CXII. THE FORMATION AND DECOMPOSITION OF URATE GELS.

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URIC acid and urates are usually considered relatively insoluble substances. A few observations have been recorded in the literature of remarkably high concentrations of uric acid in the urine and blood of the fowl [Gibbs, 1929], which were beyond the saturation limits as generally accepted [His and Paul, 1900, 1, 2; Gudzent, 1908]. The explanation seemed to be either the existence of uric acid in an unusual form or in the colloidal condition. That uric acid may be prepared in a high concentration that will gel was first demonstrated by Schade and Boden [1913], using the hydroxide of sodium, potassium or lithium. Whether these preparations are colloidal has been the subject of extended debate [Lichtwitz, 1913; Bechhold and Ziegler, 1914; Gudzent, 1914; Kohler, 1919; Schade, 1922; Keeser and Zocher, 1923; Rona and Meyer, 1923; Freundlich and Loeb, 1927; Ettisch, Loeb and Lange, 1927]. The general consensus of opinion is in favour of a portion of such preparations being in the state of colloidal aggregates. Unfortunately previous workers have not concerned themselves for the most part with the determination of the conditions controlling the formation of such gels. These gels represent supersaturated levels of urate concentration. Before attempting a study of the physiological occurrence of such solutions determination of the major variables controlling supersaturation was first attempted. This has led to a study of uric acid gels and their products of crystallisation.

EXPERIMENTAL.

Uric acid from four different manufacturing houses has been tested in the following experiments. All specimens gave rise to the phenomena studied. Three different sources, mammalian, avian and synthetic, are represented. The results of analyses have shown the moisture content to be negligible (0.1 % or less) and the total nitrogen by the Kjeldahl method to be 33.2 to 33.4 %.

The general method of procedure in the preparation of a gel has been to add

a definite weight of solid uric acid to a definite volume of water. To this mixture were added a few drops of indicator. The material was then heated to the desired temperature and alkali added slowly till the uric acid was dissolved. The resulting solution was cooled and tested for its gelation power as described in particular experiments.

Influence of temperature.

In the preparation of a gel we have frequently met with failure due to a heavy precipitate forming before all the uric acid added originally had dissolved. We have interpreted our failure to maintain a clear solution to the disturbing element of boiling in a supersaturated condition. The example of the preparation of a 1 % solution using phenolphthalein and *N*/10 NaOH may be given. At 100° solution may be almost complete but a heavy white crystalline deposit tends to form rapidly. At about 70° the rate of dissolution is too slow because after several minutes the same effect as at 100° is observed. Between 80° and 90° the uric acid dissolves rapidly and forms a typical clear gel on cooling in an ice-bath. These empirical limits have therefore been adopted in gel formation. The higher the concentration of uric acid, the more unstable is the solution.

The degree of cooling is important to the production of gels. The nature and the concentration of the solute are however modifying factors in this generalisation. Furthermore all gels tend to crystallise but at varying rates.

The following experiment will illustrate these points, using concentrations of uric acid which are minimal and maximal for the particular alkali used. The solutions were obtained by suspending solid uric acid in 100 cc. of water and adding normal alkali to complete solution at 90° and to establish a p_H of 7-8 by phenol red. This solution was rapidly divided into eight parts and suspended in water- or ice-baths at the different temperatures recorded. The various times required for gelation are listed in Table I. The limits of concentration are useful approximations from our own experience of those which will form gels. The p_H level used will be explained in the next section. The time of exposure of the preparation to a high temperature and an alkalinity of p_H 8 should be as short as possible because of the decomposition which is known to occur [Austin, 1907].

Table I. *Influence of temperature on gelation.*

The figures express time in minutes required for the formation of gel or precipitate as indicated.

