Journal of Research of the National Bureau of Standards Vol. 48, No. 1, January 1952 Research Paper 2289

Ionization Constant of 5-5′-Diethylbarbituric Acid from 0° to 60° C

George G. Manov,[1] Kathryn E. Schuette, and Floyd S. Kirk

Measurements are reported for the ionization constant and for related thermodynamic quantities from 0° to 60° C for 5-5′-diethylbarbituric acid.

Two series of solutions corresponding to molal ratios of barbituric acid:sodium barbiturate:sodium chloride (or iodide) of 1:0.5:1.667, 1:1:1.667, and 1:2:1.667 were investigated. The values obtained for the ionization constant of the acid using these three ratios of acid to sodium salt and two types of reference electrodes were found to agree within the experimental error of the measurements. Two other series of solutions in which both the ratio and the concentration of the buffer materials were maintained at a fixed value and that of the halide ion was diminished were also studied. The effect of sodium iodide on the pK' of the buffers was normal, whereas that for the sodium chloride was anomalous but could be explained in terms of a demonstrated interaction at low concentrations of sodium chloride, between the soluble barbiturate ion and the silver–silver-chloride electrode used in the cell.

The variation of pK for 5-5′-diethylbarbituric acid with the absolute temperature T, where $T=273.16+t$°C, can be expressed by the equation

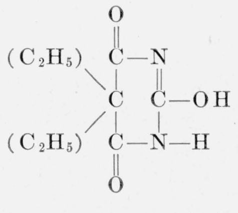
$$\mathrm{p}K=2324.47/T+0.0118562\,T-3.3491$$

over the range 0° to 60° C.

1. Introduction

Solutions of barbiturates are used to control the acidity of biological media [1][2] in the vicinity of pH 7 and are useful in blood chemistry, where the use of this buffer does not remove calcium and magnesium salts as does, for example, a phosphate buffer. Barbiturates are also used as sedatives and anaesthetics, and the time lag between the injection of the barbiturate and the onset of anaesthesia is thought by some investigators [2] to be related to the rate of absorbtion of the un-ionized molecule and hence to the ionization constant of the barbituric acid.

In general, the various substituted barbituric acids and the corresponding sodium salts are capable of easy purification and permit the preparation of a wide range of monobasic buffer mixtures. Measurements of the pH of such buffers have been made with the glass electrode [3] for a number of substituted barbiturates. The particular compound chosen for this investigation was 5-5′-diethylbarbituric acid



A number of measurements of the ionization constant of the acid and of the pH of the acid-salt buffer mixtures have been made by other investigators [1, 3, 5, 6, 7], using cells that involved a liquid junction. The specific electric conductance was measured by one worker [4]. The data reported in this paper for the ionization constant were obtained by the use of hydrogen and silver–silver-halide electrodes in a cell without a liquid junction, according to the method of Harned and associates [8].

2. Experimental Details

2.1. Materials and Solutions

The components of the buffer solutions studied were 5-5′-diethylbarbituric acid [3] and its sodium salt (hereafter abbreviated to HB and NaB, respectively), and either sodium chloride or sodium iodide. The reason for the use of the two halides is explained later.

Because of the confusion in synonyms, it was found that little credence could be placed upon the reliability of the scattered values found in the literature for the solubility of the acid or of the sodium salt. The approximate solubilities of HB and of NaB were therefore determined in the conventional manner. The approach to equilibrium was made from the directions of under- and of supersaturation; the solutions were analyzed by titration with standard acid or base. The solubility of 5-5′-diethylbarbituric acid in water at 5° and 25° C was found to be 0.019 ±0.001 and 0.028 ±0.001 mole per liter of solution. A solubility of 0.017 m at 0° C is estimated. This value is important because it limits the concentration of HB that can be used in a buffer solution at the lowest temperature of the experiments. The solubility of NaB was determined at 5° and at 25° C in a similar manner and found to be 0.79 ±0.01 and 0.82 ±0.01 mole per liter of solution.[4]

---

[1] Present address, Atomic Energy Commission, Oak Ridge, Tenn.

[2] Figures in brackets indicate the literature references at the end of this paper.

[3] Considerable confusion is present in the early, and particularly in the foreign literature by the plurality of names that have been used synonymously for 5–5′ diethylbarbituric acid (and occasionally for other barbituric acids), for example: veronal, luminal, medinal, barbitone, barbital (used indiscriminately for both the acid and the sodium salt), etc.

[4] For the solubility of HB, Squire and Cains [9] give 0.031 molal at 15° C and 0.043 m at 27° C; Casparis [10] states that 1 part of acid dissolves in 145 parts of "cold" water, corresponding to a solubility of approximately 0.04 m. For NaB, the data of Puckner and Hilpert [11] yield 0.29 m at 5° C and 0.84 m at 25° C; the requirement of the U. S. Pharmacopoeia [12] is that 1 part of the sodium salt shall dissolve in 5 parts of water at room temperature and corresponds to a minimum solubility of approximately 0.8 molal.

Small portions of barbituric acid were recrystallized three times each from ethyl alcohol and from toluene. The melting points of the products were 188.8° C (uncorrected) in both cases, whereas that of the original acid (USP grade) was approximately 0.2° C lower. The material recrystallized from alcohol was found to be wetted easily by water, whereas that from the toluene was not, and the main portion of the acid was therefore recrystallized from alcohol.

The sodium salt was purified in the following manner: 100 g of NaB (USP grade) was dissolved in 300 ml of warm water and filtered to remove any undissolved impurities, 300 ml of ethyl alcohol was added and the mixture cooled to 5° C and the product filtered. The yield was approximately 40 percent. The pH values at 25° C of 0.05-molal solutions (determined with a glass-electrode pH meter) of the original and of materials that had been recrystallized once and twice were, respectively, 9.75, 9.80, and 9.82. The distilled water used to prepare these solutions had been freshly boiled and was protected against atmospheric carbon dioxide during cooling. The pH of the water varied from 6.2 to 6.4.

