A New Myocardial Imaging Agent: Synthesis, Characterization, and Biodistribution of Gallium-68-BAT-TECH

H. F. Kung, B. L. Liu, D. Mankoff, M. P. Kung, J. J. Billings, L. Francesconi, and A. Alavi

Department of Radiology, University of Pennsylvania, Philadelphia, Pennsylvania

In order to develop a new myocardial perfusion agent for positron emission tomography (PET), a new lipid-soluble gallium complex was evaluated. Synthesis, radiolabeling, characterization, and biodistribution of a unique gallium complex, [^{67}Ga]BAT-TECH (bis-aminoethanethiol-tetraethyl-cyclohexyl), are described. The complex formation between Ga^{+3} and BAT-TECH ligand is simple, rapid, and of high yield (≥95%). This process is amenable to kit formulation. The complex has a net charge of +1 and a Ga/ligand ratio of 1:1. Biodistribution in rats shows high uptake in the heart as well as in the liver. When [^{68}Ga] BAT-TECH was injected into a monkey, the heart and liver are clearly delineated by PET imaging, suggesting that this complex may be a possible tracer for myocardial perfusion imaging.

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Generator-based radiopharmaceuticals may provide a useful and effective way of positron emission tomography (PET) imaging without an on-site cyclotron. The germanium-68/gallium-68 generator is commonly used in PET facilities as a source of positron radionuclide for physics experiments, and it is also suitable for preparing radiopharmaceuticals. The physical half-life of the parent, ^{68}Ge, is 287 days, which means that the generator is useful for about one year. The half-life of the daughter, ^{68}Ga, is 68 min, which is convenient for multi-step chemical preparation. A large number of ^{68}Ga complexes have been reported (*1–11*). However, there are only a few ^{68}Ga radiopharmaceuticals currently being used in humans. Development of lipid-soluble gallium complexes for imaging the brain and heart has not been successful. A series of lipid-soluble gallium complexes potentially useful for myocardial imaging has been reported (*3,4*). Unfortunately, these agents behave neither as freely diffusible tracers nor as microspheres; therefore, they are not useful as myocardial perfusion agents. Other types of neutral and highly lipid-soluble gallium complexes designed for brain perfusion imaging have been reported (*6,11*). These complexes showed little brain uptake, which suggests that lipid-solubility is not the sole requirement for molecules to penetrate the intact blood-brain barrier.

Despite its short half-life (75 sec), rubidium-82, produced by a strontium-82/rubidium-82 generator, is useful for myocardial perfusion imaging (*12,13*). It has now been approved for routine clinical use. The generator-produced agent can support clinical cardiac PET imaging without an on-site cyclotron. A comparable ^{68}Ga compound with a half-life of 68 min may provide significant improvements for PET myocardial imaging.

Another potentially useful positron-generator is zinc-62/copper-62 (*14–17*) ($T_{1/2}$ is 9 hr and 9 min for parent and daughter radionuclides, respectively). Several recent reports indicate that this generator may also be feasible for routine clinical use (*15–17*). Since the parent half-life is relatively short (9 hr), the generator is only useful for one to two days. Nonetheless, the clinical potential of a series of copper(II) (bisthiosemicarbazone) complexes, specifically Cu(PTSM) (Fig. 1), as myocardial and cerebral perfusion tracers has been demonstrated (*18,19*). The Cu(PTSM) is based on an N_2S_2 ligand and is a neutral and lipid-soluble compound. After an i.v. injection, the compound passes through the cell membrane, including the intact blood-brain barrier. Apparently, the compound decomposes intracellularly after interacting with sulfhydryl groups (*20*). The regional distribution is a reflection of regional perfusion, a property consistent with "chemical microspheres." Therefore, this agent in combination with the ^{62}Zn/^{62}Cu generator may provide a convenient source of radiopharmaceuticals for measuring regional blood perfusion of the brain and heart. However, ^{68}Ga-labeled compounds may offer some advantages because the longer half-lives of the parent and daughter may

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For reprints contact: Hank F. Kung, PhD, Division of Nuclear Medicine, Department of Radiology, University of Pennsylvania, 3400 Spruce St., Philadelphia, PA 19104.

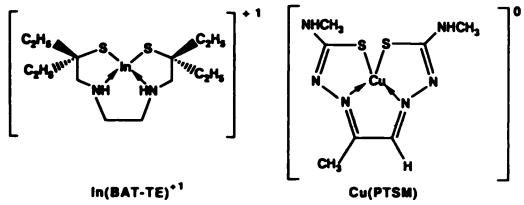

FIGURE 1
Chemical structure of In(BAT-TE)$^{+1}$ and Cu(PTSM).

greatly enhance the clinical potential as PET radiopharmaceuticals.

