Unexpected Selectivity in the Alkylation of Polyazamacrocycles

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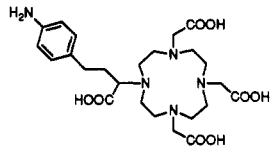
Reaction of equivalent amounts of free base polyazamacrocycles with an alkyl halide in a nonpolar, aprotic solvent affords the mono-N-alkylation product as its monohydrohalide salt in high yield with excellent selectivity. This unexpected selectivity has been explained in terms of the high affinity of the alkylated product for a single proton which attenuates the nucleophilicity of the remaining nitrogen atoms. Selectivity is dependent upon a number of factors including macrocycle ring size, solvent polarity, and the steric nature of the electrophile. The approach has allowed for a short, convergent route to bifunctional lanthanide chelators which are useful in therapeutic applications.

Introduction

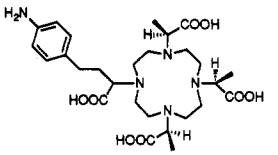
Over the past decade, a resurgence of interest in chelate chemistry for biomedical applications has emerged. In particular, chelating agents based upon 12-membered tetrazamacrocycles such as DOTA and functionalized versions of this ligand have provided a basis for useful diagnostic agents in magnetic resonance imaging.[1] Bifunctional versions of these ligands have been covalently attached to tumor selective, monoclonal antibodies and have shown promise for the delivery of diagnostic and therapeutic radioactive metals to the site of metastatic disease.[2]

In connection with our efforts in radioimmunotherapy, we have recently described approaches for two exceptional lanthanide chelators, PA-DOTA and PA-DOTMA, in which the antibody linker group is attached through one of the ring nitrogens.[2b] The synthesis of similar ligands which are functionalized on the carbon backbone of the ring are dependent upon template mediated macrocyclizations which are lengthy and less amenable to scale-up.[2c-i] In view of our need to produce multigram quantities of these bifunctional reagents for further synthetic modification and clinical investigations, we sought a short synthetic approach from readily available starting materials.

Both of these chelating agents are dependent upon methods of performing selective alkylation of free base 2.[3] Although a number of efficient techniques have been developed for the synthesis of symmetrical polyazamacrocycles, their cost is prohibitive.[4] Despite this restriction, selective monoalkylation of numerous polyazamacrocycles



PA-DOTA



PA-DOTMA

has been ensured using a large excess of free bases (5–10 equiv) relative to electrophile.[5] Other synthetic routes which afford mono-N-functional polyazamacrocycles involve protection, functionalization, deprotection schemes which can be divergent and not always general.[6]

In view of these alternatives, the direct alkylation approach seemed to be the most expedient route to the preparation of precursors to PA-DOTA and its derivatives. We noted that selectivities and yields for mono-N-alkylation products remained surprisingly high when the azamacrocycle to electrophile ratio approached unity, provided the reaction was conducted in a nonprotic solvent such as methylene chloride or chloroform and certain types of alkylating agents were used.[7] The scope and limitations of this reaction as well as the basis for this chemoselective process are addressed.

Results and Discussion

This approach to selectively functionalized macrocycles depends upon the synthetic availability of appropriately

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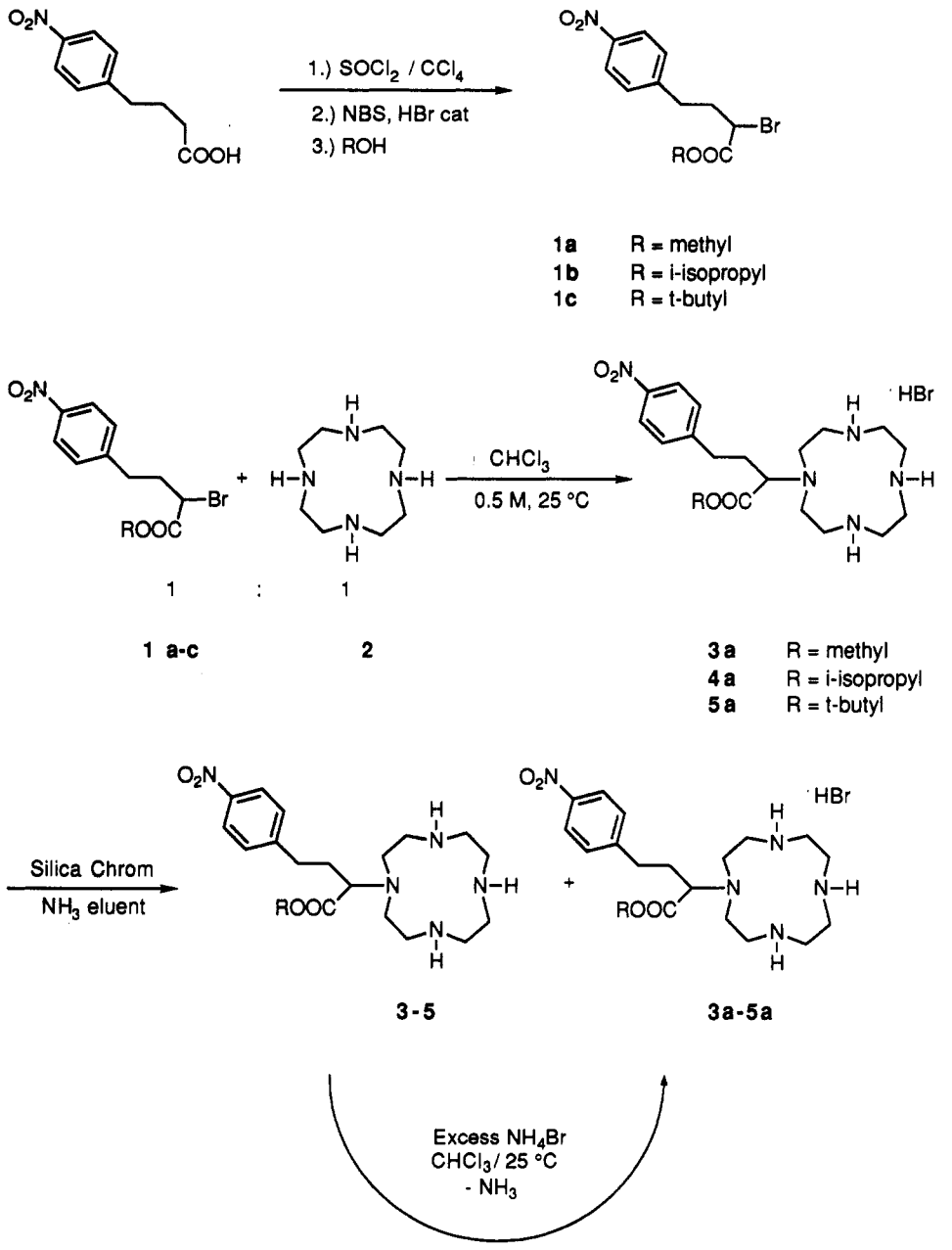
0022-3263/93/1958-3869$04.00/0

