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D E C I S I O N
of 11 January 2001

Case Number: T 0687/98 - 3.3.3

Application Number: 92906029.1

Publication Number: 0527234

IPC: C08B 37/16

Language of the proceedings: EN

Title of invention:
Separating agent

Applicant:
DAICEL CHEMICAL INDUSTRIES CO., LTD.

Opponent:
-

Headword:
-

Relevant legal provisions:
EPC Art. 56, 84, 87, 88, 89

Keyword:
"Claims (main request) - support by description (no)"
"Priority - entitlement (no)"
"Inventive step (auxiliary request) - unobvious selection"

Decisions cited:
T 0133/85, T 0409/91

Catchword:
-

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Case Number: T 0687/98 - 3.3.3

D E C I S I O N
of the Technical Board of Appeal 3.3.3
of 11 January 2001

Appellant: DAICEL CHEMICAL INDUSTRIES., LTD.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 20 February 1998 refusing European patent application No. 92 906 029.1 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: C. Gérardin
Members: P. Kitzmantel
J. De Preter

Summary of Facts and Submissions

I. This appeal, which was filed on 20 April 1998, lies against the decision of the Examining Division dated 20 February 1998, refusing European patent application No. 92 906 029.1 filed on 28 February 1992 as International application PCT/JP92/00232 in the name of DAICEL CHEMICAL INDUSTRIES, claiming a JP priority of 28 February 1991 and published under No. 0 527 234 (WO 92/15617). The appeal fee was paid together with the Notice of Appeal and the Statement of Grounds of Appeal was filed on 25 June 1998.

II. The decision under appeal was based on a set of seven claims submitted with letter dated 3 July 1996, independent Claims 1 and 7 reading as follows:

"1. A process for resolving a racemic modification into optical isomers, said process comprising the step of contacting said racemic modification with a chemically bonded body contained in a separating agent or a separating apparatus, said chemically bonded body comprising a support and a cyclic oligosaccharide derivative, at least one of the 2-, 3- and 6-position hydroxyl groups of which is chemically bonded to said support through a spacer,

with the proviso that those wherein the 6-position hydroxyl group is bonded to a support through an ether linkage are excluded, and that the chemically bonded body does not comprise a support and a cyclodextrin derivative bonded to said support through a carbamate linkage."

"7. The use of a chemically bonded body contained in a separating agent or a separating apparatus for resolving a racemic modification into optical isomers,

said chemically bonded body comprising a support and a cyclic oligosaccharide derivative, at least one of the 2-, 3- and 6-position hydroxyl groups of which is chemically bonded to said support through a spacer,

with the proviso that those wherein the 6-position hydroxyl group is bonded to a support through an ether linkage are excluded, and that the chemically bonded body does not comprise a support and a cyclodextrin derivative bonded to said support through a carbamate linkage."

The further claims 2 to 6 were dependent on Claim 1.

III. The decision under appeal held that the subject-matter of Claim 1 was novel over document

D1: EP-A-0 445 604,

but did not involve an inventive step over documents

D2: JP-A-61 237 057 (considered in the form of World Patent Index, Derwent Publications Ltd., London/GB, AN 86-321 586),

D3: JP-A-01 053 152 (considered in the form of File Supplier Patent Abstracts of Japan, Japanese Patent Office, Tokyo/JP, 1 March 1989),

D4: EP-A-0 459 530,

D5: Römpps Chemie-Lexikon, 8th ed., Franckh'sche Verlagshandlung, Stuttgart 1987, pages 3455 to 3456 and

D6 : D. Stevenson and I.D. Wilson, Chiral Separations, Plenum Press, New York and London 1988, pages 4, 5 and 37.

In particular, it was obvious to use the cyclodextrine (CD) derivatives disclosed in D2 and D3 for the chiral racemate separation techniques referred to in D5, which related to the use of CDs as chiral stationary phases, and in D6, which disclosed chiral CD phases bound to silica via a spacer unit.

IV. In the course of the appeal proceedings, partly in response to the Rapporteur's communication dated 4 August 2000, the Appellant submitted several amended sets of claims, the final versions being those of the main request (comprising six claims) and of the auxiliary request (comprising five claims) filed at the oral proceedings, which took place on 11 January 2001.

