Metal Chelating Crosslinkers to Form High Stability Nanogels

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MATERIALS AND METHODS

Materials. Unless otherwise noted, all chemicals were obtained from commercial sources and were used without further purification. All reactions were in oven-dried glassware unless otherwise noted. Flash column chromatography purification was performed using a Teledyne Isco Combiflash Companion with RediSep Rf prepacked silica or C18 columns. Thin layer chromatography was performed with EMD TLC Silica gel 60 F254 glass plates. \(^1\)H NMR spectra were acquired using a Varian 600 MHz and \(^{13}\)C NMR spectra were acquired using a Varian NMR spectrometer at 150 MHz. Particles were imaged by TEM with a FEI Tecnai Spirit at 200 kV. Mass determination was performed with a HPLC-MS Agilent 160 Infinity (binary pump, UV-vis 1260 DAD, 6120 Quadrupole LC/MS ESI source) with a RP-18 column. HR-MS measurements were done with an Agilent 6230 ESI-TOF MS. Relaxivities were measured using a Bruker Minispec mq60 contrast agent analyzer (1.4 T, Bruker, Karlsruhe, Germany). Dynamic Light Scattering (DLS) measurements were performed with a Malvern Zetasizer.

Synthesis of DTPA crosslinker 1. DTPA-bisanhydride (1.428 g, 4 mmol) dissolved in DMF (10 ml) was combined with N-(3-aminopropyl)methacrylamide hydrochloride (0.786 g, 5.5 mmol), to which triethylamine (8 ml, 57 mmol) was added dropwise. Reaction was purged with nitrogen for 1 h and stirred at room temperature for 24 h. Solvents were concentrated and the crude material was purified by reverse phase flash chromatography on C18 with water and methanol as eluents to give 1. (1.56 g, 61%) \(^1\)H NMR (600 MHz, \(D_2\)O): \(\delta\) (ppm) = 5.687 (s, 2H), 5.440 (s, 2H), 3.868 (s, 4H), 3.746 (s, 4H), 3.725 (s, 2H), 3.386 (t, 4H, \(J=6.1\) Hz), 3.319 (t, 4H, \(J=6.1\) Hz), 3.288 (q, 8H, \(J=7.0\) Hz), 1.924 (s, 6H), 1.774 (qn, 4H, \(J=7.0\) Hz). HR ESI-MS: MH\(^+\) = 642.3458 g.mol\(^{-1}\) (cacl: 642.3457 g.mol\(^{-1}\)).
Synthesis of 4. 2,4-Diaminobenzoic acid (500 mg, 3.3 mmol) was dispersed in EtOAc (20 mL) and a solution of K$_2$CO$_3$ (9 g, 66 mmol) in water (20 mL) was added. The resulting mixture was vigorously stirred at 0 °C and acryloyl chloride (1 mL, 13 mmol) was then carefully added, resulting in the formation of a light brown precipitate. The reaction mixture was then allowed to reach room temperature, leading to the dissolution of the precipitate. After 30 minutes, the reaction was complete (as confirmed by LC-MS). The organic layer was then discarded and the aqueous layer was acidified with HCl 5%, making a precipitate appear at pH < 4. EtOAc was then added and the product was extracted. The organic layers were then dried with MgSO$_4$, filtered, and evaporated. The solid residue was then suspended in water, filtered, and washed thoroughly with diethyl ether to give 4 as a gray powder (627 mg, 73%).

$^1$H NMR (600 MHz, dmso-$d_6$): δ (ppm) = 9.296 (s, 1H), 8.944 (s, 2H), 7.371 (dd, 2H, $J$=17 Hz, 10.5 Hz), 7.222 (d, 2H, $J$=17 Hz), 6.712 (d, 2H, $J$=10.5 Hz). ES-MS: MH$^+$ = 261.0 g.mol$^{-1}$ (calc: 261.09 g.mol$^{-1}$).