Scheme I



substituted electrophiles, all of which in these studies include moieties that permit covalent attachment to proteins. In the case of substituted α-halo acid esters **1a–d**, a number of acids (Scheme I) were brominated and converted to the ester in a one-pot, two-step procedure using *N*-bromosuccinimide.[8] This ionic bromination procedure proved to be tolerant of benzyl or pthalamido groups and was superior to the standard Hell–Vollard–Zielinski procedure. In the case of bromo ester **1**, the *tert*-butyl group was introduced after bromination of the corresponding acid, due to the instability of the ester under the acidic bromination conditions.[9]

When equivalent amounts of bromo ester **1a** and free base macrocycle **2** were reacted in chloroform under nondilution conditions at room temperature, monoalkylated **3a** was obtained in 70–80% yield after flash chromatography. Small amounts of bis-alkylated macrocycle (<2%) accompanied the formation of **3a**. During initial attempts to purify **3a**, variable mixtures of free base **3** and monohydrobromide salt **3a** were obtained which depended on how the chromatography was performed (duration of separation and lot number of silica gel).[10] In light of the basic nature of the chromatography eluent,[11] it is noteworthy that any hydrobromide salt remained intact during the partitioning process. In fact, macrocycles **5a** and **7a** were obtained in analytical purity as their monohydrobromide salts after similar chromatography.

Treatment of dry chloroform solutions of free base **3** with a large excess of solid ammonium bromide provided monohydrobromide **3a** which could be obtained as single, X-ray diffractible crystals. Conversely, treatment of solutions of hydrobromide with anhydrous potassium carbonate for extended periods of time at room temperature failed to produce the free base form which could only be

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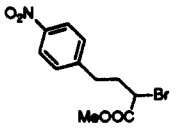
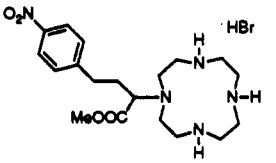
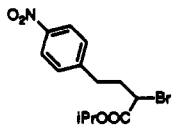
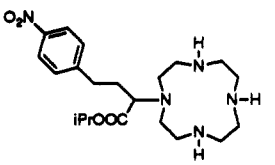
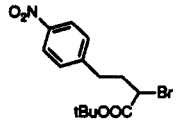
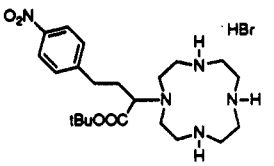
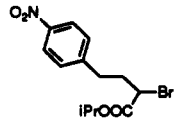
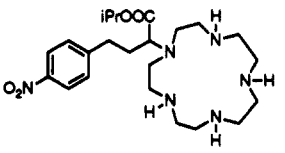
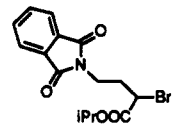
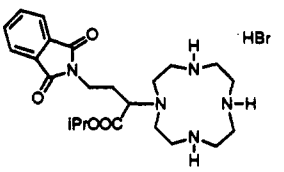
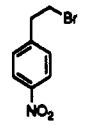
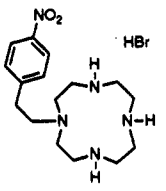
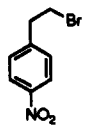
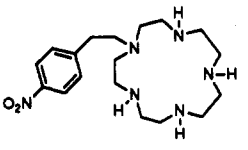
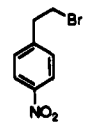
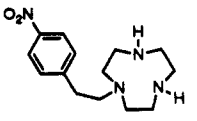
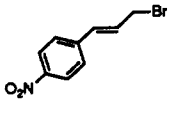
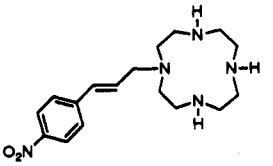
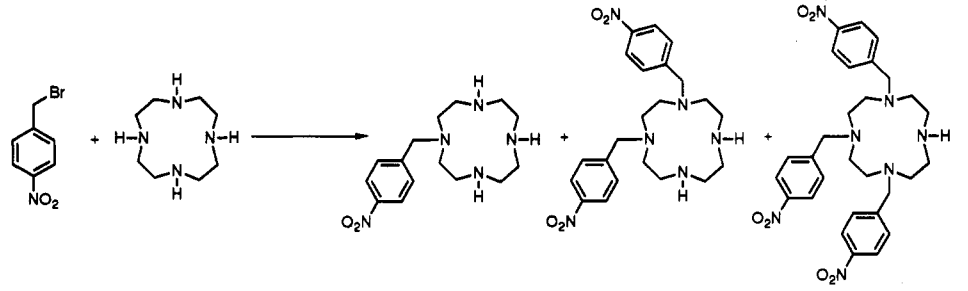
(9) Hassner, A.; Alexanian, U. *Tetrahedron Lett.* **1978**, *46*, 4475–4478.
(10) Chromatographic separation of bis adducts from mono-N-alkylated material was done to establish accurate selectivity ratios for this study; in practice, **3a** has been isolated in analytical purity on a 0.5-kg scale by precipitation of the chloroform solution in ether.
(11) The use of chloroform/methanol/ammonia eluents were common to all preparative separations.

Table I. Alkylation of Polyazamacrocycles with Alkyl Halides

electrophile	M:E	product	mono:bis[a] yield
 **1a**	1:1	 **3a**	40:1[b] 84%
 **1b**	1.2:1	 **4**	39:1 72%
 **1c**	1:1	 **5a**	40:1 79%
 **1b**	1:1	 **6**	43:1 83%
 **1e**	1:1	 **7a**	45:1 79%
	1:1	 **8**	30:1 41%
	1:1	 **9**	3.3:1[b] 39%
	1:1	 **10**	3.9:1[b] 21%
 **11**	1.1:1	 **12**	4.0:1 60%

[a] All reactions conducted at 25–30 °C in dry chloroform at 0.5–1.5 M in each reagent; selectivities and yields (for mono adduct) are based upon products isolated by flash chromatography. [b] Statistical selectivity ratios using the kinetic model predict the same product distribution for the following macrocycles at this stoichiometry (M:E = 1): mono:bis = 2.0:1 for 3-aza-9-ane, 4-aza-12-ane 2, and 5-aza-15-ane.

Table II. Mono-N-alkylation of *p*-Nitrobenzyl Bromide with 1,4,7,11-Tetraazacyclododecane 2



2 13 14 15

M:E	[E]	solvent	% isolated yield[a] mono	bis	tris	mono:bis
1:1.0	statistical					2.0:1.0
1:1.0	1 M	$CHCl_3$	49	11	5	4.5:1
1:1.5	1 M	$CHCl_3$	66	10	3	6.6:1
1:1.5	4×10^{-2} M	$CHCl_3$	73	9	2	7.4:1
1:1.5	1 M	MeOH	39	16	3	2.4:1
1:1.5	1 M	n-butanol	43	15	3	3.0:1
1:1.5	1 M	MeOH[b]	34	19	7	1.8:1

[a] Isolated yield of purified product after flash chromatography. All reactions conducted at 25 °C. [b] 1.0 equiv of potassium carbonate added relative to bromide.

partially formed upon reflux conditions. It is clear the selectivity of the alkylation does not stem from precipitation of hydrobromide salt **3a** from solution since both **3** and **3a** are highly soluble in the medium.[12] More importantly, hydrobromide **3a** was found to be *resistant toward reaction with other alkylating agents under comparable alkylation conditions, whereas free base 3 undergoes rapid alkylation with a variety of electrophiles at room temperature.* The strong affinity of free base **3** for a single proton (pK_a = 11.5 for **3b**) and resulting diminished nucleophilicity of the remaining secondary nitrogens provides an understanding for this chemoselective alkylation.

