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(57) Abrégé/Abstract:
The invention relates to a process for the preparation of sweetening salts consisting of a sweetener derived from aspartic acid and an intense sweetener not derived from aspartic acid by adding to a liquid medium, in any order, (a) a sweetener derived from aspartic acid, (b) a salt of a sweetening acid not derived from aspartic acid, and (c) a strong acid, after which the components then present in the system are allowed to react for at least one minute and the sweetening salt formed is isolated. The invention also relates to new sweetening salts having a good thermal stability and a low moisture content, as well as a new crystal modification of the sweetening salt from aspartame and acesulfamic acid. The invention furthermore relates to the use of and preparations of sweetening salts.

# A B S T R A C T

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# SWEETENER SALTS

The invention relates to a process for the preparation of sweetening salts consisting of two sweetener components. The invention relates in particular to the preparation in a liquid medium of sweetening salts consisting of two sweetener components starting from a sweetener derived from aspartic acid and from a derivative of an organic sweetening acid which corresponds to an intense sweetener not derived from aspartic acid. The invention also relates to such new sweetening salts with a good thermal stability and a low moisture content as well as in particular a new crystal modification of the sweetening salt from aspartame and acesulfamic acid. In addition, the invention relates to the application of sweetening salts in foodstuff compositions, confectionery, sweets, chewing gum, etc. The invention further relates to preparations of such sweetening salts.

ES-A-8604766 discloses such a process for the preparation of, for example, salts of the aspartic acid derived sweetener aspartame (α-L-aspartyl-L-phenylalanine methyl ester; hereinafter also referred to as APM) and saccharinic acid (3-oxo-2,3-dihydro-1,2-benzisothiazole-1,1-dioxide). ES-A-8604766 also mentions acesulfamic acid and glycyrrhizic acid as potential starting materials. According to this publication, as - derivative of - the organic sweetening acid (which in practice appears to have been carried out only for saccharinic acid), the organic sweetening acid itself is dissolved in methanol, after which a quantity of aspartame that is equimolar to the acid is added and the mixture is heated to 40-50°C until a solution is obtained; the solution is subsequently evaporated using the rotavapor (until a solid has formed or up to a predetermined concentration) and the salt formed can be recovered,

optionally by addition of a methanol-miscible organic solvent, which can be done either as an insoluble product or in the solvent added or in the solvent system obtained. The main disadvantage of this process is that use is to be made of the organic acid. As a result, the applicability of this method is essentially limited to the preparation of saccharinates, since other eligible organic sweetening acids - that is, except for saccharinic acid - generally have an unstable character and therefore are hard to obtain. Applicant has found that poor results are obtained also, for that matter, when the process described in ES-A-8604766, analogously to the preparation of the products from saccharinic acid, is carried out on the basis of an organic sweetening acid other than saccharinic acid. So far, no other suitable processes for the preparation of such salts are known, either. In addition, as will be explained in the experimental part of the present application, applicant has also found that the salts obtained using the process of ES-A-8604766, which is limited in terms of general applicability, have a relatively high moisture content and a limited thermal stability. This is particularly the case for the salt of aspartame and acesulfamic acid, prepared analogously to the process of ES-A-8604766.

At the moment a great many intensive sweeteners are known. A substantial number of these is derived from aspartic acid. Aspartame (α-L-aspartyl-L-phenylalanine methyl ester; APM), for example, now is one of the most important intense sweeteners. APM's sweetening power is about 200 times that of sugar. Examples of other sweeteners derived from aspartic acid are compounds such as the APM-corresponding lower alkyl esters, esters of L-aspartyl-D-serine and L-aspartyl-D-threonine (Aryoshi et al., Bull. Chem. Soc. Jap., 47, 326 (1974)), esters of L-aspartyl-D-alaninol and L-

aspartyl-D-serinol (US-A-3,971,822), 3-L-α-aspartyl-D-alanylamido-2,2,4,4-tetramethylthietanylamine (alitame; EP-A-0034876; approx. 2000x the sweetening power of sugar), and many others.

In addition, various other synthetic intense sweeteners are known which are derived not from aspartic acid but from other organic acids. In this patent application these are referred to as organic sweetening acids. Examples are the long-known sweeteners acesulfame-K (6-methyl-1,2,3-oxathiazin-4(3K)-one-2,2-dioxide; hereinafter also referred to as AceK; 200x sugar; US-A-3,689,486), saccharin-Na (sodium 2,3-dihydro-3-oxobenzisosulfonazole; 300x sugar) and cyclamate-Na (sodium cyclohexylsulfamate; 30x sugar). Especially the sodium, calcium and potassium salts of the relevant acids prove to have suitable sweet properties. These sweeteners, too, just like APM, are used in large quantities for sweetening of foodstuffs such as soft drinks, diet products, chewing gums, confectionery, sweets, etc. The organic sweetening acids in question themselves are as such less suitable as sweetener because either they are unstable or they exhibit a less suitable taste profile. Moreover, the organic sweetening acids are only slightly water-soluble.

It should be noted that the possibilities of using intense sweeteners in the various products may be restricted as a consequence of chemical and/or thermal instability aspects during the preparation and/or storage of (end) products containing such sweeteners. Thermal stability of sweeteners, for example, will be an important criterion governing the choice of a sweetener for use in confectionery products. The use of, for example, aspartame or its derivatives in such applications is limited due to their relatively unfavourable thermal stability. In this context it is remarked in US-A-4,439,460, column 1, line 30 ff., that

the aspartame salts known at the time generally have as a disadvantage that their thermal stability is not as it should be, for which reason they are not universally applicable. After that, it is concluded that only specific sulphate ($SO_4^=$) and organosulphate ($RSO_3^-$) salts of aspartame have sufficient thermal stability.

ES-A-8604766 does describe that salts on the basis of two intense sweetener components may have (synergistic) sweetening properties without - in solid form or dissolved - the bitter taste of the acid being noticed, as well as advantages in terms of dissolution rate, etc., but apparently such salts have so far hardly found practical application due to their limited accessibility and their limited thermal stability.

There was therefore felt to be a need for providing a more universal, simpler process for the preparation of sweetening salts consisting of two sweetener components, being built up of a sweetener derived from aspartic acid and an organic acid corresponding to an intense sweetener that is not derived from aspartic acid, it being possible for the resulting sweetening salts to be obtained in a thermally stable form and with a low moisture content without the above-mentioned drawbacks, in particular without the limitation that the preparation method must be based on the organic acid in question.

Surprisingly, it has now been found that sweetening salts consisting of two sweetener components can be prepared in a very suitable manner and in a thermally stable form and with a low moisture content in a liquid medium. Thus, according to one aspect of the invention there is provided a process for the preparation in a liquid medium of sweetening salts consisting of two sweetener

components, starting from a sweetener derived from aspartic acid and from a derivative of an organic sweetening acid which corresponds to an intense sweetener not derived from aspartic acid by adding to the liquid medium, in any order of the steps (a), (b) and (c):

a) as component (i) the sweetener derived from aspartic acid;

b) as component (ii) a salt of an organic sweetening acid which corresponds to an intense sweetener not derived from aspartic acid;

c) as component (iii) a strong acid; and

d) the components then present in the system are allowed, optionally with agitation, to react for at least one minute, so that the sweetening salt is formed, and

e) the sweetening salt is isolated from the resulting reaction mixture.

According to another aspect of the present invention, there is provided sweetening salt, consisting of two sweetener components, of a sweetener derived from aspartic acid and an organic acid which corresponds to an intense sweetener not derived from aspartic acid, with less than 0.5% degradation when heated for 60 minutes at 120°C, or less than 0.5% degradation when heated for 70 hours at 70°C, and with a moisture content < 0.5 wt.%.

In this way a universally applicable, simple method has become available for preparing the sweetening salts in question without the disadvantages inherent in the instability of most of the relevant organic sweetening acids that could be used as starting product.

In one of the first paragraphs of this application a non-exhaustive list was already given of sweeteners derived from aspartic acid that can be used as starting product in the framework of this invention. These substances are conveniently referred to as component (i) or starting material (i) in the application; with special preference aspartame and alitame are used as starting material (i) from this group of compounds, for the products derived from them according to the invention have good properties in terms of taste, low moisture content and thermal stability.

Examples are also given above, non-exhaustively, of (salts of) organic sweetening acids, corresponding to intense sweeteners not derived from aspartic acid, that can be used as starting product in the framework of this invention. Below, these substances will conveniently be referred to as component (ii) or starting material (ii); the salts of the organic sweetening acid to be used in the process

according to the invention are preferably chosen from the group formed by potassium, sodium, calcium, ammonium and secondary or tertiary amine salts. Particularly suitable starting materials are the relevant salts of organic acids from the group formed by acesulfamic acid, saccharinic acid or cyclamic acid.

