Effect of metal complexation on the radiolytic stability of DOTA

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Supplementary information

Characterization of Zr-DOTA.

Formation of the Zr-DOTA complex was confirmed by ESI-MS (Figure S1) and NMR spectroscopy (Figure S2 and Figure S3). ESI-MS spectrum show peaks at m/z = 491.1 corresponding to $ZrC_{16}H_{25}O_8N_4$ ($[ML]H^+$). Proton attribution was made by using 2D analysis (gHSQC ^{13}C and NOESY). Results are in good agreement with Parker et al. study.[1] No free ligand was observed in both techniques.

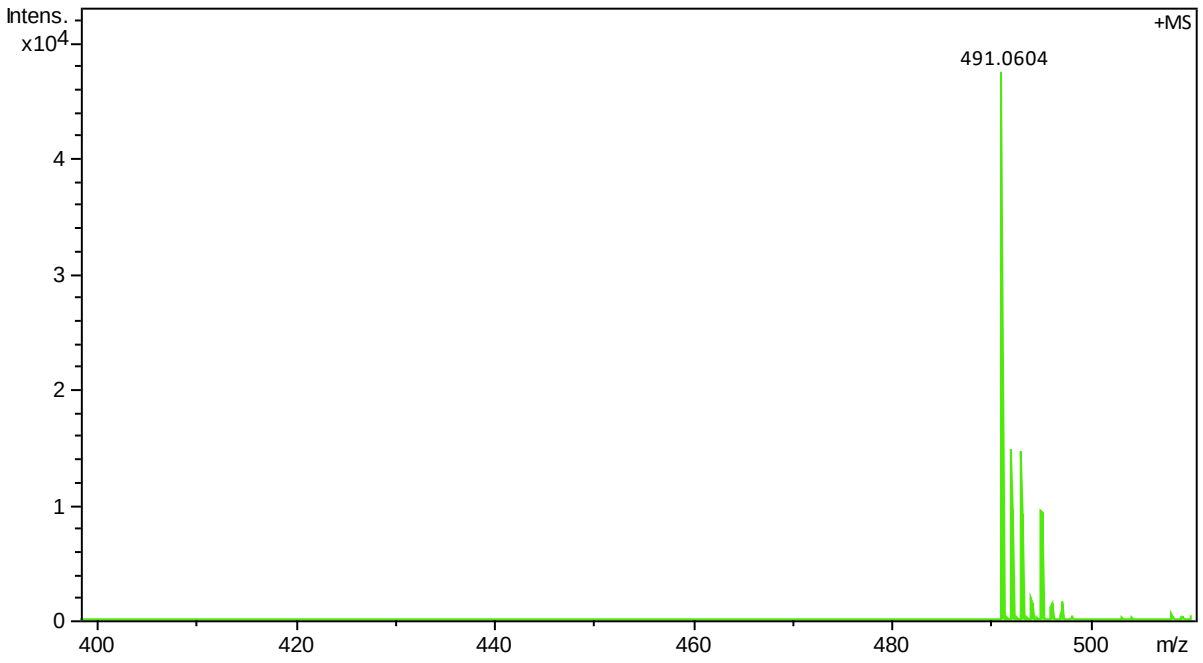

Figure S1: ESI-MS spectrum of Zr-DOTA complex in water ([Zr-DOTA] = 5mM). Diluted 50 times in water.

