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Hydrolysis and Radiation Stability of *m*-Xylylene Bis-diglycolamide: Synthesis and Quantitative Study of Degradation Products by HPLC–APCI$^+$

Hitos Galán,[a] María Teresa Murillo,[a] Rosa Sedano,[b] Ana Núñez,[c] Javier de Mendoza,[d] Amparo González-Espartero,[c] and Pilar Prados*[a]

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For nuclear hydrometallurgical separation process development, it is necessary to demonstrate the stability of the extracting systems, since it is well known that radio- and hydrolytic degradation leads to undesirable effects, such as a decrease in selectivity, poorer phase separation and third-phase formation. Recently, we have developed a new family of bis-diglycolamide (bis-DGA) molecules with high distribution coefficients (D) for Eu^{III} over Am^{III}. One of these bis-DGA extractants, namely, compound **1**, showed high distribution coefficients even under gamma irradiation at 1000 kGy with external ^{60}Co sources. We report herein a detailed account on the stability of **1** against radio- and hydrolysis. We have also identified and quantified the sub-products formed during the irradiation process. Qualitative and quantitative analyses of irradiated **1** were performed by HPLC–MS, indicating the presence of seventeen degradation compounds. All fragments (**2**–**18**) were identified and synthesized independently. To complete this study, the An^{III} and Ln^{III} extraction properties of these fragments were assessed under the same experimental conditions as those used to evaluate the An^{III} and Ln^{III} extraction by irradiated **1**. Despite the significance of a decrease in the concentration of **1**, Am/Eu D values are still quite high. This means that at least some degradation products also act as efficient extractants. It is relevant to remark that two of the major degradation products (compounds **3** and **11**) are stable to radiation and showed high D values for Am^{III} and Eu^{III} extraction.

Introduction

One of the strategies used for spent nuclear fuel management is the hydrometallurgical treatment of high level-liquid waste (HLLW), coming from the PUREX process, in two steps.[1] The first one consists of co-extraction of trivalent actinides (An^{III}) and trivalent lanthanides (Ln^{III}) by the DIAMEX process (DIAMide EXtraction), which removes part of the nitric acid and most of the fission products.[2] The second step, called the SANEX process (Selective ActiNide EXtraction), separates the An^{III}/Ln^{III} group.[3] In these processes, organic ligands are used as cation extractants in apolar solvents. Since the system is in contact with highly radioactive solutions, for process development it is not only necessary to demonstrate high extraction coefficients (D) for An^{III} and Ln^{III}, but also to demonstrate the stability of the extractant. It is well known that radio- and hydrolytic degradation during the extraction process leads to undesirable effects, such as a decrease of selectivity, poorer phase separation and third-phase formation. Most often, the new species generated have extracting properties that markedly differ from those of the original ligands.[4] Although several technologies have been used to determine the degradation process,[5] a study to assess the structure of these compounds has not been performed yet.

Previously, we have described a family of bis-DGA extractants containing either rigid spacers or flexible alkyl chains that co-extract An^{III} and Ln^{III}. Specifically, compound **1** with a *m*-xylylene spacer between the diglycolamide subunits showed higher selectivity than simple diglycolamides for Eu^{III} over Am^{III} extraction from 3 M solutions of nitric acid in a mixture (95:5 vol.-%) of hydrogenated tetrapropylene (HTP)/1-octanol (Figure 1).[6]

To evaluate the effect of hydrolysis and extended irradiation on the distribution coefficients, we have studied the degradation products of **1** by HPLC–APCI$^+$ and fragments **2**–**18** were identified (Figure 1). These compounds have been synthesized and their extraction properties have been assessed separately. Finally, quantification of **1** and its degradation products has been performed by HPLC–APCI$^+$ after irradiation of **1** under different experimental conditions and pretreatments of the organic solutions.

[a] Departamento de Química Orgánica (C-I), Facultad de Ciencias, Universidad Autónoma de Madrid
Carretera de Colmenar Viejo 15.3 km, 28049 Madrid, Spain
Fax: +34-91-4973966
E-mail: pilar.prados@uam.es
[b] Servicio Interdepartamental de Investigación (SIDI), Facultad de Ciencias, Universidad Autónoma de Madrid
Carretera de Colmenar Viejo 15.3 km, 28049 Madrid, Spain
[c] Centro de Investigaciones Energéticas, Medioambientales y Tecnológicas (CIEMAT), Avda. Complutense 22, 28040 Madrid, Spain
[d] Institute of Chemical Research of Catalonia (ICIQ), 43007 Tarragona, Spain
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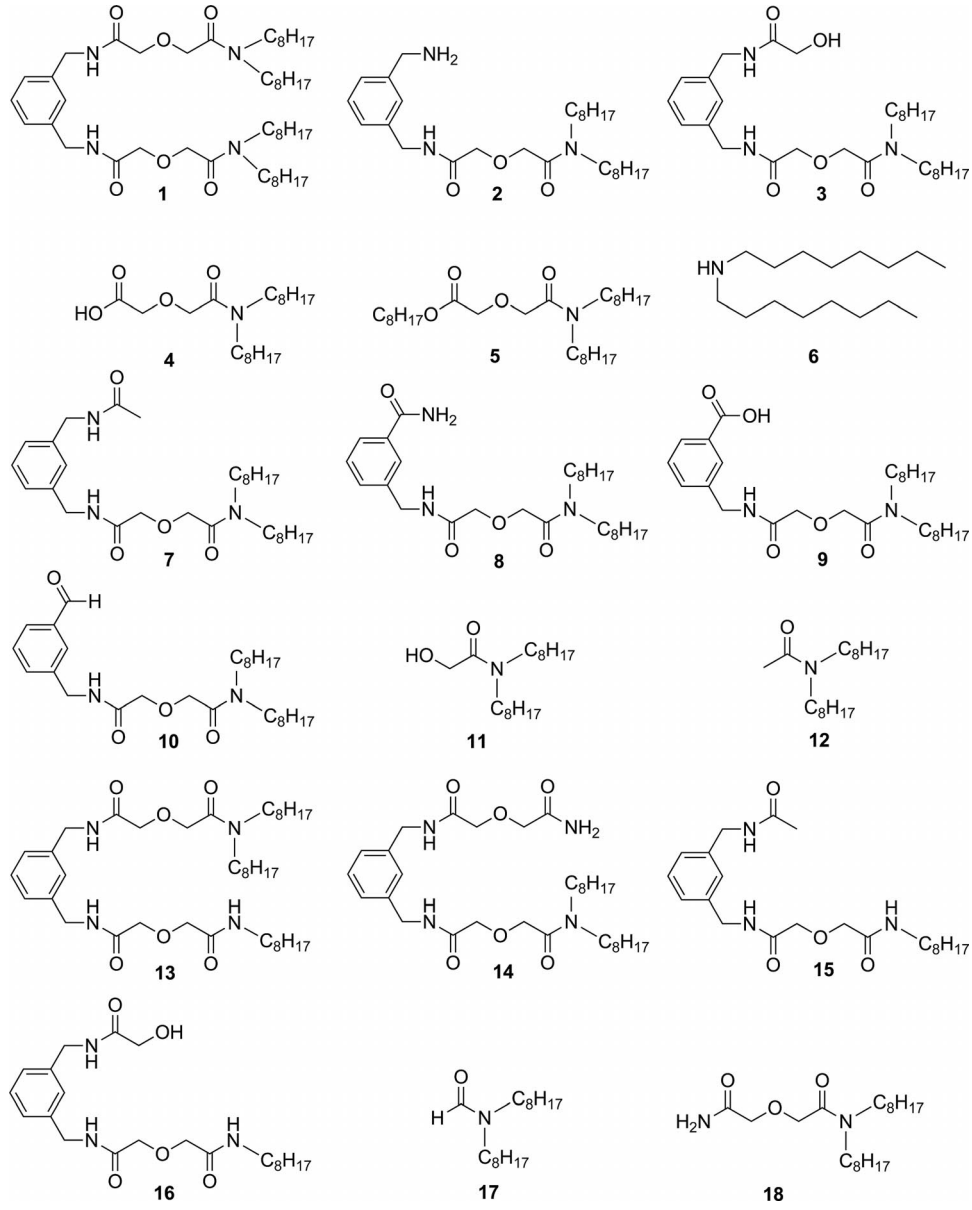


Figure 1. Radiolytic degradation products of **1**.

Results and Discussion

Synthesis

Compound **1** was prepared according to the procedure previously described by us.[6] Compound **2** was obtained from commercially available *tert*-butyl 3-(aminomethyl)-benzylcarbamate in two steps by coupling with carboxylic acid **4**[7] followed by hydrolysis of the *tert*-butoxycabonyl group (Scheme 1).

