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Synthesis of a new tricyclic tetraazatriacetic acid as ligand for gadolinium(III)

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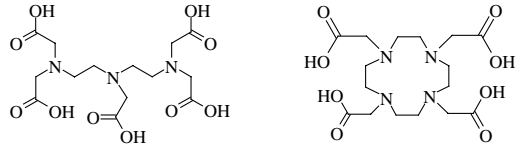
Abstract—Polyazapolycarboxylic acids are known to be efficient ligands for the development of gadolinium-based contrast agents used in magnetic resonance imaging (MRI). Given that rigidification of the ligand structure seems to be an important structural parameter to increase the relaxivity of the corresponding gadolinium complex, we have synthesized a new tricyclic tetraazatriacetate ligand from commercially available *trans*-2-aminocyclohexanol. In the synthetic routes described here, the 2-nitrobenzenesulfonamide chemistry was used to selectively functionalize the polyamine precursors.

The majority of paramagnetic contrast agents used for magnetic resonance imaging (MRI) diagnoses are complexes of gadolinium.[1] The contrast enhancement is due to the ability of the paramagnetic Gd^{3+} cation to shorten the longitudinal (*T1*) and transversal (*T2*) relaxation times of the water protons in the surrounding tissues. The effectiveness of a gadolinium chelate as MRI contrast agent is usually assessed in vitro by measuring the corresponding relaxivities *r1* and *r2*, defined as the longitudinal and transversal, respectively, relaxation rates for a millimolar solution of complex.

Gadolinium-based contrast agents routinely used for clinical diagnosis involve linear (DTPA and derivatives) or cyclic (DOTA and derivatives) polyazapolycarboxylic acid ligands with longitudinal relaxivities ranging from 3.5 to 5 $s^{-1}mM^{-1}$ (Fig. 1).[2] Despite such, substances enjoy widespread use in clinical applications, there, however, remains a need for new compounds of improved performances in terms of relaxivity as well as targeting.



DTPA ligand
$[Gd\text{-}DTPA]^{2-}$ (Magnevist™)
$r1 = 4.3\ mM^{-1}.s^{-1}$

DOTA ligand
$[Gd\text{-}DOTA]^{-}$ (Dotarem™)
$r1 = 4.2\ mM^{-1}.s^{-1}$

Figure 1. Ligands of some routinely used gadolinium-based contrast agents for MRI; relaxivity of the corresponding complexes (20 MHz, 25 °C)[2].

Among the structural parameters that influence relaxivity and, consequently, efficacy of gadolinium-based contrast agents, it had been postulated that an increased rigidity of the chelate structure would be favorable to an increased longitudinal relaxivity.[3,4] Moreover, to be clinically relevant agents, the new compounds need to be of sufficient stability to avoid the toxicity of free gadolinium together with the toxicity of the ligand free of ion. This means that both kinetic and thermodynamic stabilities are important, in addition to selectivity to avoid transmetallation with endogenic cations. Considering the thermodynamic stability of gadolinium chelates used in clinical practice, a constant of 10^{17} appeared to be a minimum requirement.

Keywords: Polyazapolycarboxylic acid; Macrocyclic ligand; Gadolinium; Contrast agent; MRI; 2-Nitrobenzene sulfonamide; Functionalized polyamine.
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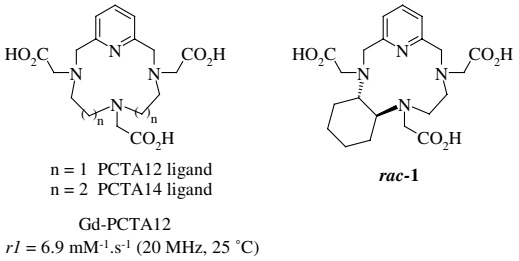
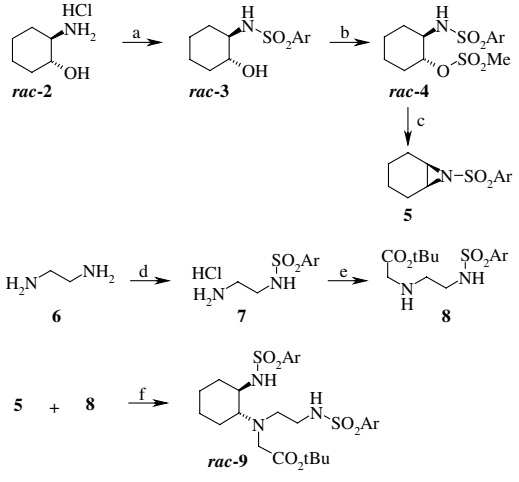


Figure 2.

