Scientific
Research

Thermodynamics of the Second Stage Dissociation Step (pK_2) of Buffer Monosodium 1,4-Piperazinediethanesulfonate from (278.15 to 328.15) K

Rabindra N. Roy, Lakshmi N. Roy, John J. Dinga, Matthew R. Medcalf, Katherine E. Hundley, Eric B. Hines, Ryan R. Parmar, Jamie A. Veliz, Clark B. Summers, Lucas S. Tebbe

Hoffman Department of Chemistry, Drury University, Springfield, USA
Email: rroy@drury.edu

Abstract

Values of the second thermodynamic dissociation constant pK_2 of the protonated form of monosodium 1,4-piperazinediethanesulfonate (PIPES) have been determined at twelve different temperatures in the temperature range from (278.15 to 328.15) K including the body temperature 310.15 K by measurement of the electromotive-force for cells without liquid junction of the type: Pt (s), H_2 (g), 101.325 kPa|Na-PIPES (m_1) + Na_2-PIPES (m_2) + NaCl (m_3)|AgCl (s), Ag (s), where m_1, m_2 and m_3 indicate the molalities of the corresponding species at 1 atm = 101.325 kPa in SI units. The pK_2 values for the dissociation of Na-PIPES are represented by the equation: pK_2 = −1303.76/T + 48.369 - 6.46889 lnT with an uncertainty of ± 0.001. The values of pK_2 for Na-PIPES were found to be 7.1399 ± 0.0004 at 298.15 K and 7.0512 ± 0.0004 at 310.15 K, respectively, and indicate that this buffer would be useful as pH standard in the range of physiological application. Standard thermodynamic quantities $\Delta G°$, $\Delta H°$, $\Delta S°$ and $\Delta C_p°$ for the acidic dissociation process of Na-PIPES have been derived from the temperature coefficients of the pK_2. These values are compared with those of structurally related N-substituted PIPERAZINE and TAURINE at 298.15 K.
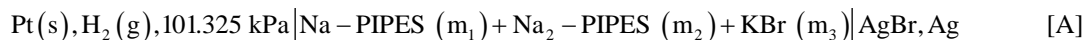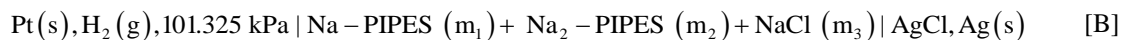
Keywords

1. Introduction

The control of pH in the physiologically important pH range is difficult because of the limitation in the number of weak acid-base systems whose pH values fall within the pH range of 6 - 8. Second-stage dissociation process and the acid-base behavior of the simplest zwitterionic amino acids, 2-aminoethanesulfonic acid (TAURINE) [1] and (PIPERAZINE) [2], have been studied. The pK_2 values of these two buffers at 298.15 K are 9.061 and 9.731, respectively. Careful thermodynamic investigation of the dissociation of other amino acids, (MES) [3], (MOPS) [4], (BES) [5], (TES) [6], and (CHES) [7], has contributed significantly to an understanding of this important subject. Biological buffers are of great importance for research in biomedicine, pharmaceutical chemistry, clinical chemistry, and oceanography. Good *et al.* [8] recommended several biological buffer substances which are useful in the physiological pH region of 6 - 8. One of the buffer compounds selected was monosodium 1,4-piperazine diethanesulfonate (PIPES) whose deprotonation constant is about 10^{-8} at 298.15 K. The compound PIPES is, therefore, a better buffer for pH control in the buffer region of greatest physiological interest than its parent compound, (PIPERAZINE) [2].