Synthesis of 5. Hydroxy-(tBu)$_4$DOTA derivative 5 was synthesized in 4 steps according to the literature, with a global yield of 10%. 37

Synthesis of 6. Hydroxy-(tBu)$_4$DOTA derivative 5 (526 mg, 0.8 mmol), 2,4-bisacrylamidebenzoic acid 4 (211 mg, 0.8 mmol) and DMAP (195 mg, 1.6 mmol) were dissolved in dry DCM (3 mL) under argon. The resulting mixture was then stirred at 0 °C for 15 minutes, DCC (329 mg, 1.6 mmol) was added, and the reaction was stirred at rt for 48 hours. After this time the reaction mixture was filtered and the precipitate was washed with DCM. The filtrate was concentrated and the solid residue was purified by flash chromatography with DCM/MeOH (2% to 5%) as eluent to give the product 6 as a white solid (320 mg, 44% - best yield: 59%). $^1$H NMR (600 MHz, CDCl$_3$): δ (ppm) = 9.541 (bs, 1H), 9.355 (bs, 1H), 8.727 (s, 2H), 8.519 (s, 1H), 6.753 (m, 2H), 6.489 (dd, 2H, $J$=17.1 Hz), 5.798 (t, 2H, $J$=9.6 Hz), 4.75-2.15 (m, 25H), 1.569 (s, 36H). $^{13}$C NMR (150 MHz, CDCl$_3$): δ (ppm)
Synthesis of 7. Alkyne-(tBu)₄DOTA derivative 7 was synthesized according to the literature with a yield of 75%. 37

Synthesis of 8. Iodo-3,5-dinitrobenzene (2.87 g, 9.76 mmol) and SnCl₂.(H₂O)₂ (15 g, 58.7 mmol) were dissolved in EtOH (24 mL) under argon and stirred at 70 °C. The reaction was monitored by LC-MS until complete conversion and the reaction mixture was allowed to reach room temperature after 60 minutes. The reaction mixture was then poured over ice and NaHCO₃ was added to reach pH 8. EtOAc (200 mL) was then added and product was extracted with EtOAc in brine and water. Organic layers were dried over Na₂SO₄, filtered, and concentrated to give the product 8 as a brown-orange solid (2.23 g, 99.8%). 1H NMR (600 MHz, CDCl₃): δ (ppm) = 6.460 (s, 2H), 5.940 (bs, 1H), 3.552 (bs, 4H). 13C NMR (150 MHz, CDCl₃): δ (ppm) = 149.90, 116.23, 102.31, 96.94. ES-MS: MH+ = 235.0 g.mol⁻¹ (cacl: 234.97 g.mol⁻¹).

Synthesis of 9. 1,3-diamino-5-iodobenzene 8 (475 mg, 2.03 mmol) was dissolved in EtOAc (20 mL) under argon and a solution of K₂CO₃ (5.61 g, 40.6 mmol) in water (20 mL) was added. The resulting mixture was vigorously stirred at 0 °C for 5 minutes and acryloyl chloride (0.66 mL, 8.12 mmol) was then carefully added. After the addition, the reaction mixture was allowed to reach room temperature. EtOAc and an aqueous solution of NaHCO₃ were added and the product was extracted first with EtOAc and then with DCM because of the poor solubility of the product. The organic layers were dried over Na₂SO₄, filtered and concentrated to give 9 as a white solid (695 mg, 100%). 1H NMR (600 MHz, dmsø-d₃): δ (ppm) = 10.374 (s, 2H), 8.114 (s, 1H), 7.945 (s, 2H), 6.513 (dd, 2H, J=16.7 Hz, 10.1 Hz),
6.361 (d, 2H, J=16.7 Hz), 5.873 (d, 2H, J=10.1 Hz). ES-MS: MH+ = 343.0 g.mol\(^{-1}\) (cacl: 342.99 g.mol\(^{-1}\)).