In the process according to the invention the starting materials (i) and (ii) do not have to be used in dry or virtually dry form. Thus, it is possible for example to use a wet crystal mass obtained in processes for the preparation of the sweetener derived from aspartic acid, for example a 2-6 wt.% APM slurry in water, or the wet APM crystal cake with a moisture content of for example 30-70 wt.% that is obtained in a further process step after solid/liquid separation using centrifuges or another separation technique. It is also possible to use aqueous suspensions containing a dispersing agent, for example a 10-70 wt.% suspension of APM in water, such as the commercially available NutraSweet Cusrom Liquid®, as starting material.

In principle the process according to the invention can be carried out in any liquid medium. It will be clear to one skilled in the art that under the reaction conditions used the medium is inert relative to (that is, does not react irreversibly with) the starting materials used and the products to be obtained. Liquid medium in the sense of this patent application is therefore understood to mean any medium that is inert relative to the reagents (the components (i) and (ii) used as starting materials), the end product and the strong acid, and that is liquid in the process temperature range chosen. If, during one or more steps of the process and depending on the liquid medium chosen, a solid is present in the liquid medium which consists of one or more of the starting materials (i) and (ii) and/or the desired sweetening salt or inorganic salt formed during the process, in the

framework of this patent application the term slurry is also used. In the process according to the subject invention in many cases a slurry will be present. This does not form an impediment to the process. It is even advantageous if at least 1.0 wt.% of solid material is present in the reaction mixture after step (d). Usually, therefore, such a slurry has a solids content of at least 1.0 wt.% relative to the weight of the total of liquid medium and starting materials used and strong acid. However, higher solids contents are quite possible; the slurry may for example have a solids content of up to for example 50 or even 60 wt.% relative to the weight of the total of liquid medium and starting materials used and strong acid, without agitation of the system becoming impossible. An exact upper limit for the solids content can therefore hardly be indicated. It is determined especially by practical considerations relating to the stirrability and viscosity of the system, during and at the end of the process. This can easily be established by one skilled in the art. The stirrability of the system can optionally be improved by adding a dispersing agent, for example hexaethyl cellulose (HEC). Depending on the liquid medium and the process conditions that have been chosen, the process according to the invention can also be carried out fully or largely in solution, i.e. without the presence of solid(s).

However, in view of the higher volume yields that can be achieved and the higher purity of the end product, the process is preferably carried out under such conditions that at least 1.0 wt.% of solid material is present in the reaction system, optionally already before step (c), but certainly at the end of step (d). The solid does not necessarily have to be the desired sweetening salt itself but may, depending on the liquid medium chosen, also be an inorganic salt. This will be explained in more detail below.

For practical and economic reasons the liquid medium is chosen in particular from the group formed by water, less or more polar organic solvents, such as for example lower alcohols (with 1-8 carbon atoms) or ketones, such as for example acetone or methylisobutylketone (MIBK) or halogenated hydrocarbons with 1-6 carbon atoms, or esters (e.g. ethyl acetate), or ethers, such as for example methyl-t-butylether (MTBE), dibutyl ether, diethyl ether and tetrahydrofuran, and apolar organic solvents such as alkanes (e.g. pentane, hexane, cyclohexane, petroleum ether), aromatics (e.g. toluene or benzene), as well as water-miscible or water-immiscible solvents, such as for example solutions, mixed in suitable proportions, of methanol and methylethylketone (MEK), MIBK or MTBE, or other mixtures with components from the above-mentioned liquids, including aqueous media. If the liquid medium contains a substantial quantity of water, for example at least 50% of the total weight of the liquid medium, it is referred to as an aqueous medium in the framework of this invention. The liquid medium may optionally already contain a quantity of the strong acid, component (iii).

As liquid medium use is preferably made of an aqueous medium. On the one hand this is to be preferred because then, if alkali (alkaline earth) metal salts of the organic sweetening acid are used, inorganic salt present at the end of the process remains in solution, while the desired sweetening salt can be recovered directly as a solid from the aqueous medium. When the process according to the invention is carried out in an aqueous medium, as a rule a slurry is obtained already after addition of component (i) and mostly solids will also be present at the end of the process, and therefore the process in aqueous media can usually also be called a 'slurry conversion' process. In more general terms, to also do justice to those processes

according to the invention which take place, depending on factors such as the liquid medium chosen, wholly or largely without the presence of solids and in which the desired sweetening salt for example remains in solution, the process can also be referred to as a 'trans-salification process'. When the conversion according to the invention is carried out in, for example, (m)ethanol, inorganic acid precipitates at the end of process and the sweetening salt formed generally remains in solution. In that case, too, the process can be called a 'slurry conversion process'.

The isolation in step (e) of the desired sweetening salt from the reaction mixture is effected by solid-liquid separation. If the sweetening salt itself is present as a solid at the end of step (d), the solid-liquid separation can be carried out directly, optionally after the reaction mixture has been concentrated to some extent by partial evaporation of the liquid medium, preferably at reduced pressure. If the sweetening salt, for example if the process is carried out in (m)ethanol, is present in solution at the end of step (d) and inorganic salt is present as a solid, first the inorganic salt can be removed by solid-liquid separation, following which the sweetening salt is crystallized out of the filtrate by cooling or by addition of a second liquid medium, optionally in combination with complete removal of liquid medium (e.g. through spray drying) or with a concentration step in which the solution is partly evaporated until a precipitate has formed. The sweetening salt then precipitated is subsequently recovered by solid-liquid separation. The sweetening salt obtained is optionally dried further. In all cases, therefore, selective crystallization of the sweetening salt can basically be said to take place.

Removal of all or part of the inorganic salt formed in the slurry conversion process is not

necessary for the process according to the invention. Through a suitable choice of the liquid medium, such that in this medium both the solubility of the sweetening salt formed and that of the inorganic salt being formed are relatively high, even at temperatures of 20 to 40°C, the reaction mixture obtained can - most expediently - be used directly in, for example, a spray-drying process. A relatively high solubility of both the sweetening salts and the inorganic salt formed can be achieved by using mixed solvent combinations, such as for example water/(m)ethanol systems with a high (m)ethanol content, for example about 60 to about 95% (v/v). One skilled in the art can easily determine under what conditions a spray-drying process can suitably be carried out without (prior or intermediate) removal of the inorganic salt.

On the other hand aqueous media are to be preferred as liquid medium because it has been found that the sweetening salts obtained when an aqueous medium is used have the best properties, particularly as regards low moisture content and thermal stability. The most preferred aqueous medium is water itself, also because in water large crystals can be obtained, which is advantageous in the solid-liquid separation. As will be explained below, when the process according to the invention is carried out with water as liquid medium, in particular the sweetening salt of aspartame and acesulfamic acid is obtained in a new, highly suitable crystal modification. In addition, water is particularly suitable as liquid medium because, apart from minute quantities of liquid, no organic solvent residues are present in the end product. The process according to the invention can be suitably carried out both in an aqueous medium and in a medium having a more organic nature also when amine salts or ammonium salts of the organic acid are used as starting material.

The concentrations of the quantities of

components (i) and (ii) to be used in the liquid medium are not critical within very wide limits. Evidently, for reasons of process economy use will preferably be made of higher concentrations, also in case solid material is present in the system, for example more than 10 wt.%, and more preferably 30-50 wt.%, or even higher concentrations, for example 60 wt.%. Moreover, it is self-evident that the highest possible concentrations are preferred not only in a so-called 'slurry conversion process', but also if the process, with the selected liquid medium and the selected process temperature, is wholly or largely carried out in solution.

The ratio between the starting materials (i) and (ii) in the process according to the invention can generally be varied within wide limits. As a rule, the molar ratio of substances (i) and (ii) can be chosen in the range from 0.2:1 to 5:1, more preferably in the range from 0.5:1 to 2:1. Within said ranges it proves to be very well possible, with a suitable choice of combinations of starting materials (i) and (ii), strong acid, liquid medium and other process conditions, to eventually obtain a sweetening salt in solid form which virtually purely consists of the 1:1 salt of the sweetener derived from aspartic acid and the organic sweetening acid. In spite of molar ratios of components (i) and (ii) that deviate from 1:1, still the 1:1 salt is mostly obtained if the liquid medium is chosen so that either a) the component (i) or (ii) remaining at the end of the process, which was the starting material that was present in an excess, remains in solution and the sweetening salt is present as precipitate, or b) the sweetening salt remains in solution while the component (i) or (ii) that is present in an excess is present as a solid. Variant a) takes place, for example, in an aqueous environment; variant b) for example in (m)ethanol.

Preferably, the quantities of components (i), (ii) and (iii) are chosen so that the product eventually obtained (the sweetening salt) consists substantially, i.e. to at least 90 wt.%, in particular at least 95%, based on the dry weight, of the desired sweetening salt. It should be noted that the presence of inorganic salt, even in quantities of up to about 15 wt.% relative to the sweetening salt, is not considered to cause any interference.