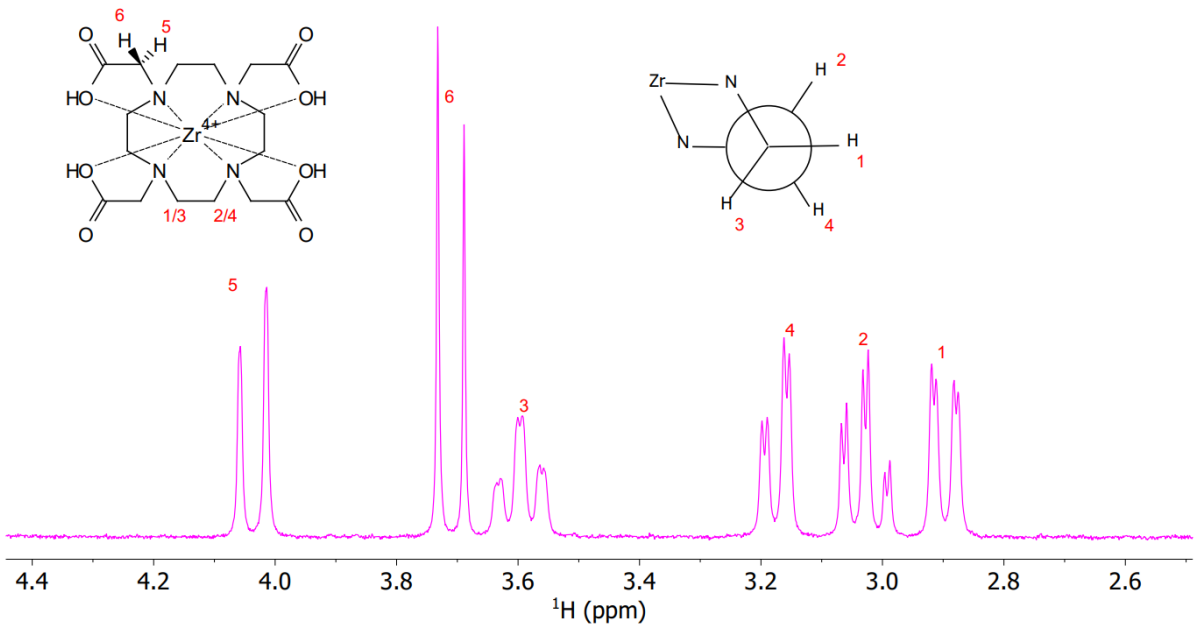

Figure S2: ^{1}H NMR spectrum of Zr-DOTA complex in H_2O ([Zr-DOTA] = 5 mM). $CDCl_3$ with 0.03%$_{Vol}$ TMS was used as external lock solvent (in a capillary tube).

