Specific Sequestering Agents for the Actinides. 1. *N,N',N'',N'''*-Tetra(2,3-dihydroxybenzoyl)tetraazacyclotetra- and -hexadecanes

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Abstract: A new synthetic procedure is presented for the 2,3-dihydroxybenzamidation of azaalkanes. Four equivalents of 2,3-dioxomethylene (or 2,3-dimethoxybenzoyl chloride) reacted with 1,4,8,11-tetraazacyclotetradecane (**1**) or 1,5,9,13-tetraazacyclohexadecane (**2**) to produce the corresponding cyclotetraamides (**3, 4, 5**). Subsequent treatment with either BBr_3 or BCl_3 in CH_2Cl_2 solution gave the desired *N,N',N'',N'''*-tetra(2,3-dihydroxybenzoyl)tetraazacyclotetradecane (**6**) or -hexadecane (**7**). The latter two compounds are the first products of a new biomimetic design concept for the preparation of selective actinide-ion sequestering agents. Preliminary data indicate that the formation constant for Pu(IV) with deprotonated **6** is greater than 10^{52}.

Introduction

In response to the biological hazards associated with the nuclear fuel cycle and nuclear research sites, we are pursuing a biomimetic design concept for the preparation of sequestering agents for eight-coordinate actinide ions in general, and Pu(IV) in particular. Plutonium is a potent carcinogen[1] since once absorbed by body tissues, it exhibits long-term retention in mammals. This is known for humans[2] as well as for test animals such as dogs.[3] Although plutonium commonly exists in aqueous solution in each of the oxidation states from III to VI, biological evidence indicates that most, if not all, exists in vivo as Pu(IV), where it is complexed by available bioorganic ligands.[4]

There are many similarities between Pu(IV) and Fe(III). These range from the similar charge/ionic-radius ratio for Fe(III) and Pu(IV) (4.6 and 4.2 e/Å, respectively) to their similar transport properties in mammals, where Pu(IV) is bound by the iron transport protein transferrin at the site which normally binds Fe(III).[4] Thus a biomimetic approach to the design of Pu(IV) sequestering agents, which are similar to naturally occurring Fe(III) sequestering agents, should be feasible. Since the 2,3-dihydroxybenzoyl group (DHB) is a component of several siderophores and in particular is found in enterobactin [cyclotris(2,3-dihydroxybenzoyl)-*N*-*l*-serine], a powerful iron transport and sequestering agent of enteric bacteria,[5] we anticipated that the macrocyclic tetra(DHB) conjugates of cyclam-14 (**6** in Figure 1) and cyclam-16 (**7** in Figure 1) might be selective Pu(IV) sequestering agents. Molecular models show that **6** and **7** can readily form octadentate complexes of Pu(IV) in which the central metal ion is completely encapsulated by the ligand. Measurements in our laboratory of tetrakis(catecholate)actinide(IV) complexes suggest that formation constants greater than 10^{52} may be expected for 1:1 complexes of Pu(IV) with **6** or **7**.[6]

The biosynthetic pathways of enterobactin (enterochelin)[7] and of DHB amides of glycine,[8] serine,[9] lysine,[9] and threonine[10] have been elucidated. Recently the biosynthesis of bis(DHB) derivatives of spermidine has been reported.[11] The products are potent iron chelators and remove Fe(III) from transferrin.[12] The chemical syntheses of N(DHB)glycine[8] and N(DHB)serine were accomplished by the condensation of the O-protected amino acids with DHB acid, mediated by *N,N'*-dicyclohexylcarbodiimide.

Our synthetic strategy has been to develop a generally applicable procedure for the preparation of DHB amides. To ensure tetrasubstitution by DHB, 2,3-dioxomethylenebenzoyl chloride[13] (4 equiv) was added to a solution of **1** or **2** and 4 equiv of pyridine in *N,N*-dimethylacetamide. The solution was maintained at 95–100 °C for 24–48 h reaction times, after which thin layer chromatography (TLC) showed only one product, the tetraamide (**3** or **5**). The 2,3-dimethoxybenzoyl chloride condensed equally well to give **4** (Figure 1 and Table I). Analytically pure products were obtained by column chromatography on silica gel.

