Diastereoselective synthesis of substituted macrocyclic complexes from achiral starting materials

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Abstract

Substituted derivatives of the DOTA framework are of general interest to alter chelate properties and facilitate conjugation of chelates to other molecular structures. However, the scope of substituents that can be introduced into the α-position has traditionally been limited by the availability of a suitable enantiopure starting materials to facilitate a stereoselective synthesis. Tetra-substituted DOTA derivatives with phenyl and benzoate substituents in the α-position were prepared. Initial syntheses used enantiopure starting materials but did not afford enantiopure products. This indicates that integrity of the stereocentres was not preserved during synthesis, despite the homo-chiral diastereoisomer being the major reaction product. The homochiral diastereoisomer could be produced as the major or sole reaction product when starting from racemic or even achiral materials. Stereochemical resolution was found to occur during chelation through formation of an enolate stabilized by the aryl substituent. This general ability of aryl groups to enable stereoisomeric resolution greatly increases the range of substituents that can be introduced into DOTA-type ligands with diastereochemical selectivity.

Introduction

Since its introduction in the late 1970s[1] the DOTA ligand framework has proven itself especially useful in a range of biomedical applications such as fluorescent probes,[2–5] MRI contrast agents,[6–13] shift reagents[14–16] and radionuclide tracers.[17–19] Many derivatization strategies have been developed to tailor the properties of this ligand system for specific applications and metal ions.[20,21] Given the extensive array of DOTA-derivatives that have been reported to date, it is somewhat surprising how few of those are tetra α-substituted derivatives (Figure 1). One possible reason for the sparsity of α-substituted DOTA derivatives is the additional complication of the stereogenic centre generated by introducing a substituent on each pendant arm. In this context these derivatives may be divided into two broad groups. The first group comprises DOTMA and DOTAZA: chelates that are obtained as single enantiomers following a stereochemically controlled synthesis from enantiopure starting materials.[22–27] The second group, made up of DOTCEA, DOTCPA and DOTA(BOM)$_4$, are prepared from racemic starting materials and a distribution of racemic diastereoisomeric chelates is obtained.[28–31] The diastereoisomeric chelates thus obtained are commonly studied as a mixture, but in the case of DOTCEA, were resolved prior to study demonstrating that the four stereoisomers have different properties and stabilities.[30,31] Notably all of the α-substituents in Figure 1 include relatively sterically unhindered sp^3 carbons at the point of attachment.

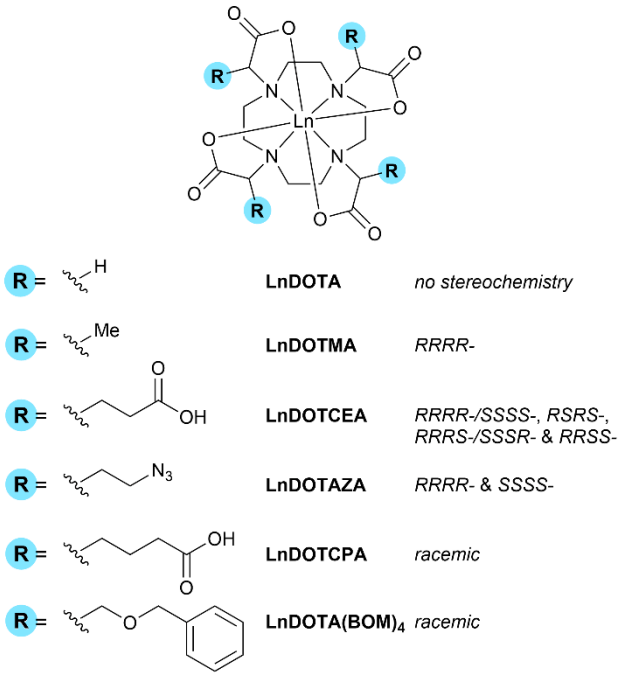


Figure 1. A summary of the tetra-α-substituted derivatives of DOTA (1,4,7,10-tetraazacyclodocane-1,4,7,10-tetraacetate) reported to date and the stereochemistries of the chelates studied. This list includes only chelates of tetraacetate derivatives; α-substituted derivatives of related ligands such as phosphonates or amides have not been included.

When fewer than four substitutions are made, a somewhat wider range of groups have been introduced into the α-position of the DOTA framework. Often this is for reasons of synthetic viability or solubility of the resulting chelate. But in many cases just one α-substituent is introduced as a means of facilitating further functionalization of the chelate. Mostly these substituents also possess relatively sterically unhindered sp^3 carbons at the point of attachment.

The effects of stereochemistry can be more complicated when fewer than four substituents are present. When only one substituent is present the effect of stereochemistry will generally not be evident: the configuration of the stereocentre defines the helicity of the pendant arms (*R*- → Λ, *S*- → Δ) and a single diastereoisomer is observed with the same outward appearance as a mixture of enantiomers.[32] However, if the substituent is small (*i.e.* methyl) a single substituent may possess insufficient bulk to define arm helicity and a mixture of stereoisomers can result (major isomers *R*-/Λ & *S*-/Δ and minor isomers *R*-/Δ & *S*-/Λ).[33] In instances where two or more substituents or mixed substituents are present – the effects of

stereochemistry have either not been discussed or all substituents are introduced enantioselectively.

The range of substituents that have been introduced into the α-position on fewer than four arms is shown in Figure 1.[32–40] Four substituents stand out as different from the others: the four aryl substituents. The two nitro-substituted aromatic groups – each of these is introduced singly onto the DOTA framework and the effects of stereochemistry are subsequently only apparent to techniques that probe enantiopurity.[32] In the case of the two polyphenyl substituents the stereochemistry was not explored.[38] It is curious that the carboxyethylene substituent is reported to have been introduced both with and without attention to stereochemistry[31,41–43] and this particular substituent can present challenges when introducing α-substituents into these types of ligand. Overall, the literature presents a situation in which, if stereochemistry is not controlled at the outset of synthesis, then a mixture of stereoisomers will result. This implies that α-substitution efforts are constrained to those groups for which a suitable enantiopure starting material can be sourced.

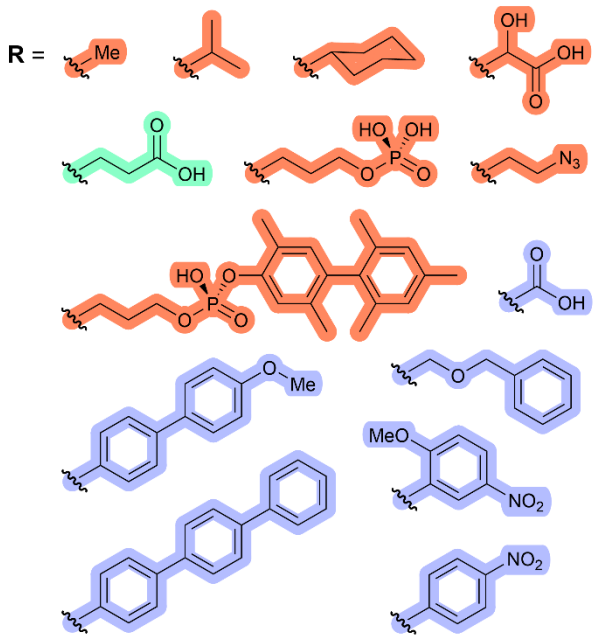


Figure 2. Substituents that have been incorporated into the α-position of fewer than four pendant arms of the DOTA frameworks. Those groups highlighted in orange are reported to have been introduced with stereochemical specificity. Those highlighted in lavender are either introduced in a non-stereoselective manner or stereochemical considerations are not discussed.

The ethyl carboxylate (highlighted in green) has reportedly been introduced both with and without regard to the resulting stereochemistry.