In order to calculate pH values with the accuracy needed for a pH buffer standard, it is essential to determine very accurate values of the thermodynamic dissociation constant pK_2 for the second-stage dissociation equilibria of PIPES. Roy *et al.* [9] determined pK_2 values and related thermodynamic quantities of PIPES at 12 temperatures using the galvanic cell without liquid junction:

$$\text{Pt}(s), \text{H}_2(g), 101.325\ \text{kPa} \big| \text{Na} - \text{PIPES}\ (m_1) + \text{Na}_2 - \text{PIPES}\ (m_2) + \text{KBr}\ (m_3) \big| \text{AgBr}, \text{Ag} \qquad [\text{A}]$$

In this cell, Ag, AgBr electrode and KBr solid were used. Because of the importance of the chloride ion Cl$^-$ in clinical samples such as blood, plasma and cerebrospinal fluids, we have undertaken to study PIPES at 12 temperatures from (278.15 to 328.15) K employing the cell:

$$\text{Pt}(s), \text{H}_2(g), 101.325\ \text{kPa} \mid \text{Na} - \text{PIPES}\ (m_1) + \text{Na}_2 - \text{PIPES}\ (m_2) + \text{NaCl}\ (m_3) \mid \text{AgCl}, \text{Ag}(s) \qquad [\text{B}]$$

in which NaCl salt and Ag, AgCl were used. Thus, there is a great difference between cell A and cell B in terms of the use of the salt and the electrode. No thermodynamic data on pK_2 of PIPES is available in the literature using Ag-AgCl electrode. This is the original research work. The monosodium salt of the (PIPES) $\text{Na}^+\text{O}_3^-\text{S}(\text{CH}_2)_2\ \text{N}(\text{CH}_2)_4\ \text{N}^+\text{H}(\text{CH}_2)\text{SO}_3^-$ is designated as P$^{\pm-}$, and the deprotonation process is represented by

$$\text{P}^{\pm-} \xrightleftharpoons{\quad K_2 \quad} \text{H}^+ + \text{P}^{-2} \qquad (1)$$

where K_2 is the thermodynamic equilibrium constant. The structure of the monosodium 1,4-piperazinediethanesulfonate (PIPES) is shown below.
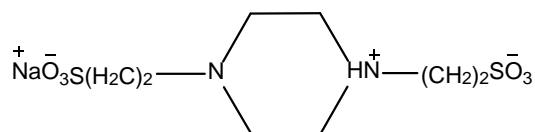
2. Experimental

The commercial sample of monosodium 1,4-piperazinediethanesulfonate (PIPES) was obtained from Research Organics (Cleveland, Ohio). The technique to determine the assay of PIPES has been previously reported [9]. It assayed 99.98% when titrated with a standard solution of NaOH. From the preliminary measurements, the difference in e.m.f (cell voltage) between a purified and unpurified sample was well within the experimental error ±0.05 mV. Thus, the commercial sample was used as received. It was always dried and stored in a desiccator. The preparation of all 16 experimental buffer solutions of Na-PIPES were made by mixing accurate amounts of the commercial sample of PIPES, CO_2-free NaOH, Fisher ACS certified grade NaCl, and CO_2-free double distilled water. The molality range of the buffer solutions varied from 0.002 to 0.04 mol·kg^{-1}, and the ionic strength range was from $I = 0.006$ to 0.12 mol·kg^{-1}. Vacuum corrections were applied to all masses with accuracy better than ±0.02 mass percent. The precise e.m.f measurement technique was originally used by Harned and Ehlers [10]. The e.m.f method used in the present study was modified by Gary *et al.* [11] and was successfully used by Sankar and Bates [12] as well as Roy *et al.* [13]. The following galvanic cell without liquid junction of the type

was used:

$$Pt(s), H_2(g), 101.325 \text{ kPa} \big| Na - PIPES(m_1) + Na_2 - PIPES(m_2) + NaCl(m_3) \big\| AgCl(s), Ag(s) \qquad (A)$$
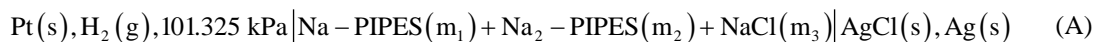
In all previous publications from this laboratory, the preparation of the platinum black hydrogen electrode and the silver-silver chloride electrode (thermal electrolytic type [14]), the cell design of all glass cells, purification of the hydrogen gas, and other experimental details have been described in detail elsewhere [15] [16]. The bias potential of the (silver + silver chloride) electrodes was within ±0.05 mV. The e.m.f measurements were made at intervals of 5 K from (278.15 to 328.15) K for all 16 buffer solutions at 12 temperatures in the molality range 0.002 to 0.04 mol·kg^{-1}. The e.m.f at 298.15 K was recorded two times (sometimes three times), namely at the beginning, in the middle, and at the end of the run. These e.m.f values, on average, agreed to within ±0.04 mV, demonstrating excellent stability and high reproducibility of the silver-silver chloride in the presence of nitrogen base. The constant temperature of the water bath was regulated to ±0.005 K within a digital thermometer (Guildline model 9540). All e.m.f measurements were made by employing Hewlett-Packard 2000 multimeter.

