Synthesis of Lipophilic Paramagnetic Contrast Agents

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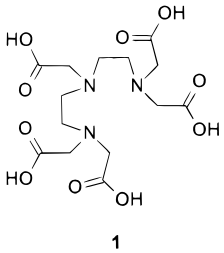
The facile, high-yielding synthesis of a series of macrocycles **7a**−**k** in 75−100% yield is reported. The transformation of these compounds to their carboxymethylated analogues **8a**−**k** in 75−90% yield and subsequent gadolinium complexes **9a**−**k** provides a series of homologous neutral paramagnetic contrast agents (PCAs) with tunable lipophilicity. Alkylated cationic intermediates **6a**−**k** are prepared in yields of 72−94% from glyoxal adduct of cyclen (**5**) and slight excesses of alkyl iodides**.** The methodology is selective for monoalkylation and amenable to large-scale synthesis.

Introduction

Since its introduction in 1978, the concept of contrast enhanced magnetic resonance imaging (CE-MRI) has evolved into a common clinical modality.[1,2] The current generation of FDA-approved T_1 contrast agents are based predominantly on amino polyacetic acid chelates of Gd(III) (**1**−**3**) and function by promoting the relaxivity of protons on solvating water. Although MRI was initially envisioned as a completely noninvasive technique, intravenously administered paramagnetic contrast agents (PCAs) can improve the overall quality and detail of images and allow for the unambiguous identification of pathologies that would otherwise be undetected. Numerous reports demonstrate how CE-MR images readily indicate the presence of lesions, tumors, and defects that are unobserved by conventional MRI techniques.[2] As a result of these successes, clinical CE-MRI applications continue to rapidly evolve. This drives the need for more efficient and pathology-specific contrast agents that increase the potential of CE-MRI as a diagnostic tool.[3]



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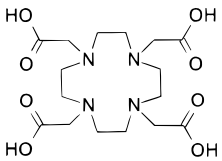

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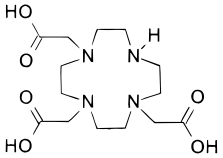

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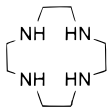

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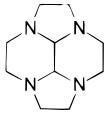

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The development of ligands which impart significant lipophilic character to the PCA are becoming increasingly important.[4] Ideally, ligands that possess substantial lipophilic character should serve as more efficient carriers for the transport of the paramagnetic gadolinium ion across cell membranes. Increased hydrophobicity of the ligand should lead to plasma protein binding and some degree of hepatobiliary excretion, thereby creating the potential for liver targeting.[2] We envisioned that the lipophilicity could be increased by substituting one of the carboxylate arms of DOTA (**2**) with a hydrocarbon chain. In this paper we report the synthesis of a series of alkylated macrocycles and their Gd(III) complexes which are intended for use as PCAs. These compounds are based on the selective monoalkylation of 1,4,7,10-tetraazacyclododecane (**4**, cyclen) with slight excesses of simple alkyl iodides.

Original work in the area of PCA design demonstrated that the polyamino carboxylate derivatives diethylenetriaminepentaacetic acid (DTPA, **1**)[5] and 1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazacyclododecane (DOTA)[6] formed stable and soluble complexes with Gd(III) in water. These macrocycles have no easily accessible sites for modification; thus, subsequent studies have focused on the preparation of ligands with differentiated sidearms on the nitrogen atoms. One of the most significant results of these studies was the synthesis of 1,4,7-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecane (DO3A, **3**) from **4** in six steps.[7] This ligand offered the synthetic advantage of having a free nitrogen on the macrocyclic ring available for derivatization.

Numerous examples of alkylated nitrogen-based macrocycles have appeared in the literature.[8] Recent efforts toward alkylated PCAs have focused on derivitization of **4**,[9] which can be efficiently synthesized using the methodology of Weisman and co-workers.[10] Alteration of the carbon skeleton of **4** has been investigated,[11] but most

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strategies have been based on N-alkylation. In addition to monoalkylation products, several instances of N^1,N^4-dialkylated cyclen derivatives have been reported in the literature.[12] Handel and co-workers used highly reactive alkyl halides and a silicon-based protection scheme to synthesize the monomethylated and monobenzylated derivatives of **4**.[13] Benzyl**,** propyl, and nonyl cyclen have been prepared in 56, 63, and 48% yield, respectively, via their molybdenum tricarbonyl complexes.[14] Other reports have demonstrated that the use of a 5−10 mol excess of **4** over the alkyl halide yields monoalkylation products.[15] Recently, Kimura and co-workers synthesized hexadecylcyclen from dioxotetramine and 1-bromohexadecane through a multiple-step, low-yielding sequence.[16]

In addition to alkylated cyclen derivatives, reports of alkylated DO3A analogues have also appeared in the literature. Tweedle and co-workers reported the cyclen-based synthesis of methyl DO3A,[7] and Chang has determined the stability constants of propyl DO3A with several alkaline-earth metals.[17] A report on EPR studies of gadolinium pentyl-DO3A (Gd-DOTA-P) in phospholipid bilayers has also recently appeared.[18]

Results and Discussion

Cyclen (**4**) was synthesized through methods reported earlier by Weisman and co-workers. It has been previously shown that reaction of cyclen with glyoxal yields bridged macrocycle **5**.[19] Subsequent alkylation of **5** with alkyl iodides over the course of 1−4 days in toluene resulted in precipitation of the monoalkylated iodo salts **6a**−**k**. In general, the use of longer-chain alkyl iodides required longer reaction times. We observed 1,7-dialkylation products in the case of the two most reactive halides (MeI and BnBr), even when less than 1 mol equiv of halide was employed. These results are consistent with those in the literature.[20]

Salts **6f**−**k** were found to be slightly soluble in toluene due to their significant lipophilic character, resulting in partial precipitation of oily amorphous residues which were subsequently purified through recrystallization. We attribute the driving force of the alkylation reaction to the precipitation of the monoalkylated cationic products from solution. Addition of a large excess of halide did not significantly hasten the course of the reaction; thus, a 1.5:1 ratio of alkyl iodide to **5** was employed in each case. The tetradecyl salt **6i** was formed in significantly higher yield than its counterparts. The origin of this effect is unknown. All iodides were pure before use; furthermore, distillation of alkyl iodides from copper mesh immediately prior to use did not significantly change the yields of subsequent alkylations.

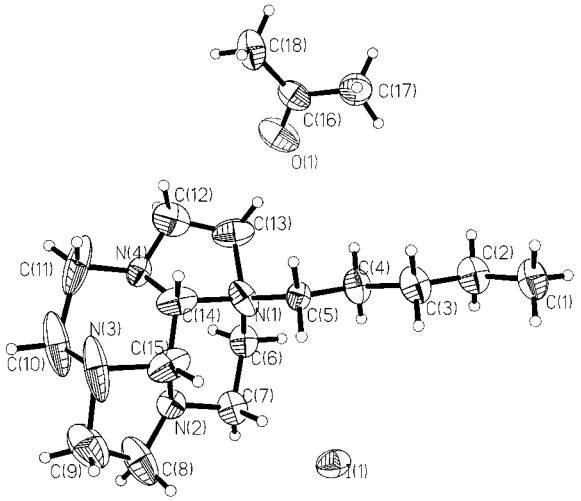

Figure 1.