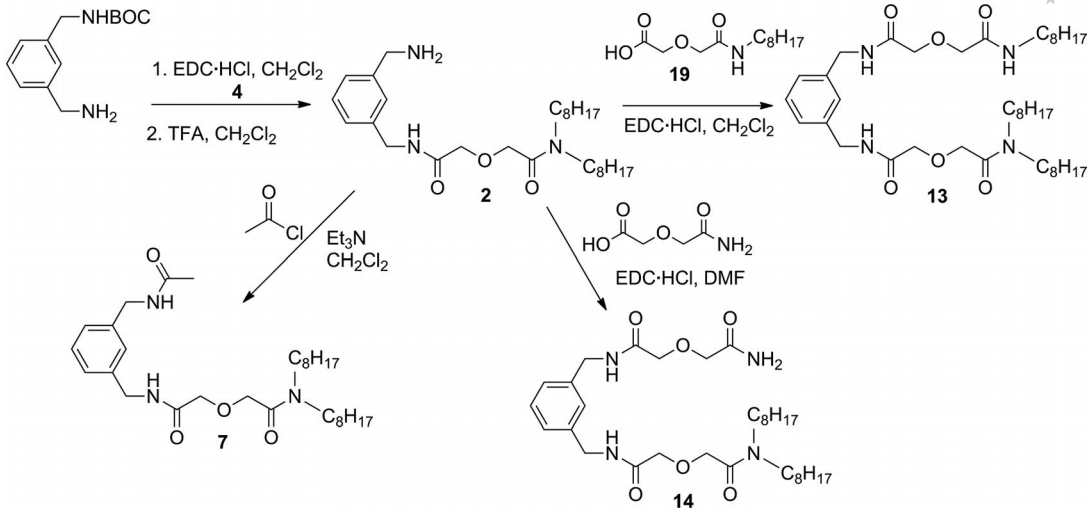
Carboxylic acid **19** was prepared from diglycolic anhydride by following the general procedure.[6] Compounds **13** and **14** were synthesized by activation of the corresponding carboxylic acids {**19** and 2-[(carbamoyl)methoxy]acetic acid} with EDC·HCl followed by addition of amine **2**, whereas compound **7** was obtained by reaction of acetyl chloride with amine **2** in the presence of triethylamine (Scheme 1).

Similar procedures were used to obtain compounds **3**, **15** and **16** (Scheme 2).

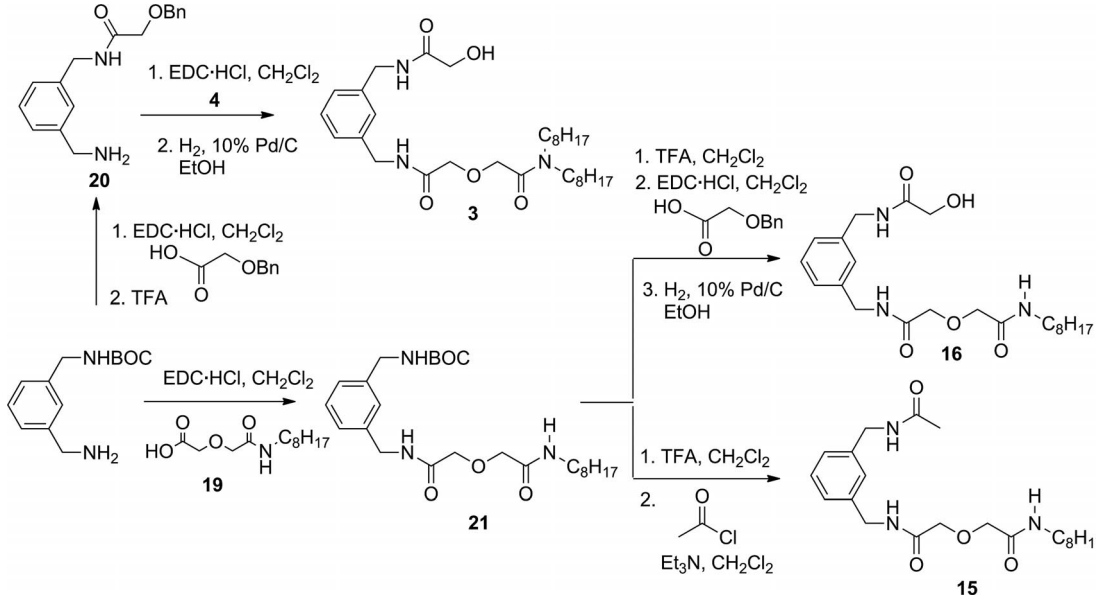
Compound **9** was obtained by basic hydrolysis of ester **22**, which was prepared from methyl [3-(methoxycarbonyl)-phenyl]methylammonium chloride by coupling with carboxylic acid **4**[7] (Scheme 3).

Compound **8** was prepared by coupling of compound **4**[7] with 3-(aminomethyl)benzamide, whereas aldehyde **10** was synthesized from amine **23**[8] by coupling with carboxylic acid **4**[7] followed by hydrolysis of the acetal (Scheme 4).

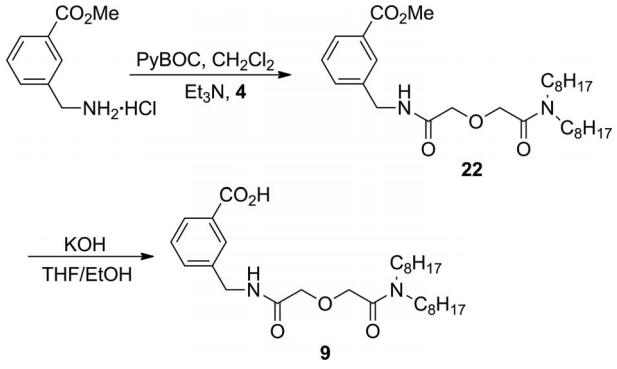
Ester **5** was prepared by *O*-alkylation of carboxylic acid **4**,[7] whereas amide **11** was obtained in two steps from 2-(benzyloxy)acetic acid followed by hydrogenolysis of amide **24** (Scheme 5).



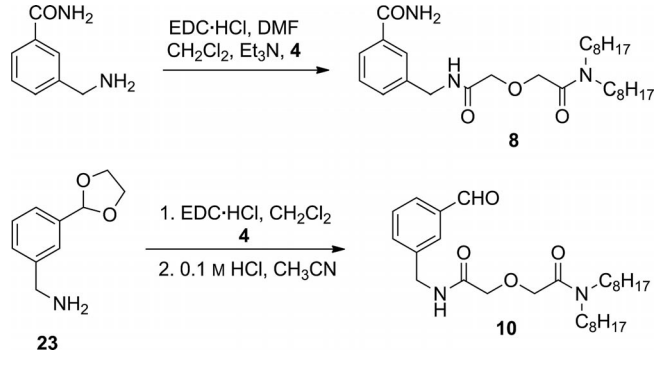
Scheme 1. Synthesis of compounds **2**, **7**, **13** and **14**. TFA = trifluoroacetic acid, EDC = *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide.



Scheme 2. Synthesis of compounds **3**, **15** and **16**.

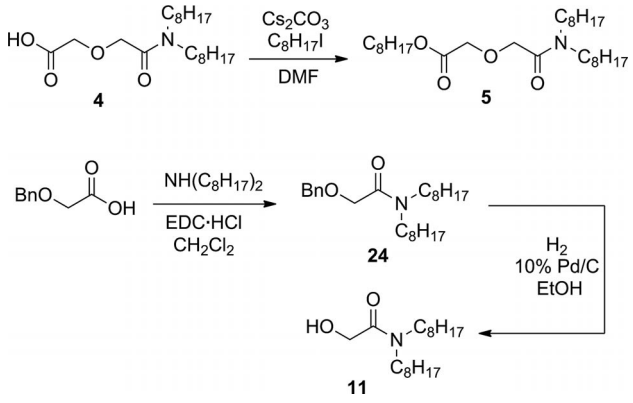


Scheme 3. Synthesis of compound **9**.

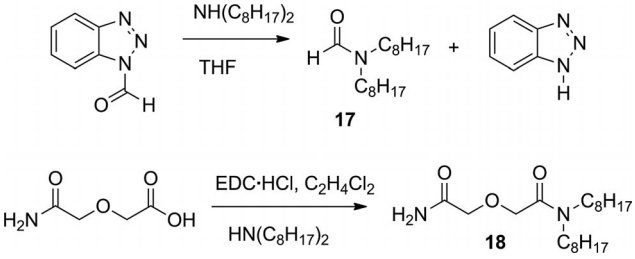


Scheme 4. Synthesis of compounds **8** and **10**.

The synthesis of **17** was carried out quantitatively from dioctylamine by using 1*H*-benzo[*d*][1,2,3]triazole-1-carbaldehyde as the acylation agent. Finally, compound **18** was obtained from 2-[(carbamoyl)methoxy]acetic acid and dioctylamine in the presence of EDC·HCl. (Scheme 6).



Scheme 5. Synthesis of compounds **5** and **11**.



Scheme 6. Synthesis of compounds **17** and **18**.

Stability of 1 towards Hydrolysis

Hydrolysis experiments were performed at 25 °C, using a 0.1 M solution of **1**[6] in a mixture of dodecane/1-octanol (95:5 vol.-%), in contact for 42 days with a 3 M solution of nitric acid. Samples were analyzed qualitatively by HPLC–APCI$^+$ after 7, 15, 36, and 42 days. Structures of compounds **2**, **5** and the methyl ester of **4** were established from the mass spectra of all peaks of the chromatograms, showing in all cases a similar qualitative composition (Figure 2). As expected, hydrolysis takes place on the amide group and compound **5** was formed from **4** due to the presence of 1-octanol in the sample. Quantitative analysis of **1** throughout the hydrolysis was performed by HPLC–APCI$^+$; 18.6% of **1** remained after 42 days of contact time. This result is in contrast with *N*,*N*,*N*′,*N*′-tetraoctyldiglycolamide (TODGA), which remains stable after four weeks in contact with 3 M nitric acid.[9] The solvents used in both cases justify the different behaviour observed, since for **1** the presence of 1-octanol facilitates hydrolysis, whereas for TODGA an apolar solvent, dodecane, was employed.

Am^{III} and Eu^{III} extraction was performed by using the organic solutions obtained after the period studied. A higher decrease in the distribution coefficients of Am (D_{Am} = 226; 42 days) than for Eu (D_{Eu} = 682; 42 d) were obtained (Figure 3, Table 1, dose 0).

Despite the significant decrease in the concentration of **1**, Am/Eu *D* values were still quite high. This means that at least some of the degradation products act as efficient extractants, compounds **2**, **4** and **5** are most likely because they possess diglycolamide groups that could coordinate to the cation.