**Synthesis of 10.** Alkyne-(tBu)\(_4\)DOTA derivative 7 (102.4 mg, 0.15 mmol), 1,3-bisacrylamide-5-iodobenzene 9 (50.3 mg, 0.15 mmol), Pd(PPh\(_3\))\(_2\)Cl\(_2\) (5 mg, 5 mol%) and CuI (6 mol%) were dissolved under argon in dry THF (2 mL) and TEA (2 mL). The resulting suspension was then stirred at 50 °C for 16 hours. After this time, the solvents were evaporated and the solid residue was purified by flash chromatography with DCM/MeOH (2% to 5%) as eluent to give the product 10 as a white solid. \(^1\)H NMR (600 MHz, CDCl\(_3\)): δ (ppm) = 9.068 (bs, 1H), 8.972 (bs, 1H), 8.184 (s, 2H), 8.103 (s, 1H), 6.755 (m, 2H), 6.488 (d, 2H, J=16.7 Hz), 5.809 (t, 2H, J=10.1 Hz), 4.46-1.96 (m, 27H), 1.551 (s, 36H). ES-MS: MH+ = 912.6 g.mol\(^{-1}\) (cacl: 911.56 g.mol\(^{-1}\)).

**Synthesis of 2.** Ester-(tBu)\(_4\)DOTA crosslinker 6 (320 mg, 0.35 mmol) was dissolved in a 1:1 mixture of TFA/DCM (2 mL) and stirred at room temperature for 16 hours. After this time, conversion was complete according to LC-MS. The solvents were evaporated and DCM was added to suspend the product and was evaporated to yield a white crystalline solid (390 mg of TFA salt, 100%). \(^1\)H NMR (600 MHz, D\(_2\)O): δ (ppm) = 7.967 (s, 1H), 7.912 (s, 2H), 6.431 (dd, 2H, J=17.1 Hz, 10.1 Hz), 6.365 (t, 2H, J=17.1 Hz), 5.911 (d, 2H, J=10.1 Hz), 4.605 (m, 2H), 4.25-2.96 (m, 23H). HR ES-MS: MH+ = 677.2774 g.mol\(^{-1}\) (cacl: 677.2777 g.mol\(^{-1}\)).

**Synthesis of 3.** Alkyne-(tBu)\(_4\)DOTA crosslinker 10 (80 mg, 0.02 mmol) was dissolved in TFA (1 mL) and stirred at room temperature for 16 hours. After this time, conversion was complete according to LC-MS. The solvents were evaporated and the residue was purified by reverse phase C18 flash chromatography with H\(_2\)O/MeOH (10% to 50% MeOH) as eluent to give the product as a white solid (27 mg, 45% - best yield: 73%). \(^1\)H NMR (600 MHz, D\(_2\)O):
δ (ppm) = 7.695 (s, 1H), 7.380 (s, 2H), 6.368 (m, 4H), 5.878 (d, 2H, J=9.2 Hz), 4.414 (bs, 2H), 3.896-2.993 (m, 25H), 1.551 (s, 36H). HR ES-MS: MH+ = 687.2980 g.mol⁻¹ (cacl: 687.2984 g.mol⁻¹).

**Gd(III) chelation and concentration measurements.** GdCl₃•6H₂O was added in excess to the crosslinkers in solution at a molar ratio of crosslinker: Gd³⁺ = 1:4. The pH of the solution was adjusted to pH 6 with 1 M KOH. The mixture was stirred at 40 °C overnight. To remove free Gd³⁺ from the remaining supernatant, Chelex-100 was added at 100 mg/mL. After stirring for another 3 h, the solution was centrifuged at 3,000 rpm for 3 min. The supernatant was filtered through a 1 µm syringe filter to ensure removal of Chelex-100. Chelex-100 is a chelating resin consisting of styrene divinylbenzene copolymer beads functionalized with iminodiacetic acid, a tridentate ligand able to chelate different metals. The filtered solution was then freeze-dried to give the chelated crosslinkers in a powder form.