3. Methods and Results

The equation for the calculation of the "apparent" thermodynamic dissociation constant pK_2' for the second dissociation step of PIPES is expressed:

$$pK_2' = pK_2 - \log\left\{ \left(\gamma_{P^{\pm-}}\right) \cdot \gamma_{Cl^-} \big/ \left(\gamma_{P^{-2}}\right) \right\} = (E - E^\circ) F \big/ (RT \ln 10) + \log\left(m_1 m_3 / m_2\right) \qquad (2)$$

where $P^{\pm-}$ is the zwitterionic species for Na-PIPES; m_1, m_2, and m_3 are stoichiometric molalities of the corresponding species; P^{-2} stands for Na$_2$-PIPES; pK_2 the thermodynamic dissociation constant; γ the activity coefficient of the respective species; E the e.m.f corrected to a hydrogen partial pressure of 101.325 kPa; F is the Faraday constant (96487 C·mol^{-1}); $RT \ln 10/F = $ k = 0.059156 at 298.15 K; and E° is the standard electrode potential of the (silver + silver chloride) electrode. The cell voltage (E) values are listed in **Table 1**. The values of (E°) [17] were obtained in the authors' laboratory by using 0.01 mol·kg^{-1} HCl solution with a value of γ_{HCl} = 0.904 at 298.15 K. The activity coefficient of Equation (2) is unknown. In such situations, the simple form of Equation (2) involves assumptions that a) the activity coefficient term $\log\left\{\gamma_{P^{\pm-}} \cdot \gamma_{Cl^-} \big/ \gamma_{P^{-2}}\right\}$ will, because of charge type, be small and is expected to become linear function of the ionic strength I, and b) the nearly neutral pH of the buffer solutions which make hydrolysis correction of the ratio m$_1$/m$_2$ unnecessary. The ionic strength of the solution of cell B is indicated by:

$$I = m_1 + 3m_2 + m_3 \qquad (3)$$

and the simplified version of Equation (2) becomes:

$$pK_2' = (E - E^\circ)/k + \log m_1 m_3 / m_2 \qquad (4)$$

As expected, pK_2' varies linearly with I at each temperature and is represented by the following equation:

$$pK_2' = pK_2 - \beta I \qquad (5)$$

where the intercept at $I = 0$ yields the value of pK_2 and β is the slope parameter. These values of pK_2 together with the standard deviation are listed in **Table 2**. The experimental values of pK_2 are fitted as a function of the thermodynamic temperature T from (278.15 to 323.15) K by the method of least squares to an equation of the form suggested by Ives and Mosely [18]. The final equation takes the form

$$pK_2 = -1303.76/T + 48.369 - 6.46889 \ \ln T \qquad (6)$$

The standard deviation of regression for Equation (6) is 0.0014. The values of the standard changes of Gibbs energy (ΔG°), enthalpy (ΔH°), entropy (ΔS°) and the heat capacity (ΔC_p°) for the dissociation process indicated by Equation (1) have been derived from the constants of Equation (6) by using simple thermodynamic relationships. The values of these thermodynamic functions, along with the estimates of the standard deviations calculated by the method of Please [19] are summarized in **Table 3**. It is of interest to compare the values of the pK_2 and thermodynamic functions of Na-PIPES with some structurally related N-substituted zwitterionic compounds of (TAURINE) [1] and (PIPERAZINE) [2]. At 298.15 K, these values are compiled in **Table 4**.

Table 1. Cell potential of cell B (in volts).

