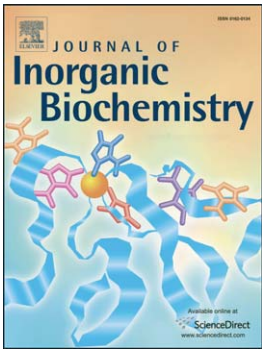

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Physico-chemical properties of Mn^{II} complexes formed with *cis*- and *trans*-DO2A†: thermodynamic, electrochemical and kinetic studies

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† *CIS*-DO2A = 1,4,7,10-tetraazacyclododecane-1,4-diacetic acid and *TRANS*-DO2A = 1,4,7,10-tetraazacyclododecane-1,7-diacetic acid

1. ABSTRACT

Manganese (Mn^{II}) is a promising alternative to gadolinium (Gd^{III}) as a magnetic resonance imaging (MRI) agent. Unlike gadolinium, this biogenic metal might be better tolerated by the body, reducing the risk of toxicity associated with dissociation of the complex. Herein we report detailed equilibrium and kinetic studies performed with Mn^{II} complexes of 1,4,7,10-tetraazacyclododecane-1,4-diacetic acid (1,4-DO2A or *CIS*-DO2A) and 1,4,7,10-tetraazacyclododecane-1,7-diacetic acid (1,7-DO2A or *TRANS*-DO2A). The protonation constants of the ligands as well as stability constants of their Mn^{II} complexes have been determined by pH-potentiometry. The stability constants of [Mn(*CIS*-DO2A)] are slightly higher than that of [Mn(*TRANS*-DO2A)] (log K_{MnL} = 15.68 and 15.22, respectively). Cyclic voltammetric (CV) experiments performed on [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] revealed quasireversible systems with a half-wave potential of +636 and +705 mV versus Ag/AgCl, respectively. These values indicate that the Mn^{II} ion in these complexes is more stabilized against the oxidation than in $[Mn(EDTA)]^{2-}$. The kinetic inertness of the complexes has been studied in transmetallation reactions with Cu^{II} or Zn^{II} ions. Kinetic measurements indicate that both Mn^{II} complexes primarily undergo acid catalyzed dissociation and positions of the acetate pendant arms do not influence kinetic inertness. The kinetic inertness of these complexes is comparable to that of $[Mn(NOTA)]^{-}$ and significantly (about twenty times) lower than that of $[Mn(DOTA)]^{2-}$. In conclusion, [Mn(*CIS*-DO2A)] displays some very interesting features (thermodynamic and redox stability as well as kinetic inertness) which makes this complex a promising platform for the development of more efficient Mn^{II} complexes as alternatives to Gd-based MRI agents.

KEYWORDS: Magnetic Resonance Imaging (MRI) / Contrast Agents (CA) / Manganese / Thermodynamic stability/ Inertness / Electrochemistry

2. INTRODUCTION

Over the past decades, research on novel Magnetic Resonance Imaging (MRI) Contrast Agents (CAs) has led to the development of structurally diverse ligands as well as the several metal ions as viable alternatives to Gd^{III}. Although the majority of approved MRI CA is still based on gadolinium complexes, manganese has gained certain attention due to its ability to form high spin complexes (Mn^{II}) with five unpaired electrons. Unlike Gd^{III}, Mn^{II} is an essential metal ion in human body and its in vivo concentration is efficiently regulated by a homeostatic mechanism.[1] Although the T_1 relaxivity of Mn^{II} complexes is not as high as that of their Gd^{III} analogues, it is a metal worth exploring considering the recent concerns on Gd^{III}-deposition in tissues and Nephrogenic Systemic Fibrosis (NSF), a disease related to Gd-deposition in patients suffering from severe renal failure.[2, 3] However, shocking recent review/editorial of E. Kanal and M. F. Tweedle[4] and N. Karabulut[5] that highlights the findings of T. Kanda[6-8], Y. Errante[9], R. J. McDonald[10] and A. Radbruch[11] clearly indicates that certain Gd^{III}-based CA's in MRI may cause problems for patients even with normal renal function. These results are raising new questions about the safety of Gd^{III}-based CA's available in the market and will trigger new research in order to design safer CA's for MRI. The lower relaxivity of several Mn^{II} complexes studied so far can partially be attributed to the lack of an inner sphere water molecule. Examples of Mn^{II}-based agents in the literature demonstrate, however, that it is possible to create Mn^{II} chelates with at least one inner sphere water molecule.[12-18] The remaining hurdle to the feasibility of Mn^{II} complexes as efficient contrast agents in vivo is their low thermodynamic stability and kinetic inertness. In contrast to the well-known chemistry of Gd^{III} chelates, the coordination chemistry of Mn^{II} with polydentate ligands and, in particular, the kinetic behavior of Mn^{II} complexes, have remained largely unexplored.[19-23] While most of the Mn^{II} complexes of open-chain ligands (such as DTPA = diethylenetriaminepentaacetic acid) were found to be kinetically too labile for *IN VIVO* applications[24] (with an exception for $[Mn(TRANS\text{-}CDTA)]^{2-}$ (*TRANS*-CDTA = *TRANS*-1,2-Diaminocyclohexane-N,N,N′,N′-tetraacetic acid) which was evaluated even in preclinical studies)[25-26], the Mn^{II} complexes of macrocyclic ligands (e.g. NOTA = 1,4,7-Triazacyclononane-1,4,7-triacetic acid and DOTA = 1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid) have been reported to have reasonably high

thermodynamic stability and kinetic inertness.[27] A detailed ^{1}H and ^{17}O NMR relaxometric and computational study on Mn^{II} complexes with cyclen-based ligands bearing one, two and three acetate pendant arms (DO1A = 1,4,7,10-Tetraazacyclododecane-1-acetic acid, *CIS*- and *TRANS*-DO2A, and DO3A = 1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid, respectively) has been recently reported.[28] Similarly to $[Mn(DOTA)]^{2-}$, the Mn^{II} complex with the heptadentate ligand DO3A has no inner sphere water molecules ($q = 0$). Interestingly, the Mn^{II} complexes of the two isomeric hexadentate DO2A ligands, *CIS*- and *TRANS*-DO2A, are markedly different from one another in this respect: [Mn(*TRANS*-DO2A)] is predominantly six-coordinated ($q = 0$) in aqueous solutions whereas for [Mn(*CIS*-DO2A)] a hepta-coordinated species with one coordinated water molecule ($q = 1$) prevails and the $q = 0$ complex represents only about 10% of the overall population. Finally, the Mn^{II} complex of the pentadentate ligand DO1A also contains a coordinated water molecule.[28] A previous study on the thermodynamic stability of the Mn^{II} complexes of the two DO2A isomers also suggested that these complexes may have promising features (e.g. stability) for further development.[29] Thus, there is continuing interest in the detailed analysis of both thermodynamic stability and kinetic inertness of the Mn^{II} complexes with these two ligands. In an effort to improve our understanding on the structural and dynamic properties of Mn^{II}-based contrast agents, here we report the thermodynamic, kinetic and electrochemical properties of Mn^{II} complexes of *CIS*-DO2A and *TRANS*-DO2A (Figure 1).

