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Positive variation of the MRI signal *via* intramolecular inclusion complexation of a C-2 functionalized β-cyclodextrin†

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The synthesis of a new contrast agent based on a β-cyclodextrin scaffold and bearing a flexible lipophilic spacer arm on its secondary face is reported. Intermolecular host–guest inclusion complexes were known to undergo an enhancement of the contrast imaging. We extend this concept to intramolecular complexation. Inter- and intramolecular interactions are compared by NMR spectroscopy, circular dichroism and magnetic resonance imaging using hydrocinnamic acid and adamantane carboxylic acid as external guests. This positive variation of the observed relaxivity is a key element of new strategies aiming at developing smart molecular MRI probes.

Introduction

Magnetic Resonance Imaging (MRI) is widely used for human non-invasive imaging of deep tissues despite its low sensitivity. To improve this weak detection threshold, 35% clinical scans are performed by administration of contrast agents. Currently, ten millions of diagnostics are carried out annually using a probe to increase the efficiency of the medical diagnosis. The most important class of contrast agents for MRI is represented by gadolinium Gd(III) chelates such as cyclic DOTA or linear DOPA developed in 1988.[1] Indeed, the free gadolinium atom is toxic and has to be polycoordinated by organic chelates.

Cyclodextrins are natural and chiral cyclic oligosaccharides composed of (α-1,4)-linked D-glucose units that can be used as an anchor for various ligands of Gd(III). Besides their ability to undergo chemical modifications, the size and shape of the cavity of this kind of macrocycle play an essential role in the formation of host–guest inclusion complexes with lipophilic molecules by hydrophobic interactions, H-bonding and van der Waals forces in aqueous media or polar solvents.[2] Cyclodextrins have been already identified as the support of gadolinium for MRI imaging applications. They were used as polyfunctionalizable scaffolds bearing one to seven DOTA or DTPA units.[3] The higher molecular weight of the contrast agent so formed exerts a positive effect on the MRI signal by decreasing the rotation rate in water. Thus, it enhances the contrast of images by increasing the water proton relaxation rates (relaxivity r_1). These properties were used to develop new MRI probes[4] based on polyrotaxanes[5] or nanoparticules.[6]

Other contrast agents have also been developed using 3,6-anhydro-α-cyclodextrin substituted by carboxylate ligands.[7] *In vivo* studies on rats were performed on a tumor model and no nephrotoxicity or hemolysis was reported.[8] We have also previously synthesized new MRI probes based on a β-cyclodextrin bearing seven carboxylate functions on its primary side. Thanks to the cyclic oligosaccharide, we observed a positive effect on the MRI signal which could be attributed to the influence of the secondary hydration sphere.[9]

The cyclodextrins' host properties were also exploited to modify the MRI signal by inclusion of organic molecules inside their internal cone in aqueous medium. Indeed, non-covalent interactions between the cyclodextrin cavity and hydrophobic compounds also act positively on the relaxivity value. Thus the influence of the formation of an intermolecular inclusion complex in MRI was described between DOTA and DTPA bearing one to three lipophilic aromatic groups in the presence of β-cyclodextrins,[10] polymers of β-cyclodextrins[11] or nanoparticules of β-cyclodextrins.[12] Surprisingly a higher relaxivity was observed even in case of a weak host–guest association constant. This correlation between relaxivity and binding constant values was confirmed with a dimer and trimer of cyclodextrins in the presence of DTPA functionalized with one to three cyclohexyl groups.[13] Host–guest interactions were

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recently applied to target tumor using a modified macrocyclic DOTA with the adamantane group. This self-assembly underwent a significant increase of the relaxivity from 3.17 to 6.36 mM^{-1} s^{-1}.[14]

Self-inclusion studies of various arms linked to cyclodextrins into their cavities have been reported in the literature.[15–21] The β-cyclodextrin and a flexible pendant introduced into the C2 position underwent the most efficient molecular sensing.[16a,c,17a,d] This balance can be influenced by various parameters such as temperature,[17a,c,18a,19b] pH,[16a,20] concentration[17b,18b,d] or solvent polarity.[17b,c,18a,b,21] However, the impact on the MRI signal of intramolecular inclusion complexation has never been studied. To evaluate this effect, we developed an innovative strategy to obtain a new contrast agent based on a β-cyclodextrin bearing a lipophilic spacer. Such a functionalized pendant can constitute a future anchor site for a biological target in order to achieve a smart MRI molecular probe.[22]

