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D E C I S I O N
of 27 March 2003

Case Number: T 0588/99 - 3.3.6

Application Number: 92870122.6

Publication Number: 0583535

IPC: C11D 3/386

Language of the proceedings: EN

Title of invention:

Liquid detergents containing a peptide trifluoromethyl ketone

Patentee:

THE PROCTER & GAMBLE COMPANY

Opponent:

Unilever N.V.

Headword:

Liquid detergents/PROCTER & GAMBLE

Relevant legal provisions:

EPC Art. 56

Keyword:

"Inventive step (no)"

Decisions cited:

T 0400/98

Catchword:

In the particular situation where a document explicitly defines any compound having a certain activity as suitable component of a detergent composition and urges the person skilled in the art to look for such compounds in publications of other technical fields, such as biochemistry and medicine, it requires no inventive activity to solve the technical problem of providing an alternative to the compositions disclosed in this prior art by replacing therein the explicitly specified compounds having said activity with any other of such compounds which may be found by exploring said other technical fields (see points 2.3.3 and 2.3.4 of the Reasons of the Decision).



Case Number: T 0588/99 - 3.3.6

D E C I S I O N
of the Technical Board of Appeal 3.3.6
of 27 September 2003

Appellant: Unilever N.V.
(Opponent) Weena 455
NL-3013 AL Rotterdam (NL)

Representative: Kan, Jacob Hendrik, Dr.
Unilever N.V.
Patent Division
P.O. Box 137
NL-3130 AC Vlaardingen (NL)

Respondent: THE PROCTER & GAMBLE COMPANY
(Proprietor of the patent) One Procter & Gamble Plaza
Cincinnati
Ohio 45202 (US)

Representative: Canonici, Jean-Jacques
Procter & Gamble European Technical Center N.V.
Temselaan 100
B-1853 Strombeek-Bever (BE)

Decision under appeal: Interlocutory decision of the Opposition Division
of the European Patent Office posted 22 March
1999 concerning maintenance of European patent
No. 0 583 535 in amended form.

Composition of the Board:

Chairman: P. Krasa
Members: P. Ammendola
C. Holtz

Summary of Facts and Submissions

- I. This appeal is from an interlocutory decision of the Opposition Division concerning the maintenance of European patent No. 0 583 535 in amended form. The patent was directed to liquid detergents containing a peptide trifluoromethyl ketone (hereafter "PTK").
- II. The notice of opposition was based exclusively on lack of inventive step and cited *inter alia*:

Document (1) = WO 92/03529

Document (3) = Imperiali et al. "Inhibition of Serine Proteases by Peptidyl Fluoromethyl Ketones", *Biochemistry* 1986, vol. 25, pp.3760-3767.

At the hearing before the Opposition Division the Appellant (Opponent) argued additionally that the invention defined in the amended claims was not sufficiently disclosed either (Articles 100(b) and 83 EPC) and the Opposition Division decided to introduce this ground of opposition into the proceedings.

- III. The Opposition Division decided to maintain the patent in amended form according to the only request of the Respondent (Patent Proprietor). The amended patent comprises 16 claims of which independent claim 1 reads as follows:

"1. A liquid aqueous detergent composition, comprising:
- from 1% to 80% of a deterative surfactant,
- from 0.0001% to 1.0% of active proteolytic enzyme or mixtures thereof,

- a reversible protease inhibitor, directed to said active proteolytic enzyme or mixtures thereof, characterized in that said reversible protease inhibitor is a peptide trifluoromethyl ketone comprising from 2 to 50 amino acids, or mixtures thereof, and is comprised at a level of from 0.00001% to 5% by weight of the detergent composition."

Dependent claims 2 to 15 relate to particular embodiments of the claimed composition and claim 16 defines four specific PTKs suitable for use in the compositions of any of claims 1 to 15.

IV. In its decision, the Opposition Division held that the amended patent complied with the requirements of Articles 83, 84 and 123 EPC and that the detergent compositions according to above claim 1 were novel and provided a non obvious alternative to the detergent composition disclosed in Document (1). In particular it found that the PTKs which are disclosed in Document (3) to produce selectively reversible inhibition of certain specific proteases in certain test conditions and in the absence any surfactant, could be expected to act also as reversible inhibitors of the proteases disclosed in Document (1) in concentrate detergent compositions, so that the protease activity would be recovered upon dilution in the washing liquor of the detergent composition.

