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August 1993

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IN VIVO CHELATION OF Am(III), Pu(IV), Np(V) and U(VI) IN MICE BY TREN-(Me-3,2-HOPO)*

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ABSTRACT

Octadentate 3,4,3-LI(1,2-HOPO), composed of the acidic hydroxypyridine isomer, 1,2-HOPO, is the most effective ligand yet prepared for *in vivo* chelation of Pu(IV) and Am(III), but it is difficult to prepare and acutely toxic. Hexadentate TREN-(Me-3,2-HOPO), composed of the less acidic Me-3,2-HOPO isomer, can be produced in relatively large quantities. TREN-(Me-3,2-HOPO) (30 $\mu mol.kg^{-1}$ injected intraperitoneally in mice 3 min to 1 h after intravenous injection of an actinide) removed significant body Pu(IV), Am(III), Np(V), or U(VI) (compared with controls), and those actinide reductions were significantly greater than were obtained with $CaNa_3$-DTPA. TREN-(Me-3,2-HOPO) was almost as effective for reducing body Pu(IV) as 3,4,3-LI(1,2-HOPO). TREN-(Me-3,2-HOPO) is of low acute toxicity in mice and its clinical potential, as a practical compromise between the effectiveness of 3,4,3-LI(1,2-HOPO) and the safety of $CaNa_3$-DTPA, merits further investigation.

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* This work was supported by the Director, Office of Energy Research, Office of Basic Energy Sciences, Chemical Sciences Division, U.S. Department of Energy under contract number DE-AC03-76F00098, the National Institute of Environmental Health Sciences grant number ES02698, and the U.S. Armed Forces Radiation Research Institute.

INTRODUCTION

Efficient ligands for the actinides are needed to accelerate their excretion from internally contaminated persons and reduce radiation and chemical damage and cancer risk in tissues that sequester them. Similar coordination behavior of Pu(IV) and Fe(III) suggested an experimental approach -- incorporation of high affinity Fe(III) binding groups into macromolecules spatially configured for stable binding of Pu(IV).[1] The most effective ligand yet prepared for Pu(IV) is octadentate 3,4,3-LI(1,2-HOPO), composed of the hydroxypyridinone isomer, 1,2-HOPO. Its potency for *in vivo* chelation of Pu(IV) and also Am(III), exceeds clinically accepted $CaNa_3$-DTPA in all tests in mice and rats.[2-6] However, it is acutely toxic: dosages ≥500 $\mu mol.kg^{-1}$ destroyed hepatic and renal tubule cells, and 50 to 100% of mice died in 8 d.[2] Multiple injections of 30 $\mu mol.kg^{-1}$ in rats produced lesions (possibly not reversible) in both tissues.[4] Starting materials for 3,4,3-LI(1,2-HOPO) are expensive and yields are small.[2] Several new ligands, composed of the less acidic Me-3,2,-HOPO isomer[7], have been prepared.[8] Easy synthesis and high yield of hexadentate TREN-(Me-3,2-HOPO), Figure 1, made it a good candidate for initial evaluation of *in vivo* chelation of Pu(IV) by ligands composed of Me-3,2-HOPO.

In vivo chelation of Am(III) by 3,4,3-LI-(1,2-HOPO) was demonstrated.[4-6] The structurally analogous tetracarboxycatecholate [CAM(C)], 3,4,3-LICAM(C), augmented excretion of Np(V).[3,9] Acute toxicity of UO_2^{2+} was reduced by Tiron, a sulfocatecholate [CAM(S)] monomer.[10,11] Those observations stimulated investigation of *in vivo* chelation of Am(III), Np(V), and U(VI) by TREN-(Me-3,2-HOPO).

