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Role of the capping bond effect on pyclen $^{nat}Y^{3+}$/$^{90}Y^{3+}$ chelates: full control of the regiospecific *N*-functionalisation makes the difference

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Thanks to a smart regiospecific *N*-functionalisation, a pyclen based ligand bearing one picolinate and two acetate arms organized in a dissymmetric manner was synthesized for Y^{3+} complexation, and compared to its symmetric analogue. The nature of the capping bonds around the metal coordination environment has a dramatic effect on the properties of the chelate, the $^{nat}Y^{3+}$ and $^{90}Y^{3+}$ dissymmetric derivatives presenting enhanced thermodynamic stability and kinetic inertness.

A large variety of metal radioisotopes is currently used in nuclear medicine due to their important diagnostic or therapeutic applications. Among the radioisotopes available for therapy ^{90}Y ($t_{1/2}$ = 64.2 h, E_{β^-} = 2.28 meV) is one of the most interesting β^- radioisotopes,[1] especially for treatment of large solid tumors.[2] As the lanthanide(III) ions, Y^{3+} typically forms eight- or nine-coordinated chelates with a preference for hard donor atoms such as negatively charged oxygen atoms of carboxylate/phosphonate groups and amine nitrogen atoms.[3] Polyazamacrocycles, such as tacn or cyclen,[‡] are recognized as convenient platforms for the coordination of lanthanide cations after a specific functionalisation of their amine functions.[4] Among the current azamacrocycles, derivatives of the 12-membered tetraaza-macrocyclic ligand that includes a pyridine unit within the ring, often denoted as pyclen (or 12-py-N4),[‡] have been less explored. However, the presence of the aromatic moiety confers to the macrocyclic backbone an important rigidity that constrains the overall structure and consequently may lead to unexpected properties compared to its cyclen analogue. For example, the aminocarboxylic acid derivative of pyclen, pcta,[‡] forms stable and neutral lanthanide complexes. Its Gd^{3+} chelate presents a relatively high proton relaxivity due to the presence of two coordinated water molecules endowed with fast water exchange rates, which makes this complex and related systems interesting alternatives to $[Gd(dota)]^{-}$[‡] as non-specific MRI contrast agents.[5] In addition, pcta has been found to present fast chelation kinetics under mild conditions,[6] making pcta and its derivatives attractive candidates for application in nuclear medicine. A fast complexation of the radioisotope compared to its half-life is of crucial importance to obtain high radiolabelling yields, in particular because of the low concentrations employed and the "soft" conditions that can be tolerated by the biomolecules used for targeting purposes.[7]

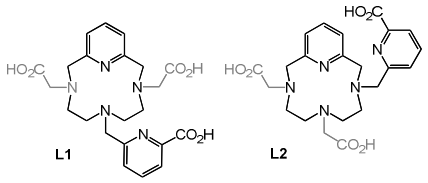

Fig 1. Structures of the pyclen-based mono-picolinate ligands.

Pyridinecarboxylate (picolinate) groups are bidentate coordinating units that are known to provide extraordinary coordination properties toward different metal ions,[8] including lanthanides,[9] particularly when appended on macrocyclic scaffolds.[10] Thus, we firstly thought judicious to conjugate the favourable binding properties of the pyclen skeleton and the pyridinecarboxylate group to obtain neutral yttrium(III) chelates that could be an interesting alternative to the negatively charged $Y(dota)^{-}$. Furthermore, we sought to investigate the effect that a different spatial arrangement of the coordinating functions may have on the properties of the complexes. Thus, two new regio-isomeric pyclen-based ligands bearing one picolinate and two acetate pendant arms, organized either in a symmetric (**L1**) or non-symmetric (**L2**) manner were synthesized, and their coordination properties towards yttrium(III) were compared (Fig. 1).

