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Highly-Iodinated Fullerene as a Contrast Agent For X-ray Imaging

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Abstract—The first fullerene-based X-ray contrast agent (CA) has been designed, synthesized, and characterized. The new CA is an externally functionalized derivative of C_{60} that is conceptually based on contemporary X-ray CA, all of which use iodine as the X-ray attenuating vehicle and are based on the 2,4,6-triiodinated-benzene-ring substructure. Using a modified Bingel-type reaction, a single addend containing 6 iodine atoms and 8 protected hydroxyl groups was appended to C_{60} followed by the addition of 4 more addends each containing 4 protected hydroxyl groups. Final deprotection afforded the highly water-soluble (>460 mg/mL), non-ionic, highly-iodinated (24% I) fullerene for application as an X-ray contrast agent.

Introduction

Since the fortuitous discovery of X-rays by Wilhelm C. Roentgen in 1895, X-ray radiography has evolved into the foundation of contemporary medical imaging. Although the past two decades have experienced an explosive growth in the ultrasound and magnetic resonance imaging (MRI) modalities (due largely to the advent of the microchip), fully 75–80% of all imaging procedures still entail the use of X-rays.[1]

Contemporary X-ray radiography is intimately dependent upon the use of X-ray contrast agents (also called X-ray contrast media, radiopaque agents, and roentgenographic agents). With the exception of $BaSO_4$ slurries for gastrointestinal imaging, all commonly employed X-ray contrast agents (CA) are based on the 2,4,6-triiodinated-5-aminoisophthalic acid substructure.[1–4] The structure of a typical, commercially-available X-ray CA, Iohexol,[5] is shown in Figure 1. Such iodinated CA are currently used in approximately 20 million procedures in the US annually.[6,7]

Iodinated, water-soluble X-ray CA like Iohexol (Fig. 1) are technically known as uroangiographic agents since they are most commonly used (and best suited) for imaging of the blood vessels and/or the urinary system. Typically, an aqueous CA commercial formulation is injected rapidly via catheter directly into the blood stream followed by immediate imaging. Contrast is enhanced by the increased X-ray attenuation caused by the multiple heavy iodine atoms. Other less common applications include imaging of the spinal fluid, the nasal sinuses, and the salivary gland ducts.[8]

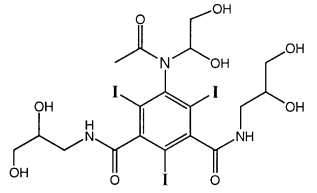

Figure 1. The structure of commercially-available Iohexol® based on the tri-iodinated benzene ring with typical 1,3-diol water-solubilizing substituents.

Upon injection, the agents diffuse throughout the bloodstream and are rapidly excreted (typically, $t_{1/2}$ = 1.5–2 h)[9] primarily through the kidneys by glomerular filtration which allows imaging of the urinary system.

Today's X-ray CA have evolved to the point where it is unlikely that a simple modification of the R groups in Figure 1 will lead to any significant improvement in tolerability or performance. Accordingly, much of the current research in X-ray CA is focused on novel systems such as tungsten clusters,[10,11] metal chelates,[12,13]

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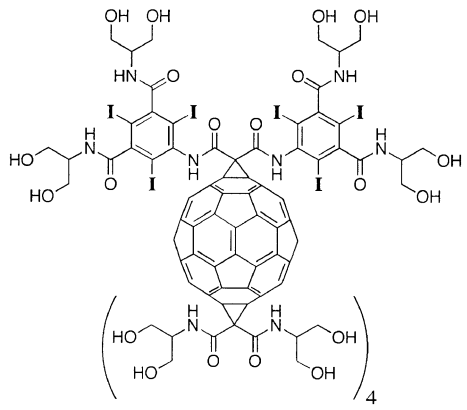


12

Figure 2. The C60-based X-ray contrast agent.

iodinated dicarbon carborane cages,[14,15] and fullerenes (this work).

The use of C_{60}-derived materials for biological applications is currently an active area of research and several reviews have been written on the subject.[16–18] The idea of using the easily derivatized, non-toxic scaffolding[19,20] of C_{60} for the development of a new X-ray contrast agent has not previously been explored. However, preliminary results of this work have been communicated[21,22] and a patent application has been filed.[23]

The target compound **12** is shown in Figure 2. Like other contemporary CA agents, **12** uses iodine as the active X-ray attenuating vehicle. However, **12** also contains the unique and synthetically versatile molecular scaffolding of C_{60}.

The spheroidal, truncated-icosahedral structure of C_{60} confers a globular shape to it's highly-functionalized derivatives. The advantage of a more globular shape (rather than the disk-like shape of a contemporary CA) is reduced viscosity in clinical formulations, which allows a more rapid intravenous injection of the agent.[3] A C_{60}-derived agent could also be expected to benefit from an enhanced masking effect in which one side of the tri-iodinated phenyl ring may be blocked by the fullerene core from having hydrophobic interactions with blood plasma proteins. This would lead to decreased protein binding and increased in vivo tolerability (this is known as the 'hydrophilic sphere concept').[24] Additionally, the possibility of having more than 3 iodine atoms per molecule would allow a solution of lower molarity to be used in CA injections.

Results and Discussion

Of the efficient methods available to functionalize C_{60},[25] one of the best approaches is nucleophilic cyclopropanation or the Bingel reaction.[26] However, the typical malonodiester fullerene adducts are easily hydrolyzed to give the diacid product,[27] an undesirable attribute for materials requiring high in vivo stability. Accordingly, the C_{60}-based CA design incorporates the more hydrolytically-stable malonodiamide functionality. Preliminary model-compound studies[28] established the viability of appending the malonodiamide group to C_{60}.

The preparation of the highly-iodinated addend **7** is shown in Scheme 1. Starting from 5-aminoisophthalic acid, three iodine atoms were introduced with $KICl_2$ in water[29] followed by treatment with $SOCl_2$ to give diacid chloride **2**.

Diacid chloride **2** was then directly condensed with malonyl dichloride to give the tetraacid chloride **3** in 83% yield.[30] Condensation with malonyl dichloride is favored over polymerization due to the steric congestion caused by the large flanking iodine atoms.[29]

A suitable method for the *O*,*O*′-protection of serinol was developed based on the reported stability of both *cis*- and *trans*-5-amino-2-phenyl-1,3-dioxane.[31] Serinol was first *N*-protected with benzylchloroformate and then *O*,*O*′-protected by condensation with benzaldehyde (cat. H_2SO_4) to give an equilibrium mixture of *cis*:*trans* substituted 1,3-dioxane in a ratio of 8:2.

