Thermodynamic Stability of Mn(II) Complexes with Aminocarboxylate Ligands Analyzed Using Structural Descriptors

Rocío Uzal-Varela, Francisco Pérez-Fernández, Laura Valencia, Aurora Rodríguez-Rodríguez, * Carlos Platas-Iglesias, * Peter Caravan, and David Esteban-Gómez

ACCESS

ABSTRACT: We present a quantitative analysis of the thermodynamic stabilities of Mn(II) complexes, defined by the equilibrium constants (log $K_{\text{Mn-L}}$ values) and the values of $p_{\text{Mn}}$ obtained as $-\log[K_{\text{Mn-L}}]$ for total metal and ligand concentrations of 1 and 10 μM, respectively. We used structural descriptors to analyze the contributions to complex stability of different structural motifs in a quantitative way. The experimental log $K_{\text{Mn-L}}$ and $p_{\text{Mn}}$ values can be predicted to a good accuracy by adding the contributions of the different motifs present in the ligand structure. This allowed for the identification of features that provide larger contributions to complex stability, which will be very helpful for the design of efficient chelators for Mn(II) complexation. This issue is particularly important to develop Mn(II) complexes for medical applications, for instance, as magnetic resonance imaging (MRI) contrast agents, number eight is more common for Mn(II) than is generally assumed, with the highest log $K_{\text{Mn-L}}$ values generally observed for hepta- and octadentate ligands. The X-ray crystal structure of [Mn(DOTA)](H$_2$O)$_2$, in which eight-coordinate [Mn(DOTA)]$^{2-}$ units are bridged by six-coordinate exocyclic Mn(II) ions, is also reported.

INTRODUCTION

Magnetic resonance imaging (MRI) often uses contrast-enhanced procedures to attain a more accurate diagnosis of different malignancies.1–4 The contrast agents (CAs) that are currently used in clinics are complexes with the paramagnetic metal ion Gd(III),5,6 which are very efficient relaxation agents of water proton nuclei in their vicinity. As a result, CAs shorten significantly the water longitudinal relaxation times, providing an enhanced signal of the tissues in which they are distributed, as fast $T_1$ relaxation allows for the accumulation of more signal intensity using short repetition times.7 The efficacy of Gd(III) as a $T_1$ relaxation agent is related to the dipolar interaction between the nuclear and electron spins, which is particularly efficient due to the presence of seven unpaired electrons and the long electronic relaxation time.8,9 While the use of Gd(III) CAs is regarded to be safe, a few cases of adverse effects have been reported.10 Long-term accumulation of Gd(III) in patients that received multiple doses was also described, which stimulated the search for alternative CAs.11

High-spin Mn(II) possesses five unpaired electrons that originate a symmetrical $^5S$ ground state term for the free ion. This leads to a slow electronic relaxation, making Mn(II) an efficient relaxation agent.12 Thus, it is not surprising that Mn(II) complexes were considered as CA candidates with the advent of MRI in the 1970s and 1980s.13,14 The Mn(II)-based CA [Mn(DPDP)]$^{4-}$ (DPDP$^{6-}$ = N,N$'$,N$''$-dipyridoxylethyleneamine-N$'$',N$''$'-diaminateS$'$',S$''$'-bis(phosphate), L11, Chart 1)15 was also introduced in clinical practice for liver imaging.16,17 Nevertheless, the problems associated with Gd(III) toxicity and deposition have provoked a renewed interest in Mn(II)-based MRI contrast agents.18 One of the main aims of the research in this field is to develop stable and inert complexes endowed with high relaxation efficiencies.19–29

In a recent paper, we proposed an empirical correlation to predict and rationalize the thermodynamic stabilities of Gd(III) complexes with polyaminopolycarboxylate ligands.20 We showed that the thermodynamic stability constants and pGd values can be approximated to a good accuracy using structural descriptors. The contribution of each structural descriptor (ligand motif) to complex stability was obtained by a least-squares fitting procedure to stability data reported in the literature. The stability constants and pGd values were

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subsequently obtained by adding the contributions of each structural descriptor. We validated the predictive character of the model by determining the stability constants of a test set of complexes. The prediction of Mn(II) complex stability is of great interest to aid ligand design and reduce synthetic efforts. Thus, we envisaged to extend to Mn(II) the methodology developed to predict Gd(III) complex stabilities.

This paper presents an overview of the stability constants of Mn(II) complexes reported in the literature, which are subsequently used to develop an empirical correlation.
RESULTS AND DISCUSSION

Coordination Numbers in Mn(II) Complexes. The analysis described in this work assumes that the thermodynamic stability of Mn(II) complexes can be predicted by adding the contributions of the different donor groups present in the ligand structure. However, the number of donor groups that contribute to complex stability is limited by the coordination number of the metal ion. Once the coordination sphere is saturated, the incorporation of additional donor groups into the ligand scaffold is not expected to contribute to an increased stability. The metal ion in Mn(II) complexes with polyaminopolycarboxylate ligands generally displays coordination numbers 6 or 7. Depending on the denticity of the ligand, water molecules present in the first coordination sphere may complete the metal coordination environment. Heptacoordinated metal complexes are relatively rare within the first-row transition-metal series but are more abundant for Mn(II) than for any other metal ion within the series.31,32 Typical seven-coordinate Mn(II) complexes are those with EDTA (L4, Chart 1) and its derivatives,33 in which a coordinated water molecule completes the metal coordination sphere.34-37 A remarkable example of this class is H2P2C3A (L10, Chart 1), which forms a very stable Mn(II) complex that generates excellent MRI contrast.38,39 Seven coordination is also favored by 15-membered macrocyclic ligands containing five donor atoms, which generally provide pentagonal bipyramidal coordination in which the equatorial positions are occupied by the donor atoms of the macrocyclic unit.40,41 The Mn(II) complex with the triethyl ester derivative of the 12-membered macrocycle H2PCTA (L37, Chart 2) was also found to be seven-coordinated in the solid state.42 However, complexes with 1,4,7-triazacyclononane derivatives such as H3NOTA and related ligands generally form six-coordinate complexes in solution.

Eight-coordinate Mn(II) complexes are rare.46,47 Eight-coordinate bispidine derivatives providing exceptionally high thermodynamic stabilities (\(\log K_{\text{MnI}} > 24\)) have been reported recently.48 Remarkable examples in the context of MRI contrast agents are the cyclen derivatives [Mn(DOTAM)]\(^{2-}\) (DOTAM = L36, Chart 2) and the analogue containing four 2-pyridyl pendants, which were both found to exhibit eight-coordinate metal ions in the solid state.49,50 However, it is not clear whether eight coordination is favored for these complexes by the presence of charge-neutral pendant arms. The charge-neutral [Mn(cis-DO2A)] complex (see L32, Chart 2) was found to display seven-coordinate Mn(II) ions in solution, thanks to the presence of a coordinated water molecule.51 A seven-coordinate structure was also observed in the solid state.52 The incorporation of a third acetic acid pendant into the cyclen structure to give H2DO3A (L25, Chart 2) yields a seven-coordinate Mn(II) complex, as demonstrated by relaxometric studies.53 The coordination number of the metal ion in [Mn(DOTA)]\(^{2-}\) (see L35, Chart 2) was never ascertained; though the small zero field splitting evidenced by electron paramagnetic resonance (EPR) measurements is compatible with a rigid and symmetrical coordination environment.53,54

Crystal Structure of [Mn2(DOTA)(H2O)3]. Crystals with formula [Mn2(DOTA)(H2O)3] were obtained from an aqueous solution of the [Mn(DOTA)]\(^{2-}\) complex in the presence of 1 equiv of Mn(II). The compound crystallizes in the tetragonal P4/m space group. Crystals contain [Mn(DOTA)]\(^{2-}\) entities joined by exocyclic Mn(II) ions with octahedral coordination, provided by four oxygen atoms of bridging \(\mu_2-\eta^1\eta^1\)-carboxylate groups and two coordinated water molecules (Figure 1). The Mn-O distances involving the coordinated water molecules (Table 1) are close to those observed in the solid state for (NH4)\(2\)[Mn(H2O)6](SO4).56 The coordinated water molecules are involved in hydrogen bonds with oxygen atoms of the carboxylate groups.

