

(19) **DANMARK**

(10) **DK/EP 4208436 T3**



(12)

Oversættelse af europæisk patentskrift

Patent- og
Varemærkestyrelsen

-
- (51) Int.Cl.: **C 07 C 227/02 (2006.01)** **C 07 C 277/00 (2006.01)** **C 07 C 279/14 (2006.01)**
- (45) Oversættelsen bekendtgjort den: **2024-07-22**
- (80) Dato for Den Europæiske Patentmyndigheds bekendtgørelse om meddelelse af patentet: **2024-05-01**
- (86) Europæisk ansøgning nr.: **21765884.8**
- (86) Europæisk indleveringsdag: **2021-08-18**
- (87) Den europæiske ansøgnings publiceringsdag: **2023-07-12**
- (86) International ansøgning nr.: **EP2021072929**
- (87) Internationalt publikationsnr.: **WO2022048909**
- (30) Prioritet: **2020-09-01 EP 20193773**
- (84) Designerede stater: **AL AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HR HU IE IS IT LI LT LU LV MC MK MT NL NO PL PT RO RS SE SI SK SM TR**
- (73) Patenthaver: **Evonik Operations GmbH, Rellinghauser Straße 1-11, 45128 Essen, Tyskland**
- (72) Opfinder: **STAHL, Timo, , 63694 Limeshain, Tyskland**
RONNEBURG, Axel, , 63457 Hanau, Tyskland
ROTH, Philipp, , 63456 Hanau, Tyskland
- (74) Fuldmægtig i Danmark: **RWS Group, Europa House, Chiltern Park, Chiltern Hill, Chalfont St Peter, Bucks SL9 9FG, Storbritannien**
- (54) Benævnelse: **FREMGANGSMÅDE TIL FREMSTILLING AF GUANIDINOEDDIKESYRE**
- (56) Fremdragne publikationer:
EP-A1- 3 677 329
CN-A- 102 329 250

DESCRIPTION

Description

[0001] Guanidino acetic acid (GAA) is a colorless crystalline organic compound used as animal feed additive (e.g., WO2005120246 A1 and US2011257075 A1). GAA is a natural precursor of creatine (e.g. Humm et al., *Biochem. J.* (1997) 322, 771-776). Therefore, the supplementation of GAA allows for an optimal supply of creatine in the organism.

[0002] The present invention concerns an improved method for preparing guanidino acetic acid (GAA) by reacting cyanamide with glycine in an aqueous reaction mixture in the presence of a base.

[0003] The production of GAA by adding cyanamide to glycine was first described in 1861 (M. Strecker, *comptes rendus* 1861, 52, 1212; cited in: *Ber. Chem. Ges.* (now: *Eur. J. Inorg. Chem.*) 1908, 41, 4385). A weakly alkaline aqueous ammonia solution was used as the reaction medium. More recent publications also include reaction conditions with sodium hydroxide, sodium bicarbonate, or sodium carbonate as the base for setting the pH (e.g., CN 102329250 A and CN 101462983 A).

[0004] EP3677329 discloses a method for preparing guanidino acetic acid (GAA) by reacting glycine and cyanamide, characterized in that the anionic impurities are removed from the process solution by electrodialysis.

[0005] An alkaline environment (pH 8-10) is necessary for the production of GAA from cyanamide and glycine. In an alkaline environment, undesirable by-products of cyanamide, such as dicyandiamide, ammonia, and urea, are also formed (Buchanan and Barsky, *J. Am. Chem. Soc.* Vol. 52, 195, 1930). An excess of glycine can be used for suppression. Two GAA production methods from cyanamide and glycine are described in the literature:

1. A) Adding a cyanamide solution to an alkaline glycine solution (fed batch; Figure 1)
 2. B) Addition of glycine and cyanamide in a continuously operated reaction system with continuous recirculation of the glycine-containing mother liquor after product separation. In the process the glycine concentration is set higher than the cyanamide concentration (Figure 2).
1. A) Fed-Batch: A large amount of base is necessary to adjust the pH value, because the glycine provided has an unfavorable pH buffering effect. During the reaction, however, glycine is consumed and the buffer effect diminishes, the pH rises too high and worsens the yield and selectivity. This undesired effect can be prevented by adding acid, but has not yet been described. The pH control with acid leads to an overall high rate of salt formation.
 2. B) Continuously operated reaction system: For technical reasons, continuous operation allows only a small excess of glycine in the reactor (typically: glycine: cyanamide = 2: 1), otherwise the circuit becomes too large. This results in poor selectivities. At the same time, by-products have to leave the cycle, otherwise there is a risk of accumulation. However, such a purge stream also removes large amounts of glycine, which are then

lost.