Because of the stoichiometry of salt formation and the process economy, the ratio between the starting materials (i) and (ii) is preferably 1:1 in moles. Optionally, one skilled in the art can, through a suitable choice of the quantities used and the ratio between components (i) and (ii) as well as, as will be elucidated below, of the strong acid, deliberately aim to obtain a sweetening salt in solid form remaining as desired product at the end of the process, with also a part of one of the components (i) or (ii) themselves being present in solid form in order to create a very special taste or stability profile.

The effects to be achieved through the attempts to secure the presence of an excess of starting material in the end product are not identical with, but can perhaps best be compared to, the effects obtained by combining various sweeteners in certain quantities. The use of combinations (blends) of intense sweeteners (which may lead to, for example, mutual reinforcement of the sweetening power (synergy)), or with other components, in order to improve the taste profile or to eliminate a bitter aftertaste or other undesirable phenomena, is known in itself in practice. Such combinations of sweeteners can generally be obtained through mixing of the individual components. A major disadvantage of such combinations of sweeteners is that - in solid form - demixing may take place.

Where this application refers to agitation,

what is meant is that the system is at least partly kept in motion, for example by stirring or shaking, so that a relatively homogeneous distribution of the various components that are present is achieved and locally too high, undesirable concentrations of the strong acid are prevented. These might give rise to undesirable side-reactions, such as hydrolysis. However, there is no need for very strong agitation, its magnitude being determined also by the thickness and the stirrability of the slurry that may be present at any moment during the process. As a rule only little agitation is required, and even without agitation good results are still possible, possibly also because the crystallization taking place during trans-salification during the process, in particular when the process is carried out in an aqueous medium, proceeds even better in the absence of agitation. In particular when the strong acid is dosed gradually, there is no or hardly any need for agitation. Moreover, if a slurry is present, as a rule sudden thickening of the slurry is found to occur upon fast addition of the strong acid, which also makes it difficult to stir the slurry.

Trans-salification according to the process of the invention generally proceeds relatively fast. In principle, it is enough to allow the components to react in step (d), even at room temperature, for at least one minute to achieve full conversion, also when the process proceeds as a 'slurry conversion reaction'.

Suitable strong acids that can be used in the framework of the invention are generally organic or inorganic acids having a $pK_a$ that is lower than the $pK_a$ of the sweetener derived from aspartic acid; however, they are preferably chosen from the group formed by hydrochloric acid, sulphuric acid or phosphoric acid. The strong acid used in step (c), component (iii), can be applied in the form of a solution (which may range from diluted to strongly concentrated) of the strong

acid in a liquid medium as used in the framework of the subject process. In particular the strong acid is used as a solution in the same liquid medium as used in the process applied. If hydrochloric acid is used as strong acid, the addition in step (c) may also be effected by means of the introduction of gaseous HCl.

At least a portion of the strong acid is added in step (c), but further addition can also take place, preferably gradually, during step (d).

The quantity of strong acid to be used in steps (a) - (c) combined, where optionally a portion of the strong acid may even be present already in the liquid medium, and in step (d), where addition of the strong acid preferably takes place gradually, is not very critical within broad limits, and generally amounts to at least 25% (in $H^+$ equivalents) of the quantity of component (i). If the total quantity of the strong acid used is less than equivalent (in $H^+$) relative to the sweetener derived from aspartic acid, 100% conversion of the latter substance into the desired sweetening salt will not be possible, so that part of this substance may remain present in the end product as a solid besides the solid sweetening salt that has been formed.

Neither are there objections to the quantity of strong acid being more than 100% (in $H^+$ equivalents) of the quantity of component (i). The strong acid excess then present generally remains behind in solution. However, the quantity of strong acid is not chosen so high that the pH of the reaction system decreases to a level where undesirable side reactions such as hydrolysis take place. If the total quantity used of the strong acid is larger than equivalent (in $H^+$) relative to the sweetener derived from aspartic acid, this will be less acceptable from an economic point of view because of the unnecessarily high consumption of strong acid and the neutralizations,

etc., needed in any further process steps. If the presence of any residual AceK in the resulting solid product is deemed undesirable, for example in view of the taste profile, which may be the case for example when an acesulfame salt excess (e.g. AceK) relative to APM is used in the preparation of the aspartame-acesulfame salt, then it is recommendable to choose the quantity of strong acid (in $H^+$) at least equivalent to the quantity of AceK used. As already explained, this partly depends on the liquid medium that has been chosen.

The order in which each of the components (i), (ii) and strong acid (iii) is dosed does not prove to be critical. If desired any order of dosing to the liquid medium can be chosen, without any substantial effect on the product obtained. It is, however, recommendable to dose one of the three components (i), (ii) and (iii), and preferably the strong acid, to the other components after these have been added to the liquid medium. Optionally, two of the three components may be added simultaneously to the liquid medium by, for example in the preparation of the aspartame-acesulfamic acid salt, simultaneously adding the aspartame and the strong acid, or alternatively acesulfame-K and the strong acid. In the latter case this can be done both separately and in the form of a mixture. Addition of the component(s) not yet present preferably takes place gradually.

Where this application refers to gradual addition of one or more of the components in one or more of the steps (a), (b), (c) or (d), in particular as regards addition of the strong acid, this is understood to mean that this component is slowly, for example in 5 minutes to 2 hours, added, continuously or in small portions, to the system, depending on the concentration in the system and the total quantities to be added, such that undesirable too high local

concentrations of, in particular, the strong acid are prevented. This can simply be determined through optimization by one skilled in the art.

In a particularly suitable embodiment of the process according to the invention components (i) and (iii) are not added separately but, instead, the addition of a salt of the sweetener derived from aspartic acid with a strong acid, for example the APM.HCl salt, is started from. Preferably this is done in a quantity above the solubility limit of that salt. Subsequently, component (ii) is added, following which the components then present in the system are allowed to react for at least one minute, yielding the desired sweetening salt. Conversely, it is also possible to first supply component (ii), after which the salt of the sweetener derived from aspartic acid is added with a strong acid. If this particularly suitable embodiment of the process according to the invention is carried out in an aqueous environment, use is preferably made of a 'slurry conversion process', which means that use is made of concentrations that are at least higher than 3.5 wt.%, but even more preferably much higher, for example higher than 10 wt.%, and even higher than 30 wt.%, for example 50 wt.%.

It is noted that a process disclosed in CA-A-1027113, in so far as carried out in an aqueous environment, shows some similarity with this specific, particularly suitable embodiment, but can certainly not be equated with it, for according to this Canadian patent specification the process carried out in an aqueous environment should be carried out at low concentrations, presumably up to max. 2.5 wt.%, because all reagents must be in solution. Furthermore, because of solvent removal that economically unattractive process leads to an end product that contains less than 90% of the desired sweetening salt. This process, therefore, is less suitable.

In another suitable embodiment the salt of the organic sweetening acid used in step (b) is prepared in situ by reacting the organic sweetening acid with a base. Suitable bases are ammonium and/or alkali (alkaline earth) metal hydroxides as well as primary, secondary and tertiary amines, and ammonia.

The process according to the invention can in principle be carried out at any suitable temperature in the range from -20 to +90°C, provided that the system remains liquid and stirrable. At too low a temperature, in an aqueous environment, there is a risk of freezing, while, also mainly in an aqueous environment, at too high a temperature decomposition of the starting materials and the products, for example by ester hydrolysis, may take place to a serious extent. If the process is carried out entirely at ambient temperature, good results are obtained, also as regards the thermal stability and the low moisture content of the solid product eventually obtained. However, step (d) of the process is preferably carried out at elevated temperature, in particular in the range from 40 to 70°C, after which the resulting system is gradually cooled to a temperature in the 0-20°C range, because according to that embodiment, in particular when effecting the conversion in an aqueous medium, a sweetening salt having excellent filtration properties and good handling properties is eventually obtained.

If desired, the sweetening salt eventually obtained in the process according to the invention can, after separation, subsequently be washed and dried in a known manner. After that, it is also possible to effect further recrystallization and/or further purification, also in the known manner. A highly suitable form of drying of the sweetening salt, in which, depending on the choice of the liquid medium, prior separation of inorganic salt is not even necessary, is spray-drying.

The invention also relates to new sweetening

salts, consisting of two sweetener components, of a sweetener derived from aspartic acid and an organic acid which corresponds to an intense sweetener not derived from aspartic acid, which new sweetening salts feature good, i.e. less than 0.5%, degradation upon 60 minutes' heating at 120°C, or less than 0.5% degradation upon 70 hours' heating at 70°C, thermal stability and a moisture content < 0.5 wt.%, in particular < 0.25 wt.%. Such sweetening salts are obtained in particular if the process according to the invention is carried out in water as a liquid medium. It has, surprisingly, been found that such sweetening salts obtained from water have a good thermal stability and can simply be obtained with a moisture content that, in comparison with other known sweeteners, is often low, < 0.5 wt.%, in particular < 0.2 wt.%, and often even < 0.15 wt.%. Good thermal stability in this context is therefore understood to mean that the products obtained do not show more than 0.5 wt.% decomposition when heated at 120°C for one hour (respectively at 70°C for 70 hours). If the decomposition occurring upon heating at 140°C for one hour does not exceed 0.5 wt.%, the thermal stability can be said to be very good.