The nature of the solvent likewise is important in determining selectivity. Nonpolar and aprotic solvents solvents such as methylene chloride and chloroform were found to be preferable to polar solvents which promote proton transfer with subsequent loss of selectivity. This observation is most pronounced for less sterically hindered electrophiles such as *p*-nitrobenzyl bromide (Table II). Temperature and concentration have little effect on governing product distribution, and the addition of auxiliary base, a practice common in similar displacement reactions,[4c] further diminishes selectivity.

Selectivity was found to be dependent upon the size of the polyazamacrocycle as well. Contrastatistical selectivity for mono-N-alkylation with *p*-nitrophenethyl bromide was observed with both 12- and 14-membered tetraazamacrocycles, yet the use of larger (5-aza-15-ane) or smaller (3-aza-9-ane) macrocycles under identical conditions gave considerably lower selectivity. Unlike 12- and 14-membered tetraazamacrocycles, we found *no evidence for preferential formation of stable monohydrobromide salt adducts of larger or smaller polyazamacrocycles.*[13]

To gain greater insight into what would be considered a normal or statistical distribution of products accompanying the process, we constructed a kinetic model in which the bimolecular rate constant for initial alkylation (k_1) was assumed to be equivalent to rate constants (k_2, k_3, ...k_n) for subsequent alkylations on the polyazamacrocycle. In addition, the rate constants were statistically corrected based upon the number of available nitrogens (e.g., k_1 = 1 for mono, k_2 = 0.75 for bis, k_3 = 0.5 for tris and k_4 = 0.25 for 4-aza-12-ane **2**) remaining in the macrocycle as the alkylation progressed. Using a program developed for SIMULSOLVE to integrate the differential equations describing the product formation and disappearance of the ester.[14] With assumed initial concentrations (e.g., M:E = 1:1), the statistical distribution of alkylation products (Tables I and II) is obtained at long times when the ester concentration has gone to zero. This model predicts a 2.0:1 mono/bis ratio starting with equimolar concentrations of electrophile and macrocycle **2**, a remarkable difference over what is observed in all cases.

The nature of the electrophile is important in determining the course of chemoselectivity in polyazamacrocycle alkylations. In contrast to benzyl halides, alkylation of more sterically hindered yet reactive electrophiles such as α-halo esters **1b** with 5-aza-(15)-ane displayed high propensity for the monoalkylation adduct **6**. The consequence of steric demands in the displacement process was further addressed in the reaction of 4-aza-(12)-ane **2** with 4-nitrocinnamyl bromide (**11**) which afforded only the S_n2 displacement product **12** and none of the more hindered S_n2' product. Curiously, there was no difference in product distribution between more sterically hindered α-halo-*tert*-butyl ester **1c** and its methyl ester derivative **1a**, with both substrates exhibiting strong preference for mono-N-alkylation with macrocycle at 1:1 stoichiometry.

Positional selectivity for the bis-alkylation adduct was subtly dependent upon the nature of the electrophile, with primary halides such as **11** and 4-nitrobenzyl bromide

(12) Similar solubilities, TLC mobilities, and NMR spectra led to initial confusion in reconciling the differences in **3** and **3a**.

(13) The formation of the monohydrazoic acid salt of a 16-membered dioxopentamine macrocycle which strongly retains its proton has been noted: Kimura, E.; Anan, H.; Koike, T.; Shiro, M. *J. Org. Chem.* **1989**, *54*, 3998–4000.

(14) SIMULSOLVE is a registered trademark of the Dow Chemical Co. and constitutes a software modeling and simulation package for modeling dynamic physical systems. Mitchell and Gauthier Assoc., 73 Junction Square Dr., Concord, MA 01742.

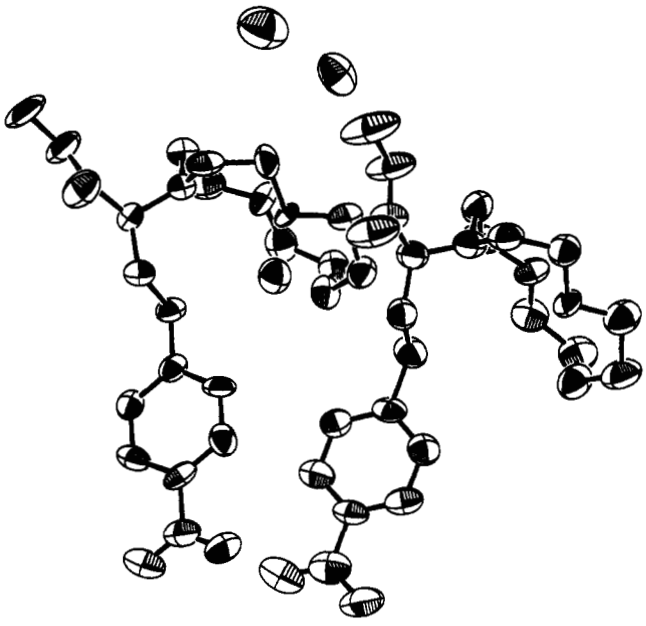
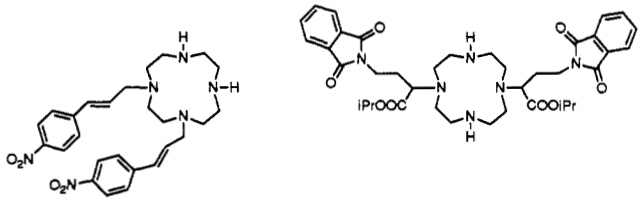


Figure 1. Ortep plot of **3a**.

giving exclusively *cis* or 1,4-diaza substitution products such as **12b** with macrocycle **2**. In contrast, more sterically



12b **7b**

hindered α-halo esters afforded *trans* or 1,7-diaza substitution such as **7b** with macrocycle **2**. The nature of the substitution pattern could be easily addressed from proton-decoupled ^{13}C spectral examination of the macrocycle carbons (*trans* adduct **7b** displays two carbon signals for the macrocycle indicating D_{2h} symmetry whereas *cis* adduct **12b** displays four carbon signals indicating C_{2v} symmetry). The tendency toward *cis*-substituted products arising from less sterically hindered alkylating agents may represent a directive effect from the more basic tertiary nitrogen which is poised to accept a proton through a five- rather than a eight-membered transition state. This directive or kinetic effect is overcome and the preference for *trans*-alkylation predominates when more hindered alkylating agents are employed.