Recent advances in technetium-99 chemistry of complexes based on N_2S_2 (bisaminoethanethiol, BAT) ligands have dramatically enhanced our ability to predict the chemical structure of the final ^{99m}Tc complexes. This series of ligands forms strong complexes with $(Tc{=}O)^{+3}$ (*21–33*). The x-ray crystallography studies of several N_2S_2 complexes developed by us and others have confirmed the $(Tc{=}O)^{+3}$ chemical state and the pyramidal core structure (*21,30,31*). We have extended the use of the BAT ligands to investigate the radiochemistry of indium, a plus three cation (*34*). We have initiated a study using the N_2S_2 ligand, bis-(aminoethanethiol) tetraethyl (BAT-TE), for complexing In^{+3}. The result suggested that a lipid-soluble and plus one charged In(BAT-TE)$^{+1}$ was formed (Fig. 1) and that it may be useful as a myocardial perfusion imaging agent. In this paper, we turn our attention to synthesis, radiolabeling, characterization, and biodistribution of a similar gallium complex, Ga(BAT-TECH)$^{+1}$ (bis-aminoethanethiol-tetraethyl-cyclohexyl) (Fig. 2). For convenience, [^{67}Ga]gallium citrate from commercial sources was employed as the tracer in this paper. However, for imaging studies, ^{68}Ga is the radionuclide suitable for PET imaging.

MATERIALS AND METHODS

General

The preparation of BAT-TECH was achieved by a method reported previously (*23*). The only difference is that lithium aluminum hydride was employed for the final reduction step of the diimine intermediate (*24,28,30*). The dimercapto hydrochloride salt of BAT-TECH was precipitated and used for this study. Gallium-67 was obtained from Mallinckrodt (St. Louis, MO) as gallium citrate. Gallium-68 was obtained by eluting a ^{68}Ge/^{68}Ga generator (NEN/DuPont, N. Billerica, MA) with 0.1 N HCl.

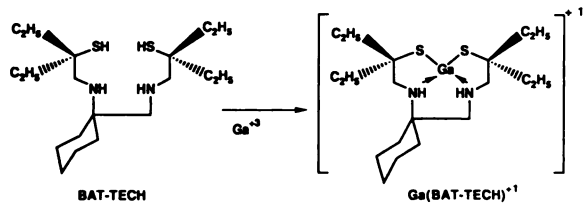

FIGURE 2
Chemical equation for the formation of Ga(BAT-TECH)$^{+1}$.

Radiolabeling

No-carrier-added ^{67}Ga-citrate (1 mCi/ml) was added to a test tube containing the BAT-TECH ligand (1 mg) in 0.5 ml of water and adjusting the pH to 3.1 ± 0.1 by the dropwise addition of a solution of 5% NaOH or 1 N HCl. The mixture was vortexed and kept in a heating block at 75°C for 0.5 hr. The percent labeling yield was measured by thin-layer chromatography (silica gel plate, developing solvent:acetone:acetic acid 3:1, V/v, R = 0.1 and 0.7 for Ga-citrate and Ga-BAT-TECH, respectively). The radiochemical purity is usually over 96%. This material was used directly for animal studies. The effects of pH, temperature, and ligand concentration on the formation of this complex was determined by the same TLC technique. For charge determination experiments, the ^{67}Ga-BAT-TECH complex was purified on preparative silica gel plates (developed by the same solvent system). The desired fraction was scraped from the plates and redissolved in water. The solution was centrifuged and the supernatant containing the ^{68}Ga-BAT-TECH complex was used (radiochemical purity >99%).

For a monkey imaging study, ^{68}Ga was eluted from a ^{68}Ge/^{68}Ga generator and extracted in a 6N HCl solution with ether (3 × 1.5 ml) (*35*). The combined extract was dried under a stream of nitrogen. To this residue, BAT-TECH ligand (3 mg/ml, pH 3.1) was added. The mixture was heated in a heating block at 75°C for 15 min. After filtration through a 0.22-micron filter, the material was assayed and injected into a monkey. The whole preparation was accomplished in 40 min (yield 40%, purity >98%).

Characterization of [^{67}Ga]BAT-TECH Complex

The same methods as those reported previously for characterization of In(BAT-TE)$^{+1}$ were also employed for identifying the Ga(BAT-TECH)$^{+1}$ complex (*34,36*).