Salts **6a**−**k** exhibited extremely complex ^{1}H NMR spectra resulting from symmetry breaking of the glyoxal ring adduct. Spectra obtained at 500 MHz lacked the necessary dispersion required for full assignment of ring protons, but ^{1}H NMR spectra could be completely assigned at 750 MHz. HMBC, HMQC, and COSY data were used to elucidate the structure of **6c**. The presence of pseudoaxial and pseudoequatorial protons on each of the four rings leads to the observation of numerous complex multiplet signals in the region from 2.40 to 4.40 ppm. Assignment of the individual ethylene fragments was achieved through the use of COSY and HMQC data, followed by positioning in the fused ring structure on the basis of long-range correlations from the HMBC experiment. In the specific case of the butyl salt **6c**, second-order signals at 1.50, 1.60, and 1.80 ppm were observed from prodiastereotopic protons on the butyl side chain. Higher chain salts were solved by analogy due to the similarity of spectra throughout the series.

Pentyl salt **6d** was recrystallized from acetone and petroleum ether over 24 h to yield crystals suitable for X-ray diffraction. This compound crystallizes in the space group $P\bar{1}$ with two molecules per unit cell (Figure 1). This structure clearly shows the hydrogen atoms of the bridging ethylene unit protruding in a cisoid fashion from the bowl-shaped fused ring system. Alkylation of glyoxal adduct may occur at N1 or N2, leading to formation of a pair of enantiomers related to each other in the unit cell by an inversion center. We also observe the iodine counterion and a single solvent molecule of acetone for each molecule of **6d** in the unit cell.

Formation of alkylated cyclen derivatives (**7a**−**k**) was achieved in good yields through hydrolysis of salts **6a**−**k**

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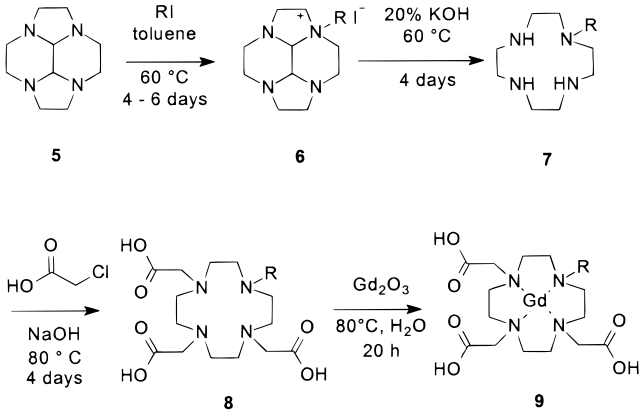
Scheme 1



in 20% (w/v) aqueous KOH solution at 60 °C. The course of these reactions was monitored by ^{1}H NMR, showing full conversion in most cases after 4 days. The resulting water-insoluble oily residues were extracted into chloroform, yielding the hydrolysis products **7a**−**k**. Extraction of cyclen adducts **7e**−**k** revealed the presence of a small amount of unknown impurity, which could not be removed by chromatographic methods or recrystallization. Dissolution of the residues in ethanol, followed by treatment with concentrated HCl, resulted in the formation of the respective hydrochloride salts of **7e**−**k**. Recrystallization of these salts from ethanol, followed by neutralization with NaOH and extraction into chloroform, resulted in removal of the unknown impurities.

Hydrolysis of salts **7j** and **7k** resulted in the initial formation of white sebacious spheres in the reaction mixture after 24 h. These structures persisted for 3 days, after which the familiar oily residue separated from the reaction mixtures. This white substance was found to be insoluble in aqueous and organic solvents and thus was not identifiable by standard NMR techniques. The mechanism of this reaction is not currently known. We postulate a hydrolysis mechanism that proceeds via nucleophilic attack on one of the bridgehead carbons of the salt **6**, resulting in the formation of a nitrogen ylide **10** (Scheme 2). Subsequent loss of formaldehyde and formate anion affords the monosubstituted cyclen derivative **7**. Attempted hydrolysis of propargylated salt **6l** resulted in elimination of the propargyl arm and regeneration of glyoxal adduct **5**. This demonstrates that **5** is stable under basic conditions and suggests that a positively charged nitrogen atom is a prerequisite for the hydrolysis. Generation of the ylide **10** is slow compared to deprotonation of the terminal alkyne hydrogen and subsequent elimination of the propargyl side chain. On the basis of this observation, we propose the formation of the nitrogen ylide **10** as the product-determining step in the hydrolysis.Reaction of **7a**−**k** with chloroacetic acid and NaOH in aqueous solution yielded DO3A analogues **8a**−**k**. During purification, **8a**−**h** were found to be water-soluble, whereas compounds **8g**−**k** showed limited solubility in water.

Additional solubility tests showed these compounds to be only moderately soluble in organic solvents due to formation of aggregates. Attempted characterization of **8g**−**k** by standard NMR techniques produced spectra with low signal-to-noise due to the poor solubility of these compounds in most deuterated solvents. These compounds are currently being tested to determine their

Scheme 2

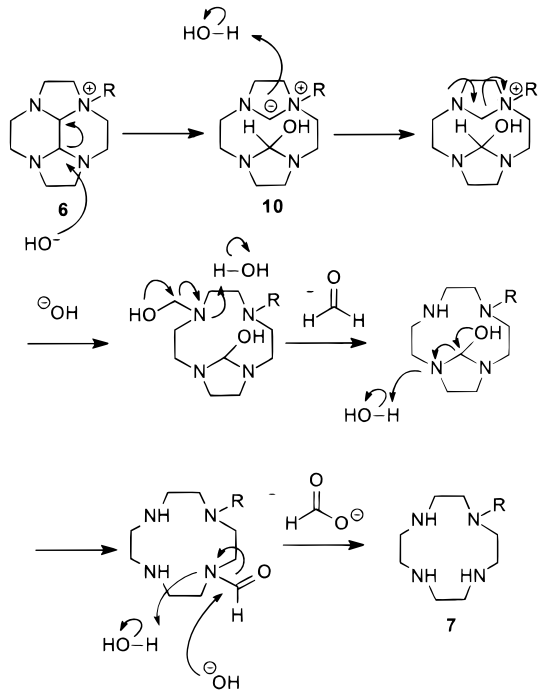


Table 1. Synthesis of Alkylated DO3A Analogues (% yield)

entry	R	6	7	8	9
a	C_2H_5	92	92	88	100
b	C_3H_7	91	95	81	100
c	C_4H_9	84	100	87	100
d	C_5H_{11}	76	100	78	100
e	C_6H_{13}	79	84	83	100
f	C_8H_{17}	77	79	90	100
g	$C_{10}H_{21}$	72	75	86	100
h	$C_{12}H_{25}$	85	82	89	100
i	$C_{14}H_{29}$	94	85	80	100
j	$C_{16}H_{33}$	74	84	77	100
k	$C_{18}H_{37}$	77	78	75	100
l	C_2H_2	94	0	−	−

critical micellular concentrations (CMC); these results will be reported separately.

Preparation of the Gd(III) complexes of **8a**−**k** was achieved using Gd_2O_3 in aqueous solution as reported in the literature.[7] After removal of excess $Gd(OH)_3$ via filtration, each solution was concentrated in vacuo to give **9a**−**k** as glassy solids. These compounds showed solubility traits similar to their gadolinium-free counterparts and exhibited decreased solubility in both organic and aqueous solvent when the lipophilic side chain contained more than eight carbons.

