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Author
Weitl, F.L.

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Frederick L. Weitl and Kenneth N. Raymond

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DISCLAIMER

SPECIFIC SEQUESTERING AGENTS FOR THE ACTINIDES.

3. POLYCATECHOLATE LIGANDS DERIVED FROM

2,3-DIHYDROXY-5-SULFOBENZOYL CONJUGATES OF

DIAZA- AND TETRAAZAALKANES.[1]

Frederick L. Weitl and Kenneth N. Raymond[*]

Contribution from the Materials and Molecular Research Division,
Lawrence Berkeley Laboratory and Department of Chemistry,
University of California, Berkeley, California 94720

ABSTRACT

As part of a program to develop specific sequestering agents for
the actinides, we have reported the synthesis of N, N', N", N''' —
tetra (2,3-dihydroxybenzoyl) tetraazacycloalkanes. These tetra (DHB)
amides are potentially octadentate ligands by coordination of the cathechol
oxygen atoms. We now report the synthesis of the DHB amides of linear
tetraaza- and diazaalkanes. Furthermore, sulfonation of these compounds
in 20-30% SO_3-H_2SO_4 yields exclusively all their 5-sulfo-DHB analogs
(2, 7, 10, 13). The sulfonated derivatives have several properties
which make them superior to their precursors with respect to actinide
coordination; these properties include increased water solubility,
enhanced phenolic acidity, and improved oxidative stability near neutral
pH. *In vivo* tests with mice have shown the tetrameric (5-sulfo-DHB)
compounds (14, 15, 16) to be generally acutely non-toxic, efficient
sequestering agents for the actinides which promote rapid urinary
excretion of [238]Pu. Compound 16, the tetra (5-sulfo-DHB) derivative of
spermine, is more effective than any other plutonium sequestering agent
yet tested.

INTRODUCTION

The biological hazard presented by plutonium is a combination of its radioactivity and chemical properties.[2-5] Plutonium is a potent carcinogen whose long-term retention in mammals is due to the immobility of Pu(IV) *in vivo*. We are pursuing a biomimetic design concept to prepare new sequestering agents which will expedite plutonium removal and isolation.[6] This approach is based on the observation that there are many chemical and biological similarities of Pu(IV) and Fe(III). In mammalian serum, Pu(IV) is bound and transported by the iron transport protein, transferrin.[5]

In microbes the transport of Fe(III) is accomplished by a class of low-molecular weight compounds called siderophores.[7] These typically incorporate hydroxamate and catecholate functional groups to form polychelate ligands which satisfy the six-coordinate geometry favored for Fe(III). We are preparing analogous tetra catechol ligands which can completely encapsulate the Pu(IV) ion and form the eight-coordinate geometry preferred by the actinide(IV) ions. We have recently reported this geometry in the structures of tetrakis(catecholate)-thorate(IV) and -uranate(IV).[1] Molecular models show that the attachment of four catechol groups to tetraza alkanes gives compounds which can form octadentate cavities of the proper size for Pu(IV). We have reported earlier the preparation of 3,3,3,3,-CYCAM[9] and related compounds. Animal tests and titration studies indicated that the low solubility and weak acidity of the dihydroxybenzoyl (DHB) groups of 14 limited its potential as a Pu sequestering agent. In response to this, a further cycle of compound modification was undertaken to prepare sulfonated derivatives

in which -SO_3H groups were added to the DHB rings. This substantially improved the solubility, stability to air oxidation, and actinide(IV) ion affinity at low pH. We next examined the effect of greater stereo-chemical freedom in an octadentate ligand by preparing tetra (sulfo-DHB) derivatives 15 and 16 of linear tetraamines. We have established that the equivalent quantity of the monomeric sulfonated dihydroxybenzamide from which the polychelate structure is derived (2, Fig. 1) causes little if any Pu excretion. While further cycles of ligand modification and improvement are continuing (currently aimed at optimization of bridge length between monomeric units), current test results for our initial Pu sequestering agents compare favorably with those of diethylenetriamine-pentaacetic acid (DTPA) and desferrioxamine B (DFOA) — the two agents presently used clinically in human actinide poisoning.[5] The syntheses and characterization of the crystalline, dimeric 5-sulfo-DHB compounds have been included here to substantiate the synthetic procedures used for the tetramers and precursors since the latter compounds are generally isolable only as amorphous hydrated tetra-sodium or -potassium salts.