Temperature °C	NaOH				KOH				LiOH			
	1 %		2 %		1 %		2 %		2 %		5 %	
-5	Gel	25	Gel	3	Gel	5	Gel	3	Gel	12	Gel	4
0	Gel	60	Gel	3	Gel	5	Gel	3	Gel	25	Gel	4
10	Ppt.	40	Gel	3	Gel	20	Gel	3	Ppt.	10	Gel	5
20	Ppt.	120	Gel	4	Ppt.	5	Gel	3	Ppt.	30	Gel	10
30	Ppt.	120	Gel	4	Ppt.	5	Gel	4	Ppt.	40	Gel	10
40	Ppt.	120	Gel	5	Ppt.	5	Gel	10	Ppt.	40	Gel	20
50	Ppt.	120	Ppt.	1	Ppt.	5	Ppt.	10	Ppt.	40	Gel	20
60	Ppt.	120	Ppt.	1	Ppt.	5	Ppt.	10	Ppt.	40	Ppt.	20

Several interesting conclusions may be drawn from Table I. The limiting temperature for gel formation is about 40° in the higher concentrations of the three urates. In the lower concentrations it is 0° . If gel formation fails to take place precipitation occurs, denoting a supersaturation at that temperature.

We have also tried ice- and salt-baths at -10° , -15° , -20° , and carbon dioxide snow with ether at -78° . Gels will form, at these temperatures but the solvent tends to freeze more rapidly than the gel will form and consequently they are not as suitable as the simple ice-bath.

Influence of surface.

Gelation has not been found to be influenced appreciably by the nature of the containing surface, whether of glass, silica, porcelain, iron or nickel. In presence of small glass beads or of coarse sand the time of gelation of the solution is much prolonged.

Influence of p_H .

Adopting the optimal temperature for dissolution of uric acid and for gelation we may now outline the results of a variation in the hydrogen ion concentration of our preparations. The determinations of p_H have been made colorimetrically by the use of methyl red, bromocresol purple, phenolphthalein, phenolphthalein and tropaeolin O. The values obtained have been frequently checked electrometrically by the hydrogen-calomel half cell method. The limits of hydrogen ion concentration within which gelation will take place have been determined for minimal and maximal concentrations of the urates of sodium, potassium and lithium. They are only sharp to the extent of about $0.5 p_H$. Sodium urate will gel between p_H 5 and 8.5, potassium urate between p_H 6 and 11.5 and lithium urate between p_H 6 and 12. We have been unsuccessful in our attempts to cause the gelation of sodium urate in the higher ranges of alkalinity possible with both potassium and lithium urate.

There is to be observed in the region of gel formation a shift to the alkaline side to the extent of $1-2 p_H$ units as the solution cools and the gel forms. A single experiment over this range will illustrate the change in a 1 % solution of sodium urate prepared at 80° with N NaOH and cooled in an ice-bath to 0° .

Initial p_H	5.4	6.2	6.8	7.2	8.7
Final p_H	6.6	7.4	8.4	8.6	9.4

These changes have been noted using bromocresol purple, phenol red and phenolphthalein as indicators. The same shift has been observed in solutions of potassium and of lithium urates under the same conditions and to about the same degree. With sodium and potassium urates the gels form rather quickly, frequently before the solution has cooled to the temperature of the ice-bath. This creates a difficulty in separating the change of indicator due to temperature changes from one which might be caused by a reaction in the urate complex. The gels of lithium urate form more slowly and are more suitable for the

observation of this phenomenon. In a 2 % solution the following changes have been observed, using phenol red as indicator.

Temperature	p_H	Physical state
80°	7.2	Clear solution
0°	7.5	Clear solution
0°	8.4	Firm clear gel
0°	8.4	Crystalline deposit

If the clear gel at p_H 8.4 is melted by raising the temperature a reversal of the shift is evident and the original p_H is re-established at 80°. The main shift takes place during the liquefaction of the gel and with a change in temperature of but a few degrees. Thus in the above experiment 8.4 became 7.5 at 5°. It is to be noted that crystallisation does not alter the p_H .

The temperature coefficients of the indicators must first be considered. Kolthoff [1921] has determined the values for p_H displacement between 18° and 70° to be for phenolphthalein — 0.4, phenol red — 0.3, bromocresol purple 0.0. Our temperature range is between 0° and 80° which should therefore increase these figures slightly. The change is accounted for in part on this basis, as has been observed in the case of lithium urate with phenol red as indicator. That it is not essentially a temperature effect can be seen however with bromocresol purple. We have confirmed electrometrically the observation of Kolthoff that this indicator is not affected by changes in temperature. Hydroxyl ions are liberated as the gel forms. An explanation of this phenomenon is offered in the discussion.

