RIGIDITY AS A TOOL TO CONTROL ISOMERIZATION: A PROMISING HBED DERIVATIVE FOR GALLIUM-68

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The hexadentate acyclic ligand, N,N'-di(2-hydroxybenzyl)-(1,2-cyclohexanediamine)-N,N'-diacetic acid (HBCD)[1] designed for the chelation of the positron-emitting radiometal ^{68}Ga was developed by replacing the flexible ethylenediamine backbone of its parent ligand, N,N′-di(2-hydroxybenzyl)ethylenediamine-N,N′-diacetic acid (HBED), with a more rigid cyclohexane diamine scaffold (DACH). This aims to hinder the formation of multiple isomers upon Ga^{3+}-complexation as observed in HBED-containing molecules,[2] which could affect the *in vivo* performance of ^{68}Ga-labelled radiopharmaceuticals. To this end, we report the synthesis of HBCD, a comprehensive investigation of its acid-base behavior, its Ga^{3+} coordination chemistry, its labelling performances with generator-produced ^{68}Ga, and the stability of the corresponding radioactive complex in physiological media.

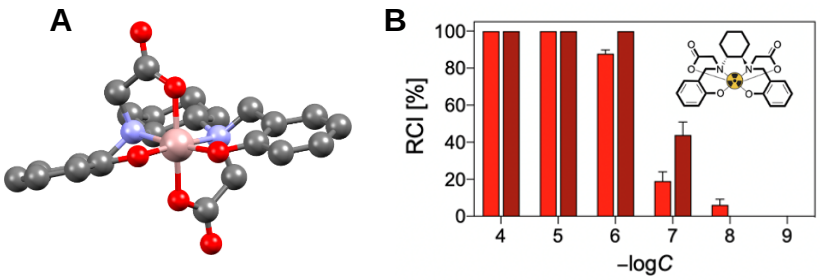

Figure 1: (**A**) DFT-optimized structure of 6-coordinated cis-trans $[GaL]^-$; (**B**) Concentration-time-dependent $[^{68}Ga]Ga^{3+}$ radiochemical incorporations (RCIs) of HBCD at 90°C and pH 4.5.

Our findings confirm that the DACH scaffold promotes the formation of a hexacoordinated single-isomer Ga^{3+} complex (Fig. 1A). As for Ga^{3+}-HBED, the prevailing species at physiological pH (7.4) is $[GaL]^-$, and the two systems have comparable thermodynamic stability. Ga^{3+}-HBCD is by far more stable than the Ga^{3+} complex formed with the clinical workhorse DOTA chelator. HBCD also demonstrated the ability to bind $[^{68}Ga]Ga^{3+}$ under extremely diluted radiochemical conditions ($C_L = 10^{-6}$ M, 90°C, pH 4.5/7) (Fig. 1B).

Notably, $[^{68}Ga][Ga(HBCD)]^-$ shows exceptional stability in biological media. These results position HBCD as a highly attractive chelator for the development of next-generation PET radiotracers, effectively addressing the issue of isomerization in its parent ligand HBED.

[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.