L1 was obtained by two successive alkylations controlled by protection/deprotection sequences starting from N^3-Boc-pyclen, which was previously described by Siaugue *et al.*[11] (see ESI†). The synthesis of the dissymmetric regio-isomer **L2** was more challenging and required the development of a new route inspired by the acylation of cyclam with diethyl oxalate, which allows a selective *cis*-N^2-N^3-dialkylation.[12] After the neutralisation of pyclen·3HCl,

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pyclen oxalate (**1**) was synthesized in good yield (90 %) by acylation with diethyl oxalate in MeOH (Fig. 2). The free amine function was then reacted with methyl 6-(chloromethyl)picolinate to lead quasi-quantitatively to **2**. After hydrolysis of the oxalate bridge and esterification of the carboxylic acid, the two other amine functions were alkylated with the acetate arm. A final hydrolysis step provided **L2**. The relatively low yields of the last step obtained for the two ligands are related to the difficulties found during HPLC purification.

The yttrium(III) complexes were synthesised in water at pH 5 and isolated in very good yields (~90%). Both regio-isomers and their complexes were characterized by ^{1}H and ^{13}C NMR in D_2O (ESI†). The assignments of the proton signals (Tables S1-S4, ESI†) were based on HMQC and HMBC 2D heteronuclear experiments as well as standard 2D homonuclear COSY experiments. At 25°C, Y**L2** presents sharp signals with methylene resonances showing a diastereotopic pattern (see Fig. S2 in ESI†). In fact, all the non-aromatic protons located on a same carbon atom give two signals, which indicates the presence of a single diastereoisomer in solution with no fluxional behaviour within the NMR timescale. Y**L1** shows however broad signals in the region 2-5 ppm at room temperature that become sharp at 55°C. At the latter temperature, the number of ^{1}H and ^{13}C NMR signals is consistent with an effective C_s symmetry, likely resulting from a fast interconversion between enantiomeric forms of the complex by rotation of the pendant arms and inversion of the macrocyclic ring (see Fig. S3 and S4 in ESI†).

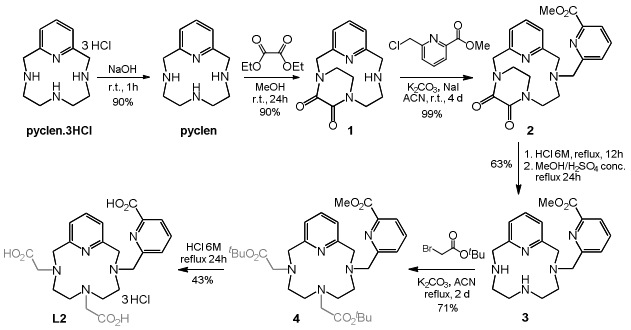

Fig 2. Synthesis of the dissymmetric pyclen-based mono-picolinate **L2**.

The thermodynamic protonation constants of **L1** and **L2** and the stability constants of their complexes with Y^{3+} were determined at 25°C in 0.15 M NaCl using potentiometric titrations. Both **L1** and **L2** present a protonation behaviour similar to H_3pcta. The first protonation constant (logK_1 = 9.69 and 10.43 for **L1** and **L2** respectively) corresponds to the protonation of the N atom *trans* to the pyridine ring.[13] The second protonation induces a rearrangement of the protonated sites, so that the two N atoms in *cis* to the pyridine unit are protonated (logK_2 = 7.63 and 6.47 for **L1** and **L2** respectively).[6] As for previous systems, a decreasing basicity occurring when carboxylate groups are replaced by picolinate moieties is observed.[14] The third protonation process is likely associated to the protonation of the picolinate unit, while the fourth protonation constant is attributed to a carboxylate group (Table S5, ESI). The protonation constants show that **L1** and **L2** have a similar overall basicity, which is lower than that of H_4dota.[15] The thermodynamic stability of the yttrium(III) complexes Y**L1** and Y**L2** were determined by competition with Gd^{3+} using the relaxometric technique (Table 1 and in the ESI†, Table S5 and Fig. S5).[16] The stability constant obtained for Y**L2** is very high and significantly higher than that of Y**L1** (log K_{YL} = 22.44 and 19.89 respectively), in spite of the similar basicity of the ligands. In addition, the stability constant of Y**L2** is higher than that of Y(pcta) (log K_{YL} = 20.28 determined at 25°C by using 1.0 M KCl), although lower than that of $[Y(dota)]^-$ (log K_{YL} = 24.9). However, a comparison of the complexation ability of ligands with different basicity might be misleading if the competition of protons is not taken into account. A better comparison is provided by the pM values, which were calculated for the Y^{3+} complexes of **L1**, **L2** and related ligands at pH 7.4 (Table 1). The pY value obtained for Y**L1** (pY = 18.14) is one log unit higher than that of Y(pcta) (pY = 17.0) and approaching that of $[Y(dota)]^-$ (pY = 18.9). More remarkable, the pY value obtained for Y**L2** (pY = 20.33) is much higher than those of the reference chelates Y(pcta) and $[Y(dota)]^-$. These results highlight the dramatic effect that the arrangement of the ligand donor atoms of the chelators has on the stability of the complexes, conferring on **L2** higher Y^{3+} complexation properties than the current reference chelators.