Influence of concentration.

Having established optimal conditions of temperature and p_H , we next worked out on pure solutions the limits of concentration which would permit of gel formation. Below the lower limit the solutions remain clear for several hours on cooling to 0°, then slowly deposit crystals. Above the upper limit the solutions deposit dense precipitates before the uric acid can be dissolved completely and hence represent the limits of supersaturation. These limits are for sodium urate 1–2 %, potassium urate 1–2 %, lithium urate 2–5.6 %. The figures are confirmatory of those found by Schade [1922]. The time required for gelation varies inversely with the concentration and is usually 3 to 60 minutes as is shown in Table I. In some dilute solutions of lithium urate it has been observed to require several hours. The presence of electrolytes and non-electrolytes influences the time and concentration required for gelation, as will be shown in a subsequent paper.

In the process of determining the saturation limits as described above we have noted the amount of *N* NaOH used to obtain complete solution of the solid uric acid at different levels of concentration, at the temperature level of 80–90°, and at the point of neutrality. These figures conform at all levels of concentration to the formation of monosodium urate. The same relationship has been found true for lithium and potassium.

Potentiometric titration of uric acid.

Because of the importance of the p_H in the formation of the supersaturated condition and of gels it was thought that potentiometric titration might yield information of interest in the definition of the limits of free uric acid, mono- and di-basic urates. The assembly used was that of Hildebrand with a Weston model 45 voltmeter of 3 volt scale reading to 5 millivolts with an accuracy of 0.5 % by calibration and a Leeds and Northrup pointer galvanometer (No. 2320). We have also used the Cenco-Wendt apparatus with voltmeter scale reading to 10 millivolts. The hydrogen electrode was a modified Hildebrand bell type and it was balanced through an agar bridge by a calomel half-cell containing 1 *N* or saturated KCl. The platinum electrode is poisoned by long contact with the urate solution and it has been our custom to clean the electrode each day by electrolysis in a dilute solution of sulphuric acid and to replatinise frequently.

Fig. 1.

Preparations of uric acid for titration have been made in several ways. Initially a saturated solution was obtained by agitating the solid in water for 30 mins. at 20°. Solutions have also been prepared by boiling uric acid with water, cooling and filtering. Titrations have been carried out at 25° and 50°, using 200 cc. of the solution of uric acid and 0.05 *N* NaOH and LiOH as alkalis. Fig. 1 represents a typical titration. The formation of the monosodium urate is complete at about p_H 6 and the disodium salt does not appear under p_H 8.5. Thus in nearly all the experiments discussed in this paper the monourate is mainly involved. There is a suggestion of the formation of a trisodium urate in the break of the curve at p_H 10.2.

Because of the low concentration of uric acid in the above experiment an endeavour was made to titrate supersaturated solutions by dissolving solid uric acid in water at 90° by adding 0.5 *N* alkali to the point of complete solution. This preparation was then cooled and the titration continued in the usual

way¹. LiOH was used because the urate formed does not tend to precipitate out as does the sodium salt. Fig. 2 represents such a titration. The range of the mono-urate is approximately the same, but the formation of the di-urate does not appear. The upper portion of the curve is unusual, as will be seen in Fig. 3. There are three plateaux occurring definitely at p_H 10.6, 10.8 and

Fig. 2.

Fig. 3.

10.95. As they have been noticed only in high concentrations which are probably colloidal, the phenomenon is interpreted as an adsorption effect.

Using the expression $p_H = -\log K_a$ at mid-point, the dissociation constants of uric acid have been calculated from the curves. $K_{a1} = 8 \times 10^{-6}$ and $K_{a2} = 7 \times 10^{-10}$ as measured in Fig. 1; $K_{a1} = 3 \times 10^{-6}$ from Fig. 2. K_{a3} would be in the vicinity of 6×10^{-11} . These figures agree fairly well with those of Kanitz [1921] who found $K_{a1} = 2 \times 10^{-6}$ and $K_{a2} = 2.6 \times 10^{-9}$ to 8.5×10^{-10} from data of conductivity.

¹ The authors wish to acknowledge their indebtedness to Mr H. C. Graham for this potentiometric titration.