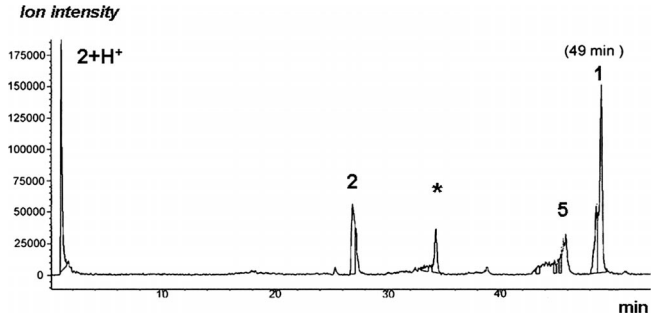


Figure 2. HPLC chromatogram of **1** (0.1 M) in dodecane/1-octanol (95:5 vol.-%) after 42 d in contact with 3 M HNO_3. * Methyl ester of compound **4**, formed during the analytical process.

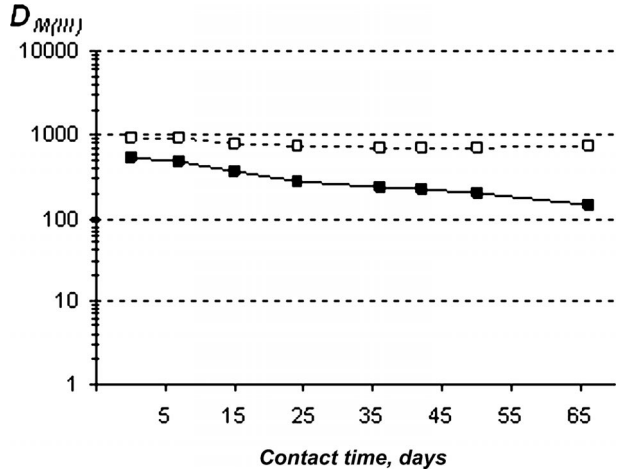


Figure 3. Stability of **1** towards hydrolysis. Organic phase: **1** (0.1 M) in dodecane/1-octanol (95:5 vol.-%). Aqueous phase: ^{152}Eu and ^{241}Am tracers in 3 M HNO_3. ■: Am, □: Eu.

Stability of 1 towards Radiolysis

Initially, the stability of **1** against radiolysis was determined in three solvents commonly employed in hydrometallurgical processes for actinide partitioning: 1-octanol and dodecane/1-octanol (90:10 and 95:5 vol.-%). Solutions of **1** (0.1 M) were pre-equilibrated with 3 M nitric acid and subsequently irradiated at 250, 500, 750 and 1000 kGy integrated doses (3.7 kGy h^{-1} dose rate) with external ^{60}Co sources. Non-irradiated samples of **1**, under the same conditions, were stored as references for aging control. Finally, the distribution coefficients for Am/Eu were determined (Table 1).

The extraction experiments showed that the Am/Eu distribution coefficients decreased as the integrated doses increased. After irradiation at 1000 kGy, samples still showed high distribution coefficients for Am^{III} and Eu^{III}, in agreement with TODGA stability under the same experimental conditions [1000 kGy, dodecane/1-octanol (95:5 vol.-%), D_{Am} = 121 and D_{Eu} = 458; see the Supporting Information]. Nevertheless, these values were lower when 1-octanol was used.

Table 1. Distribution coefficients of **1** irradiated with different integrated doses.[a]

Dose [kGy]	Solvent [vol.-%]	D_{Am}	D_{Eu}
	1-octanol	22	123
0	dodecane/1-octanol (90:10)	374	>1000
	dodecane/1-octanol (95:5)	600	>1000
	1-octanol	10	52
250	dodecane/1-octanol (90:10)	327	905
	dodecane/1-octanol (95:5)	595	880
	1-octanol	7	29
500	dodecane/1-octanol (90:10)	–	–
	dodecane/1-octanol (95:5)	361	996
	1-octanol	5	17
750	dodecane/1-octanol (90:10)	255	713
	dodecane/1-octanol (95:5)	233	885
	1-octanol	3.5	13
1000	dodecane/1-octanol (90:10)	156	652
	dodecane/1-octanol (95:5)	180	780

[a] Organic phase: **1** (0.1 M) in different solvents. Aqueous phase: ^{241}Am and ^{152}Eu tracers in 3 M HNO_3.

Qualitative analysis of the irradiated samples (1000 kGy) was performed by HPLC–APCI$^+$ under different conditions, without solvent (raw), or dissolved in 1-octanol or dodecane/1-octanol (95:5 vol.-%), previously pre-equilibrated with 3 M HNO_3. The HPLC chromatograms showed the presence of at least 17 degradation compounds, the structures of which were assigned from the mass spectra (**2**–**18**, Figure 1).

The relative amounts of the signals varied depending on the experimental conditions (Figure 4). The results show a significant decrease in the signal of compound **1** when a solvent was employed; this was more significant when its polarity increased. The sample of **1** without solvent displayed the highest resistance to radiation, in good agreement with the results obtained for TODGA.[9]

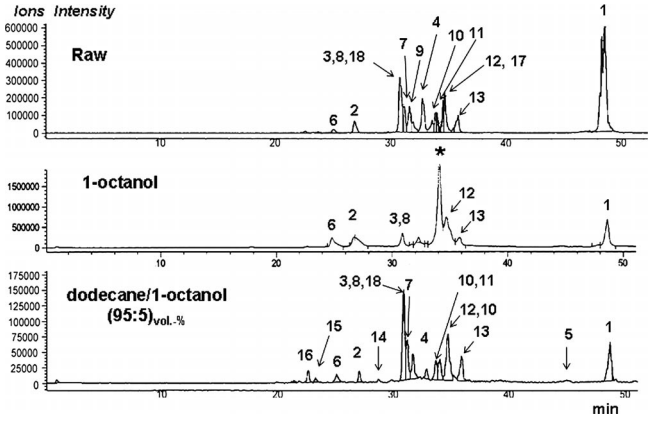


Figure 4. HPLC chromatograms of **1** after 1000 kGy of integrated dose. * Methyl ester of compound **4**, formed during the analytical process.

As in the hydrolysis study, the high distribution coefficients found after irradiation indicated that some of the degradation products also took part in the extraction. To demonstrate this, fragments **2**–**18** were synthesized and analyzed by HPLC–APCI$^+$ (SCAN method) to confirm that their mass spectra and retention times were in agreement with previously identified structures. It can be concluded that radiolysis takes place mainly at the amide (compounds **2** and **18**) and ether functions (compounds **3**, **7**, **15** and **16**). In addition, benzylic oxidation (compounds **8**, **9** and **10**) and octyl chains breaking (compounds **13** and **14**) were also produced.

Distribution coefficients of Am^{III} and Eu^{III} for each fragment were determined. Compounds **2**, **3**, **8**, **9**, **10**, **14** and **18**, which still have diglycolamide groups in their structures, showed high values for D_{Am} and D_{Eu} (Table 2). Unfortunately, during extraction a third phase was observed for compounds **7** and **13**, displaying high distribution coefficients.

Table 2. Distribution coefficients of Am^{III} and Eu^{III} for compounds **1**–**18**.[a]

Compound	D_{Am}	D_{Eu}	Compound	D_{Am}	D_{Eu}
1	600	>1000	**1** irradiated	180	780
2	125	526	**11**	1.5	1.6
3	313	433	**12**	<0.001	<0.001
4	0.071	0.18	**13**	[b]	[b]
5	<0.001	<0.001	**14**	262	245
7	[b]	[b]	**15**	0.055	0.102
8	232	>1000	**16**	0.419	0.668
9	50	300	**17**	<0.001	<0.001
10	30	150	**18**	74	277

[a] Organic phase: 0.1 M of each compound in a mixture of dodecane/1-octanol (95:5 vol.-%). Aqueous phase: ^{241}Am and ^{152}Eu tracers in 3 M HNO_3. [b] A third phase was observed.

To evaluate the effect of nitric acid during the irradiation process, quantitative analysis of irradiated samples of **1** (0.1 M) at 500 and 1000 kGy (2.6 kGy h^{-1} dose rate) was carried out in dodecane/1-octanol (95:5 vol.-%) with and without pre-equilibration. Initially, calibration curves were performed with 0.01, 0.1, 0.5 and 1 mM for **1** and for each synthesized fragment (**2**–**18**). Known concentrations of each compound and mixtures of all of them were employed for calibration, and the results are in agreement with those for the initial concentration (see the Supporting Information). Irradiated samples of **1** and compounds **2**–**18** were diluted 200 and 100 times with MeOH/1-octanol (90:10 vol-%) and data were collected in triplicate, and the final concentrations were calculated as the average of the three measurements. Quantitative analysis showed a higher final concentration of **1** in the presence of nitric acid (1000 kGy pre-equilibrated sample: 13.6 mM, without pre-equilibration: 2.2 mM). Although nitric acid causes partial hydrolysis of **1**, it seems to play a protective role during irradiation. This result is in contrast with others previously published.[10a,10c,10d] To the best of our knowledge, only one similar behaviour has been reported.[10b]

Surprisingly, comparison of data at 500 and 1000 kGy reveals that fragments **3** and **11** do not degrade with increasing the irradiation dose (Figure 5).