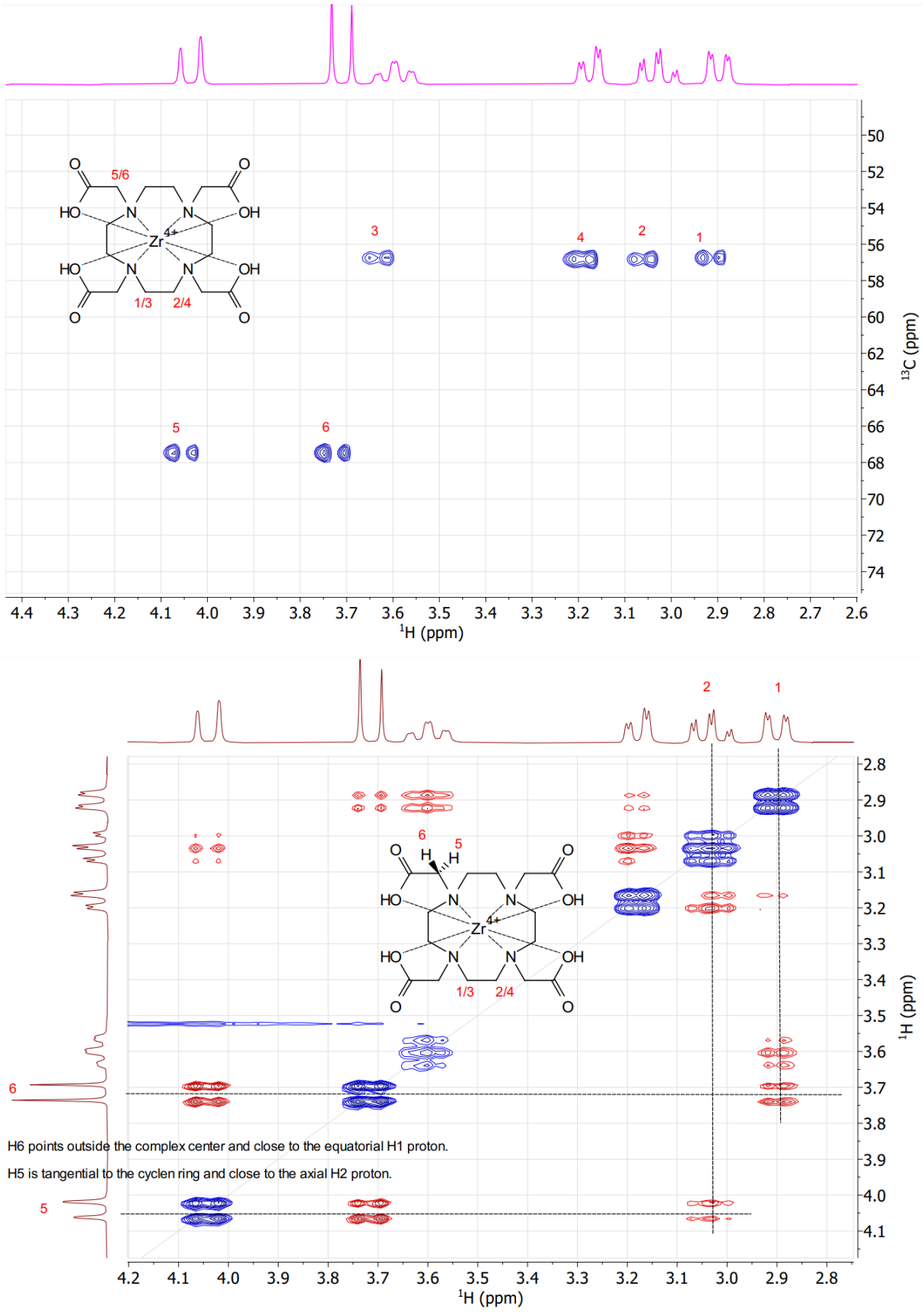

Figure S3: gHSQC ^{13}C (top) and NOESY (bottom) NMR spectra of Zr-DOTA complex in H_2O ([Zr-DOTA] = 5mM). $CDCl_3$ with 0.03%$_{Vol}$ TMS was used as external lock solvent (in a capillary tube).

NMR signals integration and determination of the dose constant.

Proton NMR signals of DOTA and Zr-DOTA between 0 and 30 kGy were integrated. Values obtained are presented in Table S1 and Table S2. This allow the calculation of C/C_0 (C_0 and C are the initial and final concentration) and thus to plot $\ln(C/C_0)$ as a function of the absorbed dose (Figure S4). As it is linear, it shows that we have an exponential decrease with a pseudo-first-order kinetics. The slope of the curve corresponds to the dose constant (d).

Table S1: Proton NMR signals integration for DOTA. NMR signals for acetate and cyclen protons correspond to those shown in Figure 2 (main text) at respectively 2.74 and 2.26 ppm.

kGy	Acetate	Cyclen	Mean %
0	100%	100%	100%
10	23%	20%	22%
20	10%	9%	10%
30	7%	4%	6%

Table S2: Proton NMR signals integration for Zr-DOTA. NMR signals number correspond to those shown in Figure S2.

kGy	6	5	3	4	2	1	Mean %
0	100%	100%	100%	100%	100%	100%	100%
10	77%	77%	83%	80%	82%	80%	80%
20	62%	62%	72%	65%	66%	63%	65%
30	56%	56%	68%	58%	59%	53%	58%