The PCTA12 ligand (Fig. 2) was reported to form a stable Gd^{3+} complex ($\log K = 20.8$)[5] with an improved longitudinal relaxivity ($r1 = 6.9\ mM^{-1}s^{-1}$, 20 MHz, 25 °C) in comparison with that of gadolinium-based contrast agents clinically used.[2] In the context of a program aimed at the development of more efficient contrast agents for MRI diagnoses, we decided to prepare the constrained PCTA12 derivative **1** (Fig. 2) in which one ethylene bridge connecting two nitrogen atoms of the triamine block will be replaced by a cyclohexylene bridge. In this letter, we report the synthesis of the new tricyclic polyazapolyacetic acid **1** in its racemic form.

Two synthetic routes were envisaged to prepare the desired compound ***rac*-1**. Both of them involve the common functionalized triamine **9** prepared in a convergent way from the two commercially available reagents *trans*-2-aminocyclohexanol hydrochloride **2** and ethylenediamine **6** (Scheme 1). Moreover, in the routes reported, the selective regiofunctionalization of the polyamine backbones was achieved by applying Fukuyama's 2-nitrobenzenesulfonamide strategy widely used for the preparation of secondary amines.[6]



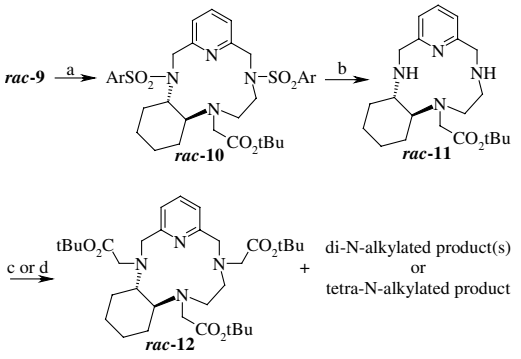
Scheme 1. Reagents and conditions: Ar = 2-NO_2–C_6H_4 (a) 2-nitrobenzenesulfonyl chloride, $NaHCO_3$, THF, 0 °C → rt, overnight, 98%; (b) methanesulfonyl chloride, Et_3N, THF, 0 °C, 30 min, 75%; (c) K_2CO_3, CH_3CN, 45 °C, 1 h, 100%; (d) 2-nitrobenzenesulfonyl chloride, THF, 0 °C, 3 h then HCl, 88%; (e) *tert*-butyl bromoacetate, Et_3N, CH_3CN, rt, 15 min, 50%; (f) CH_3CN, reflux, overnight, 79%.

An efficient synthetic method was established to prepare the activated aziridine **5** from the racemic form of *trans*-2-aminocyclohexanol **2**. Indeed, not only this method does not require the purification of the two amino-alcohol derivatives **3** and **4** but also it affords a crude form of the target aziridine **5** sufficiently pure to be involved as such in the next step. At last, this process allows the extension to large-scale preparations (up to 60 mmol) of the versatile aziridine **5** that proved to be stable during a few months at room temperature.

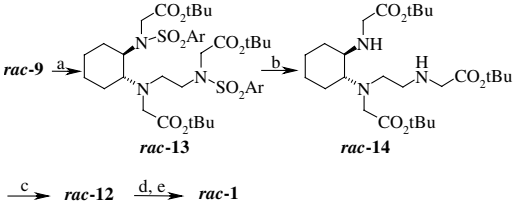
By reaction with a stoichiometric amount of 2-nitrobenzenesulfonyl chloride in the presence of sodium hydrogencarbonate, the *trans*-2-aminocyclohexanol hydrochloride **2** was chemoselectively N-sulfonylated to afford the sulfonamide **3** in 98% yield by spontaneous crystallization from the reaction medium. Subsequent activation of the hydroxyl function was chemoselectively realized by reaction with a stoichiometric amount of methanesulfonyl chloride in the presence of triethylamine. The crude mesylate **3** obtained in 75% yield then afforded quantitative aziridination in the presence of potassium carbonate.