Table 1. Stability constants of Y^{3+} complexes formed with pyclen based mono-picolinates (25°C, 0.15 M NaCl) and related ligands.

	L1	**L2**	pcta	dota
log K_{YL}	19.89(1)[a]	22.44(2)[a]	20.28[b]	24.09[c]
pY[d]	18.14	**20.33**	17.0	18.9

[a]Stability constants of the Y^{3+} complexes were determined by Gd^{3+} competition; [b]Ref. 6 (25°C, 1.0 M KCl); [c]Ref. 17 (25°C, 0.1 M Me_4NNO_3); [d]Calculated at pH = 7.4 for 100% excess of ligand with $[Y^{3+}]_{tot} = 10^{-5}$ M based on stability constants given in this Table.

Another essential feature that must fulfil chelate-based radiopharmaceuticals is a good kinetic inertness in order to avoid release of the metal ion *in vivo*. A preliminary assessment of the kinetic inertness of a chelate can be carried out by studying the dissociation of the complex in acidic media, which provides interesting information on the behaviour of a complex in very competitive media. The acid-assisted dissociation of Y**L1** and Y**L2** was studied in 0.5, 1 and 2 M HCl solutions at 25°C by following the changes in the π-π* absorption band of the complexes in the UV range (Fig. S6 and S7 in the ESI†). The different *N*-functionalization pattern has a very significant impact on the chelate properties, as an impressive gain of kinetic inertness is observed for the yttrium(III) complex of the dissymmetrical pyclen-based mono-picolinate **L2** compared to its symmetric analogue **L1** (Table 2). One can especially note that the inertness of Y**L2** is significant with respect to the reference Y(pcta)[6] complex.

Table 2. Determined half-times (in minutes) of dissociation of Y**L1** and Y**L2** in HCl media.

	HCl 0.5M	HCl 1M	HCl 2M
Y**L1**	55	27	11
Y**L2**	**1014**	**357**	**137**
Y(pcta)[6]	31.9	19.6	12.7

In the absence of crystallographic data, a DFT study was undertaken to rationalise the very different stability and dissociation kinetics of the Y**L1** and Y**L2** complexes. Our calculations provide optimised structures showing nine-coordinate Y^{3+} ions, where coordination number nine is completed by the presence of a water molecule (Fig 3). During the calculations two second-sphere water molecules were included in order to obtain more accurate bond distances involving the coordinated water molecules.[18] The two isomeric complexes present tricapped trigonal prismatic coordination environments, which are however defined by different donor

