Abstract: The purpose of this study was to design, synthesize, and initially characterize a representative set of novel constructs for large-molecular radiographic/computed tomography (CT) contrast agents, intended for a primarily intravascular distribution. A new assembly of well-known and biocompatible components consists of paired, symmetrical dendritic polyllysines initiated from both ends of a poly(ethylene glycol) (PEG) core, yielding an array of multiple free amino groups to which were conjugated highly soluble and stable triiodophthalamide ("triiodo") moieties. An array of six dendritic contrast agents was synthesized originally, using three different PEG cores (3, 6, 12 kDa) with t-Boc lysine-generated dendrimer "amplifiers" (from three to five generations) containing 16 to 64 amino groups for conjugation with reactive triiodo moieties. A clinically used, nonionic, small molecular CT contrast agent, iobitridol, was derivatized via a hydroxyl protection/deprotection strategy, introducing a new carboxyl group available for conjugation to the lysine amino groups of dendrimers. Final products were purified by size exclusion chromatography and characterized by NMR, UV, HPLC, and elemental analysis. Preliminary evaluations were conducted for physicochemical characterization and in vivo CT contrast enhancement in a rat model. All six iodinated PEG-core
dendrimer conjugates were synthesized in good yields, with a high degree of size monodispersity, large apparent molecular weight, favored physicochemical properties. A representative compound, PEG12000-carbamate-Gen4-IOB conjugate, 27% (w%) rich in iodine, demonstrated a desirable strong and persistent intravascular enhancement with a monoexponential blood half-life of approximately 35 min assayed by dynamic CT imaging and also showed high water solubility (>550 mg/mL at 25 degrees C), large apparent molecular size (comparable to a 143-kDa protein), high hydrophilicity (butanol-water partition coefficient 0.015), and stability to autoclaving conditions. This study showed the synthetic feasibility, desired basic characteristics, and potential utility for CT contrast enhancement achieved with a new type of iodinated, large-molecular PEG-core dendritic construct. Further development of this class of macromolecular contrast agents will be required to define the optimal formulation, pharmacology, safety profile, and the full range of diagnostic applications including tumor microvascular quantitative characterization by CT imaging.