The macrocyclic fragment in each of the [Mn(DOTA)]\(^{2-}\) entities is disordered into two positions, which correspond to the two square [3333] conformations57 of cyclen that are usually denoted as \(\delta\delta\delta\delta\) and \(\lambda\lambda\lambda\lambda\).58 Interestingly, the position of the pendant arms is not disordered, adopting either a \(\Delta\) or a \(\Lambda\) conformation for each [Mn(DOTA)]\(^{2-}\) entity.59 As a result, the two disordered macrocyclic units generate the \(\Delta(\lambda\lambda\lambda\lambda)\) and \(\Delta(\delta\delta\delta\delta)\) isomers, which provide square...
Table 1. Bond Distances (Å) and Angles (deg) Observed in the Crystal Structure of [Mn$_4$(DOTA)(H$_2$O)$_2$]

| Mn(1)−O(1) | 2.2687(17) | Mn(2)−O(4) | 2.2845(18) |
| Mn(1)−N(1) | 2.462(4) | Mn(2)−N(3) | 2.449(3) |
| Mn(1)−N(11) | 2.416(7) | Mn(2)−N(31) | 2.398(14) |
| Mn(1)−N$_{TSAP}$ | 1.218 | Mn(2)−N$_{TSAP}$ | 1.184 |
| Mn(1)−N$_{VTSAP}$ | 1.357 | Mn(2)−N$_{VTSAP}$ | 1.308 |

$\phi$, SAP | 43.0 | $\phi$, SAP | 41.2 |

$\phi$, TSAP | 26.6 | $\phi$, TSAP | 25.5 |

Mn(3)−O(2) | 2.2154(18) | Mn(3)−O(3) | 2.2153(19) |

Mn(3)−O(3) | 2.198(2) | Mn(3)−O(6) | 2.186(3) |

“Distance between the metal ion and the plane defined by the four N atoms of the macrocycle (N$_4$). $\theta$Twist angle of the O$_4$ and N$_4$ planes.

antiprismatic (SAP) and twisted square antiprismatic (TSAP) coordination polyhedra, respectively. Inversion center relation the $\Delta(\text{xxxx})/\Lambda(\text{xxxx})$ and $\Delta(\text{xxxx})/\Lambda(\text{xxxx})$ enantiomeric pairs of [Mn(DOTA)]$^{2-}$. Thus, all four stereoisomers of the complex are present in the crystal lattice. The crystal lattice contains two [Mn(DOTA)]$^{2-}$ entities with slightly different bond distances (Table 1). The twist angles ($\phi$) of the O$_4$ and N$_4$ planes that define the square planes of the coordination polyhedra are close to those expected for SAP (45$^\circ$) or TSAP (22.5$^\circ$) coordination. The Mn−N distances in TSAP isomers are ~0.05 Å longer than in the corresponding SAP isomers. As a result, the Mn(II) ions reside closer to the N$_4$ plane in the SAP isomers than in the TSAP counterparts (see Mn−N$_4$ distances in Table 1). All of these structural features parallel those observed for DOTA-type complexes of the lanthanide ions and Sc(III). The Mn−O distances are longer than those involving carboxylate oxygen atoms in seven-coordinate Mn(II) complexes (ca. 2.17−2.27 Å), as a result of the higher coordination number of the metal ion in [Mn(DOTA)]$^{2-}$. A similar situation is observed for the Mn−N bonds, which fall within the range 2.33−2.45 Å for seven-coordinate complexes containing amine N atoms.

**Stability Constants of Mn(II) Complexes.** The literature reports a wide collection of thermodynamic stability constants determined for Mn(II) complexes with a wide variety of ligands. In this study, we aimed at predicting the stability constants of Mn(II) complexes, relevant as MRI contrast agents, using structural descriptors. Thus, we included in our study ligands that contain structural motifs present in the ligands used for this purpose. Among the nonmacrocyclic ligands, two families have been widely investigated for Mn(II) complexation. The first class comprises H$_4$EDTA (L$_4$, Chart 1) and its derivatives, including: (1) EDTA analogues in which the ethyl spacer is replaced by propyl (H$_3$PDTA, L$_3$), cyclohexyl (H$_4$CDTA, L$_4$), phenyl (H$_4$PhDTA, L$_6$), 1,2-cyclobutyl, or 1,3-cyclobutyl (H$_4$CBDTA, L$_5$) groups. (2) Ligands bearing one of these spacers in which some of the acetic acid arms are replaced by donor groups such as phenols (i.e., L$_7$−L$_9$) or pyridine groups (i.e. H$_3$PyC3A, L$_{10}$). (3) Extended H$_4$EDTA structures such as those of H$_4$OBETA (L$_2$), H$_3$PyDTA (L$_8$), and H$_4$EGTA. (4) Ligands related to the latter three classes in which some donor groups are absent. A more exhaustive list of ligands and their protonation and stability constants is provided in Table S1 (Supporting Information).

A second ligand family comprises tripodal ligands, in which the different donor groups, up to three, are appended on an amine nitrogen atom. This family includes H$_4$NTA$^{2-}$ (L$_7$) and derivatives in which acetic acid groups are replaced by different donors like picolinic acid (i.e. H$_4$DPAAA, L$_3$), sulphonyamide (i.e. H$_4$DPASAm, L$_2$) or methylphosphonic acid$^{39}$ groups. Table 2 presents the stability constants reported for Mn(II) complexes of selected nonmacrocyclic ligands.

The class of macrocyclic ligands that have been more extensively investigated for Mn(II) complexation is certainly the family of tetraazamacrocycles (Chart 2), more commonly cyclam (1,4,7,10-tetraazacyclododecane),$^{30}$-$^{32}$ cyclam (1,4,8,11-tetraazacyclotetradecane),$^{33}$-$^{34}$ or pyclen (3,6,9,15-tetraazacyclo[9.3.1]pentadeca-1(15),11,13-triene)$^{35}$,$^{36}$,$^{37}$ functionalized with different pendant arms, typically acetic acid, primary or N-substituted acetamides, methylphosphonic, methylphosphonic, or picolinic acid groups, among others. Some of these macrocycles incorporate ether oxygen atoms into the macrocyclic structure replacing some of the amine N atoms. Alternatively, macrocyclic ligands derived from 1,4,7-triazacyclononane (TACN) functionalized with different pendant arms, and often with mixed N/O donor sets in the macrocyclic scaffold, can be used as ligands for Mn(II) (i.e. L$_{43}$, Chart 3).$^{38}$-$^{40}$ The structurally related 15-membered macrocyclic ligands containing mixed N/O donor sets form rather stable complexes as well (i.e. L$_{47}$–L$_{50}$, Chart 3).$^{41}$-$^{44}$ Macrocyclic ligands of this family incorporating acetic acid pendant arms were also investigated for Mn(II) complexation.$^{45}$ Finally, the stability of Mn(II) complexes with a few mesocyclic ligands derived from AAZTA was also explored (i.e. L$_{44}$–L$_{46}$, Chart 3).$^{46}$

The thermodynamic stability of Mn(II) complexes depends on several factors, as illustrated in Figure 2. Stability constants generally increase with increasing ligand denticity, as would be expected. The highest log $K_{\text{Mnl}}$ values are observed for complexes with hepta- and particularly octadentate ligands. This suggests that several Mn(II) complexes display coordination number eight in solution, as, for instance, the bispines reported recently by Comba$^{48}$ and some cyclen derivatives such as [Mn(DOTA)]$^{2-}$. In the latter case, stability constants of log $K_{\text{Mnl}}$ = 20.7 and 19.9 were determined using ionic strengths of 0.1 M Me$_2$N(NO$_3$)$_2$ and Me$_2$NCl$^{52}$ while that reported for [Mn(DO3A)]$^{3-}$ in 0.1 M Me$_2$NCl is slightly lower (log $K_{\text{Mnl}}$ = 19.4).$^{52}$ The log $K_{\text{Mnl}}$ values determined for a given ligand denticity spread over several orders of magnitude, highlighting the critical effect of ligand topology and the nature of the donor groups incorporated into the ligand scaffold. The data shown in Figure 2 also evidence that macrocyclic ligands derived from the 12-membered macrocycles cyclen, and particularly cyclen, tend to form Mn(II) complexes with higher stabilities than other ligand classes, with the exception of the bispine ligands described recently,$^{48}$ which form extraordinary stable Mn(II) complexes. Taken together, the stability constants reported for Mn(II) complexes span more than 20 orders of magnitude, from log $K_{\text{Mnl}}$ values of ca. 1−3 for simple bidentate ligands (i.e. picolinic acid) to log $K_{\text{Mnl}}$ ~ 24 for the mentioned bispide complexes.

