(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 June 2010 (03.06.2010)

PCT

(10) International Publication Number
WO 2010/061191 A1

(51) International Patent Classification:
G01R 33/30 (2006.01) *G01R 33/62* (2006.01)

(21) International Application Number:
PCT/GB2009/002763

(22) International Filing Date:
26 November 2009 (26.11.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
08170056.9 27 November 2008 (27.11.2008) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PE, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

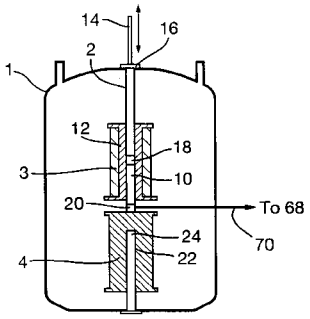
Published:

— *with international search report (Art. 21(3))*

WO 2010/061191 A1

(54) Title: APPARATUS FOR DYNAMIC NUCLEAR POLARISATION

Fig.1.



(57) Abstract: DNP apparatus comprises: a cryostat (1) within which is located a superconducting magnet (3) and defining a bore (2) having opposite inlet and outlet ends and surrounded by the magnet. A sample positioning device (14) is provided for insertion into the inlet end of the bore (2) to locate a sample at an irradiation position coupled to a microwave source. A dissolution dock (20) is located at the outlet end of the bore (2) to which the sample positioning device (14) is moved following DNP of a sample; and a solvent supply system conveys heated solvent under pressure, without passing through the bore (2), to a sample at the dissolution dock (20), and conveys the dissolved, polarised sample to NMR apparatus. The conduits of the solvent supply system extend to the dissolution position without passing through that part of the cryostat bore through which the sample positioning device is inserted.

APPARATUS FOR DYNAMIC NUCLEAR POLARISATION

The invention relates to DNP apparatus, that is apparatus for carrying out dynamic nuclear polarisation on a sample prior to subjecting the sample to a nuclear magnetic resonance (NMR) process.

Dynamic nuclear polarisation (DNP) is used to enhance the nuclear polarisation of samples for use in applications such as nuclear magnetic resonance (NMR) analysis including nuclear magnetic resonance imaging (MRI) and analytical high-resolution NMR spectroscopy (MRS). MRI is a diagnostic technique that has become particularly attractive to physicians as it is non-invasive and does not involve exposing the patient under study to potentially harmful radiation such as X-rays. Analytical high resolution NMR spectroscopy is routinely used in the determination of molecular structure.

MRI and NMR spectroscopy lack sensitivity due to the normally very low polarisation of the nuclear spins of the materials used. In view of this, the dynamic nuclear polarisation technique has been developed to improve the polarisation of nuclear spins.

In a typical DNP process, as described for example in WO-A-2006/077361, a liquid sample is mixed with a polarising agent and placed in a sample cup which is mounted to a sample holding tube or sample positioning device. The sample holding tube is then inserted into the bore of a superconducting magnet located in a cryostat so as to bring the sample to a working volume within the bore, the working volume being located in a microwave cavity defined by a DNP insert. The superconducting magnet generates a magnetic field of suitable strength and homogeneity in the working volume.

The sample is cooled and solidified by exposing it to liquid helium in the bore and then irradiated with microwaves while it is exposed to the magnetic field and in its frozen state.

The sample is then lifted out of the liquid helium to a position in which it is still subject to the magnetic field although this may be less homogeneous and remains at a low temperature.

Hot solvent is then supplied into the sample holding tube, typically through a dissolution tube or stick, to the working volume so as to dissolve the polarised sample. The solution is then rapidly extracted and transferred for subsequent use either for analysis in an NMR system or, in the case of in vivo applications, injection into a patient.

The solvent is prepared for delivery by superheating it to a temperature above its boiling point. During this process, the pressure on the solvent will increase and when a desired pressure is reached, i.e. sufficient to ensure rapid delivery, a valve is opened and the solvent released. Transfer to the NMR apparatus is further aided by the use of a chase gas.