EXPERIMENTAL DISCUSSION

Chemistry

As early as 1933 there were literature reports that neutral, stable, aqueous solutions of many metal ions — including the actinides uranium and thorium — could be prepared from monomeric disulfonated aromatic $\underline{O}$-dihydroxy compounds.[8] With this in mind we have focused upon the preparation of the tetrameric 5-sulfo-2,3-dihydroxybenzamides (CAMS)[9] which are potentially octadentate ligands for the actinides in which

the lengths of the joining methylene bridges help determine the metal specificity. All tetra-2,3-dihydroxybenzamide (CAM) precursors were prepared using the general procedures reported earlier.[6] Their direct sulfonation was accomplished at room temperature with 20-30% SO_3-H_2SO_4 — which serves as both solvent and reactant.[10] The sulfonation products were isolated at pH 4 as their hydrated tetra-sodium or -potassium salts. Both elemental analysis and pH-titration to obtain neutralization equivalents proved that monosulfonation of each catechol unit occurred. Model experiments in SO_3-H_2SO_4 indicated (by inference) regiospecific sulfonation at the 5-position resulting in isomerically pure LICAMS compounds. For example, a H^1-nmr of 2,3-dihydroxy-N,N-dimethylbenzamide ($\underset{\sim}{1}$) dissolved in 20% SO_3-H_2SO_4 showed an AB-quartet in the aromatic region with J_{AB} = 2Hz. This portion of the spectrum was superimposable upon that of 5-sulfo-2,3-dihydroxybenzenesulfonic acid, also in H_2SO_4 solution, indicating that quantitative, mono-sulfonation in the 5-position had occurred (Fig. 1). This regiospecific 5-sulfonation was also shown for three dimeric compounds ($\underset{\sim}{7}$, $\underset{\sim}{10}$, $\underset{\sim}{13}$) (Table I, Fig. 2).

Design Concept

Our goal has been the synthesis of tetrameric CAM ligands which effect the chelation of all four contiguous catechol units to a single Pu(IV) ion. We now understand that the linear catechol amides allow greater stereochemical freedom than do the corresponding cyclic compounds and butylene bridges (relative to ethylene or propylene) allow a significant improvement in the ability of the ligand to completely surround or encapsulate the actinide — while at the same time satisfying the geometrical requirement of octacoordination of Pu(IV) or Th(IV).[11] This understanding was reinforced by the

fact that mice given ^{238}Pu(IV) as its citrate complex excreted approximately 60% of the plutonium with a single (2-22 µmole/kg bw i.p.) dose of either 15 or 16 given 1 hour later.[12] This is essentially identical with the response to a 30 µmole/kg bw CaNa$_3$DTPA[13] dose give under the same conditions. A comparison of the *in vivo* results for LICAMS 15 and 16 with that for CYCAMS 14, which produced approximately 35% ^{238}Pu-excretion from mice, reveals the improvement in ligand effectiveness with greater stereochemical freedom. Furthermore, compound 16, a derivative of the natural product spermine, has shown no acute toxicity and histological studies have shown no liver damage. This compound is more effective in plutonium removal at lower dose concentrations than any other sequestering agent tested to date.

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. ^{1}H nmr spectra (D$_2$O) were recorded on a Varian T-60 or Varian A-60 instrument using 3-Me$_3$Si-1-propanesulfonic acid, sodium salt hydrate as internal standard. Evaporations were accomplished (40-60°) with a Buchi Rotovapor-RE. Microanalyses were performed by Analytical Services, Chemistry Department, University of California, Berkeley. The sulfonated products (14-16) were dried at 120° (0.1 mm Hg) *in vacuo*; the sulfonated compounds (2, 7, 10, 13) were dried at room temperature in a vacuum dessicator over P$_2$O$_5$/NaOH pellets prior to elemental analysis. The ion exchange resin used in the synthesis of 2 was Bio-Rad, AG50W-X^2 (50-100 mesh). The alumina used in the

chromatography of precursors to 15 and 16 was CAMAG basic, in a 15 × 3/4"
o.d. column. The appropriate diaza- and tetraazaalkanes were used in the
synthesis of each LICAM according to the two-step general procedure (Fig. 2)
we have earlier used to prepare precursors 3,3,3,3-CYCAM[6] and 1 [14] (Fig. 1).
The tetraazaalkanes, spermine (amine component of 16) and N,N'-bis(4- amino-
butyl)-1,4-butanediamine (amine component of 15), were purchased from Ames
Laboratory, Inc., Milford, Connecticut. The 4,5-dihydroxy-M-benzenedisul-
fonic acid, disodium salt (Fig. 1), was obtained from Eastman Kodak Co.,
Rochester, NY. Reagent 4 (2,3-dimethoxybenzoylchloride) was prepared from
an equivalent amount of the corresponding acid by treatment with excess $SOCl_2$
for 3 hours at room temperature followed by co-evaporation with CCl_4 to the
crystalline, crude acid chloride and was used without further purification.