Determination of Composition. The composition of the complex was determined by a pH titration method (Orion, pH meter 611). The formation of this complex follows the equation:

$$\text{BAT-TECH} + Ga^{+3} \rightleftharpoons (\text{Ga-BAT-TECH})^{+} + 2H^{+}.$$

When [Ga]BAT-TECH is formed, two equivalents of [H^+] are released and can be titrated by a standardized sodium hydroxide solution (0.01 N). The titration is performed under two different conditions: solution (A) containing 1.0 mg (0.391 m*M*) of BAT-TECH in 7 ml of 1 m*M* HCl solution and solution (B) containing the same amount of ligand, 1.0 mg of BAT-TECH in 3 ml of 1 m*M* HCl, and 4 ml of $Ga(NO_3)_3$ solution (1.9 mg in 50 ml of 1 m*M* HCl, 0.168 m*M*). Both of the solutions contain 0.1 N NaCl (the same ionic strength). Based on the difference between titration curves A and B, the formation function can be calculated (*34,36*):

$$\bar{n} = \frac{(\text{Ga-BAT-TECH})^{+}}{[T_M]}$$

where $[T_M]$ = total concentration of Ga^{+3}.
At the end point of titration the formation function n approaches unity if the Ga/ligand ratio is equal to one.

Determination of Net Charge. Determination of net charge

of this complex was achieved by the ion exchange method (*34,37*). Ion exchange resin (strong cation R-SO_3H, 10 mg/each experiment) was placed in a test tube with a solution of radioactive (no carrier-added) [^{67}Ga]BAT-TECH (5 ml, at pH 0.9–2.3). The mixture was shaken for 1 hr. The resin (RH_x) and the solution were separated. The residual radioactivity in the solution was measured and the distribution coefficient (D) was calculated by counts in resin/counts in solution.

$$[*\text{Ga-BAT-TECH}]_{aq}^{+X} + RH_x \rightleftharpoons \text{R-}[*\text{Ga-BAT-TECH}] + xH^+$$

where RH = cation exchange resin.

The equilibrium constant = K:

$$K = \frac{\text{R-}[*\text{Ga-BAT-TECH}][H^+]^x}{[*\text{Ga-BAT-TECH}]_{aq}^{+X}[RH_x]}$$

Distribution coefficient = D:

$$D = \frac{\text{R-}[*\text{Ga-BAT-TECH}]}{[*\text{Ga-BAT-TECH}]_{aq}^{+X}}$$

$$\log D = \log K + \log[RH_x] + xpH \Rightarrow \log D = xpH + C$$

The relationship between log D and pH is a straight line and the slope, x, is equal to the net charge of the complex.

Biodistribution in Rats

Biodistribution of [^{67}Ga]BAT-TECH was studied in male Sprague-Dawley rats (200–250 g), which were allowed access to food and water ad lib. Saline solution containing [^{67}Ga]BAT-TECH in a volume of 0.2 ml was injected directly into a femoral vein. Rats were killed at 2, 30, and 60 min postinjection by cardiac excision under ether anesthesia. The organs of interest were removed and counted using a well-type gamma counter. Percent dose per organ was calculated by comparison of tissue counts to suitably diluted aliquots of injected material. Total activities of blood and muscle were calculated assuming that they are 7% and 40% of total body weight, respectively. The % dose/gram of each organ can be calculated by dividing the % dose/organ by the mean organ weight (i.e., average 200 g rat: heart, 0.85 g; brain, 1.65 g; blood, 18 g; liver, 9 g; kidney, 1.9 g; lungs, 1.6 g). Each time point consists of a group of three rats.

Imaging Study in a Monkey

A monkey (cynomologous, male, 10 lb) was sedated with ketamine (50 mg i.m.) and then anesthetized with nembutal (0.2 ml, 65 mg/ml, additional amount was used as needed). The monkey was positioned in the PENN-PET (*38*) tomograph and the scan started at 7 min after an i.v. injection of [^{68}Ga]BAT-TECH (424 μCi/3 ml of saline). The monkey was scanned for 15 min and a total of 5.8 million counts were collected. Data were reconstructed in 45 overlapping 8-mm thick slices using filtered backprojection with a Hanning filter. In this preliminary study, no attenuation correction was performed. Slice spacing was 2 mm, yielding image data on a 2 × 2 × 2 mm grid suitable for displaying transverse sections.