**Structural Descriptors.** The descriptors used to predict the thermodynamic stability of Mn(II) complexes are essentially those used previously for Gd(III)$^{30}$ and are listed in Table 3. Linear polyaminopolycarboxylate ligands are described by the corresponding number of amine N atoms, denoted as $N$, and the number of acetic acid groups $C$. For instance, H$_4$EDTA is described as $nN = 2 + nC = 4$, where $n$ indicates the number of groups of a given class. In the case of macrocyclic ligands, the macrocyclic unit as a whole, including
Table 2. Stability Constants ($\log K_{\text{MnL}}$ Values, 25 °C), Values of pMn, Structural Descriptors, and Calculated $\log K_{\text{MnL}}$ and pMn Values for Mn(II) Complexes

| L_1 (H_4DTPA) | L_2 (H_4OBETA) | L_3 (H_4PDTA) | L_4 (H_4EDTA) | L_5 (1,3-H_4CBnDTA) | L_6 (meso-DIMEDTA) | L_7 (H_4NTA) | L_8 (H_4PyDTA) | L_9 | L_10 (H_4PyC3A) | L_11 (H_4DPDP) | L_12 (H_4DPASam) | L_14 (trans-H_4CDTA) | L_15 (cis-H_4CDTA) | L_16 (H_4PhDTA) | L_17 | L_18 | L_19 | L_20 (trans-H_2DO2A) | L_21 (H_4ODOTRA) | L_22 | L_23 (H_4TRITA) | L_24 (H_4TETA) | L_25 (H_4DO3A) | L_26 (H_4DO3P) | L_27 | L_28 | L_29 | L_30 | L_31 | L_32 (cis-H_2DO2A) | L_33 (cis-H_2DO2P) | L_34 (H_4DOTP) | L_35 (H_4DOTA) | L_36 (DOTAM) | L_37 (H_4PCTA) | L_38 (cis-H_4PC2A) | L_39 (trans-H_4PC2A) | L_40 | L_41 | L_42 (H_2NO2A) | L_43 | L_44 (H_4AAZTA) | L_45 | L_46 | L_47 | L_48 | L_49 | L_50 |
|--------------|----------------|--------------|--------------|------------------|------------------|--------------|--------------|-----|----------------|--------------|------------------|------------------|------------------|--------------|-----|-----|-----|----------------|--------------|-----|--------------|--------------|------------------|--------------|----------------|--------------|------------------|--------------|-----------------|--------------|----------------|--------------|------------------|--------------|-----------------|--------------|
| 15.50        | 14.45          | 10.01        | 12.46        | 10.78            | 14.10            | 7.44         | 14.13        | 11.37| 14.14          | 15.10         | 13.53            | 14.32            | 14.19           | 11.79        | 14.16        | 13.66        | 14.61          | 14.64         | 13.88         | 9.38          | 16.74         | 11.27          | 19.43          | 17.45         | 11.54        | 9.39          | 13.03         | 10.72          | 12.64         | 15.22         | 15.41         | 18.98         | 19.44         | 11.96        | 17.09         | 10.61         | 4.30          | 11.56        | 7.73          | 14.19         | 11.00         | 10.67         | 10.85         | 11.09         | 10.89         | 7.18          | 9.44         |
| 12.07        | 11.88          | 7.44         | 11.62        | 9.44             | 11.20            | 6.36         | 13.39        | 10.83| 12.29          | 10.34          | 11.55            | 13.59            | 11.54           | 12.67         | 9.21         | 11.06        | 8.41          | 8.95           | 13.09        | 9.32          | 11.41        | 6.51           | 13.68         | 8.82          | 7.91         | 6.58          | 10.99         | 9.34          | 9.83         | 9.99         | 7.41         | 8.64          | 13.95         | 12.65         | 15.13         | 12.15         | 13.18         | 9.99         | 7.49         | 8.02          | 6.13          | 12.52         | 9.10          | 8.72          | 7.03          | 6.09          | 6.35          | 6.09          | 4.00          | 6.00          | 6.00          | 6.00          | 6.00          |
| 3N + 5C      | 3N + 4C + SOe | 2N + 4C + SProp | 2N + 4C   | 2N + 4C + SCBu  | 2N + 4C + 2SCalk | N + 3C       | 3N + 4C + SPy | 3N + 2C + SCyhx + SPy | 2N + 3C + Py + SCyhx | 2N + 2C + 2Phe | N + 2PMe + Sulph | 2N + 4C + SCyhx | 2N + 4C + 2SCyhx | 2N + 4C + SPn | 2N + 3C + Phe | 2N + 3C + PheNO2 | 2N + 3C + PheOMe | A_12 + 2C       | A_12 + 3C + SOe | A_12 + 2C + 2SOe | A_12 + 4C + 2Spropyl | A_12 + 4C + 2Spropyl | A_12 + 3C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     | A_12 + 2C     |
| 102          | 71             | 103          | 71           | 74               | 70              | 79           | 76           | 99            | 20              | 15              | 78              | 21             | 71             | 98             | 72             | 95             | 95             | 81             | 80             | 81              | 87              | 93             | 93             | 104            | 81             | 96             | 82             | 105            | 96             | 96             | 52             | 82             | 81             | 104            | 81             | 81              | 82             | 88             | 88             | 88             | 88             | 88             | 88             | 88             | 88             | 88             | 88             | 88             | 88             |
| 17.12 (14.47°) | 12.39         | 10.41         | 13.18         | 9.95            | 13.38          | 8.39          | 14.74         | 10.14         | 13.26          | 8.46            | 11.76          | 11.48          | 12.22          | 12.22          | 11.77          | 9.98          | 10.17         | 8.24          | 10.05          | 11.92          | 8.51            | 12.49          | 7.01           | 12.69          | 16.49          | 9.29          | 6.59          | 11.57          | 8.91          | 9.29          | 10.05          | 9.15          | 16.49          | 15.33          | 12.01          | 14.70          | 12.06          | 12.06          | 6.39          | 4.19          | 8.06          | 7.29          | 12.01          | 9.37          | 6.77          | 8.56          | 7.02          |

*Calculated for 3N + 4C. 6Value calculated for A_12 + 4C + 2Spropyl. 7Calculated for A_12 + 2Pho. Excluded from the fit because the complex is nearly fully dissociated under the conditions used to define pMn. Descriptors detailed in Table 3.

the donor atoms, is represented by a single descriptor denoted as A_0, A_12, and A_15 for triaza-, tetraaza-, and pentaaza-macrocycles, respectively. These descriptors are intended to catch the peculiarities of each macrocyclic unit in terms of not only the number of donor atoms but also the match between the size of the cavity and that of the Mn(II) ion. Thus, H_4DOTA is described as A_12 + 4C, while H_2NO2A is defined as A_0 + 2C. Similarly, we used a descriptor A_AAZTA to account for the ligand 6-amino-6-methylpyridine-1,4-diazepine fragment. Thus, H_4AAZTA (L_44, Chart 3) is described as A_AAZTA
Bispidine derivatives were excluded from the analysis presented below due to the scarce thermodynamic data reported for this family of complexes.

