Office de la Propriété Intellectuelle du Canada
Un organisme d'Industrie Canada

Canadian Intellectual Property Office
An agency of Industry Canada

CA 2230774 C 2007/06/26

(11)(21) 2 230 774

(12) BREVET CANADIEN
CANADIAN PATENT

(13) C

(22) Date de dépôt/Filing Date: 1998/03/02

(41) Mise à la disp. pub./Open to Public Insp.: 1998/09/18

(45) Date de délivrance/Issue Date: 2007/06/26

(30) Priorité/Priority: 1997/03/18 (EP97104554.7)

(51) Cl.Int./Int.Cl. *C07F 9/655* (2006.01)

(72) Inventeurs/Inventors:
DLUBALA, ALAIN, FR;
NOSBERGER, PAUL, CH

(73) Propriétaire/Owner:
DSM IP ASSETS B.V., NL

(74) Agent: GOWLING LAFLEUR HENDERSON LLP

(54) Titre : FABRICATION DE MONOPHOSPHATES D'ASCORBYLE
(54) Title: MANUFACTURE OF ASCORBYL MONOPHOSPHATES

(57) Abrégé/Abstract:
A process for the manufacture of alkali metal and alkaline earth metal salts of L-ascorbic acid 2-monophosphate comprises reacting a L-ascorbic acid 2-polyphosphate under alkaline conditions with an alkali metal or alkaline earth metal salt of L-ascorbic acid in concentrated aqueous solution, the amounts of the L-ascorbic acid salt and the alkaline earth metal hydroxide used as the base being arranged such that pH value of the reaction medium is held in the range of about 8 to about 11 and a stepwise transfer of in each case one phosphate group from the polyphosphate to the L-ascorbic acid salt takes place until essentially the polyphosphate has been consumed and only L-ascorbic acid 2-monophosphate salt is present. Preferably, the L-ascorbic acid 2-polyphosphate is produced in situ and calcium hydroxide is used as the base. Independently of whether the L-ascorbic acid 2-polyphosphate is produced separately or in situ, sodium trimetaphosphate is preferably used as the phosphorylating agent. A further aspect of the present invention comprises spray drying the mixture obtained after completion of the reaction, cooling and dilution to a suitable viscosity. The product of the process according to the invention is suitable as an additive for human and animal foodstuffs; it is especially stable against oxidative and thermal degradation and has an especially high content of L-ascorbic acid monophosphate vis-à-vis polyphosphates and is accordingly primarily of use preferably for the nutritional enrichment of fish feed.

RAN 4226/106

Abstract

A process for the manufacture of alkali metal and alkaline earth metal salts of L-ascorbic acid 2-monophosphate comprises reacting a L-ascorbic acid 2-polyphosphate under alkaline conditions with an alkali metal or alkaline earth metal salt of L-ascorbic acid in concentrated aqueous solution, the amounts of the L-ascorbic acid salt and the alkaline earth metal hydroxide used as the base being arranged such that pH value of the reaction medium is held in the range of about 8 to about 11 and a stepwise transfer of in each case one phosphate group from the polyphosphate to the L-ascorbic acid salt takes place until essentially the polyphosphate has been consumed and only L-ascorbic acid 2-monophosphate salt is present. Preferably, the L-ascorbic acid 2-polyphosphate is produced in situ and calcium hydroxide is used as the base. Independently of whether the L-ascorbic acid 2-polyphosphate is produced separately or in situ, sodium trimetaphosphate is preferably used as the phosphorylating agent. A further aspect of the present invention comprises spray drying the mixture obtained after completion of the reaction, cooling and dilution to a suitable viscosity. The product of the process according to the invention is suitable as an additive for human and animal foodstuffs; it is especially stable against oxidative and thermal degradation and has an especially high content of L-ascorbic acid monophosphate vis-à-vis polyphosphates and is accordingly primarily of use preferably for the nutritional enrichment of fish feed.

Ref. 13'736

The present invention is concerned with a novel process for the manufacture of alkali metal and alkaline earth metal salts of L-ascorbic acid 2-monophosphate starting from a L-ascorbic acid salt, a L-ascorbic acid 2-polyphosphate and an alkaline earth metal hydroxide as the base.

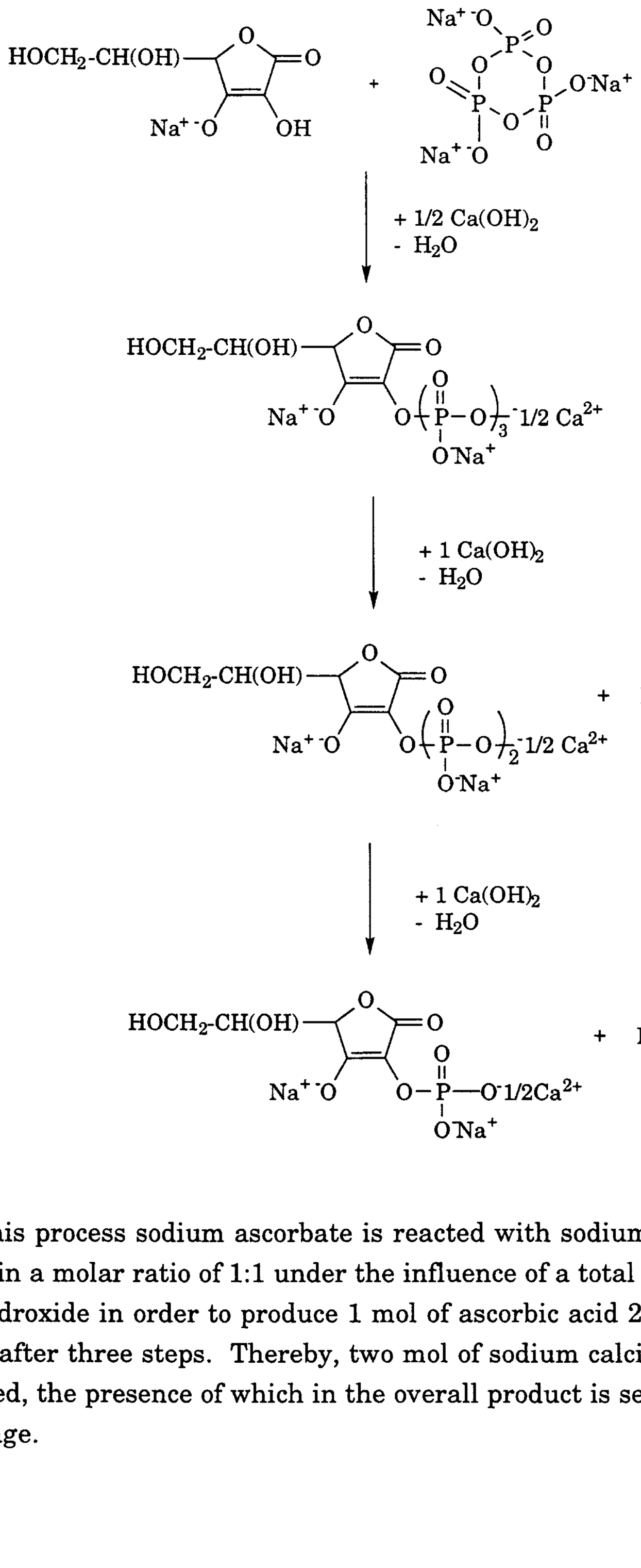
As is known, ascorbic acid (vitamin C) and its salts are used as additives for human and animal foodstuffs. However, ascorbic acid itself is temperature- and oxidation-sensitive and is decomposed to a considerable extent, for example, in the production and storage of enriched fish feed and is thus lost. The ascorbic acid phosphates in particular are, as is known, forms of ascorbic acid which are protected against oxidative and thermal degradation and are accordingly and primarily used for the nutritional enrichment of fish feed. With the use of ascorbic acid phosphates, which are substantially more stable than ascorbic acid, the problem of decomposition is almost completely eliminated and the ascorbic acid, which is active, for example, against scurvy in fish and crabs, is liberated in the host organism by the action of the enzyme phosphatase.