RESULTS

Characterization of [^{67}Ga]BAT-TECH

Effects of Acidity, Temperature, and Ligand Concentration. The formation of the complex was evaluated at various pHs to determine the optimum conditions for labeling. The results shown in Figure 3 suggest that the labeling yield reaches a plateau at pH 3–5. At a more basic pH, precipitation of the ligand, due to the limited solubility in water, is observed. The reaction temperature is also an important factor controlling the rate of complex formation, however, as shown in Figure 4, when the reaction temperature is above 40°C, the labeling yield appears to be constant at >93%. The concentration of the ligand in the reaction mixture also affects the labeling yield. When the concentration is above 3 mg/ml, the labeling yield is >97% (Fig. 5).

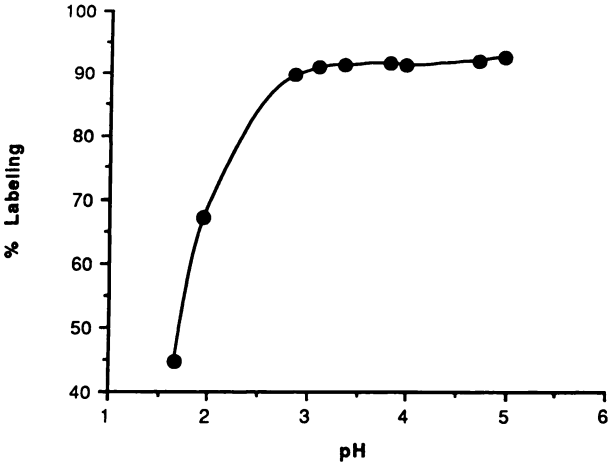

FIGURE 3
Effects of pH on the formation of Ga(BAT-TECH)$^{+1}$. The optimum pH range is between 3 and 5.

Determination of Composition of [Ga]BAT-TECH. As indicated in Figure 2, the formation of no-carrier-added [Ga]BAT-TECH produces two hydrogen ions. Due to the release of these two hydrogen ions, the pH of the reaction solution will decrease. This change can be measured by using acid-base titration techniques. The titration curves for BAT-TECH ligand at the same

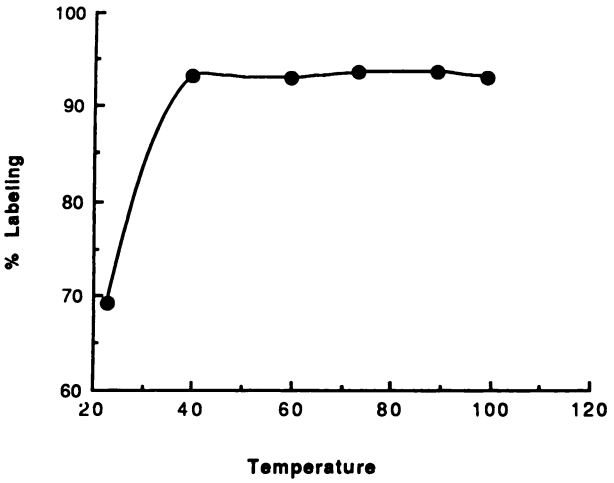

FIGURE 4
Effects of temperature on the formation of Ga(BAT-TECH)$^{+1}$. The formation of the complex reaches a plateau above 40°C.

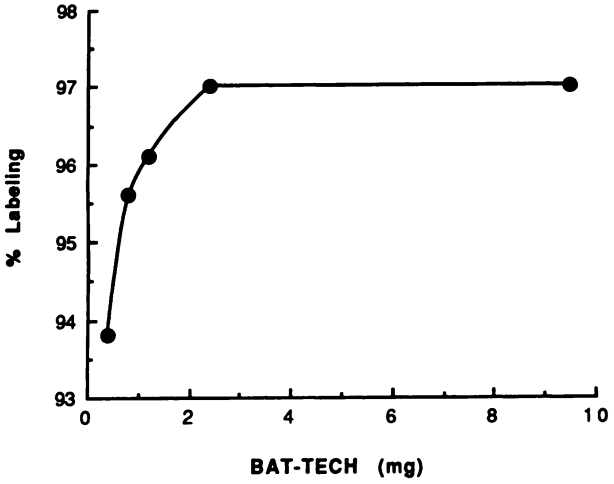

FIGURE 5
Effects of ligand concentration on the formation of Ga(BAT-TECH)$^{+1}$. The formation of the complex reaches 97% at 3 mg/ml.