(i) Independent Claims 1 and 6 of the main request read as follows:

"1. A process for resolving a racemic modification into optical isomers, said process comprising the step of contacting said racemic modification with a chemically bonded body contained in a separating agent or a separating apparatus, said chemically bonded body comprising a support and a cyclic oligosaccharide derivative, at least one of the 2- and 3-position hydroxyl groups of which is chemically bonded to said support through a spacer, with the proviso that a cyclic oligosaccharide derivative wherein the 6-position hydroxyl group is bonded to a support through an ether linkage is excluded."

"6. The use of a chemically bonded body contained in a separating agent or a separating apparatus for resolving a racemic modification into optical isomers, said chemically bonded body comprising a support and a cyclic oligosaccharide derivative, at least one of the 2- and 3-position

hydroxyl groups of which is chemically bonded to said support through a spacer, with the proviso that a cyclic oligosaccharide derivative wherein the 6-position hydroxyl group is bonded to a support through an ether linkage is excluded."

Claims 2 to 5 are dependent on Claim 1.

(ii) The auxiliary request differs from the main request

- by the insertion, before the proviso, of the passage "wherein the chemical bonding is made through at least one member selected from among ester linkages, carbamate linkages and ether linkages" into the two independent claims (i.e. Claims 1 and 5 of the auxiliary request),

- by the deletion of Claim 2, and

- by the consequential renumbering of Claims 3 to 6 of the main request into Claims 2 to 5.

V. The written and oral arguments of the Appellant may be summarized as follows:

(i) The subject-matter of Claim 1 of both requests was entitled to the claimed priority, because the feature that "at least one of the 2- and 3-position hydroxyl groups ... is chemically bonded to said support through a spacer" merely amounted to a restriction within the teaching of Claim 1 of the priority document.

(ii) Claim 1 of the main request complied with the requirements of Article 84 EPC, because the use of the term "includes" in the statement on page 3, lines 13 to 18 of the original description allowed for bonding units which were different from carbamates, esters and ethers.

(iii) The subject-matter of Claim 1 of both requests was not obvious over the citations on file, including document D1, because these did not suggest the superior enantioselectivity of cyclic polysaccharide derivatives, which were bonded to a support through a spacer on at least one of the 2- and 3-position hydroxyl groups, as compared with such cyclic polysaccharide derivatives, which were bonded through the 6-position.

(iv) This effect was demonstrated

(iv-1) by the separation factors α exhibited in Table 3 (Examples 1 to 3) of the application in suit as compared with the separation factors α exhibited in Table 3 for Examples 5 to 7, and

(iv-2) by the evidence contained in the newly cited, post-published documents

D7: Journal of Chromatography, 628(1), 11 to 22, 1993, and

D8: Journal of Liquid Chromatography, 16(4), 843 to 858, 1993.

(v) The conclusion of obviousness, which was drawn in the decision under appeal on the basis of a combination of the teachings of documents D2/D3 and documents D5/D6, could not be sustained, because documents D2 and D3 were not concerned

with the problems of optical resolution involving chiral separation and did not lend themselves, therefore, to such a combination.

VI. The Appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of the main request or the auxiliary request, both submitted at the oral proceedings.

Reasons for the Decision

1. The appeal is admissible.

2. *Late-filed evidence (Article 114(2) EPC)*

Documents D7 and D8 are not admitted for consideration, not only because they were published after the filing date of the application in suit, but also because they do not contain any information which is more pertinent to the issues under consideration than that already before the Opposition Division.

3. *Amendments (Article 123(2) EPC)*

3.1 Main request

Claims 1 and 6 are based on Claims 1, 3, 7 and 8 of the original application.

Claims 2 to 5 are based on Claims 2 and 4 to 6.

3.2 Auxiliary request

Claims 1 and 5 are based on Claims 1, 2, 3, 7 and 8 of the original application.

Claims 2 to 4 are based on Claims 4 to 6.