The influence of organic bases in gel formation.

Schade [1922] has observed that ammonium hydroxide will also form gels with uric acid but that these are the least stable of the group. It was thus anticipated that organic bases would also form supersaturated solutions with uric acid which would gel. An extended list of bases from very weak to strong has been tried. The technique was that developed above.

A known weight of solid uric acid was suspended in 50 cc. of distilled water to which were added a few drops of phenol red. To this suspension at a temperature of 80–90° was added slowly with constant stirring the base as solid, liquid or solution to the complete solution of the uric acid if possible. The rate of addition was such as never to allow the solution to become strongly alkaline and the reaction was maintained between p_H 6 and 8, usually at 7. The resulting solution was filtered if necessary and cooled quickly to 0° in an ice-bath.

In these preparations attention has been paid to the amount of base required to dissolve the uric acid, the character and duration of the gel formed and the composition of the crystalline deposit. The results permit of division of the compounds used into three groups as listed in Table II. The members of the

Table II.

Group 1		Group 2		Group 3	
Substance	K_b	Substance	K_b	Substance	K_b
Ammonia	1.8×10^{-5}	Trimethylamine	7.4×10^{-5}	Quinoline	3.2×10^{-10}
Hydroxylamine	—	Tetramethylammonium hydroxide	>1	Semicarbazide	2.7×10^{-11}
Methylamine	5.0×10^{-4}	Diethylamine	1.3×10^{-3}	Caffeine	4.1×10^{-14}
Ethylamine	5.6×10^{-4}	Triethylamine	6.4×10^{-4}	Creatinine	7.0×10^{-10}
<i>n</i> -Propylamine	4.7×10^{-4}	Tetraethylammonium hydroxide	>1	Colchicine	4.5×10^{-13}
<i>n</i> -Butylamine	4.4×10^{-4}	Pyridine	2.3×10^{-9}	Benzidine	1.2×10^{-8}
Dimethylamine	7.4×10^{-4}	Nicotine	7.0×10^{-7}	Phenylhydrazine	1.6×10^{-9}
Hydrazine	3.0×10^{-6}	Ethylenediamine	8.5×10^{-5}		
Coniine	1.3×10^{-3}	Piperidine	1.6×10^{-3}		
<i>p</i> -Phenylenediamine	1.3×10^{-3}	Piperazine	6.4×10^{-5}		
Guanidine	8.0×10^{-5}	Quinine	2.2×10^{-7}		
Hexamethylene-tetramine	2.0×10^{-3}				

first group form gels with varying degrees of ease. The members of the second group possess the power of dissolving uric acid but, under the conditions outlined, do not form gels. The solutions however will gel in the presence of traces of sodium or potassium chloride. The members of the third group neither form gels with uric acid nor aid in its dissolution perceptibly. For the purpose of comparison of basicity the dissociation constants are also listed in Table II. Ammonia is included for comparative purposes and hydroxylamine was tried because it had never been done before. Obviously basicity is an important factor but it does not account for the different behaviour of groups 1 and 2, nor for the various stabilities of the gels formed. The behaviour of ethylamine preparations is interesting in that an initial cloudiness appears on chilling the solution, which may clear with the formation of a perfectly clear gel which is ultramicroscopically empty, or which may give rise to an opalescent solution, microscopically clear but ultramicroscopically filled with submicrons.

The inability of the powerful quaternary bases to form gels without the presence of electrolyte is noteworthy. Hexamethylenetetramine differs from other bases in several respects. It forms a clear or slightly opalescent, very stable gel which does not crystallise. Gels have been kept for several months at 20° and would seem to keep indefinitely. The temperature of preparation is optimal at 100°. Gels will form almost up to this temperature. They can be melted and solidified repeatedly without precipitation. At 100° there is hydrolytic decomposition of the amine with the liberation of ammonia and formaldehyde. Both compounds have the power to dissolve uric acid at this temperature by chemical action. We have tried to effect gel formation under the adopted conditions with these substances separately and combined without success. Ammonia will form gels only in lower concentrations of urate and the latter precipitates out very readily. Formaldehyde has its characteristic solvent action but the solution will not gel. Moreover the proportion of amine used to the uric acid dissolved is well below that at which either decomposition product will act.

