

Electrical Conductances of Dilute Aqueous Solutions of Sodium Penicillin G, Potassium Penicillin G, and Potassium Penicillin V in the 278.15–313.15 K Temperature Range

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Systematic determinations of electrical conductivities of sodium penicillin G, potassium penicillin G, and potassium penicillin V in the 278.15–313.15 K temperature range are reported. These conductivities are examined by applying the Quint–Viallard conductivity equations and the Debye–Hückel equations for activity coefficients. Determined dissociation constants and the limiting conductances of penicillin anions are based on the assumption that in dilute aqueous solutions, penicillin salts behave as acidic salts of dibasic acids, which are the final products of degradation reactions in acidic media.

1. Introduction

The investigation of physicochemical properties of aqueous penicillin solutions began at an early stage, when penicillin was introduced in medical practice, albeit on a limited scale. This was in contrast to a plethora of biochemical, chemical, and pharmaceutical studies related to the structure, production, and the clinical potency of this antibiotic. The first determinations of electrical conductivity (often performed together with measurements of surface tension) from the late 1940s were associated with the question whether penicillin salts behave as strong, weak, or colloidal electrolytes. Between 1947 and 1953, conflicting opinions have been expressed on this subject. Hauser et al.^{1–3} reported that penicillin G salts lowered the surface tension, and conductometric studies indicated that the antibiotics formed negatively charged colloidal micelles. This view was supported by Vavruch^{4,5} who claimed that the crystalline or amorphous penicillins behave mostly in aqueous solutions as colloidal electrolytes. On the other hand, Woodbury and Rosenblum,⁶ Kumler and Alpen,⁷ McBain et al.,⁸ and Goyan,⁹ on the basis of conductivity experiments with sodium and potassium salts of penicillin G, concluded that no marked deviation from the behavior of completely dissociated electrolyte is observed. Canals et al.¹⁰ took a somewhat in-between view. In very dilute solutions ($m < 0.001$ M), the salts behaved as weak electrolytes, while in more concentrated solutions, they behaved as strong electrolytes. Certain properties were consistent with the possibility that the penicillin G salts are dispersed in water and that they are not true solutions. Experiments with different batches of commercial penicillin G salts showed different surface tension–concentration curves¹¹ and that the effect is time-dependent.¹⁰ After this period, no more measurements of conductivity could be found in the literature. In the

recent investigation of Martinez-Landeira et al.,¹² which deals with the colloidal properties of antibiotics, only the specific conductances of rather concentrated solutions were reported. Unfortunately, even these conductances were only presented in graphical form.

The basic structure of the penicillin molecule consists of a nucleus (the fused β -lactam-thiazolidine ring known as 6-aminopenicillanic acid) and a condensed side-chain group. The penicillins with the benzyl and methoxymethyl side groups are called penicillin G and penicillin V, respectively.^{13,14} In water, the penicillin molecule is a fairly strong organic acid, with an apparent pK_a of 2.6–2.7^{15,16} for the carboxyl group. Since these penicillins are not suitable for oral administration, the highly soluble sodium and potassium penicillin salts are used instead. For brevity, these salts will be denoted by Na-Pen G, K-Pen G, and K-Pen V.

Since the instability of penicillin in aqueous solutions has been known from the time of its discovery, considerable attention in the literature was devoted to the transformation, degradation, aging, and hydrolysis reactions of penicillins. Many kinetic, thermodynamic, and structure studies and the analytical identification of degradation products are reported.^{17–33} It is generally accepted that these reactions are associated with the reduction of antibacterial activity of the drug and with the allergic response after penicillin therapy. Also, since many antibiotics are produced semisynthetically by the chemical modification of the 6-aminopenicillanic acid, the hydrolysis reactions of penicillin G in enzymatic reactors is of significant theoretical and industrial importance.^{34–38} The pH dependence of penicillin hydrolysis is well-documented, but the exact proportion of formed degradation products and details of reaction pathways continue to be examined. The interpretation of our electrical conductivity measurements with respect to the autocatalytic hydrolysis of penicillins in water will be discussed in greater detail later.

Systematic determinations of electrical conductances of sodium and potassium salts of penicillin G and the potassium salt of penicillin V in the 278.15–308.15 K temperature range and in dilute aqueous solutions are presented in this work. The obtained results are examined by applying the Quint–Viallard

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conductivity equations,^{39–42} taking into account the dissociation of likely products of penicillin hydrolysis and degradation reactions.

2. Experimental Section

2.1. Materials. Benzylpenicillin potassium salt (penicillin G potassium salt, $\geq 98.0\%$) and benzylpenicillin sodium salt (penicillin G sodium salt, $\geq 98.0\%$) were purchased from Fluka, while phenoxymethylpenicillin potassium salt (penicillin V potassium salt VETRANAL, analytical standard) was obtained from Riedel-de Haën. All compounds were stored in a refrigerator and used as received. Demineralized water was distilled two times in a quartz bidistillation apparatus (Destamat Bi 18E, Heraeus). The final product with a specific conductance of $< 6 \times 10^{-7} \Omega^{-1} \text{ cm}^{-1}$ was distilled into a flask, permitting storage and transfer of water into the measuring cell under an atmosphere of nitrogen. Stock solutions were prepared by adding a weighed amount of water to a weighed amount of penicillin salts. All solutions were stored under nitrogen at room temperature.

2.2. Conductivity Measurements. The conductivities of the solutions were determined with the help of a three-electrode measuring cell described elsewhere.⁴³ The cell was calibrated with dilute potassium chloride solutions⁴⁴ and immersed in the high-precision thermostat described previously.⁴⁵ The temperature dependence of the cell constant was taken into account.⁴⁴ The water bath could be set to each temperature using a temperature program, with a reproducibility of 0.005 K. The temperature in the precision thermostat bath was additionally checked with a calibrated Pt100 resistance thermometer (MPMI 1004/300 Merz) in connection with a HP 3458 A. The resistance measurements of the solutions in the cell were performed using a precision LCR Meter Agilent 4284 A.

At the beginning of every measuring cycle, the cell was filled with a weighed amount (~ 660 g) of water. After measurement of the solvent conductivity at all temperatures of the temperature program, the stepwise concentration was carried out by successive additions, using a gas-tight syringe, of weighed amounts of a stock solution to weighed samples of K-Pen G. After every addition, the temperature program was run by the computer, and all measured data (frequency-dependent resistance, temperature) were stored and partially shown on a display to track the measuring process. A home-developed software package was used for temperature control and acquisition of conductance data. The measuring procedure, including corrections and extrapolation of the sample conductivity to infinite frequency, has been previously described.⁴⁵

The molar concentrations c were determined from the weights and the corresponding solution densities d . A linear change of d with increasing salt content for diluted solutions was assumed, $d = d_0 + b\tilde{m}$, where d_0 is the density of water and \tilde{m} is the molonity of the electrolyte (moles of electrolyte per kilogram of solution). The densities of the solutions were determined by the method of Kratky et al.⁴⁶ using a Paar densimeter (DMA 60, DMA 601 HT) at 298.15 K combined with a precision thermostat. As usual, the density gradient b is considered to be independent of temperature. The measured conductivity data of all investigated salts are given as a function of concentration c at 298.15 K. They can be converted to the temperature-dependent quantities by use of the relationship $c = \tilde{m}d$. Considering the sources of error (calibration, measurements, impurities), the specific conductivities are estimated to be accurate to within 0.2%.

TABLE 1: Experimental and Calculated Molar Conductivities of Sodium Penicillin G Salt as a Function of Concentration c and Temperature T^a

T/K	278.15		283.15		288.15	
$10^3 \times c^b$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$
0.876	51.05	49.30	58.78	57.18	66.91	65.42
1.197	48.83	47.54	56.38	55.11	64.29	63.10
1.568	46.60	46.19	53.87	53.52	61.51	61.31
1.959	45.04	45.19	52.07	52.34	59.56	59.99
2.361	43.97	44.42	50.91	51.43	58.24	58.97
2.788	42.78	43.77	49.52	50.68	56.70	58.12
3.373	42.39	43.09	49.03	49.87	56.14	57.21
3.981	42.12	42.53	48.77	49.22	55.81	56.47
4.603	41.83	42.06	48.41	48.67	55.42	55.85
5.293	41.51	41.63	48.09	48.16	55.05	55.28
6.026	41.30	41.25	47.81	47.71	54.73	54.77
6.879	40.95	40.86	47.37	47.27	54.29	54.26
7.695	40.66	40.54	47.05	46.87	53.91	53.81
$\sigma(\Lambda)$		0.76		0.76		0.83
		293.15		298.15		303.15
0.876	75.34	73.29	84.12	82.83	93.22	92.01
1.197	70.79	70.70	81.03	79.92	89.82	88.71
1.568	69.14	68.72	77.81	77.68	86.43	86.18
1.959	67.40	67.25	75.56	76.02	84.02	84.30
2.361	65.96	66.11	74.00	74.73	82.34	82.84
2.788	64.27	65.16	72.20	73.66	80.45	81.63
3.373	63.56	64.14	71.49	72.52	79.49	80.34
3.981	63.22	63.31	70.98	71.58	79.11	79.28
4.603	62.80	62.62	70.50	70.80	78.56	78.39
5.293	62.47	61.98	70.02	70.08	78.02	77.58
6.026	62.06	61.41	69.69	69.43	77.66	76.85
6.879	61.61	60.84	69.03	68.79	77.10	76.12
7.695	61.20	60.33	68.55	68.21	76.63	75.46
$\sigma(\Lambda)$		0.80		0.79		0.84
		308.15		313.15		
0.876	102.59	102.01	112.04	111.27		
1.197	98.72	98.35	107.57	107.35		
1.568	95.19	95.53	103.90	104.34		
1.959	92.71	93.43	101.43	102.09		
2.361	90.88	91.82	98.07	100.36		
2.788	88.99	90.47	97.75	98.91		
3.373	87.90	89.03	96.51	97.36		
3.981	87.52	87.85	96.18	96.09		
4.603	86.88	86.87	95.31	95.03		
5.293	86.32	85.96	94.88	94.05		
6.026	85.92	85.15	94.27	93.17		
6.879	85.31	84.34	93.49	92.30		
7.695	84.80	83.59	92.85	91.49		
$\sigma(\Lambda)$		0.85		1.08		