**Preparation of the nanogels.** Nanogels at 1.5% (for 2Gd(III) and 3Gd(III)) or 5% (for 1Gd(III)) crosslinking density were formed by dissolving 36.2 (45.4 µmol), 10.9 (13.1 µmol) or 11.1 (13.1 µmol) mg of 1Gd(III), 2Gd(III) or 3Gd(III), respectively, together with 61.3 mg of acrylamide in 250 µL of 10 mM Tris-HCl (pH 8), which was then added into 11 ml of 9% AOT in hexane. After vortexing for 1 min, 32 µL of 50% APS in 10 mM Tris-HCl (pH 8) was added. The reaction mixture was vortexed for 1 min, and then filtered through a 0.1 µm PVDF filter three times. After portionwise addition of 500 µL of 5% TEMED in hexane (10 µL x 50), the particle solution was left on a shaker at 60 rpm for 30 min, followed by removal of hexane by rotovap at 40 °C. Nanogels were washed with acetone (10 mL x 3) and collected each time by centrifugation at 5,000 rpm for 5 min. The white precipitate was then resuspended in 2 mL of 1X PBS buffer, pH 7.4. Gd³⁺ concentration in the nanogel stock solution was determined by inductively coupled plasma atomic emission spectroscopy (ICP-
AES). Nanogel stock solution was split into aliquots of 250 µL, frozen by liquid nitrogen, and stored at -86 °C for further evaluation.

**Nanogel density calculation.** 200 µL of nanogel solution was lyophilized in a pre-weighed Eppendorf tube. The mass of the nanogel (m) after lyophilization was then calculated (25.4 mg). As we sought the density of the nanogels themselves (not the nanogel solution) in their hydrated state, a minimal amount of water (v) was added (25 µL). The density was calculated as \( m/v = 1.016 \text{ g/mL} \), which falls between the density of water (1.00 g/mL) and that of acrylamide (1.13 g/mL).

**Transmetallation measurements.** Buffer was prepared by mixing 125 µL of 50 mM potassium phosphate buffer (pH 7.0) with 2.5 µL of 250 mM ZnCl₂ solution. Both the buffer and nanogels solution at \([\text{Gd}^{3+}] = 5.11 \text{ mM} \) were incubated at 37 °C separately. At time = 0, 125 µL of particle solution was added to buffer of the same volume and 200 µL of the resulting solution was transferred to a NMR tube. T₁ relaxation time was measured over time. The NMR tube was placed inside a heating block at 37 °C between measurements. Magnevist® or chelated crosslinkers served as a control. The control experiment was conducted as above without the addition of ZnCl₂ solution, otherwise keeping volumes and concentrations the same.

**Relaxivity measurements.** To measure relaxivity (\( r₁ \)), nanogel solutions at different Gd concentrations were prepared and an inversion recovery experiment was performed. 50, 40, 30, 20, and 10 µL of the nanogel stock solution was added to 150, 160, 170, 180, and 190 µL of 1X PBS, respectively, and incubated in a water bath at 37 °C for 10 min before relaxivity measurement. Longitudinal relaxation times (T₁) of the solutions were measured using a Bruker Minispec mq60 contrast agent analyzer (1.4 T, Bruker, Karlsruhe, Germany). The \( r₁ \) of the nanogel was calculated using the following formula: \( 1/T₁,\text{measured} = 1/T₁,\text{buffer} + r₁\text{•}[\text{Gd}] \).
where the baseline $T_1$ (buffer) is the $T_1$ relaxation time of the buffer alone. By plotting the inverse of $T_1$ ($1/T_1$) as a function of Gd concentration of the particle solutions (as determined by ICP-AES), the relaxivity can be calculated by finding the slope of the linear regression.

**Dynamic Light Scattering (DLS) measurements.** 20 µL of gel particle solution was added to 200 µL of 1X PBS (pH 7.4) for DLS measurement using a Malvern Zetasizer.

**Transmission Electron Microscopy (TEM).** Nanogel particles stained with 0.5% phosphotungstic acid (PTA) were imaged using a FEI Tecnai Spirit at 200 kV.