Two fundamentally different processes have hither to been of significance for the phosphorylation of ascorbic acid, namely phosphorylation using phosphorus oxychloride (as described, for example, in European Patent Publications 388,869 and 582,924 as well as in US Patent 4,179,445) and phosphorylation using polyphosphates, e.g. sodium trimetaphosphate (see, for example, US Patents 4,647,672 and 5,110,950), with a L-ascorbic acid salt being phosphorylated under basic conditions in both cases. The first process yields ascorbic acid 2-monophosphate as the main product and as byproducts mainly ascorbic acid 3-phosphate and 2-pyrophosphate as well as bis(ascorbic acid)-2,2'-diphosphate [see C.H. Lee et al., Carbohydrate Res. 67, 127-138 (1971)]. The reaction products require complicated purification and cannot be converted in a simple manner, e.g. by spray drying of the entire reaction mixture, into a product which can be commercialised directly. For these reasons phosphorylation using phosphorus oxychloride is a process which has little attraction economically and ecologically. The alternative process, i.e. phosphorylation using polyphosphates, yields ascorbic acid 2-polyphosphate as the primary product, for example ascorbic acid 2-

Pa/So 5.1.98

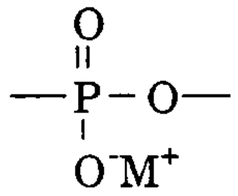
triphosphate when sodium trimetaphosphate is used. The ascorbic acid 2-polyphosphates can be degraded to the monphosphate by an excess of base. The ratio of ascorbic acid 2-monophosphate to ascorbic acid 2-diphosphate and higher phosphates is influenced by the amount of base which is used and the other reaction conditions. A disadvantage of this process is that a very large amount of phosphorylating agent, e.g. at least 1 mol of sodium trimetaphosphate per mol of ascorbic acid, is required. Moreover, when the product should contain relatively little ascorbic acid polyphosphates and more ascorbic acid 2-monophosphate, a large amount of base, e.g. calcium hydroxide, must be used. Accordingly, the product contains a large amount of inorganic phosphates; the content of ascorbic acid equivalents in a dried product amounts to a maximum of about 25 weight percent. The course of the process described in US Patent 5,110,950, insofar as it is used for the manufacture of the monophosphate, will be evident from Reaction Scheme 1 hereinafter in which, for the purpose of a clear and simple presentation, sodium ascorbate, sodium trimetaphosphate (the preferred phosphorylating agent) and calcium hydroxide (base) are used:

Reaction Scheme 1



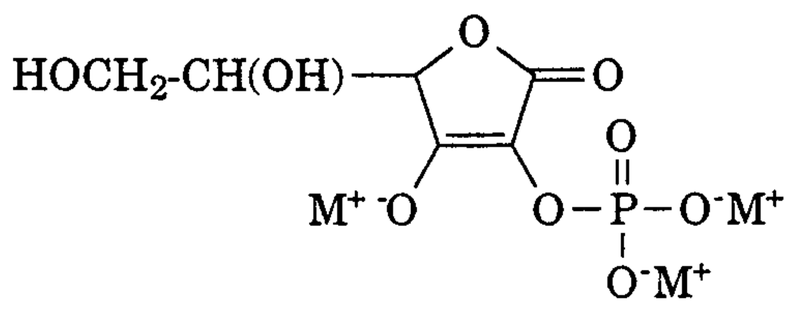
In this process sodium ascorbate is reacted with sodium trimetaphosphate in a molar ratio of 1:1 under the influence of a total of 2.5 mol of calcium hydroxide in order to produce 1 mol of ascorbic acid 2-monophosphate after three steps. Thereby, two mol of sodium calcium phosphate are liberated, the presence of which in the overall product is seen to be a disadvantage.

It has now been found that by using polyphosphate phosphorylating agents, e.g. sodium trimetaphosphate, also mainly alkali metal and alkaline earth metal salts of L-ascorbic acid 2-monophosphate can be manufactured when the initially formed L-ascorbic acid 2-polyphosphate is reacted under specific alkaline conditions with a concentrated solution of an alkali metal or alkaline earth metal salt of L-ascorbic acid, whereby in each case a stepwise transfer of one phosphate group



from the polyphosphate to the L-ascorbic acid salt takes place in the course of the reaction until essentially the polyphosphate has been used up and only L-ascorbic acid 2-monophosphate salt is present. By this means the required amounts of phosphorylating agent and base can be drastically reduced and the major disadvantages of the known processes can be eliminated.

