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Synthesis and Evaluation of a Gd (III) Complex as T_1-Weighted MRI Contrast Agent

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ABSTRACT

A hexadentate ligand, H_4mum consisting of two phenyl moieties with four acetate arms was designed and synthesized. A water-soluble Gd(III) complex (1) was synthesized by reacting ligand H_4mum with $GdCl_3 \bullet xH_2O$ in 1:1 molar equivalent. Tb (III) congener (complex 2) of complex 1 was also synthesized and used for determining the number of coordinated water molecules present in the inner-coordination sphere of the complex by luminescence lifetime measurements. It was confirmed that the complex consisted of two directly coordinated-water molecules. At 25 °C and pH ~ 7.4 in HEPES buffer, the complex offered longitudinal relaxivity r_1 value of 8.34 $mM^{-1}s^{-1}$ at a magnetic field of strength 1.41 T. However, with increasing filed strength to 14.1 T, the r_1 relaxivity value slightly deceased to 7.62 $mM^{-1}s^{-1}$ at the same experimental conditions. The complex stability under physiological conditions was investigated by measuring r_1 relaxivity in the presence of various physiological anions. In the presence of almost 100 equivalents (~ 50.0 mM) excess of these anions the r_1 value remained almost constant, justified the complex stability under physiological conditions. Finally, phantom MR imaging under clinical scanner at 1.5 T showed positive contrast efficiency of the complex.

Keywords: MRI, Contrast agents, Gadolinium (III) complex, Relaxivity, Hydration state, High field.

INTRODUCTION

Over last few decades, the use of non-invasive magnetic resonance imaging (MRI) for diagnosis has achieved great interest, as it provides anatomical tissue images at high spatial resolution without using ionising radiations. The images are developed from[1] H-NMR signals of endogenous water molecules present in tissues by monitoring variation in longitudinal (T_1) and transverse (T_2) relaxation times.[1-21] However, in some cases, low detection sensitivity is the major limitation of the technique. To deal with the issue, exogenous paramagnetic substances, which are known as contrast agents (CAs), are administered prior the imaging. The paramagnetic substances can enhance an image contrast significantly *via* reducing nuclear relaxation times (T_1 and T_2) of local water protons.[1-24] The contrast efficiency, defined as relaxivity (r_i), is the resultant increase of $1/T_i$ (i = 1 and 2) by per mM concentration of the paramagnetic metal ion; subscripts represent longitudinal (i = 1) and transverse (i = 2) relaxivity respectively.[1] Contrast agents are categorized into T_1 and T_2 types.[1] T_1 contrast agents produce positive or brighter MR images by reducing spin-lattice relaxation time of nearby protons, while, T_2 contrast agents provide negative or darker MR images by accelerating dephasing *via* spin-spin relaxation between the proton nuclear spins.[1] With seven unpaired electrons ($4f^7$, S = 7/2), Gd(III) ion possesses favourable properties of high magnetic moment, slow electronic relaxation, and fast water exchange ability. Thus, it can efficiently enhance the T_1-relaxation process. Most of the clinically used contrast agents are small inorganic coordination complexes of Gd(III) ion and show moderate r_1 value (~ 3-6 $mM^{-1}s^{-1}$) at low fields (1.5-4.7 T).[18] However, r_1 value