There are number of problems with this approach. The first is that when the desired pressure is reached, the temperature of the solvent may not be at a required level. A second problem is that when the superheated solvent is released, the accompanying sudden drop in pressure can cause bubbles of gas to form in the sample. Likewise, the use of a chase gas may lead to the formation of gas bubbles in the solvent. The presence of gas bubbles impairs the quality of the subsequent analysis of the sample in the NMR apparatus.

GB-A-2448054 describes a fluid path system for dissolution and transport of a hyperpolarised material in which solvent is supplied from a syringe.

In accordance with the present invention, we provide DNP apparatus comprising:

a cryostat within which is located a superconducting magnet and defining a bore surrounded by the magnet;

a sample positioning device for insertion into the bore to locate a sample at an irradiation position coupled to a microwave source, the sample positioning device being movable to a dissolution position following DNP of the sample;

a solvent supply system comprising one or more conduits for conveying heated solvent under pressure and is characterized in that the apparatus further comprises a pump for causing heated solvent to be conveyed along the one or more conduits to the sample at the dissolution position, and for conveying the dissolved, polarised sample to NMR apparatus connected in use to the DNP apparatus; and

a heating system for heating solvent in the pump, and in that the conduits of the solvent supply system extend to the dissolution position without passing through that part of the cryostat bore through which the sample positioning device is inserted.

With this invention, we enable the pressure and temperature of the solvent to be controlled independently so that solvent temperature can be raised to a desired level while the pressure applied to the solvent is controlled by a separate pump. In addition, the use of a pump enables solvent to be supplied under a controlled pressure and without the use of a chase gas. This reduces the risk of gas bubble generation.

Furthermore, by extending the conduits of the solvent supply system to the dissolution position without passing through that part of the cryostat bore through which the sample positioning device is inserted, the pressure under which the solvent is supplied and the temperature of the solvent can be much more accurately controlled since most of the solvent supply system is located externally of the cryostat. It also avoids the need for a chase gas since the same solvent can be used to transfer the sample.

Typically, the conduits of the solvent supply system extend through a side wall of the cryostat. This minimizes the length of conduit which will be cooled by the cryostat and consequently minimizes the time for which solvent is cooled as it is supplied to the dissolution position. Alternatively, the conduits could extend through the remote part of the bore of the cryostat to that through which the sample positioning device is inserted since typically this will be relatively short in length and again will minimize the amount of cooling.

Preferably, the pump comprises a piston/cylinder device, the piston being controllable to apply pressure in a controlled manner to solvent in the cylinder. This is similar to using a syringe.

Movement of the piston can be controlled by a mechanical device utilising a pressure monitor to maintain constant pressure on the solvent but more conveniently the piston is coupled to a control means such as a source of fluid or gas pressure, for example a pneumatic actuator.

The solvent supply device may be replenished with solvent by simply regularly filling it, for example by withdrawing the piston in the case of piston/cylinder arrangement.

Preferably, however, the apparatus further comprises a solvent reservoir which can be selectively coupled to an outlet of the pump whereby reducing the pressure applied to solvent by the pump causes fresh solvent to be delivered from the solvent reservoir to the pump. This provides a particularly convenient way to fill the pump without physically decoupling the device.

In some cases, the dissolved sample can be supplied to separate NMR apparatus in a conventional manner but in the preferred approach, NMR apparatus having a cryostat within which is located a superconducting magnet and defining a bore surrounded by the magnet is located adjacent the DNP apparatus, the bore of the NMR apparatus being coupled to the bore of the DNP apparatus. This minimises the time for the dissolved sample to lose polarisation before it reaches the NMR apparatus. Typically, the same cryostat is used for both DNP and NMR apparatus to minimize heating of the dissolved sample as it passes from one to the other but this may not be necessary in some cases.

