Synthesis of N-[^{11}C]methyl-D-aspartatic acid [^{11}C]-NMDA

M. Schönberger[2], J.M. Hooker[1], J. Fowler[1]

[1]*Brookhaven National Laboratory, 11973 Upton, NY, USA* [2]*Johannes Gutenberg Universität, 55099 Mainz, Germany*

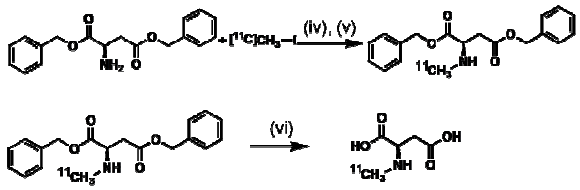
Introduction:

The *N*-methyl-D-aspartic acid (NMDA) subtype of ionotropic glutamate receptors plays a major role in excitatory synaptic transmission. It affects synaptic plasticity like long term depression and long term potentiation, which are thought to be involved in processes such as learning and memory [1]. Anomalies can lead to a broad range of neurological disorders, e.g. acute stroke, chronic neurodegeneration in amyotropic lateral sclerosis or Alzheimer desease. In order to investigate further coherences between known neurological deseases and NMDA receptor-related signaling pathways, NMDA itself was labelled with the positron emitter carbon-11 (half life = 20.38 min) for positron emission tomography (PET) studies.

Results and Discussion:

Our studies focused on the synthesis of *N*-methyl-D-aspartate (NMDA) precursors that could be conveniently labelled with [^{11}C]iodomethane and rapidly purified. First we decided to synthesize the methyl ester of L-aspartic acid using thionyl chloride in methanol as a solvent at room temperature. However, we felt it would be advantageous to have a chromophore attached so we turned our attention to the synthesis of benzyl esters by a condensation reaction in toluene with *p*-toluene sulfonic acid as a catalyst, using a Dean-Stark trap. Aware of the fact that we next wanted to radiolabel the aspartic acid dibenzyl ester, we needed to develop standards and corresponding chromatography conditions.

Scheme 1. Radioactive methylation reactions



(i) $[^{11}C]CH_3I_{(g)}$, $Ar_{(g)}$, MeCN, 0 °C (ii) 40 °C, 5 min (iii) LiOH, H_2O, 80 °C, 10 min

As a standard for the first reaction, the insertion of a [^{11}C]methyl group, we synthesized NMDA by reacting D-aspartic acid dibenzyl ester with iodomethane in acetonitrile at room temperature, scheme 1. As expected, the reaction led to a normal distribution and had to be purified by FLASH chromatography. With our precursor, standards and chromatography conditions in hand, we proceeded to radiochemistry. Briefly, [^{11}C]iodomethane carried by argon was led directly into a cooled soltion of 0.3 mg aspartic acid dibenzyl ester in 0.3 mL acetonitrile. This solution was heated to 40 °C for 5 min and then analysized by radio-TLC showing a 87% yield. The saponification occured by introduction of 4 eq of aqueous LiOH and heating to 80 °C for 10min showing a 95% radioactive yield (Fig.1).

Conclusion:

[^{11}C]-NMDA was prepared in a two step rapid and high yielding sequence. D-aspartic acid dibenzyl ester was an excellent precursor for this alkylation reaction that could be both simply synthesized and saponified. This discovery provides the possibility for *in vitro* or *in vivo* studies on NMDA like glutamate receptors using positron emission tomography.

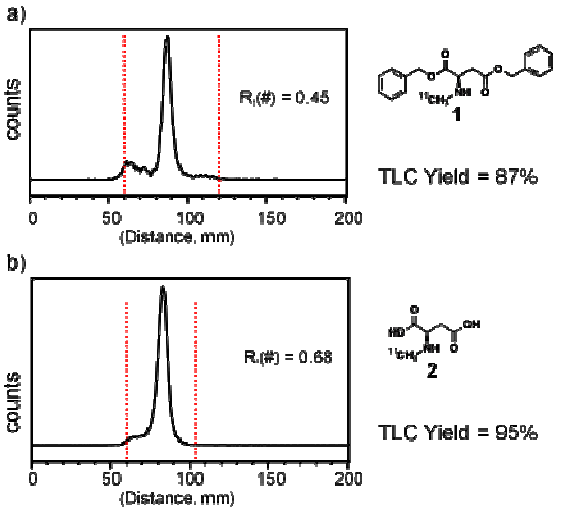


Figure 1. Radio TLC Analysis of compound **2**. The peak level is associated to the radioactive decay of the positron emitter carbon-11

References

[1] (a) Shankar, G. M.; Bloodgood, B. L.; Townsend, M.; Walsh, D. M.; Selkoe, D. J.; Sabatini, B. L. *J Neurosci* **2007**, *27*, 2866-75 (b) Villmann, C.; Becker, C. M. *Neuroscientist* **2007**, *13*, 594-615.

Acknowledgment: I want to thank Dr. Jacob Hooker, Prof. Dr. Joanna Fowler and Prof. Dr. Rösch. Funding by DAAD and DOE.