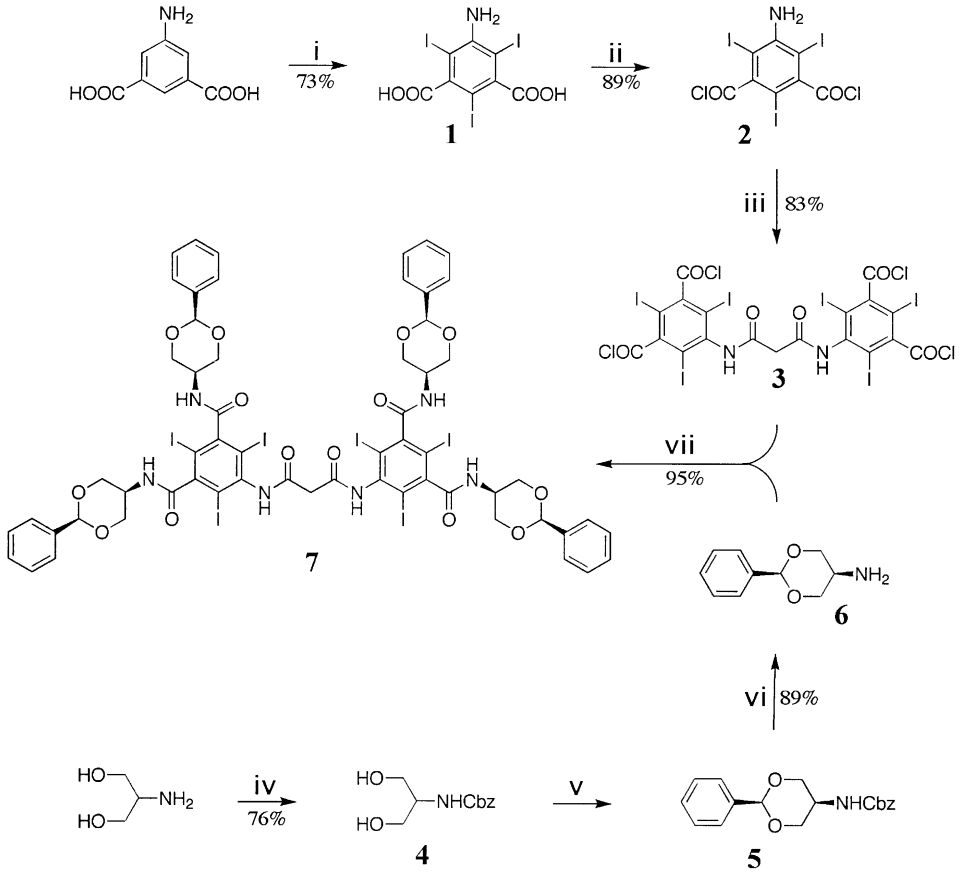
The *cis* isomer selectivity can be rationalized by the axial preference for the *N*-benzyl carbamate group due to the presence of intramolecular *N–H···O* hydrogen bonding.[32] In addition, the nucleophilicity of the *cis* isomer of 5-amino-2-phenyl-1,3-dioxane has been shown to be approximately twice that of the *trans* isomer.[33] Therefore, the *cis* isomer was chosen as the more desirable protected-serinol isomer.

Removal of the benzoxycarbonyl from the nitrogen of **5** under catalytic hydrogenation conditions (300 psi H_2, Pd/C) proceeded smoothly to give pure **6**. Condensation of **6** with tetraacid chloride **3** in DMA at room temperature proceeded in excellent yield (95%) to give the malonodiamide **7**.

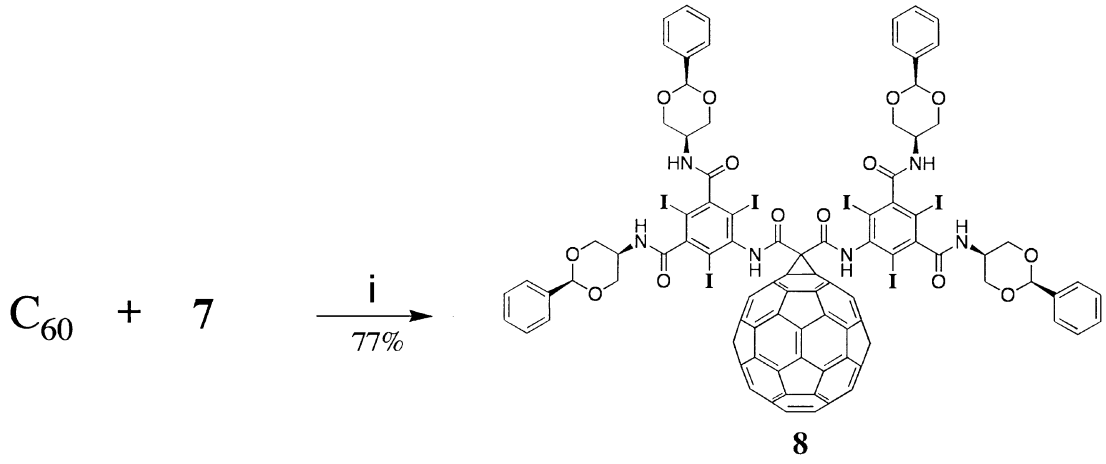
The characterization of addend **7** was complicated by the presence of up to 12 hindered rotations at room temperature caused by the sterically congested environment of the hexasubstituted benzene rings.[34] The large number of atropisomers caused the room temperature ^1H NMR to be broadened and complex. However, interpretable 500 MHz ^1H and ^{13}C NMR spectra were obtained at 70 °C.

To prepare the C_{60} monoadduct of the malonodiamide **7**, the method of Hirsch for the in situ generation (with CBr_4 and DBU) of the active brominated intermediate was used.[35] The reaction, as shown in Scheme 2, was found to proceed nicely at room temperature in toluene/pyridine, in which both **7** and C_{60} were suitably soluble, to give the monoadduct **8**.[21] The relatively good yield of 77% was somewhat surprising, considering the steric bulk of addend **7**, but indicates that the central methylene (methine after in situ bromination) in **7** is available for reaction with C_{60} in its more favored room temperature conformer(s).

The FTIR spectrum of C_{60}-monoadduct **8** was nearly superimposable on the IR spectrum of addend **7**, but additionally had the characteristic C_{60}-monoadduct



Scheme 1. Synthesis of the hexa-iodinated, *O*,*O*′-protected malondiamide addend **7**. Reagents and conditions: (i) $KICl_2$, H_2O, 55 °C, 24 h; (ii) $SOCl_2$, reflux 6 h; (iii) $CH_2(COCl)_2$, THF, reflux 6 h; (iv) benzyl chloroformate, NEt_3, EtOH, 2.25 h; (v) PhCHO, cat. H_2SO_4, toluene, reflux 6 h; (vi) 300 psi H_2, Pd/C, EtOH, 50 min; (vii) DMA, NEt_3, 24 h.



Scheme 2. Synthesis of monoadduct **8**. Reagents and conditions: (i) CBr_4, DBU, 25:14 toluene:pyridine.