Experiments were performed on separate 0.02-molal solutions of HB and NaB to determine the effect of small amounts of acidic or alkaline impurities on the pH of the mixtures. Such information is of importance in determining the extent to which the HB and NaB should be purified. The results, presented graphically in figure 1, show that 0.25 mole percent of an acidic impurity (added as HCl) lowers the pH of 0.02-molal HB from 4.69 to 4.47, whereas the same amount of an alkaline impurity (added as NaOH) raises the pH from 4.69 to 4.84. The corresponding figures for NaB are from 9.75 to 9.60 and from 9.75 to 9.95. The effect of small amounts of impurities is particularly noticeable when the HB and NaB are tested separately, because the buffer capacity of the solution in such cases is very low. The same amounts of impurities in a solution in which the buffer ratio is unity would each cause a difference in the pH of only 0.001 unit. Obviously, if the impurities were weak electrolytes, their effect on the pH of the buffer solution would be reduced still further. If the impurities were homologs of 5-5′-diethylbarbituric acid (or of the sodium salt), it would be possible, of course, for the acid (or the sodium salt) to contain an appreciable amount of impurity without changing the pH of the separate solutions significantly. The USP grade acid and sodium salt used in the determination of pK' and pH were each recrystallized twice with yields of approximately 55 and 40 percent, respectively, for each crystallization. The melting point of the USP grade acid was also 188.6° C (uncorrected), and the first and second recrystallizations both melted sharply at 188.8° C. The purification of the materials by recrystallization to the extent that the pH of successive fractions of the acid and of the salt in 0.02-m solutions changes by less than 0.1 unit evidently is adequate.

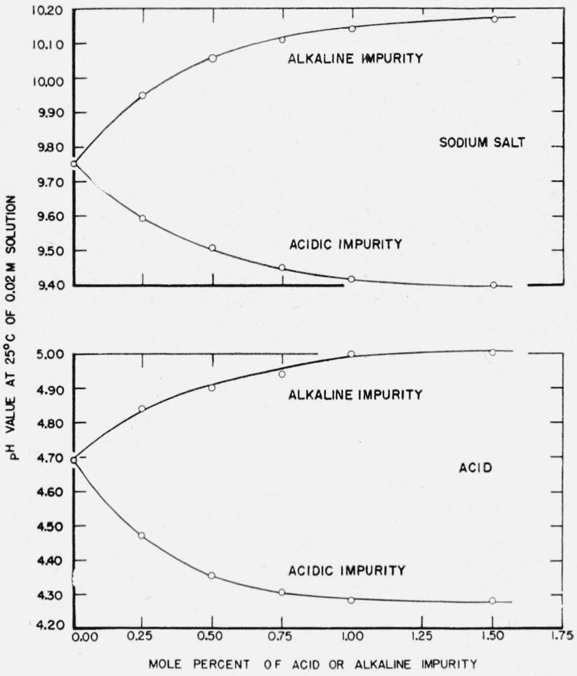


FIGURE 1. *Effects at 25° C of small quantities of acid* (HCl) *and of alkaline* (NaOH) *impurities on the* pH *of a 0.02-m solution of 5-5′-diethylbarbituric acid and of a 0.02-m solution of sodium 5-5′-diethylbarbiturate.*

The densities of solid HB and NaB (needed to reduce the weights of these materials in air to a vacuum basis) were determined with sufficient accuracy by measuring with a Westphal balance the densities at 25° C of the mixtures of benzol and chloroform in which the two solids would remain in suspension without appreciably floating or sinking. The densities thus obtained were 1.3 g/cm^3 for both the HB and NaB.

The sodium chloride was purified by passing gaseous chlorine into the boiling saturated solution that had been acidified slightly. The excess chlorine was removed by passing a stream of air through the boiling solution until the odor of free halogen disappeared and a negative test for free halogen was obtained with starch-iodide on a portion of the solution. The main portion of the solution was then cooled to room temperature and the pH adjusted to neutrality with a small amount of aqueous sodium hydroxide prepared from metallic sodium and water. An equal volume of ethyl alcohol was added to the solution, and the precipitated sodium chloride was filtered and dried at 110° C. The pH of a 0.05-molal solution of the product was not significantly different (±0.03) from that of the water used to prepare the solution. Analysis [13] of the purified sodium chloride by Gladys D. Pinching, of the Bureau, showed a bromide content of 0.002 percent. This method for the purification of sodium chloride is a modification of the one described earlier [14] and eliminates the steps [13] involving the precipitation of the salt with hydrochloric acid (which must also be free of bromide impurities) and the subsequent necessity for the fusion of the sodium chloride under special conditions to remove traces of hydrochloric acid and to prevent hydrolysis of the salt.

Sodium iodide was purified by recrystallization from water in the conventional manner. The distilled water used for the preparation of the solutions had a maximum specific conductance at 25° C of 0.7 micromho.

All solutions were prepared by weight methods, and the concentrations of the various components were known to a precision of ±0.05 percent.

2.2. Electrodes

The hydrogen and silver–silver-chloride electrodes were prepared as described previously [14]. The Ag-AgI electrodes used were of the thermal-electrolytic variety, in which a paste of silver oxide was heated to 450° C and the resulting silver partially converted (5 mole percent) to silver iodide by electrolysis in 1-*m* HI. Several lots, each containing 18 electrodes of this type, showed an average reproducibility in potential of ±0.05 mv (±0.0008 pH). The values for $E°$ obtained by Owen [15] were employed in the present paper.[5] In table 1 are given the values used for $E°$ for the two silver–silver-halide electrodes and for other constants used elsewhere in this paper.

TABLE 1. *Values used for the constants in the determination of the ionization constant of 5-5′-diethylbarbituric acid*

Temperature	$E°_{\text{Ag-AgCl}}$ [16]	$E°_{\text{Ag-AgI}}$ [15]	k
° *C*	*Int. v*[a]	*Int. v*	*Int. v*
0	0.23644	−0.14624	0.054179
5	.23396	−.14707	.055171
10	.23132	−.14808	.056163
15	.22846	−.14927	.057154
20	.22550	−.15064	.058146
25	.22238	−.15219	.059138
30	.21911	−.15392	.060129
35	.21564	−.15583	.061121
40	.21207	−.15792	.062113
45	.20822	----------	.063105
50	.20432	----------	.064096
55	.20033	----------	.065088
60	.19619	----------	.066080

[a] The work reported in this paper was completed prior to the general adoption of the absolute units of electromotive force. Inasmuch as E, $E°$, and k are all expressed consistently in international volts, the true value of pK is obtained.