Conclusion

We have prepared a series of new lipophilic Gd(III) complexes for use as paramagnetic contrast agents. This synthesis of compounds with varying lengths of alkyl side chains has resulted in the creation of potential PCAs with a tunable lipophilicity. Our methodology allows for selective monoalkylation of cyclen using slight excesses of alkyl halide in excellent yield. This procedure is restricted to the use of sidearms that do not easily undergo base-catalyzed processes. Complexes **9a**−**k** are under investigation as candidates for use as paramagnetic contrast agents for magnetic resonance imaging.

Experimental Section

General Methods. Et_2O (Mallinckrodt) was freshly distilled from benzophenone ketyl prior to use. 1-Iodotetradecane was obtained from Chemica Alta LTD, Edmonton, Alberta, Canada. All other alkyl iodides were obtained from Aldrich Chemical Co. Cyclen (**4**)[10] and glyoxal adduct of cyclen (**5**)[19] were prepared according to known procedures. Dowex 50W-8X cation-exchange resin was obtained from Bio-Rad Laboratories, Richmond, CA. Other reagents were purchased from commercial sources and used as obtained. Elemental analyses were performed by the University of Illinois Microanalysis Laboratory.

General Procedure for the Reaction of 5 with Alkyl Halides. A solution of *cis*-13−1,4,7,10-Tetraazatetracyclo-[5.5.2.0.^{4,14}0^{10,13}]tetradecane **5** in toluene (20 mL) and alkyl iodide (1.5 equiv) was stirred at 60 °C for 4 d under N_2. In the case of salts **6a**−**e**, the reaction mixture was cooled to room temperature and filtered to yield white precipitates which required no further purification. In the case of salts **6f**−**k**, the reaction mixture was concentrated in vacuo, giving a yellow solid which was recrystallized from ether/chloroform to give pure **6f**−**k**.

(1*RS*,13*SR*,14*RS*)-1-Ethyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane Iodide (6a). Yield (92%). ^{1}H NMR (500 MHz, $CDCl_3$) 1.52 (t, J = 7.0 Hz, 3H) 2.43 (ddd, J = 10.2, 7.9, 6.3 Hz, 1H), 2.67 (m, 1H), 2.70 (m, 1H) 2.80 (ddd, J = 12.5, 8.0, 6.1 Hz, 1H) 2.85 (td, J = 12.2, 3.2 Hz, 1H) 2.92 (ddd, J = 13.2, 11.7, 2.3 Hz, 1H) 3.04 (ddd, J = 11.1, 3.0, 1.9 Hz, 1H) 3.20 (m, 3H) 3.27 (td, J = 8.0, 4.5 Hz, 1H) 3.45 (td, J = 8.2, 2.5 Hz, 1H) 3.49 (d, J = 2.9, 1H) 3.78 (m, 3H) 3.91 (td, J = 13.9, 7.2 Hz, 1H) 4.19 (td, J = 10.5, 6.3 Hz, 1H) 4.20 (d, J = 2.8 Hz, 1H) 4.43 (ddd, J = 11.6, 10.1, 3.0 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 9.4 43.5 47.9 48.0 48.4 49.1 52.0 53.0 57.3 61.4 72.8 83.5. HRFAB calcd for $C_{12}H_{23}N_4$ 223.1923, found 223.1923. Anal. Calcd (found) for $C_{12}H_{23}N_4I$: C, 41.15 (40.94); H, 6.62 (6.70); N, 16.00 (15.67).

(1*RS*,13*SR*,14*RS*)-1-Propyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0^{4,14}.0^{10,13}]tetradecane Iodide (6b). Yield (91%). ^{1}H NMR (500 MHz, $CDCl_3$) 1.13 (t, J = 7.2 Hz, 3H) 1.92 (m, 2H) 2.44 (ddd, J = 9.3, 8.0, 5.9 Hz, 1H) 2.66 (m, 1H) 2.69 (m, 1H) 2.79 (ddd, J = 12.3, 8.0, 6.1 Hz, 1H) 2.83 (td, J = 11.1, 2.6 Hz, 1H) 2.93 (ddd, J = 13.6, 11.4, 2.5 Hz, 1H) 3.03 (dt, J = 12.1, 2.0 Hz, 1H) 3.19 (m, 3H) 3.26 (td, J = 8.0, 4.6 Hz, 1H) 3.44 (td, J = 8.2, 2.5 Hz, 1H) 3.51 (d, J = 2.8, 1H) 3.74 (td, J = 12.5, 5.2, 1H) 3.80 (m, 3H) 4.05 (td, J = 12.1, 5.1 Hz, 1H) 4.16 (d, J = 2.5 Hz, 1H) 4.51 (ddd, J = 12.4, 10.0, 2.8 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 10.9 17.3 43.6 47.8 48.1 48.3 49.1 52.0 57.7 58.8 62.0 72.1 83.6. HRFAB calcd for $C_{13}H_{25}N_4$ 237.2079, found 237.2079. Anal. Calcd (found) for $C_{13}H_{25}N_4I$: C, 42.86 (42.95); H, 6.92 (6.90); N, 15.38 (14.99).

(1*RS*,13*SR*,14*RS*)-1-Butyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane Iodide (6c). Yield (84%). ^{1}H NMR (750 MHz, $CDCl_3$) 0.99 (t, J = 7.2 Hz, 3H), 1.49 (m, 1H), 1.57 (m, 1H), 1.82 (m, 1H), 2.42 (ddd, J = 9.7, 8.1, 6.0 Hz, 1H), 2.66 (m, 1H), 2.68 (m, 1H) 2.78 (ddd, J = 12.5, 8.0, 5.9 Hz, 1H) 2.82 (td, J = 11.7, 2.8 Hz, 1H) 2.90 (ddd, J = 13.6, 10.5, 3.0 Hz, 1H) 3.01 (ddd, J = 13.6, 3.1, 1.9 Hz, 1H) 3.19 (m, 3H) 3.24 (td, J = 8.1, 4.6 Hz, 1H) 3.43 (td, J = 8.2, 2.6 Hz, 1H) 3.49 (d, J = 2.9, 1H) 3.73 (td, J = 12.4, 5.3 Hz, 1H) 3.78 (m, 3H) 4.03 (td, J = 12.2, 4.8 Hz, 1H) 4.19 (d, J = 2.8 Hz, 1H) 4.41 (ddd, J = 11.9, 10.1, 3.0 Hz, 1H). ^{13}C NMR (750 MHz, $CDCl_3$) 13.7 19.7 25.5 43.6 47.8 48.0 48.3 49.0 51.9 57.3 57.7 61.9 72.167 83.5. HRFAB calcd for $C_{14}H_{27}N_4$ 251.2236, found 251.2236. Anal. Calcd (found) for $C_{14}H_{27}N_4I$: C, 44.44 (44.52); H, 7.20 (7.37); N, 14.81 (14.59).

