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D E C I S I O N
of 12 October 2005

Case Number: T 0853/03 - 3.3.01

Application Number: 99963923.0

Publication Number: 1135392

IPC: C07D 487/08

Language of the proceedings: EN

Title of invention:

Process for preparing cross-bridged tetraaza macrocycles

Applicant:

THE PROCTER & GAMBLE COMPANY

Opponent:

-

Headword:

Macrocycles/PROCTER & GAMBLE

Relevant legal provisions:

EPC Art. 56

Keyword:

"All requests: inventive step (no) - obvious solution"

Decisions cited:

T 0930/94

Catchword:

-



Case Number: T 0853/03 - 3.3.01

D E C I S I O N
of the Technical Board of Appeal 3.3.01
of 12 October 2005

Appellant:

THE PROCTER & GAMBLE COMPANY
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Representative:

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Decision under appeal:

Decision of the Examining Division of the
European Patent Office posted 28 February 2003
refusing European application No. 99963923.0
pursuant to Article 97(1) EPC.

Composition of the Board:

Chairman: A. Nuss
Members: P. P. Bracke
R. Menapace

Summary of Facts and Submissions

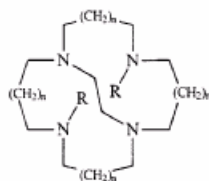
I. The appeal lies from the Examining Division's decision refusing European patent application No. 99 963 923.0, for the reason that the claimed process was not inventive over the disclosure of document

(1) WO 98/39335.

II. In particular, the Examining Division was of the opinion that document (1) suggested both catalytic and non-catalytic processes for the presently claimed reduction process and that the mere choice of temperature, pressure and pH-ranges could not render the claimed process inventive.

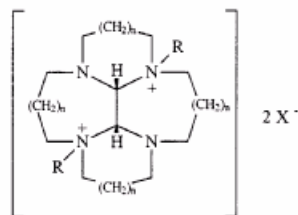
III. At the oral proceedings before the Board, which took place on 12 October 2005, the Appellant filed, as a main request, a set of fourteen claims, with Claim 1 reading:

"A process for preparing a tetraaza macrocyclic ligand having the formula:



where each R is independently C₁-C₈ linear or branched alkyl, -(CH₂)_xCO₂M, and mixtures thereof, provided both of the R units are not methyl; M is hydrogen or a salt forming cation; x is from 1 to 6; each index n is independently from 0 to 3; said process comprising the steps of:

a) catalytically hydrogenating a tetraaza macrocyclic ligand precursor having the formula:



wherein X is an anion which provides charge neutrality, **at a temperature of at least 40°C and a pH of at least 8, with from 1 ppm of a transition metal hydrogenation catalyst and a hydrogen pressure of at least 2.8×10^6 Pa (400psi)** to form a tetraaza macrocyclic ligand; and

b) optionally isolating said ligand." (emphasis added)

IV. During the written procedure, the Appellant had filed with telefax dated 21 September 2005 sets of claims according to a first to fourth auxiliary request. The claimed process differed from the one defined in the main request filed at the oral proceedings before the Board by the fact that the process was conducted

- with a hydrogen pressure of at least 5.6×10^6 Pa (800psi) (first auxiliary request);

- at a temperature of at least 60°C with a hydrogen pressure of at least 5.6×10^6 Pa (800psi) (second auxiliary request);

- at a temperature of at least 60°C with a hydrogen pressure of at least 7×10^6 Pa (1000psi) (third auxiliary request); and

- at a temperature of at least 60°C and a pH of at least 10 with a hydrogen pressure of at least 5.6×10^6 Pa (800psi) (fourth auxiliary request).

V. The Appellant essentially argued that the claimed process solves the double problem of avoiding the work-up and other problems associated with the borohydride reduction process described in document (1) and simultaneously maintaining the high yield obtained by the borohydride reduction. Neither common general knowledge nor any of the cited prior art would suggest to the skilled person how to solve such a problem by using a catalytic hydrogenation process under the pH, temperature and pressure conditions of the claimed process.

VI. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the set of claims 1 to 14 as filed during the oral proceedings, or, as auxiliary requests, on the basis of a claim 1 as filed during the oral proceedings, whereby temperature, pH and hydrogen pressure are defined as in claim 1 of each of the four auxiliary requests filed on 21 September 2005, respectively.

The wording of Claim 1 of each auxiliary request was thus identical with the wording of Claim 1 according to the main request filed at the oral proceedings before the Board, with the exception that the emphasized part therein (see point III above) read:

- first auxiliary request: "at a temperature of at least 40°C and a pH of at least 8, with at least a catalytic amount of a transition metal hydrogenation

catalyst and a hydrogen pressure of at least **5.6 x 10⁶ Pa (800psi)**" (emphasis added);

- second auxiliary request: "at a temperature of at least **60°C** and a pH of at least 8, with at least a catalytic amount of a transition metal hydrogenation catalyst and, with a hydrogen pressure of at least **5.6 x 10⁶ Pa (800psi)**" (emphasis added);

- third auxiliary request: "at a temperature of at least **60°C** and a pH of at least 8, with at least a catalytic amount of a transition metal hydrogenation catalyst and, with a hydrogen pressure of at least **7 x 10⁶ Pa (1000psi)**" (emphasis added);

- fourth auxiliary request: "at a temperature of at least **60°C** and a pH of at least **10**, with at least a catalytic amount of a transition metal hydrogenation catalyst and, with a hydrogen pressure of at least **5.6 x 10⁶ Pa (800psi)**" (emphasis added).