Description of Crystal Structure. Monohydrobromide salt **3a** was found to be readily crystallized from methylene chloride and cyclohexane, providing an opportunity to obtain single, X-ray diffractible crystals to further substantiate the structure. Unfortunately, difference electron density mapping could not provide unambiguous assignment for the position of the single proton associated with the macrocyclic framework. Figure 1 shows the monohydrobromide salt **3a** and its interaction with the adjacent water and bromine atoms. The unit cell contains two slightly different conformations of the macrocyclic molecule. A water of solvation is also present in the crystal lattice. The two unique molecules, within experimental error, have the same bond distances and angles. The main molecular differences appear to be a slight rotational twist in the $-CO_2Me$ group. The molecules

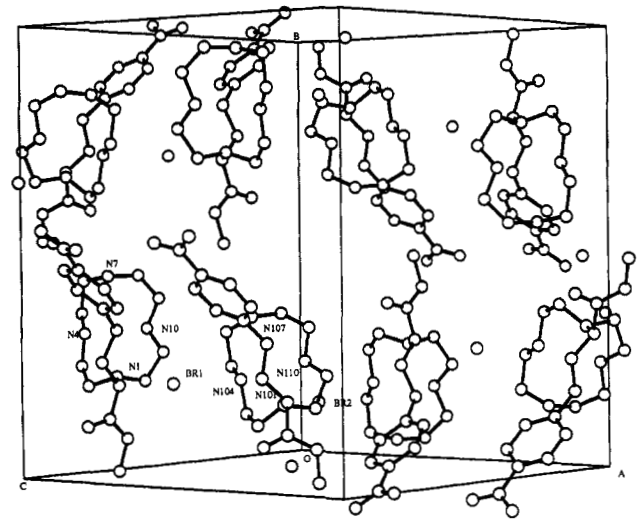


Figure 2. Unit cell of **3a**.

are held together in the crystal by N···H–Br bonds. The hydrogen bonding scheme involves Br2 which has a contact of 3.330(8) Å with N4 of molecule 1 and a longer contact of 3.585(8) Å with N110 of molecule 2. Similarly, Br1 has contacts of 3.352(8) Å with N10 of molecule 1 and 3.208(7) Å with N104 of molecule 2. These distances can be compared to O···H–Br distances which range from about 3.3 to 3.5 Å (87). This N···H–Br hydrogen bonding accounts for lone pair interaction of two of the four nitrogens in the macrocycle ring. Water, $O(H_2O)$ hydrogen bonds to N7 in molecule 1 (3.27(1) Å); however, no such contact is made in molecule 2. Other bonding holding the crystal together includes water–water hydrogen bonding at 3.40(2) Å. In both molecules, the 1-position nitrogens, N1 and N101, form no hydrogen bonding contacts. There is no evidence for the involvement of the ester group in hydrogen bonding in either an intramolecular or intermolecular fashion within the solid-state structure.

Infrared solution studies provided yet another line of evidence for differentiating the hydrobromide salt of ester **3a** (1728 cm^{-1}) from its free base form **3** (1732 cm^{-1}) but did not allow for definitive positioning of the proton. The shift to lower stretching frequency for the carbonyl group which is hydrogen bonded is expected,[15] but the magnitude of the shift is not comparable to that observed by Kimura in an intramolecular amide hydrogen bond for a 16-membered dioxopentamine macrocycle.[12] ^{13}C NMR data shows the carbon most deshielded in **3a** (2.5 ppm versus free base **3**) by the single proton is the methine carbon of the 2-butanoate side chain; this finding suggests the proton may be most intimately associated with the tertiary nitrogen in the macrocycle. Although the crystallographic, infrared, and NMR data do not necessarily substantiate a structure in which a proton is sequestered within the macrocyclic framework, we feel the proton is intimately associated with it to explain the diminished reactivity of all secondary amines toward further alkylation.

Conclusions

Although there are certain limitations to the general approach, mono-N-alkylation of 12-, 14-, and 15-membered tetraazamacrocycles proceeds with excellent selectivity

(15) Colthup, N. B.; Daly, L. H.; Wiberley, S. E. *Introduction to Infrared and Raman Spectroscopy*, 2nd ed.; Academic Press: New York, 1975; p 218.

which is not statistically predicted when α-halo esters are employed as electrophiles and the electrophile/macrocycle ratio is unity. Most importantly, the selectivity is dependent upon the nature of solvent and the highest selectivity is promoted by nonpolar, aprotic solvents such as chloroform which do not favor proton transfer. The approach has allowed for a direct and scalable synthesis of efficient lanthanide chelators stemming from **3a**, **5a**, and **7** which contain linking moieties that enable attachment to antibodies. Reduction of the nitro group of pentaazamacrocycle **9** results in formation of an antibody conjugatable reagent which forms outstandingly inert complexes with rhodium(III).[16]

Alkylation of **3a** with *tert*-butylbromoacetic acid ester or optically active *O*-mesylates of lactate esters followed by catalytic reduction of the nitro group and hydrolysis of the resulting tetraesters afforded PA-DOTA and PA-DOTMA in good overall yield. The synthetic details of these bifunctional reagents, their lanthanide complexation chemistry, and biodistributions in tumor-bearing animals as a conjugates to the monoclonal antibody, CC-49, will appear elsewhere.

Experimental Section

General Procedures. All reactions were conducted under nitrogen, and alkylations were conducted at 25 °C. Mass spectra were obtained in positive ion mode using FAB with xenon using a matrix of dithioerythritol/pentathioerthyritol, Magic Bullet, unless otherwise noted. All ^1H and ^{13}C NMR spectra were obtained at 300 and 75 MHz, respectively. Elemental analyses are reported for the major chromatographed product without further purification unless noted. All samples were vacuum dried (50–60 °C (10^{-1} mm)) overnight immediately prior to analysis.

All solvents employed were Fisher HPLC grade materials which were used without further purification. All preparative chromatography of organic compounds was performed using flash chromatography (Merck Grade 60, 230–400 mesh silica gel, 60A) and the following solvent systems unless otherwise noted: (1) solvent system 1, $CHCl_3$/MeOH/concentrated NH_4OH = 2/2/1 v/v; (2) solvent system 2, $CHCl_3$/MeOH/concentrated NH_4OH = 12/4/1. R_f values are reported using these solvent systems and commercially available Analtech silica plates (250 μm, Analtech Inc.).