2.3. Procedure

Hydrogen and silver–silver-halide electrodes were used in cells without a liquid junction in two series of experiments.

In the first series, a stock solution was prepared corresponding to the fixed ratio of HB:NaB:NaX (where X was either chloride or iodide), and a number of dilutions of this stock solution were made.

Measurements of the emf of the cells containing these dilutions were made from 0° to 60° C, and the data were used for evaluating the ionization constant of HB. In the second, the concentration of HB and of NaB were maintained at a constant value, whereas that of the NaX was progressively diminished. The emf measurements of the cells were made from 0° to 40° C, and the data were used to determine the effect of NaX on the apparent ionization constant of HB.

The arrangement of the thermostat, the construction of the solution flasks, the filling of the cells, and related matters have been described by Hamer [17].

3. Determination of the Ionization Constant of 5-5′-Diethylbarbituric Acid From 0° to 60° C

Measurements were made of the emf of the cell system

$$\text{Pt; H}_2\text{, HB, NaB, NaX, AgX; Ag} \qquad (1)$$

in which the proportions and concentrations of HB, NaB, and NaX (X=Cl or I) were systematically varied. The measured emf, E, of the cell is given by

$$E = E° - k \log (a_H)(a_X), \qquad (2)$$

where a_H and a_X are the activities ($a = fm$) of the hydrogen and halide ions. By defining

$$\text{p}K = -\log K \qquad (3)$$

where

$$K = (a_H)(a_B)/(a_{HB}) = (a_H)(f_B m_B)/(f_{HB} m_{HB}) \qquad (4)$$

and with the assumption that $f_{HB}=1$, eq 4 may be rewritten to yield

$$\text{p}K = (E - E°)/k + \log (m_{HB}/m_B) + \log m_X + \log (f_X/f_B). \qquad (5)$$

The last term in eq 5 cannot be calculated unless pK is known, and it is therefore convenient to define a new quantity, pK', such that

$$\text{p}K' = (E - E°)/k + \log (m_{HB}/m_B) + \log m_X = \text{p}K - \log (f_X/f_B). \qquad (6)$$

Equation 6 contains only terms whose values either are known or can be measured experimentally. By definition, the activity coefficients of the ions become unity at infinite dilution, and consequently a plot of pK' against the ionic strength, μ, (for univalent buffer-halide solutions, $\mu = m_B + m_X$) may be extrapolated to $\mu = 0$ to yield pK.[6] Having obtained an extrapolated value for pK, it is then possible to use eq 5, if desired, to calculate values for $\log (f_X/f_B)$ at finite concentrations.

3.1. Measurements of pK' with Hydrogen and Silver–Silver-Chloride Electrodes

For the determination of pK, three different proportions of HB:B:Cl were investigated at each temperature.

---

[5] The values for $E°$ for the Ag-AgI electrode are given by Owen [15] over the range 5° to 40° C by $E° = -0.15219 - 0.328 \times 10^{-3}(t-25) - 3.6 \times 10^{-6}(t-25)^2$. Owen found that electrodes prepared by fusion of a coprecipitated mixture of silver oxide and silver iodide were somewhat less reliable than either the thermal-electrolytic variety or those prepared from silver oxide and silver iodate.

[6] In dilute solutions, the hydrolysis of barbiturate ion results in a slight increase in the buffer ratio, (m_{HB}/m_B). The largest effect is observed at 60° C for the most dilute solution of the 1:2 buffer ratio, and amounts to +0.0012 in pK' (0.07 mv in emf). The effect of hydrolysis is considerably less at lower temperatures and is negligible for the 1:0.5 ratio at all temperatures.

In series A the proportions of HB:B:NaCl were 1:0.5:1.667; in series B, 1:1:1.667; and in series C, 1:2:1.667. The concentration of HB in the most concentrated (stock) solution for each series was approximately 0.015 molal to prevent separation of the free acid at 0° C.

Dilution of the stock solution was made by weight methods, and the resulting solutions were used to fill the cells.

Measurements of the emf of the cells were made at 25° C, then at 5-degree intervals from 0° to 60° C, and finally at 25° C, and, in general, the initial and final emf at 25° C agreed to within 0.15 mv.

The composition of the solutions and the emf of the cells (in international volts), corrected to 1-atm pressure of hydrogen gas, are given in table 2. Values for pK' at each concentration, and temperature were calculated by means of eq 6 and are given in table 3.

Figure 2 shows the variation of pK' with the ionic strength. The experimental points obtained in series A, B, and C are designated by circles. (The points designated by squares refer to the data obtained with sodium iodide and silver–silver-iodide electrodes and are discussed later).

As mentioned previously, the extrapolated values

TABLE 2. *Observed electromotive force, in international volts, of cells composed of hydrogen and silver–silver-chloride electrodes and mixtures of 5–5′-diethylbarbituric acid* (m_{HB}), *sodium 5–5′-diethylbarbiturate* (m_{B}), *and sodium chloride* (m_{Cl})