Results and Discussion

Tetraalkyl-α-substituted DOTA derivatives

The preparation of DOTMA is reported by various enantioselective syntheses starting from commercially available enantiopure *S*-hydroxy- or *S*-halo- propionates.[22–24] Thus, by convention, the acronym DOTMA refers to the *RRRR*- enantiomer.[24] The stereospecificity of each synthetic approach to DOTMA has not been tested – some purification steps (especially crystallization) may remove traces of unwanted diastereoisomers. Nonetheless, diastereoisomerically pure chelates can be readily obtained. To establish a baseline for diastereoisomeric distribution in α-substituted DOTA derivatives we prepared a sample of ±DOTMA using racemic 2-bromo propionic acid (ESI, Scheme S1). Carboxylates were protected as t-butyl esters and although the tetra-t-butyl protected ligand was subjected to column purification, this technique was not thought to have inadvertently removed of one or more diastereoisomer from the mixture. The t-butyl esters were removed in trifluoroacetic acid and Eu^{3+} introduced under standard conditions (60 ºC, pH 5.5). The NMR spectrum of ±EuDOTMA is shown (Figure 3) and each diasteroisomer identified by its symmetry and the observed SAP/TSAP ratio – comparing with EuDOTCEA.[30] (SAP = square antiprism, TSAP = twisted square antiprism.) The amount of each isomer present was determined by a line fitting analysis using the NUTS software package from Acorn NMR.[44]

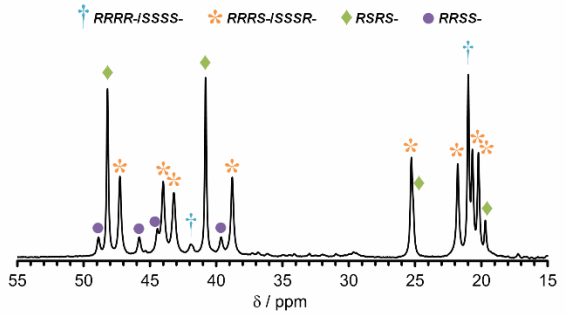


Figure 3. ^{1}H NMR spectrum, focused on the most highly shifted *ax*^{s} resonances, of ±EuDOTMA recorded at 600 MHz in D_2O at pD 6.

Table 1. A comparison of the statistical and observed diastereoisomeric distributions in ±EuDOTMA.

Isomer	Isomer Distribution		Variance
	Statistical	±EuDOTMA	
RRRR-/SSSS-	12.5%	12.8%	+0.3%
RRRS-/SSSR-	50.0%	51.3%	+1.3%
RSRS-	12.5%	29.5%	+17.0%
RRSS-	25.0%	6.4%	-18.6%

Comparing the distribution of diastereoisomers observed experimentally for ±EuDOTMA with that predicted statistically (Table 1) reveals that the *RRSS*- isomer is produced in significantly lower quantities than expected. This difference is almost entirely accounted for by over-production of the *RSRS*- isomer which is present in more than twice the amount predicted. This result is far from intuitive if the substitution sequences that lead to each of isomer are considered (Figure 4). Of the four substitution sequences that afford the *RRSS*- isomer only one is in competition with the *RSRS*- isomer the other three are in competition with the *RRRS-/SSSR*- isomer. But only a small increase in the amount of *RRRS-/SSSR*- isomer is observed.

Since each alkylation reaction is functionally irreversible the isomeric distribution is controlled by kinetic factors; each substitution sequence is presumably associated with its own individual series of energy barriers. The observed isomeric distribution is simply an aggregate of the effects of these energy barriers. Nonetheless, it is possible to conclude that the overall energy barriers to each isomer follow the trend: *RSRS*- < *RRRR-/SSSS*- < *RRRS/SSSR*- << *RRSS*-. Additionally, it is notable that the observed distribution appears to point to a non-negligible contribution from sequences that follow from *cis*- substitution. It is generally assumed that in the second alkylation reaction that *trans*- substitution is more favourable than *cis*-. However, from inspection of Figure 4 it is evident that an over-production of *RSRS*- that arises primarily through a sequence involving *trans-R,R*- would concomitantly decrease the production of *RRRR*-. But this is not observed. The sequences involving *cis*- substitution must play a significant role in the distribution of isomers.

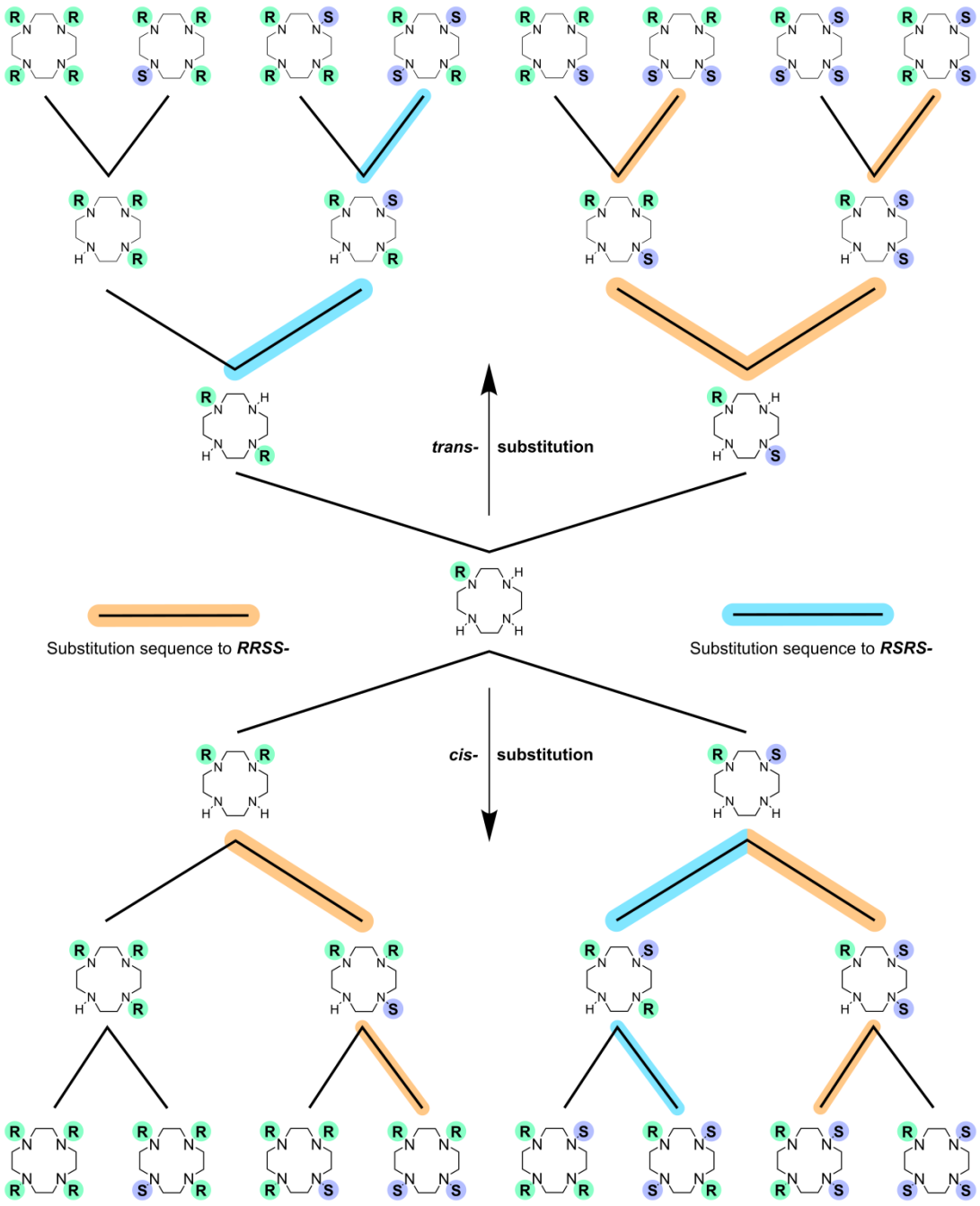
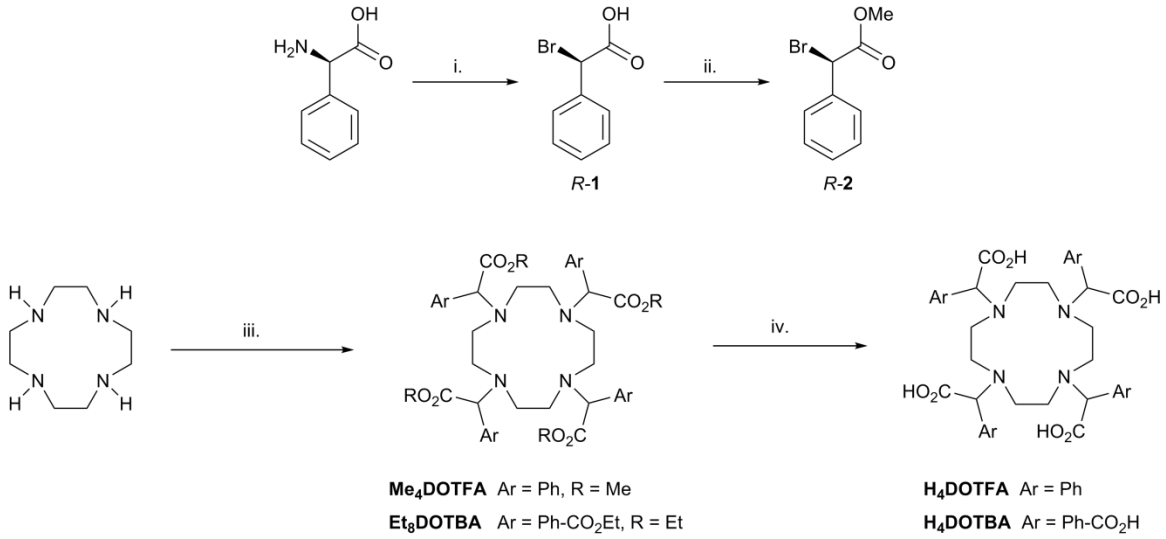