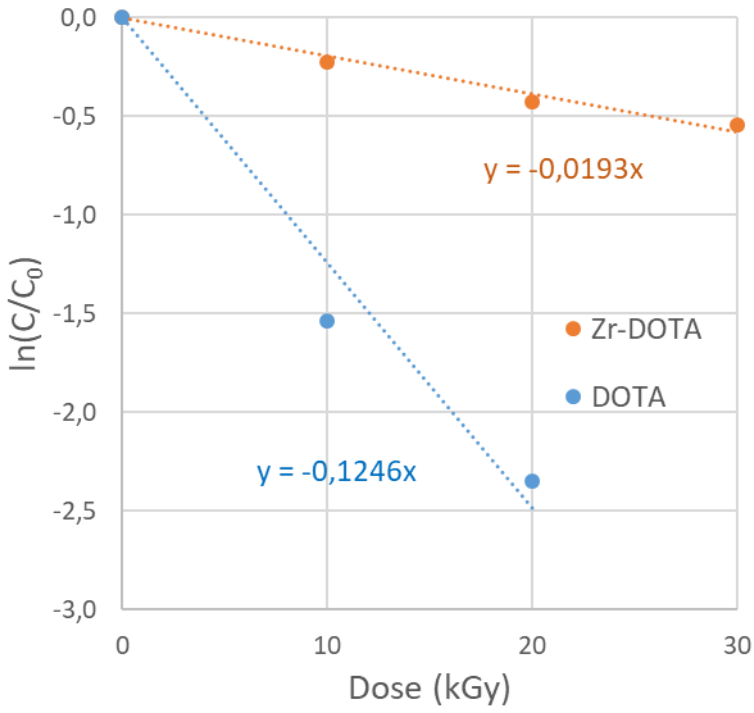

Figure S4: Determination of the dose constant for DOTA (blue) and Zr-DOTA (orange) by plotting $\ln(C/C_0)$ as a function of dose.

Tandem mass spectrometry (MS/MS) of DOTA and major degradation products.

MS/MS analysis were performed for DOTA and degradation products observed (Figure S5 to S7). Because of their low concentration, only the major ones were analysed. Results concerning the free ligand show good agreement with the study of Fiegel et al.[2]

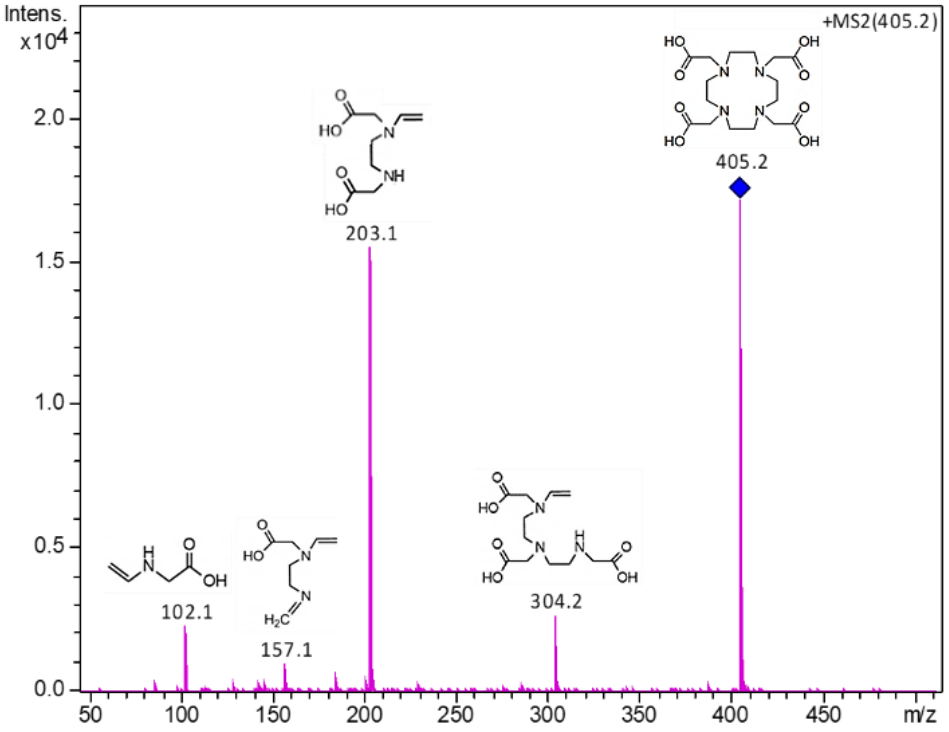

Figure S5: MS/MS of DOTA (m/z = 405.2). Collision: 25 eV.

