ФИЗИКА ЭЛЕМЕНТАРНЫХ ЧАСТИЦ И АТОМНОГО ЯДРА
2013. Т. 44. ВЫП. 6

PRODUCTION OF HYPERPOLARIZED NUCLEI FOR MRI

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The project in producing the hyperpolarized ^{3}He and ^{19}F is addressed in pursuit of radiation-free medical diagnosis. The program for production of the hyperpolarized ^{3}He by the brute force method with the Pomeranchuk cooling and the rapid melting of the solid ^{3}He started a few years ago, and is still on the way, while a new program for production of the hyperpolarized ^{19}F by means of the PHIP (ParaHydrogen Induced Polarization) has just got started. Particular attention is placed upon a new idea of the hyperpolarization catalyst to be used for ^{19}F.

PACS: 87.57.-s; 87.61.Ff; 82.56.Pp; 13.88.+e; 67.30.hp

INTRODUCTION

On March 11, 2011, Japan was attacked by the fatal earth quake and the subsequent huge tsunami. As a result, the meltdown of the nuclear reactors in Fukushima Daiichi was induced by the shortage of cooling water, and the fallout (fallen radioactive material) from the broken reactors seriously polluted the land and ocean of Japan in a broad range. It is an unavoidable fact that a lot of people will be suffering from the radiation exposure, and will have serious economical problems for a long time in future. In addition, it is a well-known fact that Japan is one of the most serious countries against the risk of cancers for patients due to the exposure of radiation from the medical diagnosis with the radiation-based diagnostic equipment such as an X-ray CT (Computer Tomography) and PET

(Positron Emission Tomography) [1]. Under these circumstances, it is of urgent importance for Japanese to alleviate the radiation exposure not only from the environment but also from the medical diagnosis.

We paid attention to the MRI (Magnetic Resonance Imaging) which has been used for the medical diagnosis as a promising imaging method free from the ionizing radiation such as X-ray and radioactivity. Since the nuclei to be used for the MRI were limited to the proton, usefulness of the MRI was keeping rather restrictive. However, since the first success of the MRI imaging for the animal brain and lung by the hyperpolarized ^{129}Xe [2], the MRI with the hyperpolarized nuclei has been developed not only for ^{129}Xe, but also for ^{3}He [3], and ^{13}C [4], where «hyperpolarized» means «polarized higher than the TE (Thermal Equilibrium) polarization». Since the NMR signals are greatly enhanced owing to the hyperpolarized nuclei relative to the TE-MRI, the hyperpolarized nuclear MRI has the substantial advantage of high resolution imaging and short measuring time. In addition, possible candidate nuclei to be hyperpolarized are not restricted to the above nuclei, but expanded into other nuclei with a spin $\frac{1}{2}\hbar$ such as ^{15}N, ^{19}F, ^{29}Si, ^{31}P, and so on.

Then, the radiation base diagnostic method like the X-ray CT and PET would give way to the radiation free MRI with the hyperpolarized nuclei. This is the primary motivation of our project to establish a novel imaging method without using the radiation in order to reduce the cancer risk caused by the medical diagnosis (note that this is not a new method since it has been used by a number of laboratories in Europe and USA by using hyperpolarized ^{3}He and ^{129}Xe).

In this report, the progress in our project on the MRI with the hyperpolarized ^{3}He and ^{19}F is presented particularly emphasizing the reason why we chose ^{3}He and ^{19}F, and the methods to create the ^{3}He and ^{19}F hyperpolarization.

1. PRODUCTION OF THE HYPERPOLARIZED NUCLEI

1.1. Hyperpolarized ^{3}He. The MRI with hyperpolarized ^{3}He has been developed mainly in Europe and the USA as a diagnostic and prognostic tool for given lung pathological diseases ^{3}He images as well as a tool for the basic study on the ventilation function of the animal and human lungs. Since the ^{3}He images gave far superior images to other methods such as ^{81m}Kr Single-Photon Emission Computed Tomography (SPECT), which uses radioactivity [5], usefulness of the hyperpolarized ^{3}He showed particularly in pathologies: emphysema and selected COPD (Chronical Obstructive Pulmonary Disease), such as bronchitis and bronchiolitis as a substitute for the SPECT. In fact, in Europe, the Phelinet project [6] that aims at promoting the study and training of the lung image with the hyperpolarized ^{3}He has widely enlightened the worldwide community on importance of the hyperpolarized ^{3}He MRI.