Figure 4. All possible sequences of substitution in a racemic synthesis of a tetra-α-substituted DOTA derivative after the first alkylation step has afforded an *R*- configuration. In addition, the mirror image of these pathways exists for when the first alkylation yields an *S*- configuration. Substitutions resulting in an *R*- configuration are shown proceeding to the left, those resulting in an *S*- configuration are shown proceeding to the right. Although this affords a total of 32 possible pathways only the 16 shown here are unique.

The ligands DOTFA and DOTBA (Scheme 1) were identified as targets of interest in a research program studying water exchange in substituted GdDOTA-type chelates (Scheme 1).[45–48] On the basis that stereochemistry must be controlled in the α-positions to avoid a mixture of diastereoisomeric chelates the synthesis of DOTFA was envisioned starting from commercially available *R*-phenyl glycine. The chiral α-amino acid was converted to the corresponding bromide *R*-**1** with complete retention of stereochemistry by diazotization of the amine with nitrous acid in the presence of potassium bromide (Scheme 1).[49] Fisher esterification of *R*-**1** in methanol afforded the suitably protected enantio-pure alkylating agent *R*-**2** (ESI, Figure S2). *R*-**2** was used to tetra-alkylate cyclen in acetonitrile with caesium carbonate at 60 ºC. To permit the evaluation of the stereochemical selectivity of this synthesis the esters were removed by saponification without performing extensive purification. The rare earth chelates of DOTFA was prepared in aqueous solution at pH 5.5 at 70 ºC from the corresponding chloride or from oxide without adjustment of the pH.



Scheme 1. The synthetic route for the preparation of an enantiomerically pure alkylating agent to introduce phenyl groups into the α-position of DOTA (top). A general synthetic route for the preparation of DOTFA and DOTBA (bottom). *Reagents and conditions*: i. $NaNO_2$/HBr/KBr; ii. MeOH/H_2SO_4; iii. *R*-**2**, ±**2** or **4**/Cs_2CO_3/MeCN/60 °C; iv. KOH followed by HCl (pH 3).

Purification of EuDOTFA was undertaken by RP-HPLC on a C18 column, the chromatogram of which is shown in Figure 5. The synthesis was found to produce one primary

product (> 90 %), consistent with the strategy of controlling stereochemistry at each α-centre. Two smaller peaks with only slightly shorter retention times were observed in the HPLC trace. After separation by RP-HPLC chromatography each peak was analyzed by ^{1}H NMR (Figure 5). The major reaction product (peak 3) exhibits C_4-symmetry and was thus assigned to the expected *SSSS*- isomer. Peak 1 is found to possess C_2-symmetry and was assigned as the *RSRS*- isomer, peak 2 exhibits no symmetry and, based on the isomeric distribution observed for ±EuDOTMA, was assigned to the *SSSR*- isomer. The alkylating agent *R*-**2** was confirmed to be enantiopure (ESI, Figure S2) and so the production of unintended diastereoisomers would seem to be the result of a small degree of racemization during the alkylation reaction.

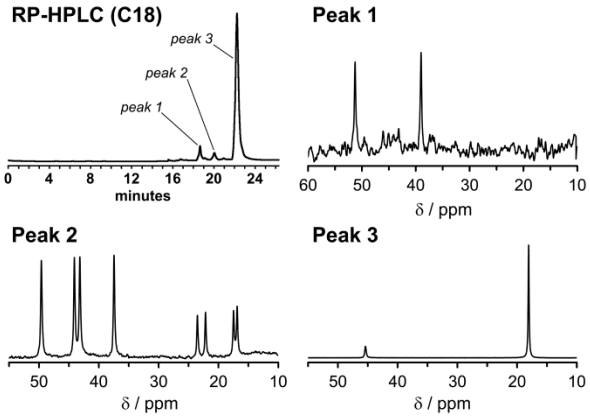
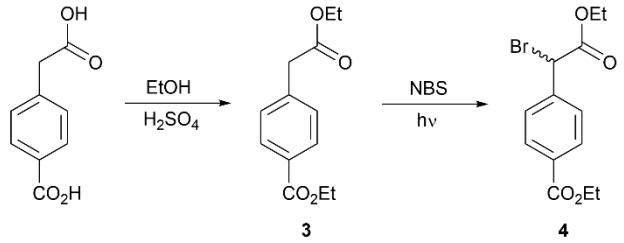


Figure 5. An analysis of the chelates produced in the synthesis of EuDOTFA. Top left: the chromatogram from the RP-HPLC separation of crude EuDOTFA (C18 column, λ – 254 nm). Top right: the ^{1}H NMR spectrum (focused on the most shifted *ax*^{S} protons) of the first peak to elute, which appears to be the *RSRS*- isomer. Bottom left: the ^{1}H NMR spectrum (focused on the most shifted *ax*^{S} protons) of the second peak to elute, which appears to be the *RRRS-/SSSR*- isomer. Bottom right: the ^{1}H NMR spectrum (focused on the most shifted *ax*^{S} protons) of the third peak to elute, which is the *RRRR-/SSSS*- isomer. NMR spectra were recorded at 400 MHz in D_2O. The SAP/TSAP ratio for isomers of EuDOTFA notably different for those found for EuDOTCEA.