Pt (s); H₂ (g), 101.325 kPa|Na-PIPES (m₁), Na₂-PIPES (m₂), NaCl (m₃)|AgCl (s), Ag (s)							

m_1	m_2	m_3	T/K					
mol·kg^{-1}			278.15 K	283.15 K	288.15 K	293.15 K	298.15 K	303.15 K
0.001999	0.000667	0.001993	0.75837	0.76320	0.76770	0.77218	0.77633	0.78021
0.003336	0.001113	0.010000	0.71954	0.72369	0.72752	0.73130	0.73477	0.73793
0.009996	0.003337	0.004991	0.73623	0.74067	0.74482	0.74890	0.75267	0.75612
0.010000	0.003333	0.009997	0.71951	0.72365	0.72750	0.73128	0.73474	0.73790
0.010000	0.003333	0.010000	0.71940	0.72354	0.72740	0.73119	0.73465	0.73780
0.006658	0.002210	0.020000	0.70276	0.70659	0.71015	0.71364	0.71678	0.71964
0.008330	0.002777	0.025000	0.69734	0.70109	0.70456	0.70795	0.71101	0.71377
0.015000	0.005000	0.015000	0.70956	0.71353	0.71722	0.72085	0.72413	0.72711
0.020000	0.006663	0.020000	0.70264	0.70648	0.71006	0.71356	0.71670	0.71956
0.020000	0.006667	0.020000	0.70264	0.70649	0.71008	0.71358	0.71673	0.71957
0.021990	0.008665	0.021990	0.70415	0.70803	0.71167	0.71520	0.71838	0.72125
0.025000	0.008333	0.025010	0.69714	0.70090	0.70441	0.70782	0.71087	0.71361
0.029999	0.010000	0.029990	0.69269	0.69636	0.69979	0.70312	0.70610	0.70876
0.033300	0.011100	0.033300	0.68995	0.69359	0.69701	0.70031	0.70323	0.70584
0.039960	0.013320	0.039960	0.68553	0.68907	0.69244	0.69566	0.69849	0.70101
0.040000	0.013330	0.040000	0.68548	0.68904	0.69241	0.69561	0.69844	0.70097

m_1	m_2	m_3	T/K					
mol·kg^{-1}			308.15 K	310.15 K	313.15 K	318.15 K	323.15 K	328.15 K
0.001999	0.000667	0.001993	0.78381	0.78502	0.78721	0.79032	0.79318	0.79582
0.003336	0.001113	0.010000	0.74081	0.74174	0.74350	0.74589	0.74804	0.74995
0.009996	0.003337	0.004991	0.75929	0.76034	0.76229	0.76498	0.76745	0.76968
0.010000	0.003333	0.009997	0.74078	0.74170	0.74347	0.74587	0.74803	0.74994
0.010000	0.003333	0.010000	0.74066	0.74158	0.74333	0.74572	0.74787	0.74978
0.006658	0.002210	0.020000	0.72220	0.72300	0.72459	0.72668	0.72854	0.73016
0.008330	0.002777	0.025000	0.71622	0.71697	0.71851	0.72050	0.72226	0.72377
0.015000	0.005000	0.015000	0.72977	0.73060	0.73226	0.73445	0.73643	0.73815
0.020000	0.006663	0.020000	0.72209	0.72286	0.72446	0.72653	0.72839	0.73000
0.020000	0.006667	0.020000	0.72210	0.72287	0.72447	0.72655	0.72840	0.73000
0.021990	0.008665	0.021990	0.72380	0.72457	0.72619	0.72829	0.73017	0.73179
0.025000	0.008333	0.025010	0.71602	0.71674	0.71828	0.72025	0.72202	0.72352
0.029999	0.010000	0.029990	0.71108	0.71175	0.71326	0.71515	0.71682	0.71823
0.033300	0.011100	0.033300	0.70809	0.70873	0.71021	0.71204	0.71366	0.71500
0.039960	0.013320	0.039960	0.70318	0.70376	0.70520	0.70695	0.70849	0.70977
0.040000	0.013330	0.040000	0.70314	0.70374	0.70518	0.70692	0.70846	0.70975

Table 2. Second dissociation constant of Na-PIPES.