We have found that in the cases of sodium, potassium and lithium hydroxides the ratio is approximately 1 : 1 for the point of complete dissolution of uric acid. Apart from the main reaction involved, this point depends, to a variable extent, upon a number of physical factors, such as rate of addition and volatility of the base, amount of stirring, p_H , etc., and the end-point is not a sharp one. The ratio for the amines forming gels will be found in Table III.

Table III. *Molecular ratio for dissolution.*

Base	Amount		Remarks
	Calculated g.	Required g.	
Methylamine	0.092	0.106	As hydrochloride
Ethylamine	0.134	0.160	As 33 % solution
Propylamine	0.176	0.208	As liquid amine
Butylamine	0.220	0.237	As liquid amine
Guanidine	0.175	0.183	As carbonate
Coniine	0.378	0.387	As hydrochloride
Hydrazine	0.095	0.105	As sulphate
Hexamethylenetetramine	0.417	0.424	As solid base
Hydroxylamine	0.049	0.349	As hydrochloride

The calculated values are based on the molar ratio of 1 : 1. The experimental values are those observed, converted into terms of free base. As might be expected, the required amounts are in all cases slightly higher than the theoretical. The value for *p*-phenylenediamine is not included because of the simultaneous reaction of oxidation. In the case of hexamethylenetetramine the values obtained vary greatly, but the smaller the amount of uric acid used, the nearer to the theoretical does the amount of the amine become in the same volume of solvent. The simultaneous reaction of hydrolysis of the amine is involved here to a variable extent along with two secondary reactions as described above. An exception to the agreement in Table III is hydroxylamine.

The instability of this compound at high temperature is the probable explanation.

Most of the members of the second group require an excess of the base over the 1 : 1 ratio to produce complete solution of the uric acid.

In general it is concluded that uric acid goes into solution at 80–90° in stoichiometrical proportions with the base used as mono-urate.

Composition of crystalline deposits.

The gels formed by using organic bases crystallise at very different rates, from one or two minutes, as in the case of pyridine and quinine, to days or weeks, as with coniine, nicotine, guanidine, piperidine and piperazine. Gels of hexamethylenetetramine have never crystallised spontaneously. The nature of the crystals from the various gels was next investigated. It was hoped to determine thereby whether any chemical reaction was involved in the destruction of the gel. Only the substances of group 1 have been analysed.

The products which resulted from the crystallisation of the gels were filtered off after the process was complete, washed with small quantities of water, alcohol and ether. They were dried first in a desiccator at 20° over calcium chloride and finally in an oven at 105°. The nitrogen values were estimated by the Kjeldahl-Gunning procedure. Complete combustions were not considered necessary because of the limited possibilities of combination and the purity of the products initially.

Table IV. *Elementary composition of crystalline deposits.*

Substance	Nitrogen		Compound ratio	Solution ratio
	Determined %	Calculated %		
Methylamine	34.6	34.3	1 : 2	1 : 1
Ethylamine	33.3	33.2	1 : 2 (?)	1 : 1
Propylamine	31.9	31.9	1 : 2	1 : 1
Butylamine	30.8	30.6	1 : 2	1 : 1
Guanidine	39.2	39.0	1 : 2	1 : 1
Coniine	27.1	27.3	1 : 2	1 : 1
Hydroxylamine	26.9	27.1	1 : 2	7 : 1
Hexamethylenetetramine	35.0	35.3	1 : 2 (?)	1 : 1
Hydrazine	27.2	—	—	1 : 1

Table IV summarises the results of the nitrogen analyses and compares these figures with the calculated values on the molar ratio nearest to them. In all cases except one the proportion is 1 mol. of base to 2 of uric acid. In the case of ethylamine the figure obtained is consistent with such a proportion but the accuracy of the method is not sufficient to permit of the definite separation from other possible combinations. The hexamethylenetetramine complex is inconstant in its composition. Since the gel did not crystallise it became necessary to obtain the complex by precipitation. This has been accomplished by pouring the warm viscous solution into an excess of ethyl alcohol (95 %) or acetone. Six such preparations yielded nitrogen analyses consistent in themselves but ranging from 30.15 to 37.52 %. Certain preparations have given

figures agreeing with the ratio of 1 : 2 as listed in the table however. Hydrazine furnishes a complete exception in that the product does not yield a figure for nitrogen to be related with any ordinary combination.

