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D E C I S I O N
of 2 July 2003

Case Number: T 0422/01 - 3.3.5

Application Number: 94109310.6

Publication Number: 0687491

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Language of the proceedings: EN

Title of invention:
Simulated moving bed chromatographic separation process

Applicant:
DAICEL CHEMICAL INDUSTRIES, LTD.

Opponent:
-

Headword:
-

Relevant legal provisions:
EPC Art. 56

Keyword:
"Inventive step (no) - obvious to try"

Decisions cited:
-

Catchword:
-

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Beschwerdekammern | Boards of Appeal | Chambres de recours

Case Number: T 0422/01 - 3.3.5

D E C I S I O N
of the Technical Board of Appeal 3.3.5
of 2 July 2003

Appellant: DAICEL CHEMICAL INDUSTRIES, LTD.
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Decision under appeal: **Decision of the Examining Division of the European Patent Office posted 17 November 2000 refusing European application No. 94109310.6 pursuant to Article 97(1) EPC.**

Composition of the Board:

Chairman: R. K. Spangenberg
Members: A. T. Liu
J. H. Van Moer

Summary of Facts and Submissions

I. The appeal is from the decision of the examining division refusing the European patent application No. 94 109 310.6.

II. The decision was based on a set of claims 1 to 3 filed during the oral proceedings of 27 September 2000, with claim 1 being directed to a chromatographic process and claims 2 and 3 dependent thereon. Claim 1 read as follows:

"A simulated moving bed chromatographic process for separating a mixture of optical isomers comprising: forming a circulation circuit consisting of a plurality of columns each provided with an inlet port and an outlet port and packed with a solid adsorbent being a filler for optical resolution, said columns being serially and endlessly connected; introducing a supercritical fluid as an eluent into a first unit column via its inlet port (a first inlet) for forced circulation through the circuit; letting said fluid desorb a substance adsorbed in said column and several columns that follow; taking out a solution (extract) rich in the substance which has been adsorbed in these columns and desorbed therefrom via an outlet port (a first outlet) of the last one of these columns; introducing a stock solution containing a plurality of substances to be separated into a next column via the inlet port thereof (a second inlet) making the object substance adsorbed on the adsorbent in said column and several columns that follow; taking out a solution (raffinate) rich in the other substance, which has not been adsorbed in these columns via an outlet port of

the last column of these columns(a second outlet); passing the remaining solution and supercritical fluid through several unit columns that follow and recirculating them to a first column; shifting the working first inlet, the working first outlet, and the working second inlet and the working second outlet, successively in the direction of the fluid flow column by column at a predetermined interval and thus separating the adsorbable substance and the non-adsorbable substances."

III. Reference was particularly made to the following prior art documents in the decision under appeal:

D2: EP-A-0 471 082

M1: Journal of Chromatographic Science, Vol. 27, July 1989, pages 383 to 394.

M2: Journal of High Resolution Chromatography and Chromatography Communications, Vol. 10, December 1987, pages 665 to 667.

M3: Bull. Chem. Soc. Jpn., 65, 2286 - 2288 (1992).

The examining division came to the conclusion that the subject-matter of claim 1 lacked an inventive step with respect to the closest prior art according to D2 in combination with M1.

IV. With the statement of the grounds of appeal, the appellant submitted that the skilled person would not have combined D2 with M1 in the expectation of an overall improvement or advantage and that M1 would

rather lead away from the process as claimed. Furthermore, it was also argued that the simulated moving bed system as well as the use of supercritical fluids as mobile phases in chromatography had been known for more than 25 years at the filing date of the present application, but the combination of these teachings for the separation of optical isomers was suggested in the present case for the first time.

V. By a communication of 11 April 2003, the Board expressed the preliminary view that M1 appeared to disclose that the use of a supercritical fluid as eluent was promising for the resolution of optical isomers. Thus, when seeking to improve the process of D2, it would seem obvious for the skilled person to try and apply that knowledge and arrive at the subject-matter of claim 1 in a straightforward manner. Furthermore, the use of a simulated moving bed system for the separation of optical isomers was only made available to the public by the publication of D2, which was approximately 2 years prior to the filing date of the present application. Seen under this aspect, the time factor would not seem to particularly work in favour of an inventive step.