The different donor groups incorporated into linear or macrocyclic structures are associated with the following descriptors: methylphosphonic acid (Pho), methylphosphinic acid (Phosphi), hydroxyethyl (HE), 2-methypyridine (Py), primary acetamide (A\(_{\text{NH2}}\)), secondary acetamide (A\(_{\text{NHR}}\)), tertiary acetamide (A\(_{\text{NR2}}\)), 2-propionic acid or \(\alpha\)-substituted acetic acid (C\(_{\alpha}\)), 2-methylpicolinic acid (Pic), and ethylsulphonamide (Sulph). The stability constants reported for 2-methylphenol derivatives appear to be very sensitive to the nature of the substituent at position 4. Indeed, the stability constants of derivatives containing the electron withdrawing \(-\text{NO}_2\) substituent (i.e. L18, Chart 1) are lower than those of unsubstituted derivatives (L17), which in turn are lower than the stability of derivatives containing an electron-donating \(-\text{OMe}\) substituent (L19, see stability constants in Table 2). We thus used three structural descriptors for 2-methylphenol groups, denoted as Phe, PheNO2, and PheOMe. Similarly, the use of different descriptors for primary (A\(_{\text{NH2}}\)), secondary (A\(_{\text{NHR}}\)), and tertiary (A\(_{\text{NR2}}\)) acetamides is justified by the stability constants of complexes with ligands such as L30, L31, and pyclen derivatives with amide groups, which indicate that complex stability increases upon increasing the number of alkyl substituents. Ligands containing \(\alpha\)-substituted acetic acid arms generally provide Mn(II) complexes with slightly lower stability than the parent derivatives (i.e. L45 and L46), and thus we used two different descriptors to consider the effect of \(\alpha\)-substitution.

The comparison of the stability constants reported for \(\text{H}_4\text{EDTA}\) derivatives bearing different spacers evidences that this structural modification has an important impact on the thermodynamic stability constants. The incorporation of a cyclohexyl ring (i.e. \(\text{H}_4\text{CDTA}, \text{L14}\)) results in increased stability, while all remaining modifications result in lower log \(K_{\text{MnL}}\) values than for the parent complex. We note that the use of 1,2-cyclobutyl or \(\text{cis}-1,3\)-cyclobutyl spacers yields complexes with very similar stabilities. Thus, these structural modifications, consisting in replacing an ethyl group such as that in \(\text{H}_4\text{EDTA}\) by a cyclobutyl ring, are described by the same structural descriptor SCybu. Similarly, the complexes of \(\text{cis}\)- and \(\text{trans}\)-\(\text{H}_4\text{CDTA}\) give also very similar values of log \(K_{\text{MnL}}\), and thus these structural modifications are described by a single structural descriptor SCyhx. Additionally, the same descriptor was used to account for the incorporation of a piperidine ring into the ligand scaffold (see L9, Chart 1). Similarly, the incorporation of a phenyl ring (i.e. \(\text{H}_4\text{PhDTA}, \text{L16}\)) and a propyl chain (i.e. \(\text{H}_4\text{PDTA}, \text{L3}\)) are denoted as SPh and Spropyl, respectively. The same descriptors are employed to account for the introduction of phenyl or propyl groups into macrocyclic units, for instance, the propyl chains in \(\text{H}_4\text{TRITA} (\text{L23})\) and \(\text{H}_4\text{TETA} (\text{L24})\).

A rather common structural modification introduced to macrocyclic systems consists in replacing amine N atoms by ether oxygen atoms (L21, L22, L40, L41, L50) or...
These structural modifications are considered by structural descriptors $SO_e$ and $SP_y$. Some nonmacrocyclic ligands also incorporate these structural motifs, for instance, H$_4$OBETA ($L_2$) and H$_4$PyDTA ($L_8$).

The log $K_{MnL}$ values of C-alkylated linear and macrocyclic complexes, such as meso-H$_4$DIMEDTA ($L_6$) and $L_48$, are slightly higher than the parent nonsubstituted derivatives. Thus, this alteration was considered with an additional descriptor (SCalk).

**Prediction of Stability Constants and Conditional Stability.** The structural descriptors presented in the previous section were used to estimate the log $K_{MnL}$ values of Mn(II) complexes using the following expression

$$\log K_{MnL} = \sum_i n_i \Delta \log K_i + \sum_j n_j \Delta \log K_j + A_{MnL}$$

where $n_i$ is the number of structural descriptors of type $i$, while $\Delta \log K_i$ represents the contribution to the stability constant of this donor group. The second term accounts for the different structural modifications present in the ligand structure, where $n_j$ is the number modifications of a given type and $\Delta \log K_j$ its contribution to complex stability. For the complexes with acyclic ligands, $A_{MnL}$ was set to zero.

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Similarly, we used a similar expression to analyze complex stabilities at pH 7.4 using $p_{Mn}$ values (eq 2), which are defined here as $-\log[Mn]_{free}$ for a total Mn(II) concentration of 1 $\mu$M and a total ligand concentration of [L]$_{tot} = 10$ $\mu$M.
\[
p_{\text{Mn}} = \sum_i n_i \Delta p_{\text{Mn}_i} + \sum_j n_j \Delta p_{\text{Mn}_j} + A_{p_{\text{Mn}}}
\]  

The values of \(p_{\text{Mn}}\) allow for a comparison of the stabilities of complexes with different ligands at physiological pH, which depend not only on \(\log K_{\text{MnL}}\) values but also on ligand basicity as well. In principle, one could define \(p_{\text{Mn}}\) using different conditions, for instance, taking equimolar concentrations of ligand and metal ions. We have chosen here the conditions proposed by Raymond, \(^{113}\) which imply using a 10-fold ligand excess. This results in higher \(p_{\text{Mn}}\) values, increasing the number of ligands that provide a \(p_{\text{Mn}}\) value >6, as \(p_{\text{Mn}} = 6\) corresponds to a fully dissociated system. Figure 2 shows that the \(p_{\text{Mn}}\) values vary in the range of ca. 6–21, and tend to increase with ligand denticity. Bidentate and tridentate ligands generally provide \(p_{\text{Mn}}\) values of 6 for the definition used here, and thus these ligands were excluded in Figure 2c.

A least-squares fit of 168 \(\log K_{\text{MnL}}\) values reported in the literature to eq 1 provided the contribution to the complex stability of the different structural descriptors, which were used as fitting parameters. The results of the analysis are provided in Table 4. The agreement between the experimental \(\log K_{\text{MnL}}\) values and those predicted by eq 1 is very good, as shown in Figure 2. The linear fit of the data provides a slope very close to 1 \([0.997(5)]\), as would be expected, with a Pearson’s correlation coefficient of 0.9978. The mean deviation of the calculated data with respect to the experimental values is only 0.63. The agreement between the experimental and calculated data is remarkable, as the mean deviation is comparable to the differences in stability constants reported for the same system by independent groups, often using different ionic strengths. For instance, \(\log K_{\text{MnL}}\) values differing by more than 1.3 and 0.7 \(\log K\) units were reported for \(\text{H}_2\text{DTPA (L1)}^{108}\) and \(\text{H}_2\text{EGTA.}^{75,76}\) Similar differences in stability constants were observed for macroyclic ligands when using different ionic strengths. \(^{80}\) Furthermore, the structural descriptors presented above predict identical \(\log K_{\text{MnL}}\) values for regioisomeric ligands such as cis-H₃PC2A \((\text{L38})\) and trans-H₃PC2A \((\text{L39})\), which were found to differ by \(\sim 1.5 \log K\) units. \(^{40}\) Thus, it is obvious that the stability constants of a given complex are affected not only by the nature of the donor groups present in the ligand scaffold but also by the arrangement of these donor groups in the ligand structure.

The analysis of the \(\log K_{\text{MnL}}\) values using eq 1 allows us to infer the coordination number of the metal ion in certain complexes, for which the assignment of a given coordination number is ambiguous. For instance, a \(\log K_{\text{MnL}}\) value of 17.12 is calculated for \(\text{H}_2\text{DTPA (L1)}\) assuming octadentate binding of the ligand to the Mn(II) ion \((3\text{N}+3\text{C})\). However, the value calculated for a seven-coordinate complex \((3\text{N}+4\text{C})\) of 14.47 is in much better agreement with the experimental values of 15.50 \(^{102}\) and 14.54. \(^{121}\) Thus, this complex is very likely heptacoordinated in aqueous solution, as observed in the solid state for bis(amide) derivatives of \(\text{H}_2\text{DTPA}.^{109}\) A similar situation is observed for \(\text{H}_2\text{TETA (L24)}\), for which the \(\log K_{\text{MnL}}\) value estimated assuming eight coordination \((14.71)\) differs considerably from the experimental value of \(\log K_{\text{MnL}} = 11.27.^{93}\) A considerably better agreement is observed by assuming the formation of a heptacoordinated complex \((\text{Table 2})\). Most likely the propyl chains present in the ligand structure introduce some steric hindrance around the metal ion, favoring a lower coordination number in comparison with \(\text{H}_2\text{DOTA}\), as observed for the corresponding Gd(III) complexes. \(^{110}\) The presence of bulky methylyphosphonic acid groups in \(\text{H}_2\text{DO3P (L26)}\) and \(\text{H}_2\text{DOTP (L34)}\) appears to favor the formation of six-coordinate complexes in solution \((\text{Table 2})\).