The synthesis of DOTFA chelates employed enantio-pure starting materials in procedures comparable to those used to obtain single enantiomers of other similar chelates.[23,24,26,27] It was somewhat surprising therefore that these chelates exhibited effectively no rotation of plane polarized light (GdDOTFA: α_D^{296} = +0.01 (water)). If racemization had occurred during the

reaction, then a mixture of stereoisomers, comparable to that found in Table 1, would be expected. But the HPLC and NMR analyses unambiguously demonstrate that the *RRRR-/SSSS*-diastereoisomer is the predominant reaction product. The only reasonable explanation for these seemingly contradictory observations is that the ligand H_4DOTFA is prepared as a single enantiomer (*SSSS*-). But during chelation, inversion of the α-chiral centre occurs easily. This will initially scramble the configuration of stereocentres, but if inversion is fast enough then eventually the mixture of stereoisomers resolves down to the thermodynamically most stable. The formation of an enol or enolate at the α-carbon has been demonstrated under either acidic (DOTCEA)[31] or basic (DOTA)[50] conditions for certain chelates. Notably methyl substituted chelates do not appear to enolize.[51] DOTFA is distinguished from other tetra-α-substituted chelates by its aryl substituents, which can potentially stabilize an enolate intermediate. During the subsequent reprotonation step bulky α-substituents will tend to drive the orientation of the pendant arms into the lowest energy diastereoisomer: *RRRR-/SSSS*-. Because this is a thermodynamically driven process the preferred isomer is not expected to be the same as that in the study of ±EuDOTMA (above).



Scheme 2. The preparation of a racemic aryl substituted alkylating agent from an achiral source for the preparation and DOTBA.

To test this hypothesis the ligands of DOTFA and DOTBA were prepared in racemic form. A suitable alkylating agent to produce DOTBA was prepared from an achiral source. 4-(Carboxymethyl) benzoic acid was protected as a diethyl ester also by Fisher esterification to afford **3** (Scheme 2). The benzylic carbon was then brominated with *N*BS in MeCN at 60 ºC with constant irradiation at 365 nm – 395 nm to afford ±**4** after column chromatography. Cyclen was then exhaustively alkylated using either ±**2** or ±**4** in acetonitrile with caesium carbonate at 60 ºC (Scheme 1). Care was taken in any purification steps to not inadvertently remove any

diastereoisomer from the mixture – the presence of multiple isomeric chelates in the preparation of DOTBA was evidenced in the carbonyl region of the ^{13}C NMR spectrum (ESI, Figure S3). Esters were removed by saponification and the Eu^{3+} and Gd^{3+} chelates prepared from the chloride salts. It is worthy of comment that although chelation of DOTFA was found to occur in the pH range commonly employed in this type of reaction (pH 5 – 6), chelation with DOTBA in this range was unsuccessful and only when a pH ≥ 12 was employed with heating could the metal ion be introduced into the ligand. NMR analysis of each reaction reveals that in each case the *RRRR-/SSSS-* isomer is the predominant reaction product (Figure 6). Non-negligible amounts of other isomers were produced in the case of EuDOTFA produced from ±**2**, the distribution of isomers being comparable to that produced by using *R*-**2**. In contrast, only trace quantities of other diastereoisomeric chelates may be discerned in the baseline of the spectrum of EuDOTBA. Appreciable quantities of another chelate can be observed in the up-field region of the spectrum although this does not correspond to a fully formed DOTA-type chelate. This chelate is attributed to residual Type I intermediate (see below).[52]

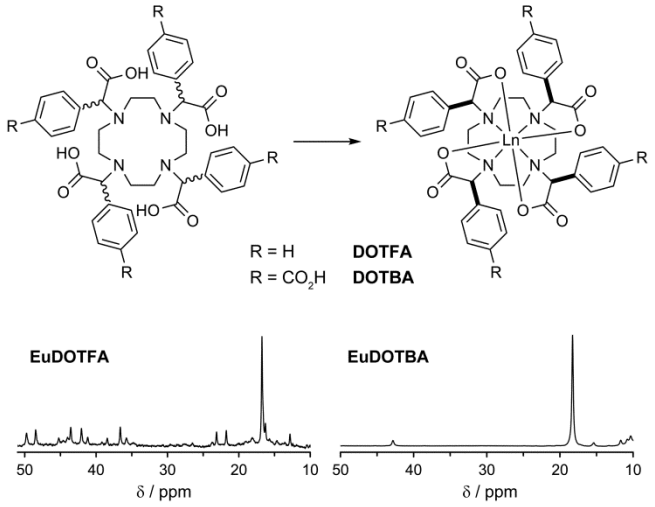


Figure 6. A racemic α-aryl substituted DOTA ligand resolves into a single predominant, C_4-symmetric (*RRRR-/SSSS-*) diastereoisomeric chelate upon instruction of a rare earth metal ion. This is seen in the ^1H NMR spectra (focused on the most shifted ax^S region of the spectrum) of samples of EuDOTFA (left) and EuDOTBA (right) both prepared from ligand samples that contained a mixture of diastereoisomers. This occurs even under the mild conditions used for chelating DOTFA and DOTMA, but at the high pHs used in the chelation with DOTBA the resolution is almost complete.

The observed distributions of isomers in these aryl-substituted chelate are important; they demonstrate that a single diastereoisomeric LnDOTA-type chelate can be prepared from an achiral starting material. This greatly expands the scope of the substituents that can be introduced into the α-position of DOTA-type chelates.

Mechanism of Stereochemical Resolution

It is comparatively easy to appreciate why *RRRR-/SSSS-* would be the most thermodynamically stable isomer. It is also easy to see how racemization at the α-carbon would lead to the conversion of the other isomeric chelates to the most thermodynamically stable. What is more difficult to understand is why *SSSS*-DOTFA should convert into *RRRR-*. To do so the chelate must pass through two other isomers both of which are higher in energy than the starting chelate. To understand why this would happen, we must understand at what stage the conversion takes place.

The α-protons of LnDOTA (Ln = Eu, Tb & Yb) can be exchanged for deuterium by heating (70 ºC) in D_2O at pD 11.5 for 24 hours.[50] The mechanism of H/D exchange – formation of an enolate at the α-carbon – is the same as that expected in the inversion of stereochemistry. Accordingly, HPLC purified Na_5EuDOTBA was incubated in a 1 mM solution of D_2O (pD 11) in a sealed NMR tube. Even when heating at 60 ºC was extended to 72 hours no significant decrease in the intensity of the α-proton resonance could be detected by ^{1}H NMR (ESI Figure S5 & Table S2). This compares with 90% incorporation for DOTA chelates.[50] The absence of deuterium incorporation indicates that enolate formation in the fully formed chelate EuDOTBA does not occur to an appreciable extent under these conditions.

Until the metal ion is introduced into the system there is no driving force for resolution of the chelate to the *RRRR-/SSSS-* isomer. If the fully formed chelate does not enolize, then presumably stereochemical resolution happens during the chelate formation. The mechanism of chelation by DOTA is a two-step process. In the first step the metal ion associates with the carboxylate groups of DOTA to form, a so-called "Type I" intermediate complex (ESI, Figure S5).[53,54] In the Type I intermediate the metal ion interacts only with the pendant arms and the cyclen ring is diprotonated. In the second step, the rate determining step, the protons are

removed from the cyclen ring, allowing the metal ion to drop down into the coordination cage of the ligand forming the final chelate. Generally the second step occurs easily at moderate pH, but occasionally unusually high pHs are required to deprotonate the cyclen ring – this is most common when ligands contain potential ligating groups in peripheral positions.[52] The requirement for a high pH when chelating DOTBA is perhaps not surprising in this context.