(1*RS*,13*SR*,14*RS*)-1-Pentyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0^{4,14}.0^{10,13}]tetradecane Iodide (6d). Yield (76%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.90 (t, J = 7.1 Hz, 3H) 1.40 (m, 3H) 1.52 (m, 1H), 1.84 (m, 1H) 2.43 (ddd, J = 10.0, 8.1, 6.3 Hz, 1H), 2.66 (m, 1H), 2.70 (m, 1H) 2.80 (ddd, J = 12.2, 8.1, 6.1 Hz, 1H) 2.82 (td, J = 12.6, 3.7 Hz, 1H) 2.88 (ddd, J = 13.6, 10.3, 4.9 Hz, 1H) 3.02 (ddd, J = 11.3, 2.7, 1.6 Hz, 1H) 3.20 (m, 3H) 3.26 (td, J = 8.1, 4.6 Hz, 1H) 3.44 (td, J = 8.3, 2.8 Hz, 1H) 3.49 (d, J = 2.9, 1H) 3.74 (ddd, J = 13.0, 10.9, 6.6 Hz, 1H) 3.79 (m, 3H) 4.04 (td, J = 10.7, 6.2 Hz, 1H) 4.22 (d, J = 2.8 Hz, 1H) 4.44 (ddd, J = 11.8, 10.0, 2.9 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 13.8 22.3 23.4 28.3 43.7 47.9 48.1 48.3 49.1 51.0 57.5 57.8 61.9 72.2 83.5. HRFAB calcd for $C_{15}H_{29}N_4$ 265.2392, found 265.2392. Anal. Calcd (found) for $C_{15}H_{29}N_4I$: C, 45.92 (46.20); H, 7.45 (7.47); N, 14.28 (13.94).

(1*RS*,13*SR*,14*RS*)-1-Hexyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0^{4,14}.0^{10,13}]tetradecane iodide (6e). Yield (79%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.87 (t, J = 7.0 Hz, 3H) 1.32 (m, 4H) 1.43 (m, 1H) 1.54 (m, 1H), 1.83 (m, 1H) 2.41 (ddd, J = 9.8, 7.8, 5.9 Hz, 1H), 2.66 (m, 1H), 2.70 (m, 1H) 2.80 (ddd, J = 12.3, 8.0, 5.9 Hz, 1H) 2.83 (td, J = 11.1, 3.4 Hz, 1H) 2.87 (ddd, J = 13.7, 9.8, 4.0 Hz, 1H) 3.02 (ddd, J = 11.1, 3.3, 1.9 Hz, 1H) 3.19 (m, 3H) 3.26 (td, J = 8.1, 4.6 Hz, 1H) 3.44 (td, J = 8.2, 2.8 Hz, 1H) 3.47 (d, J = 2.9, 1H) 3.73 (ddd, J = 12.8, 10.5, 8.2 Hz, 1H) 3.79 (m, 3H) 4.05 (td, J = 12.8, 7.9 Hz, 1H) 4.20 (d, J = 2.8 Hz, 1H) 4.44 (ddd, J = 12.6, 9.9, 2.9 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 13.9 22.3 23.6 25.9 31.2 43.6 47.8 48.0 48.3 49.0 51.9 57.4 57.8 61.9 72.2 83.4. HRFAB calcd for $C_{16}H_{31}N_4$ 279.2549, found 279.2548. Anal. Calcd (found) for $C_{16}H_{31}N_4I$: C, 47.29 (47.31); H, 7.69 (7.65); N, 13.79 (13.77).

(1*RS*,13*SR*,14*RS*)-1-Octyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.04,14.010,13]tetradecane Iodide (6f). Yield (77%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.84 (t, J = 7.1 Hz, 3H) 1.30 (m, 8H) 1.43 (m, 1H) 1.51 (m, 1H), 1.82 (m, 2H) 2.45 (ddd, J = 10.4, 8.3, 4.4 Hz, 1H), 2.68 (m, 1H), 2.71 (m, 1H) 2.80 (ddd, J = 13.9, 8.0, 3.4 Hz, 1H) 2.86 (td, J = 11.1, 3.2 Hz, 1H) 2.91 (ddd, J = 11.5, 8.7, 4.0 Hz, 1H) 3.03 (ddd, J = 10.8, 3.3, 2.0 Hz, 1H) 3.21 (m, 3H) 3.27 (td, J = 8.0, 4.8 Hz, 1H) 3.45 (td, J = 8.4, 2.9 Hz, 1H) 3.55 (d, J = 2.8, 1H) 3.74 (ddd, J = 13.0, 10.0, 7.0 Hz, 1H) 3.79 (m, 3H) 4.02 (td, J = 12.7, 7.9 Hz, 1H) 4.23 (d, J = 2.8 Hz, 1H) 4.40 (ddd, J = 12.0, 9.9, 3.0 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.0 22.5 23.6 26.3 28.9 29.2 31.6 43.6 47.8 48.1 48.3 49.1 51.9 57.4 57.8 57.8 61.9 72.2 83.4. HRFAB calcd for $C_{18}H_{35}N_4$ 307.2862, found 307.2862. Anal. Calcd (found) for $C_{18}H_{35}N_4I$: C, 49.77 (49.99); H, 8.12 (8.23); N, 12.90 (12.93).

(1*RS*,13*SR*,14*RS*)-1-Decyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane Iodide (6g). Yield (72%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.86 (t, J = 7.0 Hz, 3H) 1.24 (m, 10H) 1.35 (m, 2H) 1.49 (m, 2H), 1.82 (m, 2H) 2.43 (ddd, J = 9.7, 8.0, 5.6 Hz, 1H), 2.68 (m, 1H), 2.71 (m, 1H) 2.82 (ddd, J = 12.4, 8.1, 5.9 Hz, 1H) 2.86 (td, J = 11.7, 2.8 Hz, 1H) 2.88 (ddd, J = 13.9, 8.4, 5.9 Hz, 1H) 3.04 (ddd, J = 11.1, 4.76, 1.9 Hz, 1H) 3.20 (m, 3H) 3.27 (td, J = 8.2, 4.6 Hz, 1H) 3.45 (td, J = 8.2, 2.8 Hz, 1H) 3.49 (d, J = 2.7, 1H) 3.75 (ddd, J = 12.7, 10.0, 7.0 Hz, 1H) 3.79 (m, 3H) 4.05 (td, J = 12.9, 5.8 Hz, 1H) 4.22 (d, J = 2.9 Hz, 1H) 4.44 (ddd, J = 12.9, 10.1, 3.0 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.0 22.5 23.6 26.3 29.1 29.2 29.3 29.3 31.7 43.6 47.8 48.0 48.2 49.0 51.9 57.5 57.7 61.9 72.1 83.3. HRFABMS calcd for $C_{20}H_{39}N_4$ 335.3175, found 335.3176. Anal. Calcd (found) for $C_{20}H_{39}N_4I$: C, 51.94 (51.75); H, 8.50 (8.34); N, 12.11 (12.10).

(1*RS*,13*SR*,14*RS*)-1-Dodecyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane Iodide (6h). Yield (85%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.87 (t, J = 7.1 Hz, 3H) 1.25 (m, 14H) 1.36 (m, 2H) 1.50 (m, 2H), 1.81 (m, 2H) 2.41 (ddd, J = 9.6, 7.7, 5.4 Hz, 1H), 2.69 (m, 1H), 2.72 (m, 1H) 2.82 (ddd, J = 12.0, 8.2, 6.1 Hz, 1H) 2.83 (td, J = 11.7, 2.9 Hz, 1H) 2.85 (ddd, J = 12.3, 8.6, 5.3 Hz, 1H) 3.04 (ddd, J = 11.3, 4.5, 1.6 Hz, 1H) 3.21 (m, 3H) 3.28 (td, J = 8.1, 4.7 Hz, 1H) 3.44 (td, J = 9.0, 3.2 Hz, 1H) 3.45 (d, J = 2.8, 1H) 3.76 (td, J = 12.9, 5.6 Hz, 1H) 3.80 (m, 3H) 4.10 (td, J = 12.0, 5.1 Hz, 1H) 4.22 (d, J = 2.8 Hz, 1H) 4.44 (ddd, J = 12.3, 9.9, 3.2 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.1 17.3 22.6 23.7 26.3 29.3 29.3 29.5 29.5 31.8 43.7 47.9 48.2 48.4 49.1 52.0 57.4 58.0 62.0 72.3 83.3. HRFABMS calcd for $C_{22}H_{43}N_4$ 363.3488, found 363.3486. Anal. Calcd (found) for $C_{22}H_{43}N_4I$: C, 53.86 (53.86); H, 8.83 (8.73); N, 11.42 (11.17).

