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Perspective

Macrocyclic ligands for Fe(II) paraCEST and chemical shift MRI contrast agents

Pavel B. Tsitovich, Janet R. Morrow *

Department of Chemistry, University at Buffalo, State University of New York, Amherst, NY 14260, USA

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ABSTRACT

Fe(II) macrocyclic complexes are a relatively new addition to the class of MRI contrast agents that function through paraCEST (paramagnetic chemical exchange saturation transfer) or paraCSI (paramagnetic complex chemical shift imaging). Both methods require relatively narrow and highly shifted ligand proton resonances. For paraCEST, the protons are exchangeable with water (NH or OH); for paraCSI the protons are non-exchangeable and are on carbons (CH). We report on several macrocyclic ligands for Fe(II) including those based on CYCLEN (1,4,7,10-tetraazacyclododecane) and TACN (1,4,7-triazacyclononane) with attached pendent arms containing either benzimidazole, pyridine or amide donor groups. Paramagnetic proton NMR spectra and paraCEST spectra are reported for these complexes. Challenges include fluxionality of the macrocyclic complexes in solution which broadens the macrocycle proton resonances, especially for amide pendent groups. Despite this dynamic process, the exchangeable NH proton resonances of the amide pendent groups remain relatively sharp. These amide complexes are thus suitable for paraCEST but not paraCSI. The dynamic process is arrested in complexes containing pendent pyridine groups that lock the TACN macrocyclic Fe(II) complex into a single diastereomeric form over the temperature range of 15–45 °C to produce an Fe(II) complex that is promising for paraCSI.

Pavel B. Tsitovich *received his B.S. degree in Chemical Engineering from Mendeleyev University of Chemical Technology of Russia in 1998. He received his Ph.D. degree in Chemistry from Bowling Green State University, OH, in 2005. After holding several postdoctoral and industrial positions he joined Prof. Morrow's group at the University at Buffalo, State University of New York, in 2010 where he currently does postdoctoral work. His research focus is paraCEST MRI contrast agents and agents for chemical shift imaging that are based on transition metals.*

Abbreviations: MRI, magnetic resonance imaging; paraCEST, paramagnetic chemical exchange saturation transfer; paraCSI, paramagnetic complex chemical shift imaging; CYCLEN, 1,4,7,10-tetraazacyclododecane; TACN, 1,4,7-triazacyclononane.

* Corresponding author. Address: 526 Natural Sciences Complex, Department of Chemistry, University at Buffalo, State University of New York, Amherst, NY 14260, USA. Tel.: +1 716 645 4187; fax: +1 716 645 6963.

E-mail addresses: jmorrow@buffalo.edu, jmorrow@acsu.buffalo.edu (J.R. Morrow).

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Janet R. Morrow *received her B.S. degree in chemistry from the University of California, Santa Barbara and her Ph.D. degree in chemistry from the University of North Carolina, Chapel Hill. She did postdoctoral work at the University of Bordeaux on a National Science Foundation International Exchange Fellowship and at the University of California, San Diego prior to her appointment at the University of Buffalo, State University of New York, where she is currently Professor of Chemistry. Her research interests include the design of f-block and d-block paraCEST MRI contrast agents, optical sensing using luminescent lanthanide complexes and metal ion complex interactions with DNA and RNA.*

1. Introduction to paramagnetic MRI contrast agents

There is increasing interest in paramagnetic coordination complexes that create magnetic resonance imaging (MRI) contrast through their effect on ligand proton chemical shifts. Such contrast agents include paraCEST (paraCEST = paramagnetic chemical exchange saturation transfer) agents [1–4] as well as paramagnetic complexes that have temperature and/or pH sensitive proton resonances used for chemical shift imaging (paraCSI = paramagnetic chemical shift imaging) [5–9]. In these two methods, the paramagnetic center is used to create proton resonances that are highly shifted but have relatively narrow line widths. Interference from the proton signal of bulk water in tissue is minimized by the large shift of the proton resonances bound to the paramagnetic metal ion [2]. In paraCEST, the highly shifted proton is either in an OH or NH group of the ligand and this proton is in chemical exchange with the protons of water. The chemical exchange process must be slow on the NMR time scale so that the resonance of the exchangeable proton is distinct from that of the water protons. Irradiation at the resonant frequency of the exchangeable proton saturates the magnetization and, upon exchange, reduces the intensity of the water proton signal. Thus paraCEST contrast is produced by changes in the water proton signal. The water signal is modulated by the presaturation pulse that can be turned on or off in order to give an image with or without the effect of paraCEST. In paraCSI, the proton resonances of the contrast agent themselves are used to create the image. This technique is substantially the same as that used in chemical shift imaging with diamagnetic compounds, except that the paramagnetic contrast agent shifts the proton resonances far away from tissue water proton resonances. This leads to an increase in sensitivity of the contrast agent [5,6,9]. The proton chemical shifts of ligands in paramagnetic complexes are typically dependent on temperature and, for complexes with ionizable groups, on pH [9–11]. Thus, important applications for paraCEST and paraCSI contrast agents are for mapping temperature and pH in MR imaging studies [5,12]. These applications are referred to as “thermometry” [6,12] for temperature sensitive contrast agents or BIRDS (biosensor imaging redundant deviation in shifts) [8] for contrast agents that are pH and temperature dependent.

