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Molecular sieve based MRI contrast agents

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Abstract

The application of zeolite molecular sieves as magnetic resonance imaging contrast agents for the gastrointestinal tract is described. Results for the preparation and characterization of zeolite GdNaY, the principle component of Gadolite, are presented. Ion exchange studies suggest GdNaY is stable to relatively low pH values as well as in dilute NaCl solutions. Preliminary relaxivity (R) measurements of aqueous GdNaY suspensions at room temperature and 40 MHz indicate an increase in R with a decrease in zeolite gadolinium loading.

1. Introduction

The development of new diagnostic pharmaceuticals for contrast enhancement in magnetic resonance imaging (MRI) [1] has evolved to the point where there are now several challengers to the Shering agent, GdDTPA [2]. It is clear that competitive drugs in this market must provide more than improved relaxivity or stability. There are major opportunities for contrast agents that target specific tissues or organ systems. In particular, MR imaging of the gastrointestinal tract would be an attractive alternative to current radiological methods that involve X-rays and barium salts. The GI tract is difficult to image because of artifacts that arise from looping and movement of bowel. The harsh environment of the GI tract requires an agent that is stable at low pH with the ability to evenly coat the bowel walls without absorbing into the bloodstream. Efforts to develop contrast media suitable for the GI tract has resulted in three types of materials: positive, negative and proton displacing agents. The negative or image darkening which results from T_2 or transverse relaxation time shortening is generally achieved with superparamagnetic ferrite particles [3]. Large organic molecules such as perfluorooctyl bromide which lack protons can displace the bowel contents resulting in a black image [4]. Preliminary studies of both these agents have shown problems with image artifacts, clumping and patient side effects. The preferred strategy appears to be the application of paramagnetic species which lead to image brightening or positive contrast created by T_1 or spin-lattice relaxation time shortening. There are a number of positive contrast agents under development which largely involve organic chelation of gadolinium(III) and these are not discussed here.

In conjunction with Pharmacyclics, Inc. we have developed an inorganic zeolite based positive contrast agent which we refer to as Gadolite [5]. Zeolites are strictly defined as aluminosilicates and form a subclass of microporous metal oxides known collectively as molecular sieves [6]. These materials are characterized as low density crystalline phases having uniform pore and channel systems. Preliminary *in vivo* imaging studies have shown exceptional contrast with no observed toxicity or side effects [7]. In this paper, we describe some of the physical and magnetic properties of a gadolinium modified zeolite. Additionally, different strategies for the incorporation of paramagnetic species into molecular sieves are discussed.

2. Materials

The molecular sieves described in this paper are synthetic Y type zeolites having the FAU topology [6]. The sodium form, NaY, has an approximate formula of $Na_{56}(Al_{56}Si_{136}O_{384})\cdot 240H_2O$ where water constitutes ~25% of the zeolite by weight. The charge balancing cations, in this case Na^+, may be exchanged with a variety of ions ranging from protons to lanthanides which can be located throughout the framework. The FAU structure shown in Fig. 1, consists of a three-dimensional array of interconnected channels ~8 Å in diameter. These channels open up to larger cavities known as supercages (~12 Å). We are largely interested in those paramagnetic species located in the supercages since we expect the water exchange rate for cations in other sites to be slower than T_1 [8]. Therefore, we anticipate the only contributions to observed relaxivity will be for those supercage sites where $\tau_m \gg T_1$.

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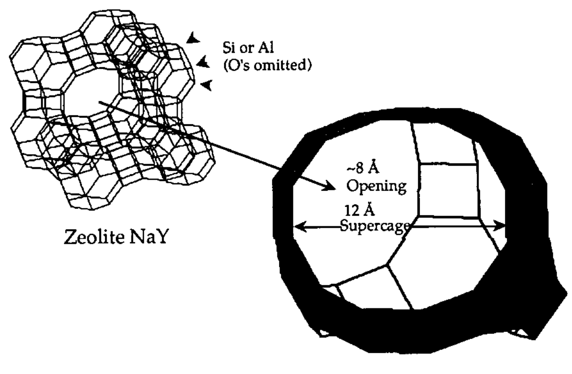

Fig. 1. FAU structure showing the arrangement of Si(Al) atoms.

Although, a variety of paramagnetic metal ions might satisfy the criteria for an effective MRI contrast agent [1], we have focused our efforts on zeolites containing gadolinium(III). Since there are commercial catalysts based on rare earth exchanged Y types zeolites, a great deal is known about their preparation and characterization. However, the pharmaceutical application of these materials presents several new issues that need to be addressed, especially the magnetic properties. In this short account we describe results for the preparation, stability and relaxivity studies of Gd^{III} exchanged NaY zeolites.