V. The Appellant appealed against this decision, presenting arguments with respect to lack of clarity (Article 84 EPC), of sufficient disclosure (Article 83 EPC) and of inventive step (Article 56 EPC).

Both parties filed conditional requests for oral

proceedings.

VI. The Appellant's argumentation in respect to lack of inventive step was based on the combination of the disclosures of Documents (1) and (3) and may be summarised as follows:

- the skilled person would have already know from Document (1) that any peptide which reversibly inhibited a serine protease could be used to produce reversible inhibition of that protease also in liquid detergent compositions;
- already the title of Document (3) defined peptidyl fluoromethyl ketones as serine protease inhibitors and the abstract and the text of this citation would have further indicated that in particular PTKs with 4 amino acid residues produced reversible inhibition thereof;
- thus it would have been obvious for the person skilled in the art who was searching for an alternative to the peptide type reversible inhibitors (hereafter "PTRIs") of the proteases used in the detergent compositions in Document (1) to try the 4 amino acid PTK suggested in Document (3) with reasonable expectation of succeeding in reversibly inhibiting these protease also in detergent compositions.

VII. In respect of inventive step the Respondent conceded that Document (1) disclosed the most relevant state of the art and that the technical problem underlying the invention was to provide other reversible protease inhibitors which were effective and suitable for use in

an aqueous liquid detergent composition containing proteases and possibly other enzymes.

It maintained however that the teaching in Document (3) related to a different technical field which would not have been considered of interest to a skilled person as it did not address the technical problem considered in the patent in suit. Moreover, the only PTKs disclosed in this document were highly specific inhibitors in analytical solutions for the specific serine proteases considered in this document. Finally, the reasons were not apparent for which the skilled person would select the PTKs among the other compounds also disclosed as reversible serine proteases inhibitors in Document (3).

Thus, it was only with the benefit of hindsight that the person skilled in the art would have combined the teaching of this document with respect to PTKs as reversible inhibitors of proteases with that of Document (1) with respect to detergent compositions and, in any case, the skilled person could reasonably expect neither that the PTKs of Document (3) effectively inhibited proteases in detergent compositions nor that in the washing liquor resulting from the dilution with water of such detergent compositions the proteases's cleaning activity would be restored.

VIII. The Appellant informed the EPO with telefax of 25 February 2003 that it would not attend the oral proceedings scheduled to take place on 27 March 2003, withdrew its request for oral proceedings and requested the Board to take a decision on the basis of the content of the file.

Also the Respondent in its telefax of 7 March 2003 announced that it would not appear at the oral proceedings and requested that a decision be taken on the basis of the content of the file.

- IX. The Appellant requested that the decision under appeal be set aside and the patent be revoked.

The Respondent requested that the appeal be dismissed.

- X. On 27 March 2003 the Chairman opened the oral proceedings and noted that none of the parties were represented. After deliberation of the Board, the Chairman announced the decision and closed the proceedings.

Reasons for the Decision

1. *Articles 54, 83, 84 and 123 EPC*

The Board is satisfied that the patent found allowable by the Opposition Division complies with the requirements of Articles 83, 84 and 123 EPC and that the subject-matter of the amended claims is novel (Article 54 EPC).

Since the subject-matter of claim 1 as upheld by the Opposition Division is found to lack inventive step it is not necessary to give further details in these respects.

2. *Article 56 EPC*

- 2.1 The subject-matter of claim 1 of the patent in suit as

amended (see point III) is a liquid aqueous detergent composition comprising a protease and a PTK acting as reversible inhibitor for such protease.

In the patent in suit this "reversible" inhibition of a protease is implicitly described (see page 2, lines 11 to 16 in combination with page 3, lines 13 to 16) as the capability of leaving unaffected the stability of other optional cleaning enzymes as long as the detergent composition remains concentrated, but regaining the proteolytic activity upon dilution with water during the washing process.