Methyl *dl*-2-Bromo-4-(4-nitrophenyl)butanoate (1a). 4-(4-Nitrophenyl)butanoic acid (10.46 g, 0.05 mol) was added to a solution of CCl_4 (5 mL) and thionyl chloride (15 mL, 0.2 mol). The solution was brought to reflux for 1 h with initial rapid liberation of HCl and SO_2. At this point, NBS (11.0 g, 0.06 mol) was added as a solution in CCl_4 (25 mL), and 3 drops of 48% aqueous HBr catalyst was added to the warm solution. The dark red solution was refluxed for an additional 35 min and became colorless. The solution was cooled and poured into MeOH (100 mL) with stirring. TLC analysis (CH_2Cl_2, silica gel plates) revealed a new product (R_f = 0.69). The excess solvent was removed, and the dark red oil was filtered through a flash silica gel pad (1- × 6-in.) using CH_2Cl_2. Evaporation of solvent gave a clear oil (14.53 g) which proved to be an 85:15 mixture of bromide **1a** and the corresponding methyl ester of the starting material: ^1H NMR ($CDCl_3$) δ 8.16 (d, 2H, J_{ab} = 8.6 Hz), 7.38 (d, 2H, J_{ab} = 8.6 Hz), 4.20 (dd, 1H, J_1 = 8.1 Hz, J_2 = 6.2 Hz methine H), 3.79 (s, 3H), 2.88 (m, 2H), 2.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 169.6, 147.5, 129.3, 123.7, 53.0, 44.4, 35.5, 33.0. Anal. Calcd for $C_{11}H_{12}N_1O_4Br$: C, 43.73; H, 4.00; N, 4.64. Found: C, 43.91; H, 4.29; N, 4.79.

Isopropyl *dl*-2-Bromo-4-(4-nitrophenyl)butanoate (1b). Compound **1b** was prepared and purified in 76% yield as was **1a** with quenching of the acid bromide in 2-propanol (R_f = 0.71 CH_2Cl_2); chromatography and vacuum drying of the oil failed to liberate 2-propanol as a nonstoichiometric solvate: ^1H NMR ($CDCl_3$) δ 8.16 (d, 2H, J_{ab} = 8.7 Hz), 7.37 (d, 2H, J_{ab} = 8.7 Hz), 5.09 (m, 1H), 4.79 (m, 0.66H solvate), 4.17 (dd, 1H, J_1 = 8.0 Hz, J_2 = 6.1 Hz methine H), 2.85 (m, 2H), 2.37 (m, 2H), 1.27–1.36 (m, 6H and 4H from solvate); ^{13}C NMR ($CDCl_3$) δ 168.6, 147.5, 129.3, 123.8, 69.8, 68.1 (solvate), 45.2, 35.5, 35.5, 33.1, 23.5 (solvate), 21.5, 21.3.

***tert*-Butyl *dl*-2-Bromo-4-(4-nitrophenyl)butanoate (1c).** 4-(4-Nitrophenyl)butanoic acid (12.5 g, 0.06 mol) was added to a solution of CCl_4 (6 mL) and thionyl chloride (15 mL, 0.2 mol). The solution was brought to reflux for 1 h. At this point, NBS (11.5 g, 0.062 mol) was added as a slurry in CCl_4 (20 mL), and 3 drops of 48% aqueous HBr catalyst was added. The dark red solution was refluxed for an additional 35 min, and at the end of this period the red color discharged rapidly. A short path still head was attached to the pot, and unreacted $SOCl_2$ and CCl_4 were distilled (a total of 30 mL). The solution in the pot was cooled and poured into dioxane (100 mL) with stirring. This dark solution was slowly added to a stirred solution of 8% aqueous dioxane (250 mL). Solvent was then removed under vacuum, and 150 mL of CH_2Cl_2 was added to the dark oil followed by removal of this solvent. Another 250-mL portion of CH_2Cl_2 was added; the solution was dried over $MgSO_4$ and filtered. To this solution was added DCC (14.2 g, 0.07 mol), DMAP (0.7 g), and t-BuOH (20 g) with stirring for 18 h. TLC analysis (50:50 CH_2Cl_2/CCl_4) revealed a new product (R_f = 0.40). The mixture was filtered to remove dicyclohexylurea, and the resulting solution was extracted with 2 × 150-mL portions of H_2O, 2 × 150-mL portions of 5% aqueous HOAc, and 2 × 150-mL portions of H_2O. The organic phase was dried over $MgSO_4$ and filtered, and the solvent was removed. The resulting oil was chromatographed (50:50 mixture of CH_2Cl_2/CCl_4) to afford **1c** (5.8 g, 0.169 mol) in 28% yield as a colorless oil: ^1H NMR ($CDCl_3$) δ 8.18 (d, 2H, J_{ab} = 8.7 Hz), 7.38 (d, 2H, J_{ab} = 8.7 Hz), 4.07 (dd, 1H, J_1 = 8.1 Hz, J_2 = 6.4 Hz, methine H), 2.84 (m, 4H), 2.32 (m, 4H), 1.49 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 168.9, 148.1, 146.9, 129.5, 124.0, 82.7, 46.3, 35.5, 33.0, 27.5; IR ($CDCl_3$ film on NaCl plates) cm^{-1} 2979, 2933, 1732 (ester), 1602, 1520, 1346, 1142.

4-(*N*-Phthalimido)butanoic Acid (1d). Phthalic anhydride (14.8 g, 100 mmol), γ-aminobutyric acid (10.3 g, 100 mmol), 1.3 mL of triethylamine, and 150 mL of toluene were placed in a round-bottom flask equipped with a Dean Stark trap and condenser. The mixture was brought to reflux, and H_2O was removed azeotropically over a 1.5-h period. The solution was allowed to cool and stand overnight, and the resulting white crystals were filtered, washed with hexane, and dried. The crude crystals were then washed with 250 mL of 5% aqueous HCl and 100 mL of cold H_2O. Drying afforded **1d** (19.0 g, 81.5 mmol) in 82% yield (mp = 114.5–115.5 °C, recrystallized from 30% MeOH in H_2O): ^1H NMR ($CDCl_3$) δ 7.84 (dd, 2H, J_1 = J_2 = 3.0 Hz), 7.72 (dd, 2H, J_1 = J_2 = 3.0 Hz), 6.05 (broad s, 1H), 3.77 (t, 2H, J = 6.8 Hz), 2.42 (t, 2H, J = 6.8 Hz), 2.02 (p, 2H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 177.9, 169.4, 134.0, 123.3, 37.1, 31.2, 23.6. Anal. Calcd for $C_{12}H_{11}N_1O_4$: C, 61.80; H, 4.75; N, 6.01. Found: C, 61.64; H, 4.72; N, 5.98.

Isopropyl *dl*-2-Bromo-4-(*N*-phthalimido)butanoate (1e). Bromide **1e** was prepared from 4-(*N*-phthalimido)butanoic acid as was **1b** and was obtained in 68% yield as a white solid (mp = 72–74.5 °C) after flash silica gel chromatography using $CHCl_3$ eluent (R_f = 0.38 in $CHCl_3$): ^1H NMR ($CDCl_3$) δ 7.85 (dd, 2H, J_1 = J_2 = 2.8 Hz), 7.73 (dd, 2H, J_1 = J_2 = 2.8 Hz), 5.04 (septet, 1H, J = 6.2 Hz), 4.23 (dd, 1H, J_1 = J_2 = 6.9 Hz), 3.85 (dt, 2H, J_1 = 6.6 Hz, J_2 = 2.4 Hz), 2.51 (m,1H), 1.29 (d, 3H, J = 3.9 Hz), 1.26 (d, 3H, J = 3.9 Hz); ^{13}C NMR ($CDCl_3$) δ 168.5, 168.0, 134.0, 132.9, 123.3, 69.9, 42.9, 35.8, 33.5, 21.4, 21.3. Anal. Calcd for $C_{15}H_{16}N_1O_4Br$: C, 50.99; H, 4.57; N, 3.97. Found: C, 50.64; H, 4.57; N, 3.87.

