tive, even when the ethanol was replaced by *n*-butanol, and the refluxing time was extended.

Quinolinecarboxylic Acid Derivatives. To prepare the quinolinecarboxylic acids, 0.01 mole of the appropriate ketone and 0.01 mole of isatin (or 5-bromoisatin) were dissolved in a solution of 0.033 mole of KOH in 30 ml. of 96% ethanol. The mixture was treated under reflux for 24 hours, diluted with five times its volume of water, treated with charcoal and filtered. Then, acetic acid or HCl was added to the filtrate until a strong acid reaction was attained. The mixture was allowed to stand in a refrigerator until the quinolinecarboxylic acid was completely precipitated. The precipitate was dissolved in acetic acid and crystallized. The yield in all cases was 85 to 95%.

The quinolinecarboxylic acids containing CF_3 groups are more soluble in water than their analogs without CF_3 groups. The prepared quinolinecarboxylic acids are listed in Table II.

Quinoline Derivatives. The decarboxylation of the above acids was carried out in a test tube, heated gently on a moderate flame, until carbon dioxide was completely evolved. The cooled residue was dissolved in 96% ethanol, the solution was treated with charcoal and filtered. A saturated alcoholic solution of picric acid was added to the filtrate, and the base was converted into its picrate. The picrate was separated and added to a mixture of 20 times its weight of chloroform and the same amount of water. An excess of ammonia was added, and the aqueous layer which dissolved the ammonium picrate was decanted off. The chloroform layer was washed with water repeatedly until the wash water was no longer colored. Chloroform was then evaporated, and the residue was dissolved in dilute methanol and crystallized. Yield, 85 to 90%. The prepared quinoline derivatives are listed in Table II.

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Thermodynamics of Ionization of Aqueous Barbituric Acid and Substituted Barbituric Acids

FRANK J. MILLERO, J. C. AHLUWALIA, and LOREN G. HEPLER
Department of Chemistry, Carnegie Institute of Technology, Pittsburgh, Pa.

Heats of ionization of barbituric acid and several substituted barbituric acids in aqueous solution have been determined calorimetrically at 298° K. Ionization constants have been determined for 5-allylbarbituric acid and 5-methylbarbituric acid. Entropies of ionization of all the acids investigated are calculated by combination of ΔG° values derived from ionization constants with our ΔH° values.

THE THERMODYNAMICS of ionization of aqueous barbituric acid and several substituted barbituric acids was investigated as a continuation of a program to determine and interpret such data for a variety of organic acids. Specific reasons for interest in the particular acids investigated are: The 5,5-disubstituted acids and their salts in solution have proved useful as buffers in the biologically important pH range from about 6 to 9; di- and tri-substituted barbituric acids are important hypnotic agents; and it has been postulated that un-ionized barbituric acids penetrate living cells more readily than do the constituent ions (*2*).

A number of investigations that are considered later in this paper have been concerned with determination of pK values for various barbituric acids, but only one of these yielded pK values of sufficient accuracy at several temperatures to permit calculation of reliable ΔH° and ΔS° values.

EXPERIMENTAL

The calorimeter used is patterned after one previously described (*7*) except that a Mueller G-2 Bridge and HS galvanometer are used with a nickel wire resistance thermometer for temperature measurements. Also, the resistance thermometer and calibration heater are contained in a glass spiral filled with mineral oil rather than wound on a silver cylinder. All of the calorimetric work reported here was carried out with 950 ml. of water or solution in the calorimeter at 25.0 ± 0.1° C.

1-Methylbarbituric acid and 1,3-dimethylbarbituric acid were prepared as follows. Diethylmalonate and the appropriate methylurea were added to absolute ethanol in which sodium had been previously dissolved. After being refluxed for 12 hours, the mixtures were acidified with HCl and stored overnight in a refrigerator. The resulting substituted barbituric acids were recrystallized twice from 95% ethanol and then vacuum dried. The melting points were 132° C. for 1-methylbarbituric acid and 122° C. for 1,3-dimethylbarbituric acid. All of the other barbituric acids investigated were supplied by Benzol Products.