Previously it has been shown that the dioxomethylene acetal moiety can be removed selectively with BCl_3, and that this occurs more readily than the corresponding demethylation.[14] This is consistent with our results which show quantitative removal of the $-CH_2-$ group in **3** and **5** using BCl_3/CH_2Cl_2, but incomplete removal of the CH_3- groups in **4** by the same procedure. However, complete demethylation of **4** was accomplished with BBr_3/CH_2Cl_2.[15]

Macrocyclic sequestering agent **6** (mp 287 °C dec) was unchanged after base (pH 12) dissolution and acid (pH 1) precipitation at room temperature and was unaffected in pH 1 aqueous solutions (1 mg/mL) after 20 h at room temperature. Neither **6** nor **7** exhibits a molecular ion in the low-voltage mass spectrum; **6** does not sublime at 200 °C at 10^{-7} mmHg. After several weeks of room exposure **6** and **7** appear unchanged, indicating considerable resistance to air oxidation.

Experimental Section

Melting points were taken on a Buchi apparatus in open capillaries and are uncorrected. Infrared spectra (KBr disks) were recorded on a Perkin-Elmer 283 instrument. ^1H NMR spectra were recorded on a Varian T-60 instrument using Me_4Si as internal standard. Evaporations were accomplished with a Buchi Rotovapor-RE at 50 °C. Thin layer chromatography (TLC) was performed on precoated silica gel 60 F-254 glass plates; plates were developed in tetrahydrofuran (93 mL)/C_6H_{12} (7 mL)/H_2O (5 mL), i.e., TCW. Spots were developed with UV and $KMnO_4$/HCl, then starch/KI. Microanalyses were performed by Analytical Services, Chemistry Department, University of California, Berkeley, except for compound **6**, which was analyzed by Galbraith Laboratories, Inc., Knoxville, Tenn. Both 2,3-dihydroxybenzoic acid and 2,3-dimethoxybenzoic acid were purchased from Aldrich Chemical Co., Milwaukee, Wis., whereas compounds **1**[16] and **2**[17] were prepared by literature methods. The *N,N*-dimethylacetamide (DMAA) (Aldrich Chemical Co.) was spectrophotometric grade and was used without purification; pyridine was dried over type 5A Linde molecular sieves before use.

1,4,8,11-*N,N',N'',N'''*-Tetra(2,3-dioxomethylenebenzoyl)tetraazacyclotetradecane (3). Refluxing 3.4 g (20.5 mmol) of 2,3-dioxomethylenebenzoic acid[18,19] in 20 mL of $SOCl_2$ under a Drierite tube for several hours gave a solution, which was evaporated to residue. Coevaporation with benzene (3 × 30 mL) removed traces of excess

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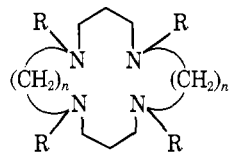
Table I. Title Compounds and Precursors



No.	*n*	R	Mp, °C	Solvent of isolation	% yield
1	2	H	182–183[a]	C_6H_5Cl	
3	2	2,3-Dioxomethylenebenzoyl	236–238	$CHCl_3$	92
4	2	2,3-Dimethoxybenzoyl	110–115	$MeOH/Et_2O$	87
6	2	2,3-Dihydroxybenzoyl	287 dec	MeOH; H_2O[b]	95
2	3	H	83–84[c]		
5	3	2,3-Dioxomethylenebenzoyl	178–180	CH_2Cl_2	63
7	3	2,3-Dihydroxybenzoyl	175–185	MeOH; H_2O[b]	100

[a] Lit. mp 184–185 °C (ref 16); purified by sublimation. [b] See Experimental Section; the reaction mixture is treated with both MeOH and H_2O resulting in hydrated products. [c] Lit. mp 83–84 °C (ref 17); purified by sublimation.

