

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

**UNITED STATES PATENT AND TRADEMARK OFFICE**

---

**BEFORE THE BOARD OF PATENT APPEALS  
AND INTERFERENCES**

---

Ex parte MICHEL G. M. PERBOST

---

Appeal No. 2004-1770  
Application No. 09/895,050

ON BRIEF

---

Before WILLIAM F. SMITH, FLEMING and GRIMES, Administrative Patent Judges.  
GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 29, 30, 32, 34, and 35. Claims 31 and 33 are also pending; the examiner has indicated that claim 31 is allowable and claim 33 would be allowable if amended to remove its dependence on a rejected claim. Claim 29 is representative of the claims on appeal and reads as follows:

29. An apparatus for fabricating an addressable array of biopolymers on a substrate according to a target pattern, comprising:

(a) a deposition system which can separately dispense onto a substrate, fluid compositions of different biomonomers each with a first linking group which must be activated for linking to a substrate bound moiety, and a fluid composition of a solid activator;

(b) a processor to operate the deposition system, which processor derives from the target array pattern a target drive pattern for operating the deposition system to form the array, the target drive pattern comprising instructions to the deposition system to perform the following at each of multiple regions at which a biomonomer is to be deposited:

(i) deposit the fluid composition of solid activator separate from and preceding deposition of the biomonomer;

(ii) allow sufficient time for evaporation to leave solid activator at the region; and

(iii) then deposit the biomonomer.

The examiner relies on the following references:

Hirschbein et al. (Hirschbein)	5,859,233	Jan. 12, 1999
Baldeschwieler et al. (Baldeschwieler)	WO 95/25116	Sept. 21, 1995

Claims 29, 30, 32, 34, and 35 stand rejected under 35 U.S.C. § 103 as obvious in view of Baldeschwieler and Hirschbein.

We reverse.

#### Background

Arrays of biopolymers (e.g., DNA or RNA) are used as diagnostic and screening tools. Specification, page 1. "Biopolymer arrays can be fabricated using either deposition of the previously obtained biopolymers or in situ synthesis methods." Id.

The "in situ" methods can be basically regarded as iterating the sequence of depositing droplets of: (a) a protected monomer onto predetermined locations on a substrate to link with either a suitably activated substrate surface (or with a previously deposited deprotected monomer); (b) deprotecting the deposited monomer so that it

can now react with a subsequently deposited protected monomer; and (c) depositing another protected monomer for linking.” Page 2.

“[I]n the conventional in situ methods for polynucleotide arrays, phosphoramidite nucleoside monomers are used. In order for the phosphoramidite group to link to a hydroxyl of a previously deposited deprotected polynucleotide monomer, it must first be activated usually by using a weak acid such as tetrazole. However, an activated phosphoramidite is highly reactive with moisture in the air.” Id. The reaction of activated monomer with ambient water leads to a reduction in the amount of monomer available for reaction with the growing oligonucleotide, a decrease in probe concentration at the perimeter of each feature in the array, and variability between batches of arrays. See id.

The specification discloses a “method includ[ing] forming on a region of the substrate carrying the substrate[-]bound moiety, a solid activator composition. A biomonomer containing fluid composition is deposited on the region so that the solid activator activates the first linking group and the biomonomer links to the substrate bound moiety.” Page 3. “As to . . . forming the solid activator composition at the region, one way of accomplishing this is to deposit a composition of solid activator as a fluid composition, and allowing fluid to evaporate. In this case, the fluid composition may have less than 20% by weight of solid activator content, for example 3% to 20% by weight.” Id.

The specification defines “solid” and “solid activator” as follows:

A “solid” may still have some amount of a carrier fluid, such as a solvent, present. However, typically a “solid” will have no more than 20% by weight (and often less than 10% or 5%, or 1%, by weight, of such carrier

fluid present). A “solid activator” is one which is solid at the operating temperature at which it is used (normally at around a typical room temperature[]], such as between 10°C to 30°C).

Pages 8-9.

“In the case of phosphoramidites, suitable activators are known and include tetrazole. . . . In the case of phosphoramidites a non-protic low boiling point solvent could be used, for example, acetonitrile, dioxane, toluene,” etc. Page 15.

#### Discussion

Claim 29 is directed to an apparatus for carrying out the disclosed method of making a biopolymer array. The claimed apparatus comprises a deposition system that can separately dispense fluid compositions of biomonomers and a fluid composition of a solid activator, in combination with a processor to operate the deposition system; “the processor derives from the target array pattern a target drive pattern . . . [which comprises] instructions to the deposition system to perform the following at each of multiple regions at which a biomonomer is to be deposited:

- (i) deposit the fluid composition of solid activator separate from and preceding deposition of the biomonomer;
- (ii) allow sufficient time for evaporation to leave solid activator at the region; and
- (iii) then deposit the biomonomer.”