Applicant has now found that with decreasing moisture content of the sweetening salt obtained a better thermal stability can be demonstrated. This is particularly advantageous when the sweetening salts in question are applied in, for example, confectionery products.

The invention particularly relates also to a new crystal modification of the sweetening salts of aspartame and acesulfamic acid. The X-ray diffraction pattern for this new crystal modification is shown in Figure 1. It is noted, incidentally, that the ratios between the intensities of the said diffraction lines may differ without this meaning that a different

crystal modification is involved. For the sake of comparison Figure 2 presents the X-ray diffraction pattern of the salt in question as would have been obtained upon application of the process according to ES-A-8604766. This will be explained in further detail in the experimental part of this patent application. The X-ray diffraction pattern of the new crystal modification is distinguished especially by characteristic X-ray diffraction lines at D-values of about 11.8, 6.04 and 5.02, while there are no intense lines at D-values of 13.5 and 6.76 (measured via X-ray diffractometry using Cu-$K_\alpha$ radiation).

It is noted that the diffractrograms of Figures 1 and 2 are represented in a form in which in particular the characteristic diffraction lines (2Theta; 2θ) can easily be read. The D-values can simply be derived from the values of 2θ according to the following formula, based on Bragg's law:

$$D = \lambda*(2\sin\theta)^{-1}$$

where $\lambda$ = 1.5418 Å (Cu-$K_\alpha$ radiation).

For the diffraction lines indicated by D-values it is conveniently noted that in Figures 1 and 2 they are present and absent, respectively, at 2θ positions of, respectively:

| | | | |
|---|---|---|---|
| D = | 11.8 | 2θ = | 7.48 |
| | 6.04 | 2θ = | 14.65 |
| | 5.02 | 2θ = | 17.65 |
| | 13.5 | 2θ = | 6.54 |
| | 6.76 | 2θ = | 13.08 |

The sweetening salts obtained according to the process of the invention, in particular when the process is carried out in an aqueous environment, with their good thermal stability, high purity and low moisture content, are new. This good thermal stability, high purity and the low moisture content further have proved to be an important and unexpected advantage as

regards the broad applicability of the products obtained.

The subject invention now offers very good potential applications for several sweetening salts consisting of a sweetener derived from aspartic acid and an organic sweetening acid corresponding to a sweetener not derived from aspartic acid. The invention therefore also relates to the use of the sweetening salts made according to the process of the invention in foodstuff compositions, confectionery products, sweets, chewing gums, etc., and in particular use of a new crystal modification of the sweetening salt of aspartame and acesulfamic acid in such products. If desired, the sweetening salts are applied in the form of preparations, as a mixture with other components or, to influence the so-called sweetness release, provided with a hydrophobic coating.

The sweetening salts according to the invention can excellently be granulated (for example via wet granulation after addition of about 30-35% water). They are also eminently suitable for compression to tablets (for example via direct compression of the salt with the other components of the tablets, or by subjecting a composition, obtained by spray-drying, of the sweetening salt with for example lactose to direct compression with the other components of the tablets).

The resulting sweetening salts according to the invention have several advantages. Because of the low residual moisture content of the dry products obtained, as well as because of the synergy that takes place between the sweet components of the salt, products are obtained, in particular in the embodiment in which the inorganic salt formed is removed prior to recovery of the sweetening salt, that, on a weight basis, have a very high sweetening power in comparison with mixtures composed of the individual sweetening

components, or with the individual sweetener components themselves. In this respect it is also important that the sweetening salts according to the invention do not contain any alkali (earth alkaline) metal - which on a weight basis does not or hardly contribute to the sweetening power. It is also noted that, because of their hygroscopic properties, it is usually hardly possible to obtain the individual components in a simple manner with such a low residual moisture content; saccharin-Na, for example, usually has a moisture content of up to 15%, and cyclamate-Ca of up to 9%. The sweetening salts that are obtained according to the process of the invention are not hygroscopic. If no further inorganic salt is present, the sweetening power per gramme of product of the salts according the invention is therefore significant, viz. for example at least 10-15% higher than for an equivalent quantity of product made by blending the individual components. In dry form the salts further have a good thermal stability at temperatures of 70-80°C and higher, certainly up to 110-140°C (which is important for so-called 'baking applications'), which stability (which is expressed particularly in a higher retention of sweetening power) is much better than that of sweetener derived 100% from aspartic acid, for example APM. The sweetness quality of the salts in solution is also more balanced than that of equi-sweet solutions on the basis of sweetener derived 100% from aspartic acid, for example APM, while the higher dissolving rate of the salts represents an advantage in various applications (both in water and in buffered systems). This advantage can be enhanced by making use of differences in the dissolution rate, etc., depending on the particle size distribution of the salt chosen. Furthermore, use of the salts, in solid form, has the additional advantage, compared with the use of virtually 1:1 blends of the components, that all individual particles offer the

same taste profile and that no segregation of the constituent components can take place, on account of which fluctuations in taste perception will occur depending on the randomly taken samples. This is important in particular in applications such as chewing gums, sweets and powder mixtures.

Since the density of the sweetening salts according to the invention is generally virtually the same as that of the sweetener derived from aspartic acid that is used as starting material (which, incidentally, is usually considerably lower than the density of the salts of the organic acid, for example potassium salts, that are also used as starting materials), the presence, if any, of an excess of the sweetener derived from aspartic acid in the residual solid product gives less rise to segregation in that solid product. Any segregation effects in those cases can, moreover, be reduced by a suitable choice of the particle size distribution. The salts are generally particularly suitable for use in powder mixtures.

In a special embodiment the sweetness release of the salts can be influenced as desired by providing the salts, optionally in a previously determined/produced particle size distribution, with a (hydrophobic) coating, by means of which the diffusion of water into the sweetener can be retarded. Examples of such coatings are several edible fats of vegetable or animal origin, mono-, di- and triglycerides, fatty acids and hydrogenated derivatives of the above-mentioned products, lipoproteins as well as natural or synthetic waxes, such as bees-wax or paraffins or polyethylene waxes.

Below, the invention will be elucidated further on the basis of some examples (experiments) and comparative examples (comparative experiments) without, however, being limited thereto.

In the following experiments use was made, in

so far as applicable, of the following techniques:

a. the chemical purity of the sweetening salts obtained was determined by means of high-pressure liquid chromatography (hplc) using a so-called reversed-phase column; approx. 0.002 molar solutions of the salts were prepared in a pH 4.0 buffer of 4% tetrabutyl ammonium hydroxide and phosphoric acid in water; as eluent an 80/20 (v/v) mixture of water and acetonitrile was used; the APM content was determined spectrophotometrically at 210 nm, and the saccharinate or acesulfamate content at 227 nm. The accuracy of this method is ± 2%. For a number of products also a $^1$H-NMR was recorded (200 MHz; Bruker) for further characterization purposes.

b. the moisture content of the products obtained was determined by means of the Karl-Fischer water determination.

c. the dissolution rate was found through spectrophotometric determination of the dissolution curve, by introducing 0.1 wt.% of the product (or a screen fraction thereof) at 23°C into a pH 5.0 buffer (Merck titrisol, pH 5.0, in 1 litre of Milli-Q water) whilst stirring continuously.

d. thermal stability tests were conducted by allowing samples of a relevant product to stand for the indicated times in an open dish placed in a thermostatted oven at the relevant temperature, and to determine, via hplc, the concentrations of possible decomposition products such as, in the case of analysis of aspartame salts, diketopiperazine (DKP) and aspartyl-phenylalanine (AP) in the initial and the final sample.

e. X-ray diffraction patterns were recorded under laboratory conditions (using a step scan from 5° to 30° (2Theta; 2Θ) with a step size of 0.05° and

a counter time of 1 second per data point) with a Philips goniometer (PW 1820) with Bragg-Brentano geometry, mounted on a Philips generator (PW 1730). Use was made of Cu-$K_\alpha$ radiation (Ni filter, 40 kV-50 mA, LFF) with a graphite monochromator in the diffracted beam; divergence and scatter slots were each 1°, the receiving slot was 0.2 mm. The D-values can simply be derived from the values of 2Θ according to the following formula, which is based on Bragg's law:

$$D = \lambda*(2\sin\Theta)^{-1}$$

where $\lambda$ = 1.5418 Å (Cu-$K_\alpha$ radiation).