^a Units: c , $\text{mol} \cdot \text{dm}^{-3}$; Λ , $\sigma(\Lambda)$, $\text{S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$. ^b The c values are molalities at 298.15 K; the b coefficient in the density equation is 0.117.

3. Results and Discussion

3.1. Electrical Conductivities of Sodium Penicillin G, Potassium Penicillin G, and Potassium Penicillin V Salts in Water. The molar conductivities of Na-Pen G, K-Pen G, and K-Pen V salts determined in this work are presented in Tables 1, 2, and 3 respectively. Na-Pen G conductivities were reported by Woodbury and Rosenblum⁶ (1947) at 303.20 K (penicillin from Merck, 95–96% in the benzyl G form with small amounts of other penicillins), McBain et al.⁸ (1949) at 298.15 K (penicillin from Bristol Laboratories, Inc., Syracuse, New York, 96.9% in the G form), and Vavrch⁵ (1950) at 293.15 K (crystalline and amorphous Czech penicillin samples). In the Kumler and Alpen⁷ note (1948), only the infinite limiting conductances of the penicillin salts are given. All conductance measurements in the Woodbury and Rosenblum⁶ experiments were made immediately after preparation of penicillin solutions. In the McBain et al.⁸ determinations (in rather concentrated

TABLE 2: Experimental and Calculated Molar Conductivities of Potassium Penicillin G Salt as a Function of Concentration c and Temperature T^a

T/K	278.15		283.15		288.15	
$10^3 \times c^b$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$
0.325	71.78	73.31	81.89	83.91	92.48	94.98
0.631	70.33	68.02	80.21	77.69	90.49	88.02
1.004	66.58	65.08	76.02	74.24	85.91	84.15
1.441	63.56	63.14	72.68	71.97	82.23	81.61
1.852	61.57	61.96	70.61	70.58	79.92	80.04
2.314	60.46	61.00	69.20	69.46	78.32	78.78
2.767	59.62	60.29	68.24	68.63	77.27	77.84
3.353	58.96	59.57	67.46	67.79	76.35	76.90
3.932	58.57	59.01	66.92	67.14	75.73	76.16
4.768 ^c	58.10	58.37	66.36	66.37	75.02	75.28
4.594	58.12	58.49	66.44	66.53	75.19	75.48
5.702 ^c	57.48	57.81	65.66	65.72	74.21	74.56
5.434	57.86	57.96	66.14	65.90	74.83	74.77
6.646 ^c	57.02	57.34	65.12	65.18	73.62	73.95
6.353	57.41	57.48	65.65	65.34	74.28	74.13
7.742 ^c	56.54	56.89	64.58	64.66	73.00	73.35
8.935 ^c	56.12	56.48	64.09	64.17	72.48	72.80
10.233 ^c	55.76	56.09	63.68	63.72	72.01	72.29
11.521 ^c	55.21	55.76	63.09	63.33	71.31	71.85
12.552 ^c	55.03	55.52	62.87	63.05	71.08	71.53
$\sigma(\Lambda)$		0.80		0.88		0.97
0.325	103.53	293.15	115.00	298.15	127.02	303.15
0.631	101.18	106.26	118.34	118.34	123.33	121.48
1.004	96.10	98.53	112.12	109.65	117.31	115.86
1.441	92.09	94.23	106.59	104.82	117.31	115.86
1.852	89.59	91.40	102.21	101.63	112.57	112.16
2.314	87.82	89.66	99.55	99.67	109.77	109.89
2.767	86.61	88.25	97.59	98.09	107.67	108.06
3.353	85.58	88.25	97.59	98.09	107.67	108.06
3.932	84.95	87.20	96.28	96.91	106.27	106.70
4.768 ^c	84.04	86.15	95.12	95.72	105.05	105.33
4.594	84.29	85.33	94.45	94.79	104.24	104.26
5.702 ^c	83.12	84.33	93.36	93.65	103.04	102.92
5.434	83.87	84.56	93.72	93.93	103.45	103.27
6.646 ^c	82.40	83.53	92.36	92.76	101.95	101.91
6.353	83.24	83.76	93.21	93.03	102.89	102.24
7.742 ^c	81.75	82.84	91.63	91.99	101.08	101.03
8.935 ^c	81.15	82.05	92.53	92.23	102.12	101.32
10.233 ^c	80.64	82.17	90.83	91.23	100.24	100.17
11.521 ^c	79.85	81.55	90.17	90.54	99.50	99.37
12.552 ^c	79.59	80.98	89.58	89.89	98.83	98.63
$\sigma(\Lambda)$		80.48	88.71	89.32	97.87	97.99
		80.12	88.42	88.92	97.55	97.53
		1.04		1.09		1.21
0.325	139.55	308.15	152.51	313.15	155.92	
0.631	134.62	143.79	145.69	144.24	137.73	
1.004	128.08	132.84	138.53	137.73	133.43	
1.441	123.10	126.75	133.52	133.43	130.79	
1.852	120.15	123.10	130.51	130.79	128.65	
2.314	117.90	120.27	126.62	127.06	125.46	
2.767	116.44	115.30	125.36	125.46	124.20	
3.353	115.14	114.14	124.12	124.20	122.58	
3.932	114.20	113.05	123.52	123.03	121.40	
4.768 ^c	113.04	111.87	121.96	121.40	121.81	
4.594	113.40	111.93	122.90	121.81	120.36	
5.702 ^c	111.87	110.59	120.86	120.36	120.72	
5.434	112.80	110.92	122.04	120.72	119.33	
6.646 ^c	110.88	109.65	119.83	119.33	118.39	
6.353	111.98	109.14	118.78	118.39	117.50	
7.742 ^c	109.96	107.96	118.15	117.50	116.73	
8.935 ^c	109.14	107.26	117.02	116.73	116.18	
10.233 ^c	108.38	106.75	116.62	116.18	1.01	
11.521 ^c	107.35	1.16				
12.552 ^c	106.99					
$\sigma(\Lambda)$						

^a Units: c , mol·dm⁻³; Λ , $\sigma(\Lambda)$, S·cm²·mol⁻¹. ^b The c values are molalities at 298.15 K; the b coefficient in the density equation is 0.126. ^c Solutions prepared from solid samples (see text).

TABLE 3: Experimental and Calculated Molar Conductivities of Potassium Penicillin V Salt as a Function of Concentration c and Temperature T^a

T/K	278.15		283.15		288.15	
$10^3 \times c^b$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$	$\Lambda_{\text{exp.}}$	$\Lambda_{\text{calc.}}$
0.824	58.79	59.53	67.20	68.13	76.03	77.14
1.087	58.70	58.87	67.12	67.37	75.89	76.28
1.415	58.31	58.30	66.69	66.71	75.42	75.54
1.820	57.71	57.78	66.14	66.11	74.81	74.86
2.278	57.29	57.33	65.68	65.59	74.26	74.27
2.794	57.03	56.93	65.23	65.13	73.83	73.75
3.393	56.67	56.56	64.81	64.70	73.32	73.27
4.090	56.37	56.21	64.43	64.29	72.88	72.80
4.821	56.05	55.90	64.08	63.93	72.51	72.39
5.615	55.74	55.61	63.71	63.60	72.07	72.01
$\sigma(\Lambda)$		0.27		0.33		0.38
		293.15		298.15		303.15
0.824	85.18	86.49	94.67	96.32	104.49	106.27
1.087	85.01	85.53	94.48	95.21	104.24	105.02
1.415	84.51	84.69	93.89	94.25	103.58	103.93
1.820	83.84	83.93	93.17	93.37	102.79	102.93
2.278	83.23	83.27	92.51	92.61	102.09	102.08
2.794	82.74	82.68	91.93	91.94	101.39	101.32
3.393	82.14	82.13	91.30	91.32	100.75	100.62
4.090	81.71	81.61	90.72	90.72	100.09	99.94
4.821	81.22	81.14	90.25	90.19	99.59	99.35
5.615	80.76	80.71	89.74	89.70	99.04	98.80
$\sigma(\Lambda)$		0.44		0.53		0.63
		308.15		313.15		
0.824	114.53	116.91	124.78	127.17		
1.087	114.20	115.50	124.22	125.65		
1.415	113.50	114.26	123.45	124.31		
1.820	112.63	113.14	122.58	123.09		
2.278	111.89	112.18	121.72	122.04		
2.794	111.01	111.33	121.02	121.12		
3.393	110.38	110.53	120.21	120.25		
4.090	109.73	109.77	119.50	119.42		
4.821	109.20	109.11	118.91	118.70		
5.615	108.59	108.48	118.33	118.02		
$\sigma(\Lambda)$		0.77		0.85		