The pendant arms of Type I complexes appear to bind cooperatively,[54] and so the same relationship between helicity and stereochemical configuration is expected. This suggests that stereochemical resolution could occur in the Type I intermediate. To test this hypothesis a solution of the DOTBA and $EuCl_3$ in D_2O at pD 13 (NaOD) was incubated in a sealed NMR tube at 60 ºC for 72 hours followed by 120 hours at 100 ºC. Reaction progress was monitored periodically by ^1H NMR spectroscopy.

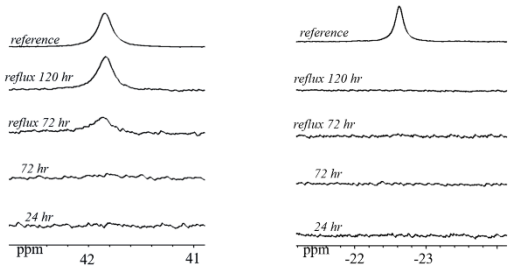


Figure 7. The up-field (right) and down-field (left) regions of the ^1H NMR spectra recorded during the chelation of Eu^{3+} with ±DOTBA in D_2O at pD 13, recorded at 600 MHz. A reference spectrum of the *RRRR-/SSSS-* isomer is shown (top). The ax^S proton of the *RRRR-/SSSS-* isomer (at ~42 ppm) is seen to grow in after the temperature is increased to 100 °C, illustrating formation of the chelate. No other isomers were observed. The acetate peak (at ~-23 ppm) does not grow in, demonstrating deuterium incorporation at the α-carbon. This shows that isomeric resolution is the result of enolization.

No change in the NMR spectrum was observed after 72 hours (Figure 7) and so the temperature was raised to 100 ºC with incubation for a further 120 hours. Analysis of the most up- and down-field regions of the ^1H NMR spectrum shows the formation of the *RRRR-/SSSS-* isomer as the axial ring proton (ax^S) resonance at 42 ppm grows in over time. But even as the chelate forms no peak is observed in the most up-field region of the spectrum where the α-CH

resonance is expected to appear. These results are consistent with incorporation of deuterium at the α-carbon. Since deuterium is not incorporated in the fully formed "Type II" chelate, it may be concluded that this occurs only in the Type I intermediate. Furthermore, despite the use of a racemic ligand sample, no other stereoisomeric chelates are observed in the reaction. This allows us to conclude that resolution of isomers occurs *via* enolate formation in the Type I intermediate during chelation.

To verify the involvement of an enolate in the mechanism of stereoisomer resolution we attempted to prepare a DOTA derivative substituted with both a phenyl and a methyl group on each pendant arm. By eliminating the α-proton, this substitution pattern would block the formation of an enolate and would therefore be expected to afford a mixture of diastereoisomer chelates despite the presence of an α-aryl substituent. Accordingly, ethyl 2-phenylpropanoate **5** was prepared from the corresponding acid prior to bromination of the benzylic positions using an identical procedure for that was used to prepare **4** (ESI, Scheme S2). However, when the disubstituted bromide **6** was used to alkylate cyclen under the same conditions used for DOTFA and DOTBA, exhaustive alkylation could not be achieved even after protracted reaction times (> 4 weeks). Presumably steric effects limit the third and fourth alkylation reaction: analyzing reaction progress by mass spectrometry showed that the extent of tri-substitution of cyclen was low, with the reaction essentially stalling at di-substitution. Unfortunately, the failure of this reaction meant that it was not possible to verify the involvement of enols in this way.

The Effect of Chelation Conditions on Isomeric Distribution

The divergence in isomeric distribution between EuDOTFA and EuDOTBA is notable. These two chelates were prepared under quite different pH regimes: the chelation of DOTBA was undertaken at significantly higher pH and exhibited almost complete resolution to the *RRRR*-/*SSSS*- isomer. This suggests that higher reaction pHs promote enolate formation, which in turn leads to more effective resolution to the most stable isomer. To test the effect of pH on the extent of isomeric resolution Eu^{3+} was introduced to samples of DOTFA in buffered media from pH 4 to pH 10.

2.2 mM solutions of ±DOTFA were prepared in 50 mM acetate buffer (pH 4, 5 & 6) and ammonium acetate buffer (pH 7, 8 & 10). 3.0 equivalents of $EuCl_3$ were added and each solution heated with stirring at 70 °C for 48 hours. Acetate buffers are considered volatile

buffers, permitting removal of most of the buffer prior to NMR analysis. They are also known to be "coordinating" buffers, which may play a role in the kinetics of the chelation reaction. But given that acetate concentration is the same in each buffer the results of these experiments can justifiably be compared with one another, although not necessarily with those of reactions with a different or no buffer. At the end of the reaction each sample was lyophilized and redissolved in D_2O. The ^1H NMR spectrum of each was recorded with pre-saturation suppression of the residual acetate buffer peak. The amount of each isomer present was determined by the line-fitting procedure described above.

Under all pH regimes the desired *RRRR*-/*SSSS*- isomer is the predominant reaction product. When the reaction is performed at the highest pH (10) this isomer makes up 80 % of the produced EuDOTFA. Unexpectedly, as the pH is reduced the proportion of the *RRRR*-/*SSSS*- isomer *increases*, eventually rising to 91 % when the reaction is performed at pH 4 (Figure 8). Of the other isomers, only *RSRS*- and *RRRS*-/*SSSR*- were produced in measurable quantities. Only 1 – 2 % of the *RSRS*- isomer was produced, the quantity of this isomers seemingly largely unaffected by pH. In contrast the amount of *RRRS*-/*SSSR*- isomer produced exhibited a clear decrease as the pH was increased.

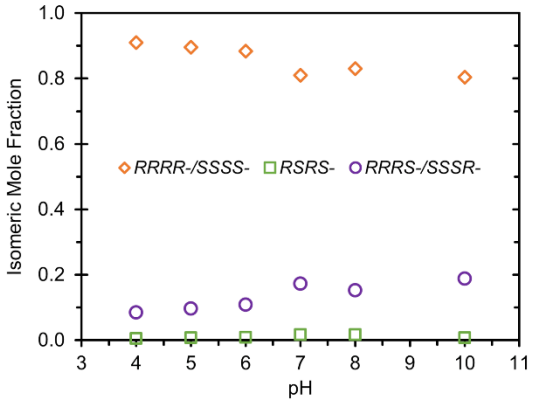


Figure 8. The proportion of each stereoisomer produced as a function of the pH at which the chelation reaction was performed.

The presence of a strongly Lewis acidic metal ion appears to be crucial to the ability of the α-stereocentre to invert rapidly – the stereocentre of phenyl glycine is not found to be so labile to inversion. We may speculate that inversion is neither an acid nor a base catalyzed

process but is initiated by the proximate Lewis acid resulting in bidentate chelation by the carboxylate (Figure 9). This would explain why inversion is found to occur during chelation when the Type I complex is present, but not once the Type II complex has formed. In the fully formed complex the carboxylates are incapable of bidentate coordination. The rate determining step for inversion of the α-stereocentre in the Type I complex is the formation of the enolate (designated by the rate constant k_1). Conversion of the Type I complex to the Type II complex is the rate determining step of the chelation reaction[53] (designated by the rate constant k_2). This process involves removing two protons from the cyclen ring and is intrinsically pH dependent. Thus, as the pH is reduced the rate at which the Type II chelate is formed decreases, while the rate at which stereochemical inversion occurs may be unaffected. The faster rate of enolization relative to that of chelate formation would explain the greater proportion of *RRRR*-/*SSSS*- isomer obtained at lower pH.