N,N-Dimethyl-(2,3-dihydroxy-5-sulfo)benzamide(2).

Solid 1 (1.3 g, 7.2 mmol) dissolved in 30% fuming H_2SO_4 (10 ml)
was allowed to stand overnight in a stoppered flask immersed in a water-
bath (22°C). A H^1-nmr of a reaction mixture aliquot revealed only an
AB-quartet (J_{AB} = 2Hz) in the aromatic region. This reaction solution
was poured onto ice, resulting in a clear aqueous solution (100 ml).
Careful, drop-wise addition of 10 N NaOH, with vigorous stirring and
(ice water bath) cooling gave a pH 4 solution at ambient temperature.
Addition of 1 volume of MeOH precipitated the inorganic salt which was
removed by filtration, washed well with MeOH-H_2O (equivol.), then discarded
The combined filtrate and wash were evaporated to a solid, redissolved in
H_2O, and eluted from a 100 meq H^+-ion exchange column. Fractions
containing 2 were identified by a (blue) color test with $FeCl_3$ solution.

These were evaporated to residue and dried in a vacuum dessicator at room temperature over P_2O_5/NaOH to yield the hygroscopic, white solid $\underset{\sim}{2}$ · 2.5H$_2$O)(2.0 g, 94%) mp 143-5°: ir 2500-3700 ($\geqslant$CH', -OH), 1670 (-$\underline{CON}\lessgtr$), 1600, 1465, 1410, 1385, 1210 (SO$_3^-$), 1160 (SO$_3^-$), 1100, 1040, 610 (SO$_3^-$) cm^{-1}; nmr δ2,97 (broad s, 6H, -CON(CH$_3$)$_2$), 7.20 (d, 1H, 4-Ar$\underline{H}$, J$_{AB}$ = 2Hz), 7.37 (d, 1H, 6-Ar$\underline{H}$, J$_{AB}$ = 2Hz).

Analysis: Calculated for C$_9$H$_{11}$NO$_6$S · 2.5H$_2$O: N, 4.59; S, 10.50. Found: N, 4.45; S, 10.55.

N,N'-Bis(2,3-dimethoxybenzoyl)-1,4-diazabutane $\underset{\sim}{(5)}$.

To 2,3-dimethoxybenzoyl chloride $\underset{\sim}{4}$ (34.3 mmol), dissolved in N,N-dimethylacetamide (DMAA, 20 ml), was added ethylenediamine (1.0 g, 17 mmol) and NEt$_3$ (3.5 g, 34.6 mmol) in DMAA (20 ml) solution. The combined ingredients were stirred in a stoppered flask immersed in a 60° oil bath for 20 hours. After evaporation to residue, the product mixture was triturated with water and collected by filtration. Crude product was washed well with dilute aqueous NaOH and HCl. Recrystallization from 95% EtOH gave $\underset{\sim}{5}$ (6.2 g, 92%): mp 141-3°.

Analysis: Calculated for C$_{20}$H$_{24}$N$_2$O$_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61.55; H, 6.21; N, 7.09.

N,N'-Bis(2,3-dihydroxybenzoyl)-1,4-diazabutane, (2-LICAM) $\underset{\sim}{(6)}$.

Under argon, a solution of $\underset{\sim}{5}$ (5.0 g, 13 mmol) in CH$_2$Cl$_2$ (40 ml) was added drop-wise to a solution of BBr$_3$ (6.5 ml, 68 mmol) in CCl$_4$ (75 ml). During the addition, the latter solution was vigorously stirred while

immersed in a room temperature water bath. An immediate precipitate formed and was allowed to stir overnight. Addition of 50 ml H_2O (CAUTION HBr evolution) followed by a 2 hour pause for completion of hydrolysis resulted in a crude white solid which was collected by filtration and washed well with H_2O to remove acids. Recrystallization of the crude white solid from aqueous MeOH gave $\underset{\sim}{6} \cdot 1H_2O$ (3.85 g, 85%): mp 214-17°.

<u>Analysis</u>: Calculated for $C_{16}H_{16}N_2O_6 \cdot 1H_2O$: C, 54.86; H, 5.18; N, 8.00. Found: C, 54.85; H, 5.20; N, 8.02.

N,N'-Bis(2,3-dihydroxy-5-sulfobenzoyl)-1,4-diazabutane, (2-LICAMS) $\underset{\sim}{(7)}$.