Solution	m_{HB}	m_{B}	m_{Cl}	μ	E_0	E_5	E_{10}	E_{15}	E_{20}	E_{25}	E_{30}	E_{35}	E_{40}	E_{45}	E_{50}	E_{55}	E_{60}
Series A. Ratio HB:NaB:NaCl=1:0.5:1.667																	
1	0.005843	0.002924	0.009737	0.012660	0.78442	0.78668	0.78915	0.79163	0.79417	0.79618	0.79832	0.80055	0.80268	0.80474	0.80663	0.80861	------
2	.005982	.002991	.010017	.013010	------	.78603	.78828	------	.79315	.79479	.79673	.79892	.80098	.80297	.80495	.80694	0.80883
3	.010000	.005000	.016745	.021750	------	.77358	.77558	.77765	.77966	.78167	78345	.78546	.78739	.78918	.79098	.79277	.79443
4	.011168	.005590	.018610	.024200	.76900	.77105	.77322	.77517	.77719	.77900	.78096	.78268	.78467	.78640	.78816	.78995	.79153
5	.015000	.007508	.024995	.032503	.76219	.76415	.76614	.76799	.76989	.77156	.77345	.77519	.77685	.77843	.77977	.78153	.78293
Series B. Ratio HB:NaB:NaCl=1:1:1.667																	
1	0.003074	0.002937	0.004896	0.007833	0.81536	0.81823	0.82123	---	---	0.82988	0.83270	0.83536	0.83802	0.84061	0.84318	0.84572	0.84806
2	.006066	.005795	.009659	.015454	.79979	.80241	.80506	0.80762	0.81015	.81270	.81511	.81743	.81976	.82202	.82422	.82636	.82837
3	.009045	.008641	.014402	.023043	.79054	.79291	.79538	.79784	.80022	.80259	80489	-	.80920	.81135	.81343	.81544	.81736
4	.012476	.011919	.019865	.031784	.78300	.78533	.78769	.78999	.79219	.79442	.79657	.79863	.80070	.80273	.80464	.80647	.80828
5	.015714	.015013	.025021	.040034	.77774	.77995	.78216	.78442	.78654	.78856	.79069	.79264	.79462	.79651	.79836	.80009	.80181
Series C. Ratio HB:NaB:NaCl=1:2:1.667																	
1	0.002681	0.005362	0.004468	0.009831	0.83522	------	0.84216	0.84533	0.84842	0.85090	0.85382	------	------	------	------	------	------
2	.003016	.006033	.005069	.011100	------	0.83561	.83863	.84178	.84515	.84781	.85092	0.85441	0.85740	0.86019	0.86317	0.86591	0.86870
3	.005362	.010724	.008935	.019659	.81893	.82198	.82496	.82798	.83075	.83350	.83612	.83895	.84161	.84436	.84714	.84983	.85236
4	.008024	.016047	.013370	.029417	.80970	.81260	.81541	.81824	.82091	.82356	.82619	.82864	.83118	.83364	.83614	.83853	.84087
5	.010000	.020000	.016804	.036804	------	------	------	------	.81540	.81719	.82019	.82268	.82496	.82717	.82945	.83154	.83357
6	.010905	.021809	.018170	.039979	.80250	.80532	.80801	.81079	.81338	.81556	------	------	------	------	------	------	------
7	.013500	.027001	.022497	.049498	.79765	.80036	.80290	.80534	.80783	.81008	.81261	.81496	.81728	.81953	.82179	.82387	.82589

TABLE 3. *Values of the negative logarithm of the apparent ionization constant,* pK', *of barbituric acid from 0° to 60° C for various ratios of 5-5′-diethylbarbituric acid, sodium 5-5′-diethylbarbiturate, and sodium chloride* [a]

Solution	μ	pK'_0	pK'_5	pK'_{10}	pK'_{15}	pK'_{20}	pK'_{25}	pK'_{30}	pK'_{35}	pK'_{40}	pK'_{45}	pK'_{50}	pK'_{55}	pK'_{60}
Series A. Ratio HB:NaB:NaCl=1:0.5:1.667														
1	0.012660	8.4033	8.3073	8.2213	8.1426	8.0690	7.9917	7.9218	7.8587	7.7980	7.7420	7.6880	7.6345	------
2	.013010	------	8.3082	8.2185	------	8.0642	7.9809	7.9080	7.8447	7.7830	7.7265	7.6725	7.6215	7.5729
3	.021750	------	8.3058	8.2156	8.1338	8.0554	7.9826	7.9104	7.8477	7.7874	7.7311	7.6777	7.6270	7.5782
4	.024200	8.4000	8.3054	8.2191	8.1360	8.0584	7.9826	7.9146	7.8477	7.7891	7.7326	7.6792	7.6292	7.5798
5	.032503	8.4023	8.3083	8.2210	8.1383	8.0617	7.9848	7.9176	7.8532	7.7912	7.7343	7.6763	7.6279	7.5776
Series B. Ratio HB:NaB:NaCl=1:1:1.667														
1	0.007833	8.3950	8.2999	8.2132	------	------	7.9825	7.9143	7.8494	7.7880	7.7317	7.6778	7.6265	7.5759
2	.015454	8.4026	8.3081	8.2203	8.1380	8.0596	7.9867	7.9167	7.8508	7.7886	7.7316	7.6765	7.6234	7.5721
3	.023043	8.4054	8.3094	8.2205	8.1404	8.0623	7.9893	7.9203	------	7.7918	7.7358	7.6813	7.6286	7.5785
4	.031784	8.4059	8.3117	8.2242	8.1428	8.0639	7.9909	7.9216	7.8562	7.7947	7.7389	7.6839	7.6305	7.5808
5	.040034	8.4091	8.3144	8.2258	8.1455	8.0669	7.9919	7.9240	7.8584	7.7970	7.7405	7.6861	7.6327	7.5831
Series C. Ratio HB:NaB:NaCl=1:2:1.667														
1	0.009831	8.4010	------	8.2253	8.1422	8.0621	7.9771	7.9049	------	------	------	------	------	------
2	.011100	------	8.3091	8.2172	8.1352	8.0641	7.9802	7.9120	7.8548	7.7943	7.7364	7.6842	7.6311	7.5828
3	.019659	8.4013	8.3082	8.2200	8.1397	8.0592	7.9839	7.9115	7.8481	7.7859	7.7313	7.6798	7.6296	7.5809
4	.029417	8.4060	8.3132	8.2250	8.1442	8.0650	7.9908	7.9214	7.8544	7.7929	7.7363	7.6829	7.6308	7.5818
5	.036804	------	------	------	------	8.0690	7.9824	7.9209	7.8562	7.7919	7.7330	7.6774	7.6222	7.5700
6	.039979	8.4064	8.3146	8.2265	8.1472	8.0697	7.9888	------	------	------	------	------	------	------
7	.049498	8.4095	8.3174	8.2283	8.1445	8.0661	7.9889	7.9215	7.8566	7.7948	7.7383	7.6848	7.6314	7.5808

[a] See table 2 for the concentrations of the solutes.