(1*RS*,13*SR*,14*RS*)-1-Tetradecyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane Iodide (6i). Yield (94%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.87 (t, J = 7.1 Hz, 3H) 1.24 (m, 18H) 1.35 (m, 2H) 1.49 (m, 2H), 1.81 (m, 2H) 2.40 (ddd, J = 9.4, 7.9, 5.6 Hz, 1H), 2.69 (m, 1H), 2.71 (m, 1H) 2.81 (ddd, J = 12.3, 7.9, 5.9 Hz, 1H) 2.83 (td, J = 10.7, 2.9 Hz, 1H)

2.85 (ddd, J = 12.8, 9.6, 5.9 Hz, 1H) 3.04 (ddd, J = 11.4, 5.1, 1.9 Hz, 1H) 3.20 (m, 3H) 3.28 (td, J = 8.2, 4.7 Hz, 1H) 3.44 (d, J = 2.9 Hz, 1H) 3.45 (td, J = 8.0, 2.5 1H) 3.75 (td, J = 12.7, 4.9 Hz, 1H) 3.80 (m, 3H) 4.08 (td, J = 12.6, 4.9 Hz, 1H) 4.22 (d, J = 2.7 Hz, 1H) 4.44 (ddd, J = 13.2, 10.0, 3.1 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.1 22.6 23.7 26.4 28.5 29.3 29.3 29.4 29.5 29.6 29.6 31.9 43.7 47.9 48.1 48.3 49.1 52.0 57.5 62.0 72.2 83.3. HRFAB calcd for $C_{24}H_{47}N_4$ 391.3801, found 391.3803. Anal. Calcd (found) for $C_{24}H_{47}N_4I$: C, 55.59 (55.34); H, 9.14 (9.31); N, 10.80 (10.55).

(1*RS*,13*SR*,14*RS*)-1-Hexadecyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane Iodide (6j). Yield (74%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.86 (t, J = 7.1 Hz, 3H) 1.25 (m, 22H) 1.35 (m, 2H) 1.48 (m, 2H), 1.81 (m, 2H) 2.41 (ddd, J = 9.5, 7.9, 5.7 Hz, 1H), 2.68 (m, 1H), 2.71 (m, 1H) 2.81 (ddd, J = 12.9, 9.6, 6.6 Hz, 1H) 2.83 (m, 1H) 2.86 (ddd, J = 12.8, 9.6, 6.6 Hz, 1H) 3.03 (ddd, J = 11.0, 4.5, 2.0 Hz, 1H) 3.19 (m, 3H) 3.27 (td, J = 8.0, 4.5 Hz, 1H) 3.42 (td, J = 8.1, 2.6 Hz, 1H) 3.46 (d, J = 2.8 1H) 3.75 (td, J = 11.4, 6.0 Hz, 1H) 3.80 (m, 3H) 4.08 (td, J = 12.5, 5.0 Hz, 1H) 4.22 (d, J = 2.6 Hz, 1H) 4.44 (ddd, J = 12.1, 10.0, 3.3 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.0 22.6 23.7 26.3 29.3 29.5 29.5 29.6 29.6 31.8 43.743 47.9 48.1 48.4 49.1 52.0 57.4 57.9 62.0 72.3 83.3. HRFAB calcd for $C_{26}H_{51}N_4$ 419.4114, found 419.4121. Anal. Calcd (found) for $C_{26}H_{51}N_4I$: C, 57.13 (57.04); H, 9.40 (9.43); N, 10.24 (9.93).

(1*RS*,13*SR*,14*RS*)-1-Octadecyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0.^{4,14}0^{10,13}]tetradecane Iodide (6k). Yield (77%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.86 (t, J = 7.1 Hz, 3H) 1.24 (m, 26H) 1.35 (m, 2H) 1.48 (m, 2H), 1.81 (m, 2H) 2.42 (ddd, J = 9.6, 7.2, 5.7 Hz, 1H), 2.68 (m, 1H), 2.71 (m, 1H) 2.81 (ddd, J = 12.0, 7.9, 5.9 Hz, 1H) 2.83 (m, 1H) 2.87 (ddd, J = 3.4, 9.5, 6.7 Hz, 1H) 3.03 (td, J = 11.3, 2.3 Hz, 1H) 3.19 (m, 3H) 3.26 (td, J = 8.0, 4.6 Hz, 1H) 3.45 (td, J = 8.2, 2.6 Hz, 1H) 3.47 (d, J = 2.7 1H) 3.74 (td, J = 11.2, 5.6 Hz, 1H) 3.79 (m, 3H) 4.08 (td, J = 11.1, 5.1 Hz, 1H) 4.22 (d, J = 2.8 Hz, 1H) 4.44 (ddd, J = 11.8, 10.2, 2.8 Hz, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.1 22.6 23.7 26.3 28.5 29.3 29.4 29.5 29.6 29.6 29.7 30.5 31.9 33.5 43.7 48.0 48.2 48.4 49.1 52.0 57.4 58.0 62.0 72.4 83.3. HRFAB calcd for $C_{28}H_{55}N_4$ 447.4427, found 447.4425. Anal. Calcd (found) for $C_{28}H_{55}N_4I$: C, 58.52 (58.17); H, 9.65 (9.71); N, 9.75 (9.45).

(1*RS*,13*SR*,14*RS*)-1-Propargyl-4,7,10-triaza-1-azoniatetracyclo[5.5.2.0^{4,14}.0^{10,13}]tetradecane Iodide (6l). Yield (94%). ^{1}H NMR (500 MHz, D_2O, benzene as internal reference) 2.30 (ddd, J = 10.0 8.6, 6.2 Hz, 1H), 2.40 (td, J = 11.7, 3.0 Hz, 1H), 2.64 (td, J = 11.7, 3.6 Hz, 1H), 2.71 (m, 3H), 2.77 (ddd, J = 12.1, 7.7, 6.1 Hz, 1H), 3.10 (m, 4H), 3.15 (td, J = 8.5, 4.3 Hz, 1H), 3.38 (td, J = 8.1, 2.5 Hz, 1H), 3.41 (d, J = 2.7 Hz, 1H), 3.61 (td, J = 12.8, 3.5 Hz, 1H), 3.74 (dt, J = 12.5, 8.4 Hz, 1H), 3.86 (d, J = 13.1, 1H), 3.94 (d, J = 2.4 Hz, 1H), 3.98 (ddd, J = 12.9, 9.9, 2.9 Hz, 1H), 4.39 (AB, Jab = 16.5, $\Delta\nu$ = 40.4, 2H). ^{13}C NMR (500 MHz, D_2O, benzene as internal reference) 43.7, 47.5, 47.9, 48.0, 48.1, 48.9, 51.1, 59.1, 63.1, 70.4, 71.4, 81.7 82.0. HRFAB calcd for $C_{13}H_{21}N_4$ 233.1766, found 233.1765. Anal. Calcd (found) for $C_{13}H_{21}N_4I$: C, 43.27 (43.40); H, 5.86 (5.77); N, 15.53 (15.77).

