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Long live the singlet state!

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ABSTRACT

The field of long-lived states in NMR is reviewed. The relationship of long-lived-state phenomena to those associated with spin isomerism is discussed. A brief overview is given of key developments in the field of long-lived states, including chemical symmetry-switching, the role of magnetic equivalence and magnetic inequivalence, long-lived coherences, hyperpolarized NMR involving long-lived states, quantum-rotor-induced polarization, and parahydrogen-induced hyperpolarization. Current application areas of long-lived states are reviewed, and a peer into the crystal ball reveals future developments in the field.

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It is now 15 years since our group published two papers demonstrating that it is possible to store nuclear spin order in solution for times much longer than the magnetization relaxation time T_1[1,2]. Both papers involved molecular systems containing well-isolated pairs of proton spins-1/2 in chemically inequivalent sites, embedded in molecules lacking a high degree of symmetry. A long-lived mode of spin order called *singlet order*, which corresponds to the population difference between the nuclear singlet and triplet states, was populated. In the first case this was done by applying a radiofrequency pulse sequence to a sample in thermal equilibrium in high magnetic field, followed by transport of the sample out of the NMR magnet into a low magnetic field region [1]. In the second case the excitation of singlet order was accomplished directly in high magnetic field [2]. In both experiments, the singlet order was allowed to evolve while suppressing singlet-triplet transitions induced by the chemical shift difference between the protons. In the first paper, chemical shift suppression was achieved by removing the sample from the NMR magnet [1]. In the second paper, the sample was retained in the high-field NMR magnet, while the chemical shift difference was suppressed by applying a resonant radiofrequency field [2]. Singlet order relaxes more slowly than ordinary magnetization, since it is immune to the dominant intra-pair dipole-dipole relaxation mechanism. It was demonstrated that the nuclear singlet order relaxes with a time constant T_S which is many factors larger than T_1.

In retrospect, the most novel feature of these experiments was *not* the demonstration that certain types of nuclear spin order may persist for times much longer than T_1. Such phenomena have been long known in the context of nuclear spin isomerism, which occurs in small, highly symmetrical molecules with a high degree of rotational freedom, *ortho*- and *para*-hydrogen being the seminal examples [3]. In spin isomerism, the Pauli principle, which constrains the overall symmetry of allowed quantum states, entangles the spatial wavefunctions and spin states, such that nuclear energy levels are invested with energy differences associated with the *spatial* quantum mechanics of the rotating molecules. Such energies may be many orders of magnitude larger than nuclear Zeeman splittings. For example, the splitting between the rotational ground states of parahydrogen (nuclear spin singlet) and orthohydrogen (nuclear spin triplet) is ~ 3.6 THz, which is about 4 orders of magnitude larger than typical nuclear Zeeman energies. This large energy difference makes it possible to generate large population differences between the nuclear singlet and triplet state simply by bringing the hydrogen gas into contact with a cold magnetic material which catalyses the singlet-triplet transitions. The population difference between the singlet and triplet state persists for very long times (up to days or weeks) when the sample is removed from the catalyst, allowing the convenient production of hydrogen gas enriched in the nuclear singlet state (parahydrogen spin isomer). The inherent long-lived singlet order in *para*-enriched hydrogen was famously exploited by Weitekamp and co-workers who showed that it may be unlocked by a chemical hydrogenation reaction, generating greatly enhanced NMR signals [4–6]. Related effects occur in compounds such as 4-methylpyridine (γ-picoline), in which the methyl (CH_3) group has a very low rotational barrier at cryogenic temperatures. In this case the splitting

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between the spatial quantum levels is called a tunneling splitting and is of the order of ~ 125 GHz, as measured by neutron scattering [7]. As in the case of parahydrogen, a large population difference can be generated between the nuclear symmetry species by cooling the sample. When the temperature is raised, strongly enhanced NMR signals may be induced, both in the solid state [8], and in solution after dissolution [9–13].