On the other hand, the sulfonylation of ethylenediamine **6** was effectively controlled by reacting diamine **6** with a sub-stoichiometric amount of 2-nitrobenzenesulfonyl chloride. The target monosulfonamide **7** was isolated as its hydrochloride salt in 88% yield and its crude form was sufficiently pure to be involved as such in the subsequent step.[7] When aminosulfonamide **7** was treated with a stoichiometric amount of *tert*-butyl bromoacetate in the presence of triethylamine, chemoselective N-alkylation of the secondary amine occurred and furnished compound **8** that was isolated in 50% yield. The ring-opening of the *meso*-sulfonylaziridine **5** occurred by reaction with the previously prepared amine **8** and furnished the expected functionalized triamine **9** in 79% yield.

Starting from triamine **9**, the first route envisaged was analogous to the synthetic ways that led us to prepare several regioselectively functionalized PCTA12 and PCTA14 derivatives (Fig. 2).[8,9] In this approach, the 2,6-bis(bromomethyl)pyridine was reacted with the activated triamine **9** in the presence of potassium carbonate and afforded the corresponding macrocycle **10** in 69% yield. While the conventional methods to remove 2-nitrobenzenesulfonyl implies a treatment with thiolate at room temperature,[10] the cleavage of the sulfonamide in macrocycle **10** required to warm the reaction mixture and led to the desulfonylated product **11** in moderate yield (44%) (Scheme 2). Unfortunately, the subsequent dialkylation step did not lead to the exclusive formation of the desired triacetate **12**. Indeed, depending on the nature of the solvent and of the base, mixtures containing the desired product **12** together with dialkylated product(s) or tetraalkylated product were obtained. Given that both mixtures were not separable by chromatography, we envisaged an alternative route in which the macrocyclization step would involve the triamine **14** bearing the three acetate pendant arms (Scheme 3).[11]



Scheme 2. Reagents and conditions: (a) 2,6-bis(bromomethyl)pyridine, K_2CO_3, *N*,*N*-dimethylacetamide, 100 °C, 4 h, 69%; (b) PhSH, Na_2CO_3, CH_3CN, 50 °C, 1 day, 44%; (c) *tert*-butyl bromoacetate, Et_3N, THF, 55 °C, 1 day; (d) K_2CO_3, CH_3CN, reflux, 2 h then *tert*-butyl bromoacetate, reflux, 40 h.



Scheme 3. Reagents and conditions: (a) *tert*-butyl bromoacetate, K_2CO_3, CH_3CN, reflux, overnight; 65%; (b) 2-mercaptoethanol, DBU, CH_3CN, rt, 2 h, 52%; (c) 2,6-bis(bromomethyl)pyridine, Na_2CO_3, *N*,*N*-dimethylformamide, 100 °C, 3 h, 59%; (d) HCl, Et_2O, rt, 6 h then ion-exchange resin chromatography, 80%.

By using an excess of *tert*-butyl bromoacetate in the presence of potassium carbonate, the previously prepared secondary disulfonamide **9** was N-alkylated to afford the corresponding tertiary compound **13** in 65% yield. The desulfonylation proceeded smoothly by using 2-mercaptoethanol in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)[12,13] and led to the functionalized triamine **14** that was involved in the macrocyclization reaction with 2,6-bis(bromomethyl)pyridine to furnish the desired macrocyclic compound in 59% yield. When treated with anhydrous hydrochloric acid, the triester **12** was converted to the target macrocyclic triacetic acid **1** isolated with high yield (80%).[†]

In conclusion, the synthesis of the rigidified pyridine containing azamacrocycle **1** was achieved in five steps from activated aziridine **5** and ethylenediamine derivative **8** in 13% overall yield. The preparation of the corresponding Gd^{3+}-complex has been realized and a preliminary assay of transmetallation in the presence of Zn^{2+} cation, at pH = 7 and at 37 °C, showed a stability of the complex equivalent to that of complexes formed with DTPA and DOTA ligands. This result encouraged us to pursue the characterization; measurements in order to evaluate the relaxivity of the complex are in due course.

Acknowledgements

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References and notes

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[†] ^1H and ^{13}C NMR analyses of compound **1** have been done in D_2O; ^1H and ^{13}C spectra are complex probably due to the co-existence of several conformers and/or protonated forms in aqueous solution. IR (KBr): ν = 3409 (broad), 2925, 2850, 1738, 1445, 1405, 1201 cm^{-1}. FAB-HRMS: *m*/*z* calcd for $C_{21}H_{31}N_4O_6$ 435.2244, found 435.2235 $[M+H]^+$.