Synthesis and ^{68}Ga-radiolabelling of several N_3S_3, N_3O_3 and NO_3-type bifunctional chelators: Low-weight lipophilic Ga-chelates

P. J. Riss, F. Rösch
Institut für Kernchemie, Johannes Gutenberg-Universität, D-55128 Mainz, Germany

Introduction: In the present years, the positron-emitter ^{68}Ga undergoes a renaissance as generator-derived PET-nuclide for clinical routine. This is due to the recent improvements in generator performance of commercially available ^{68}Ge/^{68}Ga-generator systems, and post-processing of generator eluents. The latter includes purification of the ^{68}Ga by separation of metal contaminants as well as eluate concentration for labelling purpose.[1] Thereby a chemical generator system is transformed into a medical one. However, the application of ^{68}Ga(III) for radiolabelling is somewhat limited to aqueous media and most reports on Ga-radiochemistry are concerned with polyamino-polycarboxylate chelators. The idea of lipophilic metal-chelates, dedicated for molecular imaging is not new. However, most of the earlier approaches did not specifically target bifunctional chelators, but elucidated the synthesis of rather lipophilic complex-precursors. This study reports ^{68}Ga-labelling and lipophilicity of mono- and bifunctional chelator-derivatives.

Experimental: The synthesis of a novel bifunctional N_3S_3-type chelator, derived from 1,4,7-triazacyclononane, initial ^{68}Ga-radiolabelling and the determination of stability and lipophilicity of the compound are described. For comparison, the Ga-complex of tris-mercaptoethyl-1,4,7-triazacyclononane was also studied. Furthermore tetra- (NO_3) and hexadentate (N_3O_3) bifunctional chelators bearing phenol-donors were synthesised, labelled and their octanol/water partition coefficient was assessed experimentally.
Ga was eluted with different acetone–based, non-aqueous solvent systems providing n.c.a. ^{68}Ga(acac)$_3$ as labelling synthon. ^{68}Ga-labelling was performed in chloroform in a focused microwave synthesis system.

Results: The ^{68}Ga-labelled N_3S_3 chelate was obtained in a radiochemical yield of 80 ± 5 % after a reaction time of 7 minutes. It remained intact over 3 h in a DTPA-challenge experiment, indicating sufficient stability for PET examinations. The 1-octanol/water partition coefficient log P was determined by HPLC, the results indicate rather lipophilic properties for the obtained chelate. The ^{68}Ga complexes of various mono and bifunctional chelators with lipophilic properties have been screened for their log P values. The results indicate, that these precursors indeed form stable lipophilic radiochelates. The bifunctional analogues of these complexes enable conjugation of targeting vectors for molecular imaging.

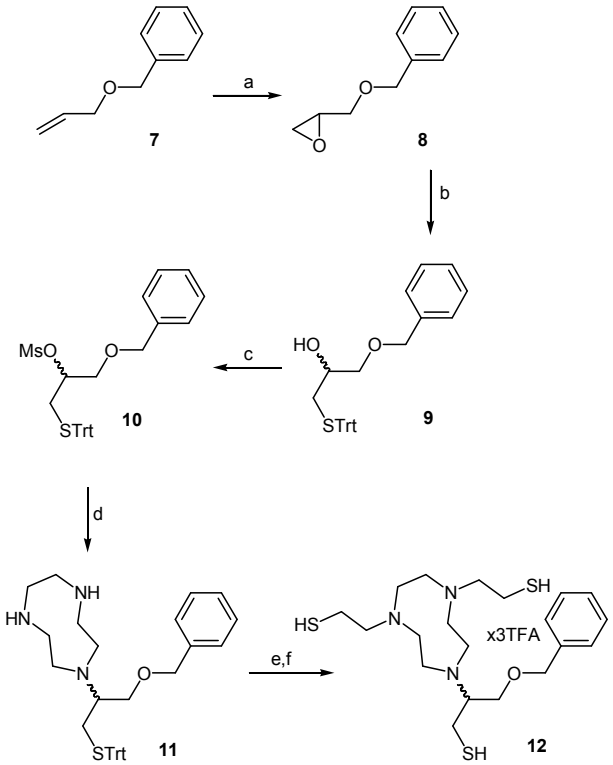

Figure 1: Synthesis of racemic model compound **12**

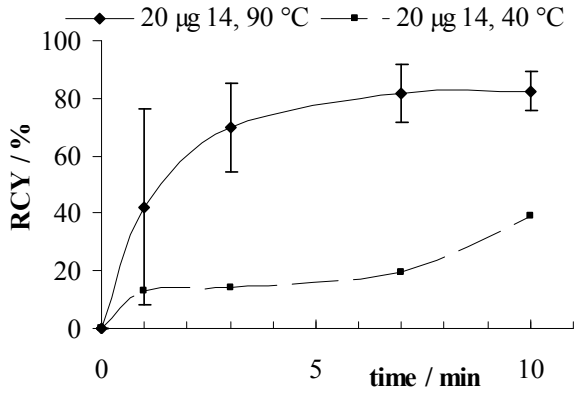

Figure 2. ^{68}Ga radiolabelling of precursor 12 at 40 °C and 90 °C.

References

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