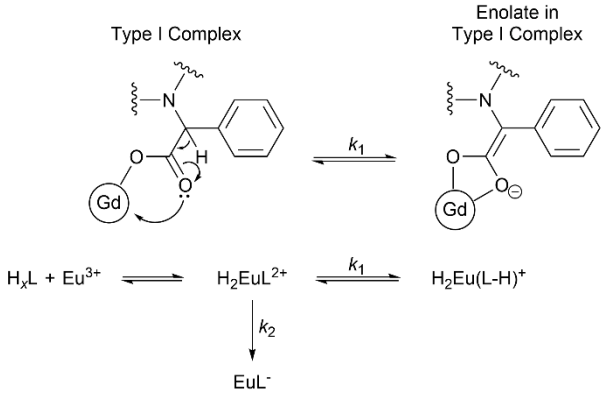


Figure 9. The proposed mechanism of enolate formation in the Type I complex (top) and the reaction steps involved in chelate formation and enolate formation (bottom). Here H_2EuL^{2+} is the Type I complex, $H_2Eu(L\text{-}H)^+$ the Type I complex in which an enolate has formed, and EuL^- is the fully formed Type II complex.

The distribution of isomers appears to be related to relative rates arising from k_1 and k_2, this may afford an opportunity to exert control by changing the temperature. However, the isomeric distribution at pH 4 was not found to vary significantly over the temperature range 40 – 70 °C (ESI, Table S3). This suggests that reaction conditions may be less important than structural consideration is determining isomeric distribution. The difference in isomeric distribution between EuDOTFA and EuDOTBA is larger than any change affected by change in conditions. The benzoate carboxylate is the only feature that distinguishes DOTBA from

DOTFA. In Figure 6, the NMR spectrum of EuDOTBA has peaks that were attributed to the residual Type I complex, this implies that the peripheral carboxylate may in some way[52] cause a decrease in k_2 by stabilizing the Type I intermediate. This would increase the lifetime of the intermediate, affording more time for inversion of stereochemistry to occur and possibly accounting the almost complete resolution of EuDOTBA to the *RRRR*-/*SSSS*- isomer.

Conclusions

The chemistry of tetra α-substituted DOTA derivatives has previously been limited by need to consider stereochemistry during synthesis and the availability of suitable enantiopure starting materials. However, we have shown that these restrictions no longer apply when the substituents are aryl groups. Achiral starting materials can be used to generate racemic a-carboxy alkylating agents, which produce substituted DOTA derivatives as a mixture of diastereoisomers. This would be a problem if alkyl substituents were used: a mixture of stereoisomeric chelates would be produced. In contrast, aryl substituents can stabilize an enolate formed at the α-position during chelation. This allows the ligand (present as a mixture of stereoisomers) to resolve to the most thermodynamically stable stereoisomer of the chelate. The resolution of the ligand into a single stereoisomer of the chelate is found to depend upon the relative kinetics of the chelation and inversion reactions. Inversion of stereochemistry occurs in the intermediate Type I complex and is thought to be initiated by bidentate ligation of the Lewis acid by the carboxyl. Formation of the final Type II complex competes with resolution of isomers because bidentate ligation and thus enolization are not possible in this chelate. Reaction conditions that slow the rate of chelate formation (lower pH) were found to improve the extent of stereoisomeric resolution. Both aryl substituents investigated here are capable of affording > 90% of the *RRRR*-/*SSSS*- isomer. These chelates were found to be freely soluble in water but crystallization from water can be used to remove the minor isomers.

Experimental

General Remarks. All chemicals were purchased from commercial sources and used as received unless otherwise noted. Water refers to deionized water with a specific impedance >18 MΩ. Preparative HPLC was performed on a Waters 2545 system equipped with a 250 × 50 mm Phenomenex Luna C18(2) column. Chelates of both DOTFA and DOTBA were purified by eluting with water (0.037 % w/w HCl) for 5 minutes followed by a linear gradient to 80 %

acetonitrile at 15 minutes with a flow rate of 50 $mLmin^{-1}$. The eluent was maintained at 20 % water and 80 % acetonitrile for a further 7 minutes. In all cases absorbance was monitored at 205 and 254 nm. ^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance IIa spectrometer operating at either 400.13 and 100.61 MHz, respectively, or a Bruker Avance III NMR spectrometer operating at 600.17 MHz and 150.93 MHz, respectively. Melting points were determined on a Bibby Scientific SMP10. Rotation of plane polarized light was measured on a Rudolph Research Analytical Autopol1. Infrared spectra we measured on a IR whatever equipped with a total attenuated reflectance sample holder. Mass spectra were measured on a ThermoScientific LTQ-Orbitrap Discovery mass spectrometer equipped with an Accula autosampler.

(*R*)-α-Bromo phenylacetate (*R*-1)

D-α-Phenylglycine (8.28 g, 55 mmol) and sodium bromide (44.1 g, 428 mmol) were dissolved in 2M HBr (80 mL) and the solution cooled to 0 °C. Sodium nitrite (4.18 g, 61 mmol) was added portion-wise to the reaction over the course of several hours allowing the brown gas that evolved to dissipate after each addition. After the addition of sodium nitrite was complete the reaction was allowed to warm to room temperature and stirred for 18 hours. After cooling to ambient temperature, the solution pH was raised to 9 by addition of potassium hydroxide. The reaction mixture was then washed with diethyl ether (3 × 60 mL). A solution of HCl added to lower the pH of the aqueous layer to 2, followed by extraction with diethyl ether (3 × 60 mL). The combined extracts were dried (Na_2SO_4) and the solvents removed *in vacuo*, the residue was then taken up in minimal methanol and hot water, upon cooling and evaporation the title compound was obtain by crystallization as a colorless solid (6.24 g, 53 %). M.p. = 119 – 120 °C (lit: 108 – 110 °C, crystallized from cyclohexane).[55]

(*R*)-Methyl α-bromo phenylacetate (*R*-2)

(*R*)-α-Bromo phenylacetate (***R*-1**) (10 g, 46.5 mmol) was dissolved in methanol (50 mL), sulfuric acid (1 mL) was added and the reaction was heated with stirring at 60 °C for 18 hours. After colling to room temperature, the solvents were removed *in vacuo* and residue taken up in Et_2O (60 mL). A solution of saturated potassium carbonate (30 mL) was added and further K_2CO_3 until the pH of the aqueous layer was 10. The aqueous phase was separated and extract twice more with diethyl ether (2 × 60 mL). The organic layers were dried (Na_2SO_4) and the

solvents removed *in vacuo* to afford a colourless oil which was purified by column chromatography over silica gel eluting with 10% diethyl ether in hexanes – 100% diethyl ether. The solvents were removed *in vacuo* to yield afford a colourless oil (7.87 g, 74% yield). R_f = 0.34 (SiO_2, 10% Et_2O in hexanes). α_D^{294} = +1.32 (c = 0.5, CH_2Cl_2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 7.55 (2H, dd, *J* = 7 Hz, *J* = 2 Hz, 3-Ar), 7.36 (2H, m, 2-Ar & 4-Ar), 5.38 (1H, s, PhC<u>H</u>), 3.78 (3H, s, OCH_3).

