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Datasheet for the decision of 30 April 2010

Case Number: T 1259/06 - 3.3.05

Application Number: 97907606.4

Publication Number: 0883574

IPC: C02F 1/42

Language of the proceedings: EN

Title of invention:
Anion-exchange resins with at least two different nitrogen containing ion-exchange groups

Patentee:
DIONEX CORPORATION

Opponent:
Metrohm AG

Headword:
Anion exchange composition/DIONEX CORPORATION

Relevant legal provisions:
EPC Art. 54, 56
EPC R. 103(1)

Relevant legal provisions (EPC 1973):
-

Keyword:
"Novelty (yes)"
"Reimbursement of appeal fee (no)"
"Inventive step (yes) - evidence for improvement (yes) - opponent's formulation of the problem not accepted"

Decisions cited:
-

Catchword:
-

Case Number: T 1259/06 - 3.3.05

DECISION
of the Technical Board of Appeal 3.3.05
of 30 April 2010

Appellant: (Opponent)	Metrohm AG Oberdorfstr. 68 CH-9100 Herisau (CH)
Representative:	Hepp, Dieter Hepp Wenger Ryffel AG Friedtalweg 5 CH-9500 Wil (CH)
Respondent: (Patent Proprietor)	DIONEX CORPORATION 1228 Titan Way Sunnyvale California 94086 (US)
Representative:	Hayes, Adrian Chetwynd Boult Wade Tennant Verulam Gardens 70 Gray's Inn Road London WC1X 8BT (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted 21 June 2006 rejecting the opposition filed against European patent No. 0883574 pursuant to Article 102(2) EPC.**

Composition of the Board:

Chairman: G. Raths
Members: H. Engl
H. Preglau

Summary of Facts and Submissions

I. European patent EP-B-0 883 574 was granted with 14 claims. Independent claims 1, 13 and 14 thereof are worded as follows:

"1. An anion-exchange composition comprising:

a) Component A comprising support resin particles containing at least 30% crosslinking monomeric units;

b) polymers containing anion-exchange functional groups, each anion exchange functional group comprising at least a first and a second nitrogen group, wherein said first nitrogen group is a quaternary amine, and said second nitrogen group is selected from the group consisting of primary, secondary, tertiary or quaternary amines;

wherein said polymers containing anion-exchange functional groups are retained directly or indirectly on Component A."

"13. A chromatographic analytical column, the column containing a packed bed of an anion-exchange chromatographic packing which comprises a composition of claim 1."

"14. A process for chromatographic separation of carbohydrates comprising

i) passing a liquid solution comprising the carbohydrates through a bed comprising a composition of claim 1;

and
ii) eluting said bed with an eluent that differentially removes the attracted carbohydrates from the bed."

II. The present appeal is from the decision of the opposition division posted on 21 June 2006 to reject the opposition lodged against the said European patent EP-B-0 883 574.

III. The following documents were *inter alia* cited in the opposition procedure:

E1: US-A-5 324 752
E2: WO-A-91/00 145
E3: K. Rengan, R. Engel, *"Ammonium Cascade Molecules"*, J. Chem. Soc., Chem. Commun., 1992, pages 757 to 758
E6: J. Prodolliet et al, *"Determination of Free and Total Carbohydrate Profile in Soluble Coffee"*, J. of AOAC international, vol. 78, No. 3, 1995, pages 749 to 761
E7: Combined CarboPac Manual, page 7: "*Comparison Table of CarboPac MA1, PA1, PA10 and PA100*"

IV. Only inventive step was under dispute during the opposition procedure. Starting from document E1 as the closest prior art, the opposition division defined the technical problem underlying the opposed patent as providing a composition for use in the ion-exchange chromatography of carbohydrates including those difficult to be separated, such as the sugar alcohols sorbitol and dulcitol and/or the amino sugars galactosamine and glucosamine.

In view of examples 6 and 8 of the opposed patent and chromatograms A to C filed by the patentee, the opposition division concluded that the claimed ion-exchange composition could separate sorbitol from dulcitol and that the above defined technical problem was accordingly solved.