3.3 Therefore, the requirement of Article 123(2) EPC is met by the claims of both requests.

4. *Consistency (Article 84 EPC)*

Article 84 EPC requires that the claims shall define the matter for which protection is sought. According to the established jurisprudence of the boards of appeal this means that an independent claim must contain all essential features of the invention concerned (cf. T 0133/85, OJ EPO 1988, 441; T 0409/91, OJ EPO 1994, 653).

4.1 Claim 1, main request

4.1.1 This claim does not comply with the afore-mentioned requirement of the EPC in that it does not comprise the feature that "the chemical bonding is made through at least one member selected from among ester linkages, carbamate linkages and ether linkages".

4.1.2 According to the wording of the statement on page 10, lines 3 to 6 of the original description "[t]he linkage through which the hydroxyl group is bonded to the support **is** at least one member ..." [emphasis by the Board], this feature belongs to the claimed invention.

4.1.3 The counter-argument presented by the Appellant during the oral proceedings is not convincing, namely that the invention was not restricted to this feature in view of the statement on page 3, lines 13 to 18 of the original description "[t]he spacer **includes** carbamates, esters and ethers, when the 2- or 3-position hydroxyl group of the oligosaccharide derivative is chemically bonded to

a support, while it **includes** carbamates and esters, when the 6-position hydroxyl group thereof is chemically bonded to a support" [emphasis by the Board].

4.1.4 The above conclusion of the Board results from a proper interpretation of the latter statement in its totality and in the context of the whole description: nowhere in the original description is there any hint at bonding variants other that through carbamate, ester and ether linkages. The double use of the word "includes" in said statement cannot, therefore, be interpreted in its literal meaning (which is anyway doubtful, because it results from a translation), but in its obvious intention **to oppose the two bonding variants** through 2-/3-position or through 6-position hydroxyl groups. Thus, the term "includes" in its context is equivalent to the term "is selected from the group consisting of".

4.1.5 Claim 1 of the main request does not, therefore, comply with the requirement of Article 84 EPC.

4.1.6 Since a request must be considered as it stands, the main request is not allowable as a whole.

4.2 Claim 1, auxiliary request

This claim meets the requirements of Article 84 EPC, because it comprises the afore-mentioned feature that "the chemical bonding is made through at least one member selected from among ester linkages, carbamate linkages and ether linkages".

Auxiliary request

5. *Priority (Articles 87 to 89 EPC)*

Claim 1 of the priority document relates to a separating agent comprising a support and a cyclic oligosaccharide derivative having repeating units of the general formula (1), part or whole of the hydroxyl groups of which are displaced by functional groups having 4 to 30 atoms, and which is bonded to the support through a carbamate or ester linkage. According to formula (1) each repeating unit of the D-glucopyranoside comprises three hydroxyl groups in the positions 2-, 3- and 6.

Accordingly this claim puts the three hydroxyl positions 2, 3 and 6 on a par and does not imply any performance-related ranking of the differently bonded derivatives. It does not, therefore, comprise the disclosure of the feature of the present independent Claims 1 and 6 of a selected subgroup of cyclic oligosaccharide derivatives, at least one of the 2- and 3-position hydroxyl groups of which is chemically bonded to the support through a spacer.

Since the priority document does not comprise any other disclosure, which could be interpreted to represent the disclosure of such a selected subgroup, the claims of the auxiliary request do not enjoy the claimed priority. Consequently, the date determining the prior art status of any publication is the international filing date of the application in suit of 28 February 1992.

6. *State of the art*

6.1 Document D1

In view of the non-entitlement of the subject-matter of the auxiliary request to the claimed priority, this document, which was published on 11 September 1991, becomes prior art within the meaning Article 54(2) EPC.

D1 relates to materials for the chromatographical separation of e.g. enantiomers, consisting essentially of a support, e.g. silica gel, and of a CD bonded thereto via a carbamic acid group (Claims 1, 3 and 7). According to Example 1 4.4 mmol β-CD are reacted with 30.8 mmol chloroformic acid p-nitrophenylester and the resulting reaction product is further reacted with 10.0 g of the carrier LiChrospher$^{(R)}$100 NH_2 (5 µm). Since one mol β-CD comprises seven D-glucopyranose repeating units, each unit bearing one 6-position hydroxyl group, 30.8 mmol (4.4 x 7) 6-position hydroxyl groups are present altogether in a molar ratio to the chloroformic acid p-nitrophenylester of 1 (= 30.8/30.8).

