

# STRUCTURE/ (RE)ACTIVITY RELATIONSHIPS IN RADIOPHARMACEUTICAL COORDINATION CHEMISTRY: IS IT NECESSARY?

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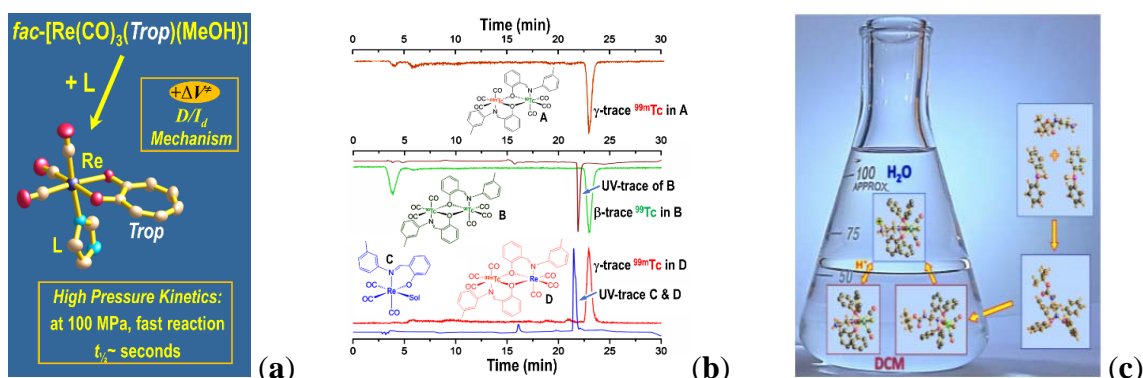
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Three examples of the delicate interplay between structure and (re)activity [kinetics] of model radiopharmaceutical agents are presented, focusing on Tc and Re as well known metal nuclides in nuclear medicine.

Firstly, the intimate mechanism of a simple substitution reaction using the model radiopharmaceutical synthon,  $fac-[M(CO)_3(H_2O)_3]^+$  is highlighted [M=Tc(I), Re(I); the  $H_2O$  easily replaced by appropriate bidentate (or tridentate) director/bio-active entities, see e.g. Fig., **a** below. Depending on the bidentate ligand used to block two coordination sites, a *Dissociative*, or at least an *Interchange Dissociative* mechanism, is induced, displaying rapid kinetics as studied by high pressure stopped flow spectroscopy. [1]

Next, using kinetic principles, and carefully manipulating conditions, dinuclear (using Schiff bases) and tetranuclear mixed nuclide  $^{99m}Tc$ ,  $^{99}Tc$ , and Re complexes are generated via self-assembly, yielding frameworks containing simple single donor atom bridges. The model theranostic complexes are confirmed by HPLC, see Fig., **b** [2,3].

Finally, a proof-of-concept to modify the water solubility/potential biological effects of a *bis*(diphenylphosphino)alkylamine (PNP) bidentate ligand for  $^{186}Re$ ,  $^{188}Re$  and  $^{99m}Tc$ , is presented, to potentially study the *radiotoxicity* of PNP complexes. A tertiary butoxycarbonyl protected *N'*-Boc-ethylenediamine-*N,N*-bis(diphenylphosphino) ligand (*N'*-Boc-PNP) and the corresponding  $fac-[Re(CO)_3(N'-Boc-PNP)Br] are synthesized, see Fig., **c**. De-protecting the *N'*-Boc amine (TFA) produces  $D_2O$  soluble (>0.05 M)  $fac-[Re(NH_3^+-PNP)(CO)_3Br].CF_3COO^-$ , in near quantitative yield).  $^{99}Tc/Re$  can be interchanged, confirmed by the isolation of  $fac-[^{99}Tc(CO)_3(N'-Boc-PNP)(Cl)]$ . [4]$



[1] M. Schutte-Smith, A. Roodt, H.G. Visser. *Dalton Trans.* 2019, 48, 9984-9997. *Back Cover featured.*

[2] A. Frei, P.P. Mokolokolo, R. Bolliger, H. Braband, M.S. Tsosane, A. Brink, A. Roodt, R. Alberto. *Chem. Eur. J.* 2018 24 (41), 10397-10402.

[3] A. Roodt, R.A. Alberto, A. Frei, P.P. Mokolokolo, R.K. Bolliger, A. Brink, D.V. Kama. PCT Patent. *PCT/IB2018/060506* | VS Ref: P3490pc00-TM6JA/LD, *WO2019/123409 A1*, 27 June 2019.

[4] D.V. Kama, A. Frei, A. Brink, H. Braband, R. Alberto, A. Roodt. *Dalton Trans.* 2021, 50 (47), 17506-17514. *Front Cover Featured.*