In a typical embodiment, the apparatus further comprises a dissolution docking device in the bore at the dissolution position which can be sealingly engaged by the sample positioning device, the solvent supply system comprising:

a solvent supply conduit having an outlet connected to an inlet port of the dissolution docking device and an inlet connected to an output port of a first valve, an inlet port of the first valve being connected to the pump; and

the dissolution docking device having an outlet port through which dissolved sample is conveyed,

whereby when the first valve is opened, solvent is delivered via the input port to the sample at the dissolution position, at least a portion of the sample dissolves in the solvent, and the dissolved sample portion is delivered to the outlet port.

This provides a relatively simple system for delivering solvent under controlled pressure and temperature.

In some cases, the dissolved sample is supplied to NMR apparatus and simply passes through that apparatus in an uncontrolled manner. Preferably, however, the apparatus further comprises a second valve downstream of the NMR apparatus through which solvent and dissolved sample can flow; and a control system for controlling both valves in synchronism. With this preferred arrangement, the dissolved sample can be incremented through the NMR apparatus enabling several NMR pulse sequences to be carried out on different portions of the sample thus allowing a variety of NMR experiments to be executed during a single dissolution. An example of this approach is described in more detail in WO-A-2007/104975.

This is a significant improvement on the more conventional use of a chase gas by instead utilising a pump to apply pressure to the solvent.

Some examples of DNP apparatus according to the present invention in combination with NMR apparatus will now be described with reference to the accompanying drawings, in which:-

Figure 1 is a schematic overview of a combined DNP NMR apparatus;

Figures 2A and 2B are schematic longitudinal sections through the dissolution dock of the Figure 1 example with the sample cup in the DNP working volume and the docking position respectively; and,

Figure 3 illustrates the solvent supply system.

Figure 1 illustrates a cryostat 1 of conventional form. Typically this will have a number of radiation shields and coolant containing vessels defining a central, elongate bore 2. A first superconducting magnet 3 is located in the cryostat 1 surrounding an upper portion of the bore 2 for use in dynamic nuclear polarisation while a second superconducting magnet 4 of NMR apparatus 74 is located in the cryostat 1 below the first magnet 3 and surrounding the bore 2 for use in an NMR process. The NMR apparatus will be of conventional form and also include gradient coils, rf coils and a control system (not shown).

Within the upper portion of the bore 2 is located a variable temperature insert (VTI) assembly 10 which can be evacuated in use. A sample positioning device 14 can be removably inserted into a first end 16 of the VTI 10 (and bore 2), the device 14 carrying a sample cup 18 at its leading end within which a sample to be hyperpolarised is located in use.

In operation, the sample positioning device 14 is inserted into the VTI 10 to bring the sample in the sample cup 18 to a working region 12. Liquid helium or other coolant is then supplied through the bore 2 to cool the sample in the sample cup to a very low temperature and it is then irradiated with microwaves to achieve hyperpolarisation in a conventional manner.

An example of suitable apparatus is described in more detail in EP-A-2028505.

Following hyperpolarisation, the frozen, hyperpolarised sample in the sample cup 18 is moved further down the bore 2 using the sample positioning device 14 until the sample cup engages a dissolution dock or docking device 20 to be described in more detail below.

Heated solvent under pressure is then supplied to the dissolution dock 20 via a conduit 70 of a solvent supply system to be described below, the conduit 70 extending through a side wall of the cryostat 1 so as to dissolve the hyperpolarised sample, the dissolved sample then being conveyed into a working region 22 defined by an NMR probe 24 of the NMR apparatus. An NMR experiment can then be performed on the sample.

As can be seen in Figure 2A, the sample cup 18 is located on the end of the sample positioning device 14. The sample cup 18 has a lower wall 34 provided with inlet and outlet ports 36, 38.

The dissolution dock 20 has a main body 44 through which extends solvent inlet and outlet conduits 40,42. The dissolution dock is sealed in the end of the VTI 10 by an O-ring vacuum seal 114.