Additionally, an experiment has been carried with compounds **3** and **11** irradiated separately. Qualitative analysis by HPLC–MS of the irradiated samples revealed that neither compound had been degraded by radiolysis, especially compound **3** (Figure 6). This is relevant because **3** shows

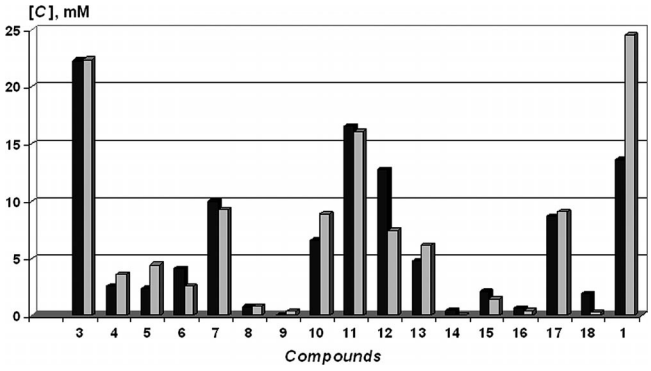


Figure 5. Concentration of **1** and fragments **2**–**18** after irradiation of **1** (0.1 M) samples in dodecane/1-octanol (95:5 vol.-%), pre-equilibrated with 3 M HNO_3. Black: 1000 kGy, grey: 500 kGy.

high distribution coefficients for Am and Eu, in addition to being stable to radiation. This structure could be considered as a model to develop a new series of extractants with enhanced resistance towards irradiation. This behaviour could be due to the formation of an enol in the acidic environment, which in turn would be stabilized by formation of an intramolecular hydrogen bond.

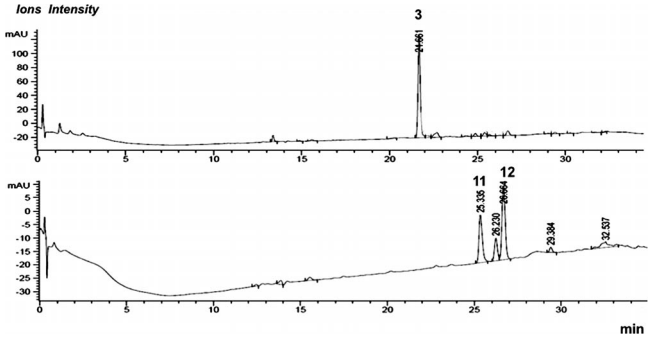


Figure 6. HPLC chromatograms of **3** and **11** in dodecane/1-octanol (95:5 vol.-%), pre-equilibrated with 3 M HNO_3, after 1000 kGy of integrated dose at 9.5 kGy h^{-1}.

To simulate the irradiation conditions for a counter-current extraction process, we repeated the quantification study up to 1000 kGy (3.1 kGy h^{-1} dose rate) in only one step, expanding the range of experimental conditions. These experimental conditions were chosen to compare samples with and without solvent [dodecane/1-octanol (95:5 vol.-%), HTP/1-octanol (95:5 vol.-%)], different treatments (with and without pre-equilibration with 3 M HNO_3, and in contact with 3 M HNO_3).

As expected, no significant differences were found between the solvents chosen but an important decrease in the concentration of **1** was observed. Figure 7 summarizes the results. An increase in the concentration of fragments **8**, **9**, and **18** was produced when a sample without solvent was irradiated (raw). For a sample that had not been pre-equilibrated, a higher concentration of fragment **12** was obtained, which was produced by cleavage of the ether group. It is worth emphasizing that compound **11**, also arising from cleavage of the ether group, was obtained in similar concentrations under all studied conditions.

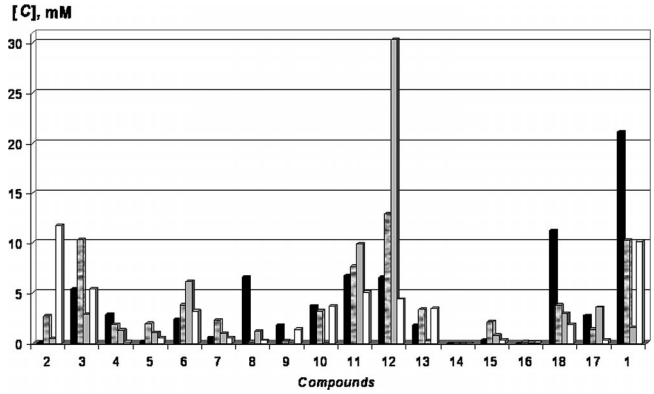


Figure 7. Concentration of **1** and fragments **2**–**18** after irradiation up to 1000 kGy of **1** (0.1 M) samples in (95:5 vol.-%) dodecane/1-octanol under several conditions. Black: raw, lines: pre-equilibrated, grey: no pre-equilibrated, white: in contact.

Conclusions

This study showed that Am/Eu *D* values of **1** in dodecane/1-octanol (95:5 vol.-%) pre-equilibrated with 3 M nitric acid were still quite high, even after irradiation up to 1000 kGy, despite the significant decrease in the concentration of **1**. This meant that at least some of the degradation products also acted as efficient extractants. The presence of nitric acid during the irradiation procedure prevented further degradation of **1**. For the first time, the identified hydrolytic and radiolytic degradation fragments have also been synthesized, allowing their extraction properties to be studied and their concentration after irradiation to be quantified. It should also be noted that two of the major degradation products in the mixture (compounds **3** and **11**) were stable to irradiation, showing high capacity to extract Am^{III} and Eu^{III}. Compound **3** could be considered as a model to develop a new series of extractants with enhanced resistance towards irradiation.

Experimental Section

General Methods: Solvents were freshly distilled and dried before use by standard methods. All chemicals were used as purchased. The NMR spectroscopy experiments (^1H,$^{13}C\{^1H\}$) were carried out at 500 (125), 400 (100) or 300 (75) MHz and reported chemical shifts (δ) are externally referenced to the residual solvent signal and are given in ppm. Mass spectra were recorded on a REFLEX spectrometer by MALDI-TOF, on a VG Autospec spectrometer by FAB^+ or on Waters LCT Premier spectrometer for ESI methods. Elemental analyses were performed on a LECO CHN 932 microanalyser and reported as percentages. TLC was performed on silica gel Alugram Sil G/UV254 (Macherey–Nagel) sheets. HTP was used in AREVA's Reprocessing Plant. *N*,*N*-Dioctylacetamide (**12**)[11] was obtained according to the procedure described.

General Procedure to Obtain Amides: A solution of the corresponding amine (1 equiv.), in dry CH_2Cl_2 or DMF was added to a solution of corresponding acid (1.2 equiv., 0.4 M) and EDC·HCl (1.2 equiv.), in dry CH_2Cl_2 and under argon atmosphere, and stirred for some time at room temp. A solution of 1 M HCl was added and the mixture was extracted with CH_2Cl_2. The organic phase was washed with a solution of 1 M HCl and water, and finally dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography.

2-{2-[3-(Aminomethyl)benzylamino]-2-oxoethoxy}-*N*,*N*-dioctylethanamide (2): Prepared by coupling *tert*-butyl 3-(aminomethyl)benzylcarbamate (1.42 mL, 6.35 mmol) in dry CH_2Cl_2 (5.0 mL) with carboxylic acid **4**[7] (2.7 g, 7.62 mmol) and EDC·HCl (1.46 g, 7.62 mmol) in dry CH_2Cl_2 (20.0 mL). The mixture was stirred for 24 h. The organic solution was washed with citric acid and brine. Purification by flash column chromatography (silica gel, 96:4 CH_2Cl_2/MeOH) gave *tert*-butyl 3-({2-[2-(dioctylamino)-2-oxoethoxy]acetamido}methyl)benzylcarbamate as a yellow oil (1.50 g, 41%). This oil was dissolved in CH_2Cl_2 (20.0 mL) and trifluoroacetic acid (0.99 mL) was added. The solution was stirred at room temp. for 2 h and the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2, and the organic phase was washed with $NaHCO_3$ and water, and finally dried ($MgSO_4$) to give **2** (1.21 g, 98%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 8.00 (br. s, 1 H, NH), 7.29–7.25 (m, 2 H, ArH), 7.18 (d, $^3J_{H,H}$ = 7.5 Hz, 2 H, ArH), 4.48 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2N), 4.21 (s, 2 H, OCH_2), 4.11 (s, 2 H, OCH_2), 3.84 (s, 2 H, CH_2N), 3.26 (t, $^3J_{H,H}$ = 7.6 Hz, 2 H, CH_2N), 3.05 (t, $^3J_{H,H}$ = 7.7 Hz, 2 H, CH_2N), 1.87 (br. s, 2 H, NH_2), 1.55–1.43 (m, 4 H, CH_2), 1.32–1.19 (m, 20 H, CH_2), 0.90–0.83 (m, 6 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, DEPT, 25 °C): δ = 169.5, 168.1 (*C*O), 138.6 (Ar), 128.8, 126.5, 126.3, 126.2 (ArH), 71.9, 69.5 (*C*H_2O), 46.8, 46.3, 46.2, 42.8 (*C*H_2N), 31.83, 31.76, 29.4, 29.3, 29.28, 29.25, 29.20, 28.9, 27.6, 27.0, 26.9, 22.7, 22.6 (*C*H_2), 14.1 (*C*H_3) ppm. MS MALDI-TOF (dithranol): *m*/*z* (%) = 476.3 (100) $[M + H]^+$. $C_{28}H_{49}N_3O_3 \cdot 1/2MeOH \cdot 1/2CH_2Cl_2$ (534.20): calcd. C 65.20, H 9.81, N 7.87; found C 65.40, H 9.37, N 7.26.