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atoms of the ligand in each case. In Y**L1**, the three capping positions of the polyhedron are taken by the nitrogen atom of the picolinate unit (N5), an amine N donor atom (N4) and the oxygen atom of a carboxylate group (O2). The capping positions in Y**L2** are delineated by the amine nitrogen atoms N2 and N4 and the oxygen atom of the coordinated water molecule (O1). The bound water molecule presents a much shorter distance in Y**L1** (2.379 Å) than in Y**L2** (2.490 Å), which is in line with the capping position occupied by the water molecule in the latter. The distances involving the metal ion and oxygen atoms of carboxylate groups are rather similar in Y**L2** (2.28-2.33 Å). However, two of these distances are considerably shorter (2.31-2.32 Å) than the third one (Y-O2 = 2.40 Å) in Y**L1**, which appears to be related to the capping position occupied by this donor atom. Indeed, we have recently shown that water molecules occupying capping positions in the coordination sphere are particularly labile because they are hindered by the environment.[19] The results reported here suggest that the labile capping bond phenomenon can be extended to donor atoms of the ligand, other than water molecules. The weak coordination of a carboxylate group at a capping position explains the lower stability of the Y**L1** complex with respect to Y**L2**, as also confirmed by the relative free energy obtained from DFT, which favours Y**L2** by 20.2 kJ mol^{-1}. The fluxional behaviour of Y**L1** evidenced by NMR measurements can be also attributed to the presence of a weakly bound carboxylate, which likely facilitates dynamic processes involving the rearrangement of the ligand donor atoms around the metal ion. The location of a negatively charged carboxylate at a capping position in Y**L1** also justifies the faster proton-assisted dissociation kinetics, which are likely the result of an easier decoordination of the carboxylate group upon protonation. This proton is then transferred to a nearby amine nitrogen atom, which in turn triggers the complex dissociation.

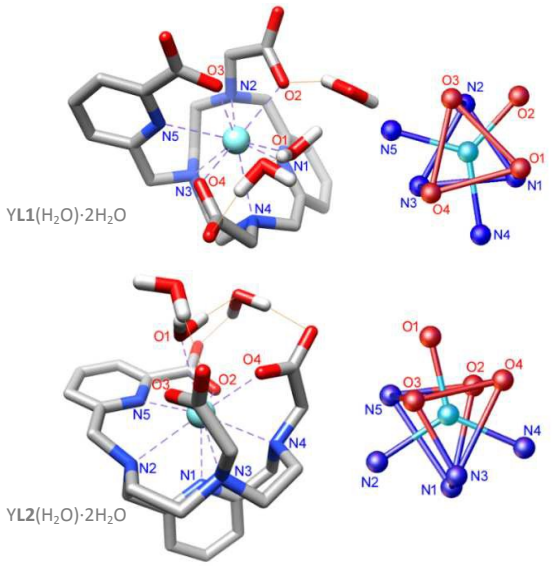

Figure 3. Optimized structures of the Y**L1**$(H_2O)\cdot 2H_2O$ (top) and Y**L2**$(H_2O)\cdot 2H_2O$ (bottom) systems obtained with DFT calculations. Bond distances (Å), Y**L1**$(H_2O)\cdot 2H_2O$: Y-N1 2.572, Y-N2 2.614, Y-N3 2.709, Y-N4 2.652, Y-N5 2.530, Y-O1 2.379, Y-O2 2.401, Y-O3 2.313 and Y-O4 2.320. Y**L2**$(H_2O)\cdot 2H_2O$: Y-N1 2.602, Y-N2 2.665, Y-N3 2.594, Y-N4 2.593, Y-N5 2.465, Y-O1 2.490, Y-O2 2.295, Y-O3 2.280 and Y-O4 2.327.