The production method of the hyperpolarized ^{3}He gases offered so far has been restricted to the SEOP (Spin Exchange Optical Pumping) [7], or MEOP (Metastability Exchange Optical Pumping) [8], both of which are based on the laser optical pumping. However, one of the drawbacks of the afore-mentioned methods comes from the fact that its production rate is limited particularly because it uses low gas pressure that has to be compressed afterwards. The production rate per day is only a few tens (a typical actual figure is mostly less than 1.5 at Mainz) of liter bar$\cdot\ell$ with ^{3}He polarization degree of about 70% [9]. With this limited production rate, one cannot make ^{3}He diagnosis of more than a few patients per day, in spite of a number of requests.

To answer this demand, we have been developing a hyperpolarization technique based on the brute force method which uses an extremely low temperature (a few mK) and a strong magnetic field ($\sim$17 T) in combination with the principle of the Pomeranchuk cooling [1]. In fact, this method is expected to produce stably a few tens bar$\cdot\ell$ of high pressure hyperpolarized ^{3}He gas per day [10], which is sufficient to be used for lung images of hundreds of patients per week. The detailed description of our hyperpolarized ^{3}He production is given in [1].

1.2. Hyperpolarized ^{19}F. It should be noted that the market price of ^{3}He gas has been unexpectedly rising more than 10 times in these years. This seems to make it more difficult to continue the development of the hyperpolarized ^{3}He MRI. Therefore, additional methods for pulmonary functional MRI are desirable to complement the capabilities of the hyperpolarized ^{3}He MRI. One of the possible candidates is to use hyperpolarized ^{19}F artificially produced in organofluoro compounds as contrast agents of MRI. The reason why ^{19}F has been chosen is that body tissues do not possess a natural ^{19}F, the gyromagnetic ratio is not far from that of ^{1}H, and the development of new drugs often involves fluorine as a component to modulate pharmacological activities of physical properties because fluorine is the most electronegative element, and therefore the synthetic introduction of fluorine can produce dramatic electronic perturbations and modify sterical tertial structures. In fact, the ^{19}F MRI at TE has been successfully used for a variety of biomedical researches in vivo [11] since the time just after the first human ^{1}H MRI in the 1970s.

As far as the lung imaging obtained by ^{19}F is concerned, there have been measurements with SF_6 gas [12], C_2F_6, C_2F_8 gases [13], and aerosol of PFC (PerFluoroCarbon) [14] at room temperature, where a PFC molecule has similar structure to usual organic compounds, for example, alkane, except that all of the hydrogens are replaced by fluorine. However, the disadvantage of the above contrast agents is that sharpness of the MRI images is inferior to those of the hyperpolarized ^{3}He MRI, and in addition, the scanning time of MRI is far longer than that of the hyperpolarized ^{3}He MRI because of the low detection sensitivity. However, if one can hyperpolarize ^{19}F in PFC, the ^{19}F MRI lung images will dramatically improve. This is a primary motivation of production

of hyperpolarized ^{19}F offered by us. So far, there has been no measurement of the hyperpolarized ^{19}F MRI except for 3-fluorostyrene [15]. They produced hyperpolarized ^{19}F by using the PHIP (ParaHydrogen Induced Polarization) method well established in the chemical society [16].