2-(2-{3-[(2-Hydroxyacetamido)methyl]benzylamino}-2-oxoethoxy)-*N*,*N*-dioctylacetamide (3): Prepared by coupling **20**[12] (350.0 mg, 1.23 mmol) in dry CH_2Cl_2 (5.0 mL) with carboxylic acid **4**[7] (661.0 mg, 1.85 mmol) and EDC·HCl (355.0 mg, 1.85 mmol) in dry CH_2Cl_2 (5.0 mL). The mixture was stirred for 48 h to give 2-[2-(3-{[2-(benzyloxy)acetamido]methyl}benzylamino)-2-oxoethoxy]-*N*,*N*-dioctylacetamide (417.0 mg, 54%). Then, a hydrogen flow was passed through a solution of this compound (417.0 mg, 0.67 mmol) and 10% Pd/C (catalytic amount) in EtOH (25.0 mL) for 30 min. The mixture was stirred under a hydrogen atmosphere at room temp. for 12 h. The mixture was filtered through Celite and the solvent was removed under reduced pressure. The residue was purified by column chromatography (silica gel, 97:3 → 95:5 CH_2Cl_2/MeOH) to give **3** (220.0 mg, 63%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.99 (br. s, 1 H, NH), 7.28–7.15 (m, 4 H, ArH), 7.12 (br. s, 1 H, NH), 4.46 (d, $^3J_{H,H}$ = 6.0 Hz, 4 H, CH_2N), 4.37 (br. s, 1 H, OH), 4.21 (s, 2 H, CH_2O), 4.09 (s, 2 H, CH_2O), 4.07 (s, 2 H, CH_2OH), 3.32–3.23 (m, 2 H, CH_2N), 3.11–3.03 (m, 2 H, CH_2N), 1.78 (br. s, 1 H, OH), 1.58–1.42 (m, 4 H, CH_2), 1.35–1.17 (m, 20 H, CH_2), 0.92–0.83 (m, 6 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, DEPT, 25 °C): δ = 172.2, 169.3, 168.1 (*C*O), 138.7, 138.5 (Ar), 128.7, 126.8, 126.7, 126.0 (ArH), 71.3, 70.0, 62.2 (*C*H_2O), 46.8, 46.3, 42.5 (*C*H_2N), 31.7, 31.6, 29.3, 29.13, 29.07, 28.8, 27.5, 26.9, 26.8 (*C*H_2), 14.0 (*C*H_3) ppm. MS (FAB^+, *m*-NBA): *m*/*z* (%) = 534.4 (100) $[M + H]^+$. $C_{30}H_{51}N_3O_5$ (533.74): calcd. C 67.51, H 9.63, N 7.87; found C 67.32, H 9.64, N 7.51.

3-({2-[2-(Dioctylamino)-2-oxoethoxy]acetamido}methyl)benzamide (8): Prepared by coupling of 3-(aminomethyl)benzamide (95.0 mg, 0.63 mmol) and Et_3N (0.09 mL, 0.63 mmol) in dry DMF (2.0 mL) with carboxylic acid **4**[7] (271.4 mg, 0.76 mmol) and EDC·HCl (145.5 mg, 0.76 mmol) in dry CH_2Cl_2 (3.0 mL). The mixture was stirred for 24 h and the solvent was removed under reduced pressure. Purification by column chromatography [using a reservoir Bond Elut (Varian) of 10 mL, with 3 cm silica gel, 95:5 CH_2Cl_2/MeOH] gave **8** (212.0 mg, 68%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.17 (t, $^3J_{H,H}$ = 6.3 Hz, 1 H, NH), 7.83 (s, 1 H, ArH), 7.76 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H, ArH), 7.44–7.28 (m, 2 H, ArH), 7.09 (br. s, 1 H, NH), 6.11 (br. s, 1 H, NH), 4.51 (d, $^3J_{H,H}$ = 6.3 Hz, 2 H, CH_2N), 4.24 (s, 2 H, CH_2O), 4.10 (s, 2 H, CH_2O), 3.30–3.16 (m, 2 H, CH_2N), 3.11–2.98 (m, 2 H, CH_2N), 1.58–1.37 (m, 4 H, CH_2), 1.36–1.12 (m, 20 H, CH_2), 0.90–0.76 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 169.8, 169.4, 168.3 (*C*O), 138.5, 133.8 (Ar), 130.9, 128.7, 126.8, 125.9 (ArH), 71.8, 69.4 (*C*H_2O), 46.9, 46.3, 42.4 (*C*H_2N), 31.8, 29.7, 29.3, 29.20, 29.16, 29.1, 28.9, 27.5, 27.0, 26.8, 22.58, 22.56 (*C*H_2), 14.0 (*C*H_3) ppm. MS (FAB^+, *m*-NBA): *m*/*z* (%) = 490.3 (100) $[M + H]^+$. $C_{28}H_{47}N_3O_4$ (489.69): calcd. C 68.68, H 9.67, N 8.58; found C 68.61, H 9.52, N 8.29.

2-[2-(3-Formylbenzylamino)-2-oxoethoxy]-*N*,*N*-dioctylacetamide (10): Prepared by coupling of **23**[8] (2.21 g, 12.35 mmol), carboxylic acid **4**[7] (3.40 g, 14.83 mmol) and EDC·HCl (2.84 g, 14.82 mmol) in dry CH_2Cl_2 (100.0 mL). The mixture was stirred for 24 h. Purification by column chromatography [using a reservoir Bond Elut (Varian) of 10 mL, with 3 cm silica gel, 95:5 CH_2Cl_2/MeOH] gave 2-{2-[3-(1,3-dioxolan-2-yl)benzylamino]-2-oxoethoxy}-*N*,*N*-dioctylacetamide as a yellow oil (3.91 g, 61%). HCl (0.1 M, 2.0 mL) was added to a solution of this oil (1.05 g, 2.02 mmol) in CH_3CN (35.0 mL) and the mixture was stirred for 24 h at room temp. The solvent was removed under reduced pressure and the residue was partitioned in CH_2Cl_2/H_2O. The organic phase was washed with $NaHCO_3$ and H_2O and finally dried ($MgSO_4$). The solvent was removed under reduced pressure to give **10** (932.0 mg, 97%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 9.92 (s, 1 H, CHO), 8.46 (br. s, 1 H, NH), 7.76 (s, 1 H, ArH), 7.69 (d, $^3J_{H,H}$ = 7.6 Hz, 1 H, ArH), 7.52 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, ArH), 7.40 (t, $^3J_{H,H}$ = 7.6 Hz, 1 H, ArH), 4.50 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2N), 4.19 (s, 2 H, CH_2O), 4.08 (s, 2 H, CH_2O), 3.27–3.14 (m, 2 H, CH_2N), 3.06–2.92 (m, 2 H, CH_2N), 1.52–1.35 (m, 4 H, CH_2), 1.31–1.05 (m, 20 H, CH_2), 0.86–0.70 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 192.2 (*C*HO), 170.0, 168.3 (*C*O), 139.7, 136.7 (Ar), 133.9, 129.2, 129.0, 128.4 (ArH), 72.1, 69.7 (*C*H_2O), 46.8, 46.3, 42.3 (*C*H_2N), 31.8, 29.3, 29.20, 29.16, 29.12, 28.9, 27.5, 27.0, 26.8, 22.6 (*C*H_2), 14.1 (*C*H_3) ppm. MS (FAB^+, *m*-NBA): *m*/*z* (%) = 475.3 (100%) $[M + H]^+$. $C_{28}H_{46}N_2O_4$ (474.68): calcd. C 70.85, H 9.77, N 5.90; found: C, 69.98, H, 9.81; N, 5.61.

***N*,*N*-Dioctyl-2-{2-[3-({2-[2-(octylamino)-2-oxoethoxy]acetamido}methyl) benzylamino]-2-oxoethoxy}acetamide (13):** Prepared by coupling of amine **2** (200.0 mg, 0.42 mmol) in dry CH_2Cl_2 (5.0 mL) with carboxylic acid **19** (155.0 mg, 0.63 mmol) and EDC·HCl (121.0 mg, 0.63 mmol) in dry CH_2Cl_2 (5.0 mL). The mixture was stirred for 24 h. Purification by column chromatography (silica gel, 98:2 CH_2Cl_2/MeOH) gave **13** (217.0 mg, 73%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.16 (br. s, 1 H, NH), 7.33–7.15 (m, 4 H, ArH), 6.92 (br. s, 1 H, NH), 6.64 (br. s, 1 H, NH), 4.51 (d, $^3J_{H,H}$ = 5.9 Hz, 4 H, CH_2N), 4.27 (s, 2 H, CH_2O), 4.15 (s, 2 H, CH_2O), 4.12 (s, 2 H, CH_2O), 4.07 (s, 2 H, CH_2O), 3.40–3.25

(m, 4 H, CH_2N), 3.20–3.15 (m, 2 H, CH_2N), 1.60–1.40 (m, 6 H, CH_2), 1.39–1.15 (m, 30 H, CH_2), 0.94–0.82 (m, 9 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 169.7, 168.6, 168.4, 168.2 (*C*O), 138.9, 138.4 (Ar), 129.0, 126.9, 126.8, 126.7 (ArH), 71.7, 71.14, 71.06, 69.4 (*C*H_2O), 46.8, 46.2, 42.8, 42.6 (*C*H_2N), 39.1, 31.8, 31.7, 29.6, 29.3, 29.23, 29.19, 29.15, 28.9, 27.6, 27.0, 26.94, 26.85, 22.61, 22.58 (*C*H_2), 14.1 (*C*H_3) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 703.4 (100) $[M + H]^+$. $C_{40}H_{70}N_4O_6 \cdot H_2O$ (721.07): calcd. C 66.63, H 10.07, N 7.77; found C 66.75, H 9.84, N 8.07.