<INSERT FIGURE 1 NEAR HERE>

2 EXPERIMENTAL

2.1 Materials. The chemicals used for the experiments were of analytical grade. The concentration of the $MnCl_2$, $ZnCl_2$ and $CuCl_2$ solutions was determined by complexometric titration with standardized Na_2H_2EDTA and *xylenol orange* ($ZnCl_2$), *murexid* ($CuCl_2$) and *Eriochrome Black T* ($MnCl_2$) as indicators. The concentration of the *cis*-H_2DO2A and *trans*-H_2DO2A (prepared as described in by Li[30] and Kovács et. al.[31], respectively) was determined by pH-potentiometric titration in the

presence and absence of a 2-5 fold excess of $MnCl_2$. The pH-potentiometric titrations were made with standardized 0.2 M KOH and NaOH solutions.

2.2 Equilibrium measurements. The protonation constants of *CIS*-DO2A and *TRANS*-DO2A, the stability and protonation constants of Mn^{II} complexes formed with *CIS*-DO2A and *TRANS*-DO2A ligands were determined by pH-potentiometric titration. The metal-to-ligand concentration ratio was 1:1 (the concentration of the ligand was generally 0.003 – 0.005 M) and the titrations were performed by allowing 45 and 300 seconds waiting time (two parallel titrations resulted in curves that were completely superimposable) to attain the equilibrium between successive points. In calculating the equilibrium constants, the best fitting of the 80-150 data pairs (mL NaOH – pH and mL KOH – pH) has been obtained by assuming the formation of ML and protonated $M(H_iL)$ complexes (where i=1 for DO2A's and i=1 and 2 for DOTA) in the pH range of 1.7-12.0. The equilibrium constants were calculated with the program *PSEQUAD*.[32] For the pH measurements and titrations, a *METROHM 888 TITRANDO* titration workstation and a *Metrohm 6.0233.100* combined electrode were used. Equilibrium measurements were carried out at a constant ionic strength (0.15 M NaCl and 0.1 M KCl) in 10 mL samples at 25 °C. The solutions were stirred, and N_2 was bubbled through them. The titrations were made in the pH range of 1.7-12.0. KH-phthalate (pH=4.005) and borax (pH=9.177) buffers were used to calibrate the pH meter. For the calculation of $[H^+]$ from the measured pH values, the method proposed by *Irving et al.* was used.[33] A 0.01M HCl solution was titrated with the standardized NaOH or KOH solution in the presence of 0.15 M NaCl and 0.1 M KCl ionic strength, respectively. The differences between the measured (pH_{read}) and calculated pH ($-\log[H^+]$) values were used to obtain the equilibrium H^+ concentration from the pH values, measured in the titration experiments. The ion product of water was determined from the same titrations (HCl/NaOH and HCl/KOH) in the pH range of 11.5-12.0.

2.3 KINETIC STUDIES. The rates of the metal exchange reactions of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] with Cu^{II} were studied with a Cary 1E spectrophotometer following the formation of the Cu^{2+} complexes at 300 nm. In order to guarantee pseudo-first-order conditions, [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] complexes were 5×10^{-4} M while that of the Cu^{II} complexes was 10 to 40

times higher in concentration. The transmetallation reactions of [Mn(*TRANS*-DO2A)] with Zn^{II} were followed by measuring the water proton relaxation rates ($1/T_1$) of the samples with a *Bruker MQ20 Minispec* spectrometer at 20 MHz owing to the large differences in the relaxivities of [Mn(*TRANS*-DO2A)] (r_{1P}=1.70 $mM^{-1}s^{-1}$) and [Mn(*CIS*-DO2A)] (R_{1P}=2.23 $mM^{-1}s^{-1}$) complexes and that of free Mn^{II} (R_{1P}=8.0 $mM^{-1}s^{-1}$) at 20 MHz and 25 °C. The longitudinal relaxation times were measured by the 'inversion recovery' method (180° - τ - 90°) by using 8 different τ values. The measurements were made with 2×10^{-3} M [Mn(*TRANS*-DO2A)] solution in the presence of 10 to 40-fold excess of Zn^{II}. The temperature was maintained at 25 °C and the ionic strength of the solutions was kept constant (0.15 M NaCl and 0.1 M KCl). For keeping the pH values constant, 1,4-dimethylpiperazine (DMP) (pH range 3.0 – 4.6) and N-ethylpiperazine (NEP) (pH range 4.6 – 6.0) buffers (0.05 M) were used. The pseudo-first-order rate constants (k_D) were calculated with the use of the Equation (1)

$$X_t = (X_0 - X_e)e^{-k_d t} + X_e \qquad (1)$$

where X_0, X_T, and X_E are the absorbance or the relaxation rate ($1/T_1$) values at the start, at time τ, and at equilibrium of the reactions, respectively. The calculations were performed using the computer program *MICROMATH SCIENTIST, VERSION 2.0* (Salt Lake City, UT, USA).

2.4 CYCLIC VOLTAMMETRY. The cyclic voltammograms (CV) of the Mn^{II} complexes were obtained using a *METROHM VA 746 TRACE ANALYZER* equipped with *747 VA STAND* driven by a common PC. The samples containing the Mn^{II} complexes were analyzed at 25 ˚C with a three-electrode assembly in a 25 mL cell. The volume of the samples was 10 mL and the concentration of Mn^{II} ion in the samples was set to 1 mM with a 1:1 metal to ligand ratio (for all experiments a 2 – 3% ligand excess was applied). The electrochemical system was calibrated with the $[Fe(CN)_6]^{3-}/[Fe(CN)_6]^{4-}$ redox system. The redox potential in the original cell was 0.449 V. This calculated redox potential was in good agreement with the published redox potential (0.458 V).[34] All cyclic voltammetric measurements were carried out at pH =7.0 in 0.15 M $NaNO_3$ aqueous solution. The pH of the solutions was measured by using *METROHM 827 PH LAB* pH-meter equipped with a combined electrode (*Metrohm 6.0234.100*).