3. Ion exchange

There are several factors that can influence the exchange of Gd^{3+} for Na^{+} in Y zeolites including time, temperature, concentration and pH. Details of these studies will be published elsewhere. In general, Gd^{III} can be incorporated in NaY zeolites reproducibly (±0.1% Gd by weight) on a scale of 1–100 g using conventional aqueous ion exchange procedures. There is a fair amount of flexibility in the synthesis parameters. For example, room temperature ion exchange using $GdCl_3$ can be achieved in the pH range 3–5 without significant variation in Gd^{3+} loadings. An exchange solution pH above 5 may lead to the formation of gadolinium hydroxide. The $GdCl_3$ concentration in the exchange solution should be in excess ($>$1:4 w/w) but small changes do not make a significant difference in the Gd^{3+} loadings. Exchange times in the range of 4–8 h are preferred as shorter or longer times may lead to less than expected exchange levels. The zeolite gadolinium content can be conveniently determined from the digested zeolite (hot perchloric acid) using an EDTA titration with Xylenol Orange as the indicator.

Two issues related to *in vivo* stability that we have evaluated are the effect of pH and the influence of cations that may be found in the GI tract. The zeolite contrast agent may encounter strong acidity in the stomach which might be detrimental to the framework resulting in release of free Gd^{III} ions. The acute toxicity of $GdCl_3$ is relatively low (LD_{50} mice $>$ 2000 mg kg^{-1} orally) whereas the long-term effects of heavy metal poisoning are uncertain. Although, stomach pH can be buffered or acid production controlled, it is important that the contrast agent be stable under physiological conditions. We have determined that GdNaY is stable to pH 2.5 (HCl) with no evidence of gadolinium leaching or framework dealumination (XRD,IR). After 3 h at pH 2.0, less than 3% of the incorporated Gd^{III} is released which is largely due to partial re-exchange with protons. At pH values less than 1 most of the Gd is released, however, this pH is well below any physiological condition that could be encountered.

The USP test solution for gastric fluid calls for a 0.03 M NaCl solution. Under these conditions, there is no release of gadolinium from exchange with sodium. If the NaCl concentration is an order of magnitude greater, then ~12% of the Gd^{3+} is exchanged for Na^{+}. However, this ionic strength is well outside any physiological conditions. The USP test solution for intestinal fluid (pH 7.5) employs a phosphate buffer which precipitates Gd^{III}. Other model solutions at this slightly basic pH indicate that no Gd leaching occurs. Further studies with Ca, Mg and K are in progress.

4. Relaxivity

Relaxivities (R) were determined from plots of $1/T_1$ versus millimoles of gadolinium per liter. The room temperature T_1 relaxation times were obtained at 40 MHz from aqueous suspensions of the zeolites using the T_{null} method. Suspensions in the range of 0.025–1.6 wt% were examined. Figure 2 shows a plot of $1/T_1$ versus Gd concentration for a GdNaY containing 9.38% Gd by weight. The observed relaxivity, $R = 4.77$ mM^{-1} s^{-1} is obtained from the slope of this plot. We anticipated difficulty in obtaining linear relaxivity plots since precipitation would introduce scatter. However,

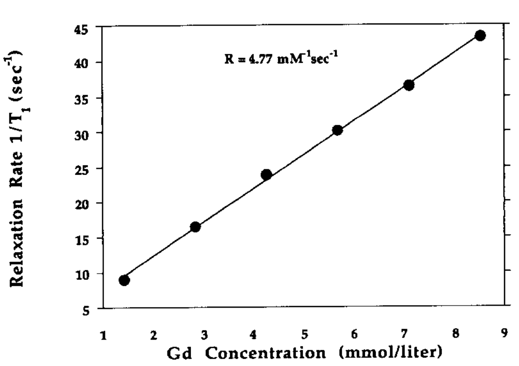

Fig. 2. Relaxivity (R) plot for GdNaY (9.38% Gd).