In portions 4.5 g (13.5 mmol) of 6, were added to 20% fuming H_2SO_4 (50 ml) contained in a stoppered round bottom flask which was immersed in a 22°C water bath, while stirring vigorously with a magnetic stir bar. The reaction solution sat overnight and was then carefully poured onto ice. The resulting solid was collected by filtration or centrifugation. Recrystallization from minimum hot H_2O, followed by filtration, an ice water wash, and drying overnight in a vacuum dessicator over P_2O_5 gave $\underset{\sim}{7} \cdot 4H_2O$ (3.3 g, 43%): mp 259-60° dec; ir 2500-3700 ($\geq$CH, OH), 1640 (-<u>CO</u>-N$\langle$), 1590, 1555, 1480, 1425, 1280, 1275 (SO_3^-), 1165 (SO_3^-), 1035, 610 (SO_3^-); nmr δ 3.72 (broad S, 4H, -<u>CH</u>$_2$<u>CH</u>$_2$-), 7.52 (d, 2H, 4-Ar<u>H</u>, J_{AB} = 2Hz), 7.82 (d, 2H, 6-Ar<u>H</u>, J_{AB} = 2Hz).

<u>Analysis</u>: Calculated for $C_{16}H_{16}N_2O_{12}S_2 \cdot 4H_2O$: C, 34.04; H, 4.29; N, 4.96; S, 11.36. Found: C, 33.88; H, 4.37; N, 4.69; S, 11.70.

N,N'-Bis(2,3-dimethyoxybenzoyl)-1,6-diazahexane (8).

Using the same procedure as in the synthesis of 5, the following

ingredients were combined: 4 (38.4 mmol); 1,4-butane-diamine · 2HCl (3.06 g,

19 mmol); NEt_3 (7.8 g, 77 mmol), DMAA (60 ml). Workup and recrystallization

from 95% EtOH gave 8 (4.3 g, 55%): mp 143-5°.

<u>Analysis</u>: Calculated for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78; N, 6.73.
Found: C, 63.06; H, 6.75; N, 6.62.

N,N'-Bis(2,3-dihydroxybenzoyl)-1,6-diazahexane, (4-LICAM) (9).

Using the procedure as in the synthesis of 6, the following

ingredients were combined: 8 (4.0 g, 9.6 mmol), BBr_3 (5.0 ml, 53 mmol),

CH_2Cl_2 (115 ml). Workup and recrystallization from H_2O/MeOH gave 9

(3.2 g, 91%): mp 203-5°.

Analysis: Calculated for $C_{18}H_2 N_2O_6$ C, 59.99; H, 5.59; N, 7.77.
Found: C, 59.76; H, 5.73; N, 7.68.

N,N'-Bis(2,3-dihydroxy-5-sulfobenzoyl)-1,6-diazahexane, (4-LICAMS) (10).

Using the same procedure as in the synthesis of 7, the following

reactants were combined: 9 (3.1 g, 8.6 mmol), 20% fuming H_2SO_4 (30 ml).

Workup and recrystallization from H_2O gave $10 \cdot 2H_2O$ (2.0 g, 42%): mp 256.5-

257.5° dec; ir 2500-3700 ($\geq$CH, -OH), 1650 (-<u>CO</u>-N<), 1595, 1550, 1470,

1430, 1330, 1280, 1225 (SO_3^-), 1160 (SO_3^-), 1110, 1040, 610 (SO_3^-) cm^{-1};

nmr δ1.6-2.0 (broad, 4H, -<u>CH</u>$_2$CH$_2$-NH-), 3.3-3.8 (broad, 4H, -CH$_2$<u>CH</u>$_2$-NH-),

7.57 (d, 2H, 4-Ar<u>H</u>, J_{AB} = 2Hz), 7.87 (d, 2H, 6-Ar<u>H</u>, J_{AB} = 2Hz).

Analysis: Calculated for $C_{18}H_{20}N_2O_{12}S_2 \cdot 2H_2O$: C, 38.85; H, 4.35; N, 5.03; S, 11.52. Found: C, 38.79; H, 4.59; N, 4.99; S, 11.45.

N,N'-Bis(2,3-dimethoxybenzoyl)-1,8-diazaoctane (11).

Using the same procedure as in the synthesis of 5, the following reactants were combined: 4 (40 mmol), NEt_3 (4.05 g, 40 mmol), 1,6-Hexane-diamine (2.32 g, 20 mmol), DMAA (60 ml). Workup and recrystallization from 95%-EtOH gave 11 (8.46 g, 95%): mp 137-9°.

Analysis: Calculated for $C_{24}H_{32}N_2O_6$: C, 64.83; H, 7.25; N, 6.30. Found: C, 64.40; H, 7.28; N, 6.06.

N,N'-Bis(2,3-dihydroxybenzoyl)-1,8-diazaoctane, (6-LICAM) (12).