From (278.15 to 328.15) K				
T/K	pK_2	$\sigma (pK_2)^a$	β	$\sigma (\beta)^b$
278.15	7.2752	0.0005	0.154	0.009
283.15	7.2413	0.0005	0.149	0.008
288.15	7.2055	0.0004	0.124	0.007
293.15	7.1734	0.0004	0.117	0.007
298.15	7.1399	0.0004	0.120	0.007
303.15	7.1048	0.0004	0.125	0.007
308.15	7.0680	0.0004	0.143	0.007
310.15	7.0512	0.0004	0.158	0.007
313.15	7.0320	0.0005	0.151	0.008
318.15	6.9950	0.0004	0.158	0.008
323.15	6.9570	0.0005	0.159	0.008
328.15	6.9175	0.0006	0.164	0.009

[a]Standard deviation of pK_2. [b]Slope parameter.

Table 3. Thermodynamic quantities for the dissociation of Na-PIPES from (278.15 - 328.15) K.

	278.15 K	288.15 K	298.15 K	308.15 K	318.15 K	328.15 K
$\Delta G°$	38.734 ± 2	39.763 ± 2	40.749 ± 3	41.694 ± 3	42.599 ± 3	43.465 ± 3
$\Delta H°$	9.487 ± 51	10.726 ± 33	11.964 ± 18	13.203 ± 19	14.441 ± 36	15.679 ± 57
$\Delta S°$	-105.1 ± 0.2	-100.8 ± 0.1	-96.5 ± 0.1	-92.5 ± 0.1	-88.5 ± 0.1	-84.7 ± 0.2
$\Delta C_p°$	124 ± 2	124 ± 2	124 ± 2	124 ± 2	124 ± 2	124 ± 2

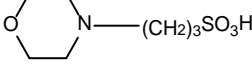Units: $\Delta G°$. $\Delta H°$, J·mol^{-1}; $\Delta S°$, $\Delta C_p°$, J·K^{-1}·mol^{-1}.
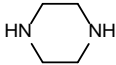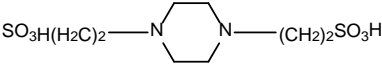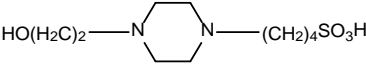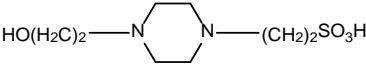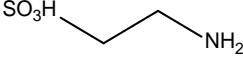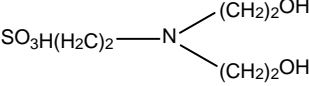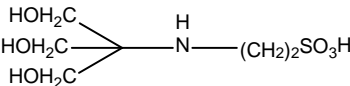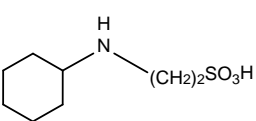
4. Discussion

For each of the structurally related compounds in **Table 4**, two methylene groups separate positive and negative charge centers. The comparison of the thermodynamic properties of some substituted compounds and the parent compound (TAURINE) [1] and the derivative of TAURINE such as (MOPS) [4], (BES) [5], (TES) [6], (CHES) [7], (MOBS) [20] and (PIPERAZINE) [2] and its N-substituted PIPERAZINE such as (HEPBS) [20], (HEPES) [21], (TAPS) [22] and PIPES [this investigation] reveal useful information in terms of acidic strength, steric and inductive effects. The parent compound PIPERAZINE has a pK_2 of 9.731 at 298.15 K whereas that of PIPES in the present work is 7.140. The interpretation is that the substitutions of methylene-$(CH_2)_2$ and hydroxymethyl-$(HOCH_2)_2$ groups on the nitrogen atom of (TAURINE) [1] and (PIPERAZINE) [2] enhance the acidic strength for the dissociation of (BES) [5] and PIPES [this study], respectively.

Table 4 clearly shows a decrease in pK_2 value (increase in acidic strength) for both N-substituted PIPERAZINE and TAURINE compounds. The alterations in acidic strength for the dissociation process of PIPES are attributable to the inductive effects of the oxygen atom from both $-SO_3^-$ groups as well as the steric effects of the $-(CH_2)_4$ groups in PIPERAZINE from which the dissociation of H^+ occurs.