With the aim of showing the role of the intramolecular inclusion process and the secondary hydroxyl groups of the oligosaccharide, a comparative study was carried out with three contrast agents denoted as **1(Gd)**, **2(Gd)** and **3(Gd)**. They are composed of seven acetate functions introduced on the primary face of the β-cyclodextrin (Fig. 1). The secondary side of **2(Gd)** was permethylated, and a flexible pendant was also introduced into the secondary position of **3(Gd)** in addition to the methyl groups in the remaining positions.

Contrast agents **1(Gd)** and **2(Gd)** were previously described and analyzed.[9] Since gadolinium is noncoordinated, two water molecules fill the inner sphere.[9] In the case of **3(Gd)**, the pendant was introduced by using a biologically stable ether function at the C-2 position. A molecular modelling approach proved that a linker involving three carbon atoms is flexible enough to form an intramolecular complex (Fig. 2).[23] The pendant was functionalized at its end with a carboxylic acid function as the future site of the anchor of a biological target.

To evaluate the role of the pendant in the MRI efficiency of **3(Gd)** (Fig. 3c), the relaxivities were measured with contrast agents **1(Gd)** and **2(Gd)** in the absence (Fig. 3a) and in the presence of an external guest (Fig. 3b and d). The first chosen external guest is hydrocinnamic acid **4** with a chemical structure close to that of the flexible arm introduced into the crown of **3(Gd)**.

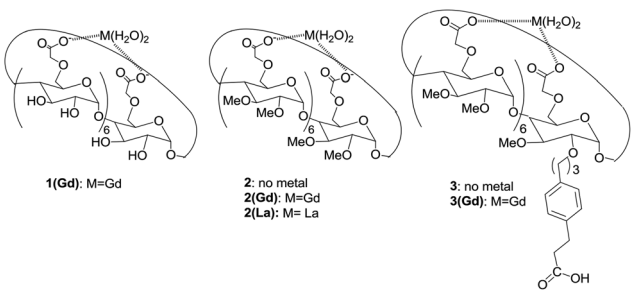


Fig. 1 Structures based on the β-cyclodextrin scaffolds **1**, **2** and **3**.

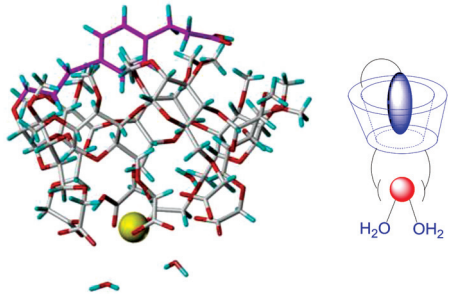


Fig. 2 Molecular modeling of the contrast agent **3(Gd)**.