Although documents E2 and E3 disclosed ion-exchange compositions having a dual nitrogen functionality, these documents did not suggest such compositions for the separation of carbohydrates. E2 and E3 and would thus not have been considered as being relevant. The opposition division therefore rejected the opposition and maintained the patent as granted.

V. With the letter stating the grounds for appeal the appellant filed *inter alia* the new documents

E9: Dionex Product Selection Guide 1991, page 47; and
E10: Laboratory Protocol 2 regarding comparative examples with chromatographic ion-exchange columns PA10 and PA100.

By letter dated 26 July 2007, the appellant filed supplemental experimental data as

E12: Laboratory protocol 07/2007

VI. The response of the patentee (respondent) included a declaration signed by Mr C. Pohl and dated 30 April 2007, and two sets of claims as auxiliary requests 1 and 2. In a further submission a supplemental declaration by Mr C. Pohl, dated 27 November 2007, was filed.

By letter dated 23 February 2009, the respondent filed C/ Technical Note 40 and C/ Technical Notes 53, 67 and 117.

Auxiliary request 1 (second page thereof), and auxiliary requests 3 to 6 were filed with letter of 30 March 2010.

VII. Oral proceedings took place on 30 April 2010.

VIII. The appellant essentially argued as follows:

The closest prior art was represented by document E1, or, in the alternative, by patentee's own prior art chromatographic ion-exchange column CarboPac PA100 whose design was based on the disclosure of E1. IN the patentee's brochure E9 the CarboPac PA100 column was recommended for the separation of mono- and oligosaccharides.

The experimental reports E10 and E12 showed that the claimed invention did not provide an improvement over the prior art column P100 as regards the separation of
a) lysine and monosaccharides;
b) amino sugars and monosaccharides; or
c) sorbitol and dulcitol.

Therefore, the objective technical problem underlying the opposed patent had to be formulated in a different manner and consisted either in

(a) increasing the pH value of the stationary phase in a chromatographic column, thereby facilitating the separation of molecules which are difficult to ionize; or in

(b) providing a chromatographic column having an increased capacity.

In case of a), it would have been obvious to increase the number of ion exchange groups, since the PA100 ion-exchange column already contained the most strongly basic anion exchange groups known, namely quaternary amino groups. Moreover, the measure was already suggested by E2 and E3. The patent itself asserted that the better separation of carbohydrates was merely an inevitable consequence of increasing the effective stationary pH.

As a solution to technical problem b), it would have been equally obvious to double the number of nitrogen ion-exchange sites, thereby as a matter of course increasing the capacity and, also automatically, increasing the pH. It was known from E2/E3 that the claimed dual nitrogen ion-exchange groups had a particular high exchange capacity and that they increased the selectivity. According to E11, *"selectivity"* meant *"relative retention"*, which in turn determined the ability of separating peaks from each other. The preferred groups of the opposed patent (*e.g.* DABCO) were specifically disclosed in E2. The claimed invention had indeed achieved a better separation of peaks, but this was not surprising in view of E2. It was true that E2 did not specifically mention carbohydrates or sugar alcohols; however, E2 mentioned biomolecules of which carbohydrates were an example.

Furthermore, it was evident to the skilled person that more functional nitrogen ion-exchanging sites in an ion-exchange composition caused a higher basicity. Species which were difficult to ionize, such as carbohydrates and sugars, could be ionized higher and better attached to the ion-exchanging sites, thereby increasing resolving power.

Therefore, the claimed invention was obvious, no matter which one of the above technical problems one chose.

The request for reimbursement of the appeal fee was justified by the fact that the opposition division had failed to provide a reasoning as to why it rejected the technical problem of increasing the capacity, as formulated by the appellant.

IX. The respondent essentially argued as follows:

E1 represented the closest prior art. The respondent rejected the appellant's versions of the technical problem as containing inadmissible pointers to the solution. In the respondent's view, the problem to be solved was to develop an anion exchange composition for the separation of a wide variety of carbohydrates, in particular of carbohydrates that are difficult to separate, e.g. sugar alcohols such as sorbitol and dulcitol. Said carbohydrates could not be separated effectively with prior art compositions. Although E9 mentioned that PA100 columns were suitable for carbohydrates, this composition was unable to separate difficult-to-separate carbohydrates, such as sorbitol and dulcitol. This was explained in the Mr Pohl's declaration and supported by the experimental reports attached thereto.