Reasons for the Decision

1. The appeal is admissible.

2. *Main request*

- 2.1 Article 123(2) EPC and novelty

Since the Board came to the conclusion that the main request does not meet the requirement of inventive step, it is not necessary to give any reasoning as to whether

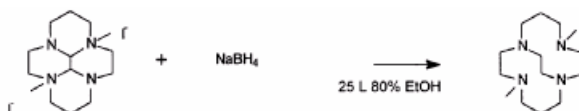
the requirements of Article 123(2) EPC and of novelty are met.

2.2 Inventive step

2.2.1 In accordance with the "problem-solution approach" applied by the Boards of Appeal to assess inventive step on an objective basis, it is in particular necessary to establish the closest state of the art forming the starting point, to determine in the light thereof the technical problem which the invention addresses and solves and to examine the obviousness of the claimed solution to this problem in view of the state of the art.

2.2.2 It was not contested that document (1) represented the closest state of the art.

Document (1) describes, as the presently claimed process, the preparation of cross-bridged tetraaza macrocyclic ligands by reducing corresponding diquaternised tetraaza macrocyclic ligand precursors. In the second paragraph on page 5 it is taught that for such reduction **any suitable reducing agent, both catalytic and non-catalytic**, may be used, but that non-catalytic reducing agents are preferred. Hydrides, and particularly borohydrides, are the preferred reducing agents. Page 10 describes in more detail a reduction reaction by using an excess of sodium borohydride and maintaining the temperature in the range of 0°C to about 80°C according to the following reaction scheme



2.2.3 According to page 1, lines 18 to 26, of the present patent application, the borohydride reduction reaction described in document (1) affords the preparation of cross bridged macropolycyclic ligands in high yield, but, due to the use of a borohydride reagent, it is necessary to break up the amine/borohydride complex during work-up and the proper recovery and disposal of boron waste products adds cost to the process. Moreover, the use of excess borohydride necessitates neutralisation with acid resulting in the evolution of large quantities of hydrogen gas.

2.2.4 Starting from the borohydride reduction process described in document (1), the Appellant submitted that the problem to be solved consisted of two parts, firstly to provide a high yield reaction and secondly to provide a reaction which avoids the work-up, waste disposal and acidification issues caused by the use of borohydride as reducing agent.

2.2.5 The application in suit claims to solve that problem by the process defined in Claim 1.

2.2.6 Therefore, the question arises whether it has been made plausible that with all the processes embraced within the wording of Claim 1 the two parts of the problem as defined in point 2.2.4 above are effectively solved.

The Appellant submitted that it was clear from the disclosure in the patent application and in the example on page 7 that the invention as claimed solves the problem.

The Board has no reason to doubt that, due to the absence of a borohydride reagent in the claimed catalytic hydrogenation process, all claimed processes avoid the work-up, waste disposal and acidification issues caused by the use of a borohydride reagent.

But, in respect of the question whether it has been made plausible that all claimed processes provide a high yield, it results from Appellant's submissions that the reduction of diquaternised tetraaza macrocyclic ligand precursors having two methyl substituents has been excluded from the wording of Claim 1, since demethylation is liable to occur and that there is less risk of dealkylation with larger alkyl groups (see letter of 14 March 2003, page 7, third paragraph). In the present application, though, it has only been shown, that 5,12-diethyl-1,5,8,12-tetraaza-bicyclo[6.6.2]hexadecane may be obtained from the corresponding diquaternised tetraaza macrocyclic ligand precursor in 81% yield and no evidence has been submitted as proof that such high yield is also obtained by catalytically hydrogenating diquaternised tetraaza macrocyclic ligand precursors substituted by higher alkyl homologs than ethyl.

From the observation that high yields are obtained when both R-substituents are ethyl and not when both substituents are methyl, however, it may not be derived that high yields are obtained with compounds having all meanings for R defined in Claim 1. This is in compliance with the principle described in decision T 930/94, according to which the knowledge of the fact that one specific member of a class of chemical compounds does not lead to the effect achieved by

several other members of this class does not, without additional indications, mean that such an effect could be attributed to all the compounds in the group.

Thus, it has not been credibly demonstrated that high yields are obtained with all claimed processes.

2.2.7 In such a case, only a less ambitious problem can be considered to be effectively solved by the claimed process, namely the provision of a process for preparing a tetraaza macrocyclic ligand from a diquaternised tetraaza macrocyclic ligand precursor, wherein the work-up, waste disposal and acidification issues caused by the use of a borohydride reagent are avoided, independent of whether a high yield is obtained or not.

2.2.8 Hence, it remains to be decided whether in the light of the teachings of the cited prior art documents a skilled person seeking to solve the problem defined in point 2.2.7 above would have arrived at the claimed catalytic hydrogenation process in an obvious way.