[0006] Both process variants presented come with disadvantages. High selectivities can only be achieved in a batch process, but relatively high amounts of base are necessary for good reaction performance.

[0007] The problem to be solved by the present invention is to provide a method for preparing guanidino acetic acid (GAA) by reacting cyanamide with glycine in an aqueous reaction mixture in the presence of a base that avoids high molar amounts of base or acid for pH control under maintaining the reaction selectivity and product yield.

[0008] This is achieved by a method for preparing guanidino acetic acid (GAA) from cyanamide and glycine, wherein cyanamide and glycine are continuously added to a pre-mixed aqueous solution comprising glycine and base characterized in that the rate of addition of cyanamide and glycine is adjusted such that the molar ratio of base to glycine within the reaction mixture is kept constant at 0.1 to 0.4 over the entire reaction period.

[0009] Suitable bases for the method according to the present invention are e.g. the hydroxides, the bicarbonates, or the carbonates of potassium or sodium.

[0010] In the method according to the present invention as described above, glycine is used as both, reagent and acid regulator. Therefore, the further addition of base, such as sodium hydroxide (NaOH), is avoided. Due to this particular reaction control the very high molar glycine : cyanamide ratio allow for high selectivities. Typical glycine : cyanamide ratios for a reaction according to the present invention in the moment when cyanamide and glycine are added to the reaction mixture are up to 100:1, whereas in conventional continuous processes the glycine : cyanamide ratios in the moment when cyanamide and glycine are added to the reaction mixture are below 5:1 leading to unwanted side products, such as dicyandiamide, ammonia, and melamine.

[0011] In a particular embodiment of the method according to the present invention cyanamide is reacted with an overall equimolar amount of glycine, wherein in a subsequent step ("Phase II" of the reaction) the remaining molar amount of cyanamide without glycine is continuously added to the glycine containing reaction mixture under maintaining the pH of the reaction mixture below 10 by adding an acid.

[0012] The pH of the reaction mixture may be measured by means of an electronic pH meter or by means of pH indicator paper.

[0013] The reaction Phase II does not only allow for full cyanamide conversion, but also for full glycine conversion (cf. Example 9).

[0014] The acid added to the reaction mixture for pH control may be sulphurous acid, acetic acid, hydrochloric acid, carbonic acid, formic acid or phosphorous acid, preferably acetic and sulphurous acid.

[0015] In a further embodiment cyanamide and glycine are simultaneously added to the reaction mixture in the form of a mixture comprising both, cyanamide and glycine.

Experimental Part

General Information

[0016] Suppliers and devices used in experiment 1:

- Glycine, p.a.: Merck KGaA, Darmstadt (Germany)
- Hydrochloric acid (aq.): Merck KGaA, Darmstadt (Germany)
- Formic acid: Merck KGaA, Darmstadt (Germany)
- Cyanamide 50% in H₂O: ABCR GmbH, Karlsruhe (Germany)
- Sodium hydroxide: Merck KGaA, Darmstadt (Germany)
- Membrane pump Fink Ritmo R05
- Piston pump Ismatec
- KPG Stirrer

[0017] Suppliers used for all other experiments:

- Glycine, p.a.: Evonik Rexim (Nanning) Pharmaceutical Co. Ltd., Nanning (China)
- Sodium hydroxide 50% in H₂O: VWR International, Radnor (USA)
- Cyanamide 50% in H₂O: Brenntag, Essen (Germany)

[0018] Analytics:

- GAA analysis via Agilent HPC
 - Derivatization: none
 - Column: Zorbax SB-Phenyl; column temperature: 30°C
 - UV-Detection at 200 nm
 - Eluent: 1780 g H₂O + 68 g *ortho*-phosphoric acid 85 wt.-% in H₂O
 - Flow: 0.4 mL/min
 - Retention time: 15.1 min
- The pH of the reaction mixture may be measured by means of an electronic pH meter or by means of pH indicator paper.