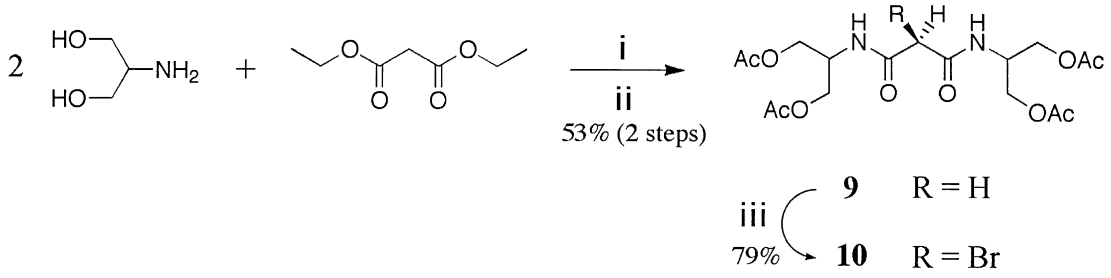
band at 526 cm^{-1}.[36,37] A molecular ion peak at 2547.5 was observed in the MALDI-TOF MS ($[M]^-$ calcd for $C_{119}H_{50}N_6O_{14}I_6$, 2547.8), with the base peak at 2453.5 corresponding to the $[M-I+S]^-$ ion.[38] Additionally, a single band was observed by thin-layer chromatography.

The NMR characterization of **8**, as with compound **7**, was hampered by the presence of multiple atropisomers. In the case of **8**, however, even after 17 h of data collection at 70 °C, the S/N ratio of the ^{13}C NMR spectrum (500 MHz, pyridine-d_5, 0.05 M, 6128 scans) was still too low and the signals too broadened to interpret, indicating that some of the rotations of the addend **7** are even more hindered upon addition to C_{60}. Higher temperature experiments were prohibited due to the thermal decomposition of the benzylidene acetal groups.

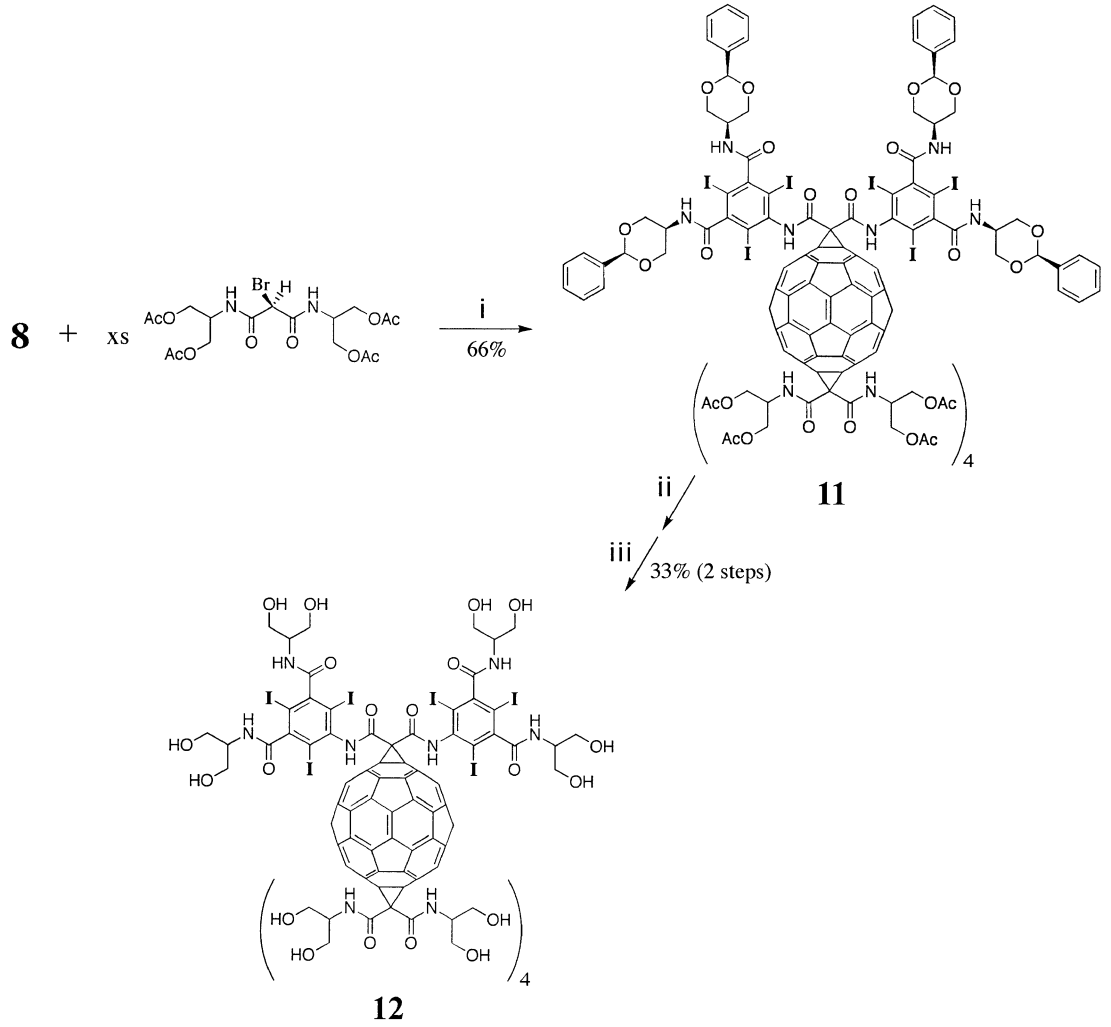
A qualitative in vitro determination of the degree of X-ray attenuation produced by hexa-iodinated **8** showed, as expected based purely on the iodine content (30%), significantly enhanced X-ray absorption relative to the blank.[21]

When C_{60} was treated with an excess of addend **7** ($\geq$3-fold relative to C_{60}), only the monoadduct formed in good yield as determined by TLC and MALDI-TOF MS. Although some bisadduct product was observed by MS, no higher adducts were detected, and the monoadduct was the major product. Apparently, the bulkiness of the addend does not allow the formation of adducts higher than the bis-, whose formation is also greatly inhibited.

Additionally, the deprotection of monoadduct **8** resulted in a material that is only sparingly soluble in water. This result is not surprising considering the highly amphiphilic nature of the material. Therefore, given the very high water solubility requirements for X-ray CA, and the lack of formation of the highly functionalized adducts (Tris-, tetrakis-, etc.), attention turned to water-solubilization of **8** by additional functionalization. This was easily accomplished using the smaller malonodiamide group $BrCH(COSer)_2$ (**10**, Ser = 2-amino-1,3-propanediol) which was previously shown to be extremely effective at water-solubilizing native C_{60} ($>$240 mg C_{60} mL^{-1}).[22] The synthesis of **10** is shown in Scheme 3.