6.2 Documents D2 and D3 (English abstracts and partial English translation of D3 submitted by the Appellant with the Statement of Grounds of Appeal)

Both documents disclose a chromatographical filler (D3: packaging material) comprising β-CD, which is chemically modified by a monoamino group (D3: chiral amino acid) in 6-position (D3: 2-, 3- or 6-position), and which is bonded to a hydrophilic porous polymer via an ionically neutral spacer.

The filler is effective for selectively absorbing and separating substances having groups like phenyl and naphthyl as well as anionic functional groups.

6.3 Document D4

In view of the non-entitlement of the subject-matter of the auxiliary request to the claimed priority, this document, which was published on 4 December 1991, becomes prior art within the meaning Article 54(2) EPC.

D4 relates to an alkyl-substituted phenylcarbamate derivative of an optical active polysaccharide, exclusive of cellulose, in which 80 to 100 percent of the hydroxyl groups have been reacted to form an all-substituted phenylcarbamoyl group. The modified polysaccharide may be supported on a porous carrier, e.g. silica, and used as chromatographical separating agent for racemic compounds (Claims 1, 3, 5 to 7; page 3, lines 10 to 36).

6.4 Document D5

The text set out in this encyclopedia under the keyword "Racemattrennung" (i.e. optical resolution) points to the technique of chromatographical separation on optical active adsorbents, including the use of CDs as chiral stationary phases (page 3456, left hand column, lines 7 to 15).

6.5 Document D6

This document states on page 4, last paragraph: "Chiral cavity type phases such as cyclodextrins bound to silica through a spacer are now also commercially available and in widespread use."

On page 37, second paragraph of the Subsection "Introduction" of the Section entitled "A note on separation of enantiomers of oxyphenonium bromide by

high-performance liquid chromatography" it is set out that β-CD, covalently bonded to silica gel, is one of four chiral HPLC-systems which were tried for the particular problem.

7. *Novelty*

None of the citations discloses a process of optical resolution which uses a separation substrate comprising a support and a cyclic oligosaccharide, at least one of the 2- and 3-position hydroxyl groups of which is chemically bonded to said support through a spacer.

7.1 The disclosure of document D1 is restricted to such separation substrates, wherein the cyclic oligosaccharide is bonded to the support through the 6-position hydroxyl group. This results from the molar ratio of 1 between the chloroformic acid p-nitrophenylester and the β-CD, from which it can be concluded that only the highly reactive 6-position primary hydroxyl groups of the β-CD (cf. original description of the present application, paragraph bridging pages 12 and 13) will react with the chloroformic ester, forming thereby a carbonic acid ester bond to the β-CD; this intermediate is further reacted with the aminated carrier "LiChrospher$^{(R)}$100 NH_2", establishing thereby the spacer bonding to the carrier through the 6-position hydroxyl group of the β-CD (cf. point 6.1 *supra*).

The disclosure of D1 does, thus, not comprise the possibility of a spacer bonding through at least one of the 2- and 3-position hydroxyl groups.

7.2 Documents D2 and D3 do not relate to optical resolution techniques for the separation of racemates.

7.3 Document D4 does not disclose the use of cyclic oligosaccharides.

7.4 Documents D5 and D6 do not identify the hydroxyl groups through which CDs, which are used for optical resolution, may be bonded to a support.

7.5 The subject-matter of Claim 1 of the auxiliary request is, thus, novel over the available citations.

7.6 The same conclusion applies *a fortiori* to the subject-matters of the independent use Claim 5 and of the dependent Claims 2 to 4.

8. *Inventive step*

8.1 Closest prior art

Document D1 represents the most appropriate starting point for the assessment of inventive step, because it is concerned with separating agents, which differ from those according to present Claim 1 solely by the fact that the spacer is bonded to the cyclic oligosaccharide (β-CD) **only** through its 6-position hydroxyl groups.