"The experiments were performed with either a glassy carbon (Metrohm 6.1204.110) or a platinum (Metrohm 6.1204.120) working electrode applied often in the CV studies of Mn^{II} complexes formed with polyamino-polycarboxylic acids". The working electrode was carefully polished before recording each voltammogram with alumina paste (particle size of 0.05 micron). The counter electrode was a platinum electrode (*METROHM 6.0343.000*) while the reference electrode was a *VYCOR* tip Ag/AgCl electrode stored in 3 M KCl (*METROHM 6.0728.020*). Aqueous complex solutions were deaerated with argon. The voltammograms were recorded in a potential range between +1.30 V and – 0.20 V at various sweep rates ranging from 20 mV sec^{-1} to 200 mV sec^{-1}. The voltammograms were analyzed with the *CACYVO* software. The half-wave potential ($E_{1/2}$) values were calculated from (E_{PA} + E_{PC})/2 (where E_{PA} and E_{PC} were the anodic and cathodic peak potentials, respectively) and converted by taking into account that $E^{\circ}_{AG/AGCL}$ versus $E^{\circ}_{NHE\ (WATER)}$ equals to +0.209 V at 25 ˚C.[35] Unless otherwise stated, all the potentials (E°) reported were referred to the normal hydrogen electrode (NHE).

3 RESULTS AND DISCUSSION

3.1 EQUILIBRIUM STUDIES. The assessment of the thermodynamic stability of Mn^{II} complexes of *CIS*- and *TRANS*-DO2A is of particular interest since these hexadentate ligands with identical donor atoms provide different coordination environments for the Mn^{II} ion resulting in the formation of isomers in solution.[28] Mn^{II} forms complexes with DOTA and DO3A and their derivatives with comparable stability because the structure of these complexes are very similar and the coordination number (CN) of the Mn^{II} (CN = 6 or 7) is lower than the number of donor atoms of the chelating ligands.[27, 36] However, the denticity (number of donor atoms) of *CIS*- and *TRANS*-DO2A is only six, which is comparable or lower than the usual CN of Mn^{II} ion. Thus, the stability of the Mn^{II} complexes is expected to be influenced by the different coordination polyhedrons formed with the *CIS*- and *TRANS*-DO2A isomers.

The thermodynamic and transmetallation kinetics of these Mn^{II} complexes in solution have been studied in order to understand the effect of different coordination environments on the equilibrium and

kinetic properties of these complexes. The protonation constants, defined by Equation (2), are determined by pH-potentiometric titrations in 0.15 M NaCl and 0.1 M KCl solutions at 25 ºC. The protonation constants of *CIS*-DO2A and *TRANS*-DO2A ligands (standard deviations are shown in parenthesis) are listed in Table 1, along with the protonation constants of DOTA and NOTA.

$$K_i^H = \frac{[H_iL]}{[H_{i-1}L][H^+]} \qquad (2)$$

where i=1, 2, 3, and 4 (for DO2A's and NOTA) or i=1, 2, … and 6 (for DOTA)

The equilibrium data obtained in the titrated solutions with 1:1 and 1:2 metal to ligand ratio have been fitted by assuming the formation of [Mn(L)] and [Mn(HL)] for both the *CIS*-DO2A and *TRANS*-DO2A ligands (Eq. (3)–(4)). We were not able to confirm the formation of the ternary hydroxido complexes in the studied pH range (detected by Bianchi et al. formerly[29]) which is fully consistent with the results of relaxometric titrations performed by G. A. Rolla and co-workers.[28]

$$K_{ML} = \frac{[ML]}{[M][L]} \qquad (3)$$

$$K_{MHL} = \frac{[M(HL)]}{[M(H_{i-1}L)][H^+]} \qquad (4)$$

where i=1 (for the DO2A's and NOTA) or 1 and 2 (for DOTA).

<INSERT TABLE 1 NEAR HERE>

The first and second protonation constants of the ligands are related to the protonation of macrocyclic amine N atoms (secondary N atoms of the cyclen ring as evidenced for the *TRANS*-DO2A by ^{1}H NMR spectroscopy[40]) whereas logK_3 and logK_4 values characterize the protonation of the acetate groups. Since the protonation constants of DO2A ligands are apparently independent of the salt used to maintain the ionic strength, it can be assumed that the interaction between these ligands and Na^I or K^I ions is rather weak.

The stability constants of Mn^{II} DO2A complexes are presented and compared with those of $[Mn(NOTA)]^-$ and $[Mn(DOTA)]^{2-}$ in Table 1. Among these complexes, $[Mn(DOTA)]^{2-}$ has the highest

stability, as evidenced by its log $K_{[MN(DOTA)]}$ value, which is four orders of magnitude higher than that of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] under the same experimental conditions. The stability constant of [Mn(*CIS*-DO2A)] is slightly higher than the value determined for the complex formed with *TRANS* derivative. Both complexes form protonated species at low pH. It is very likely that the protonation of the [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] complexes occurs at a carboxylate group of a pendant acetate arm. Altogether the log K_{MnL} values of the Mn^{II} complexes formed with DO2A's measured in this work agree well with that obtained by Bianchi and co-workers as well as Benchini et al. in the presence of Me_4NCl.[29, 38] Similar conclusions can be derived by calculating and comparing the pMn ($pMn=-\log[Mn^{2+}]_{FREE}$ at pH=7.4 and $c_{MN2+}=c_{LIG}=1\times10^{-5}$ M) values of the complexes by using the conditions proposed by Tóth et al.[39] As it can be seen from the data presented in Table 1, the pMn values are always noticeably higher for the *CIS*-DO2A systems, while the pMn values calculated for the equilibrium involving the *TRANS*-DO2A ligand are consequently lower in all cases (Table 1). It is quite difficult to account for these small differences in the stabilities of the complexes evidenced even considering the structure of the complexes suggested based on DFT calculations[28] or found in solid state (the X-ray structure of the [Mn(*TRANS*-DO2A)] complex was not determined to date, so one needs to assume that its structure is similar to the diprotonated [Mn(H_2DOTA)] complex).[41] Based on the DFT calculations the coordination polyhedron around the Mn^{II} ion both in [Mn(*CIS*-DO2A)] (non aquated complex) and [Mn(*TRANS*-DO2A)] can be described as a trigonal prism, while in the [Mn(*CIS*-DO2A)(H_2O)] the water molecule occupy the capping position resulting in monocapped trigonal prismatic structure.[28] The solid state structure of the *CIS* derivative reveales a doubly bridged dimetallic/dimeric complex in which the capping position is occupied by the carboxylate oxygen from the neighbouring complex (e.g. the place which is taken by the water molecule upon (partial to full) disintegration of the dimer in solution).[29]

3.2 ELECTROCHEMISTRY (CV). The redox stability of the Mn^{II} complexes of DO2A's was studied by using cyclic voltammetry in aqueous 0.15 M $NaNO_3$. The studies were performed initially only for

[Mn(*CIS*-DO2A)] since the complex formed with the *TRANS*-DO2A was studied by A. Bencini and co-workers a few years ago under conditions nearly identical to those applied in the current study.[38] However, based on the results obtained for [Mn(*CIS*-DO2A)] we decided to repeat the experiments with [Mn(*TRANS*-DO2A)] as the reversibility and the potential observed for [Mn(*CIS*-DO2A)] was noticeably different from the literature value of [Mn(*TRANS*-DO2A)] as the experimental observations (both complexes were redox stable at pH=7.0 as confirmed by no significant change in their relaxivity in samples exposed to air) could be accounted for these differences.