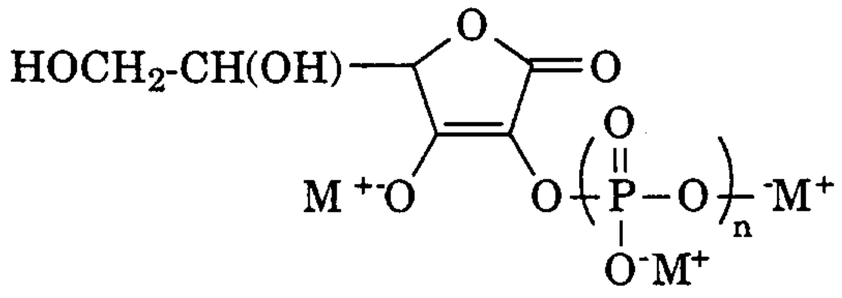
The process in accordance with the invention for the manufacture of alkali metal and alkaline earth metal salts of L-ascorbic acid 2-monophosphate of the general formula



I

wherein each M^+ signifies an alkali metal ion or the equivalent of an alkaline earth metal ion,

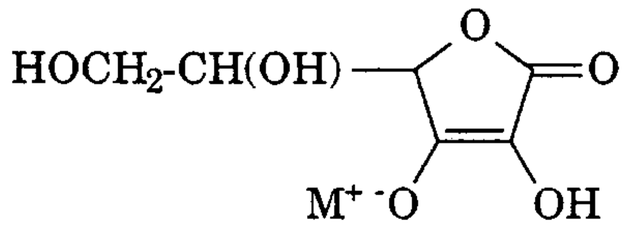
comprises reacting a L-ascorbic acid 2-polyphosphate of the general formula



II

wherein M^+ has the significance given above and n signifies a whole number from 2,

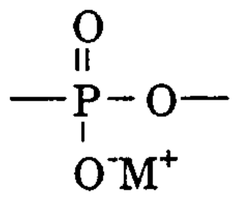
under alkaline conditions with an alkali metal or alkaline earth metal salt of L-ascorbic acid of the general formula



III

wherein M^+ has the significance given above,

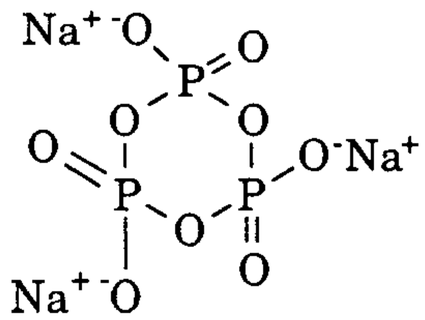
in concentrated aqueous solution, the amounts of the L-ascorbic acid salt of formula III and the alkaline earth metal hydroxide used as the base being arranged such that the pH value of the reaction medium is held in the range of about 8 to about 11 and a stepwise transfer of in each case one phosphate group



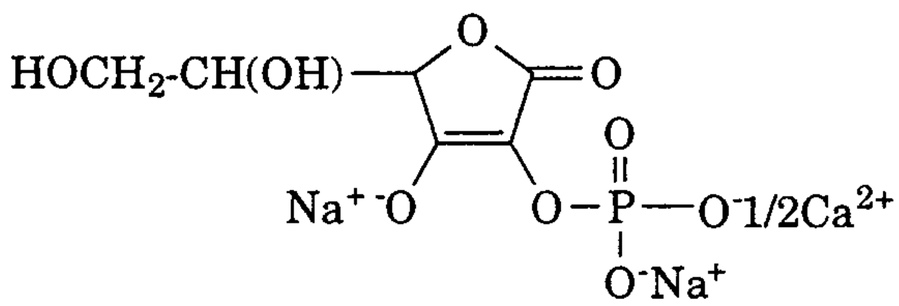
from the polyphosphate of formula II to the L-ascorbic acid salt of formula III takes place until essentially the polyphosphate has been consumed and only L-ascorbic acid 2-monophosphate salt of formula I is present.

In the scope of the above definition there is to be understood under the term "alkali metal ion" especially a sodium or potassium ion, preferably a sodium ion. The alkaline earth metal ion is especially a calcium ion or a magnesium ion, the former being preferred. In this case and taking into consideration its divalency, the alkaline earth metal ion is represented in each case as a half ion, so that, for example, a calcium ion M^+ in formula I, II or III is in this sense presented as 1/2 Ca^{2+}. Although the ions M^+ in formulae I, II and III can be the same or different, the individual meanings depend on the nature of the L-ascorbic acid salt of formula III used for the production of the polyphosphate of formula II and of the phosphorylating agent as well as on the nature of the alkaline base which is used, whereby, inter alia, ion exchange also plays a rôle. Suitably, the same base used for the production of the polyphosphate is used as the base in the process in accordance with the invention. This can be illustrated on the basis of an example: when the sodium salt of L-ascorbic acid (of formula III in which M^+ signifies Na^+) is used, sodium trimetaphosphate of the formula

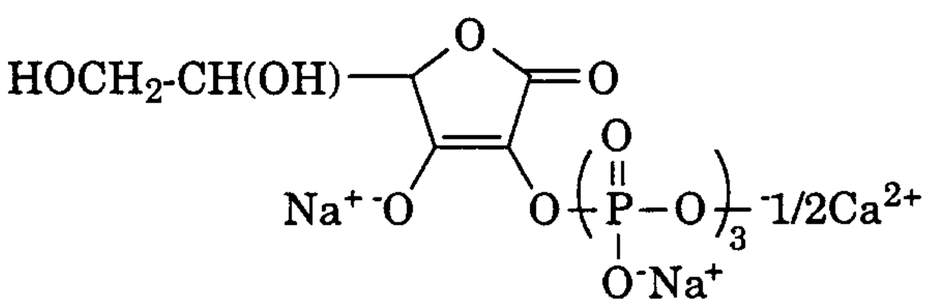
6



is used as the phosphorylating agent and calcium hydroxide [$Ca(OH)_2$] is used as the base (all preferred reactants), formulae I, II and III can be represented, inter alia and simply, as follows:

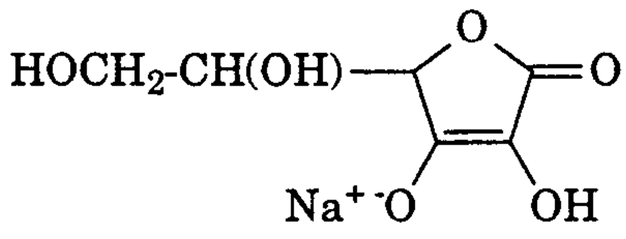


I'