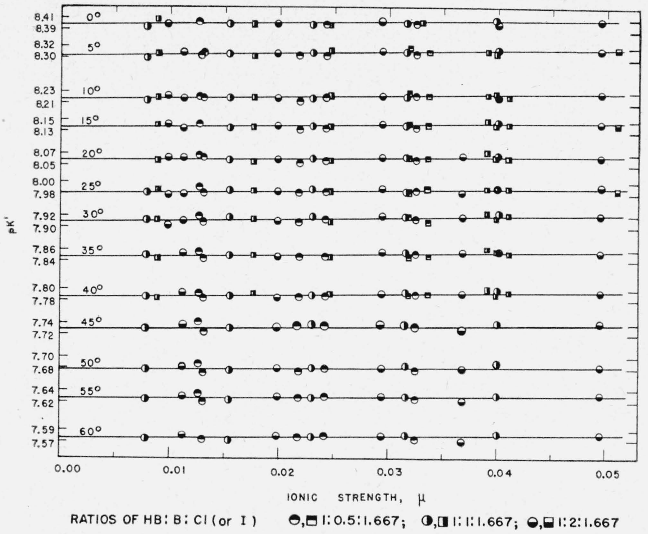


FIGURE 2. *Variation of* pK' *with ionic strength for various fixed ratios of* HB:NaB:NaCl (*or* NaI).

The data from the cells using silver–silver-chloride electrodes and sodium chloride, are designated by circles and those using silver–silver-iodide electrodes and sodium iodide are designated by squares.

obtained for pK from each series of measurements do not depend upon the validity of eq 6, because log $(f_X/f_B)=0$ when $\mu=0$. Examination of the plot of pK' against μ, however, indicated that the points fell on a straight line, of the type pK'=p$K+\beta\mu$, in which β is the slope.

The values for pK at 25° C obtained were 7.9792, 7.9815, and 7.9775 for the three series in which the buffer ratios (HB:NaB) were 1:0.5, 1:1, and 1:2. The average value for pK at 25° C weighted according to the number of experimental points in each series is 7.9792 ±0.0010.

Values for pK at several other temperatures were also calculated for each buffer ratio and show approximately the same degree of concordance.

3.2. Effect of the Concentration of Alkali Halide on pK'

In cells without a liquid junction (eq 1), the presence of a soluble alkali halide is necessary to insure the reversible functioning of the silver–silver-halide electrode.

When measurements of pH are made by means of a practical assembly, such as hydrogen-calomel or glass-calomel cells, the soluble halide in the buffer solution serves no useful purpose; in fact, it is convenient to prepare a buffer solution without the necessity of weighing out an extraneous salt.

Measurements are therefore usually made of the emf of the series of cells containing solutions in which both the ratio and the concentrations of the buffer acid and its salt are maintained at a fixed value, whereas that of the alkali halide is progressively diminished.

The values thus obtained for pK' can be plotted against the molality of the halide (usually the plot is a linear, or very nearly so), and extrapolated to zero concentration of halide to obtain the pK' for the halide-free buffer.[7]

The value for pK' at zero concentration of chloride ion (and for finite concentration of both m_{HB} and m_{B}) is designated as pwH° by Bates [18] or pwH°$\equiv\lim_{\mathrm{Cl}\to 0}$ pK'.

The value of pwH° can be used to calculate the pH of the buffer. A variety of values can be obtained, depending on the assumption used to estimate log f_{Cl}.

Although this method had been successfully applied at the Bureau in a study of a number of buffer-chloride mixtures, anomalous results were obtained with barbiturate-chloride solutions. The plot of pK' against μ was not a straight line throughout its entire length, but dropped sharply as the concentration of chloride ion relative to that of the buffer was diminished. The anomalous behavior can be explained by postulating some kind of a reaction between barbiturate ion and solid silver chloride that has an increasing tendency to take place the lower the concentration of soluble chloride in the solution. An experiment was performed in which approximately 0.01 mole of solid silver chloride (free from extraneous, soluble chloride) and approximately 0.01 mole of NaB were shaken together for several days with 100 ml of distilled water. The filtrate was acidified with nitric acid and yielded a qualitative test for chloride ion with silver nitrate. There are several possible explanations. For example, one reaction might be $AgCl+B^-=AgB+Cl^-$; another might involve the formation of undissociated, slightly soluble AgB; still another perhaps the formation of a complex ion such as AgB_2^-, etc. It was not considered necessary to delve further into the various possibilities, especially as a simple method was found to eliminate the effect entirely.

The extent to which the reactions postulated above occur can be made negligible by the use of a sufficiently high concentration of soluble chloride in the barbiturate-chloride mixture. It should also be possible to diminish them by the substitution of the chloride by iodide, both in the solution and in the reference electrode. If one considers, for example, the reaction $AgCl+B^-=AgB+Cl^-$, one may write the equilibrium constant as $K_1=K_{\mathrm{AgCl}}/K_{\mathrm{AgB}}=(a_{\mathrm{Cl}^-}/a_{\mathrm{B}^-}$, where K_{AgCl} and K_{AgB} are the solubility products for silver chloride and for silver barbiturate. Similarly, for the reaction $AgI+B^-=AgB+I^-$, the equilibrium constant is $K_2=K_{\mathrm{AgI}}/K_{\mathrm{AgB}}=a_{\mathrm{I}^-}/a_{\mathrm{B}^-}$, where K_{AgI} is the solubility product of AgI. Subtraction of the second reaction from the first yields $AgCl+I^-=AgI+Cl^-$ for which, at the same initial concentration of B^- and assuming that the occurence of the reaction does not appreciably alter the concentration of B^-, $K_3=K_{\mathrm{AgCl}}/K_{\mathrm{AgI}}=a_{\mathrm{Cl}^-}/a_{\mathrm{I}^-}$. Since the ratio of the solubility products of silver chloride and silver iodide at 25° C is approximately 10^6, substitution of chloride by iodide in the electrodes and in the barbiturate-halide solution should be quite effective in preventing any side reactions of the type postulated above.