Figure 2B illustrates the apparatus when the sample cup 18 has been docked with the dissolution dock 20. To achieve this, the sample cup 18 is pushed down to engage the dissolution dock 20, and is received within a cylindrical spigot portion 32 of the dissolution dock 20. As can be seen, the inlet port 36 is aligned with the inlet conduit 40 and the outlet port 38 is aligned with the outlet conduit 42. A seal 116 seals between the dissolution dock 20 and the sample cup 18 to isolate the solvent inlet and outlets while a seal 118 isolates the solvent outlet from the VTI sample space.

Figure 3 illustrates the solvent supply system. Solvent is provided in a pump defined by a 20ml syringe 50 formed by a cylinder 52 and piston 54.

Typical solvents are water and methanol. The syringe 50 is surrounded by a heater coil 56 whose temperature is sensed by a sensor 58. A second sensor (not shown) senses the temperature of the solvent in the syringe 50 and feeds back to a heater controller 60. In this way, the temperature of the solvent can be tracked and controlled. A typical temperature is close to the boiling point of the solvent, for example 90°C in the case of water.

The pressure under which the solvent is maintained is controlled by the piston 54 from a pneumatic actuator 62 using an electronic pressure regulator (not shown).

Independent control of temperature and pressure of the solvent is achieved by allowing sufficient room for expansion in the syringe 50 and actuator 62.

The syringe 50 is connected to an inlet port of a first valve 64 whose outlet is connected to a double flowpath valve 66. In the position shown in Figure 3, the outlet of the first valve 64 is coupled through the valve 66 to a further double flow path valve 68 and from there to a conduit 70. Conduit 70 delivers the solvent to the dissolution dock 20 via inlet 40.

The outlet 42 from the dissolution dock 20 passes through a one-way flow valve 72 and from there to the NMR apparatus 74 via a conduit 112 (see also Figures 2A and 2B). The output from the NMR apparatus 74 is connected to a second flow control valve 76 whose outlet is connected to a waste 78 or sample collection device.

The positions of the flow control valves 64, 76 are controlled by a controller 80 which turns each valve on and off together so as to increment solvent through the dissolution dock 20 and NMR apparatus 74.

In use, therefore, when a sample has been hyperpolarised and the sample cup 18 has been located at the dissolution dock 20 (Figure 2B), solvent in the syringe 50 which is maintained under pressure, is suddenly released by opening the first flow control valve 64 and, when provided, the second flow control valve 76. The solvent passes through the conduit 70 under pressure controlled by the pneumatic cylinder 62 into the dissolution dock at a typical speed of 5ml/sec, dissolves the sample, and then passes out of the dissolution dock with the dissolved sample to the NMR apparatus 74.

In order to replenish solvent in the syringe 50, the double flow path valve 66 can be adjusted to connect a solvent reservoir 100 to the outlet of the first flow control valve 64. The piston 54 is withdrawn by suitably controlling the pneumatic actuator 62 so that solvent is drawn from the reservoir 100 into the syringe 50. When the syringe 50 is full the first flow control valve 64 is closed and the double flow path valve 66 moved back to the position shown in Figure 3.

The system can also be purged when the double flow path valve 66 is in its second position (not shown) by supplying purge gas through a conduit 102 via a valve 104.

It is also possible to supply a sample to the NMR apparatus bypassing the DNP apparatus. This is achieved by supplying the sample to the dual flowpath valve 68 (in the position shown in Figure 3) along a conduit 106 from where it passes along a conduit 108 through a one-way flow valve 110 to the conduit 112. Alternatively, solvent can be supplied from syringe 50 directly to NMR apparatus 74, for instance to load the NMR apparatus with solvent prior to dissolving the polarised sample. This is achieved by selecting the second position of dual flow path valve 68 (not shown), causing the solvent to pass from the syringe 50 via conduit 108 and 112 to NMR apparatus 74.