II'

and, respectively,



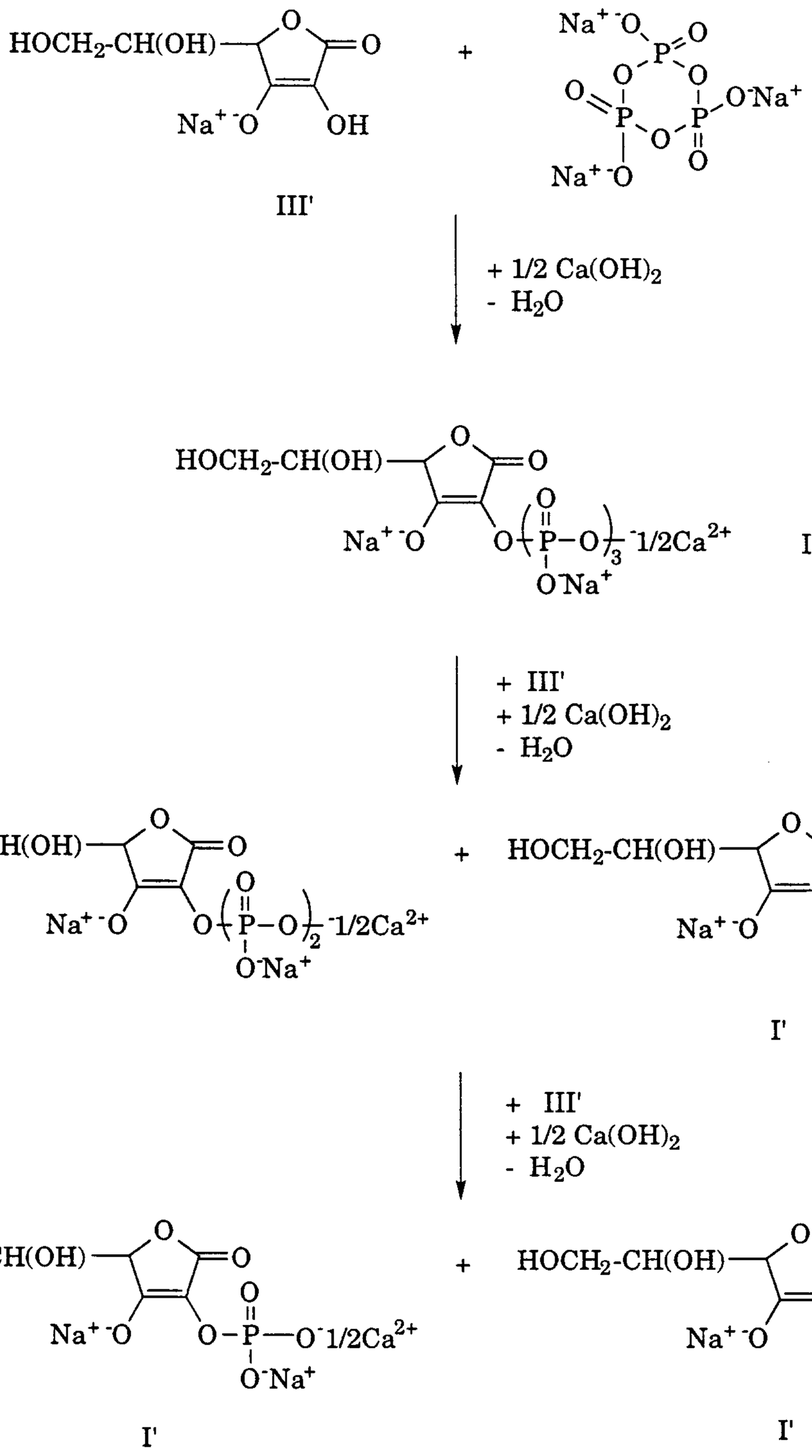
III'

From this it will be evident that n is also dependent on the nature of the phosphorylating agent: for example, n signifies 3 when sodium trimetaphosphate is used as the phosphorylating agent and signifies 6 when sodium hexametaphosphate is used for this purpose. Furthermore, it has to be borne in mind that the product of formula I or I' unavoidably occurs as a mixture of different alkali metal and alkaline earth metal salts of L-ascorbic acid 2-monophosphate and can never be represented by a single formula I.

The course of the process in accordance with the invention will be evident from Reaction Scheme 2 hereinafter in which, for the purpose of a clear and simplified presentation, L-ascorbic acid sodium salt of formula III' is used, sodium trimetaphosphate is used as the phosphorylating agent (for the production of L-ascorbic acid 2-polyphosphate of formula II') and

calcium hydroxide is used as the base; there is thus manufactured a L-ascorbic acid 2-monophosphate which features, inter alia, molecules of formula I':

Reaction Scheme 2



III'

II'

I'

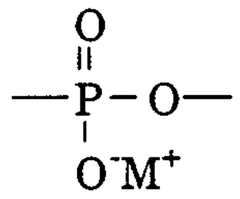
I'

I'

The production of the L-ascorbic acid 2-polyphosphate of formula II can be effected in advance (separately) or in situ, preferably in situ. Starting

from a L-ascorbic acid 2-polyphosphate of formula II, produced separately or in situ, the molar ratio of L-ascorbic acid salt of formula III to L-ascorbic acid 2-polyphosphate of formula II conveniently amounts to about n-1:1, the deviation from this ratio preferably not amounting to more than about 30%.

Where it is desired to produce the L-ascorbic acid 2-polyphosphate of formula II separately, this can be effected in a manner known per se, conveniently according to the method described in US Patent 5,110,950. The reaction product can be isolated (evaporation) or used immediately as an aqueous solution for the further reaction (with the L-ascorbic acid salt of formula III). The preferred phosphorylating agent for the separate (and also for the in situ) production of the L-ascorbic acid 2-polyphosphate is sodium trimetaphosphate, this polyphosphate having three phosphate groups



in the molecule (n = 3). Higher metaphosphates, e.g. the sodium hexametaphosphate mentioned above, or polyphosphoric acid can, in principal also be used.

With respect to the in situ production of the L-ascorbic acid 2-polyphosphate, the phosphorylating agent is conveniently added to the concentrated solution of the L-ascorbic acid salt. The phosphorylating agent, e.g. sodium trimetaphosphate, can be added, for example, as an aqueous solution or as a solid, the latter method of addition being preferred. Conveniently, the addition of the base, e.g. calcium hydroxide, is also effected either separately or in a mixture with the phosphorylating agent. The simultaneous addition of the phosphorylating agent and the base, especially by the addition of a mixture of the two, is preferred.