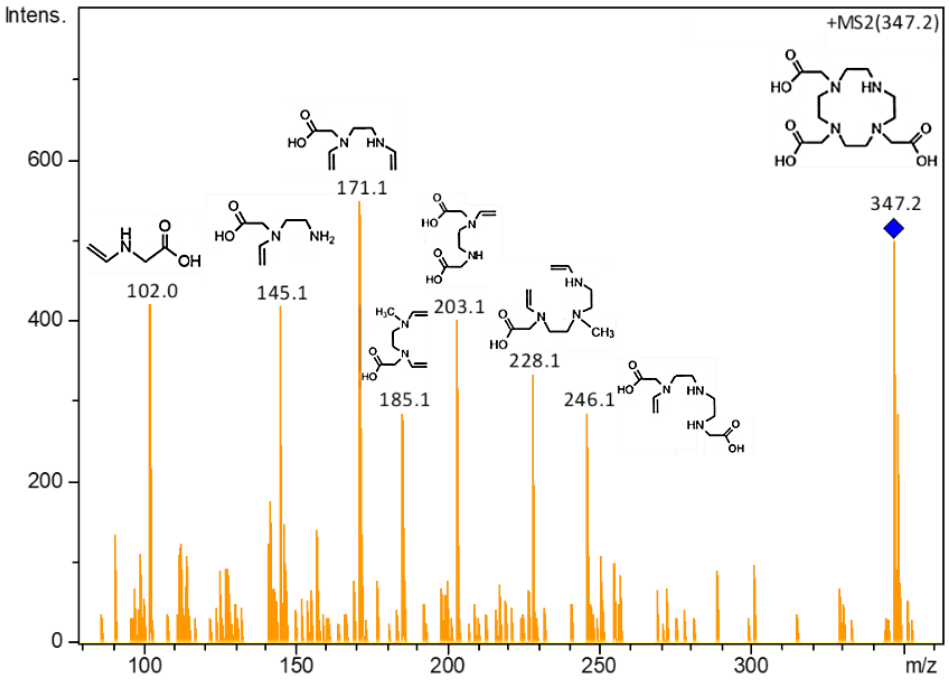

Figure S6: MS/MS of the major degradation product observed for DOTA (m/z = 347.2). Collision: 30 eV.