---

[7] Note that the extrapolation does not permit calculation of pK, because m_{HB} and m_{B} remain constant in this type of measurement.

The emf of a series of barbiturate-iodide buffers was therefore studied. The results confirmed the prediction and showed no abnormal effect of iodide on the apparent ionization constant of barbituric acid. The plots of pK' at 25° C for a ratio of HB:NaB of unity against various concentrations of sodium chloride and of sodium iodide are shown in figure 3. The concentrations of the solutions, the emf in international volts (at 25° C) of the cells corrected to 1-atm pressure of hydrogen gas, and the value for pK at 25° C are given in table 4.

TABLE 4. *Apparent effect at 25° C of sodium chloride and of sodium iodide on the value for* pK' *for 5-5′-diethylbarbituric acid*

(a) Sodium chloride

Solution	m_{HB}	m_B	m_{Cl}	$E_{25.\text{int. v}}$	pK'_{25}
1	0.014504	C.014504	0.003816	0.83513	7.9430
2	.014973	.014973	.005006	.82787	7.9381
3	.015007	.015007	.005984	.82375	7.9459
4	.014559	.014559	.007850	.81770	7.9615
5	.014951	.014951	.009978	.81171	7.9643
6	.015021	.015021	.014991	.80189	7.9751
7	.014647	.014647	.015545	.80096	7.9752
8	.015714	.015013	.025021	.78856	7.9919
9	.014864	.014864	.050000	.77118	7.9790
10	.015294	.015005	.079961	.75853	7.9773
11	.014909	.014909	.082950	.75826	7.9812

(b) Sodium iodide

	m_{HB}	m_B	m_I	$E_{25.\text{int. v}}$	pK'_{25}
1	0.014981	0.014980	0.003399	0.46629	7.9897
2	.015714	.015115	.006041	.45104	7.9831
3	.015022	.015022	.007176	.44686	7.9856
4	.014517	.014517	.010515	.43713	7.9870
5	.015036	.014977	.014689	.42838	7.9858
6	.014720	.014466	.024372	.41564	7.9902
7	.014968	.014968	.024966	.41502	7.9886
8	.014836	.014836	.026176	.41387	7.9897
9	.015098	.015098	.050343	.39362	7.9821

The value for pwH° obtained with silver–silver-iodide electrodes was 7.985 at 25° C.

In attempting to obtain data on pwH° one must not accept at face value measurements involving only sodium chloride, lest the possibility of such an anomalous reaction exist. The relative solubilities of the silver salts of the halide and of the buffer anion should be known. Unfortunately, accurate data are not available for most organic salts containing silver. Additional experiments with a soluble iodide and silver–silver-iodide electrodes may be necessary if measurements on the buffer salts have been made with only silver–silver-chloride electrodes.

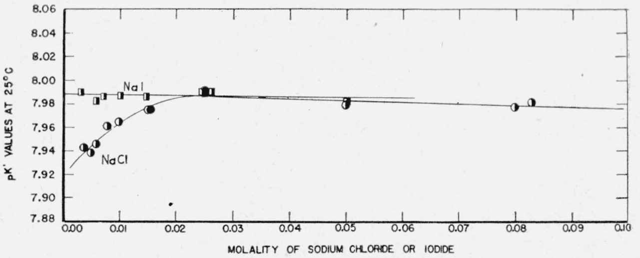


FIGURE 3. *Effect at 25° C of sodium chloride and of sodium iodide on* the pK' *for 5-5′-diethylbarbituric acid.*

3.3. Measurements of pK' with Hydrogen and Silver–Silver-Iodide Electrodes

In view of the above findings, it became of interest to determine whether the value for pK obtained by extrapolation depends on the nature of the reference electrode used in the cell shown in eq 1. Measurements were therefore made of the emf of the cells containing hydrogen and silver–silver-iodide electrodes immersed in buffer solutions composed of various concentrations of HB, NaB, and NaI. The concentrations of the solutions and the emf, in international volts, corrected to 1-atm pressure of hydrogen gas are listed in table 5. The values of pK' for buffer ratios, HB:B, of 2.0, 1.0, and 0.5, caluclated by eq 6, are given in table 6 and are designated by squares in figure 2. The plot of pK' against μ proved to be linear, and over the range 5° to 40°C the positions of these lines (calculated by least squares) were found to be very nearly the same as those obtained for the corresponding measurements for the chloride series.

The average difference in the extrapolated values for pK between the Ag-AgCl series and the Ag-AgI series over the range 5° to 40° C was −0.0018 unit in pK, or about 0.1 mv in emf.

In table 7 is given a summary of the extrapolated values obtained for pK and β, using the two types of reference electrodes.

TABLE 5. *Observed electromotive force, in international volts, of cells composed of hydrogen and silver–silver-iodide electrodes and mixtures of 5-5′-diethylbarbituric acid* (m_{HB}), *sodium 5-5′-diethylbarbiturate* (m_B), *and sodium iodide* (m_I)

Solution	m_{HB}	m_B	m_I	μ	E_0	E_5	E_{10}	E_{15}	E_{20}	E_{25}	E_{30}	E_{35}	E_{40}
$m_{HB}\approx 2m_B$:													
1	0.015014	0.007478	0.024412	0.031890	--------	0.38427	0.38768	0.39108	0.39450	0.39739	0.40099	0.40400	0.40720
2	.014916	.007458	.026176	.033634	--------	.38221	.38581	.38931	.29281	.39600	.39888	.40228	.40565
$m_B\approx m_{HB}$:													
3	.003164	.003164	.005688	.008852	0.43095	.43513	.43967	.44442	.44856	.45296	.45685	.46091	.46518
4	.006319	.006319	.011288	.017607	.41438	.41861	.42302	.42721	.43122	.43528	.43905	.44311	.44711
5	.008908	.008908	.015852	.024760	.40642	.41111	.41498	.41882	.42257	.42645	.43016	.43389	.43780
6	.011874	.011874	.021140	.033014	.40016	--------	--------	--------	--------	--------	--------	--------	--------
7	.014720	.014663	.024372	.039035	--------	.40056	.40449	.40861	.41269	.41565	.41973	.42331	.42684
8	.014968	.014968	.024966	.039934	--------	.39981	.40409	.40778	.41162	.41502	.41861	.42247	.42573
9	.014836	.014836	.026176	.041013	--------	--------	.40255	.40661	.41018	.41387	.41762	.42095	.42462
$2m_{HB}\approx m_B$:													
10	.015041	.030082	.021000	.051080	--------	.42106	--------	.42925	--------	.43719	--------	--------	--------