^{90}Y radiolabelling experiments were performed with **L1** and **L2** to evaluate their labelling rates and efficiencies under different conditions (in 0.1 M HCl (pH = 3) or in acetate buffer (pH = 4.65-9)). The optimal radiolabelling conditions were then determined by varying the reaction time, the temperature, the concentration and the pH (Fig. S8, ESI†). Influence of the temperature was evaluated with $C_L = 10^{-3}$ M at pH 5.2. A radiochemical purity (RCP) of 96% was obtained with **L2** when heating at 60°C, while the RCP dropped to 79% at rt. High RCP (85%) with **L1** could be obtained only after heating up to 100°C (Fig S8 B, ESI†). The optimal conditions for the formation of the ^{90}Y**L** complexes were found to be a reaction time of 15 min, C_L = 0.1-1 mM and pH = 3.0-7.0 for **L2** and 4.7-5.2 for **L1**. These results clearly underline the faster and more efficient radiolabelling of **L2** compared to **L1** with ^{90}Y. The ^{90}Y radiolabelling of **L2** is as efficient as the one performed in similar conditions with dota (^{90}Y-acetate, pH = 7.5, 15 min at 60°C, C_L = 1 mg/mL).[20] The stabilities of the ^{90}Y**L** complexes were studied both in human serum and in an aqueous solution containing 0.1 M EDTA (Fig. 4). ^{90}Y**L2** was found to be very stable both in serum and in the presence of an excess of EDTA, with no decrease of its RCP after 72h. Again, ^{90}Y**L1** is less stable with a progressive dissociation in human serum solution (Fig. 4a) and an immediate decrease of RCP in the EDTA solution. These results are in perfect agreement with the thermodynamic stability and kinetic inertness studies performed with the cold analogues, which already underlined the superior stability of Y**L2**.

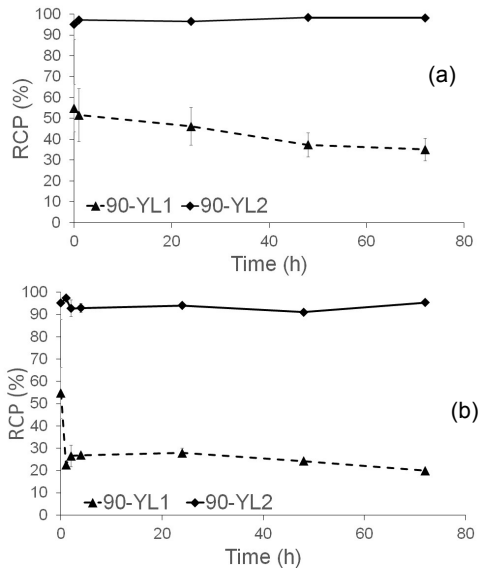

Fig. 4. Stability of ^{90}Y**L** complexes in (a) human serum, (b) EDTA 0.1 M.

In conclusion, we synthetized the two first mono-picolinate di-acetate pyclen derivatives and proved their very interesting yttrium(III) complexation properties. We developed a new regiospecific *N*-functionalization of the pyclen framework, which allows tuning the arrangement of the pendant arms. This led to the preparation of the dissymmetric **L2** chelator, which forms a very stable and inert Y^{3+} complex, representing a very attractive

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alternative to dota for $^{90}Y^{3+}$ radiotherapy applications. The different arrangement of the donor atoms of **L1** and **L2** leads to very different complexation properties. For instance, the **YL1** complex was found to be considerably more labile with respect to dissociation, which showcases the labile capping bond phenomenon. However, the **YL1** complex also shows a considerably lower thermodynamic stability with respect to **YL2**, which can be attributed to a weaker coordination of a carboxylate group occupying a capping position in Y**L1**. Therefore, the *labile capping bond phenomenon* introduced recently[19] has profound consequences not only in the water exchange and proton-assisted dissociation rates of the complexes, but also in their thermodynamic stabilities. Since the weak coordination of ligands or donor atoms at capping positions affect both kinetic and thermodynamic properties, we propose to rename this phenomenon as the *capping bond effect*.

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Notes and references

‡ Full names: tacn (1,4,7-triazacyclononane), cyclen (1,4,7,10-tetraazacyclododecane), pyclen (3,6,9,15 tetraazabicyclo[9.3.1]pentadeca-1(*15*),11,13-triene), *pcta* (3,6,9,15-tetraazabicyclo[9.3.1]pentadeca-1(15),11,13-triene-3,6,9-triacetic acid), *dota* (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid)

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