It is noted that if D is higher than 10 Å the accuracy of the D-values given is 0.1 Å; for D-values lower than 10 Å the accuracy is stated in 0.01 Å.

The abbreviations used below have the following meanings:

| | |
|---|---|
| APM: | aspartame |
| SacNa/SacK: | sodium/potassium saccharinate |
| SacH: | saccharinic acid |
| CycNa/CycH: | sodium cyclamate/cyclamic acid |
| AceK: | potassium acesulfamate |
| MTBE: | methyl-t-butylether |

Experiment 1a.-b.

Preparation of salts of APM and SacH and CycH, respectively

Exp. 1a.

A 500 ml beaker provided with a stirrer was successively charged, at room temperature, with 250 ml of water, 30.4 g of APM (0.10 mole; 3 wt.% $H_2O$) and 21.0 g of SacNa (0.10 mole). In 2 minutes 10 g of a 37% solution of HCl in water (0.10 mole) was added to the resulting slurry, which was meanwhile being stirred. Initially, a clear solution was obtained. Stirring was

continued for 30 minutes, and a voluminous white precipitate formed. The precipitate was filtered off over a Büchner filter and washed with a small quantity of cold water of 5°C and subsequently dried overnight in a vacuum stove at 40°C. 40.1 g of white product was obtained, which was unambiguously characterized via $^1$H-NMR as the 1:1 salt of APM and SacH. The moisture content was 0.03%; the APM and saccharinate contents were found to be 60% and 39%, respectively (theoretical values: 62 and 38%). The quantity of product obtained corresponds to 0.084 mole, which implies the yield of isolated product is 84%. X-ray diffractometry on this product yielded the same diffraction pattern as found for the products of comparative experiments 1A. and 1B. and experiment 4B, respectively.

Exp. 1b.

Analogously to the method of experiment 1a., 30.4 g of APM, 21.0 g of CycNa and (in 2 minutes) 10.0 g of a 37% solution of HCl in water were successively added to 200 ml of water, which was followed by stirring for 30 minutes. A voluminous slurry was obtained only after cooling down to 0°C. This slurry was filtered off at 0°C and washed with a small quantity of ice water, after which the resulting product was dried overnight in a vacuum stove at 40°C. 25.0 g of dried product (moisture content 0.16%) was obtained, which was unambiguously characterized according to $^1$H-NMR as the 1:1 salt of APM and CycH. This corresponds to an isolated yield of 53%. This value is relatively low in connection with the high solubility of the sweetening salt.

Experiment 2: preparation of the salt of APM an acesulfamic acid

Exp. 2a-g.: order of the additions

Exp. 2a.

Analogously to the method of experiment 1a., 250 ml of water, 30.4 g of APM (0.10 mole) and 21.0 g of AceK (0.10 mole) were successively added to the beaker at room temperature. In 2 minutes 10 g of a 37% solution of HCl in water (0.10 mole) was added to the slurry thus obtained, which was meanwhile being stirred. Initially a clear solution was obtained. Stirring was continued for 30 minutes, upon which a voluminous white precipitate formed. The precipitate was filtered off over a Büchner filter and washed with a small quantity of cold water of 5°C and subsequently dried overnight in a vacuum stove at 40°C. 40.2 g of white product was obtained, which was unambiguously characterized via $^1$H-NMR as the 1:1 salt of APM and acesulfamic acid. The moisture content was 0.11%; the APM content and the acesulfamate content were found to be 62% and 35%, respectively (theoretical values: 64 and 36%). The quantity of product obtained corresponds to 0.088 mole, which implies a yield of 88%.

Exp. 2b.-2g.

Experiment 2a. was repeated a few times, though the order in which the reagents were added was changed. The orders of addition were as follows: (2b.) water, AceK, APM, HCl; (2c.) water, HCl, APM, AceK; (2d.) water, APM, HCl, AceK; (2e.) water, AceK, HCl, APM; (2f.) water, mixture of APM + AceK, HCl. In all these experiments the HCl (as a 37% solution in water) was dosed in 2 minutes. In all these cases virtually identical results were achieved. The same happened when instead of solid APM use was made of a so-called wet cake, with a moisture content of 65%, formed after centrifuging of the wet crystal mass during the APM production process (2g.). Exp. 2e., for that matter, was also repeated at a higher slurry concentration (see exp. 21).

Exp. 2h.-j.: concentration of strong acid

Experiment 2a. was repeated a few times using different concentrations of the aqueous hydrochloric acid solution, viz. 73 g of 5% HCl (2h.), 37 g of 10% HCl (2i.) and 18.5 g of 20% HCl (2j.), i.e. each time with 0.10 mole HCl. In all these cases virtually identical results were achieved.

Exp. 2k.: nature of strong acid

The process of experiment 2a. was also repeated using phosphoric acid addition (11.6 g of an 85% aqueous solution) instead of HCl addition, the phosphoric acid being added in 10 minutes, followed by stirring for 10 minutes before the resulting slurry was filtered, washed and dried. During stirring slurry was constantly present. 38.9 g of white crystalline product was obtained (0.085 mole), which was characterized by means of $^1$H-NMR as being the 1:1 salt; the yield therefore was 85%. The purity was >98%, the moisture content 0.10%.

Exp. 2l.: slurry concentration

Experiment 2e. was also carried out, partly at a somewhat elevated temperature, at a solids content at the end of the reaction of about 40%. The quantities used were (in the order of addition): 50 g of water, 10 g of 37% HCl in water, 21.0 g of AceK and 30.4 g of APM. The APM was added in 5 portions of 2 g each at room temperature (in 5 minutes), and subsequently, while the temperature of the entire mixture was gradually being raised to 50°C, also in portions of about 2 g (in 15 minutes) until all APM had been added. Post-stirring was applied for 30 minutes, and then the material was cooled down to room temperature in 30 minutes, following which, after the usual upgrading treatment, 43.0 g (94%, moisture content 0.07%) of the desired 1:1 salt was obtained.

Experiment 3 (3a.-d. and 3a'): use of various liquid media

Exp. 3a.

The process of experiment 2a. was repeated in 250 ml of methanol instead of 250 ml of water. After the addition of the 37% aqueous HCl a clear solution formed, which was stirred for 30 minutes, upon which a white KCl precipitate formed. After this precipitate had been filtered off, the mother liquor was evaporated to dryness in a lukewarm water bath using the rotavapor and subsequently placed overnight in a vacuum stove at 40°C. 45.2 g of a white solid was obtained, which was identified, via $^1$H-NMR, as the 1:1 salt of APM and acesulfamic acid (99% yield). The moisture content was 2.5%; the APM content and the acesulfamate content were found to be 62% and 33%, respectively (theoretical values: 64 and 36%).

Exp. 3a. was also carried out without intermediate removal of the white KCl precipitate (Exp. 3a.'). In this experiment drying in the vacuum stove yielded 53.3 g of a white solid having a moisture content of 0.5%; the APM content and the acesulfamate content were found to be 54% and 31%, respectively (theoretical values: 55% and 31%).

Exp. 3b.

37.0 g of tri-(n-butyl) ammonium saccharinate (0.10 mole) was dissolved at room temperature in 500 ml of an 80/20 (v/v) mixture of MTBE and methanol. Subsequently 30.4 g of APM was added, so that a slurry was obtained, and 9.5 g of a 40% methanolic solution of HCl (0.10 mole) was added in 2 minutes. The slurry system present was subsequently stirred for one hour. The solid product obtained was separated by filtration and washed with MTBE before being dried under vacuum at 40°C, yielding 35.8 g (i.e. a yield of 75%) of the 1:1

salt of APM and saccharinate, its purity being >95%. Via $^1$H-NMR no presence of residual tri-(n-butyl)-ammonium salt or solvent residues could be established. The moisture content was 0.27%.

Exp. 3c.

At room temperature 2.35 g of alitame (7 mmoles), 0.65 g of a 40% solution of HCl in methanol (7 mmoles; in 2 minutes) and 1.65 g of SacK (7 mmoles) were successively added to 100 ml of ethanol, yielding a slurry. This slurry was stirred for 1 hour, upon which KCl formed as precipitate and the other components went into solution. After the solid KCl formed had been filtered off, the mother liquor was fully evaporated using the rotavapor, the residual solid material being dried further overnight in a vacuum stove at 40°C. 3.20 g (6.21 mmoles; 88% yield) of solid material remained, which was characterized as being the 1:1 salt of alitame and saccharin by means of $^1$H-NMR.

Exp. 3d.

At room temperature 1.67 g of alitame (5 mmoles), 1.05 g of AceK (5 mmoles) and 0.48 g of a 40% solution of HCl in methanol (5 mmoles; in 2 minutes) were successively added to 50 ml of ethanol, yielding a slurry. This slurry was stirred for 1 hour, upon which KCl formed as precipitate and the other components went into solution. After the solid KCl formed had been filtered off, the mother liquor was fully evaporated using the rotavapor, the residual solid material being dried further overnight in a vacuum stove at 40°C. 2.30 g (4.65 mmoles; 93% yield) of solid material remained, which was characterized as being the 1:1 salt of alitame and acesulfamic acid by means of $^1$H-NMR.