The vast majority of complexes used as paraCEST or paraCSI contrast agents are Ln(III) complexes [2]. Many of the paramagnetic Ln(III) ions other than Gd(III) give rise to large hyperfine shifts with minimal proton relaxation enhancement [13,14]. Thus the paramagnetic properties of paraCEST and paraCSI agents are quite different from those of contrast agents that increase proton relaxation through T_1 or T_2 processes. Lanthanide(III) ions including Ce(III), Nd(III), Eu(III), Tb(III), Dy(III), Tm(III) and Yb(III) are the most commonly used metal ions to date for paraCEST [2]. Tm(III) complexes are used most frequently for paraCSI [6,8]. However, several transition metal ions also have paramagnetic properties that give rise to highly dispersed proton NMR spectra with minimal paramagnetic induced proton relaxation [15]. Our work has recently focused on the design of contrast agents that contain high spin Fe(II) [16,17]. The development of iron(II) coordination complexes as MRI contrast agents is attractive from the standpoint that iron is the most abundant transition metal element in the earth’s crust and iron ores are plentiful throughout the world. Iron is also the most abundant transition metal ion in the human body which has mechanisms for handling excess iron. In order to better understand the differences in d-block versus f-block ions, a few basics about paramagnetically shifted nuclei are reviewed here.

Paramagnetic nuclei (j) placed in the vicinity of a paramagnetic ion (i) demonstrate enhanced chemical shifts [13,15]. These shifts induced by the paramagnetic ion are expressed as a sum of three contributions (Eq. (1)).

$$\delta_{ij}^{\mathrm{obs}} = \delta_{ij}^{\mathrm{dia}} + \delta_{ij}^{\mathrm{con}} + \delta_{ij}^{\mathrm{dip}} \tag{1}$$

The diamagnetic term ($\delta_{ij}^{\mathrm{dia}}$) is comprised of inductive and electric field effects, and demonstrates weak temperature dependence compared to the contact ($\delta_{ij}^{\mathrm{con}}$) and dipolar ($\delta_{ij}^{\mathrm{dip}}$) terms. Since the contact term is determined by through-bond interactions of electron spin density from paramagnetic ion to the specific nucleus, the number of bonds separating two atoms has a major effect on the magnitude of this term. Thus, the contact shift contribution decreases rapidly with increase in the number of bonds between nuclei. However, the nature of the chemical bonds contributes to the observed shift. For example, extended conjugation could lead to greater contact shift contributions even for nuclei located further away from the paramagnetic center. Moreover, the more extensive covalent bonding in transition metal ion complexes in comparison to lanthanide ion complexes is predicted to produce larger contact shift contributions in the former compared to the latter. It is thus of critical importance to consider through bond electron spin delocalization for transition metal ion paraCEST or paraCSI contrast agents.

The design of Fe(II) complexes for paraCEST and paraCSI builds on the rich coordination chemistry of transition metal ions. Fe(II) is categorized as a borderline hard/soft acid which binds well to both oxygen and nitrogen donor groups, including neutral oxygen donors and heterocyclic nitrogen donors. This allows for the incorporation of diverse sets of donor groups into macrocyclic ligands for Fe(II) contrast agents. This versatility will be useful towards realizing our goals of forming responsive contrast agents that turn on in different biological environments [18,19] and towards paraCEST agents that have exchangeable protons that are highly shifted (>120 ppm) from bulk water. The drawback in the wealth of donor group choices for Fe(II) coordination chemistry is that there are so many potential choices and so little information on paramagnetically shifted exchangeable protons to guide these choices. Theoretical methods that would