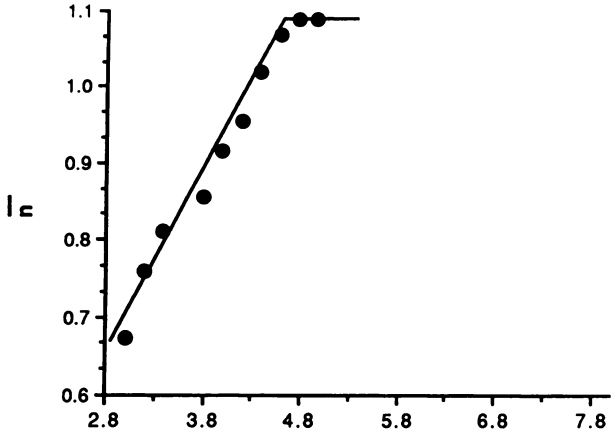

FIGURE 7
The relationship of the formation function (n) and pH. This figure indicates that the composition of the complex is 1:1, confirming the chemical structure shown in Figure 1.

concentration (0.391 m*M*) with and without the presence of the gallium metal ion (0.148 m*M*) are presented in Figure 6. From this figure, the [H^+] can be calculated. The ionic strength of the solutions for generating curves A and B is the same. At an equal pH value, curves A and B show that a different volume of sodium hydroxide is consumed. This is due to the hydrogen ion which is released during the interaction of Ga^{+3} with the ligand. The difference is a reflection of complex formation, and can be employed to calculate the concentration of the complex. Based on the titration curves and the stoichiometric relationship of hydrogen ion release and complex formation, the formation function (n) can be calculated. The relationship of formation function and pH is presented in Figure 7. This figure clearly indicates that the composition of the complex is 1:1, confirming the proposed structure shown in Figure 2.

Determination of the Net Charge of the Complex. Using the ion exchange method to determine the distribution coefficient (D) between resin and aqueous solution in the pH range 0.9–2.3, the net charge of the complex can be determined based on the following equation:

$$\log D = xpH_{aq} + C.$$

From Figure 8, the net charge, x, is determined to be 1.17. It is most likely that the net charge of this complex is +1. This evidence again suggests that the chemical structure in Figure 2 is correct. Preliminary results on elemental analysis, NMR, IR, and conductance measurement studies indicated that the structure is [Ga-

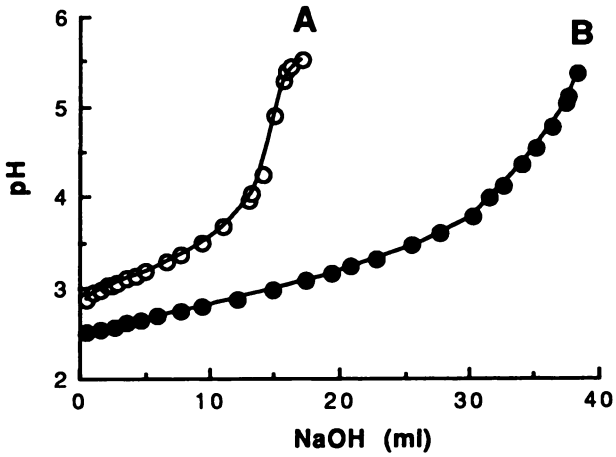

FIGURE 6
The titration curves of the ligand: BAT-TECH, with (B) and without (A) the presence of gallium metal ion (0.148 m*M*). The difference between these two curves at the same pH value is proportional to the extent of the complex formation.

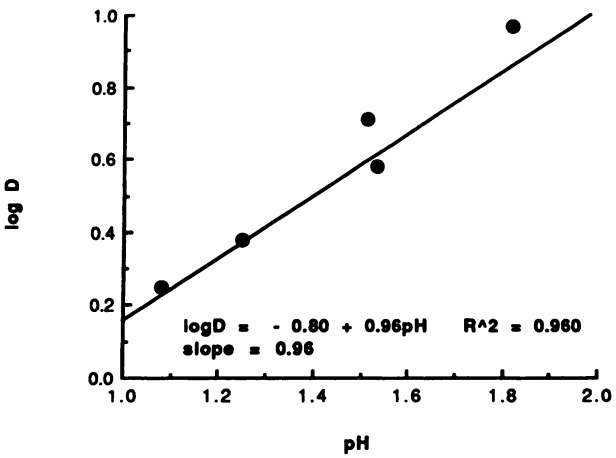

FIGURE 8
The relationship of the distribution coefficient (D) between resin and aqueous solution at various pHs. The net charge (+1) of the complex is determined based on the slope (x = 1) of this straight line.