General Procedure for the Hydrolysis of Alkylated Salts. An aqueous solution of 20% (w/v) KOH (25 mL) and alkylated salt **6** was stirred at 60 °C under N_2 for 4 d. The solution was cooled to room temperature and extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo to yield the alkylated cyclen derivative as a yellow oil. Compounds **7a**−**d** required no further purification. Compounds **7e**−**k** were purified as follows. To a solution of the oil in ethanol (3 mL) was added concentrated HCl (10 mL) to yield the tetrahydrochloride salt as a white precipitate. The solid was recrystallized from ethanol, dissolved in 20% (w/v) KOH (20 mL), and extracted with $CHCl_3$ (3 × 30 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated to yield the alkylated cyclen derivative.

1-Ethyl-4,7,10-tetraazacyclododecane (7a). Yield (92%). ^{1}H NMR (500 MHz, $CDCl_3$) 1.03 (t, J = 7.1 Hz, 3H), 2.52 (t, J = 7.1 Hz, 2H), 2.54 (t, J = 5.1, 4H), 2.59 (t, J = 4.9 Hz, 4H), 2.64 (t, J = 4.8 Hz, 4H), 2.79 (t, J = 5.0 Hz, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 11.9 45.2 45.9 47.0 48.0 50.7. HRCIMS calcd for $C_{10}H_{24}N_4$ 201.2079, found 201.2079 (M + H). Anal. Calcd (found) for $C_{10}H_{28}N_4Cl_4$: C, 34.70 (34.77); H, 8.15 (8.28); N, 16.19 (16.00).

1-Propyl-1,4,7,10-tetraazacyclododecane (7b). Yield (95%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.80 (t, J = 7.3 Hz, 3H), 1.39 (sext, J = 7.3 Hz, 2H), 2.28 (t, J = 7.2, 2H), 2.42 (t, J = 4.9 Hz, 4H), 2.47 (t, J = 5.2 Hz, 4H), 2.53 (t, J = 5.1 Hz, 4H), 2.68 (t, J = 5.1 Hz, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 11.7 20.2 44.9 45.9 46.8 41.3 56.1. HRCIMS calcd for $C_{11}H_{26}N_4$ 215.2236, found 215.2232 (M + H). Anal. Calcd (found) for $C_{11}H_{30}N_4Cl_4$: C, 36.67 (37.01); H, 8.40 (8.61); N, 15.56 (15.59).

1-Butyl-1,4,7,10-tetraazacyclododecane (7c). Yield (100%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.88 (t, J = 7.3 Hz, 3H), 1.29 (sext, J = 7.3 Hz, 2H), 1.43 (quin, J = 7.2, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.49 (t, J = 4.9 Hz, 4H), 2.54 (t, J = 5.1 Hz, 4H), 2.60 (t, J = 5.1 Hz, 4H) 2.75 (t, J = 5.0, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 13.9 22.2 29.4 45.2 45.9 47.0 51.4 54.3. HRCIMS calcd for $C_{12}H_{28}N_4$ 229.2331 found 229.2330 (M + H). Anal. Calcd (found) for $C_{12}H_{32}N_4Cl_4$: C, 38.51 (38.69); H, 8.61 (9.00); N, 14.97 (15.11).

1-Pentyl-1,4,7,10-tetraazacyclododecane (7d). Yield (100%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.87 (t, J = 7.1 Hz, 3H), 1.28 (m., 4H), 1.45 (quin, J = 7.2, 2H), 2.41 (t, J = 7.2 Hz, 2H), 2.54 (t, J = 4.9 Hz, 4H), 2.59 (t, J = 5.1 Hz, 4H), 2.65 (t, J = 5.2 Hz, 4H) 2.79 (t, J = 5.1, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.0 22.4 26.7 29.5 45.2 45.8 47.0 51.3 54.5. HRCIMS calcd for $C_{13}H_{30}N_4$ 243.2438, found 243.2437 (M + H). Anal. Calcd (found) for $C_{13}H_{34}N_4Cl_4$: C, 40.22 (40.60); H, 8.83 (8.94); N, 14.43 (14.71).

1-Hexyl-1,4,7,10-tetraazacyclododecane (7e). Yield (84%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.81 (t, J = 7.0 Hz, 3H), 1.22 (m., 6H), 1.41 (quin, J = 7.1, 2H), 2.34 (t, J = 7.2 Hz, 2H), 2.46 (t, J = 5.0 Hz, 4H), 2.51 (t, J = 5.0 Hz, 4H), 2.57 (t, J = 5.0 Hz, 4H) 2.72 (t, J = 5.0, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.0 15.6 22.4 26.8 29.5 45.6 45.9 46.9 51.3 54.3. HRCIMS calcd for $C_{14}H_{32}N_4$ 257.2732., found 257.2733 (M + H). Anal. Calcd (found) for $C_{14}H_{36}N_4Cl_4$: C, 41.80 (41.67); H, 9.02 (8.88); N, 13.93 (14.33).

1-Octyl-1,4,7,10-tetraazacyclododecane (7f). Yield (79%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.85 (t, J = 7.2 Hz, 3H), 1.25 (m., 10H), 1.44 (quin, J = 7.4, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.50 (t, J = 5.3 Hz, 4H), 2.54 (t, J = 5.2 Hz, 4H), 2.60 (t, J = 5.1 Hz, 4H) 2.76 (t, J = 5.2, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.0 22.6 27.2 27.4 29.3 29.4 31.8 44.9 45.9 46.8 51.4 54.4 HRCIMS calcd for $C_{16}H_{36}N_4$ 285.3022, found 285.3033 (M + H). Anal. Calcd (found) for $C_{16}H_{40}N_4Cl_4$: C, 44.66 (45.00); H, 9.36 (9.71); N, 13.02 (13.00).

1-Decyl-1,4,7,10-tetraazacyclododecane (7g). Yield (75%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.85 (t, J = 7.2 Hz, 3H), 1.25 (m., 10H), 1.44 (quin, J = 7.4, 2H), 2.38 (t, J = 7.2 Hz, 2H), 2.50 (t, J = 5.3 Hz, 4H), 2.54 (t, J = 5.2 Hz, 4H), 2.60 (t, J = 5.1 Hz, 4H) 2.76 (t, J = 5.2, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.1 22.6 27.2 27.4 29.3 29.5 29.6 31.8 32.5 45.2 46.0 47.1 51.5 54.5. HRCIMS calcd for $C_{18}H_{40}N_4$ 313.3331, found 313.3327 (M + H). Anal. Calcd (found) for $C_{18}H_{44}N_4Cl_4$: C, 47.16 (47.41); H, 9.67 (9.87); N, 12.23 (11.90).

1-Dodecyl-1,4,7,10-tetraazacyclododecane (7h). Yield (82%).^{1}H NMR (500 MHz, $CDCl_3$) 0.86 (t, J = 7.1 Hz, 3H), 1.24 (m., 18H), 1.45 (quin, J = 7.2, 2H), 2.39 (t, J = 7.3 Hz, 2H), 2.52 (t, J = 5.5 Hz, 4H), 2.58 (t, J = 5.1 Hz, 4H), 2.64 (t, J = 5.2 Hz, 4H) 2.79 (t, J = 5.1, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.0 22.6 27.2 29.3 29.5 29.5 29.6 29.6 31.8 45.3 46.0 47.1 52.0 52.1. HRCIMS calcd for $C_{20}H_{44}N_4$ 341.3644, found 341.3640 (M + H).