The empirical expression obtained here may be useful to aid experimental stability constant determination, as the predicted \(\log K_{\text{MnL}}\) value can help anticipate the pH range in which complex dissociation is expected to occur. Furthermore, eq 1 can be used to identify stability constant values that are likely to be incorrect. For instance, a stability constant of \(\log K_{\text{MnL}} = 14.29\) was reported for a pentadentate ligand containing a piperazine ring functionalized with a picolinic acid and an acetic acid function. \(^{25}\) The stability constant predicted with eq 1 using \(2\text{N} + 1\text{C} + 1\text{Pic} + 1\text{SCyhx}\) is 11.07. The very large discrepancy between the experimental and calculated values suggests that the experimental stability constant may be incorrect and should be taken with some caution.

The \(p_{\text{Mn}}\) values obtained from 141 complexes were fitted to eq 2 following the same strategy used for stability constants. The number of data points used in this analysis is lower than for \(\log K_{\text{MnL}}\) as ligands with \(p_{\text{Mn}}\sim 6\) had to be excluded from the analysis, and for a few systems, ligand protonation constants were not reported together with stability constants. The agreement between the experimental and calculated \(p_{\text{Mn}}\) values is reasonable good \((\text{Figure 2})\), though not as good as for \(\log K_{\text{MnL}}\) values. The linear fit of the data gives a slope of 0.993 \((7)\) and a Pearson’s correlation coefficient of 0.9967. The mean deviation of calculated versus experimental data amounts

| Table 4. Contributions of the Different Structural Descriptors to log \(K_{\text{MnL}}\) and \(p_{\text{Mn}}\) Obtained from the Least-Squares Fit of the Stability Data to Equations 1 and 2 and Total Number of Structural Descriptors of Each Type (\(\Sigma n_i\)).

| \(\Delta \log K\) | \(\Sigma n_i\) | \(\Delta p_{\text{Mn}}\) | \(\Sigma n_{p_{\text{Mn}}}\) |
|---|---|---|---|
| N | 1.29(0.10) | 136 | 0.47(0.18) | 110 |
| Pho | 3.42(0.15) | 23 | 2.19(0.18) | 16 |
| Phosphi | 0.24(0.28) | 6 | 0.91(0.48) | 2 |
| C | 2.65(0.06) | 286 | 2.64(0.10) | 256 |
| HE | –0.15(0.32) | 6 | 0.46(0.66) | 2 |
| Cu | 2.54(0.16) | 13 | 2.35(0.19) | 10 |
| ANH2 | 0.59(0.19) | 7 | 1.81(0.20) | 7 |
| ANHR | 0.92(0.26) | 5 | 2.07(0.27) | 5 |
| ANHL2 | 1.27(0.21) | 9 | 2.26(0.23) | 9 |
| Pic | 4.62(0.19) | 19 | 4.98(0.21) | 17 |
| Phe | 3.14(0.24) | 9 | 1.12(0.26) | 9 |
| PheNO2 | 1.33(0.65) | 2 | 1.31(0.67) | 2 |
| PheOMe | 2.82(0.65) | 2 | –0.62(0.67) | 2 |
| Sulph | 3.23(0.54) | 3 | 1.05(0.56) | 3 |
| Py | 1.51(0.12) | 24 | 2.29(0.16) | 15 |
| SCalk | 0.10(0.14) | 39 | 0.11(0.15) | 36 |
| SOe | –2.08(0.14) | 34 | –0.77(0.16) | 27 |
| Spropyl | –2.77(0.18) | 25 | –2.84(0.26) | 9 |
| SCyhx | 1.22(0.27) | 12 | 0.72(0.29) | 12 |
| SPH | –1.39(0.47) | 4 | 0.27(0.49) | 4 |
| SPy | 0.27(0.22) | 30 | 2.01(0.24) | 27 |
| SCybu | –1.84(0.44) | 5 | –1.55(0.46) | 5 |
| A9 | 5.79(0.26) | 17 | 2.78(0.34) | 12 |
| A12 | 9.65(0.22) | 59 | 4.77(0.30) | 47 |
| A15 | 10.88(0.31) | 24 | 6.55(0.34) | 23 |
| A2A2TA | 3.29(0.50) | 4 | 1.45(0.57) | 4 |

*Structural descriptors detailed in Table 3.*
to 0.66 pMn units. We note that the $\Delta \log K_i$ and $\Delta pMn_i$ contributions characterizing some structural descriptors were obtained with rather large standard deviations (Table 4). This situation is generally associated with structural motifs that have been seldom incorporated into ligand structures (low $\Sigma n_{ij}$ values in Table 4).

**Analysis of the Structural Descriptors.** The contributions of the different structural descriptors to $\log K_{MnL}$ and pMn provide valuable information that can be used for ligand design. Figure 3 shows the contributions of the different motifs to $\log K_{MnL}$ and pMn. The group with the highest contribution to $\log K_{MnL}$ is the picolinic acid moiety (Pic), which is characterized by a $\Delta \log K$ value of 4.65. The latter value is significantly higher than the sum of the contributions of an acetic acid (C) and a pyridyl group (Py), which amounts to 4.16. Thus, picolinate units are particularly well suited for stable Mn(II) complexation. Other groups characterized by large $\Delta \log K_i$ contributions are methylphosphonic acid (Pho), ethylsulphonamide (Sulph), and 2-methylphenol groups, either unsubstituted at position 4 (Phe) or bearing a methoxy substituent (PheOMe). However, the high basicity of these groups results in improved stability, with a particularly positive effect on $\Delta pMn$, as evidenced by $\Delta \log K_i < \Delta pMn_i$ in the latter case.11

Donor groups with low basicities are generally characterized by $\Delta \log K_i < \Delta pMn_i$ and thus are well suited to increase complex stability at physiological pH. As a result, donor groups such as 2-methylpyridine (Py) and tertiary (A$_{NH2}$) and secondary (A$_{NH}$) acetamides provide contributions to $\Delta pMn$, approaching that of carboxylates (C). The contribution of a picolinate group (4.98) is nearly identical to the sum of acetate (2.64) and pyridine (2.29).

Concerning the effect of structural modifications, the incorporation of propyl groups (Spro) or cyclobutyl (SCybu) groups has a very negative impact in both $\log K$ and $\Delta pMn$, as evidenced by their negative contributions. Replacing ethylene groups of the ligand backbone by phenyl groups has a negative impact in terms of $\log K$, but results in a slight positive contribution to pMn. The incorporation of a pyridyl group into the ligand scaffold results in improved stability, with a particularly positive effect on pMn. This can be attributed to the lower basicity of pyridine with respect to amine N atoms. Examples of ligands that exploit this effect for stable Mn(II) complexation are $H_2PyDTA$ (L8) derivatives and $H_2Py$.
derivatives L38 and L39. Cyclohexyl rings have also a beneficial impact on complex stability when replacing ethyl groups of polyaminopolycarboxylate ligands, an effect exploited in the well-known H$_2$PyC3A ligand (L10), which affords a stable Mn(II) complex with appealing properties as an MRI contrast agent. $^{38,39}$

The terms describing the contributions of macrocyclic and mesocyclic platforms indicate that 15-membered macrocycles provide the largest contribution to both complex stability and $pMn$, followed by 12-membered macrocycles, TACN and AAZTA derivatives. The same trend is observed for both log $K$ and $\Delta pMn$ values. However, one has to consider that these structural motifs contain a different number of donor groups, and thus impose some limitations to the number of additional donor atoms that can be incorporated into the Mn(II) coordination sphere. 15-Membered macrocycles generally favor seven-coordinate complexes, where two additional donor atoms coordinate to the metal ion from different sides of the macrocyclic mean plane. As a result, only one additional donor atom can be incorporated into the ligand scaffold if an inner-sphere water molecule should be present. The TACN unit contains three donor atoms, but Mn(II) complexes based on this platform do not exceed coordination number six, which greatly limits the stability that can be achieved (Figure 2). Thus, 12-membered macrocycles appear to be the best choice among those analyzed here, as they combine rather large $A_{\text{MnL}}$ and $A_{\Delta \text{Mn}}$ contributions and coordination numbers of seven or even eight in the case of cyclen derivatives, as demonstrated here for $[\text{Mn(DOTA)}]^3$.