Sodium salts of 5,5-diallylbarbituric acid, 5-methylbarbituric acid, and 5-allylbarbituric acid were prepared by mixing equivalent amounts of the barbituric acid and sodium ethoxide, both in absolute ethanol solution. Barbituric acid solutions were made up by weight, and the sodium ethoxide solution was standardized by titration with hydrochloric acid. After removal of ethanol by evaporation, the precipitated sodium salts were washed with cold absolute ethanol, vacuum dried, and analyzed by titration with hydrochloric acid. All of the other sodium salts were supplied by Benzol Products.

Solutions for pH measurements were brought to thermal equilibrium with a water bath maintained at 25.00 ± 0.05° C. The pH was measured (immediately after transfer to the pH cell, to minimize effect of CO_2 absorption) with a Beckmann Model G pH meter equipped with a shielded glass electrode.

HCl and NaOH solutions were prepared and standardized by common procedures.

Table I. pK Values for Substituted Barbituric Acids at 25°

	Neutralization			
Acid	35%	50%	60%	Av. pK
5-Allylbarbituric	4.78	4.76	4.78	4.78
5-Methylbarbituric	4.40	4.39	4.40	4.40

RESULTS AND CALCULATIONS

Ionization constants of 5-methylbarbituric acid and 5-allylbarbituric acid were calculated from results of glass electrode (calibrated with partly neutralized solutions of barbituric acid) measurements on partly neutralized solutions of the substituted barbituric acids. Details of this procedure, which is based on the assumed equality of certain activity coefficient ratios in dilute solutions of the same ionic strength, have been reported (*6*). Results are summarized in Table I.

Heats of ionization have been calculated from heats of solution of the appropriate mono-sodium salts in water and in aqueous HCl. A general calorimetric reaction equation for solution of salt in water is

$$\mathrm{NaB(c)} = \mathrm{Na^+(aq.)} + B^-\mathrm{(aq.)} \qquad (1)$$

and the experimental results, designated ΔH_1, are listed in Table II. A general calorimetric reaction equation for solution of salt in acid is

$$\mathrm{NaB(c)} + \mathrm{H^+(aq.)} = \mathrm{HB(aq.)} + \mathrm{Na^+(aq.)} \qquad (2)$$

and the experimental results, designated ΔH_2, are listed in Table II. Final concentration of HCl in these experiments was 0.050 to 0.045*M*.