1-Tetradecyl-1,4,7,10-tetraazacyclododecane (7i). Yield (85%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.87 (t, J = 7.2 Hz, 3H), 1.25 (m., 22H), 1.44 (quin, J = 7.1, 2H), 2.37 (t, J = 7.4 Hz, 2H), 2.55 (t, J = 5.2 Hz, 4H), 2.58 (t, J = 5.3 Hz, 4H), 2.61 (t, J = 5.2 Hz, 4H) 2.77 (t, J = 5.1, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.1 22.6 27.2 27.5 27.6 29.1 29.3 29.4 29.5 29.6 29.6 29.7 31.9 45.2 46.0 47.1 51.5 52.1. HRCIMS calcd for $C_{22}H_{48}N_4$ 369.3957, found 369.3951 (M + H).

1-Hexadecyl-1,4,7,10-tetraazacyclododecane (7j). Yield (84%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.87 (t, J = 7.1 Hz, 3H), 1.24 (m., 22H), 1.45 (quin, J = 7.2, 2H), 2.38 (t, J = 7.3 Hz, 2H), 2.51 (t, J = 5.3 Hz, 4H), 2.56 (t, J = 5.1 Hz, 4H), 2.62 (t, J = 5.0 Hz, 4H) 2.76 (t, J = 5.0, 4H). ^{13}C NMR (500 MHz, $CDCl_3$) 14.0 22.6 27.2 27.4 27.4 27.6 29.3 29.5 29.6 29.6 31.8 45.2 46.0 47.0 51.481 54.550. HRCIMS calcd for $C_{24}H_{52}N_4$ 397.4271, found 397.4262 (M + H).

1-Octadecyl-1,4,7,10-tetraazacyclododecane (7k). Yield (78%). ^{1}H NMR (500 MHz, $CDCl_3$) 0.86 (t, J = 7.0 Hz, 3H), 1.24 (m, 30H), 1.44 (quin, J = 6.9, 2H), 2.38 (t, J = 7.1 Hz, 2H), 2.51 (t, J = 5.1 Hz, 4H), 2.56 (t, J = 5.0 Hz, 4H), 2.62 (t, J = 5.0 Hz, 4H) 2.77 (t, J = 5.0, 4H) ^{13}C NMR (500 MHz, $CDCl_3$) 14.1 22.6 27.3 27.5 27.8 29.3 29.4 29.5 29.6 29.7 29.7 29.8 31.9 45.1 46.1 47.0 51.5 54.5. HRCIMS calcd for $C_{26}H_{56}N_4$ 425.4471, found 425.4479 (M + H).

General Procedure for Carboxymethylation. A solution of monoalkylated cyclen **7** in water (10 mL), chloroacetic acid (3.5 equiv), and NaOH (3.5 equiv) was stirred under N_2 at 80 °C for 48 h, maintaining the pH between 9 and 10 by the addition of 1 M NaOH as needed. The solution was cooled to room temperature and concentrated in vacuo to give a yellow solid which was acidified to pH 2.5 with 1 M HCl and loaded onto Dowex 50W-X8 cation-exchange resin in the H^+ form. The column was eluted with 1 L water to remove salts and excess chloroacetic acid, followed by elution with 1 L of 0.5 M NH_3 to collect the desired product. The NH_3 eluent was concentrated in vacuo and triturated with ethanol to give the respective triacetic acid **8** as a yellow solid. The solid was recrystallized as the tetrahydrochloride salt from acetonitrile and ethanol for characterization purposes.

1-Ethyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8a). Yield (88%). ^{1}H NMR (500 MHz, D_2O, benzene as internal reference) δ 1.57 (3H, t, J = 7.1, H_a), 2.94 (10H, br s, H_b), 3.05 (4H, m, H_c), 3.20 (4H, s, H_d), 3.28 (4H, m, H_e) 3.58 (2H, s, H_f). ^{13}C NMR (125 MHz, D_2O, benzene as internal reference) δ 16.0 48.5 48.7 48.9 50.1 51.1 53.5 55.2 56.4 170.2 178.1. HRFABMS calcd for $C_{16}H_{31}N_4O_6$ 375.2244, found 375.2243 (M + H). Anal. Calcd (found) for $C_{16}H_{34}N_4O_6$-Cl_4: C, 36.94 (36.80); H, 6.59 (6.41); N, 10.77 (10.71).

1-Propyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8b). Yield. (81%). ^{1}H NMR (500 MHz, D_2O, benzene as internal reference) δ 1.10 (3H, t, J = 7.3, H_a), 1.55 (2H, sext, J = 7.2 Hz, H_b), 3.00 (10H, br s, H_c), 3.04 (4H, m, H_d), 3.19 (4H, s, H_e), 3.27 (4H, m, H_f) 3.59 (2H, s, H_g). ^{13}C NMR (125 MHz, D_2O, benzene as internal reference) δ 13.1 21.3 47.6 48.3 48.6 50.1 51.3 54.1 55.5 57.1 171.1 176.7. HRFABMS calcd for $C_{17}H_{33}N_4O_6$ 389.2400, found 389.2402 (M + H). Anal. Calcd (found) for $C_{17}H_{36}N_4O_6Cl_4$: C, 38.21 (37.99); H, 6.79 (6.64); N, 10.49 (10.85).

1-Butyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8c). Yield (87%). ^{1}H NMR (500 MHz, D_2O, benzene as internal reference) δ 0.77 (3H, t, J = 7.3 Hz, H_a), 1.20 (2H, sext, J = 7.4, H_b), 1.52 (2H, quin, J = 7.2 Hz, H_c), 2.97 (10H, br s, H_e), 3.03 (4H, m, H_f), 3.18 (4H, s, H_g), 3.26 (4H, m, H_h) 3.56 (2H, s, H_i). ^{13}C NMR (125 MHz, D_2O, benzene as internal reference) δ 12.6 19.1 24.2 48.6 48.8 48.9 50.0 51.1 53.4 55.3 56.3 170.1 177.6. HRFABMS calcd for $C_{18}H_{35}N_4O_6$ 403.2556, found 403.2556 (M + H). Anal. Calcd (found) for $C_{18}H_{38}N_4O_6Cl_4$: C, 39.43 (39.11); H, 6.98 (6.64); N, 10.22 (10.16).

1-Pentyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8d). Yield (78%). ^{1}H NMR (500 MHz, D_2O, benzene as internal reference) δ 0.85 (3H, t, J = 7.2 Hz, H_a), 1.20 (4H, m, H_b), 1.66 (2H, quin, J = 7.3 Hz, H_c) 3.05 (10H, br s, H_e), 3.18 (4H, m, H_f), 3.20 (4H, s, H_g), 3.33 (4H, m, H_h) 3.60 (2H, s, H_i). ^{13}C NMR (125 MHz, D_2O, benzene as internal reference) δ 12.8 21.3 21.8 27.8 48.7 48.9 49.9 51.1 53.6 55.3 56.3 170.1 177.4. HRFAB calcd for $C_{19}H_{37}N_4O_6$ 417.2713, found 417.2713 (M + H). Anal. Calcd (found) for $C_{19}H_{40}N_4O_6Cl_4$: C, 40.58 (40.19); H, 7.17 (7.37); N, 9.96 (10.02).