In the manufacture of L-ascorbic acid 2-monophosphate itself, the manner in which the individual reactants are added is of particular significance. The L-ascorbic acid salt of formula III must always be present in the reaction medium in an excess vis-à-vis the L-ascorbic acid 2-polyphosphate. This is achieved, for example, by firstly preparing an aqueous solution of the L-ascorbic acid salt which is as concentrated as possible

(virtually saturated), conveniently by treatment of a concentrated aqueous solution of ascorbic acid with alkali hydroxide, e.g. sodium hydroxide. Then addition of the (separately produced) L-ascorbic acid 2-polyphosphate or the phosphorylating agent (for the in situ production of this polyphosphate), e.g. sodium trimetaphosphate, as well as base, e.g. calcium hydroxide, to the concentrated aqueous solution of the L-ascorbic acid salt is spread over the entire reaction period such that the L-ascorbic acid 2-polyphosphate (optionally produced in situ) and the L-ascorbic acid salt react immediately with one another under the prevailing alkaline conditions. In this case, the pH value must be held within the range of about 8 to about 11 by the addition of the base. Since the reaction medium should be as concentrated as possible, in the case of the in situ production of the L-ascorbic acid 2-polyphosphate the phosphorylating agent and the base are advantageously added as solids. The pH value can be adjusted continuously by appropriate dosage of the base, even when this is in admixture with the phosphorylating agent, namely by periodically fixing the ratio of phosphorylating agent to base. Moreover, the velocity of the addition of phosphorylating agent and base should be adjusted such that no L-ascorbic acid 2-polyphosphate precipitates; the reaction is accordingly carried out in such a manner that the polyphosphate reacts further as rapidly as possible with the L-ascorbic acid salt via the (in each case) less polyphosphorylated L-ascorbic acid salt, e.g. the L-ascorbic acid 2-diphosphate, to give the L-ascorbic acid 2-monophosphate. In practice, for this purpose the phosphorylating agent is added rather rapidly at the beginning and rather slowly towards the end of the reaction. Moreover, it is recommended to guarantee a good intermixing of the reactants in order that the added solid starting materials are brought rapidly into an intensive contact with the liquid reaction medium.

The L-ascorbic acid salt used in the process in accordance with the invention is preferably an alkali metal salt, especially the sodium salt (III = III'), since such salts are especially water-soluble. Alkali metal salts of ascorbic acid can be obtained, for example, in advance by lactonization of 2-keto-L-gulonic acid esters, e.g. methyl 2-keto-L-gulonate, with sodium bicarbonate, sodium carbonate or sodium hydroxide. In each case there is produced an aqueous solution of the salt, preferably a solution which is almost saturated at the reaction temperature.

In order to adjust the pH value within the range of about 8 to about 11, in the case of the in situ production of the L-ascorbic acid 2-polyphosphate

conveniently about 0.5 to about 0.8 mol, preferably about 0.55 to about 0.65 mol, of alkaline earth metal hydroxide is added per mol of L-ascorbic acid salt. Calcium hydroxide is the preferred alkaline earth metal hydroxide. Since the alkaline earth metal hydroxides are not particularly water-soluble, the alkaline earth metal hydroxide can be added as a suspension in water. However, the alkaline earth metal hydroxide is preferably added as a solid, especially, as mentioned above, in admixture with the phosphorylating agent (in situ production of the L-ascorbic acid 2-polyphosphate).

The amount of phosphorylating agent used is chosen such that the final content of L-ascorbic acid 2-monophosphate in the end product is as high as possible, i.e. as much L-ascorbic acid salt as possible is consumed. When sodium trimetaphosphate is used, this is achieved satisfactorily when about 0.3 to about 0.5 mol, preferably about 0.35 to about 0.45 mol, of phosphorylating agent is used per mol of L-ascorbic acid salt.

The process in accordance with the invention is conveniently effected at temperatures in the range of about 20°C to about 80°C, preferably at temperatures in the range of about 40°C to about 60°C. In general, the temperature is gradually raised in the course of the process, for example from about 40°C initially to about 60-70°C towards the end of the reaction. After completion of the reaction the temperature is advantageously lowered in order to stop the reaction.

During the reaction the pH value preferably amounts to about 9 to about 10. The reaction is too slow at too low a pH value. A pH value which is too high is also disadvantageous. The pH value should not be substantially higher than 10, in any case not higher than about 11, since the L-ascorbic acid salt has only a low stability under strongly alkaline conditions and since inorganic phosphates are increasingly formed. In the case of too high a pH value L-ascorbic acid 2-polyphosphate and less phosphorylated L-ascorbic acid salt, e.g. L-ascorbic acid 2-diphosphate, are converted into L-ascorbic acid 2-monophosphate by cleavage of phosphate groups with the base and not by reaction with L-ascorbic acid salt; thereby the content of inorganic salts in the end product increases, which is clearly a disadvantage.

The reaction time required to achieve a satisfactory yield of L-ascorbic acid 2-monophosphate of formula I depends on various factors, especially

the reaction temperature, the pH value, the amount of water in the reaction mixture as well as the stirring intensity. In general, it is preferred to add the L-ascorbic acid 2-polyphosphate rather slowly or to produce it in situ rather than to add it rapidly. When the pH value and the temperature are not unnecessarily high and an excessive amount of oxygen is not present, a somewhat long reaction time is not disadvantageous. Reaction times of about 1 to about 4 hours, preferably of about 1 1/2 to about 2 1/2 hours, are typical.

After completion of the reaction the mixture obtained can be cooled, e.g. to about 30-40°C, and diluted with water until the viscosity is suitable for a spray drying, e.g. about 100 mPa, and finally spray dried. When spray drying is carried out, practically no byproducts occur which subsequently have to be disposed of. Advantageous in the process accordance with the invention are the considerable avoidance of byproducts and the high content (high yield) of desired L-ascorbic acid 2-monophosphate of formula I. By this means the raw material costs and the energy costs in the spray drying are reduced to a minimum.

