[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE ROYAL VETERINARY AND AGRICULTURAL COLLEGE, COPENHAGEN]

The Solubility of Calcium Oxalate in Aqueous Solutions of Urea

BY KAI JULIUS PEDERSEN

It has been found by Grace Medes[1] that the solubility of calcium oxalate in aqueous solutions of urea increases considerably with increasing concentrations of urea. In 0.5 *M* urea a solubility twice as great as in pure water was measured. Knowledge of the influence of urea on the solubility of calcium oxalate is important for the estimation of its solubility in urine, and for the understanding of the conditions for the formation of calcium oxalate stones in the urinary organs. But also from a purely chemical point of view it is of interest to study and explain this surprisingly large effect. With this in mind the solubility of calcium oxalate in solutions of urea was redetermined. In disagreement with the measurements of Medes, it was found that urea has only a small influence on the solubility of calcium oxalate (about 10% increase in 0.5 *M* urea).

Calcium oxalate monohydrate was prepared by the method of Greta Hammarsten.[2] To 1 liter of 0.25 *M* sodium oxalate, containing 5% hydrochloric acid, was added (at room temperature) a small excess of 0.25 *M* calcium chloride. The solutions were prepared from analytical reagents. A few minutes after, the mixing precipitation took place. In order to obtain pure monohydrate, free from higher hydrates, the mixture was first left for two days at 40°, and then the crystals together with 500 cc. of the mother liquor were rotated at room temperature for a week. The crystals were separated by filtration on a glass filter and washed, first with 1% hydrochloric acid, then with water until the filtrate gave no reaction with silver nitrate. The crystals were now rotated for three weeks with water, separated again, washed with water, and finally dried at 40° until their weight remained constant. The crystals had no characteristic shape, but they were so large that they sank to the bottom a few minutes after they had been shaken with the solvent.

Anal. Calcd. for $CaC_2O_4 \cdot H_2O$: C_2O_4, 60.20. Found by titration with permanganate: C_2O_4, 59.86. The preparation contained a trace of chloride; 0.1 g. dissolved in 10 cc. dilute nitric acid and silver nitrate added gave a faint opalescence.

Urea ("Kahlbaum" für wissenschaftliche Zwecke) was used without purification. When the measurements in Table I had been carried out it was found that the urea contained a trace of calcium, sufficient to have an influence on the solubility. 2.6 mg. of ash was found per mole of urea. The ash was dissolved in hydrochloric acid, and calcium precipitated as oxalate and titrated with permanganate. It was found that one mole of urea contained roughly 2×10^{-5} mole of calcium. It was attempted to remove the calcium by recrystallization from alcohol, but after two crystallizations one mole of urea still contained 1.7×10^{-5} mole of calcium. No further attempt to prepare pure urea was made. Instead it was decided to correct the original measurements for the effect of the calcium in the solvent. For this purpose a more accurate estimation of the calcium was necessary, but, unfortunately, all the urea had been recrystallized. Therefore the solubility of calcium oxalate was determined in 1.00 *M* urea, made from another preparation, which contained only 1.0 mg. ash and 0.88×10^{-5} mole of calcium per mole of urea. The solubility in calcium-free 1.00 *M* urea was now calculated from the known amount of calcium by means of the law of the solubility product. It was found that the best agreement between the measurements with the two preparations of urea is obtained when we assume that the first preparation contained 1.66×10^{-5} mole of calcium per mole of urea. This is in fair agreement with the result of the first analysis, 2×10^{-5} mole.

All the solutions were made from redistilled water. The concentrations are expressed in moles per liter of solution.

The saturation with calcium oxalate took place in glass-stoppered bottles whose necks were covered with ground-on glass bells. For each solubility determination three bottles were charged, each with 0.5 g. of calcium oxalate and 300 cc. of the solvent. They were rotated in a water thermostat at 25.0° for two, four, and six hours, respectively. After the rotation the bottle was left quiet in the thermostat for some minutes. Then 250 cc. of the solution was taken out and analyzed. It was sucked from the bottle through a small sintered glass filter into a pipet. The concentrations of oxalate found after two, four, and six hours of rotation always agreed with a reasonable accuracy (±1%). Thus saturation is attained in two hours.