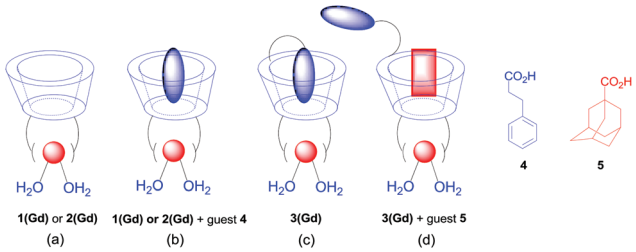


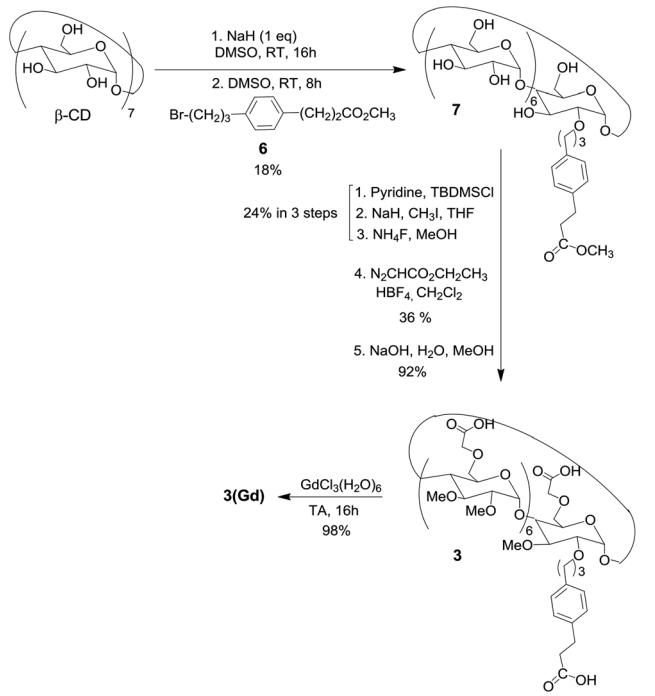
Fig. 3 Contrast agents **1(Gd)**, **2(Gd)** and **3(Gd)** in the presence of a host–guest inclusion complex: (a) no inclusion, (b) and (d) intermolecular and (c) intramolecular. The bowl in red represents the gadolinium atom, and the guests **4** and **5** are represented in blue and red shapes, respectively. Two water molecules fill the inner sphere.[9]

The in and outside isomerism was considered using adamantane carboxylic acid **5** as a second lipophilic guest. It is characterized by a high association constant value and it is assumed to totally displace the complexation equilibrium.[24] Thus, this second guest tends to disadvantage the intramolecular inclusion to the benefit of an intermolecular inclusion complex (Fig. 3d). The impact of such an inclusion is studied hereafter by NMR spectroscopy and circular dichroism.

Results and discussion

Synthesis of contrast agent 3(Gd)

Hydroxyl groups present at the C2-, C3-, and C6-positions compete with the reagent and make selective modifications extremely difficult. Among the three types of hydroxyl groups, those at the C6-position which correspond to primary alcohols are the most nucleophilic (pK_a: 15–16), those at the C2-position are the most acidic (pK_a: 12.1), and those at the C3-position are the least accessible. All these factors make the secondary side less reactive and harder to selectively functionalize than the primary face.[25] We developed a methodology to control the position and the number of substitutions on the secondary face from a native β-cyclodextrin.[26] Without any protection step, a designed spacer arm **6** † was regioselectively introduced into the native cyclodextrin in 18% yield using sodium hydride in DMSO (Scheme 1).† The follow-up of the



Scheme 1 Synthesis of the contrast agent **3(Gd)**.

reaction by HPLC-MS revealed an intramolecular transesterification reaction with another hydroxyl group of the cyclodextrin as a side reaction which explains the lower yield than expected. The C-2 regioselectivity was confirmed by 400 MHz ^{1}H NMR.† The spectrum analysis showed three characteristic peaks at 4.98 ppm (H′-1), 3.81 ppm (H′-3) and 3.22 ppm (H′-2). The attribution of the proton signal H′-1, H′-2 and H′-3 was possible, thanks to COSY NMR study. The corresponding carbons (C′-1, C′-2 and C′-3) were set to HMQC NMR. The proton H′-1 correlates with a carbon at 100.77 ppm (C′-1), the signal at 81.15 ppm is related to C′-2, and the one at 71.8 ppm with C′-3. A correlation between the methylene protons of the spacer arm (α-CH_2) and the carbon C′-2 could not be highlighted due to an overlapping with the ^{1}H signals of the cyclodextrin (H-2, H-4, H-5 and H-6). The substitution step led to a shielding of the C′-1 and C′-3 signals (1.61 ppm and 0.8 ppm respectively) while the signal of the substituted carbon C′-2 was shielded (+8.3 ppm). These observations are in agreement with the previous results published by Masurier *et al.*[26]

The next step was the protection of primary alcohols by silyl groups. Afterwards, the residual hydroxyl groups were deprotonated using an excess of sodium hydride and the permethylation step was performed by addition of methyl iodide in tetrahydrofuran. The subsequent deprotection step of the primary face by ammonium fluorine in methanol was quantitative. Seven ester functions were then introduced by the action of ethyl diazoacetate in the presence of tetrafluoroboric acid in dichloromethane with 36% yield.[9] After saponification of **3**, the contrast agent **3(Gd)** was obtained by addition of gadolinium chloride hexahydrate.