On the contrary, examples 6 and 8 of the opposed patent demonstrated the claimed composition's ability to separate the difficult-to-separate carbohydrates sorbitol and dulcitol. The appellant's experimental results (E10) using column P10 according to the invention were in all likeliness affected by a contamination of the eluent with borate and/or carbonate and were carried out at a non-standard temperature of 15°C.

Conventionally, mobile phases with very high pH would be used for the chromatographic separation of species which are difficult to ionize. The patentee had, for the first time, developed the concept of stationary phase pH. The inventors had found that a high pH of the mobile phase increased competition between OH^--ions and the carbohydrate-anions, and did not, therefore, yield a better separation. By providing more than one nitrogen group per functional anion exchange group, the inventors increased the pH of the stationary phase and thus were able to improve the separation ability of the ion exchange composition for difficult-to-ionize carbohydrates. This concept of stationary phase pH was not mentioned anywhere in the prior art.

The claimed solution was not obvious in the light of any of the prior art, as E2 and E3, for example, were silent on the separation of carbohydrates. A skilled person would not, therefore, have regarded them as relevant in view of the problem posed.

X. Requests

The appellant requests that the decision under appeal be set aside and the patent be revoked and that the appeal fee be reimbursed on the ground of a substantial procedural violation.

The respondent requests that the appeal be dismissed and the patent be maintained as granted, or, in the alternative, that the patent be maintained on the basis of one of the auxiliary requests 1 to 6.

Reasons for the Decision

1. *Novelty (main request)*

Novelty was not under dispute. None of the documents on file discloses all the claim features in combination. In particular, the anion-exchange compositions disclosed in E1 do not comprise a dual nitrogen functionality. E2 and E3 do not disclose chromatographic ion exchange compositions comprising a first component of support resin particles and polymers containing anion-exchange functional groups retained directly or indirectly on the first component. Rather, in accordance with E2, functional ion-exchange groups having a dual nitrogen functionality are coupled to the resin or gel matrix using spacer groups (page 4, lines 1 to page 5, line 35).

E7 does not belong to the prior art.

E9 is a brochure on "BioPlus" ion-exchange columns marketed by Dionex Corporation for the separation of various biomolecules, such as amino acids, proteins, peptides and mono- and oligosaccharides. Among the range of products mentioned, the CarboPac PA-100 column is specifically recommended for separating mono- and oligosaccharides. It differs from the claimed ion-exchange compositions in that its ion-exchange groups carry only one nitrogen functional group (alkyl quaternary amine).

Therefore, the subject matter of claim 1 is novel. Claims 2 to 12 depend on claim 1; therefore their subject matter is also novel. Claim 13 (relating to a chromatographic analytical column) and claim 14 (relating to a process for the chromatographic separation of hydrocarbons) refer back to claim 1; hence their subject matter is also novel.

The board is thus satisfied that the requirements of Article 54 EPC are met.

2. *Inventive step (main request)*

2.1 The patent in suit relates to anion-exchange compositions useful for the chromatographic separation of carbohydrates, comprising cross-linked resin support particles and an anion-exchange polymer bearing nitrogen functional groups retained directly or indirectly on said resin support particles.

The opposed patent also relates to chromatographic analytical columns and to processes for chromatographic separation of carbohydrates, using the above mentioned anion-exchange compositions.

2.2 Both parties regarded document E1 as representing the closest prior art. Said document discloses ion-exchange compositions of the type contemplated in the opposed patent, *i.e.*, compositions comprising synthetic cross-linked resin support particles and synthetic resin layering particles irreversibly attached thereto. The resin layering particles are functionalized, for instance by amination, to form ion-exchanging sites (column 5, lines 24 to 57; column 7, lines 20 to 39; examples 3 to 7; claims 1, 11 and 12). Chromatographic columns based on the disclosure of E1 are marketed by the respondent (Dionex Corporation) under the designations CarboPac PA-100 and PA-1 (see E7; E6, page 750, left hand column, item (o); E9, page 47, Table).