General procedure for the preparation of tetramethyl-α, α′, α″, α‴-tetraphenyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetracetate (Me$_4$DOTFA)

R-**2** or ±**2** (5.0 g, 22.0 mmol), cyclen (0.75 g, 4.4 mmol), and cesium carbonate (7.11 g, 22.0 mmol) were dissolved in acetonitrile (50 mL). The reaction was heated to 60 °C with stirring for 24 hours. After cooling to room temperature, the organic solvents were removed *in vacuo*, the residue taken up in dichloromethane (60 mL) and washed with water (30 mL). The aqueous layer was extracted with dichloromethane (2 × 60 mL) and the organics combined, dried (Na_2SO_4) and the solvents removed *in vacuo* to yield a dark yellow residue. The residue was purified by column chromatography over silica gel eluting first with CH_2Cl_2, then with 1% methanol in CH_2Cl_2 and finally 3% MeOH in CH_2Cl_2, after the solvents were removed under reduced pressure the title compound was obtained as a colorless oil (3.30 g, 98%). Data for *SSSS*- isomer only: R_f = 0.28 (SiO_2, 3% MeOH in CH_2Cl_2). ^{1}H NMR (CD_3CN, 400 MHz) δ: 7.34 – 7.27 (20H, m, Ph); 4.42 (4H, s, PhC<u>H</u>CO); 3.63 (12H, s, OCH_3); 2.6 – 3.0 (16H, m br, CH_2N). ^{13}C NMR (CD_3CN, 100 MHz) δ: 173.1 (C=O); 137.6 (1-Ph<u>C</u>H); 129.7 (2- Ph<u>C</u>H); 128.7 (3- Ph<u>C</u>H); 128.3 (4- Ph<u>C</u>H); 68.5 (OCH_3); 51.5 (CH_2N). m/z (ESI+): 765.39 ([39%, $[M+H]^+$), 787.37 (100%, $[M+Na]^+$). ν_{max} / cm^{-1}: 1731 (C=O, ester).

General procedure for the preparation of α, α′, α″, α‴-Tetraphenyl-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetracetic acid dihydrochloride (H$_4$DOTFA.2HCl)

Me$_4$DOTFA (0.5 g, 0.65 mmol) and sodium hydroxide (0.25 g, 0.62 mmol) were dissolved in tetrahydrofuran (10 mL) and water (10 mL). The reaction mixture was heated at 65 °C with vigorous stirring for 18 hours. The tetrahydrofuran was removed from the solution by evaporation. Hydrochloric acid (1 M) was added to adjust the solution pH to 3 and the solvents removed by lyophilization to afford a colorless solid (quantitative yield). The title compound

was used without further purification. Data for *SSSS*- isomer only: ^{1}H (D_2O, 400 MHz) δ: 7.43 - 7.23 (20H, m, Ph); 4.22 (4H, s, PhC<u>H</u>); 2.33 – 2.59 (16H, m br, NC<u>H</u>$_2$). *m/z* (ESI-): 707.31 (100%, $[M-H]^-$), 729.29 ($[NaM-2H]^-$, 80%). ν_{max} / cm^{-1}: 3346 (OH), 1590 (C=O).

General procedures for the preparation of HLnDOTFA Chelates

From the lanthanide chloride

DOTFA (30 mg, 34.0 μmol) and the corresponding lanthanide chloride (40.0 μmol) were dissolved in water (10 mL). The pH of the solution was adjusted to 5.5 by addition of potassium hydroxide. The reaction was heated at 70 °C with stirring for 48 hours. After cooling the reaction mixture was filtered through a 0.45 μm syringe filter and purified by RP-HPLC. The solvents were removed by lyophilization to afford the chelate as a colourless solid.

CeDOTFA: 60% yield. R_T = 21.2 minutes. ^{1}H (400 MHz, D_2O) δ: 14.0, 9.4, 8.0, 7.7, 7.6, 7.4, 0.9, 0.0, -11.4. NdDOTFA: 41% yield. R_T = 20.8 minutes. ^{1}H (400 MHz, D_2O) δ: 24.8, 13.4, 11.5, 9.4, 8.7, 8.4, 8.0, 7.9, 7.6, 7.3, 6.7, 3.9, 3.4, 0.1, -12.1, -29.0. EuDOTFA: 54% yield. R_T = 21.8 minutes. m/z (ESI-) = 857 (100%, $[M]^-$), appropriate isotope pattern was observed. ^{1}H (400 MHz, D_2O) δ: 42.2, 17.2, 7.3, 7.0, 6.7, 6.5, 5.8, 4.9, 3.3, 2.0, 1.6, -1.7, -4.9, -5.6, -9.4, -10.3, -22.9. GdDOTFA: 34% yield. R_T = 21.3 minutes. m/z (ESI-) = 862.2 (100%, $[M]^-$) $]^-$), appropriate isotope pattern was observed. TbDOTFA: 20% yield. R_T = 21.8 minutes. ^{1}H (400 MHz, D_2O) δ: 272.5, 175.69, 128.0, 94.2, 79.2, 71.5, 45.9, 41.6, 35.8, 33.2, 20.8, 9.7, -36.2, -59.4, -81.7, -88.4, -279.3, -453.2. DyDOTFA: 30% yield. R_T = 21.8 minutes. ^{1}H (400 MHz, D_2O) δ: 337.2, 214.5, 160.4, 113.5, 96.6, 86.0, 53.6, 45.4, 42.0, 0.0, -53.1, -56.5, -61.4, -86.0, -88.1, -338.7. YbDOTFA: 22% yield. R_T = 22.0 minutes. ^{1}H (400 MHz, D_2O) δ: 162.8, 96.6, 30.5, 23.6, 17.8, 13.4, 11.4, 9.69, 8.8, 7.7, 2.8, -8.6, -16.5, -35.9, -52.9, -69.9, -112.2.

From the lanthanide oxide

DOTFA (30 mg, 34.0 μmol) and corresponding lanthanide oxide (34.0 μmol)) were dissolved in water (10 mL). The reaction was heated at 70 °C with stirring for 72 hours. The reaction mixture was pH adjusted to 7 with 1M KOH. After cooling the reaction mixture was filtered through a 0.45 μm syringe filter and purified by RP-HPLC. The solvents were removed by lyophilization to afford the chelate as a colourless solid.

YDOTFA: 43% yield. R_T = 20.8 minutes. m/z (ESI-) = 793 (100%, $[M]^-$), appropriate isotope pattern was observed. PrDOTFA: 66% yield. R_T = 21.1 minutes. ^{1}H (400 MHz, D_2O) δ: 19.7, 14.8, 13.9, 12.3, 9.5, 8.8, 8.3, 7.4, 1.2, -1.6, -2.1 -6.5, -30.0, -52.6. SmDOTFA: 49% yield. R_T = 21.2 minutes. ^{1}H (400 MHz, D_2O) δ: 10.1, 8.3, 7.7, 7.5, 7.04, 7.1, 5.4, 4.1, 1.9, 1.3, 1.2, 0.6, 0.5, 0.3, -4.7. HoDOTFA: 43% yield. R_T = 21.7 minutes. ^{1}H (400 MHz, D_2O) δ: 218.9, 142.5, 1013.4, 62.7, 50.3, 33.9, 19.6, 15.6, 12.6, -40.3 -61.8, -64.3, -159.0. -293.7 (ax^S, SAP) . ErDOTFA: 46% yield. R_T = 21.6 minutes. ^{1}H (400 MHz, D_2O) δ: 207.2, 164.8, 32.4, 24.1, 18.0, 7.7, 3.6, 2.3, -0.5, -19.8, -22.7, -60.3, -66.2, -126.3, -.142.1. TmDOTFA: 28% yield. R_T = 21.9 minutes. ^{1}H (400 MHz, D_2O) δ: 511.9, 438.9, 80.5, 77.6, 58.7, 2.5, -2.9, -9.6, -10.2, -55.8, -88.0, -145.5, -206.5, -314.6, -424.5.