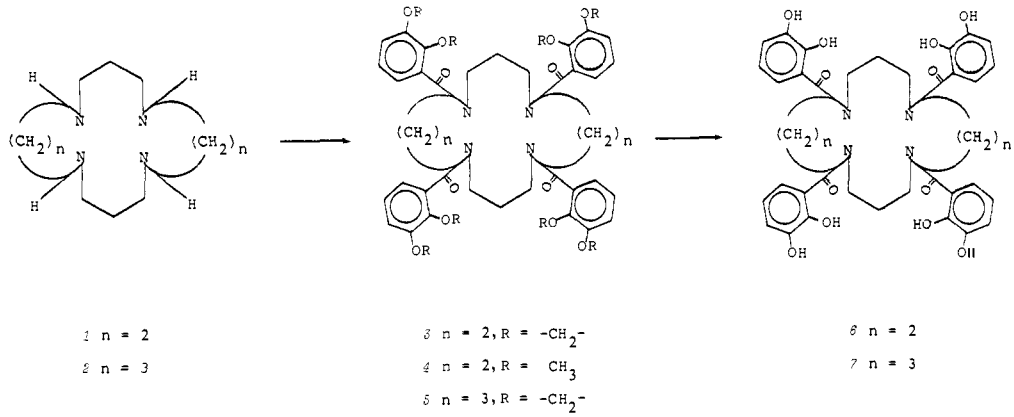


Figure 1. Synthetic scheme and formulas of the title compounds.

$SOCl_2$ to give the corresponding benzene-soluble acid chloride[18] to which 30 mL of DMAA was added followed by 1.0 g (5.0 mmol) of **1** and 1.6 g (20.2 mmol) of pyridine. The resulting mixture was heated at 95 °C for 72 h in a stoppered, 100 mL round-bottomed flask immersed in an oil bath. Evaporation of the DMAA gave a residue which was partitioned between $CHCl_3$ and H_2O. The $CHCl_3$ layer was washed several times with dilute aqueous NaOH, then concentrated and placed upon a silica gel column (15 × ¾ in. o.d.) prepared in CCl_4 The product **3,** 3.65 g (92%), was obtained after elution with 4% EtOH in $CHCl_3$ solution and crystallized from $CHCl_3$: TLC R_f 0.61; ^1H NMR (TFA) δ 2.0–2.8 (m, 4 H, $>NCH_2\underline{CH_2}CH_2-$), 3.3–4.5 (broad m, 16 H, $>N\underline{CH_2}CH_2-$), 5.90 (broad s, 4 H, $-OCH_2O-$), 6.10 (broad s, 4 H, $-OCH_2\overline{O}-$), 7.03 (broad s, 12 H, aromatic); IR 1615 and 1445 (>NCO–), 1050, 925, and 745 cm^{-1} ($-OCH_2O-$).

Anal. Calcd for $C_{42}H_{40}N_4O_{12}$: C, 63.63; H, 5.09; N, 7.07. Found: C, 63.48; H, 5.17; N, 7.04.

1,4,8,11-*N,N',N'',N'''*-Tetra(2,3-dimethoxybenzoyl)tetraazacyclotetradecane (4). To 4.55 g (25 mmol) of 2,3-dimethoxybenzoic acid was added 15 mL of $SOCl_2$ and the slurry was stirred at room temperature for 2 h under a Drierite tube. The resulting solution was evaporated to a residue, then coevaporated with benzene (3 × 30 mL) to remove traces of $SOCl_2$. To the resulting benzene-soluble acid chloride were added 1.0 g (5.0 mmol) of **1,** 40 mL of DMAA, and 2.0 g (25 mmol) of pyridine. Using the same procedure as for **3,** product **4,** 4.6 g (87%), was isolated after elution from silica gel with $CHCl_3$, then precipitated from $CHCl_3$ with Et_2O: TLC R_f 0.55; ^1H NMR ($CDCl_3$) δ 1.8–2.4 (broad m, 4 H, $>NCH_2\underline{CH_2}CH_2-$), 2.8–3.8 (broad m, 16 H, $>N\underline{CH_2}CH_2-$), 3.88 (broad s, 24 H, $-OCH_3$), 6.7–7.3 (broad m, 12 H, aromatic); IR 1635, 1475, 1425 (>NCO–), 1310, 1265, 1230, 1045, 1000, 795, 750 cm^{-1} ($-OCH_3$).