The presence of the one-way valve 72 prevents samples supplied along the conduit 106 from entering the dissolution dock 20.

CLAIMS

1. DNP apparatus comprising:

a cryostat within which is located a superconducting magnet and defining a bore surrounded by the magnet;

a sample positioning device for insertion into the bore to locate a sample at an irradiation position coupled to a microwave source, the sample positioning device being movable to a dissolution position following DNP of the sample;

a solvent supply system comprising one or more conduits for conveying heated solvent under pressure, characterized in that the apparatus further comprises a pump for causing heated solvent to be conveyed along the one or more conduits to the sample at the dissolution position, and for conveying the dissolved, polarised sample to NMR apparatus connected in use to the DNP apparatus; and

a heating system for heating solvent in the pump, and in that the conduits of the solvent supply system extend to the dissolution position without passing through that part of the cryostat bore through which the sample positioning device is inserted.

2. Apparatus according to claim 1, wherein the conduits of the solvent supply system extend through a side wall of the cryostat.

3. Apparatus according to claim 1 or claim 2, wherein the pump comprises a piston/cylinder device, the piston being controllable to apply pressure in a controlled manner to solvent in the cylinder.

4. Apparatus according to claim 3, further comprising means to control the piston to maintain a substantially constant pressure on the solvent.

5. Apparatus according to claim 4, wherein the piston is coupled to a source of fluid pressure, for example a pneumatic actuator.

6. Apparatus according to any of the preceding claims, further comprising a dissolution docking device in the bore at the dissolution position which can be sealingly engaged by the sample positioning device, wherein the solvent supply system comprises:

a solvent supply conduit having an outlet connected to an inlet port of the dissolution docking device and an inlet connected to an output port of a first valve, an inlet port of the first valve being connected to the pump; and

the dissolution docking device having an outlet port through which dissolved sample is conveyed,

whereby when the first valve is opened, solvent is delivered via the input port to the sample at the dissolution position, at least a portion of the sample dissolves in the solvent, and the dissolved sample portion is delivered to the outlet port.

7. Apparatus according to any of the preceding claims, further comprising a solvent reservoir which can be selectively coupled to an outlet of the pump whereby reducing the pressure applied to solvent by the pump causes fresh solvent to be delivered from the solvent reservoir to the pump.

8. Apparatus according to claim 7, when dependent on claim 6, wherein the solvent reservoir is coupled to the pump via a selectively operable valve located downstream of the first valve with respect to the direction of solvent flow from the pump to the dissolution position.

9. Apparatus according to any of the preceding claims, wherein the heating system comprises a heating coil attached to the pump.

10. Sample processing apparatus comprising apparatus according to any of the preceding claims, and NMR apparatus for performing a magnetic resonance experiment on a sample and having a cryostat within which is located a superconducting magnet and defining a bore surrounded by the magnet, the bore of the NMR apparatus being coupled to the bore of the DNP apparatus to enable a dissolved sample to pass from the DNP apparatus to the NMR apparatus.

11. Apparatus according to claim 10 when dependent on at least claim 6, further comprising a second valve downstream of the NMR apparatus through which solvent and dissolved sample can flow; and a control system for controlling both valves in synchronism.

12. Apparatus according to claim 10 or claim 11, wherein the solvent supply system includes a solvent bypass path selectively connectable by a valve to the NMR apparatus bypassing the dissolution position.

13. Apparatus according to any of claims 10 to 12, wherein the cryostats of the DNP and NMR apparatus are formed by the same cryostat.

Fig.1.