Example 1

[0019] Identification of best pH-value for the reaction of cyanamide with glycine to form

guanidino acetic acid (GAA)

[0020] Semi-batch trials were conducted to identify the best pH-value for the synthesis of guanidino acetic acid (GAA). For these experiments, glycine (32 g, 0.42 mol, 2.0 equiv.) in water (variable amount to adjust total glycine concentration) was placed in a 250 mL four-necked flask, equipped with a condenser, KPG-stirrer, thermometer, and pH-electrode. The pH-value was carefully adjusted by either NaOH aqueous solution (40 wt-% in H₂O), NaOH, HCl (aq.), or formic acid, thereby ending up with a total glycine concentration of 30 wt-%.

[0021] Cyanamide (50 wt-% in H₂O, 18 g, 0.21 mol, 1.0 equiv.) was added dropwise ($v = 1$ mL/min, $t = \text{ca. } 24$ min) at 80°C under stirring. After 2 h at 75°C, the formed suspension was filtered, and the wet cake was dried. HPLC analysis of the dry cake was performed to determine the GAA purity, and to calculate the yield.

[0022] The results for different pH values are shown in Table 1.

Table 1:

pH value	yield GAA [%]
8.0	63.6
9.0	81.6
9.6	82.9
10.0	78.8
11.0	45.0

[0023] Very poor yields were obtained with pH values < 8 or pH values > 11 (not shown).

Example 2

[0024] Semi-Batch at 19 GLY-Mol-% NaOH

[0025] In a 50 L reaction device, cyanamide (50 wt-% in H₂O, 4.5 kg, 54 mol, 1.0 equiv., 24 mL/min for 178 min) was added to a solution of glycine (5.8 kg, 77 mol, 1.4 equiv.) and sodium hydroxide (50 wt-% in H₂O, 1.2 kg, 15 mol) in water (16 kg, glycine content of solution: 25 wt-%) at 82°C under stirring. After stirring for another 2 h at 82°C the GAA yield was determined by HPLC analysis of the formed suspension.

[0026] GAA yield: 88% (5.6 kg).

[0027] NaOH molar content in respect of glycine: 19%

[0028] pH value at reaction start: 9, pH value at reaction end: 10.

Example 3

[0029] Semi-Batch at 13 GLY-Mol-% NaOH

[0030] In a 50 L reaction device, cyanamide (50 wt-% in H₂O, 4.5 kg, 54 mol, 1.0 equiv., 24 mL/min for 178 min) was added to a solution of glycine (5.8 kg, 77 mol, 1.4 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.77 kg, 9.7 mol) in water (17 kg, glycine content of solution: 25 wt-%) at 82°C under stirring. After stirring for another 2 h at 82°C the GAA yield was determined by HPLC analysis of the formed suspension.

[0031] GAA yield: 76% (4.8 kg).

[0032] NaOH molar content in respect of glycine: 13%

[0033] pH value at reaction start: 9, pH value at reaction end: 9.5.

Example 4

[0034] Semi-Batch at 9 GLY-Mol-% NaOH

[0035] In a 50 L reaction device, cyanamide (50 wt-% in H₂O, 4.5 kg, 54 mol, 1.0 equiv., 24 mL/min for 178 min) was added to a solution of glycine (5.8 kg, 77 mol, 1.4 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.56 kg, 7.0 mol) in water (17 kg, glycine content of solution: 25 wt-%) at 82°C under stirring. After stirring for another 2 h at 82°C the GAA yield was determined by HPLC analysis of the formed suspension.

[0036] GAA yield: 63% (4.0 kg).

[0037] NaOH molar content in respect of glycine: 9%

[0038] pH value at reaction start: 8.9, pH value at reaction end: 9.3.