Scheme 3. Synthesis of $BrCH(COSer)_2$, **10**, (Ser = 2-amino-1,3-propanediol). Reagents and conditions: (i) 225 °C, 45 min; (ii) Ac_2O, pyridine, 18 h; (iii) Br_2, EtOAc, NEt_3.



Scheme 4. Assembly and deprotection of X-ray CA **12**. Reagents and conditions: (i) $CHCl_3$, DBU, 40 h; (ii) BF_3Et_2O, $CHCl_3$; (iii) Na_2CO_3, MeOH, H_2O.

To accomplish water solubilization, **8** was treated with an 8-fold excess of **10** to give **11** as shown in Scheme 4. (All attempts to control the regiochemistry of the additions with the template dimethyl anthracene[39] were unsuccessful.) The orange-red product mixture, after workup, consisted of predominantly the pentaadduct (addition of four water-solubilizing groups, **10**, to monoadduct **8**), with small amounts ($<10\%$) of the tetraadduct present, as determined by MALDI-TOF MS.

A molecular ion peak for the deprotonated sodium adduct of **12** was observed at *m*/*e* 3211.1 (calcd 3211.1). The lack of peaks corresponding to residual protected species indicated complete alcohol deprotection. The clear presence of two higher mass peaks at $[M+Na+16]^+$ and $[M+Na+32]^+$ indicates the additional presence of oxygenated species (epoxides) which are commonly observed in C_{60}-derived materials.[40] Although very small oxygenated species peaks were observed in the mass spectra of the precursor compounds **8** and **11**, the much greater intensity of the peaks in the mass spectrum of **12** indicate that epoxide formation most likely occurs predominantly during the deprotection step (despite anaerobic conditions). Alternatively, the oxygen may have been introduced during the mass spectrum sample preparation. Additionally, fragment peaks corresponding to the loss of up to all 6 iodine atoms are clearly seen with the loss of one iodine atom $[M-I+Na]^+$ being the base peak.

The UV–vis spectra of **12** (0.62 M) has no maxima as expected for a complex mixture of isomers. In the ^1H NMR of **12**, complete deprotection is apparent and only the methine and methylenes of the serinol residues are observed. The elemental analysis is consistent with the structure of **12** and the characteristic amide carbonyl (1652 cm^{-1}) and hydroxy (3382 cm^{-1}) stretches were observed in the FT-IR spectrum.

Several water-soluble, amphiphilic C_{60} derivatives have been shown to form aggragates in aqueous solution.[41,42] However, dynamic light scattering experiments with **12** indicated that the compound does not form aggragates in the detection range of 3–3000 nm in aqueous solution (pH $\approx$7) at concentrations of $\leq$2 mM. This result is indicative of the hydrophobic shielding expected by multiple strongly hydrophilic addends, and at concentrations of around 2 mM, **12** exists as a monomer in solution.

Additionally, the *n*-octanol/water partition coefficent (K_{OW}) was determined, and within detection limits, $K_{OW}=0$ for **14**. This result compares well with the very small K_{OW} values ($<10^{-3}$) of currently-used X-ray contrast agents which are also very hydrophilic.

Conclusion

The first fullerene-based X-ray contrast agent has been designed, synthesized, and characterized. The synthetic pathway was designed to minimize the number of synthetic steps involving any C_{60} material, which in general provides overall improved yields.

Animal studies to determine the efficacy of **12** as an X-ray CA are currenty being performed.

Experimental

All compounds used were reagent grade or better, solvents were used as received unless otherwise specified. For anaerobic reactions, solvents were degassed by bubbling dry N_2 or Ar. The following reagents were used as received: C_{60} (99.5+%, MER Corp.), 1,8-diazabicyclo[5.4.0]undec-7-ene (Aldrich), diethyl malonate (Aldrich), Br_2 (Aldrich), 2-amino-1,3-propanediol (Aldrich), Pd/C (Pd 10%, Aldrich), iodine monochloride (Aldrich), 5-amino-isophthalic acid (Aldrich), malonyl dichloride (Aldrich), benzyl chloroformate (Aldrich), benzaldehyde (EM Science), CBr_4 (Aldrich), BF_3Et_2O (Aldrich), The following reagents were purified as described: NEt_3 (Acros) was refluxed and distilled from CaH_2, $SOCl_2$ (Acros) was distilled from linseed oil (Aldrich, 20% v/v) and used immediately, acetic anhydride (Fisher) was distilled.

The following solvents were purified as described: toluene (Fisher) was refluxed and distilled from Na (with benzophenone indicator), hexanes (Fisher) were dried by contact with $CaCl_2$ and either distilled or microfiltered, CS_2 (Fisher) was stirred with $CaCl_2$ 4 h then distilled from P_2O_5, $CHCl_3$ (Fisher) was refluxed and distilled from $CaCl_2$, pyridine (Fisher) was refluxed and distilled from Na or KOH, EtOAc (Fisher) was distilled from $MgSO_4$, THF (Fisher) was distilled from a K/Na alloy (made by heating 1:1 Na and K metal until molten), EtOH (Pharmco) was refluxed and distilled from $CaSO_4$, and methanol (Fisher) was distilled. Silica gel (Aldrich), grade 62, 62–200 mesh, 150 Å was used for column chromatography after activation at 200 °C for at least 24 h. TLC analyses were carried out on Whatman 250 μm layer silica gel with fluorescent indicator on polyester backing (PE SIL G/UV). Cation exchange resin (Bio-Rad) AG 50W-X2 (H^+ form) was used for the removal of cations from the fullerene materials. The resin was prepared and/or converted to H^+ form by rinsing with at least 5 bed volumes of each: deionized (DI) H_2O, 1 M HCl, DI H_2O.

NMR spectra were obtained on a Bruker Avance 250, 400, or 500 MHz NMR (for VT experiments) spectrometer. FT-IR spectra were collected on a Perkin Elmer Paragon 1000 PC spectrometer as KBr pellets.

Mass spectra were collected on either a Finnigan Mat 95 mass spectrometer or a Bruker Biflex III MALDI-TOF mass spectrometer. For the MALDI spectra, unless otherwise specified, an elemental sulfur matrix deposited from a slurry in CS_2 was used. Where resolution permitted, the isotopic distribution of the mass spectral peaks was compared to theory.

HPLC analyses were performed on Hitachi L-6200A Intelligent Pump HPLC system with a Hitachi Model

L-3000 UV–vis photodiode array detector. Elemental analyses were carried out commercially by Galbraith Laboratories (Knoxville, Tennessee). Melting points were determined on a Mel-Temp apparatus and are uncorrected.

For anhydrous reactions, all glassware was either flame-dried or dried at 200 °C for 24 h.

For the dynamic light scattering experiment, a Coulter N4 Plus dynamic light scattering particle sizer was used. Data were taken at 90°.