2-[2-(3-{[2-(2-Amino-2-oxoethoxy)acetamido]methyl}benzylamino)-2-oxoethoxy]-*N*,*N*-dioctylacetamide (14): Prepared by coupling of amine **2** (200.0 mg, 0.42 mmol), 2-[(carbamoyl)methoxy]acetic acid (67.2 mg, 0.51 mmol) and EDC·HCl (96.7 mg, 0.51 mmol) in dry DMF (2.5 mL). The mixture was stirred for 72 h. Purification by column chromatography [using a reservoir Bond Elut (Varian) of 10 mL, with 3 cm silica gel, 95:5 CH_2Cl_2/MeOH] gave **14** (175.0 mg, 70%) as yellow oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.18 (br. s, 1 H, NH), 7.62 (br. s, 1 H, NH), 7.25–7.02 (m, 5 H, ArH, NH), 6.10 (br. s, 1 H, NH), 4.45–4.32 (m, 4 H, CH_2N), 4.20 (s, 2 H, CH_2O), 4.04 (s, 2 H, CH_2O), 3.98 (s, 2 H, CH_2O), 3.89 (s, 2 H, CH_2O), 3.31–3.17 (m, 2 H, CH_2N), 3.10–2.97 (m, 2 H, CH_2N), 1.58–1.40 (m, 4 H, CH_2), 1.36–1.12 (m, 20 H, CH_2), 0.94–0.78 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 171.7, 169.9, 168.8, 168.3 (*C*O), 138.8, 138.5 (Ar), 128.8, 126.72, 126.65 (ArH), 71.6, 70.9, 70.5, 69.4 (*C*H_2O), 46.8, 46.3, 42.7 (*C*H_2N), 31.8, 31.7, 29.23, 29.15, 28.9, 27.6, 27.0, 26.9, 22.59, 22.57 (*C*H_2), 14.0 (*C*H_3) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 591.2 (100) $[M + H]^+$. Purity by HPLC–MS 81.9%.

2-(2-Amino-2-oxoethoxy)-*N*,*N*-dioctylacetamide (18): Prepared by coupling of *N*,*N*-dioctylamine (1.36 mL, 4.51 mmol), 2-[(carbamoyl)methoxy]acetic acid (500.0 mg, 3.76 mmol) and EDC·HCl (864.2 mg, 4.51 mmol) in dry 1,2-dichloroethane (15.0 mL). The mixture was stirred at 40 °C for 9 h and then 12 h at room temp. Purification by column chromatography [using a reservoir Bond Elut (Varian) of 60 mL, with 5 cm silica gel, 95:5 CH_2Cl_2/MeOH] gave **18** (683.0 mg, 51%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.80 (br. s, 1 H, NH), 5.50 (br. s, 1 H, NH), 4.25 (s, 2 H, CH_2O), 4.08 (s, 2 H, CH_2O), 3.36–3.24 (m, 2 H, CH_2N), 3.14–3.03 (m, 2 H, CH_2N), 1.60–1.45 (m, 4 H, CH_2), 1.37–1.18 (m, 20 H, CH_2), 0.92–0.83 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 172.7, 168.3 (*C*O), 71.9, 69.8 (*C*H_2O), 47.0, 46.4 (*C*H_2N), 31.9, 31.8, 29.4, 29.31, 29.26, 29.1, 28.9, 27.7, 27.1, 27.0, 26.9, 22.6 (*C*H_2), 14.2 (*C*H_3) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 357.4 (100) $[M + H]^+$. $C_{20}H_{40}N_2O_3$ (356.54): calcd. C 67.37, H 11.31, N 7.86; found C 67.55, H 11.36, N 7.77.

***tert*-Butyl 3-({2-[2-(Octylamino)-2-oxoethoxy]acetamido}methyl)-benzylcarbamate (21):** Prepared by coupling of *tert*-butyl 3-(aminomethyl)benzylcarbamate (1.35 mL, 8.46 mmol), **19** (1.48 g, 6.07 mmol) and EDC·HCl (1.16 g, 6.07 mmol) in dry CH_2Cl_2 (30.0 mL). The mixture was stirred for 36 h. Purification by column chromatography (6 × 10 cm silica gel, 100% → 95:5 CH_2Cl_2/MeOH) gave **21** (1.47 g, 50%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.35–7.17 (m, 4 H, ArH), 6.98 (br. s, 1 H, NH), 6.62 (br. s, 1 H, NH), 5.05 (br. s, 1 H, NH), 4.48 (d, $^3J_{H,H}$ = 5.9 Hz, 2 H, CH_2N), 4.30 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2N), 4.08 (s, 2 H, CH_2O), 4.01 (s, 2 H, CH_2O), 3.34–3.21 (m, 2 H, CH_2N), 1.57–1.47 (m, 2 H, CH_2), 1.47 [s, 9 H, $C(CH_3)_3$], 1.39–1.19 (m, 10 H, CH_2), 0.95–0.83 (m, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 168.1, 167.9, 155.6 (*C*O), 139.3, 137.8 (Ar), 128.7, 126.3, 126.2 (ArH), 79.3 [O*C*$(CH_3)_3$], 70.8, 70.7 (*C*H_2O), 44.0, 42.5, 38.7 (*C*H_2N), 31.4, 29.1, 28.8, 28.7 (*C*H_2), 28.0 [OC(*C*H_3)$_3$], 26.5, 22.2 (*C*H_2), 13.7 (*C*H_3) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 464.2 (17) $[M + H]^+$, 408 (18) $[M^+ - C_4H_8]$, 364 (8) [408 – CO_2], 307 (19) $[M^+ - 157]$, 57 (100) $[C_4H_8]^+$. $C_{25}H_{41}N_3O_5$ (463.61): calcd. C 64.77, H 8.91, N 9.06; found C 64.47, H 8.85, N 8.91.

2-(Benzyloxy)-*N*,*N*-dioctylacetamide (24): Prepared by coupling of *N*,*N*-dioctylamine (0.45 mL, 1.50 mmol), 2-(benzyloxy)acetic acid (250.0 mg, 1.50 mmol) and EDC·HCl (317.1 mg, 1.65 mmol) in dry CH_2Cl_2 (15.0 mL). The mixture was stirred for 24 h. Then, a solution 10% of citric acid was added and the mixture was extracted with CH_2Cl_2. The organic phase was washed with brine and water and finally dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was triturated in hexane to give **24** (378.2 mg, 65%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.44–7.27 (m, 5 H, ArH), 4.65 (s, 2 H, CH_2Ar), 4.18 (s, 2 H, CH_2CO), 3.41–3.28 (m, 2 H, CH_2N), 3.26–3.15 (m, 2 H, CH_2N), 1.64–1.45 (m, 4 H, CH_2), 1.40–1.16 (m, 20 H, CH_2), 0.96–0.83 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 168.6 (*C*O), 137.6 (Ar), 128.4, 128.1, 127.8 (ArH), 73.2 (O*C*H_2Ar), 69.0 (*C*H_2CO), 47.1, 45.7 (*C*H_2N), 31.81, 31.75, 29.4, 29.28, 29.25, 29.2, 29.0, 27.6, 27.1, 26.8, 22.64, 22.61 (*C*H_2), 14.1 (*C*H_3) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 390.3 (100) $[M + H]^+$. $C_{25}H_{43}NO_2$ (389.61): calcd. C 77.07, H 11.12, N 3.60; found C 77.04, H 11.03, N 3.77.

Octyl 2-[2-(dioctylamino)-2-oxoethoxy]acetate (5): 1-Iodooctane (0.22 mL, 1.23 mmol) was added to a mixture of compound **4**[7] (400.0 mg, 1.12 mmol) and Cs_2CO_3 (401.0 mg, 1.23 mmol) in dry DMF (12.0 mL) under argon atmosphere. The mixture was stirred at room temp. for 24 h (TLC 98:2 CH_2Cl_2/MeOH). Finally, 1 M HCl and H_2O were added and the solution was stirred for 20 min. The solution was extracted with CH_2Cl_2 and washed with $NaHSO_3$ (40%) and brine, and dried (Na_2SO_4). Solvent was removed under reduced pressure and the residue was purified by flash column chromatography (silica gel, 98:2 CH_2Cl_2/MeOH) to give **5** (380.0 mg, 72%) as a colourless oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 4.23 (s, 2 H, CH_2O), 4.19 (s, 2 H, CH_2O), 4.09 (t, $^3J_{H,H}$ = 6.8 Hz, 2 H, CH_2O), 3.29–3.20 (m, 2 H, CH_2N), 3.18–3.10 (m, 2 H, CH_2N), 1.63–1.58 (m, 2 H, CH_2), 1.53–1.40 (m, 4 H, CH_2), 1.32–1.12 (m, 30 H, CH_2), 0.87–0.77 (m, 9 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 170.1, 167.9 (*C*O), 69.4, 67.9, 64.8 (*C*H_2O), 46.9, 45.6 (*C*H_2N), 31.69, 31.66, 29.24, 29.20, 29.1, 28.9, 28.5, 27.5, 26.9, 26.7, 25.7, 22.5 (*C*H_2), 13.9 (*C*H_3) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 470.4 (100) $[M + H]^+$. $C_{28}H_{55}NO_4$ (469.74): calcd. C 71.59, H 11.80, N 2.98; found C 71.67, H 11.88, N 3.01.