decreases drastically at high fields. In this endeavour, our goal was to develop a mononuclear Gd(III)-based contrast agent. Gd(III) complexes are generally eight- or nine-coordinate. Thus, synthesis of a Gd (III) complex employing hexadentate ligand, H_4mum (Scheme 1), would allow maximum three water molecules to coordinate to Gd(III) center. It is well established that, indifferent to the field strength, r_1 relaxivity increases proportionally to the number of coordinated-water molecules (q).[1-5] Thus, it is expected to have high r_1 value even at higher fields and consequently, a high field contrast agent can be resulted. In addition, incorporation of two phenyl moieties in the ligand backbone would increase the intermolecular interaction in between aromatic core resulting into formation of aggregation and thus, the consequent increase in rotational correlation time (τ_R) would further contribute for acquiring high r_1 values.[25-27] To impose stability to the Gd(III) complex, all the four H atoms of the two -NH_2 groups were substituted by acetic acid groups in ligand H_4mum. Coordination of all the acetate units to the oxophilic Gd(III) would not only increase the stability of the complex but also decrease the Lewis acidity of the Gd(III) center. Thus, the water exchange rate (k_{ex}), which is inversely proportional to the mean residual time (τ_m) of coordinated water molecules, would be enhanced. Hence, an additional factor could also be incorporated in the molecule for the betterment of r_1 value.

Herein, the synthesis and characterization of a symmetric hexadentate ligand H_4mum and its corresponding Gd (III) complex (1) with hydration state q = 2.47 are described. The hydration state remained almost unaffected by various oxy-anions. However, at higher pH (pH ~ 10) the hydration number was relatively lower as evident by pH dependent relaxivity analysis at 25 °C (Figure 3). The complex exhibited higher longitudinal relaxivity (r_1 = 8.34 $mM^{-1}s^{-1}$) at 1.41 T, 25 °C, pH 7.4. Interestingly, even at higher field 14.1 T, the decrease in r_1 was minimal (r_1 = 7.62 $mM^{-1}s^{-1}$) at 25 °C, and pH 7.4. Thus, the complex reinforced its candidature as a high field T_1-weighted contrast agent. Furthermore, the contrast ability of complex 1 was examined under the physiological condition (25 °C, and pH ~ 7.4) by acquiring phantom images at 1.5 T and presented, herein.

MATERIALS AND METHODS

Materials: All the chemicals and solvents were obtained from commercial sources and were used as supplied, unless noted otherwise. Diphenic anhydride and $GdCl_3 \bullet xH_2O$ were purchased from Sigma-Aldrich. TFA and *tert*-butyl bromoacetate were purchased from Spectrochem. $KHCO_3$ and solvents were purchased from Merck (India). HEPES buffer was purchased from SRL. Water used for the experiments were purified by using millipore-water purifier, Milli-Q, Merck.

Physical Methods: FT-IR spectra were recorded on Perkin Elmer Instrument at normal temperature by making KBr pellet grinding the sample with KBr (IR Grade). UV-Vis/NIR spectra were recorded on Perkin Elmer, Lamda 750, UV/VIS/NIR spectrometer. Mass spectral data were obtained from either HRMS or Q-TOF/MS spectrometer. ^{1}H- and ^{13}C- NMR analyses were carried out at using BRUKER 400 MHz and 600 MHz NMR machines. The longitudinal relaxivity r_1 at 1.41 T was measured using BRUKER minispec mq60NMR Analyzer. The longitudinal relaxivity at 14.1 T were measured using Bruker Avance II 600 MHz NMR micro imager. MRI images were collected using BRIVO MR355 1.5 T NMR scanner. Lifetime fluorescence measurements were accomplished on FluoroLog®-3 spectrofluorometer, Horiba JobinYvonInc.

Luminescence lifetime measurement: Lanthanide luminescence lifetime measurements were accomplished on a FluoroLog®-3 spectrofluorometer (Horiba JobinYvonInc). 50 μM solution of the complex 2 was prepared in 10 mM HEPES

buffer maintaining pH at 7.4, 25°C. 300 μL of this solution were excited at 270 nm with a pulsed Xenon lamp having pulse width of ~3 μs and time per pulse 61ms. Emission at 544 nm was recorded and luminescence decay curves were generated by 'decay by delay' method with an initial delay of 0.1 ms and maximum delay up to 20 ms. It was then evaporated completely in aspin concentration (Eppendorf AG, Germany) under reduced pressure. Addition of 300 μL D_2O to the completely dry residue resulted in solutions of same concentrations of the complexes in D_2O-buffer. All transfers of D_2O containing samples were performed inside a glove bag under argon atmosphere to avoid contamination of moisture (H_2O) and lifetime measurements were done in a cuvette, sealed under argon maintaining all conditions same as previously in H_2O.