2.2 The closest state of the art and the technical problem solved

2.2.1 The patent in suit acknowledges that compositions similar to the claimed one were already known, e.g. from Document (1) (see page 2, line 42, of the patent in suit), and defines the technical problem to be solved with respect to the state of the art as that of providing other reversible protease inhibitors which are effective and suitable for use in an aqueous liquid detergent composition (page 2, lines 21 to 22, in combination with line 42).

2.2.2 It is undisputed that Document (1) disclosed enzymatic liquid detergent compositions comprising reversibly inhibited proteases in the sense as explained above. Therefore, the Board takes this citation as starting point for the evaluation of inventive step, as the Opposition Division did.

Since both parties also considered this citation as disclosing the most relevant state of the art, no

further details need to be given.

2.2.3 The Board has no reason to doubt that the technical problem defined in the patent in suit (see above 2.2.1) was actually solved by the claimed subject-matter. Since this was never contested, the Board accepts the technical problem as set in the patent in suit for evaluating inventive step as did the Opposition Division and the parties.

2.3 Inventive step

2.3.1 As underlined by the Appellant, Document (1) explicitly defines the PTRI to be used in the detergent compositions of this prior art as "any inhibitor of the peptide or protein type that reversibly inhibits the protease in question" (see page 3, lines 10 to 11). According to page 2, lines 15 to 17 the proteases considered in this document are preferably serine proteases of microbial origin.

The Board additionally observes that the above quoted general statement in Document (1) is followed by a large number of examples of these known PTRIs for microbial serine proteases, by making reference to publications in the technical fields of biochemistry and medicine (lines 10 to 26 of page 3).

Therefore, Document (1) provides the following clear instructions to the person skilled in the art of detergent compositions:

- (a) that microbial serine protease are useful in detergent formulations,

- (b) that these proteases may be reversibly inhibited by certain peptides,
- (c) that the reversible peptide inhibition of serine proteases is described also (and mainly) in biochemical/medical publications,
- (d) that any peptide compound which is known to produce reversible inhibition of a microbial serine protease reversibly inhibits such enzyme also in liquid detergent compositions.

2.3.2 The detergent compositions according to present claim 1 and comprising microbial serine proteases differ from those of Document (1) exclusively in that they contain other PTRIs than those disclosed in Document (1), i.e. the PTKs defined in claim 1 of the patent in suit.

The question to be answered for the assessment of inventive step is therefore whether it would have been obvious for the notional person skilled in the art of detergent compositions to solve the posed technical problem (see above point 2.2) by using in the detergent compositions of Document (1) PTKs instead of the PTRIs disclosed therein.

2.3.3 As observed above (see point 2.3.1) Document (1) teaches explicitly that **any** microbial serine protease inhibitors may be used in these prior art detergent compositions.

Therefore, the Board finds that the disclosure of said document *per se* renders it obvious for the skilled person to solve the posed technical problem by replacing the explicitly specified microbial serine

protease inhibitors of these prior art detergent compositions with **any** other compound which is known to be a PTRI of this enzyme.

- 2.3.4 The disclosure in Document (1) expressly directs the skilled person to search for further known and suitable PTRIs among those disclosed in publications precisely in the fields of **biochemistry and medicine** (see above point 2.3.1).

In this particular situation, the person skilled in the art of detergent compositions would certainly explore also these other technical fields, searching for publications disclosing further PTRIs for proteases. This would inevitably lead the skilled person to consider Document (3), whose relevance is evident already from its title (see point II above).

- 2.3.5 The Appellant has referred in particular to the general statement at lines 11 to 7 from the bottom of the abstract at page 3760 of Document (3), which reads: "In all cases, however, the difluoro- and trifluoromethyl ketones are better inhibitors than monofluoromethyl and nonfluorinated analogues. This improvement must be associated with the degree of hydration of the fluoromethyl ketones and the significant effect that fluorine substitution has on lowering the first pKa of the hemiacetal hydroxyl. The latter change would cause the more fluorinated inhibitor to be able to interact better with the anionic hole near the active site."

It is self-evident that the PTK analogues to serine proteases cited in this statement are PTRIs **according** to their general definition in Document (1) (see above 2.3.1).

It is also self-evident that the above cited passage of the abstract of Document (3) discloses the inhibition **in general** of serine proteases by substrate analogous PTKs corresponding to the targeted proteases.