The process in accordance with the invention is illustrated by the following Examples in which, with the exception of Example 2, the content of L-ascorbic acid 2-monophosphate and 2-polyphosphates is in each case given in L-ascorbic acid equivalents:

Example 1

Reaction of L-ascorbic acid 2-triphosphate (main constituent of the so-designated mixture used) with sodium ascorbate

67.3 g (340 mmol) of sodium ascorbate are added to 50 ml of water in a 750 ml double jacketed reaction vessel while stirring and under a nitrogen atmosphere at 60°C and thereby dissolved for the most part. The pH value is adjusted to 9.5 with 3.7 g of calcium hydroxide. 87 g of solid L-ascorbic acid 2-triphosphate (HPLC analysis: 4.3% ascorbic acid, 0.5% L-ascorbic acid as the 2-monophosphate, 1:4% L-ascorbic acid as the 2-diphosphate as well as 21.1% L-ascorbic acid as the 2-triphosphate) are added portionwise in the course of 2 hours, 58 g being added during the first hour and 29 g during the second hour. The pH value is held at 9.5 by the addition of 33.9 g of calcium hydroxide. Sufficient water (a total of 50 g) is added in order that the

suspension can always be stirred well. After completion of the reaction the batch is evaporated to dryness (water content: 10.5%). HPLC analysis of the dried product indicates 10.9% (residual, non-phosphorylated) L-ascorbic acid, 34.5% L-ascorbic acid as the 2-monophosphate and 0.6% L-ascorbic acid as the 2-diphosphate. L-Ascorbic acid 2-triphosphate can no longer be detected.

Example 2

a) Separate production of a L-ascorbic acid 2-polyphosphate solution

150 ml of water are cooled to 0°C in a 500 ml double jacketed reaction vessel. Then 114.44 g of sodium trimetaphosphate are added while stirring. The pH value is adjusted to 11 with slaked lime (a 20% suspension of calcium hydroxide in water), which gives the sodium trimetaphosphate solution.

67.32 g of sodium ascorbate are dissolved in 150 ml of water. The pH value is adjusted to 11 with slaked lime. Then the solution is cooled to 0°C, which gives the sodium ascorbate solution.

The sodium ascorbate solution is added rapidly to the sodium trimetaphosphate solution. The temperature is increased to 30°C in the course of 2 hours. The pH value is held at 11 with slaked lime. After 2 hours the batch is cooled to 0°C, which gives the L-ascorbic acid 2-polyphosphate solution.

b) Reaction of L-ascorbic acid 2-polyphosphate with sodium ascorbate

134.64 g of sodium ascorbate are dissolved in 100 ml of water at 60°C while stirring and under a nitrogen atmosphere in a 500 ml double jacketed reaction vessel. The pH value is adjusted to 10.5 with slaked lime. Half of the L-ascorbic acid 2-polyphosphate solution is added within one hour and the remainder is added within two hours. The pH value is held at 10.5 with slaked lime. During the last two hours water is distilled off under reduced pressure. After completion of the reaction the batch is neutralized to pH 7 with sulphuric acid and diluted with 300 ml of water. HPLC analysis indicates the following distribution of the L-ascorbic acid: 14.3% non-phosphorylated, 76.2% as the monophosphate, 7.6% as the diphosphate, <1% as the triphosphate and <2% as additional L-ascorbic acid 2-polyphosphates.

Example 3

In situ production of L-ascorbic acid 2-polyphosphate and its reaction with sodium ascorbate

100 g of water are placed in a 500 ml double jacketed reaction vessel. Thereafter it is degassed by the application of a vacuum. The vacuum is broken with nitrogen and 176 g (1 mol) of ascorbic acid are added. The ascorbic acid is neutralized with 141.6 g of 28% sodium hydroxide solution while stirring and under reduced pressure. The vacuum is broken with nitrogen and the temperature is adjusted to 50°C. A mixture of 142.8 g (0.467 mol) of sodium trimetaphosphate and 51.9 g (0.7 mol) of calcium hydroxide is added within 2 hours under nitrogen. The addition is rapid at the beginning of the reaction and slow towards the end of the reaction. The reaction mixture is stirred for 60 minutes, neutralized with 5.2 g of 98% sulphuric acid and diluted with 300 g of water. An aliquot (about 10 ml) is removed from the reaction mixture and evaporated to dryness under reduced pressure. HPLC analysis indicates 1.3% L-ascorbic acid, 34.3% L-ascorbic acid as the 2-monophosphate and 3.5% L-ascorbic acid as the 2-diphosphate, a total of 42% phosphorylated ascorbic acid.

Examples 4-7

These Examples were carried out analogously to Example 3, but under varying reaction conditions. In particular, the amount of sodium trimeta-phosphate was reduced gradually. The results obtained are compiled in the following Table.

Table

Example	4	5	6	7
Water (g)	50	50	50	50
ASC (g)	176	176	176	176
NaOH 28% (g)	163.5	166	163.5	163.5
STMP (g)	132.6	112.2	102	91.8
$Ca(OH)_2$ (g)	37	37	37	33.3
H_2SO_4 (g)	4	8.8	10.4	8.9
Water (g)	200	200	200	200
Reaction solution (g)	763.1	750	738.9	723.5
Temperature (°C)	40-60	40	40-60	40-60
pH value of the NaASC solution	9.9	10	10	10
STMP/$Ca(OH)_2$ addition in	2 h	4 h	2 h	2 h
second stirring	0.25 h	1 h	0.25 h	0.25 h
HPLC analysis (ASC equivalents):non-phosphorylated				
ASC (%)	5	7.1	8.7	11.4
ASC as the monophosphate (%)	31.6	37.9	39.4	38.1
ASC as the diphosphate (%)	6.2	2.5	1.2	0.9
ASC phosphates total (%)	39.3	41.5	41.6	39.6
ASC total (%)	44.3	48.6	50.3	51

ASC = L-Ascorbic acid

STMP = Sodium trimetaphosphate

NaASC = Sodium ascorbate

Example 8

Fluidized bed drying of the product

165 g of water are placed in a 750 ml double jacketed reaction vessel. Thereafter it is degassed by the application of a vacuum. The vacuum is broken with nitrogen and 176 g (1 mol) of ascorbic acid are added. 88.4 g of 50% sodium hydroxide solution are added while stirring. The pH value is then 9.1. The temperature is adjusted to 40°C. A mixture of 132.6 g

(0.433 mol) of sodium trimetaphosphate and 44.45 g (0.6 mol) of calcium hydroxide is added uniformly within two hours under nitrogen and the temperature in the reactor is increased to 60°C. The mixture is stirred for 30 minutes, cooled to 40°C and diluted with 200 g of water. Then the reaction mixture is evaporated under reduced pressure. The resulting solid product is ground and dried in a fluidized bed dryer with 10 m^3 of hot air at 100°C for 30 minutes. There are obtained 364 g of beige-brown powder having 6.3% residual moisture. HPLC analysis indicates 3% L-ascorbic acid, 33.2% L-ascorbic acid as the 2-monophosphate and 3.8% L-ascorbic acid as the 2-diphosphate, a total of 37.6% phosphorylated ascorbic acid.