^a Units: c , mol·dm⁻³; Λ , $\sigma(\Lambda)$, S·cm²·mol⁻¹. ^b The c values are molalities at 298.15 K; the b coefficient in the density equation is 0.138.

solutions from 0.09 to 0.53 mol·dm⁻³), the crystalline sodium penicillin G and its solutions were stored in a refrigerator, and all measurements were made with solutions less than 6 h old and with less than 0.5 h at room temperature. In order to compare conductivities at different temperatures with our results at 298.15 K, the literature-reported conductances Λ at temperature T were multiplied by the ratio of water viscosities, $\eta(T)/\eta(298.15 \text{ K})$, and they are plotted in Figure 1. As can be seen, there are two distinct concentration regions. In concentrated solutions,^{6,8} the curve of Λ versus $c^{1/2}$ is typical of strong electrolytes. However, in dilute solutions, the effect of hydrolysis is evident, and the form of the Λ curve follows the behavior of weak electrolytes or at least a marked deviation from the conduct of fully dissociated electrolytes (the Vavruch^{4,5} interpretation was that the penicillin solutions behave like colloidal electrolytes). The similar plot of Λ versus $c^{1/2}$ in the Canals et al.¹⁰ investigation also clearly shows two concentration regions. The shifted results of Vavruch⁵ (crystalline and amorphous samples) from 293.15 to 298.15 K are in reasonable agreement with our conductivities at 298.15 K. On the whole, considering that the purity of commercial penicillin samples and the applied experimental procedures are not exactly the same in the different investigations, the consistency of the Λ values presented in Figure 1 seems to be satisfactory. Absolute values of conductances of K-Pen G are larger than those of K-Pen V, and in

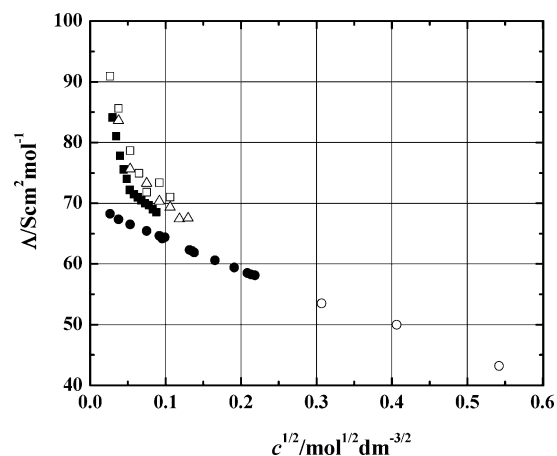


Figure 1. Molar conductivity Λ of sodium penicillin G at 298.15 K; Δ crystalline samples, ref 5; \square amorphous samples, ref 5; \bullet ref 6; \circ ref 8; \blacksquare this work.

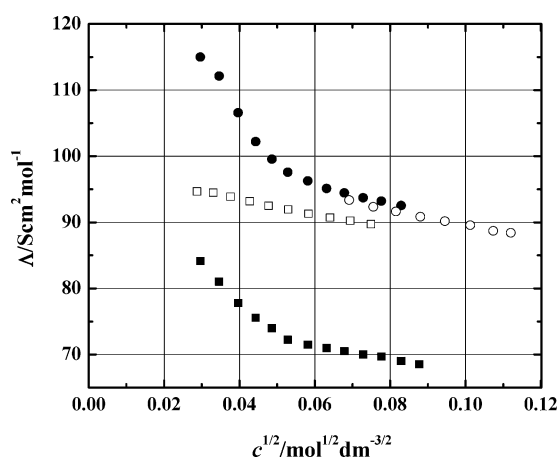


Figure 2. Molar conductivity Λ of sodium penicillin G, potassium penicillin G, and potassium penicillin V at 298.15 K; \blacksquare Na-Pen G; \bullet K-Pen G (stock solution, see text); \circ K-Pen G (solid samples, see text); \square K-Pen V.

TABLE 4: Densities, Viscosities, and Dielectric Constants of Pure Water and Limiting Ionic Conductances in Water^a

T	d_0^b	$\eta \cdot 10^{3c}$	D^d	$\lambda^0(\text{Na}^+)^e$	$\lambda^0(\text{K}^+)^e$	$\lambda^0(\text{H}^+)^e$
278.15	0.99997	1.5192	85.897	30.30	46.72	250.02
283.15	0.99970	1.3069	83.945	34.88	53.03	275.55
288.15	0.99910	1.1382	82.039	39.72	59.61	300.74
293.15	0.99821	1.0020	80.176	44.81	66.44	325.52
298.15	0.99705	0.8903	78.358	50.15	73.50	349.85
303.15	0.99565	0.7975	76.581	55.72	80.76	373.66
308.15	0.99404	0.7195	74.846	61.53	88.20	396.90
313.15	0.99224	0.6531	73.151	67.34	95.85	419.15

^a Units: T , K; d_0 , $\text{kg} \cdot \text{dm}^{-3}$; η , $\text{Pa} \cdot \text{s}$; λ^0 , $\text{S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$. ^b Ref 57. ^c Ref 58. ^d Ref 59. ^e Ref 60.

dilute solutions, the curvature of $\Lambda(\text{K-Pen V})$ is less evident than that of $\Lambda(\text{K-Pen G})$. There is a marked similarity between the $\Lambda(\text{Na-Pen G})$ and $\Lambda(\text{K-Pen G})$ curves (Figure 2). Conductances of K-Pen G and K-Pen V salts are unknown in the literature, and therefore, it is impossible to make comparison with our results.

3.2. Hydrolysis and Degradation Reactions of Penicillins. Brodersen¹⁷ (1947) postulated that in neutral solution, the carboxyl group of a penicillin molecule gives up a hydrogen ion, and a relatively stable negatively charged penicillin ion is formed. In aqueous acidic solutions, on the other hand, the penicillin is decomposed. The degradation of penicillin G is largely dependent on pH and temperature (the minimum

TABLE 5: Fractions α_i and Contributions from Dissociation Steps to the Calculated Conductance Λ_{calc} , as a Function of the NaHPenG Concentration c at 298.15 K^a

$10^3 \times c$	α_1	α_2	α_H	β	Λ_1	Λ_2
0.876	0.9252	0.0545	0.0341	0.0204	72.03	10.80
1.197	0.9273	0.0502	0.0277	0.0225	70.21	9.71
1.568	0.9286	0.0472	0.0230	0.0242	68.73	8.95
1.959	0.9293	0.0452	0.0196	0.0256	67.59	8.43
2.361	0.9296	0.0437	0.0171	0.0267	66.68	8.05
2.788	0.9298	0.0427	0.0151	0.0276	65.91	7.75
3.373	0.9299	0.0416	0.0131	0.0285	65.06	7.46
3.981	0.9299	0.0408	0.0115	0.0293	64.35	7.23
4.603	0.9298	0.0402	0.0103	0.0300	63.74	7.06
5.293	0.9297	0.0398	0.0092	0.0306	63.18	6.90
6.026	0.9295	0.0394	0.0083	0.0311	62.66	6.77
6.879	0.9294	0.0391	0.0075	0.0316	62.14	6.65
7.695	0.9300	0.0384	0.0068	0.0317	61.73	6.47

^a Units: c , $\text{mol} \cdot \text{dm}^{-3}$; Λ , $\text{S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$.

degradation is observed at $\text{pH} = 6.5^{18}$). The decomposition process is indirectly but easily observed in surface tension or optical activity measurements. For example, Canals et al.¹⁰ showed that the surface tension of different penicillins strongly decreases with the time and reaches the limit value after about 60–80 min.