TABLE 6. *Values of the negative logarithm of the apparent ionization constant,* p*K′*, *cf 5-5′-diethylbarbituric acid obtained from hydrogen and silver–silver iodide electrodes*

(See table 5 for the concentrations of the solutions)

Solution	pK'_0	pK'_5	pK'_{10}	pK'_{15}	pK'_{20}	pK'_{25}	pK'_{30}	pK'_{35}	pK'_{40}
1		8. 3211	8. 2297	8. 1446	8. 0657	7. 9835	7. 9190	7. 8497	7. 7886
2		8. 3123	8. 2250	8. 1422	8. 0652	7. 9886	7. 9125	7. 8501	7. 7922
3	8. 4084	8. 3076	8. 2201	8. 1425	8. 0600	7. 9880	7. 9131	7. 8461	7. 7873
4	8. 4002	8. 3058	8. 2212	8. 1390	8. 0595	7. 9865	7. 9144	7. 8521	7. 7936
5	8. 4008	8. 3175	8. 2257	8. 1398	8. 0583	7. 9848	7. 9139	7. 8486	7. 7911
6	8. 4057								
7		8. 3145	8. 2272	8. 1495	8. 0767	7. 9904	7. 9288	7. 8638	7. 8030
8		8. 3098	8. 2289	8. 1438	8. 0670	7. 9886	7. 9191	7. 8589	7. 7939
9			8. 2220	8. 1439	8. 0629	7. 9897	7. 9231	7. 8546	7. 7966
10		8. 3188		8. 1433		7. 9874			

TABLE 7. *Values for* p*K and for β for 5-5′-diethylbarbituric acid*

Temperature	Ag-AgCl electrodes		Ag-AgI electrodes		Average [a]	
	p*K*	*β*	p*K*	*β*	p*K*	*β*
°*C*						
0	8. 3971	−0. 25	------	------	8. 3971	−0. 25
5	8. 3036	−. 25	8. 3054	−0. 11	8. 3040	−. 24
10	8. 2167	−. 21	8. 2192	−. 19	8. 2171	−. 22
15	8. 1358	−. 19	8. 1395	−. 12	8. 1367	−. 18
20	8. 0599	− 14	8. 0566	−. 21	8. 0592	−. 15
25	7. 9792	−. 24	7. 9815	−. 16	7. 9798	−. 22
30	7. 9088	−. 32	7. 9097	−. 24	7. 9092	−. 29
35	7. 8481	−. 18	7. 8440	−. 26	7. 8471	−. 20
37	------	------	------	------	[b] 7. 8226	------
40	7. 7854	−. 21	7. 7869	−. 17	7. 7858	−. 20
45	7. 7290	−. 20	------	------	7. 7290	−. 20
50	7. 6776	−. 11	------	------	7. 6776	−. 11
55	7. 6264	−. 08	------	------	7. 6264	−. 08
60	7. 5762	−. 08	------	------	7. 5762	−. 08

[a] Averaged in proportion to the number of cells in each series.
[b] Calculated by means of eq 7.

The variation of p*K* for 5-5′-diethylbarbituric acid (col. 6 of table 7) with the absolute temperature $T(273.16+t°\mathrm{C})$ can be expressed by the equation

$$pK=2324.47/T+0.0118562T-3.3491 \qquad (7)$$

with an average deviation of ±0.0017 unit. The value for p*K* at 37° C was calculated by means of eq 7. In figure 4 the circles and the squares, respectively, correspond to the values obtained for p*K* with Ag-AgCl and Ag-AgI electrodes. The solid curve is that corresponding to eq 7.

4. Comparison With Other Values in the Literature

With one exception, all other previous measurements [1,3,5,6,7] of the ionization constant of 5-5′-diethylbarbituric acid have been obtained by the use of a reference solution of assigned pH value and a cell involving a liquid junction. Wood [4] measured the specific electric conductance of HB solutions. The values for p*K* obtained by other investigators corrected to a uniform temperature of 25° C (by means of the value for dpK/dT obtained from eq 7) and increased by 0.04 unit, when appropriate, to place them on the "activity" basis, are listed in table 8.

TABLE 8. *Comparison of the values found for* p*K for 5-5′-diethylbarbituric acid by different investigators* [a]

Year	Investigator	Method	p*K* at 25° C
1906	Wood [4]	Conductance	7. 43
1920	Kolthoff [5]	H_2-calomel cells	7. 4
1930	Michaelis [1]	do	7. 86
1931	Britton and Robinson [6]	do	7. 89
1937	Bush [7]	do	7. 93
1940	Krahl [3]		7. 91
1948	This research	Cells without liquid junction	7. 980

[a] Corrected where necessary to 25° C by means of dpK/dT obtained by differentiation of eq 7.