Syntheses

Synthesis of biphenyl-2, 2'-diyldimethanamine, [$C_{14}H_{16}N_2$], (A): The synthesis of biphenyl-2, 2′-diyldimethanamine from diphenic anhydride was already reported.[28-29]

Synthesis of [$C_{38}H_{56}N_2O_8$], (I): To a solution of *tert*-butyl bromoacetate (3.550 g, 18 mmol) in DMF (5 mL), $KHCO_3$ (3.600 g, 36 mmol) was added at 0 °C followed by the addition of biphenyl-2, 2'-diyldimethanamine (0.640 g, 3 mmol). It was then kept on stirring at 0 °C for 30 minutes and then at room temperature for 24 hours. Saturated $NaHCO_3$ solution (20 mL) was added, and mixture was extracted with diethyl ether (3×15 mL). The combined organics were washed with $NaHCO_3$ (3×15 mL) and brine (30 mL), dried (Na_2SO_4) and concentrated in vacuo to give the product on addition of hexane which was washed thoroughly with hexane to get the pure compound as white solid (1.195 g, 60%). FTIR (KBr pellet cm^{-1}): 3419, 3005, 2981, 2972, 2934, 1736, 1719, 1481, 1456, 1436, 1413, 1393, 1368, 1347, 1329, 1300, 1256, 1222, 1148, 992, 979, 944, 840, 786, 775, 747, 604. ^{1}HNMR ($CDCl_3$, 600.17 MHz): δ 7.72 (d, J = 6.0 Hz, 2H), 7.32 (t, J = 6.0 Hz, 2H), 7.23 (t, J = 6.0 Hz, 2H), 7.10 (d, J = 12 Hz, 2H), 3.54 (s, 4H), 3.27 (s, 8H), 1.38 (s, 36H) ppm. ^{13}CNMR ($CDCl_3$, 100.54 MHz): δ 170.51, 140.86, 136.93, 129.72, 129.19, 127.55, 126.60, 80.83, 55.46, 55.27, 28.31 ppm. ESI–MS (+) *m/z* for [$C_{38}H_{56}N_2O_8$ + H]$^+$: calcd, 669.4109; found, 669.4440.