Since orally active penicillins are degraded in the acidic conditions prevailing in the stomach and it is believed that degradation products are responsible for penicillin allergy, numerous investigations were devoted to understanding the instability of penicillins and to identifying the degradation products. Several schemes were suggested for the degradation of penicillin (see, for example, refs 17–32; the early reviews on the subject are given in refs 19 and 20), but there is still considerable uncertainty about the exact mechanism and final products of the penicillin degradation. In general, it can be said that penicillin has a single acidic functional group, the carboxyl group, but that the degradation products are dibasic acids. The carboxylic group is in the penicillamine portion of the penicillin molecule, and it can be easily liberated. Extensive kinetic and identification studies^{20–27} (the kinetics of K-Pen V is described in ref 28) showed that the major products of hydrogen-ion-catalyzed hydrolysis of penicillin G are benzylpenicillenic acid, benzylpenillic acid, and benzylpenicilloic acid. All of these acids have two carboxylic groups, but the proportion of each acid formed in the solution depends on the pH. In weak acidic media with $\text{pH} \geq 4.0$, (in our experiments, the pH values of solutions lie in the 4.3–5.1 range), the degradation pathways lead to the final product, which is benzylpenicilloic acid in the case of penicillin G and phenoxymethylpenicilloic acid in the case of penicillin V. The time needed for complete degradation of penicillins varies depending on temperature and pH but is relatively small and does not exceed a few hours. For example, at $\text{pH} = 2.7$ and 310 K for K-Pen G, it is about 2 h,²³ and at $\text{pH} = 2.9$ and 293 K for K-Pen V, it is about 6 h.²⁸

In the context of conductivity determinations, the exact composition of degradation products during measurements is probably not important, considering that the main contribution to the conductance comes from the hydrogen and sodium or potassium ions, which are known but not from the organic anions. Besides, since the basic structure of various benzylpenicillenic acids is similar, it is expected that differences in contributions from various organic ions to the overall conductivity will also be very small. Thus, the measured conductance is the sum of contributions from all of the cations and anions present in solution. Because the exact proportion between anions is unknown and varies during the conductivity experiments, we

TABLE 6: Coefficients of the Quint–Viallard Conductivity Equations (Na-Pen G) for Ion Pairs with HPenG[−] and PenG^{2−}, Dissociation Constants K_1 and K_2 , and Thermodynamic Functions at Different Temperatures T^a

T	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15
Λ_{12}^0	41.67	48.10	55.29	62.05	70.15	77.48	85.80	94.06
S_{12}	44.51	51.71	59.62	67.87	76.73	85.81	95.64	105.72
E_{12}	−1.01	−1.20	−1.31	−1.58	−1.64	−1.93	−2.08	−2.26
J_{112}	85.00	98.78	114.52	130.28	148.34	165.91	185.78	206.13
J_{212}	121.60	141.46	164.11	187.00	213.02	238.58	267.42	297.05
Λ_{14}^0	55.06	64.18	73.52	83.02	93.15	103.81	114.90	126.10
S_{14}	74.57	86.98	100.30	114.33	129.11	144.76	161.41	178.56
E_{14}	66.18	77.43	89.55	102.42	115.99	130.57	146.16	162.34
J_{114}	2.10	4.65	5.77	6.00	6.88	8.86	10.50	12.19
J_{214}	44.10	52.18	59.10	65.16	72.07	79.65	86.81	93.48
Λ_{23}^0	261.38	288.78	316.31	342.76	369.85	395.42	421.17	445.87
S_{23}	93.43	105.59	118.54	131.87	145.59	159.56	174.20	188.97
E_{23}	46.61	51.54	56.83	62.21	67.52	72.84	78.36	83.86
J_{123}	617	689	767	847	928	1009	1095	1180
J_{223}	1510	1686	1874	2066	2260	2456	2661	2866
Λ_{34}^0	274.77	304.86	334.54	363.73	392.85	421.75	450.27	477.91
S_{34}	144.50	163.94	184.39	205.64	227.29	249.84	273.28	297.05
E_{34}	115.12	127.27	139.71	152.49	164.52	177.31	190.00	202.66
J_{134}	998	1116	1240	1367	1493	1625	1760	1896
J_{234}	1427	1595	1768	1946	2122	2305	2490	2676
$K_1 10^3$	1.29	1.28	1.28	1.27	1.26	1.28	1.26	1.26
$K_2 10^6$	1.15	1.30	1.35	1.40	1.53	1.70	1.85	1.85
ΔG_1°	15.38	15.68	15.96	16.25	16.55	16.79	17.10	17.38
ΔH_1°	−0.44	−0.43	−0.44	−0.42	−0.41	−0.46	−0.43	−0.43
$T\Delta S_1^\circ$	−15.82	−16.11	−16.39	−16.68	−16.96	−17.25	−17.53	−17.81
ΔG_2°	31.62	31.90	32.38	32.85	33.19	33.48	33.82	34.37
ΔH_2°	10.16	10.05	10.14	10.23	10.18	10.09	10.04	10.20
$T\Delta S_2^\circ$	−21.46	−21.85	−22.24	−22.62	−23.01	−23.39	−23.78	−24.16

^a Units: T , K; K_1 and K_2 , mol·dm^{−3}; ΔG° , ΔH° , $T\Delta S^\circ$, kJ·mol^{−1}; Λ_j^0 , $S_j \times c^{1/2}$, $E_j \times c$, $J_{ij} \times c$, $J_{2j} \times c^{3/2}$, S·cm²·mol^{−1}; $j = 1-4$, 1 – Na⁺, 2 – HPenG[−], 3 – H⁺, 4 – PenG^{2−}.

TABLE 7: Limiting Equivalent Conductances λ^0 (HPen[−]) Derived from Na-Pen G, K-Pen G, and K-Pen V Conductivities as a Function of Temperature T and the Corresponding Walden Products^a

T/K	λ^0 (NaPenG)	λ^0 (KPenG)	λ^0 (KPenV)	λ_{av}^0	$\eta\lambda_{av}^0$
278.15	11.28	11.63	11.20	11.37 ± 0.23	0.1724
283.15	13.22	13.22	13.25	13.23 ± 0.02	0.1728
288.15	15.57	15.65	15.50	15.57 ± 0.08	0.1772
293.15	17.24	17.95	17.80	17.66 ± 0.37	0.1770
298.15	20.00	20.20	20.10	20.10 ± 0.10	0.1790
303.15	21.76	21.87	22.35	21.99 ± 0.31	0.1754
308.15	24.27	24.27	25.00	24.51 ± 0.42	0.1763
313.15	26.72	26.72	27.45	26.96 ± 0.42	0.1761

^a Units: λ^0 , S·cm²·mol^{−1}, $\eta\lambda^0$, S·cm²·mol^{−1}·Pa·s.

TABLE 8: Limiting Equivalent Conductances λ^0 (Pen^{2−}) Derived from Na-Pen G, K-Pen G, and K-Pen V Conductivities as a Function of Temperature T and the Corresponding Walden Products^a

T/K	λ^0 (NaPenG)	λ^0 (KPenG)	λ^0 (KPenV)	λ_{av}^0	$\eta\lambda_{av}^0$
278.15	24.67	25.25	25.05	24.99 ± 0.29	0.3788
283.15	29.30	29.36	29.00	29.22 ± 0.19	0.3816
288.15	33.80	33.72	33.50	33.67 ± 0.16	0.3832
293.15	38.21	38.38	38.20	38.26 ± 0.10	0.3834
298.15	43.00	43.00	43.50	43.17 ± 0.29	0.3843
303.15	48.09	47.97	47.80	47.95 ± 0.15	0.3824
308.15	53.37	53.00	52.90	53.09 ± 0.25	0.3819
313.15	58.76	58.63	58.00	58.46 ± 0.41	0.3818

^a Units: λ^0 , S·cm²·mol^{−1}, $\eta\lambda^0$, S·cm²·mol^{−1}·Pa·s.

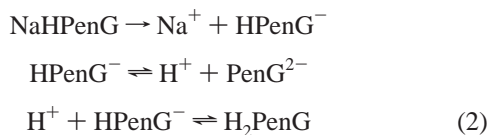
assumed that the system can be treated as containing only one acidic salt of the dibasic penicillinic acid. Most likely, the final products of degradation reactions, the salts of benzylpenicilloic acid in the case of penicillin G and those of phenoxymethylpenicilloic acid in the case of penicillin V, may play such roles. The proposed model excludes the possibility of a simple hydrolysis of Pen G or Pen V neutral salts proposed by Brodersen¹⁷ because even with a wide range of introduced

dissociation constants, it is impossible to correctly represent the conductivities of the dilute solutions. Thus, if our hypothesis is right, then the determined conductances in this work or in the literature (Figures 1 and 2) are not actually conductances of the Pen G or Pen V salts but are those of the degradation products. However, since the basic β -lactam ring is preserved in all involved molecules, it is expected that the limiting conductances with the lowest charge and the first dissociation constants K_1 are practically the same for penicillins as well as for the degradation products. Formally, we will continue to name determined conductivities as these of penicillin G or V. As a consequence, the limiting conductance associated with the first dissociation step of penicillin G will be denoted as λ^0 (HPenG[−]) and that with the second dissociation step as λ^0 (1/2PenG^{2−}). In this notation, the acidic salt of dibasic penicillinic acid is NaHPenG and KHPenG, and the corresponding acid is H₂PenG.