Intramolecular inclusion complex study

In order to confirm the intramolecular inclusion of the aromatic moiety of **3**, we compared the ^{1}H NMR spectra at various concentrations of this non-metaled compound ranging between 6.1 mM (likely to generate an intermolecular process) to 188 μM (enabling an intramolecular inclusion). Indeed, the structure of the formed supramolecular entities depends on the concentration of the solution.[17b,18b,d] The multiplet corresponding to the aromatic area initially observed at a concentration of 6.1 mM (Fig. 4a) underwent a major modification at a higher dilution (from 750 μM to 188 μM, Fig. 4b) to turn into a broad singlet.

The addition of adamantane carboxylic acid **5** as a competitive guest at 188 μM (MRI concentration level) led to a strong shielding of the aromatic signal (Fig. 4c). These NMR modifications confirm that the flexible arm stands outside the cavity of the cyclodextrin **3** in the presence of adamantane acid **5** that prevents the inclusion complex formation.

Temperature can play a key role in the stability of the inclusion complex.[17a,c,18a,19b] Thus, NMR analyses of compound **3** were done at various temperatures, *i.e.* 25 °C, 50 °C and 70 °C (Fig. 5a–c) and 6.1 mM. We observed deformation and deshielding of signals corresponding to aromatic protons from 7.2 (a) to 7.5 (b) and 7.7 ppm (c), respectively. The higher the temperature the more the deshielding of signals in the aromatic area was important. The increase of temperature modi-

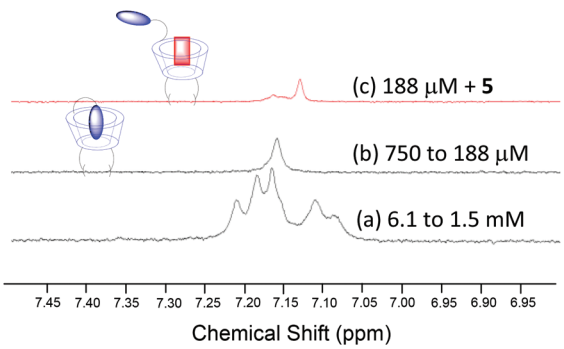


Fig. 4 ^{1}H NMR spectra of **3** (aromatic area) in the absence of adamantane acid **5** at 6.1 mM (a) and at 188 μM (b) and in the presence of 1 eq. of **5** at 188 μM (c), pH 7.4, 25 °C.

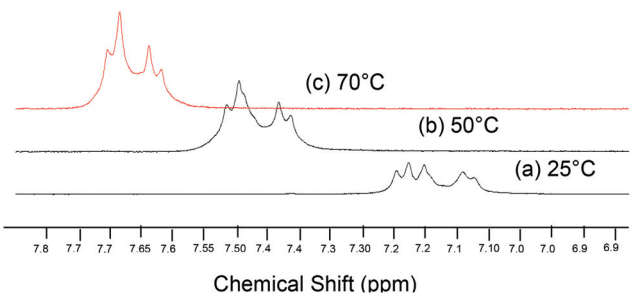


Fig. 5 Evolution of ^{1}H NMR aromatic signals as a function of temperature of **3** at 6.1 mM.

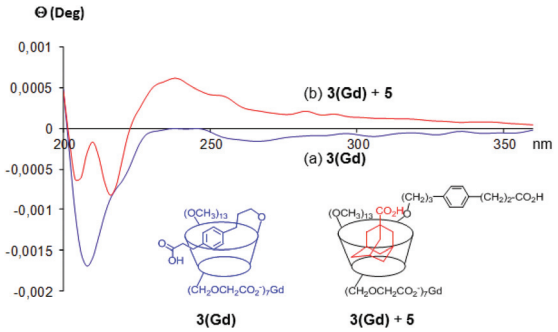


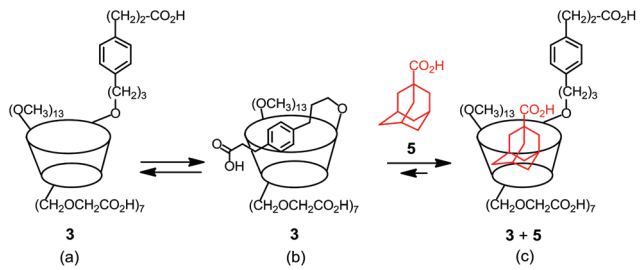
Fig. 6 Circular dichroism measurement of **3(Gd)** in the absence (curve a) and in the presence of 1 eq. of adamantane acid **5** (curve b), H_2O, 25 °C, 0.2 mM.

fied the signal shape to give a symmetric signal at 70 °C, indicating a dissociation of the inclusion complex. So, the entities formed at 6.1 mM underwent a disaggregation due to weaker binding forces at high temperature.