It is interesting to discuss the trend of the standard thermodynamic properties from **Table 4**. Usually, the decrease in pK_2 value is paralleled by the decrease in values of $\Delta H°$, which are observed for PIPERAZINE and PIPES. **Table 4** shows the value of $\Delta H°$ at 298.15 K for (PIPERAZINE) [2] is 53,390 J·mol^{-1} whereas for PIPES $\Delta H° = 11,964$ J·mol^{-1}. The explanation is that in addition to lowering the pK_2, the hydroxymethyl and hydroxyethyl substitutions lower the value of $\Delta H°$ for isoelectric dissociation process [23] [24]. This pattern is

Table 4. Thermodynamic quantities for the dissociation of a series of structurally related compounds of Taurine, Morpholine and Piperazine in water at 298.15 K.

Structure x	Common name	pK_2	$\Delta H°$	$\Delta S°$	$\Delta C_p°$	Ref.
HN⬡NH (piperazine ring)	PIPERAZINE	9.731	53.390	−33.9	88	2
SO3H(H2C)2—N⬡N—(CH2)2SO3H	PIPES	7.140	11.964	−96.5	124	This study
HO(H2C)2—N⬡N—(CH2)4SO3H	HEPBS	8.284	23.081	−84.4	77	20
HO(H2C)2—N⬡N—(CH2)2SO3H	HEPES	7.562	20.376	−76.6	46	21
SO3H···NH2 (taurine chain)	TAURINE	9.061	41.840	−33.1	−33	1
O⬡N—(CH2)3SO3H (morpholine)	MOPS	7.183	21.008	−69.7	17	4
SO3H(H2C)2—N((CH2)2OH)2	BES	7.187	24.184	−56.5	−4	5
(HOH2C)3C—N(H)—(CH2)2SO3H	TES	7.550	32.133	−36.8	−17	6
cyclohexyl-N(H)—(CH2)2SO3H	CHES	9.394	39.551	−49.1	10	7

Units: $\Delta H°$, J·mol^{-1}; $\Delta S°$, $\Delta C_p°$, J·K^{-1}·mol^{-1}.

also consistent for (TAURINE) [1] and its derivative (BES) [5]. The changes of entropy $\Delta S°$ from **Table 4** are −33.9 J·K^{-1}·mol^{-1} for (PIPERAZINE) [2], whereas that for PIPES is −96.55 J·K^{-1}·mol^{-1}. The more negative values of $\Delta S°$ for PIPES compared to PIPERAZINE might indicate that for the dissociation process, the stabilization of the solvent structure causes an increased order (orientation) of polar water molecule in the proximity of the charged species (P$^{\pm-}$, H$^+$, P^{-2}, Na$^+$). The values of $\Delta C_p°$ for the dissociation of (PIPERAZINE) [2] is 88 J·K^{-1}·mol^{-1} and that found for PIPES is 124 J·K^{-1}·mol^{-1}. Since the value of $\Delta C_p°$ for PIPES is more positive compared to PIPERAZINE, this represents a substantial change in the solvation patterns (water structure) for the dissociation process of PIPES. The charge type (electrostatic effects) appears to be the primary factor in determining the large positive P$^{\pm-}$ values of $\Delta C_p°$ [13]. The quantitative explanations for the interactions of Na$^+$, Cl$^-$, P$^{\pm-}$, H$^+$ and P^{-2} with water are complex.

5. Conclusion

The e.m.f data are stable and highly reproducible. The results of the second dissociation constant pK_2 and associated thermodynamic quantities are very accurate and reliable. The pK_2 value lies in the physiological region of pH 6 - 8. Thus buffer solutions of Na-PIPES and Na$_2$-PIPES can be considered as a pH buffer standard for the physiological use. In a separate communication, pH values of buffer solutions without and with NaCl (isotonic saline media) from (278.15 - 328.15) K at an ionic strength I = 0.16 mol·kg^{-1} will be reported as what was done for the physiological buffer (TAPSO) [25].

Acknowledgements

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