The cyclic voltammogram obtained for [Mn(*CIS*-DO2A)] (Figure S1 Supporting Information) indicates the presence of a quasireversible system with a half-wave potential of +636 mV (ΔEp = 250 mV) versus Ag/AgCl which translates to +845 mV vs. NHE. For [Mn(*TRANS*-DO2A)] we also observe a quasireversible redox response (Figure S2, Supporting Information) with +705 mV half-wave potential (ΔEp = 295 mV) versus Ag/AgCl (+914 mV vs. NHE). The somewhat higher oxidation potential for [Mn(*TRANS*-DO2A)] indicates that the divalent oxidation state of Mn is slightly more stable in this complex than in [Mn(*CIS*-DO2A)]. This may be the consequence of the slight differences in the geometries being evidenced for [Mn(*trans*-DO2A)] and [Mn(*cis*-DO2A)] complexes by DFT method[28] which are in a good agreement with the coordination polyhedron found around the metal center in [Mn(H_2DOTA)] and [Mn_2(*cis*-$DO2A)_2$] complexes by X-ray crystallography.[29, 41] This is well described in the literature for Mn^{II}/Mn^{III} as well as for Cu^{I}/Cu^{II} couples.[42-45] As mentioned above the coordination sphere around the metal centers in [Mn(*trans*-DO2A)] and [Mn(*cis*-DO2A)] complexes can be described as trigonal prisms. The mean twist angle of the two triangular faces equals to 4.9° (ideal value would be 0°) in the [Mn(*cis*-DO2A)] complex while the given angle is being larger (11.2°) in [Mn(*trans*-DO2A)] showing a somewhat larger distortion of the coordination polyhedron from a trigonal prism to an octahedron (ideal value 60°) in this structure.[28] The Mn^{III}, being a d^4 cation is expected to prefer a geometric distortion from the octahedric structure as it is experienced in [Mn(*cis*-DO2A)] agreeing well with the lower oxidation potential of the given Mn^{II} complex. The half-wave potential values of both complexes are higher than those reported for other Mn^{II} complexes such as

$[Mn(EDTA)]^{2-}$ (633 and 810 mV vs. NHE)[15, 46] or $[Mn(NOTA)]^{-}$ (740 mV vs. NHE)[46] or the redox potential of molecular oxygen (≈800 mV, depending on pH), which means that both complexes are resistant against oxidation in aqueous solution near pH=7.0. Thus, relaxivity decrease due to oxidation of Mn^{II} (d^5) to Mn^{III} (d^4) is not expected to occur in aqueous solutions of these complexes.

3.3 Dissociation Kinetics of the [Mn(*cis*-DO2A)] and [Mn(*trans*-DO2A)]. The kinetic inertness of metal complexes is an important issue for in vivo application due to the toxicity of free metal ions and ligands.[19] *In vitro* studies of the dissociation reactions of metal-complexes may provide information concerning their kinetic behavior under physiological conditions. The Mn^{II} complexes believed/considered to be very labile chelates in the literature. Among the open chain ligands the *trans*-CDTA and its derivatives were shown to form relatively inert Mn^{2+} complexes.[18, 24] To the best of our knowledge the first examples of inert Mn^{II} complexes formed with macrocyclic ligands were evidenced by D. P. Riley an co-workers about two decades ago who have synthesized and studied numerous Mn complexes formed with rigid 15-aneN_5 derivatives as highly active and stable superoxide dismutase (SOD) mimics.[47, 48] More recently É. Tóth and co-workers were shown that the Mn^{2+} complexes formed with traditional macrocyclic ligands like NOTA and DOTA (whose complexes formed with diagnostic and therapeutic metal ions employed widely widely in medicine today) were inert towards metal loss form these chelates.[27] The dissociation of $[Mn(DOTA)]^{2-}$, $[Mn(NOTA)]^{-}$ and their derivatives is very slow and generally occurs via spontaneous, proton- and metal-assisted pathways with the involvement of endogenous metal ions like Zn^{II} and Cu^{II}.[27] The kinetic inertness of Mn^{II} complexes is characterized by the rate of the transmetallation reactions, occurring in solutions with Zn^{II} and Cu^{II} ions. Therefore, the rates of metal exchange reactions occurring between [Mn(*cis*-DO2A)] and [Mn(*trans*-DO2A)] and biogenic Zn^{II} and Cu^{II} ions have been studied by ^{1}H-NMR relaxometry and UV-vis spectrophotometry, respectively. These transmetallation reactions have been investigated (metal exchange reactions, Eq. (5)) in the presence of a large excess (10-40-fold) of the exchanging metal ion

(Zn^{II} or Cu^{II}) to ensure pseudo-first-order conditions at different ionic strengths (0.15 M NaCl and 0.1 M KCl) in the pH range of 3.0 – 6.0.

$$MnL + M^{II} \rightleftharpoons ML + Mn^{II} \quad (5)$$

where $M^{II} = Zn^{II}$ or Cu^{II}. Under pseudo-first-order conditions the rate of dissociation can be expressed by Eq. (*6*), where k_D is the pseudo-first-order rate constant and $[MnL]_T$ is the total concentration of the Mn^{II} complexes.

$$-\frac{d[MnL]_t}{dt} = k_d[MnL]_t \quad (6)$$

The rate constants k_D obtained for the transmetallation of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] with Cu^{II} in 0.1 M KCl are presented in Figures 2 and 3, respectively. The k_D rate constants characterizing the exchange reaction of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] with Cu^{II} and Zn^{II} ions in the presence of 0.15 M NaCl ionic strength are shown in Figure S3 and S4.

<INSERT FIGURE 2 AND 3 NEAR HERE>

As it can be seen in Figures 2, 3, S3 and S4, the k_D values exhibit a similar dependence in the reactions of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] with the exchanging Cu^{II} or Zn^{II} ions. The k_D values increase with increasing $[H^+]$ and independent from $[Cu^{II}]$ or $[Zn^{II}]$. Considering the pH range investigated (3.0 - 6.0) and the speciation of the [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] complexes, the transmetallation reactions occur between Cu^{II} or Zn^{II} and the monoprotonated $[Mn(CIS\text{-}HDO2A)]^+$, $[Mn(TRANS\text{-}HDO2A)]^+$ and the deprotonated [Mn(*CIS*-DO2A)], [Mn(*TRANS*-DO2A)] complexes. The transmetallation reactions may take place through spontaneous dissociation of the deprotonated (k_0) and monoprotonated (k_{MNHL}) complexes, whereas the monoprotonated complex can also dissociate via proton-assisted (k^H_{MNHL}) pathways, which are followed by the fast reaction between the free ligands and the exchanging metal ions. The contribution of the different pathways to the dissociation of the complexes is shown in Figure 4.