Using the same procedure as in the synthesis of 6, the following reagents were combined: 11 (6.7 g, 15 mmol) in CH_2Cl_2 (60 ml), BBr_3 (7.5 ml, 79 mmol) in CH_2Cl_2 (75 ml). Workup and recrystallization from H_2O-MeOH gave 12 (4.2 g, 85%): mp 214-17°.

Analysis: Calculated for $C_{20}H_{24}N_2O_6$: C, 61.84; H, 6.23; N, 7.21. Found: C, 61.56; H, 6.23; N, 7.09.

N,N'-Bis(2,3-dihydroxy-5-sulfobenzoyl)-1,8-diazaoctane, (6-LICAMS) (13).

Using the same procedure as in the synthesis of 7, the following reagents were combined: 12 (4.5 g, 11.5 mmol), 30% fuming H_2SO_4 (45 ml). Workup and recrystallization from H_2O gave 13 $\cdot 2H_2O$ (3.2 g, 48%): mp 253-4° 253-4° dec; ir 2500-3700 ($\geqslant$CH, -OH), 1640 (-CO-N<), 1590, 1550, 1425, 1280, 1215 (SO_3^-), 1165 (SO_3^-), 1105, 1040, 610 (SO_3^-), cm^{-1}; nmr δ 1.2-1.9

(broad, 8H, -($\underline{CH}_2$)$_4$CH$_2$-NH-), 3.2-3.6 (broad, 4H, -(CH$_2$)$_4$C$\underline{H}_2$NH-), 7.60 (d, 2H, 4-Ar$\underline{H}$, J$_{AB}$ = 2Hz), 7.92 (d, 2H, 6-Ar$\underline{H}$, J$_{AB}$ = 2Hz).

<u>Analysis</u>: Calculated for C$_{20}$H$_{24}$N$_2$O$_{12}$S$_2$ · 2H$_2$O: C, 41.09; H, 4.83; N, 4.79; S, 10.97. Found: C, 41.41; H, 5.07; N, 4.78; S, 11.21.

N,N',N",N'''-Tetra(2,3-dihydroxy-5-sulfobenzoyl)-1,5,9,13-tetraazacyclo-hexadecane, tetrasodium salt, (3,3,3,3-CYCAMS) (14).

Crude, dry precursor 3,3,3,3-CYCAM (1.0 g, 1.2 mmol) dissolved in 30% fuming H$_2$SO$_4$ (10 ml) sat overnight in a stoppered flask immersed in a 22°C water bath. The reaction solution was poured onto ice, resulting in a clear (100 ml) solution. Careful addition of 10 $\underline{N}$ NaOH, with vigorous stirring and ice-water cooling gave a pH 4 solution at ambient temperature. Addition of 1 volume of MeOH provided a copious inorganic precipitate which was removed by filtration and discarded after washing well with 1:1 H$_2$O/MeOH. (A portion of this filtrant gave no blue color in the presence of aqueous FeCl$_3$.) The combined filtrate and wash was evaporated to dryness and then redissolved in minimum H$_2$O. Careful addition of MeOH, then EtOH, and finally Et$_2$O (to give substantial turbidity) followed by filtration gave a clear, nearly colorless solution. Subsequent addition of 2 to 3 volumes of Et$_2$O gave a white solid; this was isolated by filtration, washed well with Et$_2$O, then dried at 120° (<0.1 mm Hg) overnight. Thus was obtained hygroscopic 14 · 5H$_2$O (1.4 g, 92%): ir 2800-3700 ($\geqslant$C-H, -OH), 1610 (-$\underline{CO}$-N$\lessgtr$), 1485, 1410, 1250-1140 (SO$_3^-$), 1100, 1045, 615 (SO$_3^-$) cm^{-1}; nmr δ1.6-2.6 (broad, 8H, -$\underline{CH}_2$CH$_2$-N$\lessgtr$), 2.8-4.2 (broad, 16H, -C$\underline{H}_2$N$\lessgtr$), 7.0-8.0 (complex m, 8H, Ar$\underline{H}$); purity also established by pH-titration giving pKa, 8.12 (4 protons) and pKa$_2$ 12.0 (4 protons)

for the four constituent catechol groups.

Analysis: Calculated for $C_{40}H_{40}N_4O_{24}Na_4 \cdot 5H_2O$: C, 37.80; H, 3.96; N, 4.41; S, 10.09; Na, 7.23. Found: C, 37.52; H, 3.94; N, 4.39; S, 9.74; Na, 7.60.

N,N',N'',N'''-Tetra(2,3-dihydroxy-5-sulfobenzoyl)-1,6,11,16-tetrahexa-decane, tetrasodium salt, (4,4,4,4-LICAMS) (15).