Since the problem to be solved thus exclusively arises from the use of borohydrides in the reduction of diquaternised tetraaza macrocyclic ligand precursors into cross-bridged tetraaza macrocyclic ligands, a skilled person would have been induced to look for replacing the borohydride by an other reducing agent.

Since document (1) states on page 5, lines 8 to 11, that any suitable reducing agent may be used for such reduction reaction, and since catalytic hydrogenation is mentioned as an alternative to a borohydride

reduction, a skilled person did not have a reason to doubt that the problem defined in point 2.2.7 above would have been solved by using a catalytic hydrogenation reduction reaction.

- 2.2.9 The Appellant argued that a skilled person would not have considered the suggestion in document (1) to use a catalytic hydrogenation as reduction reaction, because no further information about the reaction circumstances are disclosed therein.

However, since the skilled person to which document (1) is addressed is an organic chemist well-acquainted with reactions commonly used in processes for synthesising organic compounds and since catalytic hydrogenation is such a commonly used reaction, it is merely a matter of routine work for a skilled person to find out the circumstances at which catalytic hydrogenation may be conducted.

- 2.2.10 The Appellant further argued that it was not suggested in document (1) to conduct the catalytic hydrogenation at the pH, temperature and pressure ranges defined in Claim 1. In particular, he argued that example 14 of document (1) is the only catalytic hydrogenation process effectively described therein and that therein less severe reaction conditions than the ones according to Claim 1 are used.

However, although in example 14 of document (1) it is stated that "The benzyl groups are removed by catalytic hydrogenation", a skilled person would immediately be aware, that such reaction actually is a hydrogenolysis reaction for splitting off a benzyl group from an amine

and that the reaction circumstances of an hydrogenolysis reaction are not directly comparable with those of a catalytic hydrogenation reaction.

- 2.2.11 What is more, the data provided by the Appellant in his letter dated 14 March 2003 are not suitable to prove any criticality of the temperature and pressure ranges in the claimed process. It is namely clear from those data that by conducting the catalytic hydrogenation outside the temperature and pressure ranges defined in Claim 1 also diquaternised tetraaza macrocyclic ligand precursors are converted into cross-bridged tetraaza macrocyclic ligands. The fact that such conversion is slower or provides lower yields is not relevant in the present case, since obtaining the final ligands in high yield is not to be considered as part of the problem to be solved (see point 2.2.7 above).

Likewise, the fact that the catalytic hydrogenation of diethyl starting material in water at pH 7, 80°C and 12×10^6 Pa (1750 psi) hydrogen pressure gave no identifiable yield of the desired end product can only be considered as proof that under those specific circumstances catalytic hydrogenation was not suitable. From this sole experiment, however, the criticality of the pH value may not be concluded, since it does not provide proof that under other circumstances of temperature and hydrogen pressure the catalytic hydrogenation reaction may result in at least some amount of desired end compounds at pH values lower than 8.

2.2.12 The Appellant also argued that it was known that the conditions for catalytic hydrogenation of imines typically are very gentle, as illustrated by documents

(6) J. Org. Chem. 67, pages 3595 to 3600, 2002, and

(7) Tetrahedron 41, 24, pages 6063 to 6066, 1985.

Therefore the literature suggests that the conditions for imine reduction would either be the same as, or less onerous than, the conditions of example 14 of document (1).

Besides the fact that document (7) was published after the filing date of the present application and thus does not form part of the state of the art, documents (6) and (7) are concerned with the hydrogenation of an intermediately formed imine into an amine. In the absence of any evidence, the reaction circumstances for such imine/amine catalytic hydrogenation cannot be considered to be suitable for splitting a part of the carbon-nitrogen bonds, as it is the case in the claimed process.

2.2.13 The Appellant further argued that document (1) described dimethyl substituted cross-bridged tetraaza macrocyclic ligands as the preferred compounds in the borohydride reduction and that, therefore, a skilled person would first try another reduction reaction on the dimethyl analogues. Since he would thereby observe that high yields are not obtained, he would be discouraged to perform the catalytic hydrogenation reaction on other analogues.

However, since the provision of high yields is not part of the problem underlying the invention (see point 2.2.7), the only relevant question in assessing inventive step is whether a skilled person would have expected that some desired final product is formed in the catalytic hydrogenation reaction, not whether such product is obtained in high yield.

2.3 Consequently, the process of Claim 1 is obviously derivable from the prior art. Therefore, Claim 1 and, thus, the claims of the main request cannot be considered to meet the requirements of the EPC.

3. *Auxiliary requests*

The first to fourth auxiliary requests differ from the main request by a further selection of the temperature, pressure and pH ranges (see the emphasised parts under point VI above).

Since, however, the criticality of such ranges has not been proven (see point 2.2.11 above), the process of Claim 1 in any of those auxiliary requests does not meet the requirement of inventive step for the reasons set out under point 2 above. Thus, also the claims of those requests cannot be considered to meet the requirements of the EPC.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar:

The Chairman:

N. Maslin

A. Nuss