Diethyl 4-(carboxymethylene) benzoate (3)

4-(Carboxymethyl) benzoic acid (2.0 g, 11 mmol) was dissolved in EtOH (100 mL) and conc. H_2SO_4 (2 mL) added. The reaction mixture was heated under reflux with stirring for 18 h before quenching with saturated $NaHCO_3$. The solvents were removed *in vacuo* and the residue taken up in water (100 mL) and Et_2O (200 mL) and separated. The aqueous layer was further extracted with Et_2O (2 × 200 mL), the organic extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to afford the title compound as a pale yellow oil (2.30 g, 85%). ^{1}H NMR data were consistent with those previously published:[56] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.00 (2H, d, *J* = 8 Hz, 3-Ar), 7.40 (2H, d, *J* = 8 Hz, 2-Ar), 4.40 (2H, q, *J* = 7 Hz, $CO_2C\underline{H}_2CH_3$), 4.17 (2H, q, *J* = 7 Hz, $CO_2C\underline{H}_2CH_3$), 3.7 (2H, s, Ar-$C\underline{H}_2$), 1.40 (3H, t, *J* = 7 Hz, $C\underline{H}_3CH_2CO_2$), 1.27 (3H, t, *J* = 7 Hz, $C\underline{H}_3CH_2CO_2$).

Diethyl 4-(Carboxybromomethyne) benzoate (4)

The diethyl ester **3** (0.20 g, 0.85 mmol) and *N*-bromosuccinimide (0.16 g, 0.89 mmol) were dissolved in CH_3CN (100 mL). The reaction mixture was irradiated under a 72-watt UV (365 nm – 395 nm) light with heating at 60 °C for four days. Upon removal of the solvent under reduced pressure a colorless crystalline solid (NHS) formed. The residue was taken up in diethyl ether (100 mL) and filtered (0.45 μm nylon membrane). The filtrate was washed with brine (50 mL), dried (Na_2SO_4) and the solvents removed *in vacuo*. The residue was purified by column chromatography over SiO_2 eluting with 20% diethyl ether in hexanes to afford the title compound as a pale-yellow oil (0.23 g, 85%). R_F (SiO_2, 20% Et_2O in hexanes) 0.3. ^{1}H NMR

data were consistent with those previously published:[57] ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 7.97 (2H, d, *J* = 8 Hz, 3-Ar), 7.54 (2H, d , *J* = 8 Hz, 2-Ar), 5.29 (1H, s, ArC<u>H</u>Br), 4.3 (2H, q, *J* = 7 Hz, $CO_2C\underline{H}_2CH_3$), 4.18 (2H, q, *J* = 7 Hz, $CO_2C\underline{H}_2CH_3$), 1.32 (3H, t, *J* = 7 Hz, $CO_2CH_2C\underline{H}_3$), 1.21 (3H, t, *J* = 7 Hz, $CO_2CH_2C\underline{H}_3$).

Tetraethyl-α,α',α'',α'''-tetra(ethylbenzoate)-1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetate (Et$_8$DOTBA)

To a solution of cyclen (37 mg, 0.21 mmol) and ±**4** (200 mg, 0.85 mmol) in acetonitrile (10 mL) was added Cs_2CO_3 (273 mg, 0.85 mmol). The reaction mixture was then heated to 60 °C with stirring and monitored by mass spectrometry. Once the reaction was determined to be complete (11 days) the solvents were removed *in vacuo*. The resulting residue was taken up in CH_2Cl_2 (200 mL) and washed with a solution of K_2CO_3 (pH 13, 100 mL). The organic layers were combined, dried (Na_2SO_4) and the solvents were removed *in vacuo* to afford an orange oil. The residue was then purified by column chromatography over SiO_2 eluting with 6% MeOH in CH_2Cl_2 to afford the title compound as a colorless oil (140 mg, 60%). R_f = 0.35 (SiO_2, 6% MeOH in CH_2Cl_2) = 0.35; ^{1}H NMR ($CDCl_3$, 400 MHz) δ = 8.12 – 7.54 (8H, m overlapping, 3-Ar), 7.43 – 7.22 (8H, m overlapping, 2-Ar), 4.31 (16H, m overlapping, $OC\underline{H}_2CH_3$), 4.05 (4H, multiple overlapping, ArC<u>H</u>), 3.06 – 2.29 (16H, m br, $NC\underline{H}_2$), 1.36 – 1.04 (24H, m overlapping, $OCH_2C\underline{H}_3$); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 171.5 (C=O), 168.8 (C=O), 166.6 – 165.3 (br, C=O), 130.6 – 124.9 (Ar), 61.4 – 60.6 (br), 50.1 – 47.1 (br), 29.4, 14.3 (due to diastereomeric mixture, peaks were not clearly assignable); *m/z* (ESI+) = 1109.5 (100%, $[M+H]^+$), 1131.5 $[M+Na]^+$); ν_{max}/cm^{-1} (ATR) = 3268 (C-H Ar), 2981 (C-H sp^3), 1714 (C=O), 1629, 1610 (C=C Ar), 1366, 1271 (C-H), 1100, 1019 (C-O), 849 (*p*-Ar), 744 (C-H), 702 (C-H).

General procedure for the preparation of 1,4,7,10-tetraazacyclododecane-1,4,7,10-α,α',α'',α'''-tetra(benzoate) tetraacetate lanthanide complexes (LnDOTBA)

Chelates were prepared from the ester of the ligand in two steps.

i. ±Et$_8$DOTBA (2.0 g, 1.8 mmol) was dissolved in tetrahydrofuran (5 mL) and 1 M solution of KOH (14.4 mL) was added. The reaction mixture heated to 60 °C and stirred vigorously for 48 hours until all THF had evaporated. The residual solvents were removed by lyophilization to afford a colorless solid. The removal of ethyl esters was confirmed by ^{1}H NMR and the ligand

used without further purification. ^{1}H NMR (D_2O, 600 MHz) δ = 7.8 (16H, br, Ar), 4.0- 1.9 (20H, br, NC<u>H</u>CO_2, NC<u>H</u>$_2$).

ii. ±K_8DOTBA and $LnCl_3 \cdot 6H_2O$ (1.2 eq., where Ln^{3+} = Eu^{3+}, Gd^{3+}) were dissolved in water (10 mL) and the pH adjusted to 13 using a 1M KOH solution. The reaction was heated at 60 °C with stirring for 96 hours while the pH was monitored and maintained between 12 – 14 by addition of KOH solution. After cooling, the reaction was filtered and the solvents removed by lyophilization. The residue was purified by RP-HPLC to afford the protonated chelates as colourless solids.

EuDOTBA: 55% yield, R_T = 15.3 minutes, ^{1}H NMR (D_2O, 600 MHz) δ = 42.2, 17.7, 7.8, 7.1, 7.1, 6.3, 5.0, 2.0, 1.9, -1.7, -4.6, -5.0, -5.5, -9.2, -10.1, -22.6; GdDOTBA: 87% yield, R_T = 16.0 minutes, ESMS-ESI(-) *m/z*: 1038.2 (23% $[H_4M]^-$, 518.6 (100%, $[H_3M]^{2-}$).

Isomeric Distribution Studies

Buffer solutions at pH 4, 5 & 6 were prepared at 50 mM from aqueous solutions of acetic acid (0.2 M), sodium acetate (0.2 M), followed by dilution with water.[58] Buffer solutions at pH 7, 8 & 10 were prepared from a 50 mM solution of ammonium acetate in water and the pH adjusted by addition of ammonia where necessary. A stock solution (600 mM) of DOTFA was prepared and the pH adjusted to 7. A stock solution (1.8 M) of $EuCl_3$ was prepared in water and the pH was not adjusted. DOTFA (55 μL), $EuCl_3$ (55 μL) buffer (15 mL) and were placed in a round bottom flask and heated with stirring for 48 hours. The solvents and some of the buffer were removed by lyophilization. The residue was taken up into D_2O and analyzed by ^{1}H NMR using a pre-saturation pulse to suppress the residual acetate peak.

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