2.3 The board considers, in accordance with the submission of the respondent and the position of the opposition division expressed in the contested decision (page 6, second full paragraph), that the problem underlying the patent in suit in the light of document E1 is to provide a composition for use in ion-exchange chromatography of carbohydrates having an improved performance in separating carbohydrates including those which are difficult-to-separate, such as the sugar alcohols sorbitol and dulcitol.

This technical problem is fully derivable from the opposed patent (paragraphs [0002], [0009], [0010], [0075] and [0076] and the examples).

2.4 As a solution to this problem, the patent in suit proposes an anion-exchange composition according to claim 1 of the main request, characterized in that it comprises polymers containing anion-exchanging functional groups, each anion exchange functional group comprising at least a first and a second nitrogen group, wherein said first nitrogen group is a quaternary amine, and said second nitrogen group is selected from the group consisting of primary, secondary, tertiary or quaternary amines.

2.5 It has to be examined whether the technical problem has been solved. The question is whether the change from functional groups having one nitrogen group (as is the case in E1) to functional groups having more than one nitrogen group has an effect on the resolution performance of the anion-exchange composition.

2.5.1 The opposed patent contains experimental evidence in the form of working examples 6 and 8 showing that the claimed ion-exchange compositions are capable of chromatographically resolving mixtures of the difficult-to-separate sugar alcohols dulcitol and sorbitol. At the same time, peaks of many carbohydrates, such as the sugars and sugar derivatives galactose, galactosamine, glucose, glucosamine and mannose are sufficiently separated from the oxygen peak, which in prior art columns (CarboPac PA-1; see E9) interferes with the individual carbohydrate signals ("oxygen dip";

see Chromatograms A to D filed by the respondent with a letter dated 11 May 2006).

Furthermore, Figure 1 annexed to the (first) declaration of C. Pohl shows the resolution of sorbitol and dulcitol on CarboPac PA-10 columns (according to the invention) with and without quaternization of the functional nitrogen moieties with CH_3I.

Additional experimental results filed with the supplementary declaration of Mr C. Pohl concern the separation ability of CarboPac PA-10 and PA-100 columns (a prior art chromatographic column comprising a quaternary ammonium functionalized latex with <u>one nitrogen moiety per functional group</u>; see E7, Table 1, right hand column) for sorbitol and dulcitol at 15°C and 30°C. Although the peaks are overlapping, at both operating temperatures the PA-10 column according to the invention achieves a better separation than the prior art PA-10 column.

For comparison, the same sugar alcohols sorbitol and dulcitol could not be sufficiently resolved on a CarboPac PA-100 column. This result was confirmed by experimental evidence filed by the appellant as document E10 (Figures 9 and 10), showing the <u>same retention time</u> for sorbitol and dulcitol on CarboPac PA100). As mentioned above, CarboPac PA-100 ion-exchange columns are based on the disclosure of document E1 (assigned to Dionex Corp.) and may, therefore, be said to represent an embodiment of the closest prior art.

2.5.2 The appellant contested the presence of an improvement over the prior art, in particular on the basis of the experiments filed as document E10. Figures 9 and 10 thereof demonstrated, so the appellant asserts, that resolution of sorbitol and dulcitol on a CarboPac PA-10 column was practically impossible, as the retention times were equal. E12, Figure 1, showed that strongly overlapping peaks of the two sugars could be obtained under certain conditions (for instance temperature of 288K = 15°C) even on the prior art CarboPac PA-100 columns. Therefore, no improvement over the closest prior art could be acknowledged.