Example 5

Method according to the present invention

[0039] at 5 GLY-Mol-% NaOH, with 20% Glycine content in reactor at start

[0040] In a 50 L reaction device, both cyanamide (50 wt-% in H₂O, 4.5 kg, 54 mol, 1.0 equiv., 24 mL/min for 178 min) and a solution of glycine (4.6 kg, 62 mol, 1.1 equiv.) in water (14 kg, glycine content of solution: 25 wt-%, in total 107 mL/min for 178 min) were added to a solution of glycine (1.2 kg, 15 mol, 0.28 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.30 kg, 3.8 mol) in water (3.2 kg, glycine content of solution: 25 wt-%) at 82°C under stirring. After stirring for another 2 h at 82°C the GAA yield was determined by HPLC analysis of the formed suspension.

[0041] GAA yield: 89% (5.7 kg).

[0042] NaOH molar content in respect of glycine: 5%

[0043] pH value at reaction start: 9.5, pH value at reaction end: 8.9.

Example 6

Method according to the present invention

[0044] at 6 GLY-Mol-% NaOH, with 30% Glycine content in reactor at start

[0045] In a 50 L reaction device, both cyanamide (50 wt-% in H₂O, 4.5 kg, 54 mol, 1.0 equiv., 24 mL/min for 178 min) and a solution of glycine (4.0 kg, 54 mol, 1.0 equiv.) in water (12 kg, glycine content of solution: 25 wt-%, in total 93 mL/min for 178 min) were added to a solution of glycine (1.7 kg, 23 mol, 0.42 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.35 kg, 4.4 mol) in water (4.8 kg, glycine content of solution: 25 wt-%) at 82°C under stirring. After stirring for another 2 h at 82°C the GAA yield was determined by HPLC analysis of the formed suspension.

[0046] GAA yield: 93% (5.9 kg).

[0047] NaOH molar content in respect of glycine: 6%

[0048] pH value at reaction start: 9.3, pH value at reaction end: 9.0.

Example 7

Method according to the present invention

[0049] at 9 GLY-Mol-% NaOH, with 20% Glycine content in reactor at start, Cyanamide 30 wt-% in H₂O

[0050] In a 50 L reaction device, both cyanamide (30 wt-% in H₂O, 7.6 kg, 54 mol, 1.0 equiv., 42 mL/min for 178 min) and a solution of glycine (4.6 kg, 62 mol, 1.1 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.24 kg, 3.0 mol) in water (14 kg, glycine content of solution: 25 wt-%, in total 107 mL/min for 178 min) were added to a solution of glycine (1.2 kg, 15 mol, 0.28 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.30 kg, 3.8 mol) in water (3.2 kg, glycine content of solution: 25 wt-%) at 82°C under stirring. After stirring for another 2 h at 82°C the GAA yield was determined by HPLC analysis of the formed suspension.

[0051] GAA yield: 93% (5.9 kg).

[0052] NaOH molar content in respect of glycine: 9%

[0053] pH value at reaction start: 9.1, pH value at reaction end: 9.1.

Example 8**Method according to the present invention**

[0054] at 8 GLY-Mol-% NaOH, with 20% Glycine content in reactor at start, Cyanamide 30 wt-% in H₂O

[0055] In a 50 L reaction device, both cyanamide (30 wt-% in H₂O, 7.6 kg, 54 mol, 1.0 equiv., 42 mL/min for 178 min) and a solution of glycine (4.6 kg, 62 mol, 1.1 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.20 kg, 2.5 mol) in water (14 kg, glycine content of solution: 25 wt-%, in total 107 mL/min for 178 min) were added to a solution of glycine (1.2 kg, 15 mol, 0.28 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.30 kg, 3.8 mol) in water (3.2 kg, glycine content of solution: 25 wt-%) at 82°C under stirring. After stirring for another 2 h at 82°C the GAA yield was determined by HPLC analysis of the formed suspension.

[0056] GAA yield: 85% (5.4 kg).