we found that the relaxation rates were quite reproducible for up to 30 min. The samples were shaken and the T_{null} recorded after a few seconds. Free gadolinium chloride was determined to have a relaxivity of 15 mM^{-1} s^{-1} (40 MHz) and this was remeasured as an external standard before every series of zeolite samples were evaluated. Figure 3 shows a plot of relaxivity versus Gd^{III} loading for several NaY zeolites. These samples cover a fairly narrow range of gadolinium concentrations which previous phantom studies [7] had indicated might be an optimum regime. A zeolite containing 8% gadolinium by weight corresponds to ~one Gd^{3+} ion per supercage (8 supercages per unit cell). If the Gd^{III} ions were located in the same positions in every sample, we might expect the same relaxivity. However, there are many more cation sites in the zeolite than there are cations so there will be some variation between zeolites with similar Gd loadings. The apparent increase in relaxivity with a decrease in Gd content may reflect the magnetic dilution as well as a variation in framework cation positions. Further work over a broader range of Gd loadings is in progress. In the fully hydrated state, we expect all of the Gd^{III} to reside in the supercages [9] with at least three waters coordinated. The two parameters that generally have a significant effect on relaxivity are the number of water molecules coordinated to gadolinium and the correlation time, τ_c [1]. The Gd^{III} aquo ion which contains 8 or 9 coordinated water molecules exhibits an $R = 15$ mM^{-1} s^{-1} which is higher than any of these Gd^{III} exchanged NaY zeolites which have less water coordinated to each metal ion. The Gd^{III} in the NaY zeolites produces solution like relaxivities that are generally greater than the multidentate chelate complexes. For example, GdDTPA which has one coordinated water, has a relaxivity of 4.8 mM^{-1} s^{-1} (25 °C, 20 MHz) [1].

The magnetic behavior of the zeolites contrasts other macromolecules used to support Gd^{III} where large increases in relaxivity have been observed. The increase in relaxivity of supported versus free Gd^{III} complexes, also referred to as the PRE effect, has been attributed to an increase in τ_r, the rotational correlation time contribution to τ_c [1]. We have observed relaxivities greater than the aquo ion only when the zeolite is suspended in a macromolecular agent. It is known that intrazeolite water behaves like a viscous liquid, lengthening T_1 in NaY [10]. Therefore, one cannot rule out the possibility that this effect may result in lower R values for GdNaY zeolites than might otherwise be expected.

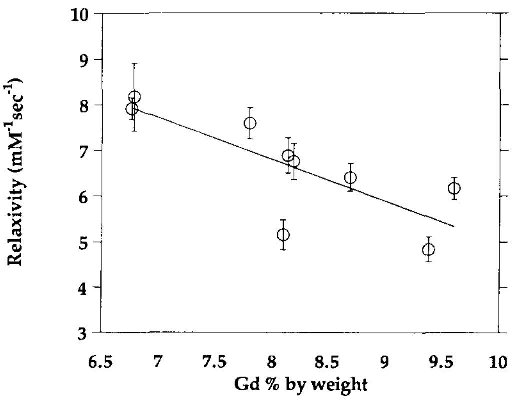

Fig. 3. Relaxivities for NaY with various Gd^{III} loadings.

The results in Fig. 3 were recorded in deionized water at pH 6. In comparison, at pH 3 there is a decrease in relaxivity for aqueous $GdCl_3$ from 15 to 12 mM^{-1} s^{-1}. Similarly at pH 3, the relaxivity for GdNaY (8.7% Gd) decreases from 6.4 to 4.4 mM^{-1} s^{-1} after 4 h and decreases further to 2.8 mM^{-1} s^{-1} after 24 h. These results are probably due to the increased hydrogen bonding and structure to the water at pH 3. This would affect the exchange rate of water as well as the molecular motion.

5. Further strategies

We have explored several methods for incorporating paramagnetic species into molecular sieves [11] as well as two-dimensional metal oxides [12]. Intrazeolite complexation of the gadolinium appears to enhance the observed relaxivity. For example, the introduction of 8-hydroxyquinoline (HQ), a potentially bidentate ligand, into GdNaY(X) or synthesis of the zeolite around Gd^{III} complexes of HQ in some cases results in modified zeolites with relaxivities greater than the ion exchanged only materials [11]. In addition to enhanced relaxivity, the encapsulated complexes are expected to be more stable to re-exchange at high proton concentrations.

The paramagnetic metal ion may also be incorporated into the oxide framework. Mn, Fe and Cr have previously been synthesized in the molecular sieve lattice [6]. Such materials may offer the advantage of a metal ion in a very stable environment but it is not clear how accessible the metal ions would be to water. We have prepared gadolinium silicates [13] having the MFI topology which exhibit room temperature relaxivities less than 3 mM^{-1} s^{-1}. There are many strategies for incorporating paramagnetic metal ions into microporous metal oxides yet to be explored, however, it may be difficult to improve on the simplicity and effectiveness of the zeolites.

Zeolite molecular sieves are inexpensive, readily available, non-toxic, chemically resistant, thermally stable and easy to modify with paramagnetic species. Preliminary animal studies indicate these materials are very promising positive MRI contrast agents.

Acknowledgments

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