Solubility of crystalline deposits.

Because of the very high values obtained for the saturation limit at a temperature of 90°, as shown in Table V for several organic bases, it was considered of interest in certain cases to determine the solubility at 20°. Two

Table V.

Base	Solubility		
	90°	20°	
	%	Trituration %	Supersaturation %
Methylamine	10	0.15	2.38
Ethylamine	8	0.28	1.69
Propylamine	10	1.54	2.88
Butylamine	8	1.47	3.79
Guanidine	1	0.50	0.90
Piperazine	7	0.57	1.41
Piperidine	20	6.65	5.41

methods have been used in obtaining these values, (a) the usual trituration for 15–20 minutes and evaporation of an aliquot portion of solution, (b) saturation at 40° and cooling at 20° with adequate time allowance for the establishment of equilibrium. The first method yields results considerably lower than the second. The values of the latter tend to be inconstant and to suggest supersaturation with the formation of colloidal aggregates even at low temperatures. This is substantiated by the impossibility of dissolving residues in their original volume of solvent, and the long time required in reaching constant concentrations. By both methods there is always a tendency for the formation of opalescent solutions. Table V illustrates these discrepancies.

The behaviour of the hexamethylenetetramine complex is worthy of note in solubility measurements. It has been found that the degree of solubility depends upon the amount of desiccation to which the urate complex has been subjected. Thus the fresh precipitate is soluble in water to the extent of 0.743 %; if dried for 36 hours in a vacuum, 0.204 %; and if dried completely at 105°, 0.154 %. This phenomenon has also been observed in the case of sodium urate. It is very similar to the behaviour of many proteins.

DISCUSSION.

Apart from the main problem under discussion, a point of interest is the evidence from the experimental details as to the existence of these urates in a colloidal state. In this communication we are not concerned with the attempt to prove or disprove the colloidal nature of our preparations. The instability of high concentrations of urates at 100° is indicative of molecular supersaturation rather than the colloidal condition, particularly since this characteristic

increases with rising concentration to an indefinite limit. The tendency of urates to form supersaturated solutions has been confirmed [His and Paul, 1900, 2] and demonstrated for numerous organic bases. Temperature is an important factor. Indefinite limits of solubility, as noted by earlier workers, [Gudzent, 1908; 1909, 1, 2; His and Paul, 1900, 2], for the alkali urates have also been observed in these cases. The stability of these supersaturated solutions is noteworthy and suggestive of colloidal aggregation. The degree of cooling is important to the formation of the gel. With increasing concentration this factor becomes less important. It is interesting that the temperature of 40° is the upper limit of gel formation. The gel condition inhibits crystallisation for a variable interval of time but appears to be a transitional stage between the condition of supersaturation and the formation of urate crystals.

From the facts which have been presented above we believe that it is possible to suggest an explanation of the phenomenon of gelation in solutions of urates. At elevated temperatures uric acid is dissolved in unimolecular ratio by substances of a basic nature possessing $K_b \leq 10^{-8}$. These aqueous solutions are capable of a high degree of supersaturation at elevated temperatures and the urates may be said to exist in them in true molecular dispersion so far as is known. These supersaturated solutions become gels on cooling within certain individual limits of concentration, this change being accompanied by a shift of the reaction of the medium to the alkaline side of the original p_H and the gels crystallise. The time required for the crystallisation of the gel is a characteristic of the particular base used. The composition of the crystalline products represents a ratio of two molecules of uric acid to one of base. We may therefore have the following reactions under the conditions specified, taking methylamine as example

The acid urate complex is deposited and the amine liberated causes an increase in the basicity of the solution. As has been shown previously, the degree of change is dependent upon the strength of base and the concentration of urate. In all cases the shift is evident during the formation of the gel, and the subsequent crystallisation does not alter the p_H materially. This observation points to the gel being an acid urate rather than the mono-urate and again raises the question of existence of the so-called quadri-urate. Whether or not we are concerned with a true molecular complex, or with the phenomenon of mixed crystals [Ringer and Schmutzer, 1912], or with a solid solution of uric acid in urate [Kohler, 1911], cannot be decided from our experiments. It is significant however that such a variety of urates formed with organic bases should all show the same phenomenon. It is also of importance that this is the type of complex deposited from supersaturated solutions at a p_H of about 7.