[0057] NaOH molar content in respect of glycine: 8%

[0058] pH value at reaction start: 8.5, pH value at reaction end: 9.5.

[0059] The results of Examples 5 to 8 are shown in Table 3 and in Figure 6.

Example 9**Method according to the present invention**

[0060] at 11 GLY-Mol-% NaOH, with 40% Glycine content in reactor at start

[0061] + Reaction phase II (Add additional Cyanamide to a final GLY:CA ration of 1:1)

[0062] Reaction Phase I:

In a 50 L reaction device, both cyanamide (50 wt-% in H₂O, 4.5 kg, 54 mol, 0.70 equiv., 24 mL/min for 178 min) and a solution of glycine (3.5 kg, 46 mol, 0.60 equiv.) in water (11 kg, glycine content of solution: 25 wt-%, in total 79 mL/min for 178 min) were added to a solution of glycine (2.3 kg, 31 mol, 0.40 equiv.) and sodium hydroxide (50 wt-% in H₂O, 0.66 kg, 8.3 mol) in water (6.5 kg, glycine content of solution: 24 wt-%) at 82°C under stirring.

[0063] Reaction Phase II:

Immediately after reaction phase I, cyanamide (50 wt-% in H₂O, 1.9 kg, 23 mol, 0.30 equiv., 24 mL/min for 74 min) was added under stirring at 82°C and the pH-value of the reaction was controlled by addition of H₂SO₄ (10% in water, threshold: pH ≤ 10). After stirring for another 5

h at 82°C the GAA yield was determined by HPLC analysis of the formed suspension.

[0064] GAA yield based on Cyanamide: 76% (5.9 kg GAA), GAA yield based on Glycine: 76%.

[0065] NaOH molar content in respect of glycine: 11%

[0066] pH value at reaction start: 10, pH value at reaction end: 10

[0067] Final GLY-concentration in process: 1.3 wt-% (aim of this experiment to keep yield high, and to minimize this value).

Table 2: Results of Examples 2-9

Ex. No.	Overall Cyanamide [mol]	Overall Glycine [mol]	Overall Base [mol]	GAA [mol]	molar ratio Base : Glycine	molar ratio Base : Cyanamide	Yield based on Cyanamide	Yield based on Glycine	Molar ratio Glycine : Cyanamide
2	54	77	15.0	47.8	0.19	0.28	89%	62%	1.4
3	54	77	9.7	41.0	0.13	0.18	76%	53%	1.4
4	54	77	7.0	34.2	0.09	0.13	63%	44%	1.4
5	54	77	3.8	48.2	0.05	0.07	89%	63%	1.4
6	54	77	4.4	50.4	0.06	0.08	93%	65%	1.4
7	54	77	6.8	50.4	0.09	0.13	93%	65%	1.4
8	54	77	6.3	46.1	0.08	0.12	85%	60%	1.4
9	77	77	8.3	58.9	0.11	0.11	77%	77%	1.0

Examples 2-4: Fed batch.

Examples 5-8: New method,

Example 9: New method + Phase II.

[0068] Compared to the new method, the fed-batch tests have relatively high base: raw material ratios, but at the same time no improved yields. On the contrary, the yield actually improves, which can be attributed to better control of the pH value. This applies to both, the yield based on cyanamide and glycine.

[0069] "New method + Phase II" (cf. Example 9) means that attention was paid to full conversion of the starting compounds by using glycine and cyanamide in a ratio of 1: 1 based on the overall reaction, wherein in a subsequent step the remaining molar amount of cyanamide without glycine is continuously added to the glycine containing reaction mixture under maintaining the pH of the reaction mixture below 10 by adding an acid. This was only made possible with the help of the new method, since the pH value can still be controlled.

[0070] The results of Examples 2-9 are also depicted in Figure 4.