Table II. Heats of Solution of Sodium Salts of Barbituric Acids

	In Water			In Dilute HCl		
Sodium Salt of	ΔH_1^0, kcal./mole	Moles salt/950 ml.	ΔH_1, kcal./mole	ΔH_2^0, kcal./mole	Moles salt/950 ml.	ΔH_2, kcal./mole
Barbituric acid	5.30	0.009526	5.29	5.24	0.006767	5.24
		0.016130	5.28		0.013408	5.25
		0.021988	5.26		0.020264	5.24
		0.028597	5.26		0.027033	5.26
		0.035459	5.25		0.033919	5.26
5-Allylbarbituric acid	1.94	0.007099	1.92	3.83	0.005992	3.82
		0.010860	1.92		0.007872	3.85
		0.013026	1.99		0.009310	3.81
					0.011987	3.86
5-Methylbarbituric acid	2.04	0.018532	2.16	3.32	0.007349	3.33
		0.018818	1.94		0.012551	3.34
		0.024588	2.08		0.012716	3.36
		0.027559	1.99		0.018771	3.38
					0.018917	3.37
5,5-Diallylbarbituric acid	1.26	0.009565	1.26	−3.66	0.004010	−3.65
		0.015230	1.24		0.004419	−3.67
		0.017452	1.31		0.004536	−3.65
		0.026673	1.24		0.004642	−3.68
5,5-Diethylbarbituric acid	0.86	0.026530	0.87	−4.95	0.007652	−4.94
		0.030421	0.87		0.012538	−4.94
		0.031284	0.85		0.016019	−4.98
		0.035547	0.85		0.020845	4.97
		0.039912	0.86		0.027086	−4.92
5-Ethyl-5-phenylbarbituric acid	−1.56	0.007106	−1.60	−6.16	0.005099	−6.11
		0.014246	−1.56		0.005892	−6.20
		0.018810	−1.53		0.006450	−6.14
		0.023359	−1.57		0.010435	−6.19
		0.026955	−1.55			
5-Ethyl-5*n*-amylbarbituric acid	−2.56	0.006557	−2.54	−7.78	0.004258	−7.78
		0.010539	−2.59		0.004744	−7.75
		0.013293	−2.50		0.005101	−7.78
		0.016610	−2.46		0.006003	−7.78
		0.016610	−2.46		0.006831	−7.79
5-Ethyl-5-(α-methylbutyl)barbituric acid	−3.17	0.004608	−3.13	−8.98	0.004164	−8.96
		0.006072	−3.18		0.004437	−9.02
		0.008953	3.17		0.005152	−8.97
		0.011355	3.17		0.006240	−9.00
		0.013076	−3.20		0.007370	−8.96
5-Allyl-5-(α-methylbutyl)barbituric acid	−2.50	0.004699	−2.51	−7.50	0.004305	−7.51
		0.009972	−2.54		0.005271	−7.42
		0.011508	−2.55		0.005582	−7.50
		0.012325	−2.64		0.006071	−7.52
		0.012715	−2.59		0.006751	−7.47
		0.016492	−2.65			

Table III. Thermodynamics of Ionization of Aqueous Barbituric Acids at 298° K.

Acid	ΔH_i^0, Kcal./Mole	ΔG_i^0, Kcal./Mole	ΔS_i^0, Cal./Deg. Mole
Barbituric	0.06	5.51	−18.8
5-Allylbarbituric	−1.89	6.52	−28.2
5-Methylbarbituric	−1.28	6.00	−24.4
5,5-Diallylbarbituric	4.92	10.61	−19.1
5,5-Diethylbarbituric	5.81	10.89	−17.0
5-Ethyl-5-phenylbarbituric	4.60	10.15	−18.6
5-Ethyl-5-*n*-amylbarbituric	5.22	10.85	−18.6
5-Ethyl-5(α-methylbutyl)-barbituric	5.81	11.07	−17.6
5-Allyl-5(α-methylbutyl)-barbituric	5.00	11.02	−20.2
1,3-Dimethylbarbituric	−0.05[a]	6.38	−21.6
1-Methylbarbituric	~0[b]	5.93	~−20[b]

[a] This enthalpy was determined as described below (see Table IV). [b] These ΔH_i^0 and ΔS_i^0 values are estimated on the basis of similar values for barbituric acid and 1,3-dimethylbarbituric acid. The ΔG_i^0 value is derived from the pK measured by Biggs (*1*).

The ionization of an aqueous barbituric acid is indicated by the equation

$$HB(aq.) = H^+(aq.) + B^-(aq.)\ \Delta H_i^0 \quad (3)$$

and ΔH_i^0 may be obtained from the experimental heats as $\Delta H_i^0 = \Delta H_1^0 - \Delta H_2^0$. The small heats of dilution and correction for hydrolysis effects have been estimated for use in converting ΔH_1 values to ΔH_1^0 values in Table II. Heats of dilution for the symmetrical reactions of Equation 2 are nearly zero in dilute solutions. Resulting ΔH_i^0 values, free energies of ionization, ΔG_i^0, and entropies of ionization calculated from $\Delta S_i^0 = (\Delta H_i^0 - \Delta G_i^0)/T$ are listed in Table III. Ionization constants leading to ΔG_i^0 values have been taken from Table I and from (*1, 4, 5*).