**Phantoms Imaging.** Phantom images were taken with a Bruker 7 T Biospec small animal imaging system (20 cm bore). The MR sequence used was an inversion recovery spin echo sequence with following the parameters: field of view: 67 mm, matrix: 128 x 128, 1 slice : 2 mm thick, repetition time (TR): 2000 ms, echo time (TE): 12.6 ms. Solution volumes were 300 µL.

**Nuclear Magnetic Relaxation Dispersion (NMRD).** $^1$H NMRD profiles were measured on a Stelar Spinmaster FFC fast field cycling NMR relaxometer (Stelar, Mede, Pavia, Italy) over a range of magnetic fields extending from 0.24 mT to 0.7 T and corresponding to $^1$H Larmor frequencies from 0.01 to 30 MHz using 0.5 ml samples in 7.5 mm o.d. tubes. The temperature was kept constant at 37 °C. Additional relaxation rates at 20, 60 and 300 MHz were obtained with Bruker Minispec mq20, mq60 relaxometers and Bruker Avance 300 spectrometers (Bruker, Karlsruhe, Germany), respectively. The diamagnetic contribution of unloaded particles was measured and subtracted from the observed relaxation rates of the Gd-loaded nanoparticles.

**MTT assay.** To evaluate cell viability in the presence of the nanogel, an MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyl tetrazolium bromide) assay was performed. RAW 264.7 macrophages were seeded in a 96-well plate at a density of 10,000 cells per well and
incubated overnight. Solutions of PAA/1Gd(III), PAA/2Gd(III) and PAA/3Gd(III) at 8 different concentrations in 1XPBS were prepared. 100 µl of the various dilutions of the nanogel or PLGA nanoparticles (control) were added to the cells. Dead cells (negative control) were prepared by adding Triton-X (to a final concentration of 0.1%) to cells. After 24 h, 10 µl of thiazolyl blue tetrazolium bromide reagent (5mg/ml) was added to each well and incubated for 3 h. The resulting formazan crystals were dissolved with 100 µl acidified isopropanol, and the absorbance was measured at 570 nm and 690 nm (background) with a FlexStation microplate reader (Molecular Devices, Sunnyvale, CA) (n=4).
Table S1. Molecular parameters extracted from the fittings of NMRD profiles.

<table>
<thead>
<tr>
<th></th>
<th>$\rho$ (mM$^{-1}$s$^{-1}$)</th>
<th>$\tau_R$ (ps)</th>
<th>$\tau_M$ (ns)</th>
<th>$\tau_{SO}$ (ps)</th>
<th>$\tau_V$ (ps)</th>
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<tr>
<td>1Gd(III)</td>
<td>4.8±0.2</td>
<td>117±4</td>
<td>554±26.3</td>
<td>84.2±1.1</td>
<td>28.5±1.6</td>
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<tr>
<td>2Gd(III)</td>
<td>4.3±0.2</td>
<td>83.5±1.8</td>
<td>100*</td>
<td>547±59</td>
<td>15±3.9</td>
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<tr>
<td>3Gd(III)</td>
<td>5.0±0.3</td>
<td>107±2.4</td>
<td>100*</td>
<td>523±51.8</td>
<td>10.3±1.9</td>
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<tr>
<td>PAA/1Gd(III)**</td>
<td>9.7±0.5</td>
<td>1800±150</td>
<td>1960±47</td>
<td>145±15.2</td>
<td>41±1.7</td>
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<tr>
<td>PAA/2Gd(III)$^\text{a}$</td>
<td>17.6±0.9</td>
<td>3500±320</td>
<td>774±22</td>
<td>412±27.1</td>
<td>7.2±0.4</td>
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<tr>
<td>PAA/3Gd(III)$^\text{ss}$</td>
<td>14.8±0.7</td>
<td>15000±300</td>
<td>1190±24</td>
<td>417±14</td>
<td>12.5±0.5</td>
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*: fixed value

**: second sphere contribution: $r_{SS}=0.36$ nm, $q_{SS}=0.75±0.26$, $\tau_{SS}=62.8±10$ ps

$^\text{a}$: second sphere contribution: $r_{SS}=0.36$ nm, $q_{SS}=1.97±0.20$, $\tau_{SS}=69.3±1.5$ ps