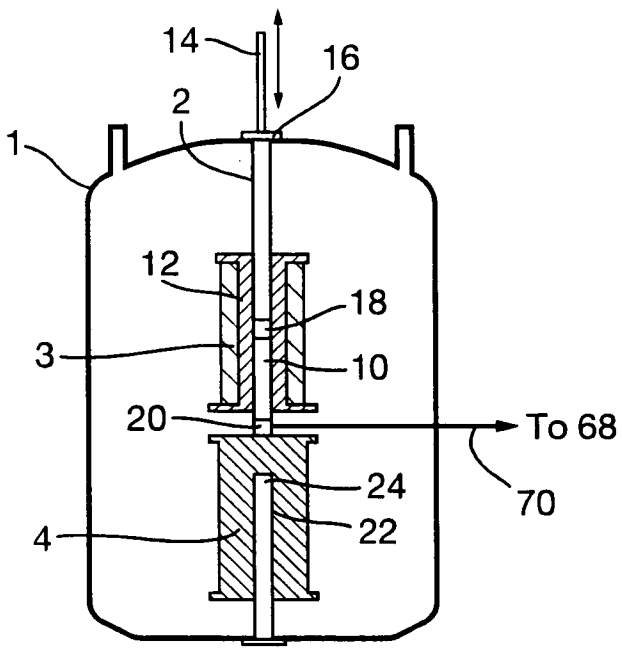


Fig.2A.

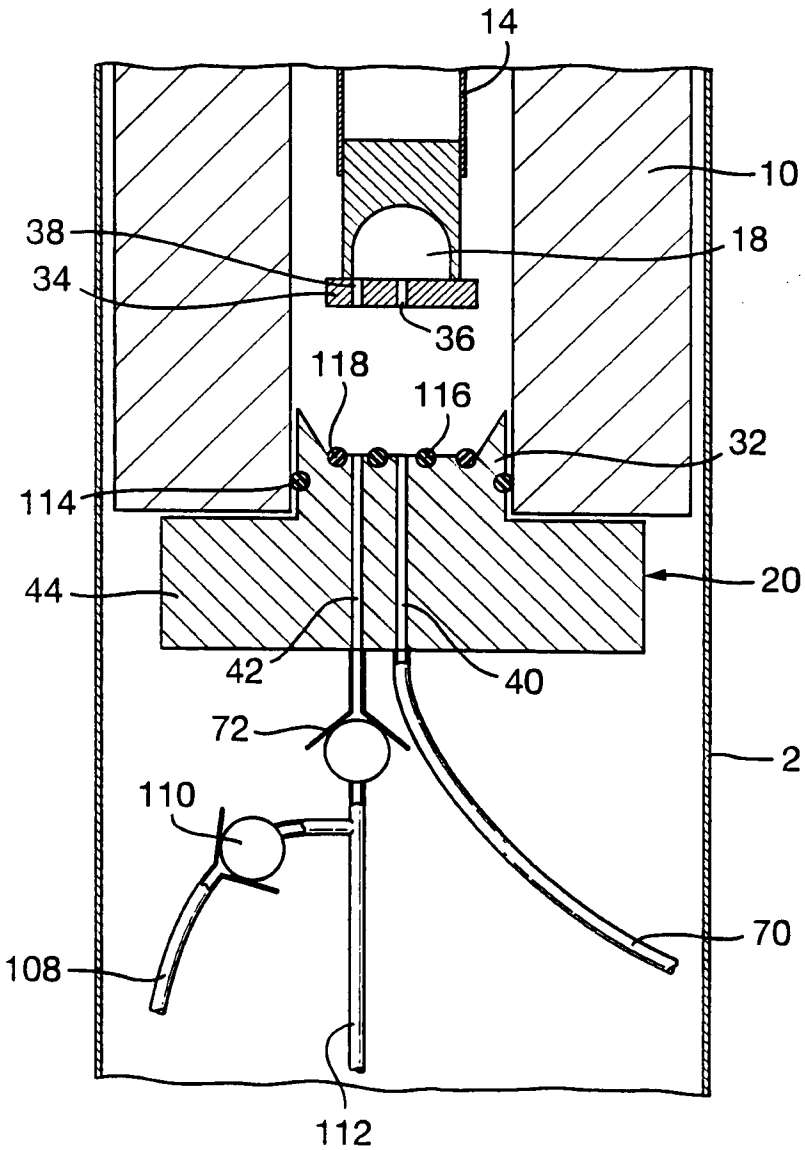


Fig.2B.