The examiner rejected the claims as obvious in view of Baldeschwieler and Herschbein. As the examiner noted, Baldeschwieler discloses an apparatus meeting most of the limitations of claim 29. The disclosed apparatus that separately dispense fluid compositions of different biomonomers (e.g., phosphoramidite-derivatized nucleotides, see page 13, lines 3-10 and 10-21) and is also capable of dispensing a

fluid composition of a solid activator (e.g., tetrazole (see page 13, lines 16-17) in acetonitrile (see page 21, lines 19-20)).

Baldeschieler's tetrazole solution meets the instant specification's definition of a "fluid composition of a solid activator" because the specification defines "solid activator" by reference to whether the activator is solid at room temperature, not by reference to whether it is in solution. See page 9. See also page 3 ("[T]he fluid composition [of solid activator] may have less than 20% by weight of solid activator present, for example 3% to 20% by weight.") and page 15 (tetrazole is a suitable activator and acetonitrile is a suitable solvent). Baldeschieler also discloses that the apparatus deposits the tetrazole onto the substrate before it deposits the phosphoramidite-derivatized monomer. See page 13, lines 16-21 and claim 28.

However, as the examiner recognized, Baldeschieler does not disclose the claim limitation requiring the target drive pattern to instruct the deposition system to "allow sufficient time [after the activator is applied] for evaporation to leave solid activator" before the biomonomer is applied. The examiner cited Hirschbein as suggesting this limitation. The examiner pointed to Example 2 of Hirschbein as teaching a method comprising allowing sufficient time for solvent evaporation, and Hirschbein's guidance that "[t]he use of very dry reagents and solvents . . . allows the use of less phosphorylating agent in the monomer syntheses and the generation of less of the impurity." See Examiner's Answer, pages 3-4. The examiner concluded that the combined references would have suggested the instantly claimed apparatus:

An ordinary practitioner would have been motivated to combine and substitute a method wherein sufficient time is allowed for evaporation to leave solid activator . . . in order to achieve the express advantages, as

noted by Hirschbein et al., of an invention which provides the use of very dry reagents and solvents, and environment free of water (inherently including allowing sufficient time for evaporation to leave a solid activator) during the synthesis of the monomers that is very helpful and which allows the use of less phosphorylating [sic, phosphitylating] agent in the monomer syntheses and the generation of less of the impurity.

Examiner's Answer, page 4.

Appellant argues that the examiner has misinterpreted Hirschbein's disclosure. See the Appeal Brief, page 6: "Hirschbein et al. makes it clear that 'dry' is used in the sense of no water being present, not that a solid form of the activator is somehow present. See in particular, column 12, lines 35-39: 'A great amount of care should be exercised to use very dry (free from water) monomer, activator, and solvent for the coupling step.'" Appellant also argues that Hirschbein's Example 2, which the examiner relies on, deals only with the preparation of phosphoramidite monomers, not linking monomers into oligomers. Appellant concludes that "while the examiner correctly points out that Hirschbein et al. refers to using a dry solvent (i.e. free of water) for the activator, he has not pointed to anything in Hirschbein et al. where this dry solvent is allowed sufficient time to evaporate to leave a solid activator before a biomonomer is then applied." Appeal Brief, page 7.

We agree with Appellant that the examiner has not made out a prima facie case of obviousness. In particular, and for the reasons stated in the Appeal Brief, we agree that the examiner has not adequately explained how Hirschbein would have suggested the claim limitation requiring allowing sufficient time for evaporation to leave a solid activator before depositing the biomonomer.

As Appellant points out, although Hirschbein teaches the advantage of using “dry” reagents during oligonucleotide synthesis, the reference uses the term “dry” to mean that the solvents used do not contain water. Hirschbein does not suggest any advantage to removing the (non-aqueous) solvent from the activator before adding the monomer to be reacted. Hirschbein teaches, in fact, that the activator-containing solution and the monomer-containing solution should be mixed. See column 12, lines 7-26:

The reaction is performed by adding a solution of the phosphoramidite monomer and a solution of an activator (or a solution containing the phosphoramidite monomer and the activator) to the reaction vessel. . . . The monomer and the activator either can be premixed, mixed in the valve-block of a suitable synthesizer, mixed in a pre-activation vessel and preequilibrated if desired, or they can be added separately to the reaction vessel.

Summary

Baldeschwieler and Herschbein would not have suggested the instantly claimed invention to a person of ordinary skill in the art having no knowledge of the present disclosure. We therefore reverse the rejection under 35 U.S.C. § 103.

REVERSED

William F. Smith	)	
Administrative Patent Judge	)	
	)	
	)	
	)	BOARD OF PATENT
Michael R. Fleming	)	
Administrative Patent Judge	)	APPEALS AND
	)	
	)	INTERFERENCES
	)	
Eric Grimes	)	
Administrative Patent Judge	)	

Appeal No. 2004-1770  
Application No. 09/895,050

Page 9

Legal Department DL429  
Intellectual Property Administration  
P.O. Box 7599  
Loveland, CO 80537-0599