazole and all the methylsubstituted compounds whereas they are notably smaller for the two *t*-butyl thiazoles.

For the methyl substituted compounds the increase in ΔG_i° and ΔH_i° values relative to the unsubstituted thiazole is interpreted as being mainly due to polar effects. A methyl group is electron donating in comparison with hydrogen and methyl substitution is therefore expected to stabilize the thiazolium ion, *i.e.* to decrease the acid strength (increase ΔG_i° and ΔH_i°). From Table 2 it may be seen that there is an increase in ΔG_i° and ΔH_i° by about 1 kcal/mole for each methyl group. Similar effects have been observed for the picolines and lutidines⁸ and also for imidazoles.⁹ Only minor differences can be noted for the different isomeric compounds although the effect for substitution in the most distant 5-position is the smallest.

The increments in ΔH_i° values when going from thiazole to the methyl thiazole are 1.19 ± 0.04 (Me-2), 0.97 ± 0.04 (Me-4), and 0.86 ± 0.04 (Me-5)

Table 3. Estimation of ΔH_i° for di- and tri-methyl thiazoles from the values for thiazole and the monomethyl thiazoles.

Compound	ΔH_i° , kcal/mole		Δ , kcal/mole
	Observed	Estimated	
2,4-Dimethyl thiazole	4.21 ± 0.03	4.18 ± 0.06	-0.03
2,5-Dimethyl thiazole	3.99 ± 0.04	4.07 ± 0.06	+0.08
4,5-Dimethyl thiazole	3.97 ± 0.05	3.85 ± 0.06	-0.12
2,4,5-Trimethyl thiazole	4.95 ± 0.02	5.04 ± 0.07	+0.09

kcal/mole. As seen from Table 3, ΔH_i° values for the di- and tri-substituted compounds are very close to those which can be estimated from ΔH_i° for thiazole by addition of the appropriate increments. The fact that the di-*ortho* substituted compounds (2,4 di-Me and 2,4,5 tri-Me) do not show any deviation from this additivity scheme indicates that the methyl groups do not interfere sterically. The same conclusion was arrived at for picolines and for lutidines.⁸

Substitution by a *t*-butyl group shows a somewhat different picture. This group is a slightly stronger electron donator than the methyl group¹⁰ and as expected, ΔG_i and ΔH_i are increased with respect to unsubstituted and the monomethyl substituted compounds.

If Taft's σ^* values* are taken as a measure of the polar effect one would expect the increase in the ΔH_i° value by *t*-Bu substitution to be 1.6 times the effect of the corresponding methyl group, or 3.95 and 3.59 kcal/mole for 2-*t*-butyl thiazole and 4-*t*-butyl thiazole, respectively. The experimental values, 3.71 and 3.86 kcal/mole, respectively, seem to be within the expected uncertainty range although it can be noted that the order between the two isomers is reversed as compared with the methyl compounds.

The $-\Delta S_i$ values for the two *t*-butyl substituted thiazoles are nearly the same but markedly smaller than for all the other compounds listed in Table 2. Corresponding effects have been noted earlier for other types of ionization reactions where bulky substituents are close to the reaction centre. Following the suggestion by King and King⁵ (*cf.* Ref. 6) this effect is believed to be due to a structure promoting effect by the alkyl group in the disordered region outside the primary hydration sphere of the thiazolium ion.

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* $\sigma_{\text{H}^*} = +0.5$, $\sigma_{\text{Me}^*} = 0$, $\sigma_{\text{t-Bu}^*} = -0.3$.