Experiment 4 (4a.-c.): gradual addition of strong acid

Exp. 4a.

To 2 l water of 20°C were successively added 608 g of APM and 410 g of AceK (2.0 moles each), after which the temperature of the resulting slurry was adjusted to 50°C and 370 g of 20% HCl in water was added in 30 minutes while the slurry was being stirred. The slurry, which had initially been rather voluminous, changed into a less voluminous slurry. At the end of the HCl addition the slurry obtained was cooled down to 10°C in about 30 minutes, via indirect heat transfer using a 0°C cooling medium, and filtered off. The resulting crystalline mass was washed with a minimal quantity of ice water and dried under vacuum at 40°C. Thus, in total 820 g (i.e. a 90% yield) of a white product was obtained, which according to $^{1}$H-NMR consisted entirely of the 1:1 salt of APM and acesulfamic acid, with a purity >99%. The moisture content was 0.12%. The product was further characterized by means of an X-ray diffraction pattern as shown in Figure 1. This crystal modification of the APM-acesulfamic acidic salt is new, and differs strongly from that which is obtained on application of the process as described in comparative experiments 1C. and 1D. (see also Figure 2). Products such as obtained in experiments 2a.-l. have the same crystal modification as that belonging to Figure 1. X-ray diffractometry in all cases proved that the products had diffraction lines at D-values of about 11.8, 6.04 and 5.02, but not at 13.5 and 6.76.

Exp. 4b.

30.4 g of APM and 21.0 g of SacNa (each 0.10 mole) were successively added to 200 ml water of 20°C, following which the temperature of the resulting slurry was raised to 60°C and 19 g of 20% HCl (0.10 mole) was added in 30 minutes with stirring. The slurry, which

had initially been rather voluminous, changed into a thinner slurry. At the end of the HCl addition the slurry obtained was cooled down to 10°C in about 30 minutes, via indirect heat transfer using a 0°C cooling medium, and filtered off. The resulting crystalline mass was washed with a minimal quantity of ice water and dried under vacuum at 50°C. Thus, in total 39.1 g (i.e. a 82% yield; moisture content 0.04%) of a white, crystalline product was obtained, which according to $^1$H-NMR consisted entirely of the 1:1 salt of APM and saccharin, with a purity >98%. The moisture content was 0.05%. The product was also analyzed by recording an X-ray diffraction pattern; however this diffraction pattern did not differ from that obtained by application of the state-of-the-art process as described in comparative experiments 1A. and 1B.

Exp. 4c.

Experiment 2h. was repeated, but this time the addition of the 73 g of 5% HCl solution in water took place gradually in 1 hour (rather than in 2 minutes). A slurry with good filtering properties was obtained, from which, after the treatment described above, 38.0 g (83% yield) of white product was obtained, which was unambiguously characterized by means of $^1$H-NMR as being the 1:1 salt of APM and acesulfamic acid. The moisture content was 0.04%; the APM content and the acesulfamate content were found to be 63% and 35%, respectively (theoretical values: 64% and 36%). X-ray diffractometry showed that the product exhibited diffraction lines at D-values of about 11.8, 6.04 and 5.02, but not at 13.5 and 6.76.

Experiment 5 (5a.-b.): ratio of starting materials

Exp. 5a.

Analogously to the process of experiment 2a., 250 ml of water, 15.2 g of APM (0.05 mole)

and 21.0 g of AceK (0.10 mole) were successively added to the beaker at room temperature. In 2 minutes 5 g of a 37% solution of HCl in water (0.05 mole) was added to the slurry thus obtained, which was meanwhile being stirred. The experiment further proceeded as in experiment 2a. 19.0 g (83% yield) of white product, with a moisture content of 0.09%, was obtained, which was characterized via $^1$H-NMR as being the 1:1 salt of APM and acesulfamic acid. The excess AceK remained behind in the filtrate.

Exp. 5b.

In a similar manner an experiment was conducted using again different quantities of starting materials, notably 30.4 g of APM (0.10 mole), 10.5 g of AceK (0.05 mole) and 10 g of 37% HCl (0.10 mole). 18.3 g (80% yield) of the 1:1 salt of APM and acesulfamic acid was obtained.

Experiment 6: process on the basis of 2 salts

34.0 g of APM.HCl was added at room temperature to 200 ml of water, yielding a slurry. Next, 21.0 g of AceK was added in 10 minutes with stirring, this being done in 10 portions of 2.1 g each. Stirring was continued for another hour. After filtration, washing and drying of the resulting solid product, 38.4 g (84% yield) of the 1:1 salt of APM and acesulfamic acid was obtained ($^1$H-NMR; >98% pure), its moisture content being 0.15%.

Experiment 7: product with excess APM

The process of experiment 2a. was repeated, this time with a quantity of APM that was twice as large, viz. 60.8 g of APM, all other quantities and activities being the same. In this experiment slurry remained present during the entire stirring period. After filtration and the customary treatment, 76.3 g of

solid material was obtained, which according to $^1$H-NMR contained about twice as much APM as acesulfamate.

Comparative experiments 1A.-D.: in conformity with ES-A-8604766

Examples 1 and 2 of ES-A-8604766 were repeated (1A. and 1B., respectively) using the quantities of SacH and APM in cmole there indicated, as well as by analogy, though not described in ES-A-8604766, using acesulfamic acid (obtained by rapidly upgrading a slurry of AceK with HCl in methanol by first filtering off the KCl formed and then evaporating the filtrate using the rotavapor) rather than SacH (1C. and 1D., respectively).

Comp. Exp. 1A.

In 200 ml of methanol 9.15 g of SacH (5 cmoles) was dissolved to which 15.2 g of APM (5 cmoles) was added, yielding a slurry which had to be heated to 45°C (rather than 40-41°C as described) to obtain a clear solution. Rotavapor evaporation at 36-37°C (35 minutes) produced 24.3 g of a white substance, which was unambiguously characterized via $^1$H-NMR as being the 1:1 salt of APM and SacH; its melting point was 203°C. The quantity of product obtained corresponds to roughly 5 cmoles, which means the isolated product yield is almost 100%. X-ray diffractometry on this product produced a similar diffraction pattern as found for the products of, for example, experiments 1a. and 4b.

Comp. Exp. 1B.

18.3 g of SacH (10 cmoles) was dissolved in 450 ml of methanol of 25°C and then 30.4 g of APM (10 cmoles) was added, followed by rinsing using 50 ml of methanol, upon which a white slurry was obtained which, after 15 minutes' stirring, was heated to 45°C in 6 minutes so that a solution was obtained. The solution

was subsequently cooled down to 26°C in 6 minutes and then evaporated at 36°C using the rotavapor (in 40 minutes). This yielded 38.6 g of a white solid, which was unambiguously characterized via $^1$H-NMR as being the 1:1 salt of APM and SacH; its melting point was 203°C. The quantity of product obtained corresponds to roughly 10 cmoles, which means the isolated product yield is almost 100%. X-ray diffractometry on this product produced a similar diffraction pattern as found in comparative experiment 1A. It is noted that in the comparative experiments 1A and 1B carried out by applicant no differences in the end product formed could be observed, although ES-A-8604677 suggests this.

Comp. Exp. 1C.

Using a method analogous to that of comparative experiment 1A. an experiment was carried out using 8.2 g of acesulfamic acid (5 cmoles) instead of SacH. The solid white product eventually obtained weighed 23.1 g and was unambiguously characterized as being the 1:1 salt of APM and acesulfamic acid by means of $^1$H-NMR. The moisture content was 0.76%; the APM content and the acesulfamate content were found to be 62% and 35%, respectively (theoretical values: 64% and 36%). The quantity of product obtained corresponds to about 5 cmoles, which means the yield of isolated product was almost 100%. X-ray diffractometry on this product yielded a diffraction pattern as shown in Figure 2. This is clearly a different crystal modification than in the products of, for example, experiments 4a. and 2a.-2k.

Comp. Exp. 1D.

Using a method analogous to that of comparative experiment 1B. an experiment was carried out using 16.4 g of acesulfamic acid (10 cmoles) instead of SacH. The solid white product eventually

obtained weighed 46.4 g and was unambiguously characterized as being the 1:1 salt of APM and acesulfamic acid by means of $^1$H-NMR. The moisture content was 0.89%; the APM content and the acesulfamate content were found to be 63% and 34%, respectively (theoretical values: 64% and 36%). The quantity of product obtained corresponds to about 10 cmoles, which means the yield of isolated product was about 100%. X-ray diffractometry on this product yielded a diffraction pattern that is comparable to that of Figure 2.