***trans*-*p*-Nitrocinnamyl Bromide (11).** This compound was made using the general procedure of Schaffer and co-workers.[17] Triphenylphosphine (7.3 g, 27.9 mmol) was dissolved in 35 mL of dry acetonitrile, and Br_2 (4.31 g, 27.0 mmol) was added dropwise over a 15-min period with cooling to maintain the solution at T = 0–10 °C. The solution was allowed to warm to room temperature, and *p*-nitrocinnamyl alcohol (5.0 g, 27.9 mmol) was

(16) Kruper, W. J.; Fordyce, W. A.; Pollock, D.; Fazio, M.; Inbasekaran, M. U.S. Patent 4,994,560 to Dow Chemical Co., 1991.

(17) Schaffer, J. P.; Higgins, J. O.; Shenkov, P. K. In *Organic Synthesis*; Baumgarten, H. E., Ed.; John Wiley and Sons, Inc.: New York, 1973; Collect. Vol. V, 249–250.

added as a slurry in 50 mL of acetonitrile whereupon an exotherm occurred (T = 45 °C). The dark red solution was heated for 1 h at 60 °C and then poured into 500 mL of ether. Triphenylphosphine oxide precipitated from this solution upon standing overnight. The solution was filtered, and 15 g of flash silica gel was added to the solution followed by solvent removal. The resulting powder matrix was applied to a 3- × 8-in. flash column, and the product was eluted with hexane followed by 20% EtOAc in hexane (R_f = 0.81 product, 0.37 starting alcohol, and 0.26 for triphenylphosphine oxide using a 60:40 mixture of EtOAc/hexane) affording *trans*-bromide (5.8 g, 23.9 mmol) in 86% yield (mp = 75–76 °C (lit.[18] mp = 52–55 °C): ^{1}H NMR ($CDCl_3$) δ 8.17 (d, 2H, J_{ab} = 8.7 Hz), 7.51 (d, 2H, J_{ab} = 8.7 Hz), 6.70 (dd, 1H, J_1 = 15.6 Hz), 6.56 (dt, 1H, J_1 = 15.6 Hz, J_2 = 7.4 Hz), 4.16 (dd, 2H, J_2 = 7.4 Hz, J_3 = 0.8 Hz); ^{13}C NMR ($CDCl_3$) δ 147.3, 142.1, 132.0, 129.8, 127.2, 123.9, 31.8.

1,4,7,10-Tetraaza-1-*N*-(1-carbomethoxy-3-(4-nitrophenyl)propyl)cyclododecane. To a stirred solution of free base **2** (5.80 g, 33.7 mmol) in 60 mL of pentene-stabilized $CHCl_3$ was added crude bromide **1a** (10.00 g containing 15 mol % of unbrominated ester) over a 5 min period. The reaction solution was stirred for 48 h at 25 °C. TLC analysis (solvent system 2) revealed conversion to the monoalkylation product **3** (R_f = 0.73). The $CHCl_3$ solution was applied to a 2- × 10-in. flash silica gel column which had been preeluted with 5% concd NH_4OH in EtOH. Fractionation with this solvent deposited NH_4Br (R_f = 0.69), followed by the bis adduct (R_f = 0.65) and free base **3** (R_f = 0.25, all using 5% concd NH_4OH in EtOH) as a light yellow oil (8.12 g, 20.7 mmol) in 74% yield: ^{1}H NMR ($CDCl_3$) δ 8.16 (d, 2H, J_{ab} = 8.8 Hz), 7.40 (d, 2H, J_{ab} = 8.8 Hz), 3.71 (s, 3H), 3.39 (dd, 1H, J_1 = 8.3 Hz, J_2 = 6.3 Hz), 2.5–3.0 (m, 21H), 2.08 (m, 1H), 2.01 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 172.7, 149.3, 146.4, 129.2, 123.6, 62.3, 51.2, 48.9, 47.2, 45.8, 45.4, 32.8, 30.9. IR ($CDCl_3$ film on NaCl plates) cm^{-1} 2939, 2844, 1732 (ester), 1598, 1521, 1457, 1344. Anal. Caclcd for $C_{19}H_{31}O_4N_5$: C, 58.00; H, 7.94; N, 17.80. Found: C, 58.21; H, 7.59; N, 17.50.

Conversion of 3 to Monohydrobromide Salt 3b. Free base **3** (5.70 g, 14.5 mmole, FW = 393.49) was dissolved in 16 mL of $CHCl_3$, and NH_4Br (1.89 g, 19.2 mmol) was added with vigorous stirring. The suspension was stirred for 45 min, and NH_3 was liberated over this interval. The remaining bromide was filtered through glass wool, and the flask was washed with 2 × 7 mL of $CHCl_3$. The combined golden filtrate was evaporated in a nitrogen stream to approximately 15 mL. This oil was then added to 200 mL of dry ether, and the resulting gum was allowed to stand in the stoppered flask for several hours. Trituration of the gum resulted in formation of off-white powder which was filtered, washed with 150 mL of ether, and vacuum dried to afford monohydrobromide salt **3b** (6.75 g, 14.2 mmol) in 98% yield (mp = 156.5–159 °C). X-ray diffractable crystals of **3b** were obtained by diffusion of cyclohexane into a CH_2Cl_2 solution of **3b** (mp = 162–163.5 °C). The crystals were sealed in a quartz capillary tube which contained a small amount of CH_2Cl_2/cyclohexane solvent: ^{1}H NMR ($CDCl_3$) δ 8.12 (d, 2H, J_{ab} = 6.9 Hz), 7.49 (d, 2H, J_{ab} = 6.9 Hz), 3.70 (s, 3H), 3.34 (t, 1H, J_1 = 7.4 Hz), 2.5–3.1 (m, 22H), 2.12 (q, 2H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8, 149.2, 146.4, 129.5, 123.6, 64.7, 51.5, 49.3, 48.5, 47.2, 45.5, 32.7, 30.6; IR ($CDCl_3$ film on NaCl plates) cm^{-1} 2939, 284 c4, 1732 (ester), 1598, 1521, 1457, 1344; MS *m/e* 394 (100, (M + H)$^+$); negative ion 554 (85, (M + 2Br − H)$^-$), 79.81 (100, Br$^-$). Anal. Calcd for $C_{19}H_{31}O_4N_5$·1HBr: C, 48.10; H, 6.80; N, 14.76. Found: C, 48.63; H, 7.02; N, 14.32.