Analysis of the Saturated Solutions.—The problem was to determine a very small concentration of oxalate (about 5×10^{-5} *M*) in the presence of a large concentration of urea (up to 2 *M*). Direct titration with permanganate in the usual way was not possible. More permanganate than corresponding to the oxalate was used. Very satisfactory results, however, were obtained when the method was modified as follows.

To 250 cc. of the solution for analysis (at room temperature) was added 10 cc. of 25% sulfuric acid, 2 cc. of 5% manganous sulfate, and 2.048 cc. of 0.01943 *N* potassium permanganate. After two minutes 1 g. of potassium iodide was added, and finally 5 cc. of 1% starch solution. The iodine set free was titrated with 0.003858 *N* sodium thiosulfate. A blank analysis of 250 cc. of the urea solution without oxalate was carried out in exactly the same way. The concentration of oxalate was calculated from the difference between the volumes of thiosulfate used in the two titrations.

(1) Grace Medes, *Proc. Soc. Exptl. Biol. Med.*, **30**, 281 (1932).

(2) Greta Hammarsten, *Compt. rend. trav. lab. Carlsberg*, **17**, No. 11 (1928).

As a test of the method the following two solutions were prepared and analyzed: (1) 5.03×10^{-5} M sodium oxalate in pure water; (2) 5.03×10^{-5} M sodium oxalate in 2 M urea. 250 cc. of solution 1 used 3.60 cc. of 0.003858 N thiosulfate, while 250 cc. of water used 10.14 cc. Hence we calculate that solution 1 contained 5.05×10^{-5} M oxalate. 250 cc. of solution 2 used 2.76 cc. of thiosulfate, while 250 cc. of 2 M urea used 9.25 cc., from which we calculate 5.01×10^{-5} M oxalate.

For the solubility measurements the method described above was altered slightly. The blank analysis of the solvent was not carried out. Instead 250 cc. of 5.03 M sodium oxalate in the same solvent was prepared by dilution of a standard sodium oxalate solution. It was titrated in the same way as the saturated solution. From the difference between the volumes of thiosulfate used in the two titrations was found how much the solubility is greater than 5.03×10^{-5} M.

The numerical results of the solubility determinations are given in Tables I and II. Table I contains the results obtained with the first preparation of urea, which is assumed to contain 1.66×10^{-5} mole of calcium per mole of urea. The solubility s in the calcium-free solvent is found by means of the equation $s = \sqrt{(s' + 1.66 \times 10^{-5}\,(\text{urea}))\,s'}$, where s' is the solubility measured, and (urea) is the concentration of urea. Table II gives the results of experiments with the second preparation of urea, which by analysis was found to contain 0.88×10^{-5} mole of calcium per mole of urea. In two of the experiments sodium oxalate had been added to the solvent (a M sodium oxalate). s', the apparent solubility, is the oxalate concentration of the saturated solution minus that of the solvent. s' is always the average of three determinations. The solubility in pure 1.00 M urea is found by means of the equation

$$s = \sqrt{(s' + 0.88 \times 10^{-5})\,(s' + a)}$$

In addition to the measurements given in Tables I and II, the following experiments with water as solvent were carried out. 0.5 g. of calcium oxalate was rotated with 300 cc. of water for three hours. The solubility 4.87×10^{-5} was found. Then the same crystals were again rotated with 300 cc. of water for three hours. Now the solubility 4.85×10^{-5} was found. The good agreement between the results shows that the calcium oxalate does not contain any soluble impurity which affects the determination.