<INSERT FIGURE 4 NEAR HERE>

By taking into account all the possible pathways, the rate of the transmetallation of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] can be expressed by Eq. (7), where [Mn(HL)] is the concentration of the protonated complexes:

$$-\frac{[\mathrm{MnL}]_{\mathrm{tot}}}{\mathrm{d}t} = k_0[\mathrm{MnL}] + k_{\mathrm{MnHL}}[\mathrm{Mn(HL)}] + k^{\mathrm{H}}_{\mathrm{MnHL}}[\mathrm{Mn(HL)}][\mathrm{H}^+] \qquad (7)$$

Considering the total concentration of the complex species ($[\mathrm{MnL}]_{\mathrm{TOT}}=[\mathrm{MnL}]+[\mathrm{Mn(HL)}]$) and the equation defining their protonation constants (Eq. (3)) and Eq. (6), the pseudo-first-order rate constant can be expressed as follows:

$$k_{\mathrm{d}} = \frac{k_0 + k_1[\mathrm{H}^+] + k_2[\mathrm{H}^+]^2}{1 + K_{\mathrm{H}}[\mathrm{H}^+]} \qquad (8)$$

The rate constants, K_0, $K_1=K_{\mathrm{MNHL}}\times K_{\mathrm{MNHL}}$ and $K_2=K^{\mathrm{H}}{}_{\mathrm{MNHL}}\times K_{\mathrm{MNHL}}\times K_{\mathrm{MNH2L}}$ are characteristic for the spontaneous and proton-assisted dissociation of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)], respectively. Using the protonation constants of the Mn^{II} complexes obtained by pH-potentiometry (Table 1.), the rate constants have been calculated by fitting the K_D values to Eq. (8). The rate constants and the half-lives calculated at physiological pH characterizing the transmetallation reactions of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] are listed in Table 2 along with the corresponding values for $[\mathrm{Mn(NOTA)}]^-$ and $[\mathrm{Mn(DOTA)}]^{2-}$.[27]

<INSERT TABLE 2 NEAR HERE>

The calculations afforded either negative value for K_0 or high standard deviation comparable with the value of the calculated rate constant (K_0= and $(-5\pm3)\times10^{-5}$ s^{-1} and $(6\pm10)\times10^{-5}$ s^{-1} for [Mn(*TRANS*-DO2A)] and [Mn(*CIS*-DO2A)] complexes, respectively), which indicates that the spontaneous dissociation of these complexes is negligible. This finding is unexpected since the spontaneous dissociation pathway has an important role in the decomplexation of $[\mathrm{Mn(NOTA)}]^-$ and $[\mathrm{Mn(DOTA)}]^{2-}$. As seen in Scheme 2, the mechanisms of the dechelation of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] complexes are rather similar to those of the Gd^{III} analogs.[19]

The proton-assisted dechelation of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] occurs orders of magnitude faster than that of $[Mn(NOTA)]^-$ and $[Mn(DOTA)]^{2-}$.[27] The proton-assisted dissociation likely proceeds by the initial protonation of the complex at the donor atom of the pendant arms followed by proton transfer to a ring nitrogen. This results in an electrostatic repulsion in the cage, which leads to the release of the Mn^{II} ion from the coordination cavity. The proton-assisted decomplexation of [Mn(*CIS*-DO2A)], [Mn(*TRANS*-DO2A)] and $[Mn(DOTA)]^{2-}$ can also occur with the formation of diprotonated intermediate characterized by the K_2 second-order rate constant.[27] The K_2 rate constants of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] are three orders of magnitude higher than that of the $[Mn(DOTA)]^{2-}$ indicating the fast proton transfer from the second protonated pendant arm to the ring nitrogens.

In general, the role of metal-assisted pathway is more important in the dissociation of the complexes (Gd^{III} as well as Mn^{II}) formed with open-chain than with macrocyclic ligands.[19, 24, 27,47, 48] In case of macrocyclic DOTA-based CAs, the contribution of all but the proton assisted reaction are negligible, in accordance with the structure showing full coordination of the donor atoms to the Gd^{III} with CN= 9. The metal-assisted dissociation in most of the open-chain Mn^{II} complexes takes place by the formation of a dinuclear intermediate, [Mn(L)M], in which the coordinating groups of the ligand migrate from the Mn^{II} metal ion to the incoming one in a stepwise manner.[24, 27] The dissociation of $[Mn(DOTA)]^{2-}$ and $[Mn(NOTA)]^-$, having non- or weakly coordinated donor groups to the Mn^{II} with CN= 6 or 7, can also take place by the metal-assisted pathways via the formation of the mixed dinuclear complexes (e.g. [Mn(DOTA)Zn]).[27] However, the stepwise transfer of the donor atoms from the chelated Mn^{II} to the exchanging metal ion is hindered by the structural rigidity of DOTA or NOTA skeleton and thus the contribution of the given pathway to the overall reaction remains relatively small. It is more pronounced in the recent study, our kinetic data presented in Figures 2, 3 and S4 show that the dissociation reactions of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] do not take place by the Cu^{II} or Zn^{II}-assisted pathways which can be rationalized by the absence of the mixed dinuclear intermediate complexes in these systems.

For practical purposes, the kinetic inertness of a complex can conveniently be characterized/compared by the half-life ($\tau_{1/2}$) of the dissociation under a given condition. Therefore, the dissociation half-life ($\tau_{1/2}$) of these complexes has also been calculated for pH=7.4 (Table 2) and for pH=6.0 as pH in renal system is know to be considerably lower than the physiological pH (pH=5.5-6.5). A comparison of the dissociation half-lives clearly shows the most inert complex is the $[Mn(DOTA)]^{2-}$ followed by $[Mn(NOTA)]^{-}$, [Mn(*TRANS*-DO2A)] and [Mn(*CIS*-DO2A)].

4. Conclusions

The protonation constants of the ligands *CIS*-DO2A and *TRANS*-DO2A as well as the stability and protonation constants of their Mn^{II} complexes have been determined using pH-potentiometry. The stability constants of these complexes are higher than the value reported for $[Mn(EDTA)]^{2-}$ (log K_{MnL} = 13.8, 0.1 M $NaClO_4$ and 20 °C) but lower than that of $[Mn(DOTA)]^{2-}$ (log K_{MnL} = 19.44, 0.1 M KCl and 25 °C).[21] The value of the stability constant and the pMn were found to be higher for [Mn(*CIS*-DO2A)]. Cyclic voltammetric experiments (performed in 0.15 M $NaNO_3$ at 25 ^{O}C in order to prevent the superimposition of the oxidation of the chloride ion with those of the complexes) indicate that the position of the acetate arms on the 1,4,7,10-tetraazacyclododecane base affects notably the tendency of these complexes towards oxidation. The half-wave potentials determined for [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] were found to be +636 and +705 mV vs. Ag/AgCl, respectively which indicate that the Mn^{2+} ion in [Mn(*TRANS*-DO2A)] complex is more stabilized against oxidation than in [Mn(*CIS*-DO2A)].