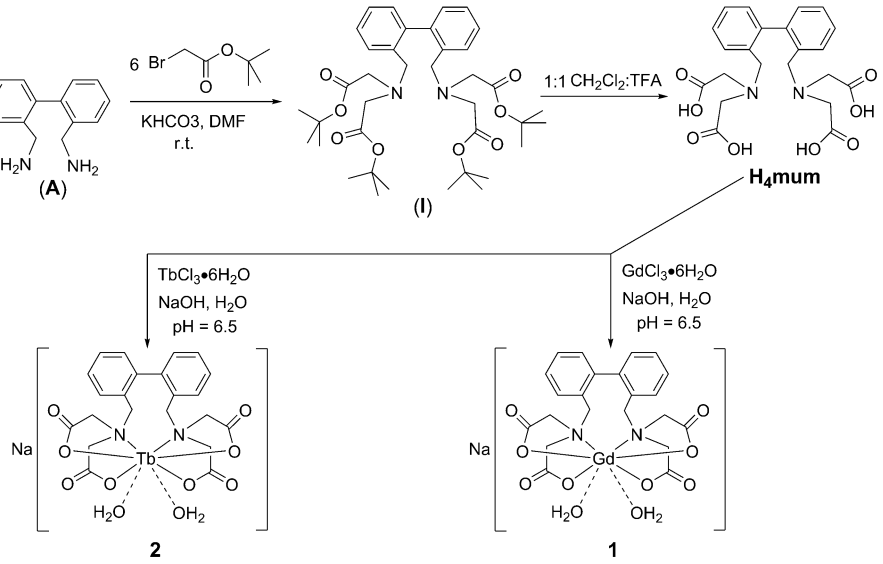
Synthesis of [$C_{22}H_{24}N_2O_8$], (H_4mum): Compound I (0.512 g, 0.85 mmol) was stirred in CH_2Cl_2/TFA 1:1 (4 mL) for 18 hours. After complete removal of TFA, diethyl ether was added to it that gave white solid compound which was washed with diethyl ether several times that finally gave white hygroscopic powder (0.375 g, 99%). FTIR (KBr pellet cm^{-1}): 3444, 3007, 1734, 1637, 1480, 1397, 1256, 1202, 1142, 1049, 1007, 947, 896, 764, 721. ^{1}HNMR (D_2O, 399.85 MHz): δ 7.74 (d, J = 8.0 Hz, 2H), 7.64 (t, J = 8.0 Hz, 4H), 7.49 (d, J = 8.0 Hz, 2H), 4.48 (d, J = 12.0 Hz, 2H), 4.16 (d, J = 12.0 Hz, 2H), 3.74 (s, 8H) ppm.[13] CNMR (CD_3OD, 150.93 MHz): δ 170.24, 141.43, 131.88, 131.08, 130.42, 128.78, 128.04, 55.93, 53.78 ppm. ESI–MS (+) *m/z* for [$C_{22}H_{24}N_2O_8$+H]$^+$: calcd, 445.1605; found, 445.1625.

Synthesis of [$C_{22}H_{24}N_2O_{10}Gd$], (1): Ligand H_4mum (0.268 g, 0.60 mmol) was dissolved in water (5 mL) and $GdCl_3$•$6H_2O$ (0.154 g, 0.58 mmol) was added to the above solution. After 5 minutes when solution became clear its pH was adjusted to 6.5 by addition of aqueous NaOH drop wise and the reaction mixture was allowed to stir for 24 hours. Then it was filtered and from the filtrate white solid compound was obtained after complete evaporation of water which was finally washed with MeOH several times to get the compound as white solid (0.128 g, 36%). FTIR (KBr pellet cm^{-1}): 3505, 3015, 1607, 1480, 1410, 1341, 1325, 1250, 1187, 1101, 984, 924, 876, 761, 619. ESI–MS (–) *m/z* for [$C_{22}H_{20}N_2O_8Gd$] $^-$: calcd, 598.04; found, 598.17.

Synthesis of [$C_{22}H_{24}N_2O_{10}Tb$], (2): Ligand H_4mum (0.145 g, 0.32 mmol) was dissolved

in water (5 mL) and $TbCl_3 \bullet 4H_2O$ (0.115 g, 0.30 mmol) was added to the above solution. After 20 minutes its pH was adjusted to 6.5 by adding aqueous NaOH and the reaction mixture was allowed to stir for 24 hours. Then it was filtered off and from the filtrate white solid compound was obtained after complete evaporation of water which was then washed with MeOH several times to get the compound as white solid (0.065 g, 35%). FTIR (KBr pellet cm^{-1}): 3440, 3004, 1629, 1486, 1446, 1424, 1396, 1341, 1282, 1186, 1125, 1061, 1026, 954, 916, 904, 701, 523. ESI–MS (–) *m/z* for $[C_{22}H_{20}N_2O_8Tb]^-$: calcd 599.05; found 599.09.

RESULTS AND DISCUSSIONS



Scheme 1. Schematic pathway for syntheses of H_4mum, complex 1, and complex 2.