The average of the ten determinations of the solubility of calcium oxalate in water in this paper is 4.84×10^{-5}. This value is in good agreement with 4.85×10^{-5} calculated from the conductivity measurements of Kohlrausch.[3]

It is seen from the last two columns of Table I that the increase of the solubility of calcium oxalate is proportional to the concentration of urea. In the last column the fraction $(s - s_0)/s_0$(urea), where s_0 is the solubility in pure water, has been calculated. The average value of the fraction is 0.19. Hence, the solubility of calcium oxalate in solutions of urea at 25.0° may be expressed as follows

$$s = 4.84 \times 10^{-5}\,[1 + 0.19\,(\text{urea})]$$

The influence of urea on the solubility of other sparingly soluble salts has been investigated by the author of this paper. In most cases the fraction $(s - s_0)/s_0$(urea) has a value between 0.18 and 0.20. The experimental data will be given, and the effect discussed, in another publication.

The influence of urea on the solubility of calcium oxalate, found in this paper, is so small that it can have no great importance for the solubility of calcium oxalate in urine, which contains from 0.2 to 0.8 M urea. The effect found in this paper is about ten times as small as that found by Medes.[1] It is possible that the reason for this disagreement is to be found in her method of analysis: 25 cc. of saturated solution was dried and heated in a

(3) F. Kohlrausch, *Z. physik. Chem.*, **64**, 163 (1908); "International Critical Tables," Vol. VI, p. 257.

TABLE I

THE SOLUBILITY s OF CALCIUM OXALATE ($CaC_2O_4 \cdot H_2O$) IN AQUEOUS SOLUTIONS OF UREA AT 25.0°

Calculated from the solubility s' in solutions of urea containing 1.66×10^{-5} mole of calcium per mole of urea. The concentrations are in moles per liter of solution.

(urea)	$s' \times 10^5$ Rot. 2 hours	$s' \times 10^5$ Rot. 4 hours	$s' \times 10^5$ Rot. 6 hours	$s' \times 10^5$ av.	$s \times 10^5$	$\frac{s - s_0}{s_0\,(\text{urea})}$
0.00	4.83	4.82	4.86	4.84	4.84	
	4.79	4.83	4.83			
		4.87	4.85			
.25	4.83	4.87	4.84	4.85	5.06	0.18
.50	4.84	4.87	4.91	4.87	5.27	.18
.75	4.86	4.90	4.93	4.90	5.48	.18
1.00	5.04	5.03	4.99	5.02	5.79	.20
2.00	5.16	5.26	5.26	5.23	6.69	.19

TABLE II

THE SOLUBILITY s OF CALCIUM OXALATE IN 1.00 M UREA AT 25.0°

Calculated from the apparent solubility s' in 1.00 M urea containing 0.88×10^{-5} M calcium ion and a M sodium oxalate.

$a \times 10^5$	$s' \times 10^5$	$s \times 10^5$
0.00	5.31	5.73
0.61	5.03	5.77
1.22	4.70	5.75
		Mean 5.75

platinum crucible. The ash was dissolved in an excess of 0.02 *N* hydrochloric acid and titrated back with 0.02 *N* sodium hydroxide. No blank analysis of the urea was carried out. A small amount of an impurity in the urea may produce the apparent increase in solubility found by Medes.

I wish to thank the head of the laboratory, Professor Niels Bjerrum, for his kind interest in my work.

Summary

The solubility of calcium oxalate at 25.0° in aqueous solutions of urea, from 0 to 2 *M*, may be expressed by the equation

$$s = 4.84 \times 10^{-5} [1 + 0.19 (\text{urea})]$$

where the concentrations are given in moles per liter of solution.