Example 9

Spray drying of the product

100 g of water are placed in a 500 ml double jacketed reaction vessel. Thereafter it is degassed by the application of a vacuum. The vacuum is broken with nitrogen and 176 g (1 mol) of ascorbic acid are added. The ascorbic acid is neutralized with 142.8 g of 28% sodium hydroxide solution while stirring and under reduced pressure. The pH value is adjusted to 10 by the addition of 18.6 g of calcium hydroxide. The vacuum is broken with nitrogen and the temperature is adjusted to 40°C. A mixture of 132.6 g (0.433 mol) of sodium trimetaphosphate and 48.2 g (0.65 mol) of calcium hydroxide is added within 4 hours under nitrogen. The reaction mixture is stirred for 90 minutes, neutralized with 7.1 g of 98% sulphuric acid and diluted with 300 g of water. The entire reaction mixture is spray-dried in a laboratory spray tower. According to HPLC analysis the powder contains 3.7% L-ascorbic acid, 38% L-ascorbic acid as the 2-monophosphate and 2.8% L-ascorbic acid as the 2-diphosphate, a total of 46.9% of phosphorylated ascorbic acid.

Example 10

Use of sodium ascorbate from the lactonization of methyl 2-keto-L-gulonate

208.4 g of methyl 2-keto-L-gulonate are dissolved in 500 g of methanol and the solution is heated to boiling while stirring. 52 g of sodium carbonate are added in the course of 2 hours. The pH value is then 8. The mixture is stirred for 30 minutes, cooled to 40°C and the precipitated sodium ascorbate

is filtered off and washed with 100 g of methanol. The moist sodium ascorbate is dried in a drying oven at 40°C under reduced pressure. There are obtained about 198.1 g of crude sodium ascorbate with a content of pure sodium ascorbate of about 94%.

198.1 g of crude sodium ascorbate are dissolved in 230 g of water at 40°C in a 500 ml double jacketed reaction vessel. The temperature is increased to 60°C within 2 hours and a mixture of 132.6 g (0.433 mol) of sodium trimetaphosphate and 44.45 g (0.6 mol) of calcium hydroxide is added. The mixture is stirred for 30 minutes, cooled to 40°C and diluted with 200 g of water. The entire reaction mixture is evaporated as rapidly as possible on a rotary evaporator under reduced pressure at a bath temperature of 60°C and the residue is ground in a mortar and subsequently dried in a drying oven at 60°C under reduced pressure (weight yield: 375.8 g). The water content is 6.7%. According to HPLC analysis the powder contains 3.7% L-ascorbic acid, 31.0% L-ascorbic acid as the 2-monophosphate, 3.6% L-ascorbic acid as the 2-diphosphate as well as 1.9% L-ascorbic acid as the 2-triphosphate.

Example 11

Use of sodium ascorbate from the lactonization of methyl 2-keto-L-gulonate without isolation of the sodium ascorbate

208.4 g of methyl 2-keto-L-gulonate are dissolved in 500 g of methanol and the solution is heated to boiling while stirring. 52 g of sodium carbonate are added in the course of 2 hours, during which the pH value does not rise substantially above 8. The mixture is stirred for a further 30 minutes, diluted with 230 g of water and the majority of the methanol is distilled off over a Vigreux column. The distillation residue (439 g) is cooled to 40°C. Then the temperature is increased from 40°C to 60°C in the course of 2 hours under nitrogen and a mixture of 132.6 g of sodium trimetaphosphate and 44.45 g of calcium hydroxide is added. The mixture is stirred for a further 30 minutes. The entire reaction mixture is evaporated as rapidly as possible under reduced pressure at a bath temperature of 60°C and the residue is ground in a mortar and subsequently dried in a drying oven at 60°C under reduced pressure (weight yield: 388 g). The water content is 9%. According to HPLC analysis the powder contains 3.6% L-ascorbic acid, 30.2% L-ascorbic

acid as the 2-monophosphate, 4.9% L-ascorbic acid as the 2-diphosphate as well as 0.9% L-ascorbic acid as the 2-triphosphate.

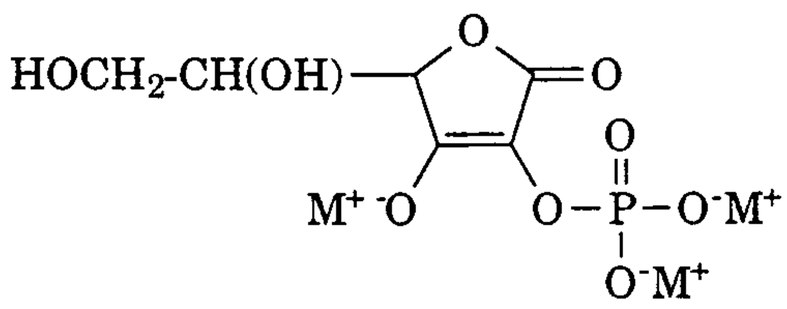
Example 12

Use of potassium hydroxide as the base

175.6 g of water are placed in a 750 ml double jacketed reaction vessel and degassed by the application of a vacuum. The vacuum is broken with nitrogen and 176 g (1 mol) of ascorbic acid are added. The ascorbic acid is neutralized with 113.2 g of 55.9% potassium hydroxide solution while stirring and under reduced pressure. The vacuum is broken with nitrogen and the temperature is adjusted to 40°C. The temperature is increased from 40°C to 60°C within 2 hours under a nitrogen atmosphere and a mixture of 132.6 g (0.433 mol) of sodium trimetaphosphate and 48.2 g (0.65 mol) of calcium hydroxide is added. The mixture is stirred for a further 15 minutes and diluted with 200 g of water. The entire reaction mixture is evaporated as rapidly as possible under reduced pressure at a bath temperature of 60°C, and the residue is ground in a mortar and subsequently dried in a drying oven at 60°C under reduced pressure (weight yield: 391.7 g). The water content is 5%. According to HPLC analysis the powder contains 4.7% L-ascorbic acid, 32.5% L-ascorbic acid as the 2-monophosphate, 3.9% L-ascorbic acid as the 2-diphosphate as well as 1.1% L-ascorbic acid as the 2-triphosphate.