REFERENCES CITED IN THE DESCRIPTION

Cited references

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Patent documents cited in the description

- [WO2005120246A1](#) [0001]
- [US2011257075A1](#) [0001]
- [CN102329250A](#) [0003]
- [CN101462983A](#) [0003]
- [EP3677329A](#) [0004]

Non-patent literature cited in the description

- HUMM et al. Biochem. J., 1997, vol. 322, 771-776 [0001]
- Ber. Chem. Ges. Eur. J. Inorg. Chem., 1908, vol. 41, 4385- [0003]
- BUCHANANBARSKY J. Am. Chem. Soc., vol. 52, 1951930- [0005]

Patentkrav

1. Fremgangsmåde til fremstilling af guanidinoeddikesyre (GAA) fra cyanamid og glycin, hvor cyanamid og glycin tilsættes kontinuerligt til en forblandet vandig opløsning, der omfatter glycin og base, kendetegnet ved, at hastigheden af tilsætning af cyanamid og glycin justeres, således at molforholdet mellem base og glycin i reaktionsblandingen holdes konstant på 0,1 til 0,4 i hele reaktionsperioden.

10

2. Fremgangsmåde ifølge krav 1, hvor cyanamid reageres med en stort set ækvimolær mængde af glycin, og hvor den resterende molære mængde af cyanamid uden glycin i et efterfølgende trin tilsættes kontinuerligt til den glycin-indeholdende reaktionsblanding under opretholdelse af pH i reaktionsblandingen under 10 ved tilsætning af en syre.

15

3. Fremgangsmåde ifølge krav 1 eller 2, hvor cyanamid og glycin tilsættes samtidigt til reaktionsblandingen i form af en blanding, der omfatter både cyanamid og glycin.

20

DRAWINGS

Drawing

Figure 1: Fed Batch

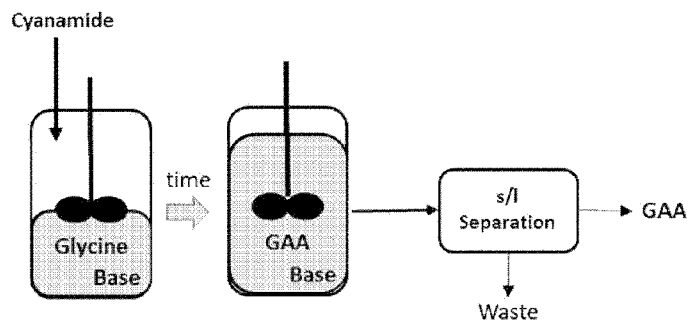


Figure 2: Continuously operated reaction system

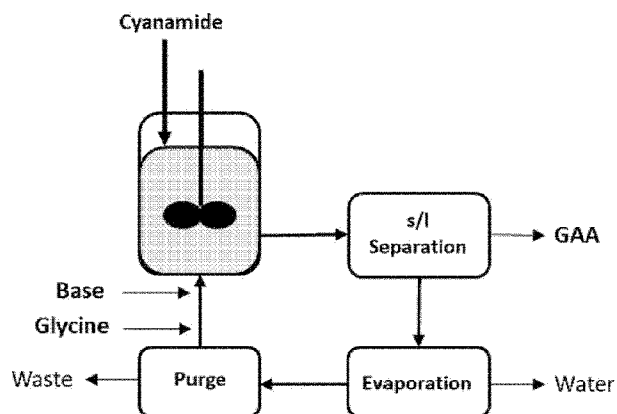


Figure 3: Fed Batch Concept according to the invention

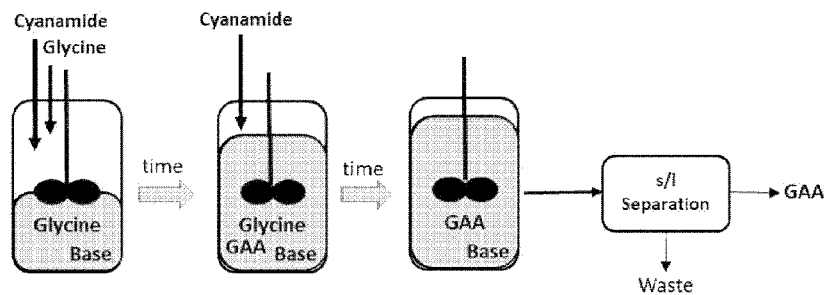


Figure 4: Overall Results of Examples 2 - 9