The half-lives ($\tau_{1/2}$) of the decomplexation reactions of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] obtained by using the calculated rate constants are similar, 48 and 57 hours, respectively, under physiologically relevant conditions (at pH = 7.4). These half-lives indicate that the kinetic inertness of these complexes are comparable to that of $[Mn(NOTA)]^{-}$ ($\tau_{1/2}$=73.2 h) but significantly, about twenty times lower than that $[Mn(DOTA)]^{2-}$ ($\tau_{1/2}$=1061 h).[27] Therefore, one can conclude that the relative position of two acetate pendant arms on the 1,4,7,10-tetraazacyclododecane base affects the inertness of

the Mn^{II} complexes only slightly. Apparently the two extra acetate pendant arms of DOTA significantly contribute to the kinetic inertness and resistance towards acid catalyzed dissociation. On one hand, these arms are capable of binding the proton and exchanging metal ion resulting in the formation of protonated or dinuclear complexes which expected to increase the rate of dissociation. In the case of $[Mn(DOTA)]^{2-}$ the contribution of the direct attack of the exchanging metal ion to the overall dissociation represent a small increase in the half-lives (0.2 h in the presence of $c_{ZN2+}=1.0\times10^{-5}$ M Zn^{II} ion).[27] On the other hand the protonation of $[Mn(DOTA)]^{2-}$ occurs on the *TRANS* positioned acetates (as evidenced by X-ray crystallography)[41] resulting in the formation of a thermodynamically stable complex with six donor atoms coordinated to the Mn^{II} ion. In a sharp contrast to this avenue the protonation of either [Mn(*CIS*-DO2A)] or [Mn(*TRANS*-DO2A)] is expected to occur on the pendant which originally coordinates the metal ion resulting in the formation of protonated species in which the metal ion is bound only by five donor atoms. In the light of this information it is not very surprising that the protonated complexes of DO2A ligands are more labile.

In conclusion, [Mn(*CIS*-DO2A)] displays some very interesting features (thermodynamic and redox stability as well as kinetic inertness) which makes this complex a promising platform for the development of more efficient Mn(II) complexes as alternatives to Gd-based MRI agents. However, to achieve this goal these properties need to be further improved by designing more rigid ligands to slow down the structural rearrangements involved in the dechelation/dissociation.

While the data concerning the stability and inertness of the Mn^{II} complexes formed with the DO2A's are very promising we feel important to underline that these complexes based on their properties (pM and half-lives of dissociation extrapolated to physiological conditions) lie closer to the open-chain Gd-based commercial CA's (e.g. Omniscan ([Gd(DTPA-BMA)] pGd = 11.06 and $t_{1/2}$ = 49.4 h at pH = 7.4 and 25 ^{o}C by taking into account the catalytic effect of the endogenous ligands discovered recently).[49] On the other hand, recent studies have confirmed that these pathways are absent for the $[Gd(DOTA)]^{-}$ (Dotarem) for which the acid catalyzed dissociation is in fact the only one pathway responsible for the loss of toxic Gd^{III}. These studies have confirmed that the $[Gd(DOTA)]^{-}$ remains the

best Gd^{III}-based MRI CA as far as the kinetic inertness of the MRI CA complexes concerned ($t_{1/2}$ = $2.7x10^9$ h at pH = 7.4 and 25 ^oC).[50]

ABBREVIATIONS

MRI	Magnetic Resonance Imaging
CA	Contrast Agent
CIS-DO2A	1,4,7,10-Tetraazacyclododecane-1,4-diacetic acid
TRANS-DO2A	1,4,7,10-Tetraazacyclododecane-1,7-diacetic acid
EDTA	Ethylenediaminetetraacetic acid
NOTA	1,4,7-Triazacyclononane-1,4,7-triacetic acid
DOTA	1,4,7,10-Tetraazacyclododecane-1,4,7,10-tetraacetic acid
NSF	Nephrogenic Systemic Fibrosis
DTPA	Diethylenetriaminepentaacetic acid
*TRANS*CDTA	*TRANS*-1,2-Diaminocyclohexane-N,N,N′,N′-tetraacetic acid
DO1A	1,4,7,10-Tetraazacyclododecane-1-acetic acid
DO3A	1,4,7,10-Tetraazacyclododecane-1,4,7-triacetic acid
DMP	1,4-Dimethylpiperazine
NEP	1-Ethylpiperazine
DFT	Density functional theory
CV	Cyclic voltammetry
NHE	Normal hydrogen electrode

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TABLE 1.

	CIS-H_2DO2A			*TRANS*-H_2DO2A			H_3NOTA[B]	H_4DOTA[C]
I	0.15 M NaCl	0.1 M KCl	0.1 M Me_4NCl[A]	0.15 M NaCl	0.1 M KCl	0.1 M Me_4NCl[A]	0.1 M Me_4NCl	0.1 M KCl
LOG K_1	11.44(2)	11.40(1)	11.07	11.69(1)	11.66(1)	11.29, 11.29[D]	13.17	11.41
LOG K_2	9.51(5)	9.58(2)	9.76	9.75(3)	9.75(2)	9.84, 9.84[D]	5.74	9.83
LOG K_3	4.14(6)	3.74(3)	3.84	3.97(5)	4.06(3)	3.97, 3.97[D]	3.22	4.38
LOG K_4	1.55(6)	1.65(3)	1.75	2.68(4)	2.58(4)	2.59, 2.59[D]	1.96	4.63
LOG K_5	–	–	–	–	–	–	–	1.92
LOG K_6	–	–	–	–	–	–	–	1.58
$\sum$LOG K_I^H	26.64	26.37	26.42	28.09	28.05	27.69, 27.69[D]	24.09	33.75
LOG K_{MnL}	15.68(1)	15.22(2)	16.13	14.64(1)	15.07(1)	14.54, 14.66[D]	16.30	19.44
LOG K_{MnHL}	4.15(2)	4.15(2)	[F]	4.40(8)	4.48(2)	4.25[F], 4.60[D, F]	2.87	3.96[F]
pMn[E]	7.27	7.03	7.41	6.52	6.75	6.60, 6.66[D]	7.75	9.02

[A] Ref. [29]; [B] Ref. [37]; [C] Ref. [36]; [D] Ref. [38]; [E] The pMn values were calculated at pH = 7.4, $c_{Mn} = 10^{-5}$ M, $c_L = 10^{-5}$ M (Ref. [39] under these conditions its minimal value equals to 5.0 (in the absence of any complexation);. [F] Some other equilibrium data for [Mn(*CIS*-DO2A)]: logβ_{MnH2L}=8.31 (Ref. [29]); [Mn(*TRANS*-DO2A)]: logK_{MnH2L}=4.45 (Ref. [29]), or logK_{MnH2L}=4.01 (Ref. [38]) and $[Mn(DOTA)]^{2-}$: logK_{MnH2L}=3.70 (Ref. [36]));

TABLE 2.

