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Communication

Optimisation of dynamic nuclear polarisation of [1-^{13}C] pyruvate by addition of gadolinium-based contrast agents

Lanette Friesen-Waldner [a,b,*], Albert Chen [c], Will Mander [d], Timothy J. Scholl [b], Charles A. McKenzie [a,b]

[a] Robarts Research Institute, London, Ontario, Canada N6A 5K8
[b] Department of Medical Biophysics, The University of Western Ontario, London, Ontario, Canada N6A 5C1
[c] GE Healthcare, 11 Brunel Crt., Suite 5116, Toronto, Ontario, Canada
[d] Oxford Instruments, 8403 Cross Park Drive, Suite 3F, Austin, TX 78754, USA

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ABSTRACT

Dynamic nuclear polarisation (DNP) of carbon-13 (^{13}C) enriched endogenous compounds provides a novel means for magnetic resonance imaging and spectroscopy of biological processes. Adding small amounts of gadolinium-based contrast agents (GBCAs) to the ^{13}C-enriched substrate matrix increases the amount of hyperpolarisation that can be achieved, but also may decrease the longitudinal relaxation time (T_1) of the ^{13}C nucleus in solution. This study examined the effects of five different GBCA at concentrations of 0.5, 1, 2, and 3 mM on [1-^{13}C]-enriched pyruvic acid. It was found that contrast agents with an open chain structure (Gadobenate dimeglumine, Gadopentetate dimeglumine, Gadodiamide) caused the largest enhancement (up to 82%) in solid state polarisation relative to solutions without GBCA. In the liquid state, T_1 of pyruvate decreased by as much as 62% and polarisation was much lower (70%) relative to solutions without GBCA added. Conversely, for GBCA with macrocyclic structures (Gadoterate meglumine, Gadoteridol), the solid state polarisation enhancement was only slightly less than the open chain GBCA, but enhanced polarisation was retained much better in the liquid state with minimal decrease in T_1 (25% at the highest GBCA concentrations). Near maximum polarisation in the solid state was obtained at a GBCA concentration of 2 mM, with a higher concentration of 3 mM producing minimal improvement. These results indicate that the macrocyclic contrast agents provide the best combination of high solid state and liquid state polarisations with minimal loss of T_1 in experiments with hyperpolarised ^{13}C-enriched pyruvate. This suggests that macrocyclic contrast agents should be the GBCA of choice for maximising signal in experiments with hyperpolarised ^{13}C-enriched pyruvate, particularly for *in vivo* measurements where shortened substrate T_1 is especially problematic.

1. Introduction

Magnetic resonance imaging and spectroscopy of non-hydrogen nuclei has, in the past, been challenging in biological specimens due to the low natural abundance of non-hydrogen nuclei and/or the poor polarisation of these nuclei due to their smaller gyromagnetic ratios. Dynamic nuclear polarisation (DNP) of carbon-13 (^{13}C) enriched substrates with rapid dissolution has enabled novel applications for magnetic resonance imaging [1,2]. These hyperpolarisation techniques provide signal-to-noise enhancements on the order of 10,000-fold over non-hyperpolarised ^{13}C imaging methods [3,4]. *In vivo* imaging with hyperpolarised compounds has been applied to imaging the perfusion of cardiac abnormalities, to vasculature in diseases, and to measuring metabolic processes in cancer, among other applications [5–7].

The addition of small quantities of gadolinium-based contrast agents (GBCAs) to the ^{13}C-enriched substrate matrix containing a trityl radical significantly increases the amount of hyperpolarisation that can be obtained via DNP [8,9]. Although the mechanism for this increase is not fully understood, it is hypothesised that the GBCA shortens the relaxation time of the free electron of the trityl radical making the transfer of electronic magnetisation to the ^{13}C nucleus more efficient. The addition of GBCA, however, has the potential side effect of shortening the relaxation time of the ^{13}C nucleus in solution. Gabellieri et al. [10] measured the relaxivities of non-hyperpolarised ^{13}C-enriched pyruvate and glycine in the presence of each of four GBCA (Omniscan, Magnevist, Dotarem, Gadovist), and the changes in the longitudinal relaxation times (T_1) of hyperpolarised ^{13}C-enriched pyruvate when Omniscan or Magnevist were injected during acquisition of the T_1 decay curves. To the knowledge of the authors, no study has been published comparing the effects of various GBCA on amount of

* Corresponding author at: Robarts Research Institute, The University of Western Ontario, 100 Perth Drive, London, Ontario, Canada N6A 5K8.
E-mail addresses: lfriesen@imaging.robarts.ca (L. Friesen-Waldner), albert.chen@ge.com (A. Chen), will.mander@oxinst.com (W. Mander), scholl@uwo.ca (T.J. Scholl), cmcken@uwo.ca (C.A. McKenzie).