The real novelty in our 2004 experiments was the demonstration that long-lived modes of nuclear spin order are not limited to systems with high degrees of symmetry and extreme rotational freedom and which display spin isomerism, but may be exhibited by rather "ordinary" molecules, and may be accessed using relatively conventional radiofrequency pulse sequences, supplemented in some cases by changes in the static magnetic field. It is now clear that such long-lived state phenomena are relatively widespread for clusters of coupled nuclear spins. Spin isomerism is a special case, in which the Pauli-principle entanglement of spin and spatial modes for freely rotating symmetrical moieties allows large amounts of order to be deposited in long-lived states by thermal means alone (Fig. 1).

In the years since 2004, our group and several others have researched intensively on long-lived states (LLS) and related phenomena. Some key developments are as follows:

- It was shown that *chemical symmetry switches* may be used to access long-lived spin order modes, as an alternative and supplement to magnetic field procedures. The local symmetry of the nuclear spin hamiltonian is broken by chemical and physical transformations of the sample, allowing access to the long-lived modes of spin order. This can provide access to long-lived states even in cases of complete magnetic equivalence [19–26].
- The use of magnetic inequivalence, as opposed to chemical equivalence, to access long-lived states in systems of more than 2 coupled spins-1/2 [27–29]. Most demonstrations of this principle have required that the degree of magnetic inequivalence (as defined in Ref. [30]) is very small. However, for some molecular geometries, a class of LLS persists even for strong magnetic inequivalence [30].
- The design and synthesis of molecular systems which support extremely long-lived states. For example, a $^{13}C_2$-labelled naphthalene derivative exhibits a T_S value exceeding 1 h in room-temperature solution, in low magnetic field [31]. Compounds called diazirines, which contain a three-membered ring formed by two nitrogen atoms and one carbon, are particularly promising [25,32].
- Demonstrations of long-lived coherences (LLCs) with very long lifetimes, and which in some cases oscillate coherently for tens of minutes [33–40].
- The use of long-lived states for the storage of hyperpolarized nuclear spin order [15,18,19,41–43]. Dynamic nuclear polarization (DNP) sometimes generates long-lived spin order directly, as a by-product of strong nuclear polarization [15–18,44].
- The development of methods for converting nuclear magnetization into long-lived spin order, and back again [45,46], including radiofrequency pulse sequences combined with field cycling [1,15,33,40,43,46–50], pulse sequences that operate in the weakly-coupled (strong inequivalence) regime [2,46,51,52], the M2S/S2M (magnetization-to-singlet and singlet-to-magnetization) pulse sequences and related methods for the near-equivalence regime [29,46,49,53–57], the simple and elegant SLIC (spin-lock-induced crossing) method [54,58–60], and the robust schemes which exploit adiabatic passage through avoided level crossings [39,40,61–63].
- The identification of long-lived states in rapidly rotating methyl groups, and their involvement in nuclear hyperpolarization phenomena observed when certain substances are warmed rapidly from the cryogenic solid state to ambient temperature [9–11].
- The study of heteronuclear long-lived states in ultralow-field NMR [64].
- The use of minuscule chemical shift differences to access long-lived singlet order, including the chemical shift differences between CH_2D protons in some chiral molecules [65–67], and mass-induced shift differences in compounds labelled with spin-0 isotopes such as ^{18}O[68].
- The elucidation of relaxation mechanisms for long-lived-states [31,69–76], including unusual mechanisms such as spin-rotation and spin-internal-motion [31,33,48,71,75], the antisymmetric components of the chemical shielding tensors [31,74], and scalar relaxation of the second kind [73,76].
- The use of long-lived states for the preparation of hard-to-access spin isomers, such as para-$^{15}N_2$[77].