	[Mn(*cis*-DO2A)]		[Mn(*trans*-DO2A)]		[Mn(NOTA)]$^{-}$, A	[Mn(DOTA)]$^{2-}$, A
I	0.15 M NaCl	0.1 M KCl	0.15 M NaCl	0.1 M KCl	0.1 M KCl	0.1 M KCl
K_0 (S^{-1})	–	–	–	–	2.6×10^{-6}	1.8×10^{-7}
K_1 ($M^{-1}S^{-1}$)	100 ± 4	99 ± 5	85 ± 3	84 ± 8	0.78	0.04
K_2 ($M^{-2}S^{-1}$)	$(1.6 \pm 0.1)\times10^{6}$	$(1.5 \pm 0.1)\times10^{6}$	$(3.0 \pm 0.1)\times10^{6}$	$(2.5 \pm 0.1)\times10^{6}$	–	1.6×10^{3}
$K_D^{PH=7.4}$ (S^{-1})	4.0×10^{-6}	3.9×10^{-6}	3.4×10^{-6}	3.3×10^{-6}	2.6×10^{-6}	1.8×10^{-7}
$T_{1/2}^{PH=7.4}$ (H)	48.3	48.9	56.8	57.5	73.2	1060.9
$K_D^{PH=6.0}$ (S^{-1})	1.0×10^{-4}	1.0×10^{-4}	8.8×10^{-5}	8.7×10^{-5}	3.4×10^{-6}	2.2×10^{-7}
$T_{1/2}^{PH=6.0}$ (H)	1.90	1.92	2.19	2.23	57.0	884.7

[A] Ref. [27]; Only spontaneous and the proton-assisted dissociations were considered for the calculation of the K_D and $T_{1/2}$ values of $[Mn(NOTA)]^{-}$ and $[Mn(DOTA)]^{2-}$ complexes.

LEGENDS

TABLE 1. Protonation constants of the investigated ligands, the protonation and stability constants and pMn values of Mn^{II} complexes (25 ºC, 0.15 M NaCl and 0.1 M KCl).

TABLE 2. Rate constants and half-lives ($T_{1/2}$=ln2/K_D, at pH=6.0 and pH=7.4) for the dissociation reactions of [Mn(*CIS*-DO2A)], [Mn(*TRANS*-DO2A)], $[Mn(NOTA)]^-$ and $[Mn(DOTA)]^{2-}$ complexes (25 °C).

FIGURE 1. The structure of the ligands discussed in the text.

FIGURE 2. The pseudo-first order rate constants (K_D) for the transmetallation reaction of [Mn(*CIS*-DO2A)] as a function of $[H^+]$ ([MnL]=0.5 mM, $[Cu^{II}]$=2.5 (◆), 5.0 (■), 7.5 (▲) and 10.0 mM (●), [DMP]=[NEP]=0.05 M, 0.1 M KCl, 25 °C)

FIGURE 3. The pseudo-first order rate constants (K_D) for the transmetallation reaction of [Mn(*TRANS*-DO2A)] as a function of $[H^+]$ ([MnL]=0.5 mM, $[Cu^{II}]$=2.5 (◆), 5.0 (■), 7.5 (▲) and 10.0 mM (●), [DMP]=[NEP]=0.05 M, 0.1 M KCl, 25 °C)

FIGURE 4. Assumed reaction pathways for the dissociation of [Mn(*CIS*-DO2A)] and [Mn(*TRANS*-DO2A)] complexes.

FIGURE 1.

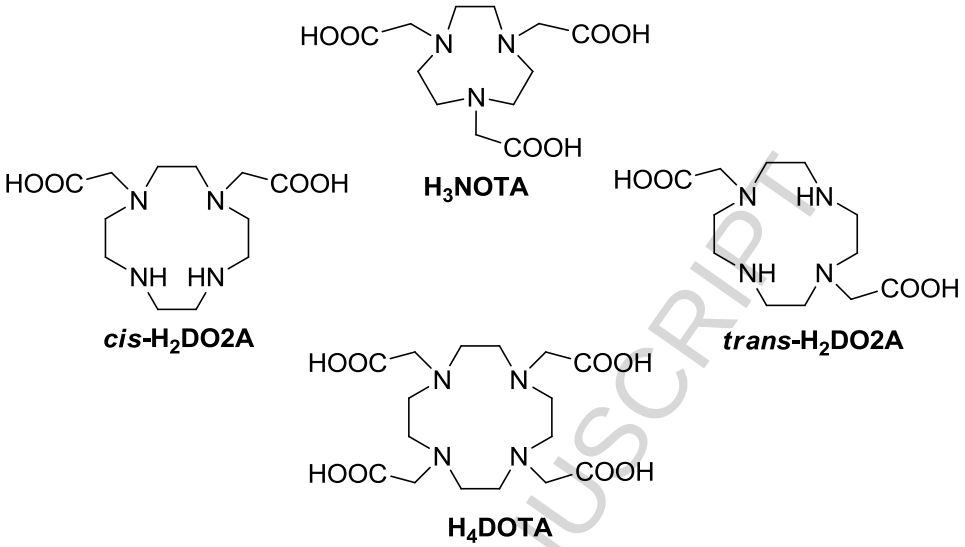


FIGURE 2.