The schematic representation for the synthesis of ligand H_4mum and its corresponding Gd(III) complex is given in scheme 1. Compound I was isolated in 60% yield by reacting 1:6 molar ratio of biphenyl-2,2'-diyldimethanamine (A) and *tert*-butyl bromoacetate in DMF in the presence of $KHCO_3$. Ligand H_4mum was obtained in 99% yield by treating compound I with trifluoroacetic acid in CH_2Cl_2. Complex 1 was synthesised by reacting equimolar amounts of $GdCl_3 \bullet xH_2O$ and the ligand in water at pH ~ 6.5. The complex was isolated in 36% yield by slow solvent-evaporation technique. Several attempts for growing X-ray diffraction quality single crystal were unsuccessful. Therefore, the surrogate complex (2) with luminescence lanthanide Tb(III) ion was synthesized to discern indirectly the number of Gd(III)-coordinated water molecules (*q*) in complex 1. In this synthesis, $TbCl_3 \bullet 6H_2O$ was reacted with equimolar amount of ligand H_4mum in water at pH ~ 6.5.

Electrospray ionization (ESI) mass spectrometric measurements in negative mode in aqueous solutions showed molecular ion peak at *m/z* = 598.17(1) and 599.09(2) [parenthesis indicates the complex]. Isotope distribution patterns analyses for the observed mass peaks indicated composition $C_{22}H_{20}N_2O_8Gd$ for complex 1 and $C_{22}H_{20}N_2O_8Tb$ for complex 2 and supported the formation of the expected complexes.

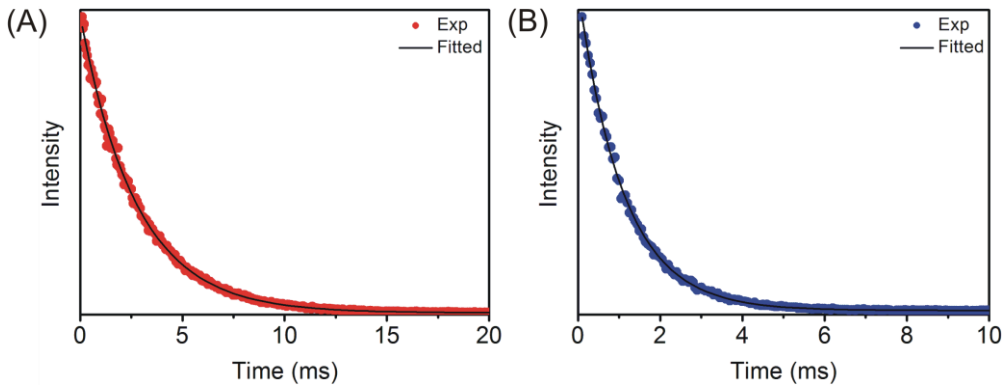


Figure 1. Lifetime decay curves of complex 2 in (A) D_2O and (B) H_2O.

The hydration state (q) of the complex was confirmed by luminescence lifetime measurement. For this purpose, the surrogate complex (2) with luminescent Tb (III) was used since Gd(III) does not emit in the visible region. Due to similar ionic radii and habit of forming similar type of complexes, it was assumed that both the complexes will have same hydration state. The correlation between luminescence life time (τ) and q results by the efficient energy transfer from the excited state of Tb(III) to O–H oscillator of the coordinated water molecule.[30-34] Replacement of O–H by O–D increases the luminescence lifetime of the complex due to less efficient energy transfer. Consequently, the luminescence decay lifetime of the Tb (III) excited state in D_2O is greater than H_2O. And luminescence decay constant is directly proportional to the number of water molecules present in the inner-coordination sphere of the metal ion. Herein, 50 μM H_2O and D_2O solutions of complex 2 in 10 mM HEPES buffer were excited at 270 nm, 25 °C, pH ~ 7.4, and the emissions were recorded at 544 nm. The decay curves were generated by 'decay by delay' method. The luminescence lifetime was then estimated by fitting the curve using single exponential model (Figure 1), and was estimated to be 1.09 ms and 2.75 ms in the presence of H_2O and D_2O, respectively. The number of coordinated water molecules to Tb(III) center was calculated as q = 2.47 by using modified Horrock´s equation: $q = 5\ (1/\tau_{H2O} - 1/\tau_{D2O} - 0.06)$.[35] The obtained q value implied the coexistence of almost equal proportions of tris(aquo) and bis(aquo) species in the aqueous solution at 25 °C, pH ~ 7.4.