However, according to the explanations of the respondent submitted in the letter dated 1 May 2007 (page 3, paragraph 3) and according to the declaration of Mr C. Pohl (dated 30 April 2007, paragraphs 7, 9 and 10), the appellant's results in E10 and E12 were likely to be influenced by contamination of the eluant with borate and/or carbonate. The document "*Product Manual: Boratetrap Column (P/N 047078*) (1997)" by Dionex Corp., (attached to the Pohl declaration dated 30 April 2007), advises that said contaminants may cause monosaccharide peak asymmetry even in the low ppb range (page 4, top) on CarboPac PA-10 columns. According to the respondent, strong peak asymmetry, such as discernable in the graphs of Figures 7 to 10 of E10, hinted at such a contamination and could explain the appellant's failure to achieve separation of sorbitol and dulcitol on a CarboPac PA-10 column and no separation at all or poor separation on a CarboPac PA-100 column. The board finds these explanations, which were not contested, plausible.

2.5.3 For the above reasons, the board concludes that the technical problem defined above has indeed been solved.

2.6 It remains to be examined whether or not the claimed solution is obvious in view of the prior art.

2.6.1 Instead of arguing lack of inventive step, the appellant contested the formulation of the technical problem to be solved. The arguments of the appellant on obviousness focus on answering the question of whether the claimed solution to the technical problem(s), as the appellant formulated it, was obvious.

2.6.2 The appellant did not agree with the formulation of the technical problem underlying the patent in suit in the light of E1.

The appellant referred to documents E10 and E12 and argued that the claimed invention did not provide any improvement over the prior art column P100 as regards the separation of

a) lysine and monosaccharides;
b) amino sugars and monosaccharides; or
c) sorbitol and dulcitol.

Because said improvement had not been achieved, in the appellant's view, the objective technical problem underlying the opposed patent had to be formulated differently than the one adopted by the opposition division and also during oral proceedings before the board. The appellant also referred to the opposed patent, paragraph [0010], according to which the improvement in separation of a wide variety of carbohydrates was a mere consequence of increasing the pH of the stationary phase.

In its submission, the objective technical problem underlying the opposed patent consisted either in
a) increasing the pH value of the stationary phase in a chromatographic column, thereby facilitating the separation of molecules which are difficult to ionize; or in
b) providing a chromatographic column having an increased capacity.

2.6.3 The board can neither accept these arguments nor can it, as a consequence, accept the appellant's formulations of the technical problem underlying the opposed patent, for the following reasons.

As discussed under points 2.5.1 and 2.5.2, the experimental evidence on file, taking into account the plausible explanations of the respondent, sufficiently supports the achievement of an improvement over the closest prior art (as represented by E1 and ion-exchange column CarboPac PA-100). Therefore, the problem formulated under 2.3 has indeed been solved and there is no reason for formulating a different or less ambitious problem.

Moreover, the first problem suggested by the appellant contains clear pointers to the claimed solution, in that increasing the pH value of the stationary phase is a feature belonging to the solution, not to the problem. Such a formulation (or reformulation) of the technical problem involves knowledge of the solution now claimed and is therefore inadmissible.

To be sure, paragraph [0010] of the opposed patent states that it was *"an object of the present invention to provide compositions for use in ion exchange chromatography that can increase the effective stationary phase pH and thus to improve the separation of a wide variety of carbohydrates".* It is, however, clear in the context that the ultimate goal of the invention is to improve separation, whereas increasing the effective stationary pH constitutes the means for achieving this goal. The board considers that the person skilled in the art of ion exchange chromatography is not primarily interested in the theoretical concept of increasing the effective stationary pH. The skilled person's aim is to extend the application range of ion exchange compositions, for instance by improving its separation performance. Indeed, as mentioned above, the opposed patent frequently refers to the separation of carbohydrates (see paragraphs [0002], [0009], [0010], [0075] and [0076]), and examples 6 and 8 specifically demonstrate the separation of the sugar alcohols dulcitol and sorbitol.

The appellant's second problem formulation also takes one of the effects of the claimed invention, namely a possible increase in ion exchange capacity, as a part of the underlying problem. This is inadmissible for the reasons set out above. Moreover, the formulation is unspecific for the invention, because the problem of increasing the ion exchange capacity may be regarded as a general *desideratum* in the art and because there is no evidence on file that the capacity of a chromatographic ion-exchange column is related to its separation performance for carbohydrates. Besides, this technical problem is not directly derivable from the patent.