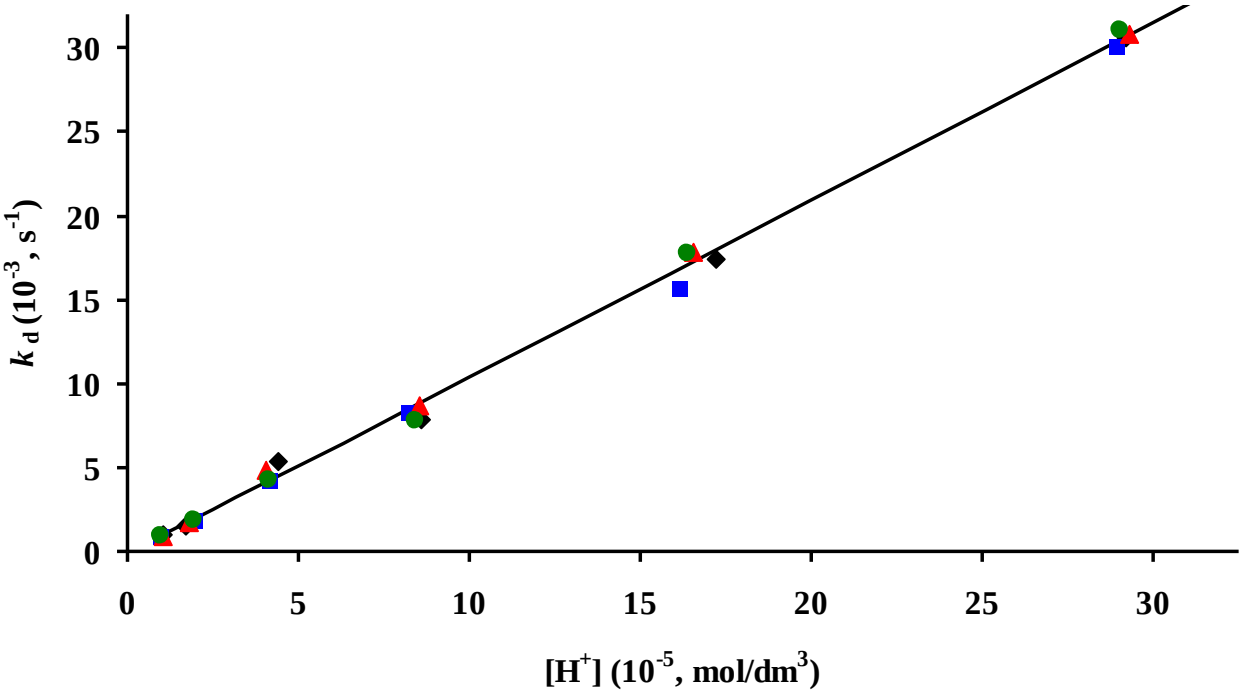


FIGURE 3.

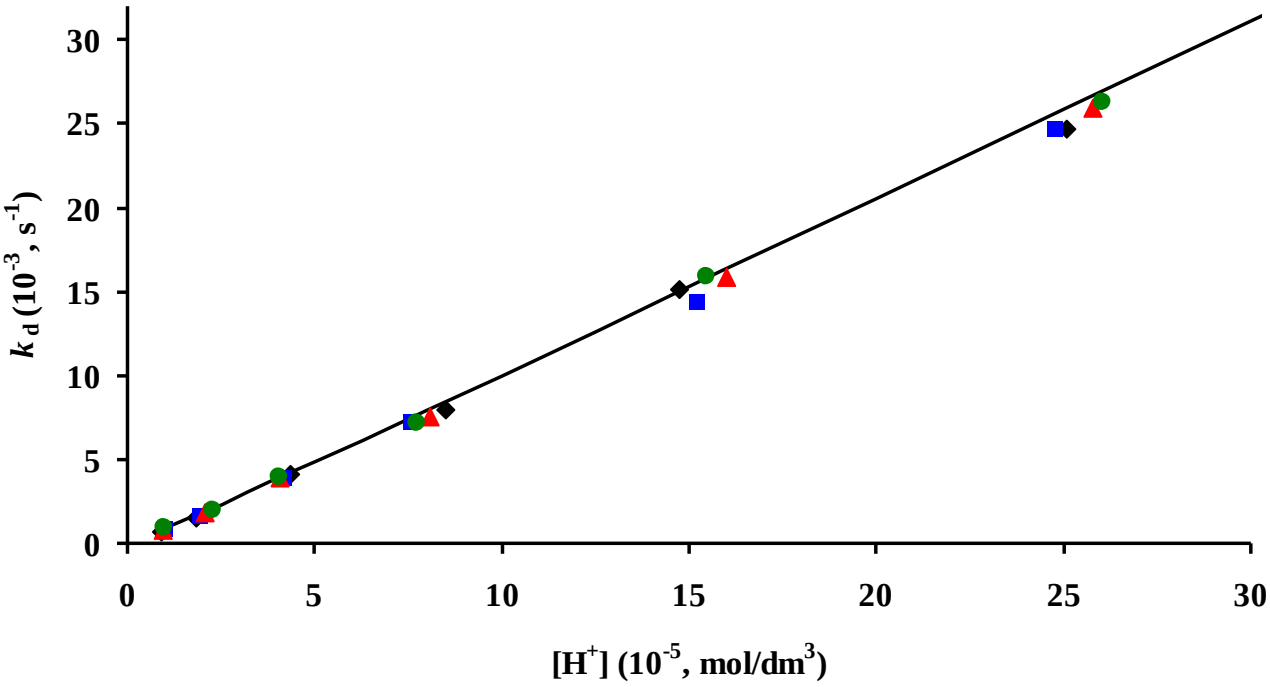
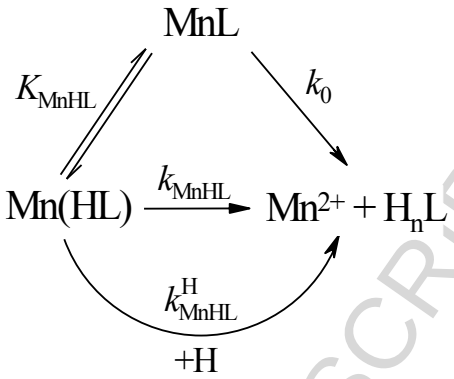
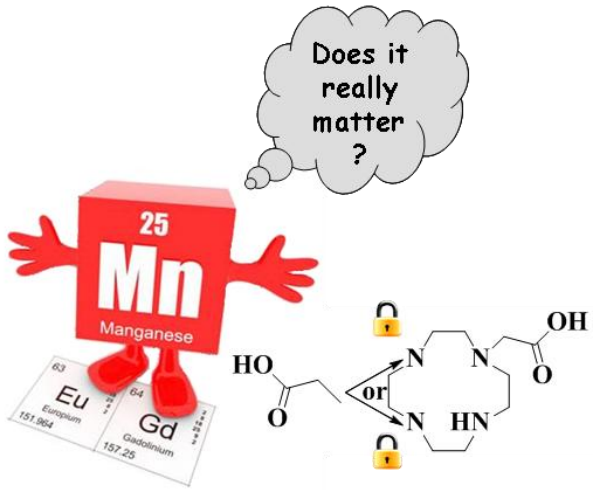


FIGURE 4.



PICTOGRAM FOR THE GRAPHICAL ABSTRACT



Mn^{II} complexes formed with *CIS*- and *TRANS*-DO2A chelators have been investigated by pH-potentiometry, ^{1}H relaxometry, UV-vis spectrophotometry and cyclic voltammetry. The physico-chemical characteristics of Mn^{II} complexes of these structure isomers do not differ dramatically, however the *CIS*-DO2A platform has better potential for further development owing to its coordinated water molecule.

HIGHLIGHTS

> The stability constants of Mn^{II} complexes agree well with those published in the literature

> The redox potentials of the complexes follow the expected (based on the structure) order

> Both Mn^{II} complexes are inert and they primarily undergo acid catalyzed dissociation

> The positions of the acetate moieties have little effect on the properties of the complexes