Figure 4 provides a comparison of the contributions of the different structural descriptors to Mn(II) and Gd(III). $^{10}$

![Figure 4](https://pubs.acs.org/doi/10.1021/acs.inorgchem.2c02364)

**Figure 4.** Comparison of the contributions of the different structural descriptors to the stability constants of Gd(III) and Mn(II) complexes. Data above the dashed line provide more favorable contributions to Mn(II) complex stability than to Gd(III).

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.inorgchem.2c02364.
Ligand protonation constants and stability constants of Mn(II) complexes and crystallographic data (PDF)

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AUTHOR INFORMATION

Corresponding Authors
Aurora Rodríguez-Rodríguez — Centro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química, Facultad de Ciencias, Universidad da Coruña, 15071 A Coruña, Galicia, Spain; orcid.org/0000-0002-4951-4470; Email: aurora.rodriguez@udc.es
Carlos Platas-Iglesias — Centro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química, Facultad de Ciencias, Universidad da Coruña, 15071 A Coruña, Galicia, Spain; orcid.org/0000-0002-6989-9654; Email: carlos.platas.iglesias@udc.es

Authors
Rocio Uzal-Varela — Centro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química, Facultad de Ciencias, Universidad da Coruña, 15071 A Coruña, Galicia, Spain
Francisco Pérez-Fernández — Centro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química, Facultad de Ciencias, Universidad da Coruña, 15071 A Coruña, Galicia, Spain
Laura Valencia — Departamento de Química Inorgánica, Facultad de Ciencias, Universidad de Vigo, 36310 Pontevedra, Spain
Peter Caravan — The Institute for Innovation in Imaging and the A. A. Martins Center for Biomedical Imaging, Massachusetts General Hospital, Harvard Medical School, Charlestown, Massachusetts 02129, United States; orcid.org/0000-0002-3179-6537
David Esteban-Gómez — Centro de Investigaciones Científicas Avanzadas (CICA) and Departamento de Química, Facultad de Ciencias, Universidad da Coruña, 15071 A Coruña, Galicia, Spain; orcid.org/0000-0001-6270-1660

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.inorgchem.2c02364

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Notes
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REFERENCES
(1) Wahnsn, J.; Gale, E. M.; Rodríguez-Rodríguez, A.; Caravan, P. Chemistry of MRI Contrast Agents: Current Challenges and New Frontiers. Chem. Rev. 2019, 119, 957–1057.
(2) Li, H.; Meade, T. J. Molecular Magnetic Resonance Imaging with Gd(III)-Based Contrast Agents: Challenges and Key Advances. J. Am. Chem. Soc. 2019, 141, 17025–17041.
(3) Lux, J.; Sherry, A. D. Advances in Gadolinium-Based MRI Contrast Agent Designs for Monitoring Biological Processes in Vivo. Curr. Opin. Chem. Biol. 2018, 45, 121–130.
(4) Bonnet, C. S.; Töth, E. Molecular Magnetic Resonance Imaging Probes Based on LnIII Complexes. In Advances in Inorganic Chemistry, Elsevier, 2016; Vol. 68, pp 43–96.
(5) Aime, S.; Botta, M.; Terreno, E. Gd(III)-Based Contrast Agents for MRI. In Advances in Inorganic Chemistry, Elsevier, 2005; Vol. 57, pp 173–237.
(6) Tircsó, G.; Molnár, E.; Csupász, T.; Garda, Z.; Botár, R.; Kálmán, F. K.; Kovács, Z.; Brücher, E.; Töth, I. Gadolinium(III)-Based Contrast Agents for Magnetic Resonance Imaging. An Appraisal. In Metal Ions in Bio-Imaging Techniques; Sigel, A.; Freisinger, E.; Sigel, R. K. O., Eds.; De Gruyter, 2021; pp 39–70.
(7) Doan, B.-T.; Meme, S.; Beloivell, J.-C. General Principles of MRI. In The Chemistry of Contrast Agents in Medical Magnetic Resonance Imaging; Merbach, A.; Helm, L.; Töth, É., Eds.; John Wiley & Sons, Ltd.: Chichester, U.K., 2013; pp 1–23.
(8) Helm, L. Relaxivity in Paramagnetic Systems: Theory and Mechanisms. Prog. Nucl. Magn. Reson. Spectrosc. 2006, 49, 45–64.
(9) Luchinat, C. Relaxometry and Paramagnetic Metal Ions in Biological Systems. Magn. Reson. Chem. 1993, 31, S145–S153.
(10) Rogosnitzky, M.; Branch, S. Gadolinium-Based Contrast Agent Toxicity: A Review of Known and Proposed Mechanisms. BioMetals 2016, 29, 365–376.
(11) Le Fur, M.; Caravan, P. The Biological Fate of Gadolinium-Based MRI Contrast Agents: A Call to Action for Bioinorganic Chemists. Metallomics 2019, 11, 240–254.
(12) Botta, M.; Carniato, F.; Esteban-Gómez, D.; Platas-Iglesias, C.; Tei, L. Mn(II) Compounds as an Alternative to Gd-Based MRI Probes. Future Med. Chem. 2019, 11, 1461–1483.
(13) Lauffer, R. B. Paramagnetic Metal Complexes as Water Proton Relaxation Agents for NMR Imaging: Theory and Design. Chem. Rev. 1987, 87, 901–927.
(14) Koenig, S. H.; Brown, R. D.; Goldstein, E. J.; Burnett, K. R.; Wolf, G. L. Magnetic Field Dependence of Proton Relaxation Rates in Tissue with Added Mn2+; Rabbit Liver and Kidney. Magn. Reson. Med. 1985, 2, 159–168.
(15) Rocklage, S. M.; Cacheris, W. P.; Quay, S. C.; Hahn, F. E.; Raymond, K. N. Manganese(II) N,N’-Dipyridoxylethylenediamine-N,N’-Diacetate 5,5’-Bis(Phosphat). Synthesis and Characterization of a Paramagnetic Chelate for Magnetic Resonance Imaging Enhancement. Inorg. Chem. 1989, 28, 477–485.
(16) Chung, J.-J.; Kim, M.-J.; Kim, K. W. Mangafodipir Trisodium-Enhanced MRI for the Detection and Characterization of Focal Hepatic Lesions: Is Delayed Imaging Useful? J. Magn. Reson. Imaging 2006, 23, 706–711.
(17) Regge, D.; Cirillo, S.; Macera, A.; Galatola, G. Mangafodipir Trisodium: Review of Its Use as an Injectable Contrast Medium for Magnetic Resonance Imaging. *Rep. Med. Imaging 2009*, 2, 55–68.

(18) Cloyd, R. A.; Koren, S. A.; Abisambra, J. F. Manganese-Enhanced Magnetic Resonance Imaging: Overview and Central Nervous System Applications With a Focus on Neurodegeneration. *Front. Aging Neurosci.* 2018, 10, No. 403.

(19) Pan, D.; Caruthers, S. D.; Senpan, A.; Schmieder, A. H.; Wickline, S. A.; Lanza, G. M. Revisiting an Old Friend: Manganese-Based MRI Contrast Agents. *Wiley Interdiscip. Rev.: Nanomed. Nanobiotechnol.* 2011, 3, 162–173.

(20) Gale, E. M.; Atanasova, I. P.; Blasi, F.; Ay, I.; Caravan, P. A Manganese Alternative to Gadolinium for MRI Contrast. *J. Am. Chem. Soc.* 2015, 137, 15548–15557.