VI. By letter of 18 June 2003, the appellant filed a new set of claims 1 to 3 as basis for Auxiliary Request I. The introductory part of claim 1 of this request was amended to read as follows:

"A simulated moving bed chromatographic process for separating a mixture of optical isomers comprising: forming a circulation circuit consisting of a plurality of columns each provided with an inlet port and an

outlet port and packed with a solid adsorbent being a filler for optical resolution selected from the group consisting of optically active polysaccharide carbamate derivatives, ..."

VII. Oral proceedings before the Board of Appeal took place on 2 July 2003.

VIII. The appellant's arguments can be summarised as follows:

- The preliminary view expressed by the Board was the result of hindsight.

- With respect to the closest prior art D2, the technical problem to be solved was the provision of an improved simulated moving bed chromatographic process for separating a mixture of optical isomers.

- When taking the documents M1, M2 and M3 in the order of their publication date, the skilled person would not have the incentive for replacing the liquid eluent as used in D2 with a supercritical fluid for the separation of optical isomers.

- Concerning claim 1 of the auxiliary request, the advantage of using a polysaccharide carbamate derivative as solid adsorbent was demonstrated in Example 1 of the patent application. This was particularly surprising in view of the experimental results in M3.

IX. The appellant requested that the decision under appeal be set aside and that a patent be granted on the basis of claims 1 to 3 as submitted during the oral proceedings of 27 September 2000 or, auxiliarily, with claims 1 to 3 as submitted by letter of 18 June 2003.

Reasons for the Decision

1. *Main request*

1.1 Claim 1 is directed to a simulated moving bed (SMB) chromatographic process for separating a mixture of optical isomers wherein a supercritical fluid is used as an eluent.

1.2 The Board concurs with the appellant in that the starting point for the assessment of inventive step is D2 which discloses a simulated moving bed chromatographic process for separating a mixture of optical isomers using a liquid eluent (claim 1). Specifically, the eluent comprises an organic solvent and/or an aqueous solution containing a salt (page 4, lines 1 to 4).

1.3 The appellant has submitted that, with respect to D2, the technical problem to be solved is the provision of a simulated moving bed chromatographic process which is more efficient for separating a mixture of optical isomers.

1.4 In order to solve the stated problem, claim 1 proposes process using a supercritical fluid instead of the

liquid eluent of D2 (see Statement of the grounds of appeal, items 4.1 to 4.3).

1.5 As was confirmed at the oral proceedings, there are no data on file which allow a direct comparison between the results obtained with the claimed process and that of D2. Furthermore, the appellant has not refuted the fact that the efficiency of the chromatographic separation for a given feedstock is strongly influenced by the choice of the solid adsorbent. Claim 1, however, neither stipulates a particular mixture of optical isomers to be separated, nor the optimal - or at least appropriate - adsorbent therefor. It is directed, in general terms, to "a simulated moving bed chromatographic process for separating a mixture of optical isomers comprising: forming a circulation circuit consisting of a plurality of columns each provided with an inlet port and an outlet port and packed with a solid adsorbent being a filler for optical resolution ..." (see claim 1, point II above). In the Board's judgment, it is therefore not conceivable that an improvement could be obtained over the whole range of the claim. The appellant has not contested this finding, let alone provided any evidence to the contrary.

As a consequence, the Board concludes that the technical problem as stated in point 1.3 above is not solved over the whole range of claim 1. The Board, however, can see the technical problem with respect to D2 in the provision of a further SMB process for separating optical isomers. There is no doubt that the technical problem thus stated is solved by the process of claim 1.

1.6 As the Board has already observed in the communication dated 11 April 2003, the supercritical fluid chromatography (SFC) with chiral stationary phases was hailed as a promising coupling for the resolution of various racemates as early as 1989 (see M1, Title). In that paper, several aspects of SFC chiral separations on packed chiral stationary phases are presented. The intention of the report is "to give a systematic comparison of LC and SFC in order to better understand chiral recognition processes and to determine whether SFC presents a real interest" (page 385, left hand column, first full paragraph). More specifically, it is indicated in that paper that polysaccharide-derived chiral stationary phases (CSPs) are growing in importance for chiral separations. Among commercially available cellulose-based CSPs, the cellulose tribenzoate ChiralCel OB was evaluated (see M1, page 390, right hand column, first paragraph). The results obtained in M1 are said to demonstrate that "it was always interesting to use the ChiralCel OB CSP in SFC instead of in LC. A significant increase of the resolution per unit of time was systematically observed ... Several comparative chromatograms are given ... to illustrate this superiority" (page 392, paragraph bridging left hand column and right hand column).