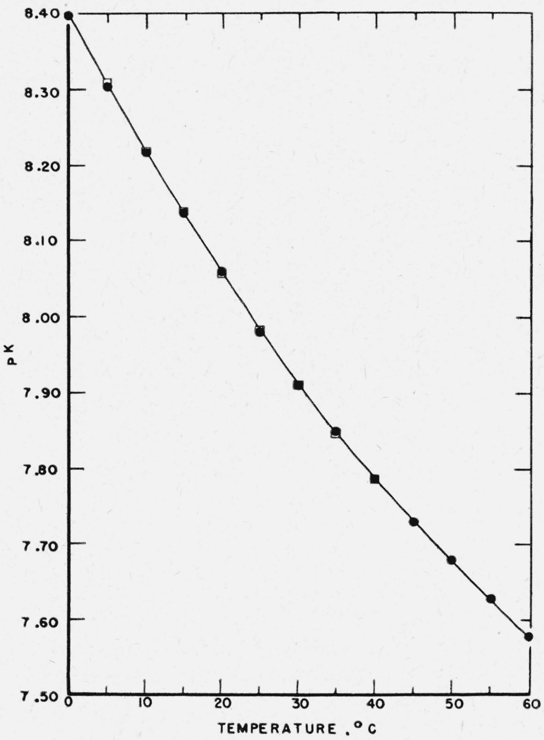


FIGURE 4. *Variation of* p*K for 5-5′-diethylbarbituric acid with temperature.*

The circles and the squares, respectively, designate the data from the chloride and from the iodide cells, respectively. The solid line is that obtained from equation 7.

5. Derived Thermodynamic Quantities

The relation between the ionization constant of a weak acid and the temperature can be used to compute a number of derived thermodynamic properties.

The free energy [19] of ionization is given by

$$\Delta F^\circ = -RT \ln K = 2.3026RT \text{ p}K = \Delta H^\circ - T\Delta S^\circ, \tag{8}$$

from which the change in entropy, the heat of the reaction, and the change in the heat capacity can be obtained by suitable differentiation [19] of eq 7 and 8:

$$\left.\begin{aligned} \Delta S^\circ &= -\partial \Delta F/\partial T \\ \Delta H^\circ &= \partial(\Delta F^\circ/T)/\partial(1/T) \\ \Delta Cp^\circ &= \partial \Delta H^\circ/\partial T. \end{aligned}\right\} \tag{9}$$

The values for ΔF°, ΔS°, ΔH°, and ΔCp° for the ionization process $HB_{(aq)} = H^+ + B^-$ are given in table 9.

TABLE 9. *Derived thermodynamic quantities for the ionization process:* $HB_{(aq)} = H^+ + B^-$

Temperature	ΔF°		ΔH°		ΔS°		ΔCp°	
° C	*Int. j/° C*	*cal/° C*	*Int. j/° C*	*cal/° C*	*Int. j/° C*	*cal/° C*	*Int. j/° C*	*cal/° C*
0	43, 916	22, 100	27, 560	13, 869	−59. 88	−30. 13	−123. 9	−62. 4
5	44, 222	22, 254	26, 934	13, 554	−62. 15	−31. 28	−126. 3	−63. 6
10	44, 538	22, 413	26, 297	13, 233	−64. 42	−32. 42	−128. 5	−64. 7
15	44, 866	22, 578	25, 649	12, 907	−66. 69	−33. 56	−130. 8	−65. 8
20	45, 205	22, 748	24, 989	12, 575	−68. 96	−34. 70	−133. 1	−67. 0
25	45, 555	22, 924	24, 317	12, 237	−71. 23	−35. 84	−135. 3	−68. 1
30	45, 917	23, 107	23, 635	11, 894	−73. 50	−36. 97	−137. 6	−69. 2
35	46, 290	23, 294	22, 944	11, 546	−75. 76	−38. 12	−139. 9	−70. 4
40	46, 675	23, 488	22, 240	11, 192	−78. 03	−39. 27	−142. 1	−71. 5
45	47, 071	23, 688	21, 523	10, 831	−80. 30	−40. 41	−144. 4	−72. 7
50	47, 478	23, 892	20, 795	10, 465	−82. 57	−41. 55	−146. 7	−73. 8
55	47, 896	24, 102	20, 055	10, 092	−84. 84	−42. 69	−148. 9	−74. 9
60	48, 326	24, 319	19, 304	9, 714	−87. 11	−43. 84	−151. 2	−76. 1

[a] $R = 8.3130$ int. j/°C; 1 defined calorie = 4.1833 int. j.

6. References

[1] L. Michaelis, J. Biol. Chem. **87,** 33 (1930).

[2] K. Klimesch, Arch. f. Exper. Path. u. Pharmakol. **176,** 494 (1934).

[3] M. E. Krahl, J. Phys. Chem. **44,** 449 (1940).

[4] J. K. Wood, J. Chem. Soc. **89,** 1831 (1906).

[5] I. M. Kolthoff, Pharm. Weekblad. **57,** 514 (1920).

[6] H. T. S. Britton and R. A. Robinson, J. Chem. Soc. 1456 (1931).

[7] M. T. Bush, J. Pharmacol. **61,** 134 (1937).

[8] H. S. Harned and R. W. Ehlers, J. Am. Chem. Soc. **55,** 2179 (1933); H. S. Harned and B. B. Owen, Physical chemistry of electrolytic solutions (Reinhold Publishing Co., New York, N. Y., 1943).

[9] P. W. Squire and C. M. Cains, Pharm. J. **74,** 720, 784 (1905).

[10] P. Casparis, Schweiz. Apoth. Ztg. **57,** 255 (1919).

[11] W. A. Puckner and W. S. Hilpert. J. Am. Med. Assoc. **52,** 488 (1909).

[12] U. S. Pharmacopoeia **XII,** 78 (1942).

[13] G. D. Pinching and R. G. Bates, J. Research NBS **37,** 311 (1946) RP1749.

[14] G. G. Manov, N. J. DeLollis, P. W. Lindvall, and S. F. Acree, J. Research NBS **36,** 543 (1946) RP1721.

[15] B. B. Owen, J. Am. Chem. Soc. **57,** 1526 (1935).

[16] W. J. Hamer, J. O. Burton, and S. F. Acree, J. Research NBS **24,** 269 (1940) RP1284.

[17] W. J. Hamer and S. F. Acree, J. Research NBS **23,** 647 (1939) RP1261.

[18] R. G. Bates, Chem. Rev. **42,** 1 (1948).

[19] G. N. Lewis and M. Randall, Thermodynamics and the free energy of chemical substances, (McGraw-Hill Book Co., Inc., New York, N. Y., 1923).

WASHINGTON, August 20, 1951.