A circular dichroism study was then carried out with the contrast agent **3(Gd)**. Indeed, this experiment can provide information on the inclusion conditions into the cyclodextrin cavity.[27] The analysis was performed at 0.2 mM (close to MRI concentration conditions).

The transition negative band in the wavelength range of 200–230 nm corresponding to a transition of type ^1B_b (Fig. 6a) proved an orthogonal intramolecular inclusion towards the axis of the cyclodextrin cavity. Addition of one equivalent of adamantane carboxylic acid **5** in the medium led to a modification of the signal that turns positive (Fig. 6b). This change revealed a variation of the environment of the cavity. Due to its higher affinity for the hydrophobic cavity of cyclodextrin, **5** perturbs the initial equilibrium and forces the formation of an intermolecular inclusion (Scheme 2).[24] The positive band indicates that the adamantane acid **5** stands parallel to the axis of the cyclodextrin **3(Gd)**. Thus, the aromatic linker could be oriented above the cavity of the cyclodextrin as a cap-like conformation and could not be totally included directly due to the high polarity of the carboxylate function.

Three states can exist in equilibrium: the open form "self-unlocked" (a), the closed form "self-locked" (b) and the adamantane complex form (c) (Scheme 2).



Scheme 2 Competitive study: open (a), closed (b) and adamantane (c) forms.

The conformation (a) (Scheme 2) observed at high concentrations could be due to an inter-supramolecular assembly which could lead to an intramolecular complex (b) at high dilutions. The behavior of a flexible and functionalized pendant grafted on position C-2 of a β-cyclodextrin has been only studied by Park by circular dichroism and NMR spectroscopy.[28] The authors also observed two conformations depending on the concentration used, assigned to the formation of a self-inclusion or a head-to-head type dimer. The formation of different types of inclusion complexes was shown to depend on the concentration and temperature. The assignment of an intermolecular complex at high concentrations justifies the hypothesis of an intramolecular complex at weaker concentrations, consistent with an IRM examination.

Host–guest intermolecular study

To prove the inclusion between hydrocinnamic acid **4** and the β-cyclodextrin derivative **2**, ^1H NMR experiments were firstly performed at various concentrations of **4**.† The gradual addition of **4** in the medium (0.12 to 1.5 equivalents *versus* **2**) led to a shielding of the signals related to the protons H-3 and H-5 of the macrocycle, and showing the interaction between compounds **4** and **2**. To study the inclusion mode of **4**, the lanthane derivative **2(La)**[9] was used since it is closer to the structure of contrast agent **2(Gd)**.

In the presence of one equivalent of hydrocinnamic acid **4** *versus* **2(La)** only the methyl group in the alpha position of the aromatic group undergoes a shielding of 0.2 ppm (2.6 ppm to 2.4 ppm) and complex signals were observed around the aromatic area. A ROESY NMR experiment showed a spatial correlation between the aromatic proton and the internal H-3 (3.6 ppm) of the oligosaccharide (Fig. 7). No correlation was detected between the protons of the aliphatic chain of the acid **4** and the internal protons of the macrocycle. Consequently, only the aromatic part is included in the cavity through the secondary face of **2(La)**. It can be noticed that similar NMR experiments were carried out in the absence of lanthane with compound **2** and similar correlations were observed.†

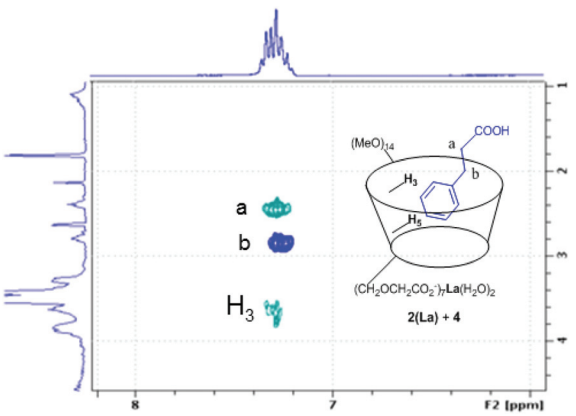


Fig. 7 Zoom of the aromatic proton area of the NMR ROESY spectrum of the inclusion complex **2(La)** + **4**, 25 °C, pH 7.4, D_2O.