The efficiency of the complex as a T_1 contrast agent was investigated by measuring longitudinal (T_1) relaxation times of water protons in the presence and the absence of complex 1 at 25 °C and at pH ~ 7.4. Four different solutions of complex 1 with variable concentrations were prepared in HEPES buffer for the measurements. The respective r_1 values were then calculated from the slopes of the linear plots of $1/T_1$ *versus* exact [Gd(III)]. The exact Gd (III) ion concentration was determined by ICP-AES technique. The complex showed r_1 value of 8.34 $mM^{-1}s^{-1}$ at 1.41 T and 7.62 $mM^{-1}s^{-1}$ at 14.1 T under the conditions [Figure 2(A) and 2(B)]. The high r_1 value is consistent with the previously reported Gd(III)-based contrast agent with q = 3.[12-14] Noteworthy, herein the measurement was also performed at high field 14.1 T. Thus, complex 1 showed promise as a high field T_1 contrast agent.

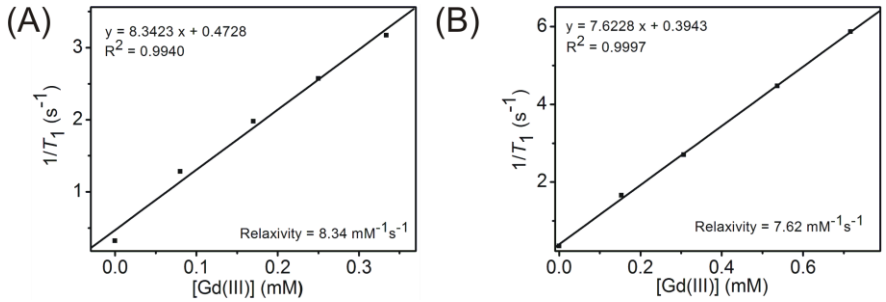


Figure 2. $1/T_1$ *vs* [Gd(III)] plot; (A) at 1.41 T and (B) at 14.1 T (at 25 °C and pH ~ 7.4).

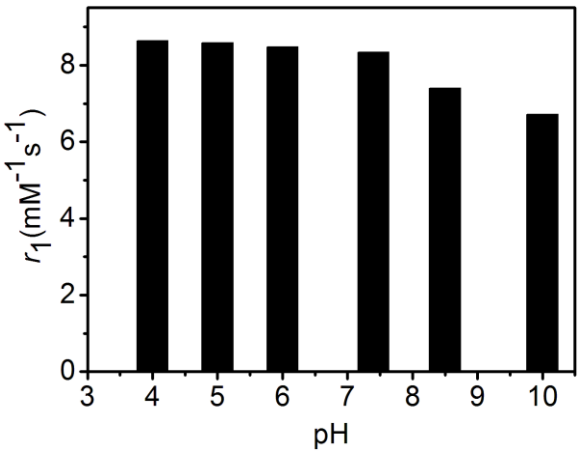


Figure 3. r_1 *vs* pH plot at 1.41 T and 25 °C.

The formation of possible equilibrium states of the complex in solution were further investigated by acquiring r_1 relaxivity values in a pH range of 4.0-10.0 (Figure 3). No appreciable change in rlaxivity values in the range of 4.0-7.4 implied the existence of complex 1 as such in that pH range. While decrease in r_1 value at pH ~ 10.0 indicated the decrease of hydration state of the complex under basic condition due to formation of hydroxyl species. The formation of hydroxyl species was due to deprotonation of coordinated water molecule or might be due to substitution by hydroxyl ion.