The Board notes that such general teaching in Document (3) is explicitly supported by a well founded reasoning (as to the existence of an inhibition mechanism involving formation of an hemiacetal hydroxyl intermediate and an interaction with the anionic hole neighbouring the active site of such enzymes). In addition, the Board finds that the introductory part of this document (page 3760 left column, line 1 to right column, line 5) explicitly states that there is one recognised "mode of action" for serine proteases, and that this common mode of action is sufficient justification for expecting that any peptide having a trifluoromethyl ketone segment and an amino acid sequence mimicking a serine protease substrate should be an effective inhibitor for such an enzyme (see page 3760 from left column, line 1 to right column lines 5).

Therefore, the authors of the investigation reported in this document clearly have had several grounds for justifying the generalization of their admittedly limited experimental work: i.e. to state that the peptidyl fluoromethyl ketone analogues to the substrates of a serine protease **generally** provide inhibition of this enzyme. Accordingly, the Board finds that in the present case this generalization cannot be considered as an unfounded allegation which a skilled person would have disregarded, but rather a statement based on specifically reasoned considerations on a common "mode of action" of serine proteases, on the

influence of fluorine substitution on the chemical affinity and reactivity on peptidyl methyl ketone inhibitors in general, on expected similarities in the active site region of all serine proteases and on the hypothesised formation of a common intermediate in all these inhibition reactions.

In addition, Document (3) clarifies (see the whole section with the heading "Discussion" and in particular page 3766, right column, lines 8 to 9, also referred to by the Appellant) that the substrate analogous PTKs corresponding to the targeted proteases produce **reversible** inhibition of those enzymes.

Finally, no difficulty could arise in reducing to practice such reasoned general instruction of Document (3): it is apparent from the whole content of this citation that the incorporation of a trifluoromethyl ketone group at the C-terminal of a peptide amounts to conventional practice (see the first 6 lines of the left column at page 3760 and the already cited paragraph bridging the two columns, as well as the fact that the authors of this scientific paper have considered it not necessary to give much detail as to the synthetic method actually used to prepare the several PTKs of the experiments). This is also explicitly confirmed by the description at page 3, lines 11 to 12, of the patent in suit.

For all these reasons, the Board finds that Document (3) renders available to the person skilled in the art PTK analogues to serine protease substrates as further PTRIs for those enzymes (according to the definition in Document (1)): i.e. this citation teaches to the skilled person how to prepare for any targeted serine

protease - and thus also for any microbial serine protease specified in Document (1) - a corresponding PTRI, by providing via conventional synthetic methods a trifluoromethyl ketone terminal group to a sequence of few (preferably 4) amino acids identical to that at the C-terminal of the substrate of such serine protease.

2.3.6 The Board concludes that, since Document (1) renders obvious to solve the technical problem of providing an alternative to the compositions disclosed in this prior art by replacing therein the explicitly specified PTRI for serine proteases with any other of such compounds and instructs the notional skilled person to search for these alternative PTRI for such enzymes in publications in the technical field of biochemistry and medicine, the skilled person would have found Document (3) and replaced the PTRI specified in Document (1) by a corresponding PTK which, although not being explicitly mentioned in Document (3), was rendered available by the simple reduction into practice of the motivated general instruction given in this latter citation, in the reasonable expectation that such replacement would solve the existing technical problem.

2.3.7 The Respondent objected to the possibility of combining the disclosure of Document (1) and (3) by observing that Document (3) did not belong to the technical field of liquid detergent compositions, did not mention the same technical problem addressed in the patent in suit and in Document (1) and did not use detergent matrixes but analytical solutions to measure the inhibition performance of PTKs on proteases.

2.3.8 The Board observes that, in the absence of any evidence casting doubts as to its credibility, there is no

reason to ignore the **explicit instruction** given in Document (1) (see above point 2.3.1, instruction "d") that **any** peptide compound which has been disclosed as reversible inhibitor for a microbial serine protease may be used to reversibly inhibit the latter also in liquid detergent compositions. In addition, and as already indicated (see point 2.3.1, instruction "c"), Document (1) explicitly teaches also that the examples of further PTRIs for serine proteases may be found in **biochemical or medical** publications and, thus, urges the notional skilled person to turn to such papers when looking for a further embodiment of the invention defined in general therein.