3.3. Dissociation Equilibria and Conductivity Equations. The molar conductivities, Λ , are the sum of ionic contributions

$$\Lambda = \frac{\kappa}{c} = \sum_{j=1}^n \frac{|z_j|c_j\lambda_j}{c} \quad (1)$$

where κ is the measured specific conductance, λ_j are the ionic conductances, c_j and z_j are the concentrations and charges of the individual ions present in the solution, and c denotes the analytical concentration of the electrolyte. Thus, the representation of the determined conductances must include the evaluation of all of the concentrations of each species making up the solution. The dissolution of an acidic salt of a dibasic acid in water (NaHPen G represents both sodium and potassium salts of Pen G and Pen V) in terms of the dissociation reactions is governed by the following equations



Denoting concentrations of existing species by

$$\begin{aligned}
 [\text{Na}^+] &= c \\
 [\text{H}^+] &= c\alpha_{\text{H}^+} \\
 [\text{HPenG}^-] &= c\alpha_1 \\
 [\text{PenG}^{2-}] &= c\alpha_2 \\
 [\text{H}_2\text{PenG}] &= c\beta = (1 - \alpha_1 - \alpha_2)c
 \end{aligned} \quad (3)$$

and taking into account the charge balance in the solution (the effect of water dissociation is very small and is neglected) the

$$c(1 + \alpha_{\text{H}^+}) = c(\alpha_1 + 2\alpha_2) \quad (4)$$

dissociation equilibria can be expressed by

$$\begin{aligned}
 K_1(T) &= \frac{[\text{H}^+][\text{HPenG}^-]}{[\text{H}_2\text{PenG}]} F_1 = \frac{c(\alpha_1 + 2\alpha_2 - 1)\alpha_1}{1 - \alpha_1 - \alpha_2} F_1 \\
 K_2(T) &= \frac{[\text{H}^+][\text{PenG}^{2-}]}{[\text{HPenG}^-]} F_2 = \frac{c(\alpha_1 + 2\alpha_2 - 1)\alpha_2}{\alpha_1} F_2
 \end{aligned} \quad (5)$$

where F_1 and F_2 denote the quotients of the activity coefficients

$$\begin{aligned}
 F_1 &= \frac{f_{\text{H}^+} f_{\text{HPenG}^-}}{f_{\text{H}_2\text{PenG}}} \\
 F_2 &= \frac{f_{\text{H}^+} f_{\text{PenG}^{2-}}}{f_{\text{HPenG}^-}}
 \end{aligned} \quad (6)$$

The activity coefficients of the individual ions in dilute solutions, f_j , can be approximated by the Debye–Hückel equations

$$\begin{aligned}
 \log[f_j(T)] &= -\frac{z_j^2 A(T) \sqrt{I}}{1 + a_j B(T) \sqrt{I}} \\
 A(T) &= \frac{1.8246 \times 10^6}{[D(T)T]^{3/2}} \quad B(T) = \frac{50.29 \times 10^8}{[D(T)T]^{1/2}}
 \end{aligned} \quad (7)$$

where $D(T)$ is the dielectric constant of water, a_j is the ion size parameter, and I denotes the ionic strength of the solution, which is $I = c(\alpha_1 + 3\alpha_2)$. Values of the size parameters ($a(\text{H}^+) = 9.0$, $a(\text{Na}^+) = 4.0$, $a(\text{K}^+) = 3.5$, $a(\text{HPenG}^-) = 5.0$, and $a(\text{PenG}^{2-}) = 5.8$ Å) were prescribed, and they are assumed to be independent of temperature.^{47,48}

If the equilibrium constants $K_1(T)$ and $K_2(T)$ and the activity coefficients are available, the concentration fractions α_1 and α_2 can be successively evaluated for every concentration c by an iterative solution of two quadratic equations (eq 5)

$$\begin{aligned}
 \alpha_1 &= \frac{1}{2} \left\{ 1 - 2\alpha_2 - \frac{K_1}{cF_1} + \sqrt{\left(1 - 2\alpha_2 - \frac{K_1}{cF_1}\right)^2 + \frac{4K_1(1 - \alpha_2)}{cF_1}} \right\} \\
 \alpha_2 &= \frac{1}{4} \left\{ 1 - \alpha_1 + \sqrt{(1 - \alpha_1)^2 + \frac{8K_2\alpha_1}{cF_2}} \right\}
 \end{aligned} \quad (8)$$

In this work, the ionic conductances λ_j in eq 1 are represented by the Quint–Viallard conductivity equations^{39–42}

$$\lambda_j = \lambda_j^0 - S_j \sqrt{I} + E_j I \ln I + J_{1j} I - J_{2j} I^{3/2} \quad (9)$$

where λ_j^0 is the limiting conductance of the j th ion. The coefficients S_j , E_j , J_{1j} , and J_{2j} are rather complex functions of the viscosity η , the dielectric constant of pure water, and the average cation–anion distances of closest approach (explicit expressions for these coefficients are given also elsewhere^{49–54}).

The molar conductivities of NaHPenG are the contributions from the four ion pairs

$$\begin{aligned}
 \Lambda_1^{(1)} &= [\lambda(\text{H}^+) + \lambda(\text{HPenG}^-)] \\
 \Lambda_2^{(1)} &= [\lambda(\text{H}^+) + \lambda(1/2\text{PenG}^{2-})] \\
 \Lambda_1^{(2)} &= [\lambda(\text{Na}^+) + \lambda(\text{HPenG}^-)] \\
 \Lambda_2^{(2)} &= [\lambda(\text{Na}^+) + \lambda(1/2\text{PenG}^{2-})]
 \end{aligned} \quad (10)$$

In order to yield equations of pairs, the organic ions should be “distributed” between the hydrogen and sodium ions⁵⁵ (the corresponding pairs of ions are denoted with the superscripts (1) and (2)), and the final result is

$$\begin{aligned}
 \Lambda(\text{NaHPenG}) &= \left\{ \frac{\alpha_{\text{H}^+}}{\alpha_1 + 2\alpha_2} [\alpha_1 \Lambda_1^{(1)} + 2\alpha_2 \Lambda_2^{(1)}] + \right. \\
 &\quad \left. \frac{1}{\alpha_1 + 2\alpha_2} [\alpha_1 \Lambda_1^{(2)} + 2\alpha_2 \Lambda_2^{(2)}] \right\} \quad (11)
 \end{aligned}$$

Thus, the proposed molecular model for the conductivity of NaHPenG in water includes the evaluation of the concentrations of all species present in solution (from eqs 3 and 8) and the use of eight Quint–Viallard conductivity equations. The representation of the experimental conductivity–concentration data set (Λ, c) can formally be expressed in the form $\Lambda = f[c; K_1, K_2, \lambda^0(\text{HPenG}^-), \lambda^0(1/2\text{PenG}^{2-}), a_j]$. At a given temperature T , the physical properties of pure water and the limiting ionic conductances $\lambda^0(\text{H}^+)$, $\lambda^0(\text{Na}^+)$, and $\lambda^0(\text{K}^+)$ are known from the literature (Table 4), and the distances of closest approach in the Quint–Viallard conductivity equations can be taken as the average value of the ion size parameters in the ion pairs. Therefore, the optimization problem requires the determination of four unknown parameters, namely, the dissociation constants K_1 and K_2 and the limiting conductances $\lambda^0(\text{HPenG}^-)$ and $\lambda^0(1/2\text{PenG}^{2-})$.

In the iterative process, starting with the assumed dissociation constants K_1 and K_2 , the values of α_1 and α_2 , f_j , and I for each concentration c were calculated and introduced into the computer program with the Quint–Viallard conductivity equations to obtain the limiting conductances of the organic anions. The calculations were repeated with new values of K_1 and K_2 until the satisfactory agreement between the measured and calculated

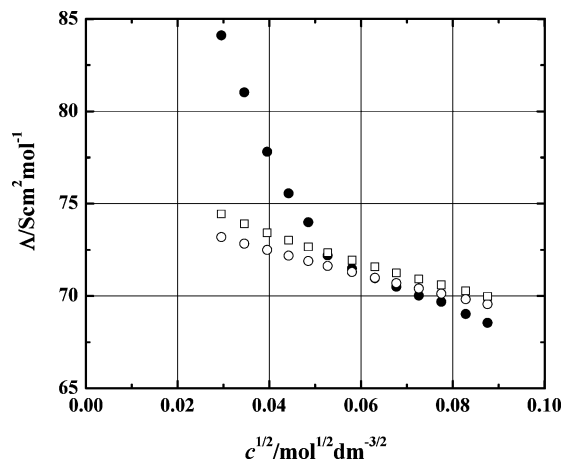


Figure 3. Molar conductivity Λ of sodium penicillin G at 298.15 K; ● Na-Pen G (experimental values); ○ Na-Pen G (calculated values, $K = 2 \times 10^{-3} \text{ mol} \cdot \text{dm}^{-3}$, see text); □ Na-Pen G (calculated values, $K = 2 \times 10^{-7} \text{ mol} \cdot \text{dm}^{-3}$, see text).

conductivities $\Lambda(c)$ was reached. The degree of agreement of the obtained fit is expressed by the mean value of standard deviations

$$\sigma(\Lambda) = \sqrt{\frac{\sum_{j=1}^N (\Lambda_{j,\text{exp.}} - \Lambda_{j,\text{calc.}})^2}{N-1}} \quad (12)$$

where N is the number of experimental points at a given T .