2-{2-[3-(Acetamidomethyl)benzylamino]-2-oxoethoxy}-*N*,*N*-dioctylacetamide (7): A solution of **2** (300.0 mg, 0.63 mmol) and Et_3N (0.176 mL, 1.26 mmol) in dry CH_2Cl_2 (5.0 mL) was added dropwise to a solution of acetyl chloride (0.067 mL, 0.95 mmol) in dry CH_2Cl_2 (10.0 mL) stirred at 0 °C under argon atmosphere. The mixture was stirred at room temp. for 12 h. The organic solution was washed with 1 M HCl and water, and finally dried ($MgSO_4$). The solvent was removed under reduced pressure to afford **7** (204.0 mg, 63%) as an oil. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.09 (br. s, 1 H, NH), 7.35–7.16 (m, 4 H, ArH), 6.05 (br. s, 1 H, NH), 4.50 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2N), 4.43 (d, $^3J_{H,H}$ = 5.6 Hz, 2 H, CH_2N), 4.26 (s, 2 H, CH_2O), 4.15 (s, 2 H, CH_2O), 3.36–3.25 (m, 2 H, CH_2N), 3.15–3.06 (m, 2 H, CH_2N), 2.04 (s, 3 H, CH_3), 1.62–1.44 (m, 4 H, CH_2), 1.40–1.18 (m, 20 H, CH_2), 0.98–0.84 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 170.0, 169.5, 168.1 (*C*O), 138.8, 138.6 (Ar), 128.9, 127.1, 126.90, 126.85 (ArH), 71.8, 69.5 (*C*H_2O), 46.8, 46.2, 43.6, 42.7 (*C*H_2N), 31.8, 31.7, 29.3, 29.24, 29.21, 29.16, 28.9, 27.6, 27.0, 26.9 (*C*H_2),

23.22 (*C*H$_3$CO), 22.61, 22.58 (*C*H$_2$), 14.1 (*C*H$_3$) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z*: (%) = 518.2 (100) [M + H]$^+$. $C_{30}H_{51}N_3O_4$ (517.74): calcd. C 69.59, H 9.93, N 8.12; found C 69.30, H 9.92, N 7.90.

3-({2-[2-(Dioctylamino)-2-oxoethoxy]acetamido}methyl)benzoic Acid (9): KOH (41.7 mg, 0.74 mmol) was added to a solution of **22** (250.0 mg, 0.50 mmol) in THF/EtOH (40 mL, 7:1) stirred at room temp. The mixture was stirred at 70 °C for 3 h. The solvent was eliminated under reduced pressure and the residue was partitioned in CH_2Cl_2/HCl (1 M). The organic solution was washed with water and finally dried ($MgSO_4$). The solvent was removed under reduced pressure to give **9** (196.9 mg, 81%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.26 (br. s, 1 H, NH), 7.90–7.80 (m, 2 H, ArH), 7.46 (d, $^3J_{H,H}$ = 7.9 Hz, 1 H, ArH), 7.30 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, ArH), 4.48 (d, $^3J_{H,H}$ = 5.5 Hz, 2 H, CH_2N), 4.21 (s, 2 H, CH_2O), 4.10 (s, 2 H, CH_2O), 3.30–3.15 (m, 2 H, CH_2N), 3.10–2.95 (m, 2 H, CH_2N), 1.55–1.35 (m, 4 H, CH_2), 1.30–1.10 (m, 20 H, CH_2), 0.90–0.75 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 170.6, 170.0, 169.0 (*C*O), 139.1 (Ar), 132.9 (ArH), 130.7 (Ar), 129.6, 129.3, 129.0, (ArH), 72.1, 69.9 (*C*H$_2$O), 47.4, 46.8, 43.0 (*C*H$_2$N), 32.23, 32.17, 29.8, 29.7, 29.64, 29.60, 29.3, 28.0, 28.4, 27.3, 23.0 (*C*H$_2$), 14.5 (*C*H$_3$) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 491.3 (100) [M + H]$^+$. $C_{28}H_{46}N_2O_5$ (490.68): calcd. C 68.54, H 9.45, N 5.71; found C 68.54, H 9.43, N 5.27.

2-Hydroxy-*N*,*N*-dioctylacetamide (11): A hydrogen flow was passed through a mixture of **24** (378.2 mg, 0.97 mmol) and 10% Pd/C (catalytic amount) in EtOH (12.0 mL) for 30 min. The mixture was stirred under a hydrogen atmosphere at room temp. for 7 h. Then, the mixture was filtered through Celite, and the solvent was eliminated under reduced pressure and the residue was purified by flash column chromatography (silica gel, 99:1 CH_2Cl_2/MeOH) to give **11** (223.2 mg, 77%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 4.13 (s, 2 H, CH_2OH), 3.69 (s, 1 H, OH), 3.38–3.33 (m, 2 H, CH_2N), 3.07–3.02 (m, 2 H, CH_2N), 1.70–1.50 (m, 4 H, CH_2), 1.45–1.15 (m, 20 H, CH_2), 1.00–0.75 (m, 6 H, CH_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 171.0 (*C*O), 59.7 (*C*H$_2$O), 46.1, 45.8, (*C*H$_2$N), 31.8, 31.7, 29.3, 29.2, 29.1, 28.5, 27.5, 27.0, 26.8, 22.6 (*C*H$_2$), 14.0 (*C*H$_3$) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 300.3 (100) [M + H]$^+$. Purity by HPLC–MS 94.4%.

***N*-[3-(Acetamidomethyl)benzyl]-2-[2-(octylamino)-2-oxoethoxy]acetamide (15):** Trifluoroacetic acid (0.88 mL, 11.43 mmol) was added to a solution of **21** (1.06 g, 2.29 mmol) in CH_2Cl_2 (13.0 mL) stirred at room temp. The mixture was heated at 40 °C for 3 h. Solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. The organic solution was washed with $NaHCO_3$ and water, and finally dried ($MgSO_4$). Solvent was removed under reduced pressure to give *N*-[3-(aminomethyl)benzyl]-2-[2-(octylamino)-2-oxoethoxy]acetamide (0.896 g, quantitative) as a yellow oil. A solution of this oil (250.0 mg, 0.69 mmol) and Et_3N (0.19 mL, 1.38 mmol) in dry CH_2Cl_2 (5.0 mL) was added dropwise to a solution of acetyl chloride (0.073 mL, 1.03 mmol) in dry CH_2Cl_2 (10.0 mL) stirred at 0 °C under an argon atmosphere. The mixture was stirred for 24 h at room temp. The organic solution was washed with 1 M HCl and water, and finally dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 99:1 → 96:4 CH_2Cl_2/MeOH) to afford **15** (235.4 mg, 85%) as an oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.38–7.21 (m, 4 H, ArH), 6.81 (br. s, 1 H, NH), 6.48 (br. s, 1 H, NH), 5.97 (br. s, 1 H, NH), 4.52 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2N), 4.45 (d, $^3J_{H,H}$ = 5.9 Hz, 2 H, CH_2N), 4.13 (s, 2 H, CH_2O), 4.06 (s, 2 H, CH_2O), 3.34–3.23 (m, 2 H, CH_2N), 2.05 (s, 3 H, CH_3CO), 1.56–1.46 (m, 2 H, CH_2), 1.39–1.22 (m, 10 H, CH_2), 0.94–0.83 (m, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 170.3, 168.6, 168.4 (*C*O), 139.1, 138.5 (Ar), 129.1, 126.9, 126.8 (ArH), 71.1, 71.0 (*C*H$_2$O), 43.4, 42.8, 39.1 (*C*H$_2$N), 31.8, 29.5, 29.22, 29.18, 26.9 (*C*H$_2$), 23.2 (*C*H$_3$CO), 22.6 (*C*H$_2$), 14.1 (*C*H$_3$) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 406.3 (100) [M + H]$^+$. $C_{22}H_{35}N_3O_4$ (405.53): calcd. C 65.16, H 8.70, N 10.36; found C 65.31, H 8.70, N 10.35.

2-Hydroxy-*N*-[3-({2-[2-(octylamino)-2-oxoethoxy]acetamido}methyl)benzyl]acetamide (16): Trifluoroacetic acid was added (0.88 mL, 11.43 mmol) to a solution of **21** (1.06 g, 2.29 mmol) in CH_2Cl_2 (13.0 mL) stirred at room temp. The mixture was heated at 40 °C for 3 h. Solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2. The organic solution was washed with $NaHCO_3$ and water, and finally dried ($MgSO_4$). Solvent was removed under reduced pressure to give *N*-[3-(aminomethyl)benzyl]-2-[2-(octylamino)-2-oxoethoxy]ethanamide (0.896 g, quantitative) as yellow oil. Then, 2-(benzyloxy)acetic acid (201.5 mg, 1.15 mmol) was added at room temp. under an argon atmosphere to a solution of this oil (350.0 mg, 0. 96 mmol) and EDC·HCl (221.5 mg, 1.15 mmol) in dry CH_2Cl_2 (10.0 mL). The mixture was stirred for 48 h at room temp. Then, 1 M HCl was added and the mixture was extracted with CH_2Cl_2. The organic phase was washed with 1 M HCl and water, and finally dried ($MgSO_4$). The solvent was removed under reduced pressure, and the residue was purified by column chromatography (silica gel, 98:2 → 95:5 CH_2Cl_2/MeOH) to give 2-(benzyloxy)-*N*-[3-({2-[2-(octylamino)-2-oxoethoxy]acetamido}methyl)benzyl]acetamide (378.0 mg, 77%). A hydrogen flow was passed through a solution of this compound (378.0 mg, 0.74 mmol) and 10% Pd/C (catalytic amount), in EtOH (15.0 mL) for 30 min. The mixture was stirred under a hydrogen atmosphere at room temp. for 3 h. The mixture was filtered through Celite and the solvent was removed under reduced pressure to give **16** (251.0 mg, 80%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 7.34 (br. s, 1 H, NH), 7.24–7.15 (m, 4 H, ArH), 7.09 (br. s, 1 H, NH), 6.72 (br. s, 1 H, NH), 4.47 (d, $^3J_{H,H}$ = 5.6 Hz, 4 H, CH_2N), 4.08 (s, 4 H, CH_2O), 3.99 (s, 2 H, CH_2O), 3.28–3.19 (m, 2 H, CH_2N), 2.43 (br. s, 1 H, OH), 1.57–1.42 (m, 2 H, CH_2), 1.36–1.18 (m, 10 H, CH_2), 0.93–0.80 (m, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 173.3, 169.4, 169.2 (*C*O), 138.6, 138.5 (Ar), 128.9, 126.8, 126.7, 126.4 (ArH), 70.69, 70.65 (*C*H$_2$O), 61.9 (*C*H$_2$OH), 42.7, 42.6, 39.3 (*C*H$_2$N), 31.8, 29.7, 29.4, 29.23, 29.18, 28.4, 26.9, 22.6 (*C*H$_2$), 14.1 (*C*H$_3$) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 422.1 (25) [M + H]$^+$. $C_{22}H_{35}N_3O_5 \cdot {}^1/_3H_2O$ (427.53): calcd. C 61.80, H 8.41, N 9.83; found C 61.86, H 8.30, N 9.73.