2.6.4 For the reasons explained above, the appellant's approach for formulating the technical problem is tainted with hindsight. The technical problem must remain as stated above under point 2.3. It follows that the conclusions drawn by the appellant cannot be taken into account.

2.7 As regards the technical problem as defined under point 2.3, the board essentially concurs with the reasoning of the opposition division in the contested decision, point 2.4. which found the claimed solution not obvious.

2.7.1 As admitted by the appellant, both E2 and E3 are silent about the problem of chromatographic separation of carbohydrates. The appellant referred however to E2, page 2, last paragraph, and page 3, first paragraph, discussing the binding of biomolecules to ion exchange compositions. In fact, E2 states that *"the charge properties of the protein will have an influence on the degree of binding. []… Selectivity and capacity of strong anion exchangers may be improved considerably by means of introducing functional groups with charges arranged pairwise, these charges being located in a special structure in which they are exposed in an optimum manner to the ambient medium due to minimization of charge shielding"*. Thus, in the appellant's view, E2 pointed at the importance of designing the anion exchanger according to the kind of biomolecules to be separated.

Indeed, the dual nitrogen functional ligands disclosed in E2 are specifically selected for the separation / resolution of proteins, peptides and DNA fragments (see description, pages 10 to 15: Chapters V to VIII). While these compounds are of course biomolecules, they are chemically distinct from carbohydrates, and so would be their binding mechanism and binding strength to the ion-exchanging groups. In view of these differences, there was no incentive for the skilled person to look at E2 when confronted with the problem of separating difficult-to-separate carbohydrates. This is all the more so as the anion exchange compositions must be designed according to the kind of biomolecules to be separated, as the appellant itself asserted with reference to E2.

2.7.2 E3 is a paper on ammonium cascade molecules (dendrimers) having core and branching points of ammonium ion sites (involving DABCO structures). Such materials are reported as efficient high capacity ion exchange materials (page 758, right hand column, penultimate paragraph). However, E3 does not disclose or suggest these materials for the chromatographic separation of particular substances, let alone carbohydrates. The appellant did not rely on this document during oral proceedings. In the board's view, the skilled person would have had no particular reason to look at E3 in view of the problem posed.

2.7.3 The appellant also argued that it was evident for the skilled person that more functional nitrogen ion-exchanging sites in an ion-exchange composition caused a higher basicity. Species which were difficult to ionize, such as carbohydrates and sugars, could therefore be ionized to a higher degree and attached better to the ion-exchanging sites, thereby increasing resolving performance. The respondent contested this.

As the appellant did not provide evidence for what it asserts to be general knowledge and as the board is also not aware of prior art supporting the allegation that the basicity of an ion-exchange composition was related to its resolving performance for carbohydrates, the appellant's argument must fail.

2.8 The board concludes that the subject matter of claim 1 of the main request involves an inventive step. The dependent claims 2 to 12 relate to particular embodiments of the ion-exchange composition of claim 1 and therefore also involve an inventive step. Claims 13 and 14 refer back to claim 1, so that the same findings as for claim 1 apply.

The requirements of Article 56 EPC are thus met for claims 1 to 14 according to the main request (claims as granted).

2.9 In view of the above there is no need to consider the auxiliary requests.

3. *Request for reimbursement of the appeal fee*

3.1 The appellant requested a reimbursement of the appeal fee on the ground of a substantial procedural violation in first instance proceedings.

3.2 Pursuant to Rule 103(1)a EPC, the appeal fee shall be reimbursed in the event of an interlocutory revision or when the Board of Appeal deems an appeal to be allowable, if such reimbursement is equitable by reason of a substantial procedural violation (emphasis added by the board).

3.3 In the present case, the appeal is not allowable for the reasons given above. The appellant's request for a reimbursement of the appeal fee must therefore fail.

Order

For these reasons it is decided that:

1. The appeal is dismissed.

2. The request for reimbursement of the appeal fee is rejected.

The Registrar	The Chairman
C. Vodz	G. Raths