It is irrefutable that the CSP evaluated in M1 is the same material used in the examples of D2, as can also be seen from the appellant's letter dated 18 June 2003 (see page 2, item 2.1). The skilled person, when seeking to solve the technical problem as stated in point 1.5 above, would get a strong incentive for

modifying the process of D2 according to M1. The Board therefore finds that it is obvious for the skilled person to try and use a supercritical fluid as eluent and thus arrive at the subject-matter of claim 1 in a straightforward manner. As a consequence, the claimed process lacks an inventive step with respect to D2 in combination with M1.

1.7 The appellant has submitted that it is hindsight on the part of the Board to judge the usefulness of the SFC method in view of a single document (here M1). The skilled person would rather evaluate that method against the historical background formed by all the three documents M1, M2 and M3 reporting the progress on that subject. It is thus argued that the oldest of these documents, M2, reveals that "chiral SFC separations have been achieved which have different (and lower) enantioselectivities, under the reported conditions, than the analog LC system" (page 667, right hand column, point 4: "Conclusion"). In the later document M1, it is indicated that "several discrepancies in the LC and SFC behaviour of these CSPs *(chiral stationary phases; remark added*) show that carbon dioxide-alcohol and hexane-alcohol mixtures are not interchangeable as mobile phases: solubilities of apolar compounds are lower in carbon dioxide than in hexane and the solvation state of both solutes and CSPs differ." (page 383, left hand column: "Abstract"). Finally, M3 reports that "phenycarbamates of cellulose and amylose showed lower optical resolving abilities in SFC using carbon dioxide modified with alcohols as a mobile phases (sic) than in HPLC using hexane and 2-propanol as an eluent. However, 4-methylbenzoate of cellulose in SFC showed a high optical resolving

ability, comparable to that in HPLC." (page 2288, right hand column. "Conclusion"). The appellant has then gone on to assert that the skilled person thus cannot deduce from M2, M1 and M3 that the implementation of SFC would decisively lead to an improvement over the LC method. Since the separation of optical isomers is a highly complex process, he would not have combined the SFC method with the SMB chromatography as known from D2 (see Statement of grounds of appeal, point 4.5, in particular page 3, last paragraph to page 5, paragraph 4 and paragraph bridging pages 6 and 7).

1.7.1 Re: the disclosure of M2

M2 is directed to a comparison of enantiomeric selectivity in SFC and LC using a same stationary phase of the Pikle type (see title). In conclusion to the experiments, it is expressly indicated that "the SFC separations shown have not yet been optimised with regard to efficiency or the influence of instrumental contributions to band broadening. Further experimental investigations on the procedure of immobilization and on the optimization of the SFC system are being executed at present." (see page 667, right hand column, last two sentences. Clearly, the experimental data reported in M2 are only considered preliminary results on which further experiments could be based.

1.7.2 Re: the disclosure of M1

As is already indicated in the communication of 11 April 2003, and reiterated at the oral proceedings, the remark in M1 concerning the discrepancies in the LC and SFC behaviour of the CSP's is made for distinct

combinations of isomers and mobile phases. The tenor of the report, however, is that the use of ChiralCel OB CSP in SFC leads to a significant increase in resolution per unit of time. Explicitly, it is stated in M1 that "as a rule, the SFC-CSP coupling is a promising technique for the resolution of racemates: It usually leads to higher resolutions per unit of time than LC and sometimes allows new types of chiral separations" (see M1, abstract, in particular the last sentence and point 1.6 above).

1.7.3 Re: the disclosure of M3

As a preliminary remark, it is stated in M3 that "the development of supercritical fluid chromatography (SFC) is remarkable; it has been becoming one of the practically useful separation methods. However, the optical resolution by SFC using chiral-packed columns is still not very familiar, although some data are available." (see M3, page 2286, left hand column: "Synopsis", first two sentences of second paragraph). The data contributed by M3 result from the investigation of the optical resolution of ten racemates by SFC on three cellulose phenycarbamates and a benzoate as chiral stationary phases (CSPs). These data show that "the optical resolving ability of cellulose tris(3,5-dimethyl-phenylcarbamate depended on the kind and compositions of the modifiers. The SFC using the cellulose benzoate may be useful not only for the analytical optical resolution of racemates but also for preparative separation to obtain optically pure isomers." (page 2288, right hand column: "Conclusion", last two sentences).