Using the same procedure as in the synthesis of 5, the following materials were combined: 4 (35 mmol); 1,6,11,16-tetraazahexadecane (2.0 g, 8.7 mmol), NEt$_3$ (3.54 g, 35 mmol), DMAA (40 ml). The reaction mixture was evaporated to residual oil which was partitioned between H_2O/CHCl$_3$. Next the CHCl$_3$ layer was washed well with aqueous HCl, H_2O, then aqueous NaOH before drying with MgSO$_4$ and elution from an alumina column with mixtures of 0-5% EtOH in CH_2Cl_2. Column fractions were monitored with tlc. Thus was obtained the tetra(2,3-dimethoxybenzoyl)-precursor to 15 as a glassy solid (6.6 g, 86%): ir 3400 (-N$\underline{H}$-CO), 2940 ($\geqslant$CH), 1655 and 1635 ($>$N-$\underline{CO}$-) cm^{-1}. This material was used in the next step.

Analysis: Calculated for $C_{48}H_{62}N_4O_{12}$: C, 64.99; H, 7.05; N, 6.32. Found: C, 65.18; H, 6.82; N, 6.23.

Using the same procedure as in the synthesis of 6, the following materials were combined: Tetra(2,3-dimethoxybenzoyl)-precursor-of-15 (3.7 g, 4.2 mmol), BBr$_3$ (4 ml, 42 mmol), CH_2Cl_2 (115 ml). After hydrolysis with H_2O (50 ml), the crude product was collected by filtration and washed

well with H_2O to remove acids, then with Et_2O, and dried in a vacuum dessicator over P_2O_5/NaOH (pellets) to obtain crude, dry 4,4,4-LICAM (2.1 g, ~62%), which was satisfactory for use in the next step.

The dry, crude 4,4,4-LICAM (1.0 g, 1.2 mmol) was sulfonated and isolated precisely as in the synthesis of 14 to obtain hygroscopic white solid 15 · $4H_2O$ · $\frac{1}{4}Na_2SO_4$ (1.4 g, 88%): ir 2800-3700, 1600 ($>$N-C$\underline{O}$-), 1475, 1150-1300 (SO_3^-), 1100, 1045, 620 (SO_3^-) cm^{-1}; nmr 1.3-2.1 (broad, 12H, -C$\underline{H}_2$C$\underline{H}_2$C$\underline{H}_2$N$\langle$), 2.8-3.8 (broad, 12H, -C$\underline{H}_2$N), 7.2-8.0 (complex m, 8H, Ar$\underline{H}$): pH-titration gave pKa_1, 7.49 (4 protons) pKa_2 12.10 (4 protons) for four catechol units.

<u>Analysis</u>: Calculated for $C_{40}H_{42}N_4O_{24}S_4Na_4$ · $4H_2O$ · $\frac{1}{4}Na_2SO_4$: C, 37.22; H, 3.91; N, 4.34; S, 10.56; Na, 8.02. Found: C, 37.27; H, 4.02; N, 4.51; S, 10.87; Na, 8.42.

N,N',N'',N'''-Tetra(2,3-dihydroxy-5-sulfobenzoyl)-1,5,10,14-tetraaza-tetradecane, tetrasodium salt, (3,4,3-LICAMS) (16).

Using the same procedure as in the synthesis of 5, the following materials were combined: spermine (2.0 g, 9.9 mmol), 4 (40 mmol), NEt$_3$ (4.05 g, 40 mmol), DMAA (40 ml). Evaporation of the reaction mixture gave oily residue which was partitioned between H_2O/CH_2Cl_2. Purification of this crude product in CH_2Cl_2 solution was accomplished as in the synthesis of the corresponding precursor to 15. In this way a 4 g fraction of the tetra(2,3-dimethoxybenzoyl)-precursor-to-16 was obtained for use in the next step.

Using the same procedure as in the synthesis of 6, the following reagents were combined: precursor-to-16 (4 g, 4.6 mmol), BBr$_3$ (4.2 ml,

44 mmol), CH_2Cl_2 (115 ml). Hydrolysis (50 ml, H_2O), filtration, and
thorough water wash, then vacuum drying at room temperature over P_2O_5/NaOH
pellets gave 3,4,3-LICAM (3 g), satisfactory for the sulfonation step.