8.2 Problem and solution

8.2.1 With respect to the separating agents disclosed in D1 the problem underlying the present subject-matter is the provision of separating agents of improved optical resolution performance.

8.2.2 According to present Claim 1 this problem is to be solved by the provision of separating agents wherein the cyclic oligosaccharide derivative is bonded to the spacer through at least one of the 2- and 3-position hydroxyl groups.

8.2.3 It can be concluded from the separation factors α, which are disclosed in Tables 3 and 4 for the "inventive" Examples 1 to 3 and for the "comparative" Examples 5 to 7 that this problem has effectively been solved by the measure referred to in point 8.2.2 *supra*.

The separation factors α exhibited in Table 3, which are achieved according to the "inventive" Examples 1 to 3 for various racemic compositions, are in many cases higher, but at least equal to the separation factors α exhibited in Table 4 for the "comparative" Examples 5 to 7.

A meaningful comparison of these results is possible, since the preparation conditions of the separation agents of the "inventive" Examples 1, 2 and 3 differ from those of the respective corresponding "comparative" Examples 5, 6 and 7 only by the different position of the spacer-bonding: According to Examples 1 to 3 (pages 14 to 19 of the original description) β-CD is first reacted with the monoisocyanate compound 3,5-dimethylphenyl isocyanate. This reaction leads to the formation of a carbamide bond at the more reactive 6-position hydroxyl groups of the β-CD which renders them, thus, inaccessible to the subsequent reaction with 4,4'-diphenylmethane diisocyanate, which is therefore bonded to the less reactive 2- and/or 3-position hydroxyl groups of the β-CD. Contrastingly, the reaction conditions of the "comparative" Examples 5 to 7 (pages 22 to 23 of the original description) lead to the bonding of the 4,4'-diphenylmethane diisocyanate to the more reactive 6-position hydroxyl groups, because this reaction is carried out prior to the reaction of the β-CD with the monoisocyanate compound.

9. *Obviousness*

9.1 The subject-matter of Claim 1 of the auxiliary request is non-obvious over the available prior art, which does not comprise any clue that the existing technical problem (cf. point 8.2.1 *supra*) can be solved by the feature, which distinguishes it from the closest prior art (cf. point 8.2.2 *supra*).

9.2 Documents D1, D2, D5 and D6, which all disclose the use of CDs (i.e. cyclic oligosaccharides) for the chromatographical separation of chemical compounds, do not specify the position of the hydroxyl group through which the spacer is to be bonded to the CD, nor is there anything in these documents, on the basis of which it could be speculated that the bonding position of the spacer is considered to be of any importance for the optical resolution performance.

9.3 The only citation on file, which explicitely discloses that there are three differently positioned hydroxyl groups on the β-CD (i.e. in 2-, 3- and 6-position) is D3. While this document states that the β-CD may be mono-amino-modified with an amino acid at any of these positions, and while it appears that the β-CD is then bonded to the support (packing material) by reaction with an ionically neutral spacer compound (cf. point 7.2 *supra*), there is again no information in the available abstract and translation concerning a possible different performance of the differently bonded materials.

9.4 The skilled person cannot foresee therefore, on the basis of the disclosure of the available citations, that the bonding position of the spacer on the CD will have any importance for the optical resolution

performance, let alone could he expect that the bonding of the spacer through the 2- and/or 3-position hydroxyl groups will have a favourable influence on the separation factor α.

9.5 Consequently, the subject-matter of Claim 1 of the auxiliary request involves an inventive step.

9.6 The same conclusion applies *a fortiori* to the subject-matters of the independent use Claim 5 and of the dependent Claims 2 to 4.

10. Although the claims meet the requirements of the EPC a patent cannot be granted at this stage according to the Appellant's request because of the substantial amendments required in the description following the new wording of the claims. To that end the case has to be remitted to the Examining Division.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the Examining Division with the order to grant a patent on the basis of Claims 1 to 5, submitted as auxiliary request at the oral proceedings and after any necessary amendment of the description.

The Registrar: The Chairman:

E. Görgmaier C. Gérardin

Pk - 08-02-01