(21) Forgacs, A.; Pujales-Paradela, R.; Regueiro-Figueroa, M.; Valencia, L.; Esteban-Gómez, D.; Botta, M.; Platas-Iglesias, C. Developing the Family of Picolinate Ligands for Mn^{2+} Complexation. *Dalton Trans.* 2017, 46, 15456–15558.

(22) Regueiro-Figueroa, M.; Rolla, G. A.; Esteban-Gómez, D.; de Blas, A.; Rodríguez-Blas, T.; Botta, M.; Platas-Iglesias, C. High Relaxivity Mn^{2+}-Based MRI Contrast Agents. *Chem.—Eur. J.* 2014, 20, 17300–17305.

(23) Loving, G. S.; Mukherjee, S.; Caravan, P. Redox-Activated Manganese-Based MR Contrast Agent. *J. Am. Chem. Soc.* 2013, 135, 4620–4623.

(24) Khanmam, M.; Weyhermüller, T.; Goswami, U.; Mukherjee, C. A Highly Stable α-Alanine-Based Mono(Aquated) Mn(II) Complex as a T₁-Weighted MRI Contrast Agent. *Dalton Trans.* 2017, 46, 10426–10432.

(25) Phukan, B.; Mukherjee, C.; Goswami, U.; Sarmah, A.; Mukherjee, S.; Safari, S. K.; Moi, S. C. A New Bis(Aquated) High Relaxivity Mn(II) Complex as an Alternative to Gd(III)-Based MRI Contrast Agent. *Inorg. Chem.* 2018, 57, 2631–2638.

(26) Drahoš, B.; Kotej, J.; Cisarová, I.; Hermann, P.; Helm, L.; Lukeš, I.; Tóth, E. Mn^{2+} Complexes with 12-Membered Pyridine Based Macrocycles Bearing Carboxyloxy or Phosphonate Pendant Arm: Crystallographic, Thermodynamic, Kinetic, Redox, and 1H/17O Relaxation Studies. *Inorg. Chem.* 2011, 50, 12785–12801.

(27) Ndiaye, D.; Sy, M.; Pallier, A.; Même, S.; Silva, I.; Lacerda, S.; Nonat, A. M.; Charbonnière, L. J.; Tóth, É. Unexpected Interactions of a Mn^{2+}-Bispyridine Chelate: A Novel Structural Entry for Mn^{2+} -Based Imaging Agents. *Angew. Chem., Int. Ed.* 2020, 59, 11958–11963.

(28) Gale, E. M.; Caravan, P. Gadolinium-Free Contrast Agents for Magnetic Resonance Imaging of the Central Nervous System. *ACS Chem. Neurosci.* 2018, 9, 395–397.

(29) Anbu, S.; Hoffmann, S. H. L.; Carniato, F.; Kenning, L.; Price, T. W.; Prior, T. J.; Botta, M.; Martins, A. F.; Stasiuk, G. J. A Single-Pot Template Reaction Towards a Manganese-Based T₁ Contrast Agent. *Angew. Chem., Int. Ed.* 2021, 60, 10736–10744.

(30) Uzal-Varela, R.; Valencia, L.; Lalli, D.; Maneiro, M.; Esteban-Gómez, D.; Platas-Iglesias, C.; Botta, M.; Rodríguez-Rodríguez, A. Understanding the Effect of the Electron Spin Relaxation on the Relaxivities of Mn(II) Complexes with Triaazacyclononane Derivatives. *Inorg. Chem.* 2021, 60, 15055–15068.

(31) de Sá, A.; Bonnet, C. S.; Geraldes, C. F. G. C.; Tóth, É.; Ferreira, P. M. T.; André, J. P. Thermodynamic Stability and Relaxation Studies of Small, Triaza-Macrocyclic Mn(II) Chelates. *Dalton Trans.* 2013, 42, 4522.

(32) Balogh, E.; He, Z.; Hsieh, W.; Liu, S.; Tóth, E. Dinuclear Complexes Formed with the Triaazacyclononane Derivative ENOTA*: High-Pressure 17O NMR Evidence of an Associative Water Exchange on [Mn^{2+}(ENOTA)H₂O]. *Inorg. Chem.* 2007, 46, 238–250.

(33) Casanova, D.; Llunell, M.; Alemany, P.; Alvarez, S. Rich Stereochemistry of Eight-Vertex Polyhedra: A Continuous Shape Measures Study. *Chem.—Eur. J.* 2005, 11, 1479–1494.

(34) Dube, K. S.; Harrop, T. C. Structure and Properties of an Eight-Coordinate Mn(II) Complex That Demonstrates a High Water Relaxivity. *Dalton Trans.* 2011, 40, 7496.

(35) Cieslik, P.; Comba, P.; Dittram, B.; Ndiaye, D.; Tóth, É.; Velmurugan, G.; Wadepohl, H. Exceptional Manganese(II) Stability and Manganese(II)/Zinc(II) Selectivity with Rigid Polyanion Ligands**. *Angew. Chem., Int. Ed.* 2022, 61, No. e202115580.

(36) Bu, X.-H.; Chen, W.; Mu, L.-J.; Zhang, Z.-H.; Zhang, R.-H.; Clifford, T. Syntheses, Crystal Structures and Properties of New Manganese(II) Complexes with Macrocyclic Polyanime Ligands Bearing Pyridyl Donor Pendants. *Polyhedron* 2000, 19, 2095–2100.

(37) Wang, S.; Westmoreland, T. D. Correlation of Relaxivity with Coordination Number in Six-, Seven-, and Eight-Coordinate Mn(II)
Complexes of Pendant-Arm Cyclen Derivatives. Inorg. Chem. 2009, 48, 719–727.

(51) Rolla, G. A.; Platas-Iglesias, C.; Botta, M.; Tei, L.; Helm, L. \(^{1}H\) and \(^{2}H\) O NMR Relaxometric and Computational Study on Macrocyclic Ln(II) Complexes. Inorg. Chem. 2013, 52, 3268–3279.

(52) Bianchi, A.; Calabi, L.; Giorgi, C.; Losi, P.; Mariani, P.; Palano, D.; Paoli, P.; Rossi, P.; Valtancoli, B. Thermodynamic and Structural Aspects of Manganese(II) Complexes with Polyaminopolycarboxylic Ligands Based upon \(1,4,7,10\)-Tetraazacyclododecanecyclen (Cyclen). Crystal Structure of Dimeric [MnL\(_2\):2CH\(_2\)OH Containing the New Ligand 1,4,7,10-Tetraazacyclododecanecyclen-1,4-Diaceatate. J. Chem. Soc., Dalton Trans. 2001, 917–922.

(53) Corzilius, B.; Smith, A. A.; Barnes, A. B.; Luchinin, C.; Bertini, L.; Griffin, R. G. High-Field Dynamic Nuclear Polarization with High-\(\chi\) Transition Metal Ions. J. Am. Chem. Soc. 2011, 133, 5648–5651.

(54) Akhmetzhanov, D.; Ching, H. Y. V.; Denysenko, V.; Demay-Drouhard, P.; Bertrand, H. C.; Tabares, L. C.; Policar, C.; Prisner, T. F.; Un, S. R. SIRDME Spectroscopy on High-Spin Mn\(^{2+}\) Centers. Phys. Chem. Chem. Phys. 2016, 18, 30857–30866.

(55) Gao, J.; Ye, K.; He, M.; Xiong, W.-W.; Cao, W.; Lee, Z. Y.; Wang, Y.; Wu, T.; Huo, F.; Liu, X.; Zhang, Q. Tuning Metal–Carboxylic Coordination in Crystalline Metal–Organic Frameworks through Surfactant Media. J. Solid State Chem. 2013, 206, 27–31.

(56) Cotton, F. A.; Daniels, L. M.; Murillo, C. A.; Quesada, J. F. Exchange Dynamics. Complexes: Aqua Species, Chirality, Excited-State Chemistry, and Higher Kinetic Inertness. Inorg. Chem. 1997, 36, 2059–2068.