1-Hexyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8e). Yield (83%). ^{1}H NMR (500 MHz, D_2O, benzene as internal reference) δ 0.86 (3H, t, J = 7.2 Hz, H_a), 1.20 (6H, m, H_b), 1.66 (2H, quin, J = 7.3 Hz, H_c) 3.10 (10H, br s, H_e), 3.25 (4H, m, H_f), 3.34 (4H, s, H_g), 3.43 (4H, m, H_h) 3.70 (2H, s, H_i). ^{13}C NMR (125 MHz, D_2O, benzene as internal reference) δ 13.1 21.6 21.8 22.0 25.4 26.4 30.4 30.9 48.8 51.2 51.3 52.5 53.7 55.3 56.6. HRFABMS calcd for $C_{20}H_{39}N_4O_6$ 431.2869, found 431.2869 (M + H). Anal. Calcd (found) for $C_{20}H_{42}N_4O_6Cl_4$: C, 41.68 (41.77); H, 7.34 (6.99); N, 9.72 (10.01).

1-Octyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8f). Yield (90%). ^{13}C NMR (125 MHz, D_2O, benzene as internal reference) δ 13.2 21.7 22.0 25.3 25.6 28.0 28.1 28.1 30.8 48.7 48.7 48.9 49.9 51.1 53.6 55.2 55.3 56.4. HRFABMS calcd for $C_{22}H_{43}N_4O_6$ 458.3214, found 459.3217 (M + H). Anal. Calcd (found) for $C_{22}H_{46}N_4O_6Cl_4$: C, 43.71 (44.01); H, 7.67 (7.81); N, 9.27 (8.90).

1-Decyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8g).[21] Yield (86%). HRFABMS calcd for $C_{24}H_{47}N_4O_6$ 487.3496, found 487.3495 (M + H). Anal. Calcd (found) for $C_{24}H_{50}N_4O_6Cl_4$: C, 45.58 (45.64); H, 7.96 (7.87); N, 8.86 (8.46).

1-Dodecyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8h). Yield (89%). HRFABMS calcd for $C_{26}H_{51}N_4O_6$ 515.3698, found 515.3699 (M + H).

1-Tetradecyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8i). Yield (80%). FABMS calcd for $C_{28}H_{55}N_4O_6$ 543.4023, found 543.4023 (M + H).

1-Hexadecyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8j). Yield (77%). HRFABMS calcd for $C_{30}H_{59}N_4O_6$ 571.4232, found 571.4232 (M + H).

1-Octadecyl-1,4,7,10-tetraazacyclododecane-1,4,7-triacetic Acid (8k). Yield (75%). HRFABMS calcd for $C_{32}H_{63}N_4O_6$ 599.4531, found 599.4532 (M + H).

General Procedure for the Formation of Gadolinium Complexes. A solution of the ligand **8** in water (2 mL) was brought to pH 3 with glacial acetic acid. Gd_2O_3 (1.1 equiv based on Gd) was added and the solution stirred under N_2 for 24 h at 80 °C. The cloudy solution was cooled to room temperature, filtered through a 0.2-μm filter, and concentrated in vacuo to yield **9a**−**k** as glassy solids, which were subsequently recrystallized from acetonitrile and water.

[1-Ethyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9a). Yield (100%). HRFABMS calcd for $C_{16}H_{28}N_4O_6Gd$ 530.0905, found 530.0907 (M + H). Anal. Calcd (found) for $C_{16}H_{27}N_4O_6Gd\cdot H_2O\cdot 2.5NaOAc$: C, 33.57 (33.53); H, 4.89 (5.14); N, 7.45 (7.43).

[1-Propyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9b). Yield (100%). HRFABMS calcd for $C_{17}H_{30}N_4O_6Gd$ 544.1176, found 544.1176 (M + H). Anal. Calcd (found) for $C_{17}H_{29}N_4O_6Gd\cdot 3.5H_2O\cdot 1.5$ NaOAc: C, 32.96 (32.81); H, 5.60 (5.41); N, 7.68 (7.74).

[1-Butyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9c). Yield (100%). HRFABMS calcd for $C_{18}H_{32}N_4O_6Gd$ 558.1449, found 558.1450 (M + H). Anal. Calcd (found) for $C_{18}H_{31}N_4O_6Gd\cdot 2.5H_2O\cdot 1.5$ NaOAc: C, 34.80 (34.96); H, 5.63 (5.69); N, 7.73 (7.73).

[1-Pentyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9d). Yield (100%). HRFABMS calcd for $C_{19}H_{34}N_4O_6Gd$ 572.1719, found 592.1718 (M + H). Anal. Calcd (found) for $C_{19}H_{33}N_4O_6Gd\cdot 4H_2O\cdot 1.5NaOAc$: C, 33.71 (33.66); H, 5.85 (5.75); N, 7.14 (7.49).

[1-Hexyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9e). Yield (100%). HRFABMS calcd for $C_{20}H_{36}N_4O_6Gd$ 586.1980, found 586.1979 (M + H). Anal. Calcd (found) for $C_{20}H_{35}N_4O_6Gd\cdot 2H_2O\cdot 1.5$ NaOAc: C, 37.13 (36.78); H, 5.89 (5.66); N, 7.53 (7.78).

[1-Octyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9f). Yield (100%). HRFABMS calcd for $C_{22}H_{40}N_4O_6Gd$ 614.2524, found 614.2521 (M + H). Anal. Calcd (found) for $C_{22}H_{39}N_4O_6Gd\cdot H_2O\cdot 4NaOAc$: C, 37.57 (37.33); H, 5.57 (5.66); N, 5.84 (5.87).

[1-Decyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9g). Yield. (100%). HRFABMS calcd for $C_{24}H_{44}N_4O_6Gd$ 642.3062, found 642.3060 (M + H).

(21) Insolubility of compounds with alkyl chains longer than eight carbons rendered elemental analysis impossible.

Anal. Calcd (found) for $C_{24}H_{43}N_4O_6Gd \cdot 6NaOAc$: C, 38.16 (38.54); H, 5.42 (5.73); N, 4.94 (4.95).

[1-Dodecyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9h). Yield (100%). HRFABMS calcd for $C_{26}H_{48}N_4O_6Gd$ 670.3604, found 670.3604 (M + H).

[1-Tetradecyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9i). Yield (100%). HRFABMS calcd for $C_{28}H_{52}N_4O_6Gd$ 698.4146, found 698.4140 (M + H).

[1-Hexadecyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9j). Yield (100%). HRFABMS calcd for $C_{30}H_{56}N_4O_6Gd$ 726.4687, found 726.4689 (M + H).

[1-Octadecyl-4,7,10-tris(carboxymethyl)tetraazacyclododecanato]gadolinium (9k). Yield (100%). HRFABMS calcd for $C_{32}H_{60}N_4O_6Gd$ 754.5221, found 754.5222 (M + H).

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Supporting Information Available: X-ray structure tables for **6d**; ^{1}H NMR and ^{13}C NMR spectra for **6a**−**l, 7a**−**k, 8a**−**e**; ^{13}C NMR data for **8f**; spectral assignments for **6a**−**k, 7a**−**k**. This material is available free of charge via the Internet at http://pubs.acs.org.

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