1.3. Parahydrogen Induced Polarization (PHIP). Bryndza, in 1981, found strangely enhanced antiphase signals on the protons of the homogeneously hydrogenated tricobaltalkylidyne complexes by using molecular hydrogen [16]. Though at that time, the signal (polarization) enhancement was caused by the CIDNP (Chemically Induced DNP) which needs formation of radical, Bowers and Weitekamp, in 1986, proposed that this phenomenon was caused not by the CIDNP but by the hydrogenation of substrates carrying unsaturated carbon bonds with parahydrogen. Since then, this principle was named PHIP. Basically, the PHIP has two types, namely, PASADENA and ALTADENA according to the condition of external magnetic field, the details of which are referred to [16]. Here, a conceptual expression of the PHIP principle applied to the ^{1}H hyperpolarization is briefly touched for the ALTADENA method, in which hyperpolarization is generated when the hydrogenation by parahydrogen is performed outside the NMR field followed by a transfer of the hydride substrate into the NMR field. Needless to say, the parahydrogen itself shows no NMR signal because two-proton spins are coupled to spin 0. However, if a substrate is hydrogenated by the parahydrogen, two protons are influenced with chemical shift, and the NMR peaks split into 4 peaks. Then, NMR signals are observable depending on the population difference determined by the Boltzmann factor as shown in Fig. 1, *a*, where α, and β are spin-up and spin-down states of proton, respectively. If the ALTADENA condition is satisfied, the spin wave function of the parahydrogen changes to the so-called adduct state expressed by $|\beta\alpha\rangle$. Consequently, the state denoted by $\beta\alpha$ is predominantly populated, and NMR signals are enhanced, i.e., hyperpolarized, as shown in Fig. 1, *b*. Here, negative peaks are due to the photon emission. It is also established that a heteronucleus in the substrate such as ^{19}F in fluorinated stylene and phenylacetylene [17] can be hyperpolarized through the spin–spin interactions between protons and heteronucleus.

The Wilkinson catalyst [18], an organic complex with transition metal (Rh), has been used for hydrogenation of a substrate to be hyperpolarized. This is a homogeneous catalyst, i.e., soluble catalyst in a solvent. Ligands of Rh atom bind both a parahydrogen molecule and a substrate with unsaturated bonds, the hydrogenated substrate is formed, and the two protons of the hydrogenated substrate are polarized. Simultaneously, the heteronucleus is also hyperpolarized. Finally, the hydrogenated substrate is released from the catalyst. In case of a substrate whose carbon bond is saturated, however, the hyperpolarization cannot be expected because the hydrogenation could not be expected.

Recently, Adams et al. [19] succeeded in the hyperpolarization not only for proton, but also for heteronuclei, ^{13}C, and ^{15}N in pyridine and nicotinamide

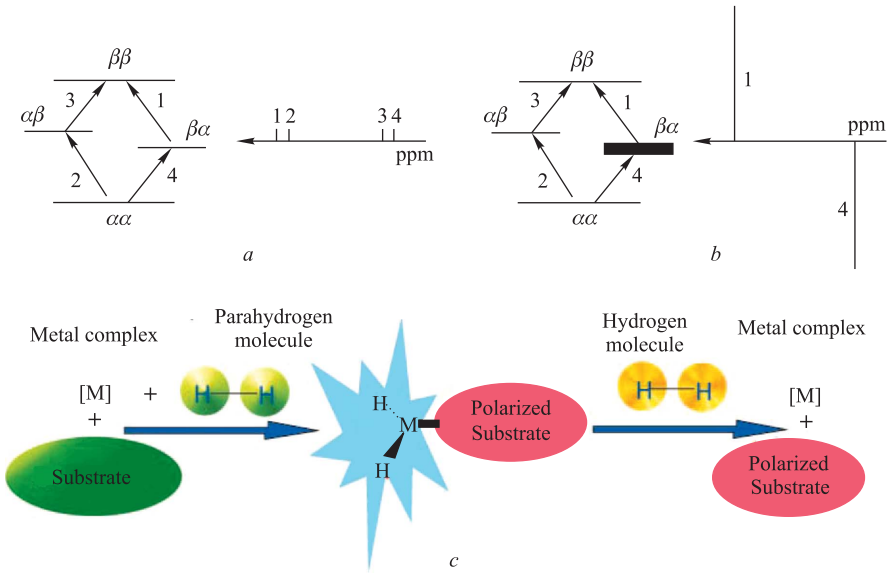

Fig. 1. *a*) Standard NMR system; *b*) ALTADENA NMR system; *c*) principle of hyperpolarization catalyst

without hydrogenation. They used a complex with an Ir atom (Crabtree's catalyst with acetonitrile ligand). Since this catalyst is labile, it keeps a parahydrogen molecule and a substrate molecule having an amine group with a lone pair close each other during a certain time enough for hyperpolarization, and, then, both the hydrogen molecule and the substrate are liberated followed by the next cycles. In other words, this catalyst does not influence the chemical reaction, but contributes only in generating the hyperpolarization. In fact, this is a novel concept of catalyst. Therefore, we named it «hyperpolarization catalyst», and its principle is illustrated in Fig. 1, *c*.