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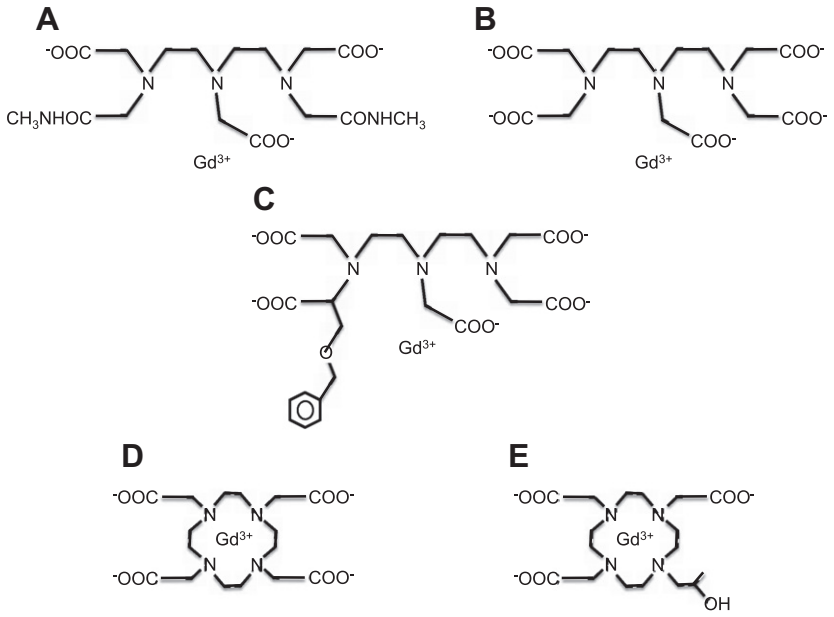

Fig. 1. Molecular structures for (A) Gadodiamide (Omniscan), (B) Gadopentetate dimeglumine (Magnevist), (C) Gadobenate dimeglumine (MultiHance), (D) Gadoteric acid (Dotarem), and (E) Gadoteridol (ProHance). The gadolinium based contrast agents A–C have open chain structures, while D and E have macrocyclic structures.

hyperpolarisation obtained and loss of hyperpolarisation in the liquid state.

The T_1 of ^{13}C nuclei are typically less than 1 min, and all data acquisition must be completed before the non-equilibrium magnetisation is lost due to T_1 decay. For this reason, additional shortening of the substrate T_1 by the GBCA is not desirable, particularly for *in vivo* experiments where the time required for the substrate to be delivered to the subject and to reach the tissue of interest may be significant. This is an important constraint for use of hyperpolarised media *in vivo* and motivates finding methods to maximise polarisation without unduly shortening T_1. Ideally, the GBCA would increase the amount of polarisation achieved via DNP with minimal effect on the relaxation time of the ^{13}C nucleus in solution. This study examines the effects of several GBCAs at varying concentrations on the T_1 relaxation time and on the relative amount of polarisation obtained in one of the more commonly used substrates, [1-^{13}C]-enriched pyruvic acid. The optimal contrast agent and concentration is determined for maximum enhancement of hyperpolarisation of the ^{13}C nucleus and minimal effect on its longitudinal relaxation time.

2. Materials and methods

[1-^{13}C]-enriched pyruvic acid (CIL, Cambridge MA) samples containing 15 mM OX63 trityl radical (Oxford Instruments Molecular Biotools, Abingdon, UK) were doped with 0.5, 1.0, 2.0, and 3.0 mM concentrations of GBCA. The volume of pyruvic acid was 15 μL and the volume of the contrast agent solution added was held constant at 1.5 μL for each sample by diluting the commercial formulations to the desired concentrations. Five contrast agents were examined – two with macrocyclic structures: Gadoterate meglumine (Dotarem, Gd-DOTA, Guebert S.A.), Gadoteridol (ProHance, Gd-HP-DO3A, Bracco Diagnostics Inc.), and three with open chain structures: Gadobenate dimeglumine (MultiHance, Gd-BOPTA, E7155, Bracco Diagnostics Inc.), Gadopentetate dimeglumine (Magnevist, Gd-DTPA, Bayer Schering Pharma AG), Gadodiamide (Omniscan, Gd-DTPA-BMA, GE Healthcare). The chemical structures for these gadolinium-based contrast agents are shown in Fig. 1. These solutions were hyperpolarised using a Hypersense DNP polariser (Oxford Instruments, Abingdon, UK). The polarised sample was dissolved in a solution containing

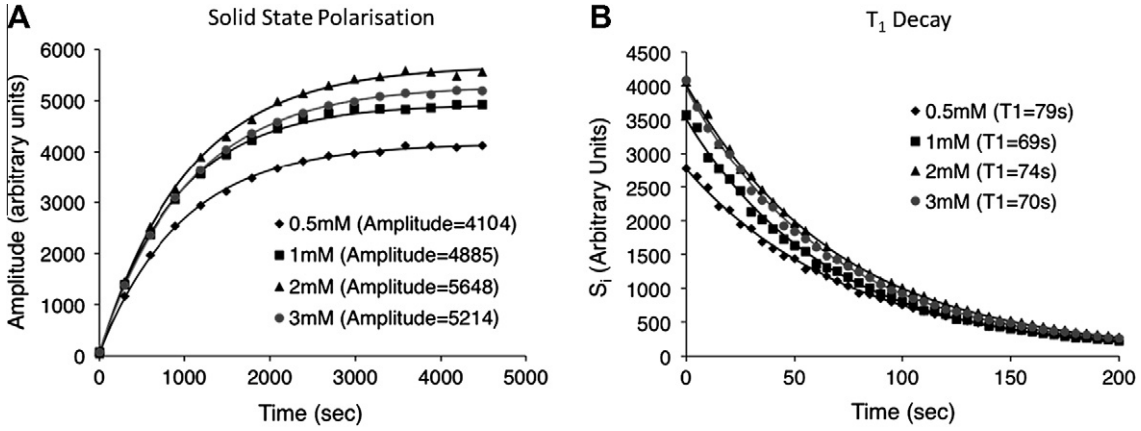

Fig. 2. (A) Polarisation build-up curves for varying concentrations of Gadoterate meglumine (0.5–2 mM). The solid lines indicate the curve fit to determine the equilibrium solid state signal. (B) T_1 decay curves for the same set of concentrations of Gadoterate meglumine. The solid lines indicate the curve fits used to determine T_1 of the [1-^{13}C] pyruvic acid/trityl radical mixture.