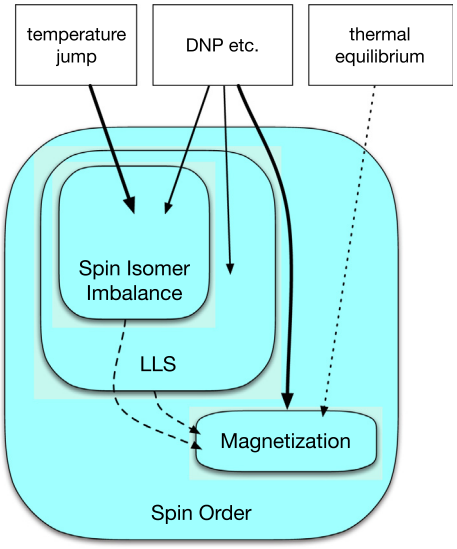

Fig. 1. The relationships between spin isomerism, long-lived states, hyperpolarization methods and thermal equilibrium. Magnetization and long-lived spin order (LLS) are both types of nuclear spin order. A population imbalance between spin isomers is a special type of long-lived spin order which may arise in symmetrical moieties with high rotational freedom, such that the Pauli principle constrains the allowed combinations of spin and spatial quantum states. Spin-isomer population imbalances may be generated by temperature changes, as in parahydrogen-induced hyperpolarization (PHIP) [4–6] and quantum-rotor-induced polarization (QRIP) [9–13]. Hyperpolarization techniques such as dynamic nuclear polarization (DNP) generate enhanced magnetization [14], but may also directly generate long-lived spin-order [15], including spin-isomer population imbalances [16–18]. Long-lived spin order may be converted into magnetization by radiofrequency pulse sequences or relaxation and/or chemical transformations (dashed arrows). Most NMR experiments exploit the small amount of thermal equilibrium magnetization in a strong magnetic field at non-cryogenic temperatures (dotted line).

In addition, promising proof-of-concept applications have been reported in several areas, including:

- Ligand binding and screening in biomolecular NMR [78–81].
- The study of diffusion, transport and chemical exchange [51,82–87].
- Quantum computation [88].
- Nuclear hyperpolarization using parahydrogen as a singlet-polarized source [20,23–25,32,54,57,77,89–96].

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- Hyperpolarized NMR sensors for molecular imaging and spectroscopy [32,40,77,97,98].

There are even speculations that long-lived nuclear spin states might be involved in human cognition [99,100].

In my view, there have been two big disappointments in the long-lived state field:

- No important metabolite has yet been found that supports a long-lived state with a really substantial lifetime in biologically relevant conditions, and which could be used to transport hyperpolarized nuclear spin order in biomolecular imaging applications. Although $^{13}C_2$-labelled pyruvate does support a long-lived singlet state with a longer lifetime that the $^{13}CT_1$ in low magnetic field [101], the extension of lifetime is not observed in magnetic fields high enough for typical imaging experiments, and is not significant enough to compensate for the increased complexity and increased losses of NMR experiments involving long-lived states. The recent demonstration that singlet-hyperpolarized fumarate may be generated by a direct catalytic reaction of parahydrogen [57] holds out somewhat more hope in this direction.
- The substance $^{15}N_2O$ ($^{15}N_2$-labelled nitrous oxide) initially seemed to be a promising target for hyperpolarized long-lived state NMR. The two ^{15}N spins-1/2 are isolated, possess a chemical shift difference (providing access to singlet order from magnetization). Nitrous oxide is biocompatible and widely used as an anaesthetic and for recreational purposes. $^{15}N_2O$ displays a long T_S of up to 20 min in solution [48], and 7 min in blood [102], and may be hyperpolarized in frozen solution by DNP [103]. Unfortunately attempts to exploit this material have so far been defeated by the very efficient nuclear spin-rotation relaxation of $^{15}N_2O$ in the gas phase.

