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Radiopharmaceutical chemistry of iodine

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Introduction:

Among the SPECT nuclides, iodine is used for the longest time in nuclear medicine, because of it´s extensive use in thyroid diagnostic and therapy with sodium iodide. It´s important role today derived from the variety of available iodine isotopes useful for in-vitro procedures (I-125; $t_{1/2}$=60d; EC;α=35 keV), in-vivo diagnostic (I-123; $t_{1/2}$=13h; EC; α=159 keV for SPECT and I-124; $t_{1/2}$=4.18d; part.α; α=511 keV for special PET appl.) and therapeutic applications (I-131; $t_{1/2}$= 8d; α; α=364 keV). In addition, the well known iodine chemistry and well working radio-labeling protocols extended it´s use to a wide variety of SPECT-tracers.

Since the occurence of drugs having iodine atoms within their structure is quite limited, the great usefulness of iodinated compounds stems from the ease of detection, availability and useful radiochemistry. Problems with iodinated tracers often arise from insufficient in-vivo stability and in addition out of the rather large sterical hindrance of the iodine label accompanied by lipophilicity changes with respect to the unlabeled drugs.

Radiolabeling Techniques:

Oxidative radio-iodination:

The majority of radioiodination techniques were created for labeling proteins. As well known from thyroid hormones, tyrosyl residues readily react with positive iodine species to form the iodinated compounds. In the same way, tyrosyl residues in peptides and protein, can be labeled with excellent yields. Mechanistic studies showed that the phenolate anion (of Tyr) is attacked by electrophilic aromatic substitution. In the early days, molecular iodine (I_2)or ICl was applied for radioiodination as in such molecules iodine carries a formally positive charge allowing electrophilic attack. Today, iodine is almost exclusively available in the form of iodide (ox-state –1) and some means of oxidation must be employed to obtain reactive iodine species (ox-state +1). Chloramine-T and Iodogen are the main used reagents for direct labeling of peptides, proteines and activated aromatic compounds. The disadvantage of this method is the relative low specificity and proteins containing more than one tyrosine moiety will be randomly labeled. In small aromatic molecules ortho and para products as well as diiodinated products may be obtained and therfore a number of more specific methods were developed:

Iododemetallation:

A variety of organometallic compounds react with iodide at very mild oxidizing conditions to form iodinated compounds. Most often stannylated precursors are used for this purpose. However, Tl, Hg, B, Si, and Ge can also be employed. In contrast to the direct electrophilic substitution, also non-activated aromatic or vinylic compounds can be regioselectively labeled. Furthermore, this reaction is of particular importance in creating metabolic stable iodinated compounds. It´s limitation is usually the synthetic availability of metallated precursors. Therefore, this approach is also used in prosthetic group labeling (see below).

Nucleophilic Substitution:
The least complex means of radioiodination is the substitution of radioactive iodide for a stable iodide already incorporated in the molecule of interest. This can be acchieved by simply heating the compounds in an appropriate solvent such as water or acetone. However, such compounds are accompanied by the stable iodine analog and therefore often not useful in nuclear medicine. A way to avoid this is to employ brominated precursors and very high specific activities can be achieved after chromatographic separation of the bromo- and iodo analogs. The disadvantage is the high temperature needed to obtain useful yields making this method practical only for very stable small molecules. Efforts to improve radiochemical yields have led to copper catalyzed substitution reactions, proven useful to obtain a number of interesting iodinated receptor ligands mainly used in brain research.

Prosthetic groups:
Many organic molecules do not have activated aromatic groups that lend themselves to direct oxidative radioiodination. A way to label those is the use of prosthetic groups. A prosthetic group for iodination contains some type of activated moiety to receive the label and some linker to covalently attach it to the molecule to be labeled. The famous Bolten-Hunter method employed N-succinimidyl 3-(4-hydroxyphe nyl)propanoate. The prosthesis is first labeled by the chloramine-T method and then coupled under mild conditions to the protein or any other reactive amine containing molecule. This type of prosthetic group labeling was extensively optimized in especially with respect to metabolic stability of the radiolabel (such as iododemetallation). An interesting newer approach is the use of residualizing prosthetic groups (1), which are designed in order to be metabolized to products that would be retained within the cell after internalization by the target cells.

Recent developments:
With the increasing role of PET and highly sophisticated Tc-99^{m} chemistry for new SPECT tracers, the clinical use of iodinated radiopharmaceuticals decreased significantly. However, in especially with small molecules, Tc-99^{m} can often not displace iodinated SPECT tracers. In radiopharmaceutical drug discovery, iodine will keep it´s strong importance, mainly in earlier development stages. For example, major radiopharmaceuticals like somatostatin analogs or antibodies like zevalin started their "radioactive career" as iodinated compounds.

References
For a recent review see:
Adams M.J., Wilbur D.S. Radiohalogens for imaging and therapy. Chem. Soc. Rev. 2005; 34: 153-163

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