Precisely as in the synthesis of 15, the following reagents were
combined: 3,4,3-LICAM (2.5 g, 3.3 mmol), 30% fuming H_2SO_4 (30 ml).
After pouring on ice, then neutralization with 10 N NaOH to pH 4 and
subsequent workup as for 15, hydroscopic, white solid 16 · $6.5H_2O$ (2.1 g,
50%) was obtained: ir 3700-2500 ($\geq$CH, -OH), 1640-1590 (-CO-N$\leq$), 1470,
1420, 1380, 1210-1180 (SO_3^-), 1100, 1040, 615 (SO_3^-) cm^{-1}; nmr δ 1.3-2.3
(broad, 8H, -CH$_2$CH$_2$N$\leq$), 2.8-3.8 (broad, 12H, -CH$_2$N$\leq$), 7.1-7.9 (broad m,
8H, ArH).

Analysis: Calculated for $C_{38}H_{38}N_4O_{24}S_4Na_4$ · $6.5H_2O$: C, 35.88; H, 4.04;
N, 4.40; S, 10.08; Na, 7.23. Found: C, 36.38; H, 3.73; N, 4.24;
S, 9.26; Na, 7.13.

TABLE 1. Dimeric 2,3-dihydroxy-5-sulfo-benzamides and precursors.

$$RO\text{-}\underset{RO}{\overset{X}{\bigcirc}} \cdot mH_2O \quad X\text{-}\underset{OR}{\overset{OR}{\bigcirc}}$$

$$O = C - NH - (CH_2)_n - NH - C = O$$
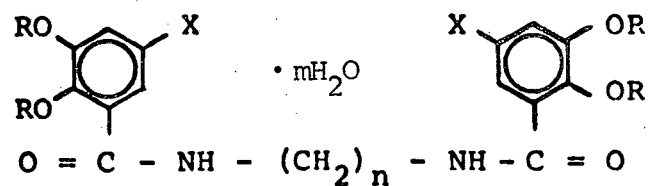
Compound	n	m	X	R	mp, °C (Recrystallization solvent)		Yield (%)	Abbreviated name
5	2	0	H	CH_3	140-2	(95% EtOH)	92	--
6	2	1	H	H	214-17	(MeOH/H_2O)	85	2-LICAM·H_2O
7	2	4	SO_3H	H	259-60d	(H_2O)	43	2-LICAMS·$4H_2O$
8	4	0	H	CH_3	143-5	(95% EtOH)	55	--
9	4	0	H	H	203-6	(MeOH/H_2O)	91	4-LICAM
10	4	2	SO_3H	H	256.5-7.5d	(H_2O)	42	4-LICAMS·$2H_2O$
11	6	0	H	CH_3	137-9	(95% EtOH)	95	--
12	6	0	H	H	186-8	(MeOH/H_2O)	85	6-LICAM
13	6	2	SO_3H	H	253-4d	(H_2O)	48	6-LICAMS·$2H_2O$

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9. The structures, as well as our abbreviated nomenclature for some of the title compounds appears in Table I. For IUPAC names see Experimental Section. Our system of abbreviation, based on CAM as an acronym for Catechol AMide, uses prefixes CY and LI to indicate a cyclic or linear compound, respectively. The numbers in the prefix indicate the length of the methylene chains connecting the CAM moieties and, should letters appear in the prefix, they indicate N-terminal substituents in a linear compound. The suffix indicates substituents on each benzene ring of the CAM ligand.

10. For a discussion of the direct sulfonation of aromatic hydrocarbons, see Adams, R., editor, Organic Reactions, Vol. 3 (John Wiley & Sons, Inc., NY, 1946), pp. 141-197.

11. The two highest symmetry coordination geometries for eight coordination are D_{4d} (Archimedian antiprism) or D_{2d} (trigonal-faced dodecahedron). We have found the latter in the $[Ac(cat)_4]^{4-}$ structure.

12. P.W.Durbin, to be submitted for publication.

13. $CaNa_3DTPA$ is the complex salt agent presently used in the treatment of actinide ion poisoning in humans.