In explanation of the fact that two groups of substances exist, the one forming more or less transitory gels with uric acid and the other tending to

crystallise without gel formation, we would recall a paper by Haber [1922]. By a study of solidification from a supersaturated condition using X-ray interference fringes two processes are distinguishable, the formation of unarranged molecular aggregates as amorphous masses and the rearrangement to form crystals depending on the formation of nuclei. These two processes are opposed to one another. Thus if the rate of aggregation is fast, amorphous precipitates result which gradually turn crystalline. If the rate of aggregation is slow as in slight supersaturation, the formation of nuclei may be sufficiently rapid for only crystals to appear. These two processes are evident in our studies, with the modification that the aggregate may appear as a gel in place of an amorphous precipitate. Our first group of urates may be said to aggregate rapidly forming gels, while the second crystallises rapidly and hence does not gel. That the structure of lithium urate gel is non-crystalline has been claimed by Keeser and Zocher [1923] from X-ray analysis. Thus in passing from a supersaturated solution of the mono-urate in molecular dispersion at high temperature a chemical reaction ensues and the particles of acid urate so formed associate in the process of cooling in such a way as to form a gel. How then does this happen?

Haber has further found that the presence of electrical charges on the surface of the original particles modifies the rate of aggregation. An explanation of this behaviour and of gel formation under the conditions of our experiments has been suggested by Usher [1929], who has shown that the presence of an electrolyte such as sodium chloride causes gel formation in gamboge suspensions if in sufficient concentration. The explanation offered is the reduction of the ionic field around the particle under the influence of the electrolyte, so that collisions result in the linear aggregation of particles. These form eventually a mesh-work which is a gel. Usher further states that "a gel is therefore to be regarded as an intermediate stage in the formation of a precipitate. . . ." His photomicrographs are remarkably similar to pictures which we have seen ourselves at times under the microscope with gelatinous precipitates of urate. This would tend to explain urate gels on the micellar theory as a separation of the disperse phase in the form of interlacing fibrils associated with some of the solvent and enclosing the remaining solution enmeshed in the network so produced. Our preparations of gels are optically clear under the ultramicroscope.

The behaviour of urate gels as recorded at present would relate them to the class of colloidal electrolytes such as the soaps as studied by McBain and his co-workers, and such other gel-forming compounds as quinine, eucupine and optochine [Thomas and Sibi, 1929], dibenzoylcystine [Gortner and Hoffman, 1921], benzoyltyrosine, and sorbitol benzoacetal [Thomas and Sibi, 1930].

SUMMARY.

A study has been made of the conditions governing the formation of supersaturated solutions of urates, their gelation and crystallisation. The hydroxides of sodium, potassium, lithium and numerous organic bases have been used to form the urates in unimolecular ratio.

The optimal temperature for supersaturation was found to be 80–90°. The degree of cooling required to produce gelation varied with the concentration of urate between 0° and 40°. The limiting concentrations for gel formation have been determined for the different urates. p_H is an important factor and is limited to 6–8. A shift to the basic side is observable in the formation of gels. The limiting values of p_H relating free acid, mono- and di-urates have been determined by potentiometric titration. The dissociation constants for uric acid have been calculated to be $K_{a1} = 8 \times 10^{-6}$, $K_{a2} = 7 \times 10^{-10}$ and a possible $K_{a3} = 6 \times 10^{-11}$.

The organic bases may be divided into three groups, the first forming gels with uric acid spontaneously, while the second do so only in the presence of certain electrolytes, and the third not at all.

The gels crystallise, with one exception, in the course of a few minutes to several weeks, depending on the nature of the base and the concentration of uric acid used. The crystalline deposits reveal on analysis an acid urate complex consisting of two molecules of acid and one of base.

A hypothesis is advanced in explanation of the phenomenon of gelation and crystallisation in urate solutions.

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