Other experimental results:

Of a number of the products obtained in the above-mentioned experiments and comparative experiments the following values were determined: (a) thermal stability (at 70°C and/or at 120°C) and (b) dissolution rate. By way of comparison the same was done for a number of reference substances. As regards the thermal stability of the APM containing substances, attention was paid in particular to the increase in the diketopiperazine decomposition product (DKP) in wt.% relative to the dry product. The results are summarized in the following table. It was also established that the salts included in the table are not hygroscopic. These results clearly prove that the products obtained via the process of the invention and the new crystal modification of the salt of APM and acesulfamic acid have particularly good properties.

| Experiment/ Comparative experiment or reference substance | moisture content (wt.%) | DKP content (wt.%) | Increase in DKP content (wt.%) 70 hours, 70°C | Increase in DKP content (wt.%) 1 hour, 120°C | Dissolution rate (minutes) |
|---|---|---|---|---|---|
| exp. 1a. (APM-Sac) | 0.03 | 0.01 | 0 | 0 | 1 |
| exp. 1b. (APM-Cyc) | 0.16 | 0.18 | * | 0.14 i) | * |
| exp. 2a. (APM-Ace) | 0.11 | 0.01 | 0 | 0 | 1 |
| exp. 4a. (APM-Ace) | 0.12 | 0.01 | * | 0 ii) | 1 |
| exp. 4c. (APM-Ace) | 0.04 | 0.01 | 0 | 0 ii) | 1 |
| comp. exp. 1A (APM-Sac) | * | 0.53 | 0 | ≃ 0 | * |



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| Experiment/ Comparative experiment or reference substance | moisture content (wt.%) | DKP content (wt.%) | Increase in DKP content (WT.%) 70 hours, 70°C | Increase in DKP content (wt.%) 1 hour, 120°C | Dissolution rate (minutes) |
|---|---|---|---|---|---|
| comp. exp. 1B (APM-Sac) | * | 0.21 | 0 | ≃ 0 | * |
| comp. exp. 1C (APM-Ace) | 0.76 | 0.35 | 1.27 iii) | 2.04 iv) | * |
| comp. exp. 1D (APM-Ace) | 0.89 | 0.32 | 0.52 iii) | 2.18 iv) | * |
| APM granulate<br>APM powder (ref) | 2.30<br>2.60 | 0.18<br>0.04 | 0.75<br>0.20 | 2.09<br>2.34 | 4 **)<br>2-3 |
| AceH (ref) | * | * | * | degradation v) | * |
| SacH (ref) | * | * | * | stable | * |

Notes to the table:

* not determined

i) pale yellow discolouration; no significant

decomposition of the cyclamate part

ii) fully stable, white product

iii) pale yellow; with hplc some degradation of the Ace part can be observed

iv) yellow/yellow-brown colour, with some degradation of the Ace part

v) yellow/orange colour; strong degradation; hydrogen sulphide odour

**) < 200 $\mu$m fraction (NB: 200-700 $\mu$m fraction: 7 minutes)

Explanation of the annexed figures

Figure 1 X-ray diffraction pattern of the new crystal modification of the salt of APM and acesulfamic acid. This diffraction pattern was made of the product of experiment 4a. For recording technique, etc., see point e. of the introduction to the experimental part.

Figure 2 X-ray diffraction pattern of the crystal modification of the salt of APM and acesulfamic acid as would have been obtained upon application of the process according to ES-A-8604766. This diffraction pattern was made of the product of comparative experiment 1C. For recording technique, etc., see point e. of the introduction to the experimental part.

CLAIMS:

1. Process for the preparation in a liquid medium of sweetening salts consisting of two sweetener components, starting from a sweetener derived from aspartic acid and a derivative of an organic sweetening acid which corresponds to an intense sweetener not derived from aspartic acid, wherein the following are added to the liquid medium, in any order of the steps (a), (b) and (c):

a) as component (i) the sweetener derived from aspartic acid;

b) as component (ii) a salt of an organic sweetening acid which corresponds to an intense sweetener not derived from aspartic acid;

c) as component (iii) a strong acid; and

d) the components then present in the system are allowed, optionally with agitation, to react for at least one minute, upon which the sweetening salt is formed, and

e) the sweetening salt is isolated from the resulting reaction mixture.

2. Process according to claim 1, wherein at least at the end of step (d), at least 1.0 wt.% of solid material is present in the reaction mixture.

3. Process according to claim 1 or 2, wherein the sweetener derived from aspartic acid and the salt of the organic acid which corresponds to an intense sweetener not derived from aspartic acid are applied in a molar ratio in the range from 0.2:1 to 5:1.

4. Process according to any one of claims 1-3, wherein the sweetener derived from aspartic acid and the

salt of the organic acid which corresponds to an intense sweetener not derived from aspartic acid are applied in a molar ratio in the range from 0.5:1 to 2:1.

5. Process according to any one of claims 1-4, wherein the sweetener derived from aspartic acid and the salt of the organic acid which corresponds to an intense sweetener not derived from aspartic acid are applied in a molar ratio of about 1:1.

6. Process according to any one of claims 1-5, wherein the liquid medium is chosen from the group formed by water, polar organic solvents, apolar organic solvents as well as water-miscible or water-immiscible solvent blends, and mixtures with components of the above-mentioned liquids, including aqueous media.

7. Process according to claim 6, wherein the liquid medium is an aqueous medium.

8. Process according to claim 6, wherein the liquid medium is water.

9. Process according to any one of claims 1-8, wherein the strong acid has been chosen from the group formed by hydrochloric acid, sulphuric acid or phosphoric acid, and that the acid used in (c) is applied in the form of a solution, concentrated or not, of the strong acid or, if the acid is hydrochloric acid, as gaseous HCl.

10. Process according to any one of claims 1-9, wherein the total molar quantity of $H^+$ of the strong acid is at least equal to 25% of the molar quantity of the sweetener derived from aspartic acid.

11. Process according to any one of claims 1-9, wherein the total molar quantity of $H^+$ of the strong acid is equimolar to the sweetener derived from aspartic acid.

12. Process according to any one of claims 1-11, wherein the reaction of the components in step (d) takes place while agitation is being applied.

13. Process according to any one of claims 1-12, wherein one or two of the three components (i), (ii) and (iii) are added to the liquid medium and subsequently the components(s) not yet present is (are) added.

14. Process according to claim 13, wherein the addition of the components(s) not yet present is carried out gradually.

15. Process according to claim 13 or 14, wherein components (i) and (iii) are added to an aqueous medium in the form of a salt of component (i) with a strong acid.

16. Process according to claim 13 or 14, wherein the salt of the organic sweetening acid that is used in step (b) is prepared in situ by allowing the salt of the organic sweetening acid to react with a base.

17. Process according to any one of claims 1-14, wherein at least a part of the strong acid is added in step (c), and during step (d) gradual addition of strong acid is continued.

18. Process according to any one of claims 1-17, wherein the reaction of the components in step (d) is carried out at elevated temperature and the system obtained is subsequently gradually cooled down to a temperature in the 0-20°C range.

19. Process according to any one of claims 1-17, wherein the reaction of the components in step (d) is carried out in the 40-70°C range and the system obtained is subsequently gradually cooled down to a temperature in the 0-20°C range.

20. Process according to any one of claims 1-19, wherein the sweetening salt is isolated in step (e) by separating the sweetening salt in the form of a product already precipitated in the liquid medium, or by crystallizing out and separating the sweetening salt in a known manner from the liquid medium after separation of any inorganic salt precipitate that has formed, the choice depending on the liquid medium chosen.

21. Process according to any one of claims 1-20, wherein the sweetening salt isolated in step (e) is subsequently washed and dried in a known manner, and is optionally recrystalized and/or purified further in a known manner.

22. Process according to any one of claims 1-21, wherein the salt of the organic acid which corresponds to an intense sweetener not derived from aspartic acid has been chosen from the group formed by potassium, sodium, calcium, ammonium and secondary or tertiary amine salts.

23. Process according to any one of claims 1-22, wherein the sweetener derived from aspartic acid is aspartame or alitame.

24. Process according to any one of claims 1-19, wherein the organic acid which corresponds to an intense sweetener not derived from aspartic acid has been chosen from the group formed by acesulfamic acid, saccharinic acid or cyclamic acid.

25. Sweetening salt, consisting of two sweetener components, of a sweetener derived from aspartic acid and an organic acid which corresponds to an intense sweetener not derived from aspartic acid, with less than 0.5% degradation when heated for 60 minutes at 120°C, or less than 0.5% degradation when heated for 70 hours at 70°C, and with a moisture content < 0.5 wt.%.

26. The sweetening salt of claim 25, wherein the moisture content is < 0.2 wt.%.

27. Crystal modification of a sweetening salt according to claim 25 or claim 26 of aspartame and acesulfamic acid, wherein the presence of characteristic X-ray diffraction lines at D-values of about 11.8, 6.04 and 5.02, and by the absence of intense lines at D-values of 13.5 and 6.76 (measured by X-ray diffractometry using Cu-$K_\alpha$ radiation).

