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From Speciation to Thermodynamic Stability: A Rigid HBED Analogue Controls Isomerization in Gallium-68 Complexes.

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The hexadentate acyclic ligand N,N′-di(2-hydroxybenzyl)-(1,2-cyclohexanediamine)-N,N′-diacetic acid (HBCD) was designed to improve the coordination chemistry of the positron-emitting radiometal ^{68}Ga by introducing rigidity into the ligand backbone. Specifically, the flexible ethylenediamine spacer of the parent HBED ligand[1] was replaced with a cyclohexanediamine (DACH) scaffold to limit the formation of multiple coordination isomers, a well-known issue of Ga^{3+}–HBED systems that can impact *in vivo* performances[2].

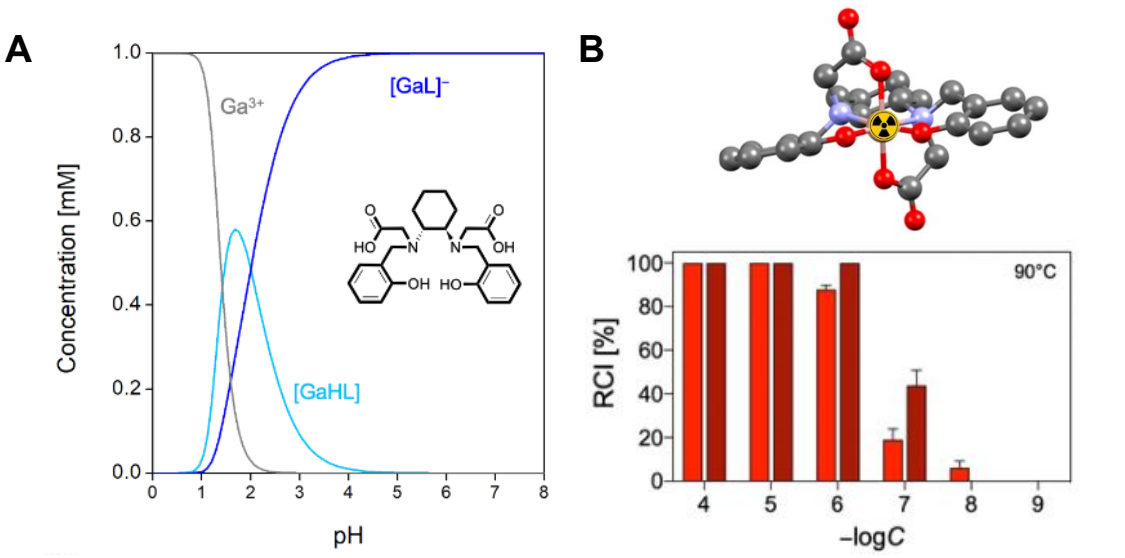

Figure 1. *(**A**) Distribution diagram of Ga^{3+}-HBCD (C_{Ga} = C_L = 1 mM); (**B**) DFT-optimized structure of 6-coordinated cis-trans $[GaL]^-$ (top) and concentration-time-dependent $[^{68}Ga]Ga^{3+}$ radiochemical incorporations (RCIs) of HBCD at 90°C and pH 4.5.*

Here, we report the synthesis of HBCD and a comprehensive investigation of its solution behavior, including protonation equilibria, Ga^{3+} complexation, radiolabeling with generator-produced $[^{68}Ga]Ga^{3+}$, and stability under physiological conditions. Speciation studies, carried out by means of UV-Vis/NMR spectroscopy and MS spectrometry, reveal that the rigid DACH framework directs the formation of a single, well-defined hexacoordinated Ga^{3+} complex, in

contrast to the isomeric mixtures observed for HBED[2]. At physiological pH (7.4), the predominant species is $[GaL]^-$ (**Fig. 1A**), with thermodynamic stability comparable to that of Ga^{3+}–HBED and significantly exceeding that of the clinically workhorse DOTA chelator.

HBCD efficiently coordinates $[^{68}Ga]Ga^{3+}$ under highly diluted radiochemical conditions ($C_L = 10^{-6}$ M, 90 °C, pH 4.5–7) (**Fig. 1B**), and the resulting complex $[^{68}Ga][Ga(HBCD)]^-$ exhibits remarkable stability in biological media.

Overall, these results demonstrate that ligand rigidification is an effective strategy to control solution speciation and suppress isomerization equilibria in Ga^{3+} complexes. HBCD thus emerges as a promising platform for the development of next-generation ^{68}Ga-based radiopharmaceuticals.

References

[1] F.L. Eplattenier, I. Murase, A. Martell, *J. Am. Chem. Soc.* **1967**, *89*, 837–843.

[2] M. I. Tsionou et al., *RSC Adv.* **2017**, 7, 49586–49599.