Claims

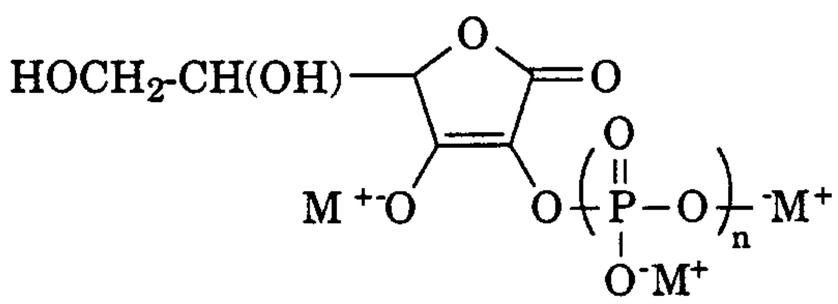
1. A process for the manufacture of alkali metal and alkaline earth metal salts of L-ascorbic acid 2-monophosphate of the general formula



I

wherein each M^+ signifies an alkali metal ion or the equivalent of an alkaline earth metal ion,

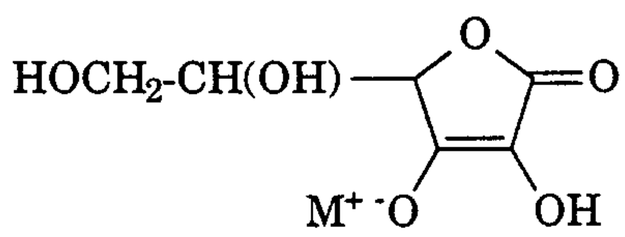
which process comprises reacting a L-ascorbic acid 2-polyphosphate of the general formula



II

wherein M^+ has the significance given above and n signifies a whole number from 2,

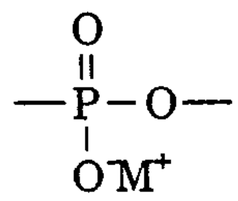
under alkaline conditions with an alkali metal or alkaline earth metal salt of L-ascorbic acid of the general formula



III

wherein M^+ has the significance given above,

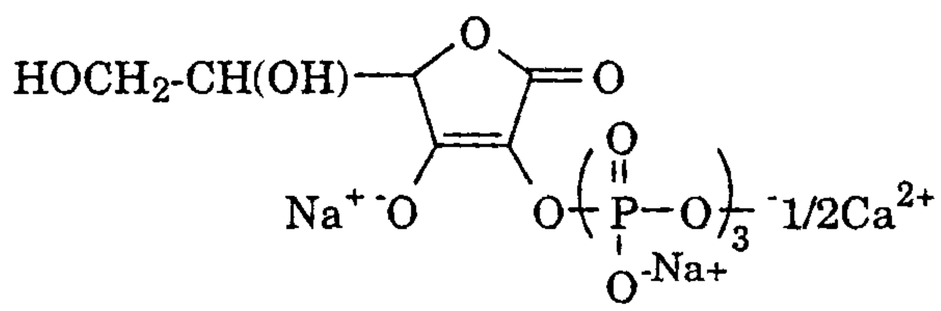
in concentrated aqueous solution, the amounts of the L-ascorbic acid salt of formula III and the alkaline earth metal hydroxide used as the base being arranged such that the pH value of the reaction medium is held in the range of about 8 to about 11 and a stepwise transfer of in each case one phosphate group



from the polyphosphate of formula II to the L-ascorbic acid salt of formula III taking place until essentially the polyphosphate has been consumed and only L-ascorbic acid 2-monophosphate salt of formula I is present.

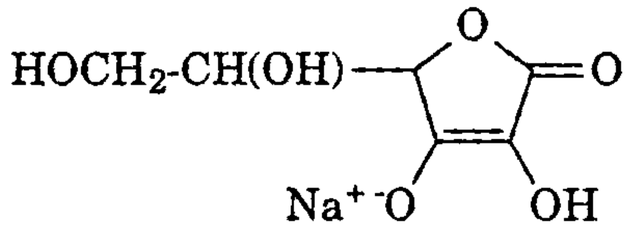
2. The process according to claim 1, wherein the L-ascorbic acid 2-polyphosphate of formula II is produced in situ.

3. The process according to claim 1 or 2, wherein the L-ascorbic acid 2-polyphosphate used has the formula



II'

the alkali metal salt of L-ascorbic acid used has the formula



III'

and calcium hydroxide is used as the base.

4. The process according to any one of claims 1 to 3, wherein the L-ascorbic acid 2-polyphosphate of formula II or II' is produced separately or produced in situ using sodium trimetaphosphate as the phosphorylating agent.

5. The process according to any one of claims 1 to 4, wherein the L-ascorbic acid 2-polyphosphate of formula II is produced in situ and for this purpose a mixture of sodium trimetaphosphate as the phosphorylating agent with the base is added.

6. The process according to claim 5, wherein the base is calcium hydroxide.

7. The process according to any one of claims 1 to 6, wherein the L-ascorbic acid 2-polyphosphate of formula II is produced in situ and about 0.5 to about 0.8 mol of alkaline earth metal hydroxide is used per mol of L-ascorbic acid salt of formula III.

8. The process according to claim 7, wherein about 0.55 to 0.65 mol of alkaline earth metal hydroxide is used per mol of L-ascorbic acid salt of formula III.

9. The process according to any one of claims 1 to 8, wherein the L-ascorbic acid 2-polyphosphate of formula II is produced in situ and about 0.3 to about 0.5 mol of sodium trimetaphosphate as the phosphorylating agent is used per mol of L-ascorbic acid salt of formula III.

10. The process according to claim 9, wherein about 0.35 to about 0.45 mol of sodium trimetaphosphate as the phosphorylating agent is used per mol of L-ascorbic acid salt of formula III.

11. The process according to any one of claims 1 to 10, wherein the reaction is effected at a temperature in the range of about 20°C to about 80°C.

12. The process according to claim 11, wherein the reaction is effected at a temperature in the range of about 40°C to about 60°C.

13. The process according to any one of claims 1 to 12, wherein the pH value is about 9 to about 10.

14. The process according to any one of claims 1 to 13, wherein, after completion of the reaction, cooling and dilution to a viscosity suitable for spray drying, the mixture obtained is spray dried.