The *n*-octanol/water partition coefficient (K_{OW}) of **12** was determined at 25 °C by the method of Leo.[43] Accordingly, a solution (~1 mM) of **12** in water (pre-saturated with *n*-octanol) was vigorously stirred for 5 min with an equal volume of *n*-octanol, then centrifuged. The absorbance in the UV–vis spectra of the *n*-octanol 'extracted' solutions was compared to the spectra of the starting solutions.

The qualitative determination of X-ray attenuation of compound **8** was carried out as follows: In 1 mL syringes, a 0.197 M (150 mg I/mL) solution of **8** in 5:1 DMF:toluene, 4 standard aqueous solutions of Omnipaque® at concentrations of 300, 225, 150, and 75 mg I/mL (diluted with saline), and 2 samples containing the saline (0.9% NaCl) and the DMF:toluene backgrounds were exposed to diagnostic wavelength (0.087–8.5 nm) X-rays in a Faxitron 43855A imager. The X-ray image was captured on standard Kodak MIN-R 2000 film.

5-Amino-2,4,6-triiodo-1,3-benzenedicarboxylic acid (1). The preparation of **1** was modified from a literature procedure.[29] Thus, 98.11 g of ICl (600 mmol) was added to a solution of 72.11 g KCl (970 mmol) in 300 mL H_2O and stirred at room temperature for 5 min. The mixture was filtered to remove insolubles, and the orange solution of $KICl_2$ was added via addition funnel over 1 h to a stirring slurry of 33.22 g of 5-aminoisophthalic acid (180 mmol) in 1100 mL DI H_2O at 55 °C. After complete addition, the tan slurry was stirred at 55 °C for 24 h. The slurry was cooled on an ice bath for 3 h and filtered to give a light tan solid. The crude product was rinsed on a fritted glass filter 2× with 40 mL H_2O, 1×20 mL H_2O, 2×20 mL 0.5 N $NaHSO_3$, 2×10 mL H_2O, dissolved in minimal 0.66 M KOH to give a clear-brown solution, neutralized with concd HCl, and treated repeatedly with 0.5 g activated charcoal at 40–50 °C for 10 min with stirring and filtered until nearly colorless (6–8×). The product was then precipitated with concd HCl with stirring until no further precipitation was observed, allowed to stand for several hours, then filtered and dried at 100°C under vacuum to give 73.68 g (130 mmol) of analytically pure off-white tan solid, 73% yield. TLC R_f 0.60 in 2:1 MeOH:EtOAc; HPLC (anal. C-8) detection at 255 nm, retention time 2.79 min in phosphate buffer (pH 7): MeOH (7:3), flowrate 0.3 mL/min; ^{13}C NMR (400 MHz, DMSO-d_6, solvent ref) δ 70.6 (1C, *C*-I) , 77.9 (2C, *C*-I), 147.7 (2C, *C*–COOH), 148.9 (1C, *C*–NH_2), 170.1 (2C, *C*OOH); FT-IR (KBr) ν (cm^{-1}) 3629, 3442, 3378, 3305 (N–H), 2990, 2480 (COO–H), 1719 (C=O); MALDI-TOF MS (MeOH, + ion) calcd for $C_8H_4O_4NI_3$ (M^+) 558.7, found 558.6.

5-Amino-2,4,6-triiodo-1,3-benzenedicarbonyl dichloride (2). In 400 mL of freshly purified $SOCl_2$, 52 g **1** (93 mmol) was refluxed for 6 h. The $SOCl_2$ was then removed under reduced pressure. The product was dispersed in 400 mL EtOAc by sonication (1 min). The EtOAc was removed under reduced pressure to give a dark yellow solid. The crude material was again dispersed in 425 mL EtOAc (the material dissolved fully upon washing) and washed with 40 mL portions of a saturated solution of 250 g NaCl/100 g $NaHCO_3$ in 1.25 L H_2O until the aqueous phase remained basic (5×), followed by satd NaCl. The clear dark yellow-orange organic phase was flash chromatographed on toluene slurry packed SiO_2 (10 cm height×7.9 cm ID) with toluene and rotovapped to give 49.1 g (83 mmol) of a pure beige solid, yield 89.3%. TLC R_f 0.62 in 1:3 C_6:EtOAc; HPLC (anal. C-8) detection at 285 nm, retention time 7.80 min in 8:2 AcCN:H_2O, flowrate 0.25 mL/min; ^{13}C NMR (400 MHz, acetone-d_6, solvent ref) δ 64.8 (1C, *C*-I) 77.0 (2C, *C*-I), 150.3 (1C, *C*–NH_2), 150.8 (2C, *C*–COCl), 170.0 (2C, *C*OCl); FT-IR (KBr) ν (cm^{-1}) 3469, 3370 (N–H), 1769 (C=O); MALDI-TOF MS (acetone, −ion) calcd for $C_8H_2O_2NI_3Cl_2$ [$(M–H)^-$] 593.7, found 593.3.

***N,N′*-Bis(2,4,6-triiodo-3,5-benzenedichlorocarbonyl)-malonamide (3).** In 200 mL anhydrous THF, 25.7 g **2** (43 mmol) was dissolved (500 mL rbf) and brought to reflux under argon. To the solution, 2.0 mL (21 mmol) malonyl dichloride was added dropwise over 5 min and the orange solution refluxed for 6 h (under Ar sparge). Anhydrous hexanes were added until slight precipitation was noted (~10 mL). Stirring was stopped and the heat removed. Crystals formed when the flask was allowed to cool overnight. It was then placed on an ice bath for 3 h and filtered to give 19.65 g (16 mmol) of a fluffy, white, microcrystalline solid. The mother liquor was stirred and precipitated with hexanes followed by filtration to give crude product. The crude tan solid was dissolved in minimal boiling THF and hexanes added until near precipitation. Upon cooling to room temperature, followed by an ice bath (2 h), a second crop of 1.91 g (1.5 mmol) pure material was obtained. An additional 2.53 g of crude material was obtained upon full precipitation and filtration of the mother liquor. Pure yield 83%. TLC R_f 0.66 in 2:1 EtOAc:C_6s; HPLC (anal. SiO_2) in 4:1 $PhCH_3$:THF, detection at 300 nm, retention time 5.92 min, flowrate 1.0 mL/min; ^{1}H NMR (400 MHz, acetone-d_6, TMS ref) δ 3.85 (s, 2H, CH_2), 10.0 (bs, 2H, N*H*); ^{13}C NMR (400 MHz, acetone-d_6, solvent ref) δ 43.0 (1C, *C*H_2), 83.1 (2C, *C*-I), 98.3 (4C, *C*-I), 146.2 (2C, *C*–NH_2), 151.8 (4C, *C*–COCl), 166.1 (2C, *C*ONH), 169.9 (4C, *C*OCl); FT-IR (KBr) ν (cm^{-1}) 3190 (N–H), 2960 (C–H), 1760 (C=O, acid chloride),

1650 (C=O, amide); MALDI-TOF MS (acetone, −ion) calcd for $C_{19}H_4O_6N_2I_6Cl_4$ [(M–H)$^-$] 1256.3, found 1256.7.