3.4. Conductivities of Sodium Penicillin G Salt. The results of the calculations for the NaHPenG salt, denoted as $\Lambda_{\text{calc.}}$, are presented in Table 1 together with the standard deviations $\sigma(\Lambda)$. As can be observed, there is a very satisfactory agreement between the experimental and calculated conductivities over the investigated concentration region and at all temperatures. Evidently, in very dilute solutions, it is expected that $\Lambda_{\text{exp.}}$ values are less accurate, and therefore, the difference between $\Lambda_{\text{exp.}}$ and $\Lambda_{\text{calc.}}$ is slightly larger. A detailed analysis of the conductivity data is given only at 298.15 K, but at other temperatures, the behavior of $\Lambda(c, T)$ is similar. The speciation of various ions in solutions of NaHPenG (Table 5) shows that the first dissociation step is predominant ($\alpha_1 \approx 0.93$ when $\alpha_2 \approx 0.04$ – 0.05). The ion pairs ($\text{Na}^+ + \text{HPenG}^-$) and ($\text{H}^+ + \text{HPenG}^-$) are responsible for 87–91% of the calculated conductivity $\Lambda_{\text{calc.}}$, and the ion pairs ($\text{Na}^+ + \text{PenG}^{2-}$) and ($\text{H}^+ + \text{PenG}^{2-}$) are responsible for the rest (these contributions are denoted in Table 5 as Λ_1 and Λ_2). Coefficients of the Quint–Vialard conductivity equations together with evaluated K_1 and K_2 constants and thermodynamic functions of the dissociation process are reported in Table 6. As expected, the value of the first dissociation constant ($\text{p}K_1 = 2.90$ at 298.15 K) is similar to those reported for various penicillins in the literature ($\text{p}K_1 = 2.6$ – 2.8^{20}), and it is practically independent of T . The standard thermodynamic functions of the dissociation process are defined by

$$\begin{aligned} \Delta G_j^\circ &= -RT \ln K_j \quad j = 1, 2 \\ \Delta G_j^\circ &= \Delta H_j^\circ - T \Delta S_j^\circ \\ \Delta S_j^\circ &= -\left(\frac{\partial \Delta G_j^\circ}{\partial T}\right)_P \end{aligned} \quad (13)$$

From eq 13, it follows that the first dissociation step is only controlled by the entropic term because $\Delta G_1^\circ \approx |-T\Delta S_1^\circ|$

(Table 6). The second dissociation constant K_2 increases slightly with temperature ($\text{p}K_2 = 5.7$ – 5.9), and the entropic term continues to dominate the dissociation process. However, with $\Delta G_2^\circ > |-T\Delta S_2^\circ| > \Delta H_2^\circ$, the enthalpic term cannot be neglected.

The Gibbs free energy can be linearly correlated with T , $\Delta G_1^\circ(T)/\text{kJ} \cdot \text{mol}^{-1} = -0.4315 + 0.0569(T/\text{K})$, $R^2 = 0.9996$; $\Delta G_2^\circ(T)/\text{kJ} \cdot \text{mol}^{-1} = 10.137 + 0.0772(T/\text{K})$, $R^2 = 0.9946$.

Woodbury and Rosenblum⁶ estimated that the limiting conductance of sodium penicillin G should be greater than $78 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ at 303.20 K, which gives the value of $\lambda^0(\text{HPenG}^-) > 22.3 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ using $\lambda^0(\text{Na}^+) = 55.7 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$. Kumler and Alpen⁷ reported $76.1 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ at 298.15 K, which with $\lambda^0(\text{Na}^+) = 50.1 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ gives $\lambda^0(\text{HPenG}^-) = 26.0 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$. These results are based on the assumption that Na-Pen G is a strong electrolyte (Figure 1). Our values are smaller, for example, at 298.15 K, $\lambda^0(\text{HPenG}^-) = 22.0 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$, but they are derived differently, by considering that penicillins behave as weak electrolytes having two dissociation steps. The limiting conductances determined from the Na-Pen G conductivities $\lambda^0(\text{HPenG}^-)$ and $\lambda^0(1/2\text{PenG}^{2-})$ are presented in Tables 7 and 8. As can be observed, the Walden products of both anions are practically independent of temperature, $\lambda^0(\text{HPenG}^-) \cdot \eta = 0.1743 \pm 0.0024 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1} \cdot \text{Pa} \cdot \text{s}$ and $\lambda^0(1/2\text{PenG}^{2-}) \cdot \eta = 0.3823 \pm 0.0034 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1} \cdot \text{Pa} \cdot \text{s}$.

If the Eyring approach is applied to the temperature dependence of the limiting conductances, then⁵⁶

$$\left(\frac{\partial \ln[\lambda^0(T)d_0^{2/3}(T)]}{\partial T}\right)_P = \frac{\Delta H_\lambda^\ddagger}{RT^2} \quad (14)$$

where $\Delta H_\lambda^\ddagger$ is the partial molar enthalpy associated with the ion movement. When $\Delta H_\lambda^\ddagger$ is independent of temperature, the integral form of eq 14 is

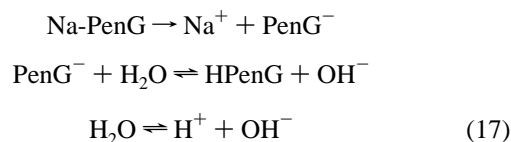
$$\ln[\lambda^0(T)d_0^{2/3}(T)] = -\frac{\Delta H_\lambda^\ddagger}{RT} + \text{const.} \quad (15)$$

Using the densities of pure water d_0 from Table 4 and the limiting conductances from Tables 7 and 8, we have

$$\begin{aligned} \ln[\lambda^0(\text{HPenG}^-; T)d_0^{2/3}(T)] &= 10.053 - \frac{2114.1}{(T/\text{K})} \quad R^2 = 0.9965 \\ \ln[\lambda^0(1/2\text{PenG}^{2-}; T)d_0^{2/3}(T)] &= 10.853 - \frac{2118.3}{(T/\text{K})} \quad R^2 = 0.9948 \end{aligned} \quad (16)$$

where, for both anions, $\Delta H_\lambda^\ddagger = 17.6 \text{ kJ} \cdot \text{mol}^{-1}$.

If the simplest version of the hydrolysis process is applied to the deviation of the Na-Pen G salt from the behavior of a strong 1:1 electrolyte, then the following reactions occur



The mass-action equations of the hydrolysis process are therefore

$$K = \frac{a_{\text{H}^+} a_{\text{PenG}^-}}{a_{\text{HPenG}}} = \frac{[\text{H}^+][\text{PenG}^-] f_{\text{H}^+} f_{\text{PenG}^-}}{[\text{HPenG}] f_{\text{HPenG}}} = \frac{[\text{H}^+][\text{PenG}^-]}{[\text{HPenG}]} F_1$$

$$F_1 = f_{\text{H}^+} f_{\text{PenG}^-} \quad f_{\text{HPenG}} = 1 \quad (18)$$

and

$$K_w = a_{\text{H}^+} a_{\text{OH}^-} = [\text{H}^+][\text{OH}^-] f_{\text{H}^+} f_{\text{OH}^-} = [\text{H}^+][\text{OH}^-] F_2$$

$$F_2 = f_{\text{H}^+} f_{\text{OH}^-} \quad (19)$$

Denoting

$$[\text{Na}^+] = c$$

$$[\text{PenG}^-] = c\alpha_{\text{PenG}^-} = c\alpha$$

$$[\text{H}^+] = c\alpha_{\text{H}^+} = c\beta$$

$$[\text{OH}^-] = c\alpha_{\text{OH}^-}$$

$$[\text{HPenG}] = c\alpha_{\text{HPenG}} \quad (20)$$

the material and charge balance equations are

$$[\text{NaPenG}] = [\text{PenG}^-] + [\text{HPenG}]$$

$$c = c\alpha_{\text{PenG}^-} + c\alpha_{\text{HPenG}} = c\alpha + c\alpha_{\text{HPenG}}$$

$$\alpha_{\text{HPenG}} = 1 - \alpha$$

$$[\text{Na}^+] + [\text{H}^+] = [\text{OH}^-] + [\text{PenG}^-]$$

$$c + c\alpha_{\text{H}^+} = c\alpha_{\text{OH}^-} + c\alpha_{\text{PenG}^-}$$

$$1 + \beta = \alpha_{\text{OH}^-} + \alpha$$

$$\alpha_{\text{OH}^-} = 1 + \beta - \alpha \quad (21)$$

In terms of the concentration fractions α and β , the mass-action equations are expressed by

$$K = \frac{[\text{H}^+][\text{PenG}^-]}{[\text{HPenG}]} F_1 = \frac{c\alpha\beta}{1 - \alpha} F_1 \quad (22)$$

$$K_w = [\text{H}^+][\text{OH}^-] F_2 = c^2\beta(1 + \beta - \alpha)F_2 \quad (23)$$