1.7.4 Inference from M1 - M3

In the Board's judgment, the skilled person will therefore deduce from the prior art documents M1, M2 and M3 the following with respect to the practical application of a SFC process:

- one cannot draw a conclusion from M2 which concerns preliminary works with non-optimised SFC procedures (see point 1.7.1 above).

- the optical resolution of optical isomers, be it by SFC or by LC (or HPLC), depends on the materials used in the investigation. The results obtained with one particular system of optical isomers and CSP do not necessarily apply to another system (see points 1.7.2 and 1.7.3 above).

- in general, however, the optical resolution by SFC using chiral-packed columns is a promising method (see points 1.7.2 and 1.7.3 above).

The three documents M1, M2 and M3, when taken into consideration in the order of their publication date, clearly reflect the increasing importance of the SFC method. The Board therefore holds that the prior art does give the skilled person a strong incentive to try and apply this method when seeking an alternative to the SMB process according to D2. By so doing, he would arrive at the subject-matter of claim 1 in a straightforward manner, without involving any hindsight.

1.8 The appellant has also alleged that the claimed process is for separating optical isomers on an industrial scale. Due to the investments involved, the skilled person would not make any change to the existing process (according to D2) unless he is certain of obtaining concrete advantages thereby.

As is undisputed by the appellant, it is known in the art that the SFC method has at least the advantage of using an eluent which is easier to remove than a liquid. Once it is known (from D2) to use the SMB method for separating optical isomers, the skilled person would naturally be led to consider using a supercritical fluid as eluent for the same purpose. The advantage of using a supercritical fluid is, of course, counterbalanced by the need for designing the apparatus accordingly. The decision as to whether or not to make the investments in order to implement the SFC method for a SMB process depends, however, on other considerations than those requiring inventive activity.

2. *Auxiliary request*

2.1 Claim 1 of this request differs from claim 1 of the main request in that it stipulates that the solid adsorbent for optical resolution is "selected from the group consisting of optically active polysaccharide carbamate derivatives" (see claim 1, point VI above).

2.2 The appellant has submitted that it is known from M3 that the optical resolving abilities of phenylcarbamates of both cellulose and amylose in SFC were low compared with those in high-performance liquid chromatography (HPLC). The skilled person therefore

would not, in view of M3, be motivated into modifying the SMB chromatographic process of D2 by using a supercritical fluid as eluent. On the other hand, Example 1 of the present application uses cellulose tris-(3,5-dimethylphenyl carbamate) as adsorbent material. It also demonstrates that with the use of that adsorbent material, the technical problem of an improved SMB chromatographic process for separating a mixture of optical isomers can be solved in a highly satisfactory manner. The appellant has gone on to conclude that, since it is surprising to obtain superior results in a SBM-SFC process using a carbamate derivative as filler material, the subject-matter of claim 1 must be regarded as involving an inventive step (see letter dated 18 June 2003, page 2, point 2.1).

2.3 The Board wishes to point out that the results of optical resolution reported in M3 concern the SFC separation of defined racemates, using distinct adsorbents. The appellant has not argued, and there is no evidence on file that an improvement could be obtained with the same systems of racemates and adsorbents by applying the SMB method. Example I of the present application is therefore irrelevant for comparative purposes.

In addition to the above, the appellant has also conceded that the stipulated carbamates are not universally suitable for all optical isomers. Rather, for different racemates, the skilled person would need to find the appropriate adsorbent. The Board finds that, in consequence, the additional feature in present claim 1, that the solid adsorbent for optical resolution be "selected from the group consisting of

optically active polysaccharide carbamate derivatives", does not substantially change the situation as stated in point 1.5 above. Consequently, the objections of lack of inventive step raised in respect of the subject-matter of claim 1 of the main request apply mutatis mutandis to the subject-matter of present claim 1.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

U. Bultmann R. Spangenberg