(57) Parker, D.; Dickins, R. S.; Pushmann, H.; Crossland, C.; Howard, J. A. K. Being Excited by Lanthanide Coordination Complexes: Aqua Species, Chirality, Excited-State Chemistry, and Exchange Dynamics. Chem. Rev. 2002, 102, 1977.

(58) Platas-Iglesias, C. The Solution Structure and Dynamics of MRI Probes Based on Lanthane(III) DOTA as Investigated by DFT and NMR Spectroscopy. Eur. J. Inorg. Chem. 2012, 2012, 2023–2033.

(59) Kálmán, F. K.; Tóth, É.; Ortuño, R. M. Stability, Relaxometric and Computational Studies on Mn\(^{2+}\) Complexes with Ligands Containing a Cyclobutane Scaffold. Dalton Trans. 2021, 50, 1076–1085.

(60) Uzal-Varela, R.; Lalli, D.; Brandariz, I.; Rodríguez-Rodríguez, A.; Platas-Iglesias, C.; Botta, M.; Esteban-Gómez, D. Rigid Versions of PDTA Incorporating a 1,3-Diaminocyclobutyl Spacer for Mn\(^{2+}\) Complexation: Stability, Water Exchange Dynamics and Relaxivity. Dalton Trans. 2021, 50, 16290–16303.

(61) Laine, S.; Bonnet, C. S.; Kálmán, F. K.; Garda, Z.; Pallier, A.; Caille, F.; Suzenet, F.; Tircsó, G.; Tóth, É. Mn\(^{2+}\) Complexes of Open-Chain Ligands with a Pyridine Backbone: Less Donor Atoms Lead to Higher Kinetic Inertness. New J. Chem. 2018, 42, 8012–8020.

(62) Anderegg, G. Critical Survey of Stability Constants of NTA Complexes. Pure Appl. Chem. 1982, 54, 2693–2758.

(63) Arancibia, A.; Rodríguez-Rodríguez, A.; Martínez-Calvo, M.; Carniato, F.; Lalli, D.; Esteban-Gómez, D.; Brandariz, I.; Pérez-Lourido, P.; Botta, M.; Platas-Iglesias, C. Mn\(^{2+}\) Complexes Containing Sulfonamide Groups with PH-Responsive Relaxivity. Inorg. Chem. 2020, 59, 14306–14317.

(64) Sawada, K.; Duan, W.; Ono, M.; Satoh, K. Stability and Structure of Nitrilo(Acetate–Methylphosphonate) Complexes of the Alkaline-Earth and Divalent Transition Metal Ions in Aqueous Solution. J. Chem. Soc., Dalton Trans. 2000, 919–924.

(65) Garda, Z.; Forgács, A.; Do, Q. N.; Kálmán, F. K.; Timár, S.; Baranyai, Z.; Tei, L.; Tóth, I.; Kovács, Z.; Tircsó, G. Physico-Chemical Properties of Mn\(^{2+}\) Complexes Formed with cis- and trans-DO3A: Thermodynamic, Electrochemical and Kinetic Studies. J. Inorg. Biochem. 2016, 163, 206–213.

(66) Garda, Z.; Molnár, E.; Kálmán, F. K.; Botár, R.; Nagy, V.; Baranyai, Z.; Briecher, E.; Kovács, Z.; Tóth, I.; Tircsó, G. Effect of the Nature of Donor Atoms on the Thermodynamic, Kinetic and Relaxation Properties of Mn(II) Complexes Formed With Some Trisubstituted 12-Membered Macroyclic Ligands. Front. Chem. 2018, 6, No. 232.

(67) Bárta, J.; Hermann, P.; Kotej, J. Coordination Behavior of 1,4-Disubstituted Cyclen Endowed with Phosphonate, Phosphonate Monooethylster, and H-Phosphonate Pendant Arms. Molecules 2019, 24, No. 3324.

(68) Molnár, E.; Camus, N.; Patinec, V.; Rolla, G. A.; Botta, M.; Tircsó, G.; Kálmán, F. K.; Fodor, T.; Tripier, R.; Platas-Iglesias, C. Picolinate-Containing Macroyclic Mn\(^{2+}\) Complexes as Potential MRI Contrast Agents. Inorg. Chem. 2014, 53, 5136–5149.
Based MRI Agents Derived from NO2A Complexes of NOTA and Complexes of 1-Oxa-4,7,10,13-Tetraazacyclopentadecane and Properties of Its Pendant Arms.

Dissociation Kinetics of Mn(II) Complexes of NOTA and DOTA. Dalton Trans. 2011, 40, 10131.

Pujales-Paradal, R.; Carniato, F.; Esteban-Gómez, D.; Bottà, M.; Platas-Iglesias, C. Controlling Water Exchange Rates in Potential Mn(II) Complexes: Oxa-Aza Macrocycles Make the Difference. Molecules 2021, 26, No. 1524.

Drahoš, B.; Pniok, M.; Hlavíčková, J.; Kotek, J.; Císařová, I.; Hermann, P.; Lukeš, I.; Tóth, E. Dissociation Kinetics of Mn(II) Complexes of NOTA and DOTA. Dalton Trans. 2011, 40, 1945.

Cabral, M. F.; Delgado, R. 4,7,10,13-Tetraazacyclopentadecane and Properties of Its Metal Complexes. Polyhedron 1999, 18, 3479–3489.

Tei, L.; Gugliotta, G.; Fekete, M.; Kálmán, F. K.; Tóth, E.; Tóth, I.; Tircsó, G. Expanding the Ligand Classes Used for Mn(II) Complexation: Oxa-Aza Macrocycles Make the Difference. Molecules 2021, 26, No. 1524.

Drahoš, B.; Kubiček, V.; Bonnet, C. S.; Hermann, P.; Lukeš, I.; Tóth, E. Dissociation Kinetics of Mn(II) Complexes of NOTA and DOTA. Dalton Trans. 2011, 40, 10131.

Pujales-Paradal, R.; Carniato, F.; Esteban-Gómez, D.; Bottà, M.; Platas-Iglesias, C. Controlling Water Exchange Rates in Potential Mn(II) Complexes Based MRI Agents Derived from NO2A. Dalton Trans. 2019, 48, 3962–3972.

Chaves, S.; Delgado, R.; Da Silva, J. J. R. F. The Stability of the Metal Complexes of Cyclic Teta-Aza-Tetra-Acetic Acids. Talanta 1992, 39, 249–254.

Anderegg, G. Pyridinderivate als Komplexbildner I. Pyridincarbosäuren. Helv. Chim. Acta 1960, 43, 414–424.

Gale, E. M.; Mukherjee, S.; Liu, C.; Loving, G. S.; Caravan, P. Structure–Redox–Relaxivity Relationships for Redox Responsive Manganese-Based Magnetic Resonance Imaging Probes. Inorg. Chem. 2014, 53, 10748–10761.

Föröcs, A.; Tei, L.; Baranyai, Z.; Esteban-Gómez, D.; Platas-Iglesias, C.; Bottà, M. Optimising the Relaxivities of Mn(II) Complexes by Targeting Human Serum Albumin (HSA). Dalton Trans. 2017, 46, 8490–8504.

Föröcs, A.; Tei, L.; Baranyai, Z.; Tóth, I.; Zékány, L.; Bottà, M. A Bisamide Derivative of [Mn(II)-DO3A] - Solution Thermodynamic, Kinetic, and NMR Relaxometric Studies. Eur. J. Inorg. Chem. 2016, 2016, 1165–1174.

Mohár, E.; Váradi, B.; Garda, Z.; Botár, R.; Kálmán, F. K.; Tóth, É.; Platas-Iglesias, C.; Tóth, I.; Brücher, E.; Tircsó, G. Remarkable Differences and Similarities between the Isomeric Mn(II)-cis- and Trans-1,2-Diaminocyclohexane-N,N,N’,N’-Tetraacetate Complexes. Inorg. Chim. Acta 2018, 472, 254–263.

Su, H.; Wu, C.; Zhu, J.; Miao, T.; Wang, D.; Xia, C.; Zhao, X.; Gong, Q.; Song, B.; Ai, H. Rigid Mn(II) Chelate as Efficient MRI Contrast Agent for Vascular Imaging. Dalton Trans. 2012, 41, 14480.