Using eq 22, we have from the Taylor expansion series

$$\alpha = \frac{K}{K + c\beta F_1} = \frac{1}{1 + \frac{c\beta F_1}{K}} = 1 - \frac{c\beta F_1}{K} + \left(\frac{c\beta F_1}{K}\right)^2 - \dots \quad (24)$$

Since $c\beta F_1/K \ll 1$, the linear term is enough in the expansion, and therefore, introducing α from eq 24 into eq 23 gives the fraction of hydrogen ions as

$$\beta = \sqrt{\frac{KK_w}{c^2 F_2 (K + cF_1)}} \quad (25)$$

Thus, in terms of concentrations, we have

$$[\text{H}^+] = c\beta = \sqrt{\frac{KK_w}{(K + cF_1)F_2}}$$

$$[\text{PenG}^-] = c\alpha = \frac{Kc}{K + c\beta F_1}$$

$$[\text{OH}^-] = c(1 + \beta - \alpha)$$

$$[\text{HPenG}] = c(1 - \alpha) \quad (26)$$

The ionic contributions to the molar conductance Λ are given by

$$\Lambda = \lambda(\text{Na}^+) + \beta\lambda(\text{H}^+) + \alpha\lambda(\text{PenG}^-) + (1 + \beta - \alpha)\lambda(\text{OH}^-) \quad (27)$$

It was observed that since β is small, the ionic strength, $I = c(1 + \beta)$, in the calculation of activity coefficients f_j and the conductances λ_j can be replaced in most cases simply by $I = c$.

The calculation procedure as applied to aqueous solutions of Na-Pen G salt at 298.15 K by using eq 27 shows that $\Lambda_{\text{calc.}}$ is clearly unable to represent $\Lambda_{\text{exp.}}$ in dilute solutions. To illustrate this point, calculations were performed using $K_w = 1.008 \times 10^{-14} \text{ (mol} \cdot \text{dm}^{-3})^2$, $K = 2 \times 10^{-3} \text{ mol} \cdot \text{dm}^{-3}$, $K = 2 \times 10^{-7} \text{ mol} \cdot \text{dm}^{-3}$, and $\lambda^0(\text{PenG}^-) = 25.16 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ (Figure 3). For penicillin salts, this disagreement cannot be overcome by changing the dissociation constant and the limiting conductance even if the values of K and $\lambda^0(\text{PenG}^-)$ are largely varied. Thus, this model, which is based on the early assumptions in the literature that penicillins in aqueous solutions have only one carboxylic group, is in complete disagreement with experimental conductivities in dilute solutions, as can be observed in Figure 3. Nevertheless, it is worthwhile to present the mathematical representation of this hydrolysis process (eq 17) because of its general value and possible application for other systems.

3.5. Conductivities of Potassium Penicillin G Salt. For K-Pen G, two sets of experiments were performed by us. In the first set, the solutions were prepared by dilution of the stock solution, whereas in the second set, the solutions were made by directly dissolving the solid salt in water (Table 2). At the time of the measurements, it was believed that the hydrolysis effect could be considerably reduced, and therefore, the second set covers more concentrated solutions. Although the overlapping concentration region is not large, there is a very reasonable consistency between both sets (Figure 2). Values of the $\Lambda_{\text{exp.}}$ and $\Lambda_{\text{calc.}}$ are reported in Table 2, and once again, the agreement is very satisfactory. Coefficients of the Quint–Viallard conductivity equations together with the evaluated K_1 and K_2 constants and thermodynamic functions of the dissociation process are reported in Table 9. The speciation of the various ions in solutions of KHPenG is similar to that of NaHPenG ($\alpha_1 \approx 0.93$ and $\alpha_2 \approx 0.04$ – 0.07). The ion pairs ($\text{K}^+ + \text{HPenG}^-$) and ($\text{H}^+ + \text{HPenG}^-$) are responsible for 83–91% of the calculated conductivity $\Lambda_{\text{calc.}}$ and the ion pairs ($\text{K}^+ + \text{PenG}^{2-}$) and ($\text{H}^+ + \text{PenG}^{2-}$) for the rest. Thus, the parameters associated with the penicillin anions and the first and second dissociation constants and, therefore, the thermodynamic functions are very close to those determined for Na-Pen G solutions.

Kumler and Alpen⁷ reported that the limiting conductance of potassium penicillin G is $99.5 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ at 298.15 K, which with $\lambda^0(\text{K}^+) = 73.5 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$ gives $\lambda^0(\text{HPenG}^-) = 26.0 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$. Our value, as explained previously, is expected to be lower than that of ($\lambda^0(\text{HPenG}^-) = 22.0 \text{ S} \cdot \text{cm}^2 \cdot \text{mol}^{-1}$, Table 7). The limiting conductances from Tables 7 and 8 can be correlated by

$$\ln[\lambda^0(\text{HPenG}^-; T) d_0^{2/3}(T)] = 9.894 - \frac{2063.9}{(T/K)} \quad R^2 = 0.9931$$

$$\ln[\lambda^0(1/2\text{PenG}^{2-}; T) d_0^{2/3}(T)] = 10.691 - \frac{2070.1}{(T/K)} \quad R^2 = 0.9980 \quad (28)$$

where, for both anions, $\Delta H_{\lambda}^\ddagger = 17.2 \text{ kJ} \cdot \text{mol}^{-1}$.

TABLE 9: Coefficients of the Quint–Viallard Conductivity Equations (K–Pen G) for Ion Pairs with HPenG[−] and PenG^{2−}, Dissociation Constants K_1 and K_2 , and Thermodynamic Functions at Different Temperatures T^a

T	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15
Λ_{12}^0	58.35	66.25	75.26	84.39	93.70	102.63	112.48	122.57
S_{12}	48.22	55.77	64.13	72.96	82.14	91.64	101.89	112.47
E_{12}	2.60	2.78	3.14	3.49	3.79	3.99	4.32	4.72
J_{112}	104.21	119.58	137.46	156.37	175.67	195.26	217.04	239.86
J_{212}	136.90	157.25	180.91	205.98	231.61	257.75	286.76	317.18
Λ_{14}^0	71.97	82.39	93.33	104.82	116.50	128.73	141.21	154.48
S_{14}	79.89	92.62	106.45	121.22	136.50	152.69	169.80	187.75
E_{14}	75.55	87.55	100.73	115.00	129.65	145.42	162.13	179.95
J_{114}	53.07	59.48	66.24	74.18	80.80	89.07	96.48	106.98
J_{214}	102.77	116.09	129.84	144.59	158.53	173.70	188.12	204.92
Λ_{23}^0	261.73	288.78	316.39	343.47	370.05	395.53	421.17	445.87
S_{23}	93.51	105.59	118.56	132.03	145.64	159.58	174.20	188.97
E_{23}	46.69	51.54	56.85	62.37	67.56	72.87	78.36	83.86
J_{123}	617	689	767	849	928	1010	1095	1180
J_{223}	1512	1686	1875	2070	2262	2457	2661	2866
Λ_{34}^0	275.35	304.92	334.46	364	393	422	449.90	477.78
S_{34}	144.78	163.97	184.35	206	227	250	273.10	296.98
E_{34}	115.63	127.32	139.64	153	165	177	189.65	202.53
J_{134}	1001	1117	1239	1368	1493	1624	1757	1895
J_{234}	1432	1595	1768	1948	2122	2304	2487	2675
$K_1 10^3$	1.29	1.28	1.28	1.27	1.27	1.28	1.26	1.26
$K_2 10^6$	1.15	1.30	1.35	1.40	1.52	1.80	1.85	1.85
ΔG_1°	15.38	15.68	15.96	16.25	16.53	16.79	17.10	17.38
ΔH_1°	−0.44	−0.43	−0.44	−0.42	−0.41	−0.46	−0.43	−0.43
$T\Delta S_1^\circ$	−15.82	−16.11	−16.39	−16.68	−16.96	−17.25	−17.53	−17.81
ΔG_2°	31.62	31.90	32.38	32.85	33.21	33.48	33.82	34.37
ΔH_2°	10.15	10.04	10.13	10.22	10.19	10.08	10.03	10.19
$T\Delta S_2^\circ$	−21.47	−21.86	−22.25	−22.63	−23.02	−23.40	−23.79	−24.18

^a Units: T , K; K_1 and K_2 , mol·dm^{−3}; ΔG° , ΔH° , $T\Delta S^\circ$, kJ·mol^{−1}; Λ_j^0 , $S_j \times c^{1/2}$, $E_j \times c$, $J_{ij} \times c$, $J_{2j} \times c^{3/2}$, S·cm²·mol^{−1}; $j = 1-4$, 1 – K⁺, 2 – HPenG[−], 3 – H⁺, 4 – PenG^{2−}.