Anal. Calcd for $C_{46}H_{56}N_4O_{12}$: C, 64.47; H, 6.59; N, 6.54. Found: C, 62.97; H, 6.57; N, 6.20.

1,5,9,13-*N,N',N'',N'''*-Tetra(2,3-dioxomethylenebenzoyl)tetraazacyclohexadecane (5). Using the same procedure as for **3,** the following were heated together at 95 °C for 88 h: 2,3-dioxomethylenebenzoyl chloride [prepared from 3.5 g (21.0 mmol) of the benzoic acid]; 1.10 g (5.0 mmol) of **2;** 1.7 g (21.5 mmol) of pyridine; 30 mL of DMAA. Workup as for **3** resulted in the title compound, **5,** 2.6 g (63%), which was crystallized from CH_2Cl_2: TLC R_f 0.58; ^1H NMR ($CDCl_3$) δ 1.6–2.4 (broad s, 8 H, $>NCH_2\underline{CH_2}CH_2$), 2.9–3.8 (broad s, 16 H, $>N\underline{CH_2}CH_2-$), 5.93 (s, 8 H, $-OCH_2\overline{O}-$), 6.80 (s, 12 H, aromatic); IR 1625 and 1595 (>NCO–), 1445, 1250, 1055, 1030, 925, 745 cm^{-1} ($-OCH_2O$).

Anal. Calcd for $C_{44}H_{44}N_4O_{12}$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.11; H, 5.31; N, 6.70.

1,4,8,11-*N,N',N'',N'''*-Tetra(2,3-dihydroxybenzoyl)tetraazacyclotetradecane (6). Method A. To a solution of 0.79 g (1.0 mmol) of **3** in 15 mL of CH_2Cl_2 under argon atmosphere, vigorously stirred with a magnetic bar and immersed in an ice bath, was added via syringe and septum 30 mL of 1 M BCl_3/CH_2Cl_2 solution. A precipitate formed immediately; the mixture was stirred overnight, while the ice was allowed to warm up to room temperature. Addition of 20 mL of H_2O via syringe (4 × 5 mL aliquots added over 20 min) quenched the excess BCl_3 and the resulting mixture was stirred for an additional 1.5 h at room temperature. Evaporation to residue followed by coevaporation with MeOH (3 × 50 mL) removed all boron as methylborate. The white residue was then dried in a vacuum oven at 95 °C overnight to obtain 0.75 g (~95%) of **6:** ^1H NMR (Me_2SO-d_6–D_2O) showed the complete absence of the $-OCH_2O-$ (δ ~6.0) moiety and the NMR sample turned deep blue when treated with aqueous $FeCl_3$.

Anal. Calcd for $C_{38}H_{40}N_4O_{12}\cdot 2.5H_2O$: C, 57.79; H, 5.74; N, 7.09; O, 29.38. Found: C, 57.86; H, 5.92; N, 6.92; O, 29.50.

Method B. To a solution of 1.0 g (1.2 mmol) of **4** in 20 mL of CH_2Cl_2 under argon atmosphere and cooled by an ice bath was added via syringe and septum 3 mL (7.8 g, 31 mmol) of neat BBr_3. The resulting slurry was stirred overnight as the ice bath was allowed to warm to room temperature. Workup in the same way as for method A gave 0.9 g (~95%) of **6:** ^1H NMR (Me_2SO-d_6–D_2O) showed the complete absence of the $-OCH_3$ ($\delta \approx 3.9$) moiety and the product was identical with that produced in method A.