$^\text{ss}$: second sphere contribution: $r_{SS}=0.36$ nm, $q_{SS}=4.21±0.07$, $\tau_{SS}=80.0±0.1$ ps

$\tau_R$: rotational correlation time

$\tau_M$: water residence time in the first coordination sphere

$\tau_{SO}$: electronic relaxation time at very low field

$\tau_V$: correlation time modulating the electronic relaxation

$q_{SS}$: number of water molecules in the second hydration sphere

$\tau_{SS}$: correlation time modulating the second sphere dipolar interaction

The distance between the water protons of the first coordination sphere and the paramagnetic center was fixed to 0.31 nm and the distance of closest approach was fixed to 0.36 nm, whereas the diffusion constant was set to $3.3 \times 10^{-9}$ m$^2$s$^{-1}$ for 1Gd(III), 2Gd(III), 3Gd(III) and to $3 \times 10^{-9}$ m$^2$s$^{-1}$ for PAA/1Gd(III), PAA/2Gd(III) and PAA/3Gd(III). The NMRD profiles of 1Gd(III), 2Gd(III), 3Gd(III) were fitted using the classical inner sphere and outer sphere theories, whereas for the profiles of PAA/1Gd(III), PAA/2Gd(III) and PAA/3Gd(III), an additional second sphere contribution was included.
Figure S1. MTT assay measuring metabolic activity. a) PAA/1Gd(III) is shown in solid and PLGA nanoparticles in stripes. B) PAA/2Gd(III) is shown in stripe and PAA/3Gd(III) in checker.
Figure S2. a) Effect of crosslinking density on the size and relaxivity ($r_1$) of the DTPA-based nanogel PAA/1Gd(III) and b) relaxivity plot for the 5% crosslinked nanogel at 37 °C and 60 MHz.

<table>
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<tr>
<th>Crosslinking density (%)</th>
<th>Relaxivity (mM⁻¹·s⁻¹)</th>
<th>Size (nm)</th>
<th>PDI</th>
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<tr>
<td>2</td>
<td>10.0</td>
<td>76</td>
<td>0.34</td>
</tr>
<tr>
<td>5</td>
<td>9.9</td>
<td>61</td>
<td>0.18</td>
</tr>
<tr>
<td>10</td>
<td>9.9</td>
<td>69</td>
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Figure S3. Control experiments in phosphate buffer at 37 °C without ZnCl₂. Stability of the Gd³⁺ complexes of a) DTPA-based crosslinker 1 and its corresponding PAA nanogel, b) DOTA-based crosslinker 2 and its corresponding PAA nanogel and b) DOTA-based crosslinker 3 and its corresponding PAA nanogel.
Figure S4. Phantom MRI images at 7 T of a) Magnevist®, 1Gd(III) and PAA/1Gd(III) with $[\text{Gd}] = 350 \, \mu\text{M}$, b) Dotarem®, 2Gd(III) and PAA/2Gd(III) with $[\text{Gd}] = 196 \, \mu\text{M}$, c) Dotarem®, 3Gd(III) and PAA/3Gd(III) with $[\text{Gd}] = 196 \, \mu\text{M}$.
Crosslinker 1 - $^1$H NMR Spectrum

Crosslinker 1 - ES-HRMS Spectrum

<table>
<thead>
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<th>Mass Measured</th>
<th>Theo. Mass</th>
<th>Delta (ppm)</th>
<th>Composition</th>
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Crosslinker 2 - $^1$H NMR Spectrum

Crosslinker 2 - ES-HRMS Spectrum

<table>
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<th>Mass Measured</th>
<th>Theo. Mass</th>
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<th>Composition</th>
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<td>677.2774</td>
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Crosslinker 3 - $^1$H NMR Spectrum

Crosslinker 3 - ES-HRMS Spectrum

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<th>Mass Measured</th>
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