(2-Hydroxy-1-hydroxymethyl-ethyl)-carbamic acid benzyl ester (4). In 60 mL dry EtOH, 11.03 g of serinol (120 mmol) and 18.5 mL NEt_3 were dissolved in a 150 mL rbf and placed on an ice bath. Benzyl chloroformate (19.2 mL) was added via an addition funnel over 15 min without allowing the temperature to rise above 35 °C. After complete addition, stirring was continued for 2 h at room temperature with the formation of a colorless ppt (NEt_3HCl). The mixture was filtered and concentrated to 50 mL. Allowed to stand at room temperature overnight, the product crystallized to give 26.72 g. A second crop of 2.5 g was obtained by seeding the mother liquor and cooling at −10 °C 18 h. Pure product was obtained by recrystallization from H_2O in two crops to give colorless crystals, 20.64 g, 76% yield. Mp 104–105 °C; TLC R_f 0.58 in 10:1 EtOAc:MeOH; ^{1}H NMR (400 MHz, acetone-d_6, TMS ref) δ 2.91 (s, 2H, O*H*), 3.66 (m, 4H, CH_2), 3.86 (p, 1H, C*H*), 5.06 (s, 2H, CH_2), 6.03 (bs, 2H, N*H*), 7.28–7.40 (m, 5H, Ar*H*); ^{13}C NMR (400 MHz, acetone-d_6, solvent ref) δ 55.70 (1C, *C*H), 62.39 (2C, *C*H_2), 66.60 (1C, *C*H_2), 128.66, 128.71, 129.26, 138.45 (Ar*C*), 157.21 (1C, C=O); FT-IR (KBr) ν (cm^{-1}) 3320 (O–H), 1695 (C=O); EI-MS calcd for $C_{11}H_{15}N_1O_4$ (M^+) 225.1, found 225.1.

***cis*-(2-Phenyl-[1,3]dioxan-5-yl)-carbamic acid benzyl ester (5).** To a refluxing solution of 17.13 g **4** (76 mmol) in a 500 mL flask in 290 mL toluene was added 7.34 mL benzaldehyde (72 mmol). 15 μL of concd H_2SO_4 was suspended in 3 mL toluene by sonication and added to the flask. After 1.5 h at reflux, 25 mL of the reaction sovent was distilled off to azeotropically remove water. A second aliquot of 15 μL concd H_2SO_4 suspended in 3 mL toluene was added and reflux was continued for 3 h and an additional 45 mL distilled off. The heat was removed and crystals allowed to form by cooling the flask to room temperature overnight under in Ar atmoshpere. The colorless crystals were filtered to give 11.5 g of 80–90% starting material 19 and 10–20% *trans*-(2-phenyl-[1,3]dioxan-5-yl)-carbamic acid benzyl ester as determined by ^{1}H NMR. The filtrate was treated with 0.5 g $MgSO_4$, filtered, and the solvent removed under reduced pressure to give a clear oil which was recrystallized from 9:1 EtOH (200 proof): H_2O in two crops to give 6.13 g of pure 20 as colorless crystals. Mp 67.0–69.0 °C; TLC R_f 0.39 in 7:3 C_6s:EtOAc; mp 67–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$, TMS ref) δ 3.76 (d, J = 8.8 Hz, 1H, C*H*), 4.14 (m, 4H, CH_2), 5.18 (s, 2H, CH_2), 5.55 (s, 1H, C*H*), 5.95 (bd, 1H, N*H*), 7.36–7.45 (m, 8H, Ar*H*), 7.54 (m, 2H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$, solvent ref) δ 46.04 (1C, N*C*H), 67.31 (1C, *C*H_2), 71.14 (2C, *C*H_2), 102.11 (1C, acetal *C*H), 126.38, 128.62, 128.76, 129.02, 129.56, 136.87, 138.31 (12C, ArC), 156.40 (1C, C=O); FT-IR (KBr) ν (cm^{-1}) 3337 (N–H), 1685 (C=O), 1524; EI-MS calcd for $C_{18}H_{19}N_1O_4$ (M–H)$^+$ 312.1, found 312.

***cis*-5-Amino-2-phenyl-1,3-dioxane (6).** In a typical preparation, 1.4 g of **5** (4.5 mmol) was dissolved in 50 mL anhydrous EtOH in a 50 mL Erlenmeyer flask. 0.14 g of 10% Pd/C was added. The slurry was stirred at room temperature under 300 psi H_2 (in a Parr hydrogenator) for 50 min. The catalyst was removed by syringe microfiltration, followed by careful solvent removal under reduced pressure (bp 22: 50 °C, 0.65 Torr44). The colorless residue was dissolved in minimal anhydrous Et_2O (~5–10 mL) and microfiltered to remove insolubles. The Et_2O was removed under reduced pressure to yield 0.72 g of pure **6** as a colorless oil (89%) which was used immediately. ^{1}H NMR (400 MHz, $CDCl_3$, TMS ref) δ 1.98 (bs, 2H, NH_2), 2.77 (m, 1H, C*H*NH_2), 4.03–4.16 (m, 4H, CH_2), 5.55 (s, 1H, ArC*H*), 7.30–7.40 (m, 3H, Ar*H*), 7.48–7.51 (m, 2H, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$, solvent ref) δ 45.96 (1C, *C*HNH_2), 73.49 (2C, *C*H_2), 101.97 (1C, acetal *C*H), 126.06 (2C, Ar*C*), 128.44 (2C, Ar*C*), 129.14 (1C, Ar*C*), 138.36 (1C, Ar*C*).