Our project on the hyperpolarized ^{19}F for PFC is based on this new idea. Since the PFC has no unsaturated bond, the hyperpolarization by PHIP is impossible. However, FPTA (PerfluoroTripropylAmine), one of the PFCs, often used for an artificial blood has an amine group. We believe that production of the hyperpolarized ^{19}F by the hyperpolarization catalyst must be in a feasible extent. In the next section, further plan on this subject will be continued.

2. PRESENT AND FUTURE DEVELOPMENT

In this section, a brief report on the present situation and future plan of our development is presented. The development of the hyperpolarized ^{3}He is still

under way. The principle of hyperpolarization is based on the production of highly polarized solid ^{3}He by means of the brute force method which needs an extremely low temperature (a few mK) and a strong external magnetic field and rapid melting of the polarized solid ^{3}He at low temperature into polarized ^{3}He liquid then followed by heating to obtain polarized gas. To realize an extremely low temperature, combination of a ^{3}He/^{4}He dilution cryogenic system and the principle of Pomeranchuk cooling were introduced. For providing an external field, a 17-T superconducting solenoid coil was employed. For rapid melting, a special device consisting of a mechanical thermal switch, and a polarized ^{3}He gas extraction system were designed and constructed [1]. For the polarization measurement, we constructed a compact NMR system which uses a cutting-edge digital technology for the fast ADC and rewritable logic circuits with a high speed computer [20]. One of full scanned NMR spectra and a temperature dependence of the ^{3}He polarization are shown in Figs. 2 and 3, respectively. The ^{3}He polarization at a low ^{3}He pressure follows the theoretical curve (green curve) assuming TE, while that at high ^{3}He pressure reduces from the TE values by a factor of about 4 (blue curve). A repeated measurement is necessary.

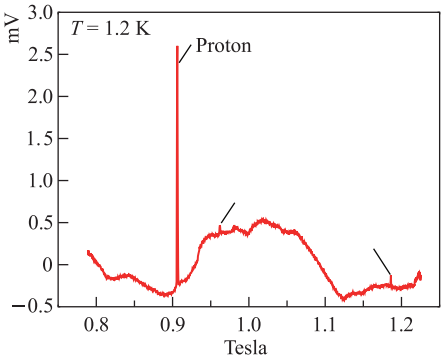

Fig. 2. (Color online) Full NMR spectrum from the Pomeranchuk cell

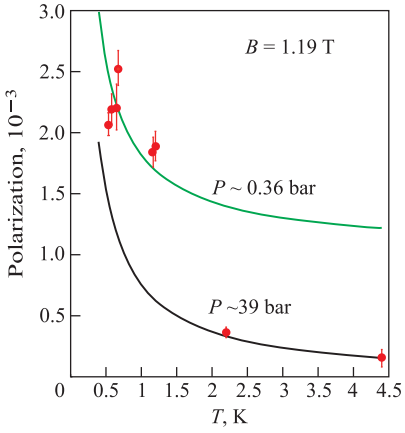

Fig. 3. Temperature dependence of the ^{3}He polarization

Finally, future development is touched on the hyperpolarized ^{19}F in PFC by means of the hyperpolarization catalyst proposed by us. The primary aim of this project is to produce aerosol of the hyperpolarized ^{19}F in PFC for lung imaging. Secondly, we pay attention to an emulsified PFC. The emulsified PFC has been used for an artificial blood, because its oxygen-carrying capacity is about three times as much as that of blood at 25°C, and the CO_2-carrying capacity is approximately four times greater than that for oxygen. If ^{19}F in emulsified PFC

shall be hyperpolarized, it will be a high contrast agent of MRI for a radioactivity-free angiography of blood vessel.

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