Since Document (3) belongs to the technical fields of biochemistry and renders available to the skilled reader peptide compounds which act as reversible inhibitors for microbial serine protease, these instructions make less relevant the fact that Document (3) does not belong to the technical field of liquid detergent compositions and, of course, addressed other technical problems, as well as the fact that the reversible inhibition of the microbial serine protease has been disclosed in this citation in chemical systems different from that present in detergent compositions.

2.3.9 The Respondent has additionally stressed the (undisputed) facts that in Document (3) the reversible inhibition of serine protease was only experimentally observed with respect to two specific serine proteases different from those considered in Document (1) and that the inhibitors disclosed in Document (3) were highly specific for the targeted proteases. Hence, the skilled person searching for further PTRIs for the serine proteases disclosed in Document (1) would not

have found in Document (3) any information relevant in this respect.

- 2.3.10 The Board cannot share the Respondent's (and Opposition Division's) view that the technical teaching in Document (3) is restricted to the specific inhibitors used for this experimental work and which are undisputedly highly selective for the corresponding targeted proteases.

On the contrary, it encompasses (see point 2.3.5 above) also a reasoned general teaching as to the occurrence and the nature of the inhibition of targeted serine proteases by the corresponding PTKs. In particular, this general teaching is given in the portions of the abstract and of the text of Document (3) specifically referred to by the Appellant and is supported by well founded reasons.

- 2.3.11 Finally, the Respondent stressed the fact that Document (3) also disclosed other effective PTRIs for serine proteases (e.g. **di**fluoromethyl ketone derivatives of substrate analogues) and that it was not evident on which grounds the skilled person should have preferred PTKs to the other equivalent alternatives.

- 2.3.12 According to the established case law of the Boards of Appeal to apply one of the several equally promising solutions to a technical problem which were available to the skilled person requires no particular skills and for this reason does not involve an inventive step (see for instance T 400/98 of 19 September 2002, unpublished in the OJ, No. 4.4.6 of the reasons).

Accordingly, the Board finds that in the present case

the above fact stressed by the Respondent does not imply the exercise of any inventive skill for deriving from Document (3) that substrate analogues PTKs are alternative PTRIs for serine proteases.

2.3.13 Therefore, the Respondent's arguments are not convincing and the combination of the disclosures of Documents (1) and (3) is found to render obvious the claimed solution to the existing technical problem according to the reasoning given at points 2.3.1 to 2.3.6 above.

Consequently, the subject-matter of claim 1 does not involve an inventive step and, therefore, does not comply with the requirements of Articles 52(1) and 56 EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The European patent No. 0 583 535 is revoked.

The Registrar:

The Chairman:

G. Rauh

P. Krasa



Case Number: T 0588/99 - 3.3.6

D E C I S I O N of 23 June 2003
correcting errors in the decision
of the Technical Board of Appeal 3.3.6
of 27 March 2003

Appellant: Unilever N.V.
(Opponent) Weena 455
NL-3013 AL Rotterdam (NL)

Representative: Kan, Jacob Hendrik, Dr.
Unilever N.V.
Patent Division
P.O. Box 137
NL-3130 AC Vlaardingen (NL)

Respondent: THE PROCTER & GAMBLE COMPANY
(Proprietor of the patent) One Procter & Gamble Plaza
Cincinnati
Ohio 45202 (US)

Representative: Canonici, Jean-Jacques
Procter & Gamble European Technical Center N.V.
Temselaan 100
B-1853 Strombeek-Bever (BE)

Decision under appeal: Interlocutory decision of the Opposition Division
of the European Patent Office posted 22 March
1999 concerning maintenance of European patent
No. 0 583 535 in amended form.

Composition of the Board:

Chairman: P. Krasa
Members: P. Ammendola
C. Holtz

In application of Rule 89 EPC the decision given in case T 588/99 on 27 March 2003 is hereby corrected as follows:

The date "27 September 2003" in the decision heading in the front page is replaced by "27 March 2003"

At page 2, line 19 (point IV of the Summary of Facts and Submissions): "could be expected" is replaced by "could not be expected"

The Registrar:

The Chairman:

G. Rauh

P. Krasa