The heat of ionization of 1,3-dimethylbarbituric acid was determined by measuring the heat of reaction of the aqueous acid with aqueous NaOH. Ten-milliliter aliquots of 4.946*M* NaOH were mixed with 950 ml. of H_2O containing a known amount of acid. A general reaction equation for this process is

$$HB(aq.) + OH^-(conc.) = B^-(aq.) + H_2O(liq.) \quad (4)$$

Separate determination of the total heat associated with breaking the bulb containing NaOH and diluting the NaOH permitted the calculation of heats for the reactions

$$HB(aq.) + OH^-(aq.) = B^-(aq.) + H_2O(liq.) \quad (5)$$

These values, designated ΔH_n, are listed in Table IV. Combination of ΔH_n^0, derived from small, estimated heats of dilution and ΔH_n values in Table IV, with $\Delta H^0 = 13.34$ kcal. per mole for the heat of ionization of water (*3, 8*) leads to the desired ΔH_i^0 that is listed in Table III.

DISCUSSION

Manov, Scheutte, and Kirk (*5*) have determined pK for 5,5-diethylbarbituric acid at several temperatures. Their data lead to $\Delta H_i^0 = 5.81_2$ kcal. per mole and $\Delta S_i^0 = -17.02$ cal. per deg. mole, in excellent agreement with authors' values listed in Table III. Manov, Scheutte, and Kirk (*5*) have made a numerical error in converting from joules to calories. Krahl (*4*) has determined pK for 5-ethyl-5-isoamylbarbituric acid at several temperatures. These data lead to $\Delta G_i^0 = 10.82$ kcal. per mole, $\Delta H_i^0 = 9.92$ kcal. per mole, and $\Delta S_i^0 = -3.1$ cal. per mole, all at 298° K. Since entropies of ionization of uncharged acids, including all those listed in Table III, are generally about −20 cal. per deg. mole, the authors believe that Krahl's ΔH_i^0 and ΔS_i^0 values are probably incorrect. However, comparison of his pK values (at 298° K.) with those of other investigators suggests that the pK values and free energies may not include large errors.

Table IV. Heats of Neutralization of 1,3-Dimethylbarbituric Acid

Moles Acid/950 Ml.	$-\Delta H_n$, Kcal./Mole
0.004790	13.43
0.005359	13.37
0.006112	13.36
0.006879	13.39
0.007102	13.42
0.008305	13.39
0.009167	13.37

$\Delta H_n^0 = -13.39$ kcal./mole

The considerations above indicate once again that ΔH_i^0 and ΔS_i^0 values can be obtained reliably from d ln K/dT or dΔG^0/dT only if highly accurate pK values have been determined at several temperatures, as was done by Manov, Scheutte, and Kirk (*5*) for 5,5-diethylbarbituric acid.

Interpretation of effects of substituents on acidity of barbituric acid is complicated and uncertain for several reasons. One reason is that the data in Table III indicate that four pairs of acids in Table III [5-allylbarbituric and 1,3-dimethylbarbituric, 5-methylbarbituric and 1-methylbarbituric, 5-ethyl-5(α-methylbutyl)barbituric and 5-allyl-5(α-methylbutyl)barbituric, 5,5-diethylbarbituric and 5-ethyl-5-*n*-amylbarbituric acid] undergo change in order of acidity at temperatures between 0 and 100° C. In some cases, differences in acidity are due to differences in ΔH_i^0, while in other cases differences in ΔS_i^0 are the determining factor. For instance, both 5-allylbarbituric and 5-methylbarbituric acids are weaker than barbituric acid because of differences in ΔS_i^0, in spite of ΔH_i^0 values favoring ionization of the substituted acids.

The data in Table III show several interesting features which may be summarized as follows. A methyl substituent in either the 1 or 5 positions has nearly the same effect on ΔG_i^0, but not on ΔH_i^0 and ΔS_i^0. The effect of two methyl substituents (not 5,5) on ΔG_i^0 is about twice that of a single methyl substituent. A single substituent in the 5 position increases ΔG_i^0 by about 0.5 to 1.0 kcal. per mole (owing to an entropy effect) while two substituents in the 5 position increase ΔG_i^0 by about 4.6 to 5.6 kcal. per mole (owing to an enthalpy effect).

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