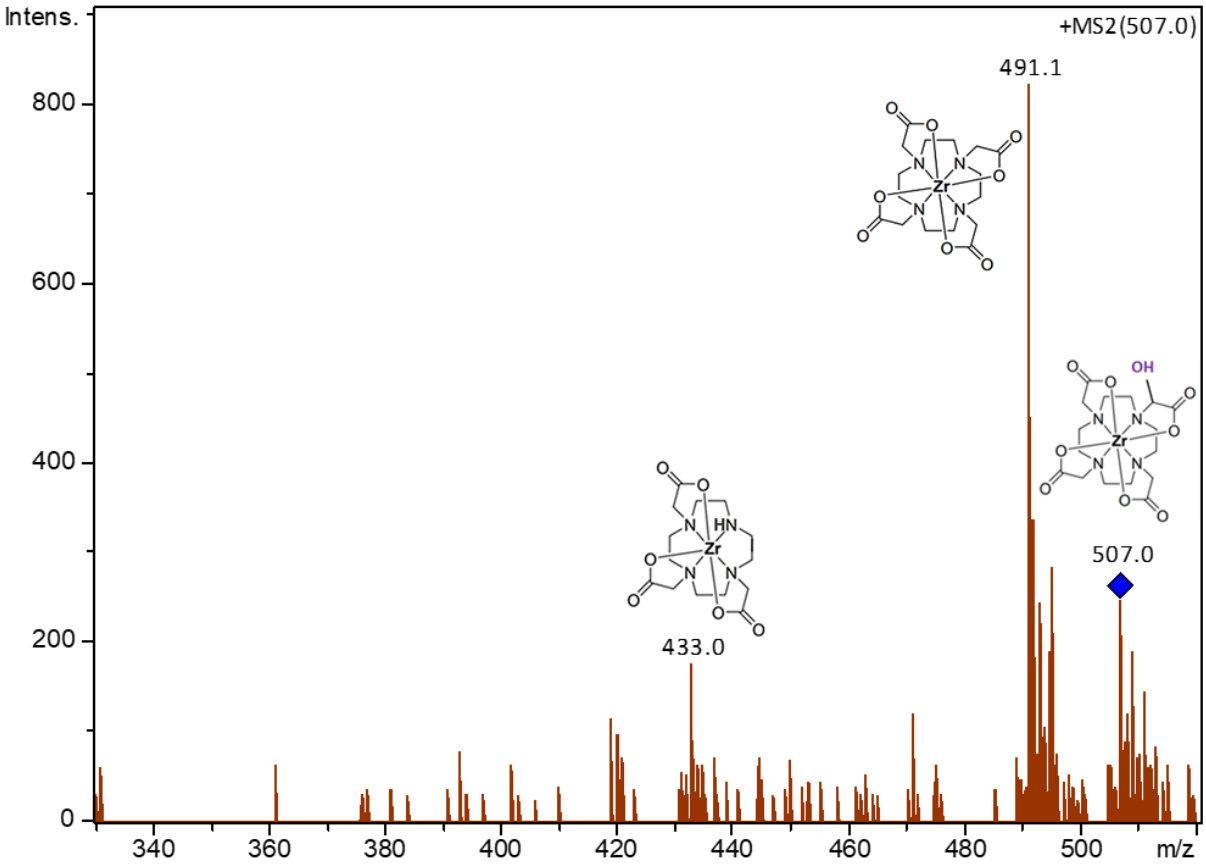

Figure S7: MS/MS of the major degradation product observed for Zr-DOTA (m/z = 507). Collision: 20 eV.

Fukui indices and CDD values for all atoms of H_4DOTA and Zr-DOTA.

Table S3 and Table S4 list Fukui indices and CDD values of H_4DOTA and Zr-DOTA respectively. Figure S8 and Figure S9 present the structures of H_4DOTA and Zr-DOTA with atomic numbering.

Table S3: Fukui indices (f^0) and CDD values for all atoms of H_4DOTA.

Number	Atom	f^0	CDD
1	C	-0.003	0.0001
2	H	0.009	-0.0059
3	H	0.002	-0.0015
4	C	-0.007	0.0108
5	H	0.016	-0.0151
6	H	0.007	-0.0042
7	C	-0.004	0.0151
8	H	0.015	-0.0083
9	H	0.004	-0.0081
10	C	-0.002	-0.0001
11	H	0.008	-0.0050
12	H	0.005	-0.0035
13	C	0.002	0.0046
14	H	0.01	-0.0068
15	H	0.007	-0.0085
16	C	0.003	-0.0061
17	C	0.012	0.0413
18	H	0.045	0.0437
19	H	0.009	0.0145
20	C	0.079	0.1578
21	N	0.003	-0.0008
22	H	-0.002	-0.0035
23	N	0.049	-0.0846
24	O	0.103	-0.1946
25	O	0.039	-0.0853
26	O	0.026	0.0354
27	H	0.017	0.0288
28	O	0.047	0.0887
29	C	-0.003	0.0001
30	H	0.009	-0.0059
31	H	0.002	-0.0015
32	C	-0.007	0.0108
33	H	0.016	-0.0151
34	H	0.007	-0.0042
35	C	-0.004	0.0152
36	H	0.015	-0.0083
37	H	0.004	-0.0081
38	C	-0.002	-0.0001
39	H	0.008	-0.0050
40	H	0.005	-0.0035
41	C	0.002	0.0046
42	H	0.01	-0.0068
43	H	0.007	-0.0086
44	C	0.003	-0.0061
45	C	0.012	0.0419
46	H	0.045	0.0440
47	H	0.009	0.0145
48	C	0.079	0.1581
49	N	0.003	-0.0008
50	H	-0.002	-0.0035
51	N	0.049	-0.0845
52	O	0.103	-0.1945
53	O	0.039	-0.0853
54	O	0.026	0.0355
55	H	0.017	0.0290
56	O	0.047	0.0889

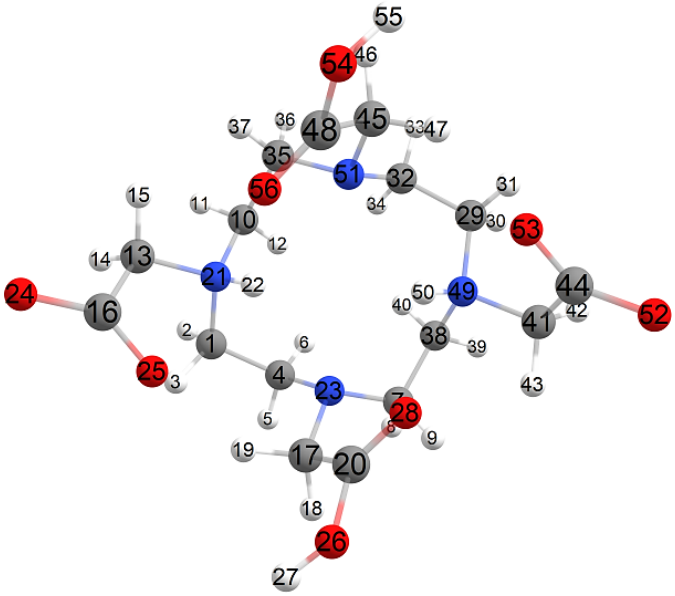

Figure S8: H_4DOTA with atomic numbering for Fukui indices and CDD values.