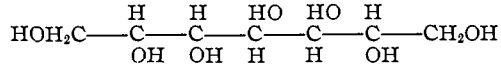
COPENHAGEN, DENMARK RECEIVED OCTOBER 19, 1938

[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Proof of the Structure and Configuration of Perseulose (L-Galaheptulose)[1]

BY RAYMOND M. HANN AND C. S. HUDSON

The polyhydric alcohol perseitol[2] was discovered in the avocado by Avequin[3] and was long regarded as a hexahydric alcohol, isomeric with mannitol. Maquenne[4] first proved that it belonged in the seven carbon series, and shortly thereafter Fischer and Passmore[5] synthesized it by reduction of *d*-α-mannoheptose (D-manno-D-gala-heptose)[6] with sodium amalgam; this synthesis established the configurations of four of the asymmetric carbon atoms (those derived from D-mannose) of perseitol, but that of the fifth remained unknown, because the configuration of carbon 2 of D-manno-D-gala-heptose had not been established. Bertrand[7] discovered that perseitol is oxidized by *Bacterium xylinum* (syn. *Acetobacter xylinum*) to a ketoheptose, which he crystallized and named perseulose; its ketose character was shown by the observations[8] that (1) it was not oxidized by bromine water and (2) its reduction by sodium amalgam generated two alcohols, namely, perseitol and a new alcohol which he named "perséulite" and characterized as having a relatively high levorotatory power of "more than 8° to the left." It was not possible to establish the structure or configuration of perseulose from these data because the configuration of "perséulite" was quite unknown and that of perseitol was known only in part. The next step was made by Peirce[9] when he proved that D-α-galaheptitol (D-gala-L-manno-heptitol) is the enantiomorph of perseitol, from which it follows that the full configuration of perseitol must be (I). The structure and configuration of perseulose remained unknown, however, because the position of its ketone group was still undisclosed. Bertrand's[10] study of the action of *B. xylinum* on numerous polyatomic alcohols led him to the generalization that the oxidation to a ketose, if it occurs, always takes place at a penultimate carbon atom. When La Forge[11] discovered D-mannoheptulose (II) in the avocado and proved its configuration (2-ketoperseitol, if the carbon atoms of (I) are numbered from right to left) and its non-identity with perseulose, he was led by Bertrand's generalization to regard perseulose as probably 6-ketoperseitol (III). If such were the case, perseulose



(I) Perseitol
(D-Manno-D-gala-heptitol or L-Gala-D-manno-heptitol)

(1) Publication authorized by the Surgeon General, U. S. Public Health Service. Presented in part before the Divisions of Organic Chemistry and of Sugar Chemistry and Technology, at the Milwaukee meeting of the American Chemical Society, Sept. 5–9, 1938.

(2) The alcohol was named perséite (from the name of the avocado genus, *Persea*) by Muntz and Marcano [*Ann. chim. phys.*, [3] **6**, 280 (1884)], and no advantage is seen in changing the established English equivalent, perseitol, to persitol (Armstrong and Armstrong, "The Carbohydrates," 5th ed., 1934, p. 146). We also advocate retention of the original name perseulose (assigned by Bertrand, discoverer of the sugar) rather than its replacement by perselose [Isbell, *J. Research Natl. Bur. Standards*, **18**, 513 (1937)].

(3) J. B. Avequin, *Journal de chimie médicale, de pharmacie et de toxicologie*, [1] **7**, 467 (1831); available in the Library of the Surgeon General of the Army, Washington, D. C. Avequin was a pharmacist of Port-au-Prince, Santo Domingo, in 1831; his discovery of perseitol appears to be the first isolation in the Western Hemisphere of a new naturally occurring pure organic substance. A bibliography of Avequin's publications appears in the "Catalogue of Scientific Papers," 1800–1863, published by the Royal Society of London.

(4) Maquenne, *Ann. chim. phys.*, [6] **19**, 5 (1890).

(5) Fischer and Passmore, *Ber.*, **23**, 2231 (1890).

(6) Hudson, THIS JOURNAL, **60**, 1537 (1938).

(7) Bertrand, *Compt. rend.*, **147**, 201 (1908).

(8) Bertrand, *ibid.*, **149**, 225 (1909).

(9) Peirce, *J. Biol. Chem.*, **23**, 327 (1915).

(10) Bertrand, *Compt. rend.*, **126**, 762 (1898).

(11) La Forge, *J. Biol. Chem.*, **28**, 511 (1917).