14. Weitl, F.L.; Raymond, K.N., J. Am. Chem. Soc., 1979, in press.
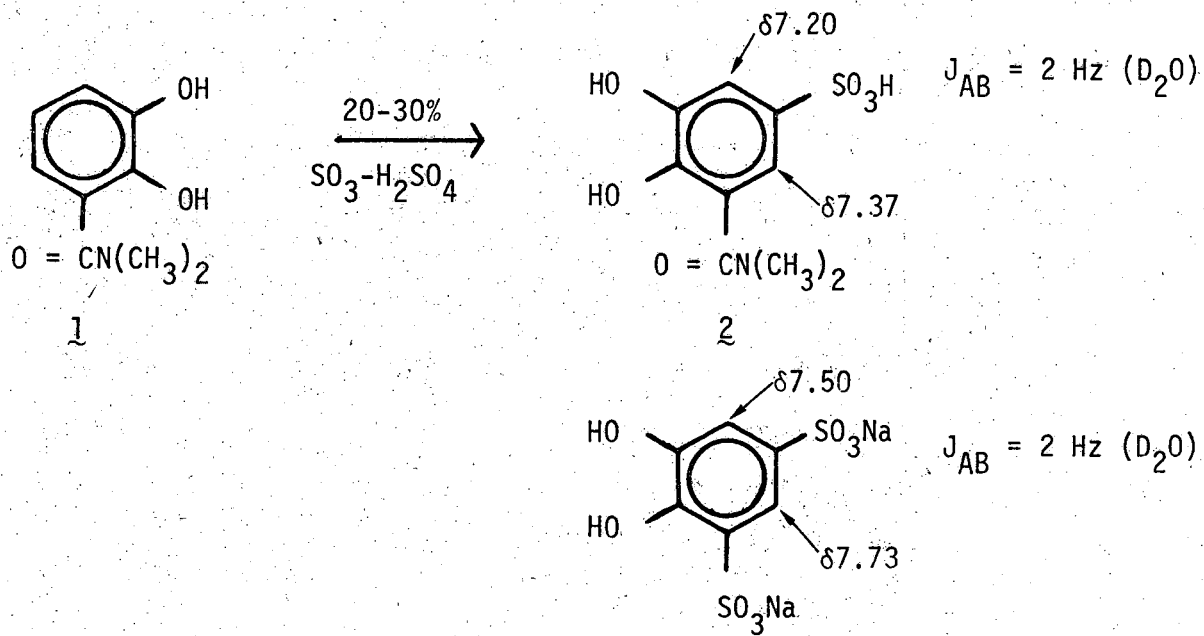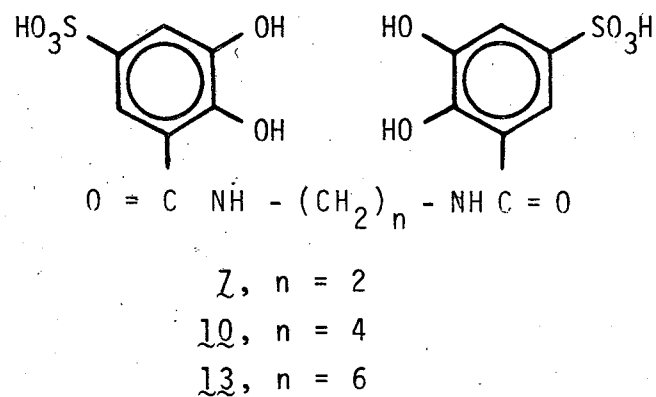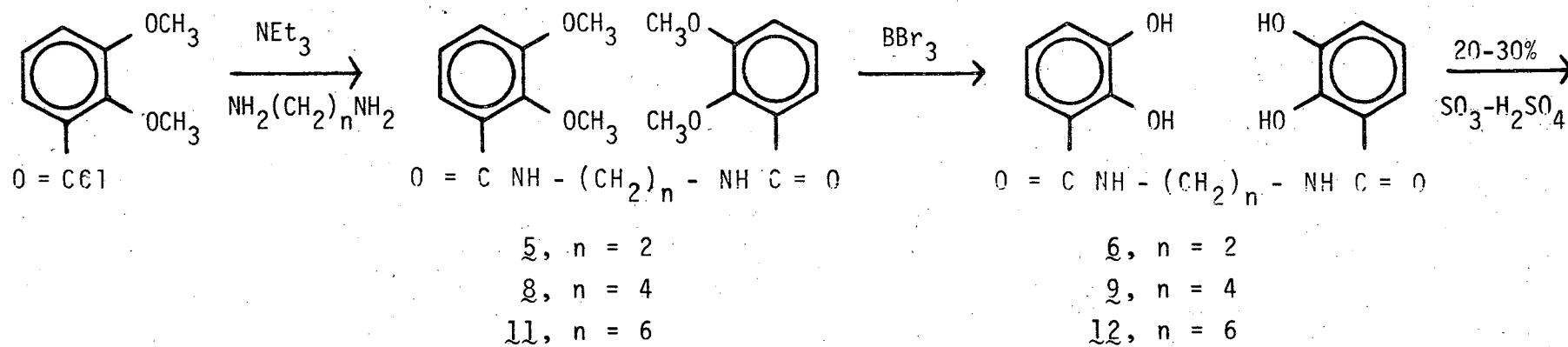
Figure 1. Quantitative, regiospecific, 5-sulfonation of 1.

Figure 2. Synthesis of dimeric 2,3-dihydroxy-5-sulfobenzamides and precursors.