***N*,*N*-Dioctylformamide (17):** A solution of *N*,*N*-dioctylamine (100.0 mg, 0.41 mmol) in dry THF (3.0 mL) under argon atmosphere was added dropwise to a solution of 1*H*-benzo[*d*][1,2,3]triazole-1-carbaldehyde (57.6 mg, 0.39 mmol) in dry THF (2.5 mL). The mixture was stirred at room temp. for 40 min. The solvent was removed under reduced pressure and the residue was dissolved in CH_2Cl_2 (10.0 mL). The organic solution was washed with 2 M NaOH and water, and dried ($MgSO_4$). The solvent was removed under reduced pressure to give **17** (101.8 mg, 98%) as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.03 (s, 1 H, CHO), 3.36–3.22 (m, 2 H, CH_2N), 3.20–3.14 (m, 2 H, CH_2N), 1.60–1.44 (m, 4 H, CH_2), 1.37–1.14 (m, 20 H, CH_2), 0.94–0.79 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 162.7 (*C*HO), 47.5, 42.2 (*C*H$_2$N), 31.8, 31.7, 29.3, 29.20, 29.15, 28.7, 27.3, 27.0, 26.5, 22.61, 22.60 (*C*H$_2$), 14.0 (*C*H$_3$) ppm. MS (FAB$^+$, *m*-NBA) *m*/*z* (%) = 270.3 (100) [M + H]$^+$. Purity by HPLC–MS 99.3%.

2-[2-(Octylamino)-2-oxoethoxy]acetic Acid (19): 1-Octylamine (3.06 mL, 20.68 mmol) was added to a solution of diglycolic anhydride (2.40 g, 20.68 mmol) in dry THF (25.0 mL, 0.8 M) stirred at room temp. The mixture was kept under the same conditions for 48 h. The mixture was washed three times with 1 M HCl and water. The organic phase was dried (Na_2SO_4) and the solvent was removed. Petroleum ether was added to the resulting orange oil and a white solid appeared. The precipitate was filtered, dried and purified by column chromatography (95:5 CH_2Cl_2/MeOH) to give **19** (980.0 mg, 19%) as a colorless wax. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.75 (br. s, 1 H, NH), 4.21 (s, 2 H, OCH_2), 4.12 (s, 2 H, OCH_2), 3.33–3.28 (m, 2 H, CH_2N), 1.55–1.50 (m, 2 H, CH_2), 1.30–1.27 (m, 10 H, CH_2), 0.90–0.86 (m, 3 H, CH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.2 (*C*O_2H), 170.2 (*C*ONH), 70.5, 68.2 (O*C*H_2), 39.2 (*C*H_2N), 31.7, 29.2, 29.13, 29.10, 26.8, 22.6 (*C*H_2), 14.0 (*C*H_3) ppm. HRMS (ES): *m*/*z* calcd. for $C_{12}H_{22}NO_4$ 244.1549 [M^+]; found 244.1551.

Methyl 3-({2-[2-(Dioctylamino)-2-oxoethoxy]acetamido}methyl)-benzoate (22): A solution of [3-(methoxycarbonyl)phenyl]methanaminium chloride (850.0 mg, 4.21 mmol) and Et_3N (1.75 mL, 12.6 mmol) in dry CH_2Cl_2 (5.0 mL) was added to a mixture of **4**[7] (1.96 g, 5.48 mmol) and benzotriazole-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOC; 2.85 g, 5.48 mmol) in dry CH_2Cl_2 (5.0 mL) at room temp. The mixture was stirred under the same conditions for 24 h. Then, a solution of 1 M HCl was added and the mixture was extracted with CH_2Cl_2. The organic phase was washed with 1 M HCl and water, and finally dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue was purified by column chromatography (silica gel, 95:5 CH_2Cl_2/MeOH) to give **22** (1.33 mg, 63%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 8.25 (br. s, 1 H, NH), 7.97–7.91 (m, 2 H, ArH), 7.52 (d, $^3J_{H,H}$ = 7.7 Hz, 1 H, ArH), 7.39 (t, $^3J_{H,H}$ = 7.7 Hz, 1 H, ArH), 4.54 (d, $^3J_{H,H}$ = 6.0 Hz, 2 H, CH_2N), 4.24 (s, 2 H, CH_2O), 4.15 (s, 2 H, CH_2O), 3.90 (s, 3 H, OCH_3), 3.29–3.24 (m, 2 H, CH_2N), 3.09–3.03 (m, 2 H, CH_2N), 1.60–1.40 (m, 4 H, CH_2), 1.35–1.15 (m, 20 H, CH_2), 0.95–0.85 (m, 6 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, DEPT, 25 °C): δ = 169.7, 168.1, 166.9 (*C*O), 138.8 (Ar), 132.3 (ArH), 130.4 (Ar), 128.8, 128.7, 128.5 (ArH), 72.0, 69.6 (*C*H_2O), 52.1 (*C*H_3O), 46.8, 46.2, 42.5 (*C*H_2N), 31.8, 31.7, 29.3, 29.24, 29.21, 29.15, 28.9, 27.6, 27.0, 26.9, 22.6 (*C*H_2), 14.0 (*C*H_3) ppm. MS (FAB$^+$, *m*-NBA): *m*/*z* (%) = 505.3 (100) [M + H]$^+$. $C_{29}H_{48}N_2O_5 \cdot {}^1/_4H_2O$ (509.21): calcd. C 68.40, H 9.60, N 5.50; found C 68.39, H 9.35, N 5.53.

Extraction Procedure: Solutions were prepared by dissolving weighed amounts of the corresponding compounds in the appropriate volume (700 μL) of corresponding solvent up to 0.1 M. Clear organic solutions were pre-equilibrated twice for 5 min with the same volume (700 μL) of the aqueous phase having the same nitric acid concentration (3 M) as the aqueous phase to be used in the subsequent extraction experiment. Nitric acid solutions were prepared by diluting concentrated nitric acid (65%) with ultrapure water (18 MΩ cm^{-1}). The behaviour of trivalent actinides and lanthanides were simulated by ^{241}Am and ^{152}Eu, respectively, which were supplied by Isotope Products Laboratories, California (USA). The extraction experiments were performed by mixing the aqueous phase (500 μL) and the pre-equilibrated organic phase (500 μL) for 30 min. Both phases were separated by centrifugation at 5000 rpm and 400 μL aliquots of each phase were spiked and conditioned into a 5 mL glass vial for high- and low-energy gamma spectrometry measurements (Canberra-Packard, CIEMAT, Spain), using the γ lines at 59.5 and 121.8 keV for ^{241}Am and ^{152}Eu determination, respectively. The distribution coefficients (D_M^{III}) were calculated as $[M^{III}]_{org}/[M^{III}]_{aq}$.

Hydrolytic Procedure: The stability studies of **1** against hydrolysis were performed by using six samples (700 μL) of the organic phase [0.1 M of **1** in a mixture of dodecane/1-octanol (95:5 vol.-%)] pre-equilibrated with 3 M nitric acid, which were contacted with an equal volume of 3 M nitric acid as the aqueous phase. Mixtures were agitated for 5, 12, 19, 26, 36 and 42 d, respectively, with an oscillating mixer at 900 rpm at room temp. [(22 ± 2) °C]. After this period, ^{241}Am and ^{152}Eu extraction was assessed by following extraction procedure described.

Irradiation Procedure: The stability studies of **1** against irradiation were performed at the CIEMAT Nayade facility, which was a pool 1.2 m^2 by 4.5 m deep. It consisted of 60 sources of ^{60}Co distributed in six lots with a total activity of 1.1×10^{14} Bq, with a dose rate of 2.6–9.5 kGy h^{-1}. The irradiation container used provided homogeneous irradiation flux. The 2 mL bottles were sealed with a plastic lid that was loosely screwed on to allow potential over-pressure to level out. No volume decrease was observed during the irradiations, hence evaporation of the solvent was assumed to be negligible. The Am^{III} and Eu^{III} extraction with the irradiated samples of **1** were assessed immediately after irradiation. The bottles were then stored in a freezer while awaiting further HPLC–MS analyses.

HPLC–APCI$^+$ Procedure: HPLC–MS studies were performed by using an HPLC–MS Agilent 1100 (Quadrupole detector 6120A) with a Protonsil C-8 column (50 × 2 mm, 5 μm) at 40 °C using a gradient of mobile phase [(A: 0.1 vol.-% CH_3CN/HCOOH), (B: 0.1 vol.-% H_2O/HCOOH)] in the APCI$^+$ ionization mode (SCAN). Samples from irradiation were used without pre-evaporation and were diluted in (90:10) MeOH/1-octanol until 10^{-3} M. Calibration curves and verification of these curves were realized with **1** and with each of the synthesized fragments. A quantitative study was carried out by HPLC–APCI$^+$ (SIM mode) by using irradiated samples of **1**, which were diluted 100 and 200 times. Data were collected in triplicate and the final concentrations of all fragments were calculated as the average of the different dilutions.

Supporting Information (see footnote on the first page of this article): Spectral characterization data (**1–18**). HPLC–MS data of the qualitative and quantitative studies. Distribution coefficients of Am^{III} and Eu^{III} by TODGA after irradiation.

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