***N*,*N*′-Bis[2,4,6-triiodo-*N*,*N*′-bis-[*cis*-(2-phenyl-[1,3]dioxan-5-yl)]-3,5-benzene-dicarbamoyl]-malonamide (7).** In a typical preparation, 0.94 g **3** (0.75 mmol) was dissolved in 40 mL anhydrous DMA. A solution of 0.72 g of **6** (4.0 mmol, 1.33 molar excess) and 560 μL anhydrous NEt_3 (4.0 mmol) in 10 mL anhydrous DMA was added via a cannulating needle. A white ppt slowly formed as the colorless solution was stirred for 20 h under Ar at room temperature. After filtration, the DMA was removed under reduced pressure to give a colorless solid. The material was flash chromatographed on a slurry packed column (silica, THF) with 10:3 THF:pyridine, the solvent removed under reduced pressure and flash chromatogpraphed a second time on a slurry packed column (silica, THF) with pure THF. Solvent removal under reduced pressure gave 1.30 g (0.71 mmol) of an analytically pure colorless to very pale yellow solid, yield 94.7%. TLC R_f 0.50 in 1:1 $PhCH_3$:THF; ^{1}H NMR (500 MHz, DMSO-d_6, 70 °C, solvent ref) δ 3.57 (s, 2H, –COCH_2CO–), 3.99 (distorted d, J = 6.5 Hz, 4H, –NHC*H*(CH_2–)$_2$), 4.22 (distorted q, J = 8.4 Hz, 16H, –CH(CH_2O–)$_2$), 5.63 (s, 4H, acetal C*H*), 7.35 (m, 12H, ArH), 7.50 (m, 8H, PhH), 7.98 (bs, 1H, N*H*), 8.7–9.3 (bm, 3H, N*H*), 10.08 (s, 2H, N*H*); ^{13}C NMR (500 MHz, DMSO-d_6, 70 °C, solvent ref) δ 41.95 (1C, –CO*C*H_2CO–), 43.70 (4C, –NH*C*H(CH_2–)$_2$, 68.45 (8C, –CH(*C*H_2O–)$_2$), 90.21, 98.10 (Ar*C*), 100.40 (4C, acetal *C*H), 126.14, 127.40, 128.23, 138.27, 142.07, 149.22 (Ar*C*), 164.55, 168.90 (*C*=O); FT-IR (KBr) ν (cm^{-1}) 1654 (s), 1103 (s); UV λ_{max} 285; MALDI-TOF MS calcd for $C_{59}H_{52}N_6O_{14}I_6$ [M]$^-$ 1829.8, found 1828.7 [M–H]$^-$; anal. ($C_{59}H_{52}N_6O_{14}I_6$) calcd: I, 41.60; C, 38.71; H, 2.86; N, 4.59, found: I, 41.86; C, 39.17; H, 3.34; N, 4.41.

1′,1′-Bis[*N*-[2,4,6-triiodo-*N*,*N*′-bis-[*cis*-(2-phenyl-[1,3]dioxan-5-yl)]-3,5-benzene-dicarbamoyl]carbamoyl]-1,2-methano[60]fullerene (8). All of the solvents in the preparation and purification of **8** were degassed. In a 2000 mL rbf, 800 mg of C_{60} (1.1 mmol) was added to 500 mL $PhCH_3$ and 200 mL pyridine and stirred until dissolved (>2 h). 2.0 g of **7** (1.1 mmol) in 80 mL pyridine was then added. 0.36 g of CBr_4 (1.1 mmol) was added followed by 245 μL DBU (1.6 mmol). A darkening of the color of the solution was noticeable almost immediately. Under N_2

sparge, the reaction mixture was stirred 14 h at room temperature. The solvent was removed and 150 mL $CHCl_3$ and 10 mL MeOH added to the dark solid. After stirring and 20 s sonication, the mixture was filtered and the solution flash chromatographed on SiO_2 (slurry packed with $CHCl_3$, 10×7.7 cm ID) with 30:1 $CHCl_3$:MeOH (degassed) and the solvent removed under reduced pressure. The dark product was redissolved in ~100 mL $CHCl_3$ and rechromatographed on SiO_2 (slurry packed with $CHCl_3$, 10×7.7 cm ID) first with $CHCl_3$ to remove C_{60} and then with 30:1 $CHCl_3$:MeOH. After solvent removal, 2.17 g of dark brown solid obtained (0.85 mmol), 77% yield (based on C_{60}). TLC R_f 0.75 in 1:1 THF:toluene; ^{1}H NMR (400 MHz, $CDCl_3$, solvent ref) δ 4.0–4.5 (bm, 20H, –NHC*H*(CH_2O–)$_2$, –NHCH(C*H*$_2$O–)$_2$), 5.6 (bs, 4H, PhC*H*(O–)$_2$), 7.2–7.6 (bm, 20H, ArH), 8.89 (N*H*); MALDI-TOF MS ($CHCl_3$, −ion) calcd for $C_{119}H_{50}N_6O_{14}I_6$ $[M]^-$ 2547.8, found 2547.5; FT-IR (KBr) ν (cm^{-1}) 1654 (s), 1103 (s), 526 (m); UV λ_{max} (nm) 273, 328; anal. ($C_{119}H_{50}N_6O_{14}I_6$) calcd: C, 56.07; H, 1.98; N, 3.30; O, 8.79; I, 29.87; found: C, 54.76; H, 2.60; N, 3.05; O, 8.34; I, 31.26 (O by subtraction).

***N,N′*-Bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-malonamide (9).** In a loosely capped 16.5×3.7 mm ID Pyrex tube, 10.59 g of serinol (2-amino-1,3-propanediol, 120 mmol) and 7.94 mL diethyl malonate (52 mmol) were combined and heated with vigorous stirring at 200–225 °C for 45 min. After this time, the loose cap was removed the EtOH was allowed to boil off. The heat was removed and, upon cooling, the solid, colorless residue was treated with 40 mL each of freshly distilled Ac_2O and pyridine and stirred 18 h at room temperature. Methanol (20 mL) was added carefully with stirring and cooling at 0 °C. The sovents were removed and the residue disssolved in 75 mL of EtOAc and extracted with dilute $CuSO_4$ (5×10 mL) followed by H_2O, and saturated NaCl. The organic phase was dried by contact with $MgSO_4$ and filtered. Recrystallization from EtOAc:hexanes (~2:1) in two crops gave 11.57 g (28 mmol) of pure **9** as a colorless crystalline solid, yield 53%. Mp 91.5–92.5 °C; TLC R_f 0.58 in 1:1 EtOAc:C_6s; mp 91.5–92.5 °C; HPLC (anal. C-8) in 7:3 AcCN:H_2O, detection at 240 nm, retention time 3.06 min, flowrate 0.30 mL/min; ^{1}H NMR (400 MHz, $CDCl_3$, TMS ref) δ 2.08 (s, 12H, C*H*$_3$), 3.21 (s, 2H, C*H*$_2$), 4.18 (m, 8H, C*H*$_2$), 4.43 (m, 2H, C*H*), 7.50 (d, J=8.36, 2H, N*H*); ^{13}C NMR (400 MHz, $CDCl_3$, solvent ref) δ 20.70 (4C, *C*H$_3$), 42.49 (1C, *C*H$_2$), 47.42 (2C, *C*H), 62.47 (4C, *C*H$_2$), 167.27 (2C, C=O), 170.68 (4C, C=O); FT-IR (KBr) ν (cm^{-1}) 3254 (N–H), 3085, 1740 (C=O, ester), 1646 (C=O, amide), 1241 (asym. –OCOCH$_3$); EI-MS calcd for $C_{17}H_{26}N_2O_{10}$ (M^+) 418.2, found 418.1.