Furthermore, the stability of complex 1 was examined in the presence of biologically abundant phosphate (PO_4^{3-}), carbonate (CO_3^{2-}) and bicarbonate (HCO_3^{1-}) anions. Since, these anions which are present in blood serum can reduce the efficiency of the complex by substituting inner-sphere water molecules.[36-37] In this regard, the effect on r_1 relaxivity of complex 1 in the presence of the oxy-anions was investigated. The complex exhibited r_1 = 8.34 $mM^{-1}s^{-1}$ at 1.41 T, 25 °C, pH ~ 7.4 in HEPES buffer. No appreciable changes in the relaxivity, even in the presence of 100 fold excess (50.0 mM) of the oxy-anions, was observed (Figure 4). This demonstrated that neither the stability of the complex was challenged by the anions nor the coordinated water molecules were replaced, *i.e.*, the hydration state (*q*) remained unaffected. An overall mono-negative charge of the complex and lowered-Lewis acidity of the Gd (III) ion by the coordination of the ligand-acetate anions were the possible factors for the inertness of the complex towards the oxy-anions.

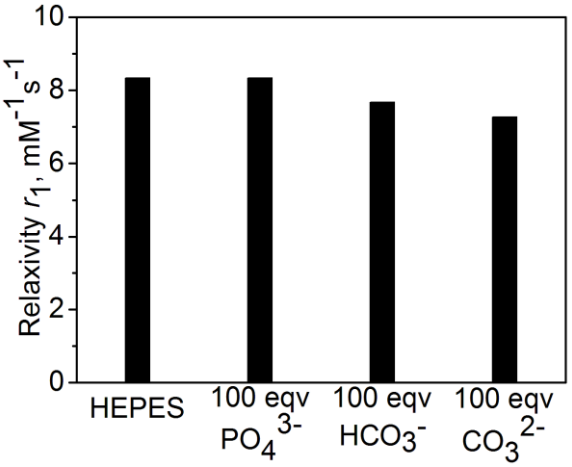


Figure 4. Values of r_1 of complex 1 in the presence of various anions at 1.41 T, 25 °C, and pH ~ 7.4.

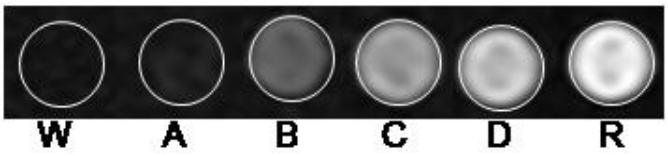


Figure 5. T_1-weighted MR images of micro-centrifuge tubes (phantom images) containing aqueous solution of the complex; where W = water, A = 0.25 mM, B = 0.50 mM, C = 0 .70 mM, D = 1.00 mM concentrations of the complex along with R = 0.50 M MultiHance® at 1.5 T, 25 °C.

The effectiveness of complexes 1 as a positive contrast agent was examined under physiological condition using BRIVO MR355 clinical imager at 1.5 T. The signal-intensity was found to increase with increasing concentration of the complex. Interestingly, the MR intensity exhibited by 1 mM solution of the complex was almost comparable to the clinically approved and commercially available 0.50 M MultiHance® contrast agent (Figure 5). The higher contrasting-behaviour was because of the higher number of coordinated water molecules in complex 1 (q = 2.47) compared to MultiHance® (q = 1.0).

CONCLUSION

To summarize, the symmetric hexadentate ligand H_4mum and its corresponding Gd(III) complex with q = 2.47 have been successfully synthesized. The complex remains stable and unaffected in the presence of 100-fold (50.0 mM) excess of phosphate, bicarbonate and carbonate anions. The complex offers high r_1 = 7.62 $mM^{-1}s^{-1}$ even at high magnetic field 14.1 T under physiological conditions. The high values can be rationalized due to large q value and possible slow tumbling of the molecule owing two phenyl rings in the ligand backbone. Noteworthy, the r_1 values for the complex is not only superior; but also T_1-weighted images at 1.41 T reinforce the possibility of application of the complex as positive contrast agent.

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