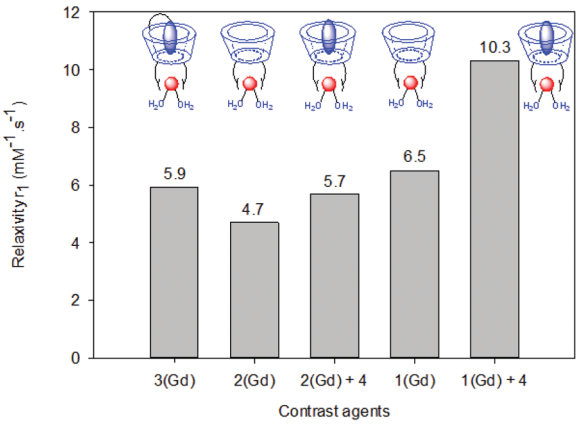


Fig. 8 Relaxivity values for contrast agents **1(Gd)**, **2(Gd)**, and **3(Gd)** in the absence and in the presence of the hydrocinnamic acid guest **4**.

Relaxivity comparison study

The relaxivity study was performed with contrast agents **1(Gd)**, **2(Gd)** and **3(Gd)** at 0.5 Tesla (minispec mq20) with solution concentrations varying from 1 to 0.0625 mM in TRIS buffer at pH 7.4. The results obtained are summarized in Fig. 8.

At the concentration levels used, the contrast agent **3(Gd)** is mainly under its intramolecular form (Scheme 2b). Compared to the relaxivity value of **2(Gd)** (r_1 = 4.7 mM^{-1} s^{-1}), **3(Gd)** shows 26% increase (r_1 = 5.94 mM^{-1} s^{-1}). The addition of one equivalent of hydrocinnamic acid **4** *versus* **2(Gd)** improved the relaxivity r_1 by 21% (4.7 to 5.7 mM^{-1} s^{-1}). Intra- and intermolecular inclusion complexes have a similar impact on the relaxivity, although the covalent bond between the aromatic group and the macrocycle is likely to promote with more efficiency the positive interactions on the relaxation rate. Consequently, even if the intramolecular complex is not deeply embedded in the cavity in the case of **3(Gd)**, the pendant is close enough to perturb the hydration spheres of the gadolinium atom and so to improve the MRI image. This positive impact opens a pathway to new MRI applications.

When **1(Gd)** was used instead of **2(Gd)**, the addition of one equivalent of guest **4** increased the relaxivity r_1 by 58% (6.5 to 10.3 mM^{-1} s^{-1}). We also observed an enhancement of the signal by 43% between the two contrast agents with methylated **2(Gd)** (4.7 mM^{-1} s^{-1}) and hydroxylated **1(Gd)** (6.5 mM^{-1} s^{-1}) and by 80% in the presence of an external guest **4** (5.7 to 10.3 mM^{-1} s^{-1}). These results are in accordance with previous observations confirming the key role of hydroxyl groups of the crown of the cyclodextrin **1(Gd)**.[9] Indeed the second hydration sphere of the cyclodextrin cavity **1(Gd)** could yield stronger interactions with water molecules at the surface of the complex.

Conclusions

A new contrast agent based on the permethylated β-cyclodextrin scaffold with a flexible arm linked on its upper face was synthesized. The positive influence of self-inclusion complex formation on the MRI signal was proved. The phenomenon was compared to intermolecular complexes using a similar external guest structure. A higher enhancement of the relaxivity value was observed for the intramolecular inclusion complex. In perspective, new contrast agents will be designed to optimize the variation of the signal using an adapted pendant to improve the inclusion inside the cavity. The functionalized spacer arm will become the key intermediate to fix specific biological targets in the future and to achieve new smart molecular MRI probes.[29]

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