TABLE 10: Coefficients of the Quint–Viallard Conductivity Equations (K–Pen V) for Ion Pairs with HPenG[−] and PenG^{2−}, Dissociation Constants K_1 and K_2 , and Thermodynamic Functions at Different Temperatures T^a

T	278.15	283.15	288.15	293.15	298.15	303.15	308.15	313.15
Λ_{12}^0	57.92	66.28	75.11	84.24	93.60	103.11	113.21	123.30
S_{12}	48.13	55.78	64.10	72.93	82.12	91.76	102.06	112.64
E_{12}	2.51	2.79	3.11	3.46	3.77	4.10	4.50	4.90
J_{112}	103.59	119.63	137.24	156.15	175.52	196.01	218.18	241.02
J_{212}	136.13	157.32	180.64	205.71	231.42	258.67	288.18	318.62
Λ_{14}^0	71.77	82.03	93.11	104.64	117.00	128.56	141.11	153.85
S_{14}	79.79	92.44	106.34	121.12	136.76	152.60	169.75	187.42
E_{14}	75.42	87.32	100.59	114.88	129.98	145.31	162.07	179.51
J_{114}	52.27	58.03	65.35	73.41	82.92	88.32	96.05	104.19
J_{214}	102.10	114.88	129.10	143.96	160.27	173.09	187.78	202.64
Λ_{23}^0	261.30	288.81	316.24	343.32	369.95	396.01	421.90	446.60
S_{23}	93.42	105.60	118.53	132.00	145.62	159.69	174.37	189.15
E_{23}	46.60	51.55	56.82	62.34	67.54	72.98	78.54	84.04
J_{123}	616	689	767	848	928	1011	1096	1182
J_{223}	1509	1686	1874	2069	2261	2460	2665	2870
Λ_{34}^0	275.15	304.56	334.24	363.72	393.35	421.46	449.80	477.15
S_{34}	144.68	163.80	184.25	205.63	227.53	249.70	273.05	296.67
E_{34}	115.45	127.01	139.44	152.48	164.98	177.04	189.55	201.93
J_{134}	1000	1114	1238	1367	1496	1623	1757	1891
J_{234}	1430	1592	1766	1946	2126	2302	2486	2669
$K_1 10^3$	1.30	1.30	1.30	1.30	1.30	1.30	1.30	1.30
$K_2 10^7$	1.10	1.19	1.23	1.30	1.50	1.70	1.95	2.00
ΔG_1°	15.37	15.64	15.92	16.20	16.47	16.75	17.02	17.30
ΔH_1°	−0.44	−0.43	−0.44	−0.42	−0.41	−0.46	−0.43	−0.43
$T\Delta S_1^\circ$	−15.82	−16.11	−16.39	−16.68	−16.96	−17.25	−17.53	−17.81
ΔG_2°	37.05	37.53	38.12	38.64	38.95	39.28	39.58	40.16
ΔH_2°	7.38	9.06	10.91	12.76	14.45	16.23	18.04	20.18
$T\Delta S_2^\circ$	−29.67	−28.47	−27.21	−25.88	−24.50	−23.05	−21.54	−19.97

^a Units: T , K; K_1 and K_2 , mol·dm^{−3}; ΔG° , ΔH° , $T\Delta S^\circ$, kJ·mol^{−1}; Λ_j^0 , $S_j \times c^{1/2}$, $E_j \times c$, $J_{ij} \times c$, $J_{2j} \times c^{3/2}$, S·cm²·mol^{−1}; $j = 1-4$, 1 – K⁺, 2 – HPenG[−], 3 – H⁺, 4 – PenG^{2−}.

3.6. Conductivities of Potassium Penicillin V Salt. Values of the Λ_{exp} and Λ_{calc} are reported in Table 3 and again show a very satisfactory agreement between them. The first dissociation constant K_1 continues to be the same as that for the penicillin G salts, but the second dissociation constant K_2 is 1 order of magnitude smaller (Table 10). Therefore, the speciation

of ions ($\alpha_1 \approx 0.98$ and $\alpha_2 \approx 0.02$, Table 11) is much closer to that of monobasic acid. This is also clear from the fact that the ion pairs (K⁺ + HPenV[−]) and (H⁺ + HPenV[−]) are responsible for 96–97% of the calculated conductivity Λ_{calc} , and the ion pairs (K⁺ + PenV^{2−}) and (H⁺ + PenV^{2−}) for only 3–4%. The lower value of K_2 and its temperature dependence leads to the

TABLE 11: Concentration Fractions α_i and Contributions from Dissociation Steps to the Calculated Conductance Λ_{calc} as a Function of the KHPen V Concentration c at 298.15 K^a

$10^3 \times c$	α_1	α_2	α_H	β	Λ_1	Λ_2
0.824	0.9753	0.0180	0.0114	0.0067	92.12	4.19
1.087	0.9763	0.0166	0.0094	0.0071	91.40	3.82
1.415	0.9768	0.0156	0.0079	0.0077	90.70	3.55
1.820	0.9771	0.0148	0.0066	0.0082	90.03	3.34
2.278	0.9772	0.0142	0.0056	0.0086	89.43	3.18
2.794	0.9773	0.0138	0.0048	0.0090	88.88	3.06
3.393	0.9773	0.0134	0.0041	0.0093	88.36	2.96
4.090	0.9773	0.0131	0.0036	0.0096	87.84	2.88
4.821	0.9773	0.0129	0.0032	0.0098	87.38	2.81
5.615	0.9772	0.0128	0.0028	0.0100	86.94	2.76

^a Units: c , mol·dm⁻³; Λ , S·cm²·mol⁻¹.

parabolic expression for the Gibbs free energy $\Delta G_2^\circ(T)/\text{kJ}\cdot\text{mol}^{-1} = -40.00 + 0.4475(T/\text{K}) - 0.0061(T/\text{K})^2$, $R^2 = 0.9933$. The entropic term dominates the second dissociation step, but the enthalpic term is also important, and similar as that to penicillin G, we have $\Delta G_2^\circ > |-T\Delta S_2^\circ| > \Delta H_2^\circ$.

The limiting conductivities $\lambda^0(\text{HPenV}^-)$ and $\lambda^0(1/2\text{PenV}^{2-})$ (Tables 7 and 8) continue to be very close to those of $\lambda^0(\text{HPenG}^-)$ and $\lambda^0(1/2\text{PenG}^{2-})$, and they can be fitted to

$$\ln[\lambda^0(\text{HPenV}^-; T)d_0^{2/3}(T)] = 10.379 - \frac{2206.3}{(T/\text{K})} \quad R^2 = 0.9955$$

$$\ln[\lambda^0(1/2\text{PenV}^{2-}; T)d_0^{2/3}(T)] = 10.731 - \frac{2083.1}{(T/\text{K})} \quad R^2 = 0.9964 \quad (29)$$

where $\Delta H_\lambda^\ddagger(\text{HPenV}^-) = 18.3 \text{ kJ}\cdot\text{mol}^{-1}$ and $\Delta H_\lambda^\ddagger(1/2\text{PenV}^{2-}) = 17.3 \text{ kJ}\cdot\text{mol}^{-1}$.

4. Conclusions

Systematic determinations of the conductivities of sodium and potassium salts of penicillin G and potassium salt of penicillin V in dilute aqueous solutions over the 278.15–308.15 K temperature range are reported for the first time. It is suggested that the dissociation of the final products of penicillin degradation in acetic media is responsible for the measured conductance and not the hydrolysis of neutral sodium or potassium penicillin salts. This means that the acidic salts of dibasic acids NaHPen G, KHPen G, or KHPen V and not NaPen G, KPen G, or KPen V are actually present in solutions during the conductivity measurements. The observed agreement between the Λ_{exp} and Λ_{calc} values strongly supports the proposed molecular model. However, it is worthwhile to emphasize that the electrical conductivity is an integral property of solutions and alone, without additional support, is insufficient proof that the suggested solution of the problem is not only correct but also unique. What makes the applied model plausible is the fact that the determined dissociation constants K_1 are very close to those reported for various penicillins. It is expected that the limiting mobility of penicillin anions would be very similar because the effect of various side-chain groups in penicillin molecules is rather small. This is actually observed, considering a very small differences in the values of $\lambda^0(\text{HPenG}^-)$, $\lambda^0(\text{HPenV}^-)$, $\lambda^0(1/2\text{PenG}^{2-})$, and $\lambda^0(1/2\text{PenV}^{2-})$ as determined from different salts. In fact, they can be replaced by the average values given in Tables 7 and 8. In addition, the literature-reported kinetic and surface tension investigations are also consistent with the proposed interpretation of the conductivity measurements.

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