28. Use of a sweetening salt prepared according to the process of any one of claims 1-24 or of a sweetening salt according to any one of claims 25-27 in foodstuff compositions, confectionery, sweets or chewing gums.

29. Use of a crystal modification of a sweetening salt of aspartame and acesulfamic acid according to claim 22 in foodstuff compositions, confectionery, sweets or chewing gums.

30. The use of a crystal modification of a sweetening salt of aspartame and acesulfamic acid according to claim 29 in confectionery.

31. Preparations of sweetening salts according to any one of claims 25-27.

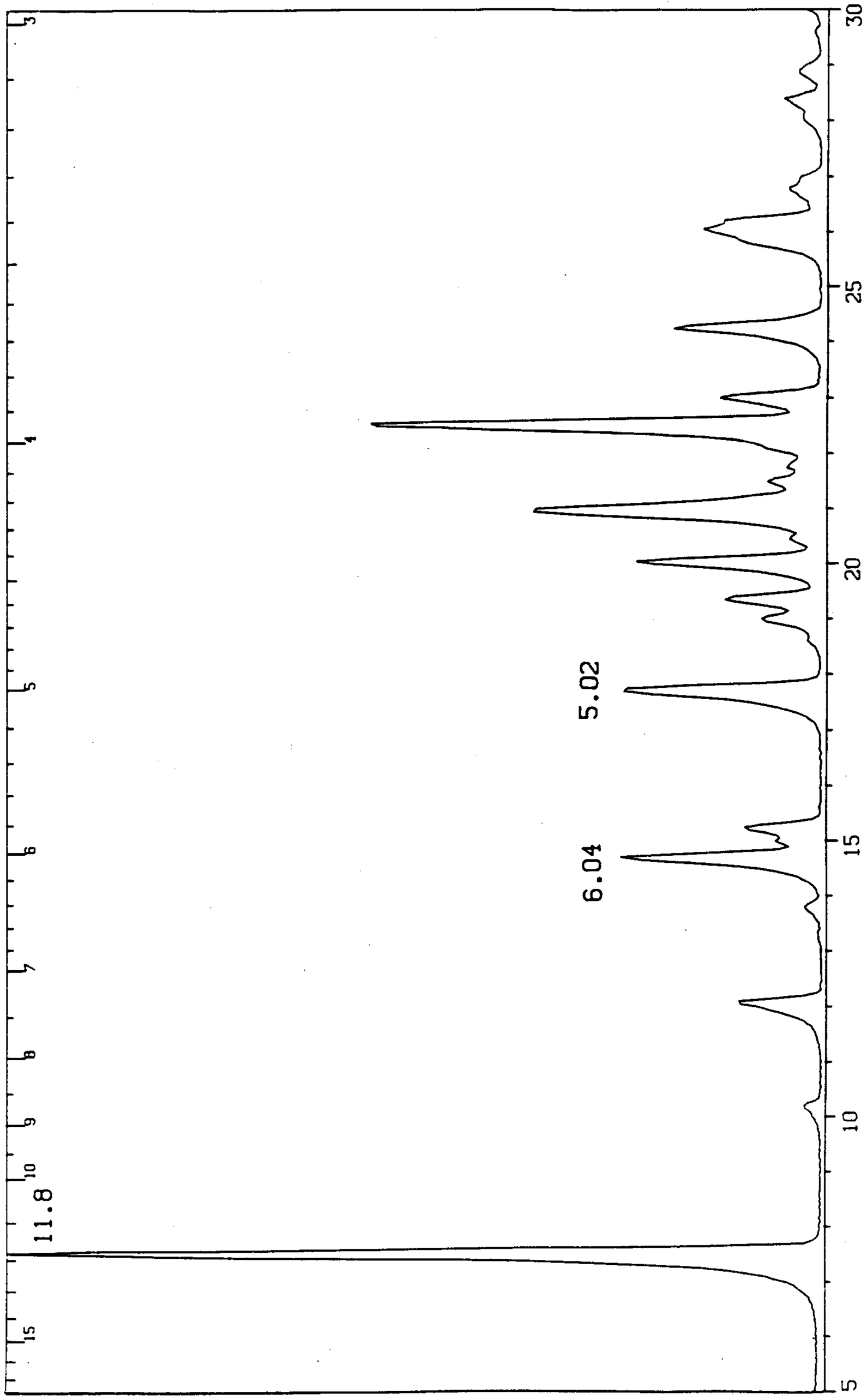
D-VALUE (Å)
3
4
5
6
7
8
9
10
11.8
15
Intensity
5.02
6.04
30
25
20
15
10
5
2 theta (degrees)

FIG. 1

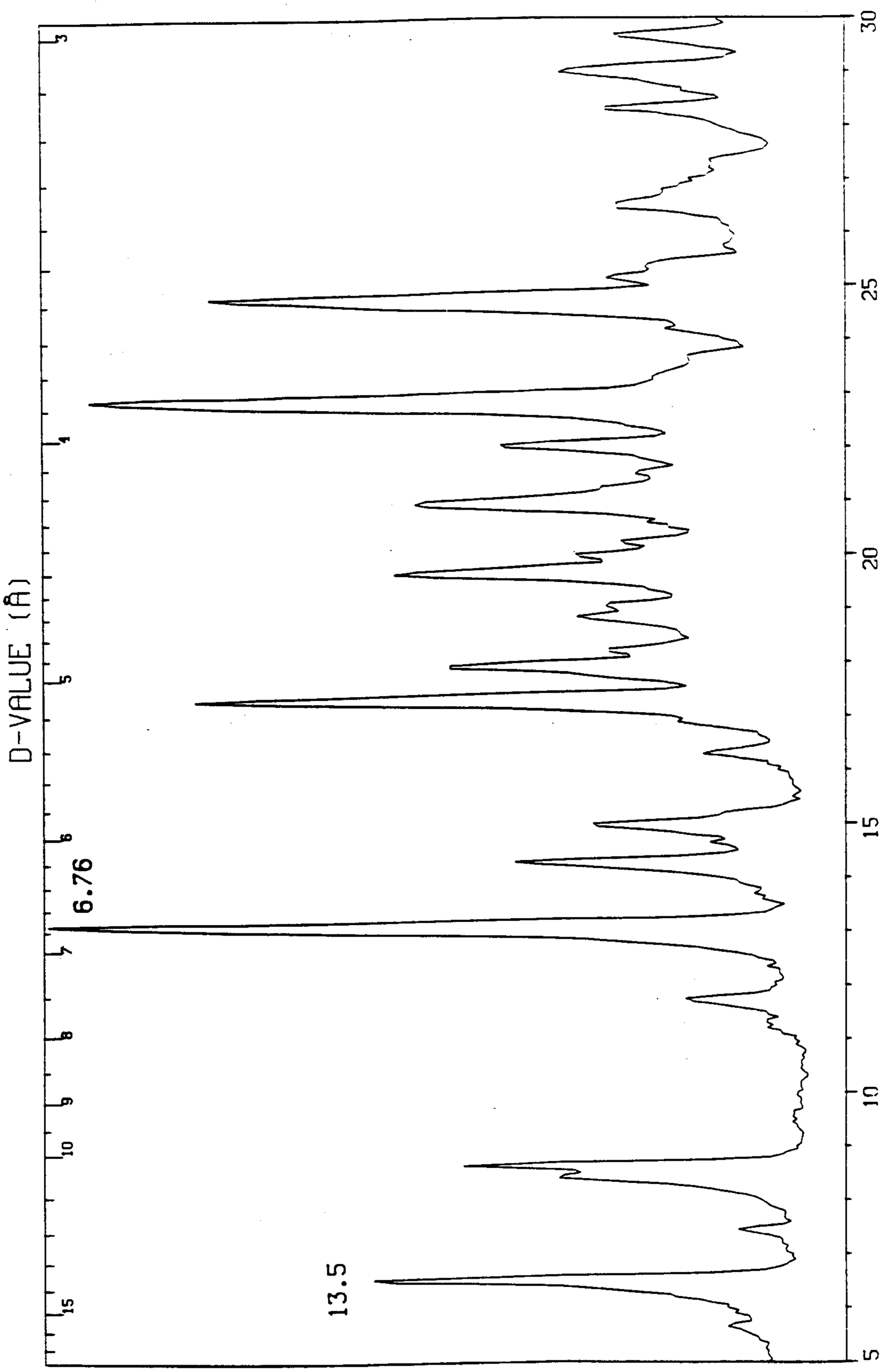
D-VALUE (Å)
3
4
5
6
7
8
9
10
15
6.76
13.5
30
25
20
15
10
5
2 theta (degrees)
Intensity

FIG. 2