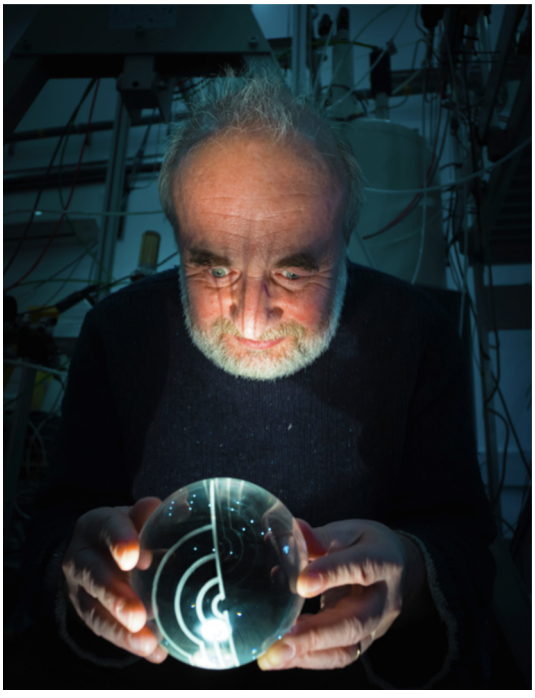

Fig. 2. My crystal ball was given to me in 2019 as a wonderful present from my research group, and is decorated with an occult inscription resembling magnetization vector trajectories for a composite pulse [104]. Unfortunately its picture quality has deteriorated – possibly through overuse (I am writing this in England in March 2019). Photograph by Karel Kouřil.

So where do we go from here?.

Despite the limited picture quality of my crystal ball (Fig. 2), the outline of future developments may be guessed.

- It is likely that the promising applications for long-lived states, as sketched above, will continue to develop. In particular the use of LLS phenomena for the characterization of ligand binding looks close to applications in realistic contexts [78–81].
- Long-lived states have always held promise as a way of extending the lifetime of hyperpolarized spin order, potentially extending the reach of hyperpolarization techniques such as dissolution-DNP in biomolecular imaging. Time has gone by and this potential has not yet been fully realised, despite some promising demonstrations. In this respect, long-lived states resemble nuclear fusion: A technology which has a great future, and which will always have a great future. Nevertheless long-lived states might still realise their potential in molecular imaging, if a hyperpolarized substance with a sufficiently long lived state is identified which has real significance as a metabolite or as a tag for functional molecular imaging. A lot of progress has been made [32,40,77,97,98], but we are not there yet.
- The fields of long-lived states and parahydrogen-induced hyperpolarization have a natural synergy, since parahydrogen is itself a long-lived nuclear singlet state. Insights from LLS spin dynamics have already played a major role in elucidating the mechanisms of important hyperpolarization methods such as SABRE (Signal Amplification by Reversible Exchange) [91,92,105]. The close contact between the fields is likely to continue into the future, specially in the context of low-field and ultra-low-field NMR [64,96,106].
- Long-lived states have also strengthened the productive contact between NMR and the related fields of quantum rotors and spin isomers. For example the powerful theories of molecular symmetry [107,108] have a clear relationship with the theory of long-lived states.
- In my mind, one of the most robust achievements of long-lived nuclear spin states is the convergence of language and concepts between the study of nuclear spins and the study of electron spins. The language of singlets and triplets is commonplace in electronic spectroscopy and molecular quantum mechanics but was quite rarely used in NMR before the demonstrations of long-lived singlet states – with some notable exceptions, such as the treatment of magnetically equivalent spin systems [109,110]. This is because the prevailing conceptual language of NMR has been largely determined by the "weak coupling" approximation, which has broad validity in high-field solution NMR. Key conceptual tools such as the product operator formalism [111,112] were developed within the context of the weak-coupling approximation and have become part of everyday NMR language. Singlet and triplet spin states do not fit well into this formalism.

  The opposite is true in multi-electron systems where the large electron exchange interaction is dominant. Electronic singlets and triplets are everyday concepts in molecular quantum mechanics and electronic spectroscopy, and are taught at undergraduate level.

  The study of nuclear singlet and triplet states establishes a productive analogy with electron-spin phenomena which involve electron singlet and triplet spin dynamics. This facilitates a two-way transfer of information and experience between ordinary NMR and phenomena in related fields including chemically-induced dynamic electron polarization (CIDEP) [113], chemically-induced dynamic nuclear polarization (CIDNP) [114,115], electrically-detected magnetic resonance

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[116], and spintronics [117].

Despite the annoying flicker of my crystal ball, the continuation of this synergy into the future is plain.

To conclude: Ladies and gentlemen – be upstanding, and raise your glasses: Long live the singlet state!

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