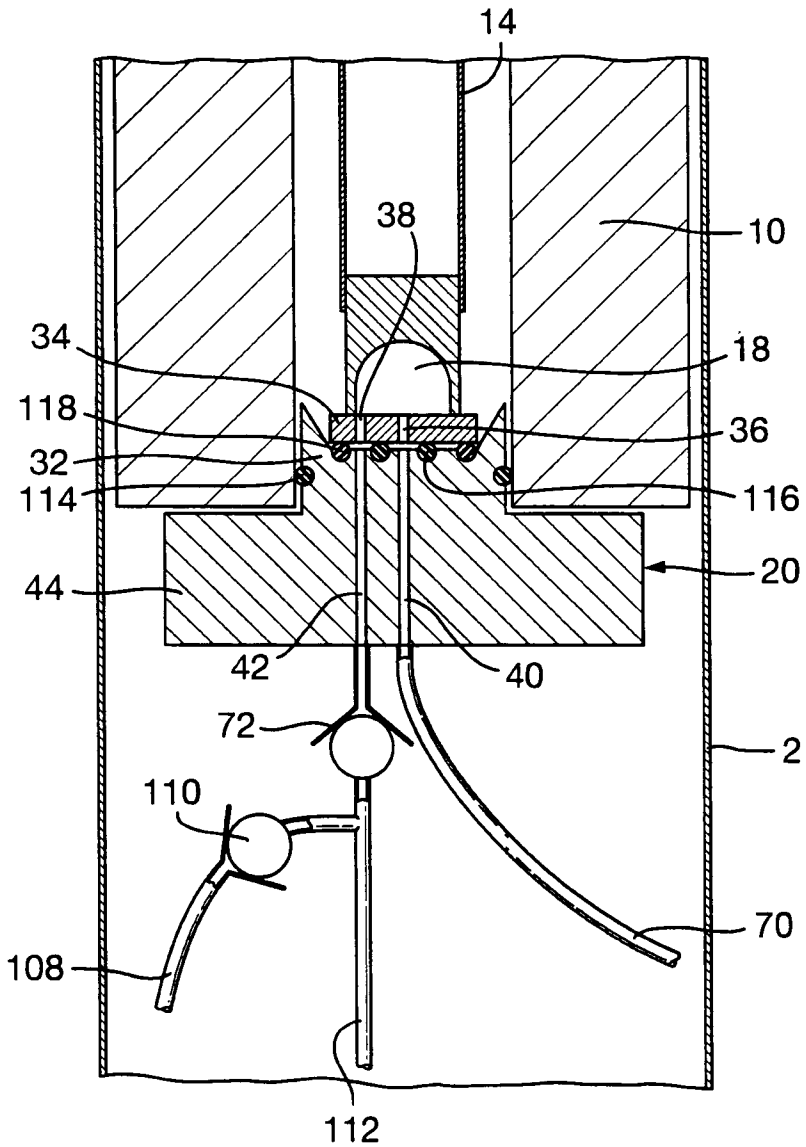
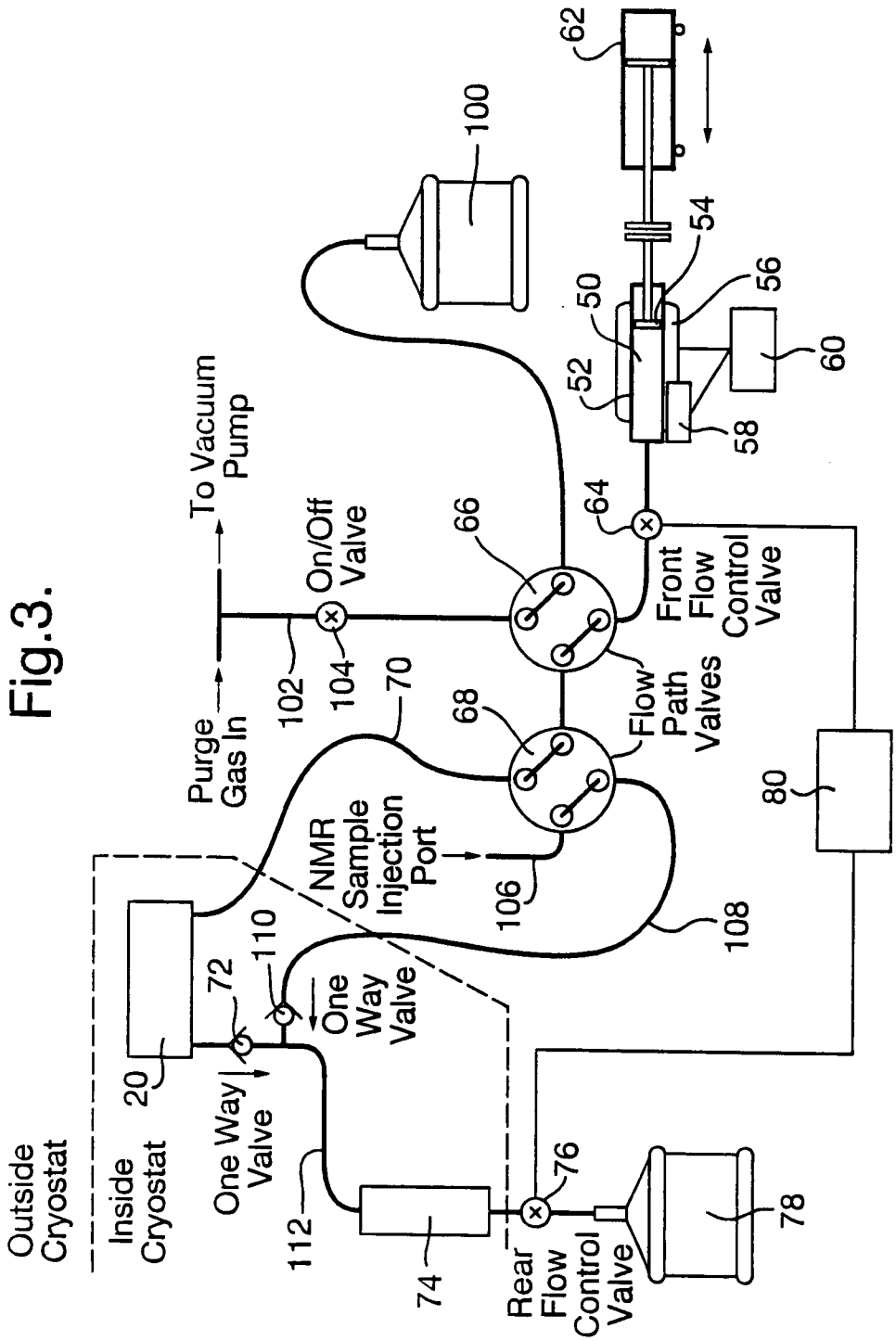


Fig.3.


Outside Cryostat
Inside Cryostat
20
One Way Valve
72
One Way Valve
110
112
74
Rear Flow Control Valve
76
78
NMR Sample Injection Port
106
108
Purge Gas In
102
On/Off Valve
104
To Vacuum Pump
70
68
Flow Path Valves
66
Front Flow Control Valve
64
80
100
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INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2009/002763

A. CLASSIFICATION OF SUBJECT MATTER
INV. G01R33/30 G01R33/62

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
G01R

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, INSPEC, EMBASE, COMPENDEX, BIOSIS, MEDLINE, FSTA, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
26 February 2010	04/03/2010

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Skalla, Jörg

Form PCT/ISA/210 (second sheet) (April 2005)

INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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3

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/GB2009/002763

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