1,5,9,13-*N,N',N'',N'''*-Tetra(2,3-dihydroxybenzoyl)tetraazacy-

clohexadecane (7). Using method A the following reagents were combined: 0.82 g (1.0 mmol) of **5**, 30 mL of 1 M BCl_3/CH_2Cl_2 solution, and 15 mL of CH_2Cl_2. Workup gave 0.8 g (~100%) of **7**: ^1H NMR (Me_2SO-d_6-D_2O) showed the complete absence of the $-OCH_2O-$ ($\delta \approx 6.0$) moiety. A sample dried at 100 °C in vacuo gave the correct elemental analysis for $7 \cdot 2H_2O$.

Anal. Calcd for $C_{40}H_{44}N_4O_{12} \cdot 2H_2O$: C, 59.40; H, 5.98; N, 6.93. Found: C, 59.09; H, 5.70; N, 6.82.

Summary

The similar coordination chemistry of Pu(IV) and Fe(III) in vitro and in vivo has led to a biomimetic approach in the synthesis of specific sequestering agents for Pu(IV) and other actinide(IV) ions. The octadentate chelating agents **6** and **7** have been prepared and their coordination properties and biological activity are under investigation. Both **6** and **7** are much less susceptible to hydrolysis than is enterobactin and both **6** and **7** are less sensitive to air oxidation than 2,3-dihydroxybenzoic acid. Qualitative observations have shown that Pu(IV) dissolves in the presence of **6** even at high pH. Since the K_{sp} for $Pu(OH)_4$ is approximately 10^{-52},[20] this indicates a formation constant which is greater than 10^{52} for the Pu(IV) complex of deprotonated **6**.

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Mechanisms of Photochemical Reactions in Solution. 77. The Effect of Configuration in Some Bicyclic Di-π-methanes with Simple Chromophores

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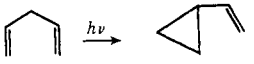
Abstract: Direct and sensitized irradiations of 5-methylenebicyclo[2.2.1]hept-2-ene and three related di-π-methanes have been conducted. The rearrangement occurring upon direct irradiation of 5-ethylidenebicyclo[2.2.1]hept-2-ene is demonstrated to be nonconcerted. In addition to the expected di-π-methane rearrangement product, 5-(3-methylbut-2-enylidene)-bicyclo[2.2.1]hept-2-ene yielded 5-methylene-3-(3-methylbut-2-enylidene)cyclohexene. Of the four compounds investigated, only bicyclo[2.2.1]hept-2-en-5-isopropylimine did not undergo a di-π-methane rearrangement.

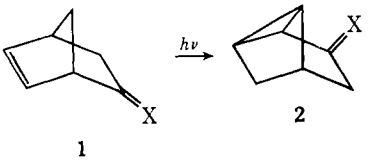
The di-π-methane rearrangement,[2] exemplified by the reaction in eq 1, has been the subject of continued intensive



(1)

investigation both for its own sake and as an example of bichromophoric interaction. In spite of this, relatively few solution-phase examples of di-π-methane rearrangements in which the chromophores are unsubstituted (or alkyl substituted) double bonds have been reported.[2b] Vapor phase photolyses, many with mercury as sensitizer, have been conducted on several simple di-π-methanes.[3] However, experience has shown that vapor- and solution-phase photochemistry of di-π-methanes can be completely different.[2b,3c,4] Frequently, the participating chromophores of di-π-methanes in solution-phase photolyses are substituted with highly absorbing auxochromes which mask the energetic details of the rearrangement. This and a number of other variables which appear to govern reactivity (e.g., excited state multiplicity, alternate routes of reaction, and relative orientation of participating chromophores) can be controlled at least partially by judicious design of the reactant molecules.

Herein, we report results from the irradiation of a series of di-π-methanes (**1a–d**) which do not contain extensive auxochromic substituents and in which the relative orientations of the chromophoric groups are rigid and essentially invariant.[5] The comportment of these compounds is compared to di-π-methanes with similar chromophores of different relative orientations.



1 2

a, X = CH_2
b, X = $CHCH_3$
c, X = $CHCH{=}C(CH_3)_2$
d, X = $NCH(CH_3)_2$

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