Table S4: Fukui indices (f^0) and CDD values for all atoms of Zr-DOTA.

Number	Atom	f^0	CDD
1	Zr	0.285	0.532
2	O	0.010	-0.039
3	O	0.096	-0.0909
4	N	0.001	-0.0233
5	C	-0.006	-0.0039
6	H	0.007	0.0019
7	H	0.014	0.0066
8	C	-0.004	-0.0033
9	H	0.014	0.0047
10	H	0.005	0.0031
11	C	0.002	-0.0095
12	H	0.017	0.0027
13	H	0.013	0.0003
14	C	0.011	0.0175
15	O	0.010	-0.0389
16	O	0.096	-0.0908
17	N	0.001	-0.0232
18	C	-0.006	-0.0039
19	H	0.007	0.0019
20	H	0.014	0.0065
21	C	-0.004	-0.0033
22	H	0.014	0.0046
23	H	0.005	0.0031
24	C	0.002	-0.0095
25	H	0.017	0.0028
26	H	0.013	0.0003
27	C	0.011	0.0176
28	O	0.010	-0.0389
29	O	0.096	-0.0908
30	N	0.001	-0.0232
31	C	-0.006	-0.0039
32	H	0.007	0.0019
33	H	0.014	0.0065
34	C	-0.004	-0.0033
35	H	0.014	0.0046
36	H	0.005	0.0031
37	C	0.002	-0.0095
38	H	0.017	0.0028
39	H	0.013	0.0003
40	C	0.011	0.0176
41	O	0.010	-0.039
42	O	0.096	-0.0909
43	N	0.001	-0.0233
44	C	-0.006	-0.0039
45	H	0.007	0.0019
46	H	0.014	0.0066
47	C	-0.004	-0.0033
48	H	0.014	0.0047
49	H	0.005	0.0031
50	C	0.002	-0.0095
51	H	0.017	0.0027
52	H	0.013	0.0003
53	C	0.011	0.0175

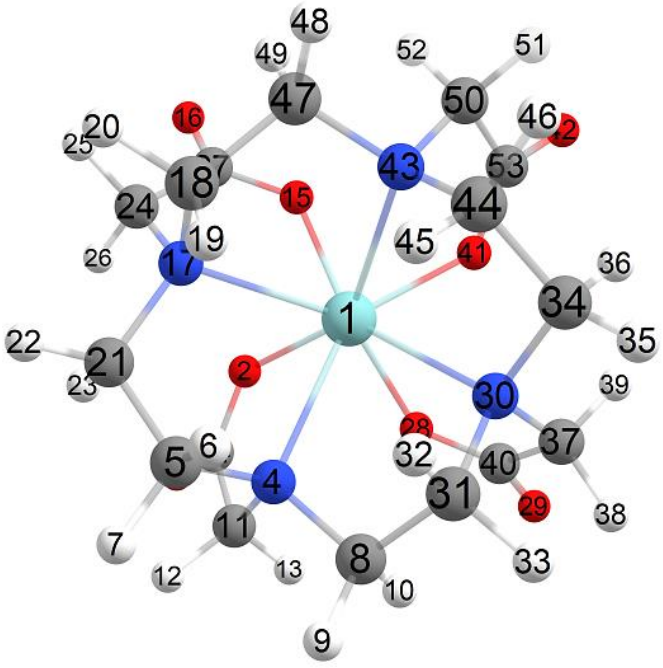

Figure S9: Zr-DOTA with atomic numbering for Fukui indices and CDD values.

1 D. Parker, K. Pulukkody, F. C. Smith, A. Batsanov and J. A. K. Howard, *Journal of the Chemical Society, Dalton Transactions*, 1994, **0**, 689–693.
2 V. Fiegel, C. Berthon, A. Costagliola, G. Blain, J. Vandenborre, J. Vermeulen, G. Saint-Louis, L. Guerin, T. Sauvage, M. Fattahi-Vanani, L. Venault and L. Berthon, *Radiation Physics and Chemistry*, 2019, **165**, 108409.