FIGURE 9
PET images of the chest of a monkey (transverse and sagittal views) after an i.v. injection of $^{68}Ga(BAT\text{-}TECH)^{+1}$(0.42 mCi).

BAT-TECH.Cl]. When this complex is dissolved in aqueous solution it is expected that the chloride ion is ionized and the proposed structure in solution is correct (Kung, unpublished data).

Biodistribution in Rats

After an i.v. injection of [^{67}Ga]BAT-TECH in rats, a significant heart uptake (1.68% dose/organ) at 2 min was observed. The heart uptake dropped to 0.52% dose/g at 30 min and 0.26% dose/g at 1 hr (Table 1). The heart uptake values are better than those reported for [^{68}Ga](5-MeOSal)$_3$TAME (0.97, 0.23 and 0.14% dose/whole heart in rats at 1, 30, and 60 min postinjection, respectively) (*3,4*). The heart-to-lung and heart-to-blood ratios for this complex are also comparable to or superior to those reported for [^{68}Ga](5-MeOSal)$_3$TAME. There is significant uptake in the liver which does not wash out with time.

Imaging Study in a Monkey

After an i.v. injection of [^{68}Ga]BAT-TECH (424 μCi in 3 ml saline), the compound quickly localized in the heart and liver. Images taken with the PENN-PET at 7 min postinjection clearly show that the agent is localized in the heart (Fig. 9). In all views, the myocardial cavity is clearly delineated, indicating an acceptable heart/blood tracer concentration ratio.

TABLE 1
Biodistribution of [^{67}Ga]BAT-TECH in Rats after Intravenous Injection

	(% dose/organ)		
Organ	2 min	30 min	60 min
Blood	10.18 ± 0.30	3.58 ± 0.08	4.54 ± 1.10
Heart	1.68 ± 0.12	0.52 ± 0.08	0.26 ± 0.02
Muscle	13.89 ± 3.21	21.14 ± 2.18	10.79 ± 1.85
Lung	2.07 ± 0.07	0.46 ± 0.09	0.37 ± 0.009
Kidney	6.94 ± 0.31	2.00 ± 0.10	1.06 ± 0.14
Spleen	0.50 ± 0.06	0.15 ± 0.009	0.11 ± 0.001
Liver	21.52 ± 1.11	33.54 ± 4.42	46.41 ± 2.39
Skin	5.44 ± 1.65	7.56 ± 1.60	5.78 ± 0.92
Brain	0.02 ± 0.004	0.01 ± 0.001	0.01 ± 0.002

DISCUSSION

The complex formation between Ga^{+3} and BAT-TECH ligand is very rapid, simple, and occurs in high yield (≥95%). The high labeling efficiency and excellent purity of this labeling reaction yields a product that requires no further purification before animal study. It is possible that this process is amenable for kit formulation.

The labeling reaction is pH sensitive, the optimum pH range is 3–5. This pH can be easily maintained by the addition of buffer solution and is, therefore, easily adaptable for a simple one-step reaction. The Ga^{+3} and BAT-TECH apparently form a 1:1 complex with release of two hydrogen ions and the net charge of the no-carrier-added [^{67}Ga]BAT-TECH is probably +1. In view of the fact that the corresponding In(BAT-TE) complex showed a net charge of +1, it is not surprising that [^{67}Ga]BAT-TECH may have the same net charge. The [^{67}Ga]BAT-TECH^{+1} also displays good heart uptake and retention. In rats, this agent displays fast myocardial uptake and rapid blood and lung washout. The biologic behavior of [^{67}Ga]BAT-TECH suggests that this agent is potentially useful for myocardial perfusion imaging. Further studies examining the structure and chemistry of "cold" Ga-BAT-TECH are in progress. An examination of the quantitative relationship of tracer distribution and the regional blood flow of this agent, or agents in this series, will also be necessary before a successful agent can be developed for clinical use.

In conclusion, ^{67}Ga or [^{68}Ga]BAT-TECH can be readily prepared by direct complexation of [^{67}Ga]gallium citrate or [^{68}Ga]$GaCl_3$, respectively, with BAT-TECH. Biodistribution in rats and a monkey showed significant heart uptake. When labeled with ^{68}Ga, this agent, or related complexes in this series, may be useful as possible radiotracers for myocardial perfusion imaging for PET.

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