2-Bromo-*N,N′*-bis[2-(acetyloxy)-1-[(acetyloxy)methyl]ethyl]-malonamide (10). In a typical bromination, 7.19 g of **9** (17 mmol) was dissolved in 140 mL EtOAc. With stirring at room temperature, four 299 μL aliquots of Br_2 (23 mmol, 1.35 molar excess) were added in 4 min intervals with the orange color disappearing each time. After complete addition, some yellow color remained and 3.22 mL of distilled NEt_3 (23 mmol) was quickly added with large amounts of salt precipitation and a return to a colorless mixture. After filtration, analysis by ^{1}H NMR indicated ~77% mono-bromination with no dibromo compound formed. The residue was redissolved in 150 mL EtOAc with warming and, after cooling to room temperature, 282 μL Br_2 added (5.5 mmol, 1.35 molar excess relative to unbrominated material) with stirring. After 15 min, 765 μL NEt_3 (5.5 mmol) was added. The slurry was filtered and rotavapped as before. ^{1}H NMR analysis of the residue indicated ~90% monobromination and ~10% dibromination. Recrystallization from 25:16 EtOAc:hexanes in two crops gave 6.75 g of pure **10** (14 mmol), 79% yield. Mp 111.0–112.5 °C; TLC R_f 0.10 in 1:1 EtOAc:hexanes; ^{1}H NMR (400 MHz, $CDCl_3$, TMS ref) δ 2.10 (s, 12H, C*H*$_3$), 4.15–4.26 (m, 8H, C*H*$_2$), 4.42–4.43 (m, 2H, C*H*), 4.71 (s, 1H, C*H*), 7.36 (br d, J=5.25 Hz, 2H, N*H*); ^{13}C NMR (400 MHz, $CDCl_3$, solvent ref) δ 20.90 (4C, *C*H$_3$), 43.02 (1C, *C*H$_2$), 48.46 (2C, *C*H), 62.39, 62.43 (4C, *C*H$_2$, signal split), 165.66 (2C, N*C*=O), 170.91, 170.96 (4C, O*C*=O, signal split); FT-IR (KBr) ν (cm^{-1}) 3247 (m, N–H), 1741 (s, ester C=O), 1665 (s, amide C=O), 1225 (s, asym. –OCOCH$_3$); HPLC (anal. C-8 column) in 7:3 AcCN:H_2O, retention time 3.30 min, detection at 250 nm; UV (7:3H_3CCN:H_2O) λ_{max} 225 nm; EI-MS calcd for $C_{17}H_{25}N_2O_{10}Br$ (M^+) 496.1, found 496.1 (M^+), 423.0 (–CH_2OCOCH_3), 357.1 (base peak –Br, –OCOCH$_3$).

Compound 11. All of the solvents in the preparation and purification of **11** were degassed. In a typical preparation, 1.28 g **8** (0.50 mmol) was dissolved in 250 mL $CHCl_3$ (degassed). To the solution, 1.61 g of **10** (3.2 mmol) was added. DBU (616 μL, 4.1 mmol) in 50 mL $CHCl_3$ was added dropwise via addition funnel over 1 h. The brown solution was stirred under N_2 for 40 h at room temperature. After removal of the solvent under reduced pressure, the reddish-brown residue was dissolved in 50 mL acetone and then 25 mL toluene was added followed by chromatography on SiO_2 (slurry packed with toluene, 10×7.7 cm ID) first with 1:5 acetone:toluene causing a small amount of colored material to elute which was discarded. The eluent was then changed to 1:1 toluene:acetone and 1200 mL of a brown solution was collected. The solvent was removed under reduced pressure to give 1.4 g of brownish solid. 66% yield (calculated for pentaadduct). ^{1}H NMR (400 MHz, $CDCl_3$, solvent ref) δ 1.9–2.2 (multiple bs, C*H*$_3$), 4.1–4.5 (bm, serinol C*H* and C*H*$_2$), 5.6 (bs, 4H, PhC*H*(O–)$_2$), 7.1 (bd, N*H*), 7.3–7.5 (bm, Ar*H*), 7.6 (bd, N*H*); FT-IR (KBr) ν (cm^{-1}) 1740 (ester C=O), 1675 (amide C=O), 1234 (asym –OCOCH$_3$); MALDI-TOF MS avg calcd for pentaadduct $C_{187}H_{146}N_{14}O_{54}I_6$ 4214.7, found 4214.4, avg calcd for tetraadduct $C_{170}H_{122}N_{12}O_{44}I_6$ 3798.3, found 3798.5; anal calcd for pentaadduct $C_{187}H_{146}N_{14}O_{54}I_6$: C, 53.3; H, 3.49; N, 4.65; O, 20.5; I, 18.1, found: C, 49.6; H, 4.45; N, 5.40; I, 18.6; O, 22.0 (O by difference).

Compound 12. All of the solvents in the preparation and purification of **12** were degassed. In a typical preparation, 421.7 mg of **11** was dissolved in 50 mL $CHCl_3$ in a 100 mL rbf. The dark reddish-brown solution was

cooled for 5 min on an acetone/dry ice bath but not allowed to freeze. 210 μL BF_3ET_2O was added with stirring under N_2. After 15 min, the flask was allowed to room to room temperature over 1 h during which some orange ppt formed. With stirring, an additional 110 μL of BF_3Et_2O was then added. Increased precipitation occurred and stirring was continued at room temperature for 2.5 h. The product was collected by centrifuge and washed with 3 aliquots of fresh $CHCl_3$ (10 mL) by repeated sonication and centrifugation to give the acetal deprotected intermediate (as verified by ^1H NMR). The brown solid was then washed with 5 aliquots of ice cold H_2O (3 mL) until neutral (5×). The brown solid was then dissolved in 12 mL of 4:1 MeOH:H_2O. A solution of 200 mg Na_2CO_3 in 3 mL H_2O was then added. After 1 h of stirring at room temperature under N_2, the dark reddish-brown solution was diluted up to 75 mL with 50 mL H_2O and 10 mL MeOH and stirred with ~1 g (dry weight) cation exchange resin (H^+ form) over 1 h. The solution was filtered and the cation exchange resin reconverted to H^+ form with 1 M HCl. The solution was again treated with the same resin (to minimize product adsorption, which caused loss of material) for 1 h. After this time, the complete removal of Na^+ was verified by flame test on a Pt wire. The solution was filtered and the solvent was removed to give 106 mg of deprotected material **12**. Yield for two steps 33%. 400 MHz ^1H NMR (D_2O, solvent ref) δ 3.5–4.2 (bm, C*H*, CH_2); FT-IR (KBr) ν (cm^{-1}) 3382 (O–H), 1652 (amide C=O); MALDI-TOF MS (2,5-dihydroxy benzoic acid matrix from 1:1 H_3CCN:H_2O) avg. calcd for pentaadduct $C_{127}H_{98}N_{14}O_{38}I_6$ $[M–H+Na]^+$ 3211.1, found 3211.1, base peak $[M–I+Na]^+$ 3085.1; anal. calcd for pentaadduct $C_{127}H_{98}N_{14}O_{38}I_6$: C, 47.8; H, 3.10; N, 6.15; I, 23.9; O*, 19.1, found: C, 43.8; H, 3.20; N, 5.80; I, 27.6; O, 19.6 (O by difference).

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