1,4,7,10-Tetraaza-1-*N*-(1-carboisopropoxy-3-(4-nitrophenyl)propyl)cyclododecane (4a). The purified product was isolated by flash chromatography in 70% yield as the free base (R_f = 0.79 in solvent system 2): ^{1}H NMR ($CDCl_3$) δ 8.15 (d, 2H, J_{ab} = 8.7 Hz), 7.42 (d, 2H, J_{ab} = 8.7 Hz), 5.09 (septet, 1H, J_1 = 6.2 Hz), 4.86 (s, 5H), 3.38 (dd, 1H, J_1 = 9.3 Hz, J_2 = 4.3 hz), 2.62–3.1 (m, 15H), 2.5–2.6 (m, 4H), 2.14 (m, 1H), 1.98 (m, 1H), 1.29 (dd, 6H, J_1 = 6.2 Hz, J_2 = 2.7 Hz); ^{13}C NMR ($CDCl_3$) δ 171.6, 149.5, 146.5, 129.2, 123.6, 68.1, 62.7, 49.1, 47.5, 45.9, 45.7, 32.9, 32.1, 22.1, 22.0; Anal. Calcd for $C_{21}H_{35}O_4N_5$: C, 59.84; H, 8.37, N, 16.61. Found: C, 58.94; H, 8.09; N, 16.41.

1,4,7,10-Tetraaza-1-*N*-(1-carbo-*tert*-butoxy-3-(4-nitrophenyl)propyl)cyclododecane Monohydrobromide (5a). To a stirred solution of free base **2** (1.90 g, 10.5 mmol) in 25 mL of $CHCl_3$ was added bromide **1c** (3.44 g, 9.50 mmol) over a 5-min period. The reaction solution was stirred for 48 h. TLC analysis (solvent system 2) revealed conversion to the monoalkylation product **5a** (R_f = 0.79). The yellow chloroform solution was applied to a 1.5- × 14-in. flash silica gel column which had been preeluted with 10% MeOH in $CHCl_3$. The oil was then eluted with this solvent until passage of a light yellow band, and then solvent system 1 was applied to afford the monohydrobromide salt of **5a** as a thick oil (3.7 g, 7.64 mmol) in 80% yield. The oil was dissolved in a minimum amount of $CHCl_3$, and this solution was triturated with ether to provide a gum which upon standing in this solvent became a white powder (decomposed between 70 and 110 °C to a brown oil) and proved to be analytically pure **5a** upon vacuum drying: ^{1}H NMR ($CDCl_3$) δ 8.13 (d, 2H, J_{ab} = 8.6 Hz), 7.48 (d, 2H, J_{ab} = 8.8 Hz), 3.71 (s, 3H), 3.23 (dd, 1H, J_1 = 8.2 Hz, J_2 = 6.3 Hz), 2.5–3.0 (m, 20 H), 2.65 (m, 2H), 1.46 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 171.9, 149.7, 146.4, 129.6, 123.7, 81.4, 64.8, 48.9, 48.1, 46.6, 45.3, 45.4, 32.5, 30.5, 27.9; IR ($CDCl_3$ film on NaCl plates) cm^{-1} 2979, 2936 2844, 1718 (ester), 1602, 1519, 1457, 1343. Anal. Calcd for $C_{22}H_{37}O_4N_5$ HBr: C, 51.16; H, 7.42; N, 13.56. Found: C, 51.34; H, 7.57; N, 13.46.

1,4,7,10,13-Pentaaza-1-*N*-(1-carboisopropoxy-3-(4-nitrophenyl)propyl)cyclopentadecane (6). The purified product **6** was obtained in 77% isolated yield after chromatography on silica gel (R_f = 0.82, solvent system 2) as a light yellow, waxy solid: ^{1}H NMR ($CDCl_3$) δ 8.14 (d, 2H, J_{ab} = 8.8 Hz), 7.49 (d, 2H, J_{ab} = 8.8 Hz), 5.09 (septet, 1H, J_1 = 6.2 Hz), 4.86 (s, 5H), 3.38 (dd, 1H, J_1 = 9.3 Hz, J_2 = 4.3 Hz) (s, 3H), 2.5–3.0 (m, 18H), 2.30 (m, 1H), 2.11 (m, 1H), 1.29 (d, 6H, J_1 = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.9, 149.1, 146.5, 129.5, 123.6, 68.7, 61.9, 49.5, 46.8, 46.7, 45.5, 45.3, 32.9, 32.1, 22.1, 22.0; IR ($CDCl_3$) cm^{-1} 3450, 2860, 1735 (ester carbonyl), 1350, 915. Anal. Calcd for $C_{23}H_{40}O_4N_6$: C, 59.46; H, 8.68; N, 18.09. Found: C, 59.21; H, 8.98; N, 18.07.

1,4,7,10-Tetraaza-1-*N*-(1-carboisopropoxy-3-(*N*-phthalimido)propyl)cyclododecane Monohydrobromide Salt (7a). To a stirred solution of free base **2** (2.00 g, 11.6 mmol) in 40 mL of $CHCl_3$ was added bromide **1e** (3.50 g, 10.00 mmol). TLC analysis (solvent system 2) revealed conversion to the monoalkylation product **3** (R_f = 0.57 versus bis diastereomers **7b** R_f = 0.71, 0.73). The yellow solution was applied to a 2- × 12-in. flash silica gel column which had been preeluted with 5% MeOH in $CHCl_3$. The column was eluted with this solvent (500 mL), and then solvent system 1 was applied. The bis adduct (190 mg) was separated from the major UV-active compound (4.22 g, 8.01 mmol) which was obtained as a white glass in 81% yield (note that solvent removal of ammonium hydroxide should be done with an efficient vacuum to *avoid phthalimide hydrolysis*): ^{1}H NMR ($CDCl_3$) δ 7.89 (m, 2H), 7.75 (m, 2H), 5.01 (sextet, 1H, J = 6.2 Hz), 3.95 (m, 1H), 3.81 (m, 1H), 3.34 (dd, 1H, J_1 = 11.6 Hz, J = 3.7 Hz), 2.85–3.1 (m, 20H), 2.12 (m, 1H), 1.93 (m, 1H), 1.24 (d, 3H, J = 6.2 Hz), 1.23 (d, 3H, J = 6.2 Hz); ^{13}C NMR ($CDCl_3$) δ 171.2, 168.4, 134.2, 131.9, 123.3, 68.7, 62.9, 49.1, 48.5, 47.0, 45.3, 35.1, 28.3, 22.0, 21.9; IR ($CDCl_3$ film on NaCl plates) cm^{-1} 2980, 2940, 2845, 1765, 1705, 1395, 1105; MS *m/e* 446 (100, (M + H)$^+$), 464 (5%, (M + H)$^+$ for phthalamic acid impurity); negative ion mode 606, 608 (6, (M + 2Br − H)$^-$), 462 (10, (M − H)$^-$ for maleamic acid impurity), 445 (20, (M$^-$), 79.81 (100, Br$^-$). Anal. Calcd for $C_{23}H_{35}N_5O_4$·HBr: C, 52.47; H, 6.89; N, 13.30. Found: C, 52.06; H, 6.70; N, 13.67.

1,4,7,10-Tetraaza-1-*N*-((4-nitrophenyl)methyl)cyclododecane (13). The free base **2a** (3.5 g, 20.3 mmol) and *p*-nitrobenzyl bromide (2.9 g, 13.5 mmol) in 50 mL of $CHCl_3$ were stirred for 24 h. The $CHCl_3$ slurry of hydrobromide salt was then applied to a 1- × 17-in. column of silica gel (solvent system 2), and careful fractionation provided tris adduct **15** (54 mg, 0.094 mmol) (R_f = 0.86), *cis*-bis adduct **14** (315 mg, 0.71 mmol) R_f = 0.68) and product **13** (1.76 g, 5.74 mmol) which was obtained as a pale yellow solid in 73% yield (R_f = 0.58, solvent system 2, mp = 128–29 °C): ^{1}H NMR ($CDCl_3$) δ 8.18 (d, 2H, J = 8.6 Hz), 7.49 (d, 2H, J = 8.6 Hz), 3.69 (s, 3H, amino H), 2.82 (t, 4H, J = 4.8 Hz), 2.70 (t, 4H, J = 4.4 Hz), 2.59 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 147.2, 128.4, 123.8, 58.8, 51.7, 47.1, 46.3, 45.1. Anal. Calcd for $C_{15}H_{25}N_5O_2$: C, 58.61; H, 8.20; N, 22.78. Found: C, 58.4; H, 7.29; N, 22.56.

1,4,7,10-Tetraaza-1-*N*-(2-(4-nitrophenyl)ethyl)cyclododecane (8). To a stirred solution of free base **2** (3.50 g, 20.3 mmol) in 50 mL of $CHCl_3$ was added the title bromide (4.00 g, 17.4

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mmole) dropwise over 5 min. After 24 h the contents of the flask were applied to a flash silica gel column (1 × 18 in.) which had been preeluted with 5% MeOH in $CHCl_3$, and 200 mL of this solution was applied as an eluent followed by elution with a 16:4:1 (vol/vol) mixture of $CHCl_3$/MeOH/ concd NH_4OH. *p*-Nitrostyrene (1.45 g, 9.7 mmol) (R_f = 0.98 solvent system 2) was clearly separated from the desired monofunctional macrocycle **8** (2.27 g, 7.06) which was isolated as an orange yellow oil (40.6%) which solidified upon standing (R_f = 0.73). An analytical sample was recrystallized from $CHCl_3$/cyclohexane (mp_{dec} = 146.5–8.5 °C): ^1H NMR ($CDCl_3$) δ 8.135 (d, 2H, J = 8.9 Hz, m aromatic H), 7.395 (d, 2H, J = 8.9 Hz, *o*-aromatic H), 2.91 (t, 2H, J = 6.6 Hz, CH_2-C_1 ethyl), 2.77 (t, 2H, J = 6.6 Hz, CH_2-C_2 ethyl), 2.72 (t, 4H, J = 5.1 Hz, CH_2 of cyclen ring), 2.50 (t, 4H, J = 5.1 Hz, CH_2 of cyclen ring), 2.60 (s, 11 H, ring CH_2 and NH); ^{13}C NMR ($CDCl_3$) δ 148.5, 129.6, 123.4, 55.5, 51.4, 46.9, 45.9, 45.1, 33.7. Anal. Calcd for $C_{16}H_{27}N_5O_2$: C, 59.79; H, 8.47; N, 21.79. Found: C, 60.01; H, 8.6; N, 21.9. The free base was converted to the monohydrobromide salt by NH_4Cl exchange in $CHCl_3$.

1,4,7,10,13-Pentaaza-1-*N*-(2-(4-nitrophenyl)ethyl)cyclopentadecane (9). 5-Aza-(15)-ane (2.5 g, 11.6 mmol) was reacted with 2-(4-nitrophenyl)-1-bromoethane (2.67 g, 11.6 mmol) in 30 mL of chloroform (48 h). The crude reaction product was applied to a 1- × 18-in. flash silica gel column and eluted with solvent system 2. The void volume contained nitrostyrene, and a second yellow band (*cis*-bis-alkylated, 700 mg, 1.36 mmol, R_f = 0.79) eluted before macrocycle **9** (2.00 g, 4.49 mmol, R_f = 0.56): ^1H NMR ($CDCl_3$) δ 8.16 (d, 2H, J = 8.9 Hz), 7.44 (d, 2H, J = 8.9 Hz), 2.91 (t, 2H, J = 6.5 Hz), 2.58–2.8 (m, 26H); ^{13}C NMR ($CDCl_3$) δ 148.9, 146.4, 129.6, 123.5, 55.4, 53.72, 48.6, 47.75, 47.3, 33.2; IR ($CDCl_3$ film on NaCl plates) cm^{-1} 3400, 2920, 1600, 1520, 1349. Anal. Calcd for $C_{18}H_{32}N_6O_2 \cdot H_2O$: C, 56.52; H, 8.96; N, 21.97. Found: C, 56.41; H, 8.66; N, 21.62.

1,4,7-Triaza-1-*N*-(2-(4-nitrophenyl)ethyl)cyclononane (10). Compound **10** was purified as an oil in 21% yield by chromatography (R_f = 0.31 in solvent system 2 versus R_f = 0.56 for bis-adduct) in a fashion analogous to **9**: mp = 201–204 °C as tris-HCl salt: ^1H NMR ($CDCl_3$) δ 8.16 (d, 2H, J = 8.7 Hz), 7.39 (d, 2H, J = 8.7 Hz), 2.90 (s, 4H), 2.62–2.76 (m, 12H with singlet at 2.72), 2.28 (broad s, 2H); ^{13}C NMR ($CDCl_3$) δ 148.5, 146.4, 129.5, 123.6, 58.3, 53.3, 47.0, 46.9, 34.2; IR ($CDCl_3$ film on NaCl plates) cm^{-1} 3200, 2925, 1591, 1513, 1337. Anal. (free base) Calcd for $C_{14}H_{22}N_4O_2$: C, 60.39; H, 7.97; N, 20.14. Found: C, 60.85; H, 7.74; N, 19.90.

1,4,7,10-Tetraaza-1-(*E*)-*N*-((4-nitrophenyl)-2-propenyl))cyclododecane (12): ^1H NMR ($CDCl_3$) δ 8.15 (d, 2H, J = 8.8 Hz), 7.57 (d, 2H, J = 8.8 Hz), 6.58 (m, 2H), 5.1 (br s, 3H), 3.46 (d, 2H, J = 5.1 Hz), 2.94 (m, 2H), 2.84 (m, 16H); ^{13}C NMR ($CDCl_3$) δ 146.6, 143.1, 132.2, 130.7, 127.0, 123.8, 58.0, 51.3, 48.1, 46.7, 45.6. Anal. (free base) Calcd for $C_{17}H_{27}N_5O_2$: C, 61.05; H, 8.44; N, 21.00. Found: C, 61.35; H, 8.14; N, 20.90.

Supplementary Material Available: Experimental data for **2**, bis alkylation adducts **7b**, **9b**, **12b**, and **14** as well as a description of the kinetic model using the SIMUSOLVE program and atomic coordinates, important bond lengths and bond angles, anisotropic thermal parameters, least-squares planes, torsion angles, and intermolecular contacts for the monohydrobromide salt **3a** (20 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.