METHODS

TREN-(Me-3,2-HOPO) [N,N′,N′′-Tris((1,2-didehydro-3-hydroxy-1-methyl-2-oxopyrid-4-yl-(carbonyl)-2,2′,2′′-triaminotriethyleneamine, Figure 1] was synthesized.[8] $CaNa_3$-DTPA was obtained as a 25% solution. Ligands were dissolved in 0.14 mol.L^{-1} NaCl, pH 7.1: 0.5 mL contained the standard dosage of 30 μmol. kg^{-1} for a 35 g mouse. Actinide solutions were prepared such that 0.2 mL administered to a mouse contained the following radioactivities and metal masses: ^{238}Pu(IV) (1.8 kBq, 0.003 μg) or ^{241}Am(III) (1.1 kBq, 0.25 μg) in 0.0084 mol.L^{-1} sodium citrate and 0.09 mol.L^{-1} NaCl, pH 4; $^{237}NpO_2Cl$ (0.1 to 0.3 kBq, 5 to 10 μg) or $^{232}UO_2Cl_2$ (0.15 kBq plus $^{234,235}UO_2Cl_2$ 3.6 μg) in 0.14 mol.L^{-1} NaCl, pH 4. The ^{232}U was used within 10 d after ion-exchange separation from its daughters. At the standard ligand dosage (30 μmol.kg^{-1}), molar ratios of administered ligand to administered metal are, as follows: ^{238}Pu, 9 x 10^4; ^{241}Am, 3 x 10^4; ^{237} Np, 25 to 50; total U, 70.

Female Swiss-Webster mice (85 d, 35 g) in groups of five were each injected (0.2 mL) with an actinide into a tail vein (i.v.) under light anesthesia* Ligands (0.5 mL) were given intraperitoneally (i.p.) or orally by gastric tube. Actinide-injected controls were given a saline injection or intubation. Actinine-removal protocols are, as follows: *prompt injection, dosage-effectiveness* -- ligand i.p. 3 min. to 1 h after actinide (more concentrated or dilute solutions used for dosage-effectiveness groups), kill at 24 h; *delayed injection* -- ligand i.p. 24 h after actinide, kill at 48 h; *prompt oral administration* -- mice fasted about 16 h, ligand by gastric tube, 3 min. after actinide, kill at 24 h.

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* Animal work approved by Lawrence Berkeley Laboratory Animal Welfare and Research Committee (protocol 1703, Sept. 30, 1992), in accordance with USPHS Policy on Human Care and Use of Laboratory Animals.

Autopsy, sample preparation, and radioanalysis procedures have been published for studies with ^{238}Pu and ^{241}Am.[2,3,11-13] Similar procedures were used for ^{237}Np and ^{232}U studies, except that radioanalysis was by liquid scintillation counting. "Significant" is used throughout in the statistical sense, t-test, $p \leq 0.01$.[14]

RESULTS

Distribution of Pu in tissues and excreta of mice given TREN-(Me-3,2-HOPO) are shown in Table I: For comparison, results obtained in the same protocols with 3,4,3-LI(1,2-HOPO), 3,4-LI(1,2-HOPO), or $CaNa_3$-DTPA are included.[2,3] Removal of Pu as a function of TREN-(Me-3,2-HOPO) dosage is compared in Figure 2 with published results for 3,4,3-LI(1,2-HOPO) and $CaNa_3$-DTPA.[3] If ligand was given when much of the Pu was circulating (i.p. at 1 h or oral at 3 min), potency of TREN-(Me-3,2-HOPO) for removing Pu from mice was significantly greater than $CaNa_3$-DTPA or 3,4-LI(1,2-HOPO) and about the same as 3,4,3-LI(1,2-HOPO). If ligand was given after most of the Pu was deposited in tissues (i.p. at 24 h), potency of TREN-(Me-3,2-HOPO) for removing Pu was significantly greater than $CaNa_3$-DTPA but less than that of 3,4,3-LI(1,2-HOPO). Ligand potencies for removing Pu from mice were generally in the order of effectiveness at low dosages: 3,4,3-LI(1,2-HOPO) $\geq$ TREN-(Me-3,2-HOPO) > $CaNa_3$-DTPA.

Distributions of Am, Np, or U in tissues and excreta of mice treated with TREN-(Me-3,2-HOPO) or $CaNa_3$-DTPA are shown in Table II. Injection of TREN-(Me-3,2-HOPO) when much of the injected actinide is still circulating (i.p. at 3 to 5 min after actinide), significantly reduced Am in all tissues and total body, Np in liver and total body, and U in kidneys and total body compared with their appropriate actinide-injected controls. All of those reductions of total body actinide were significantly greater than was achieved with $CaNa_3$-DTPA. Greater reductions of total body Np or U should be achievable with larger ratios of ligand to metal.

Large fractions of the Am, Np, or U excretion promoted by TREN-(Me-3,2-HOPO) were fecal, providing convincing evidence for *in vivo* chelation.

In mice, TREN-(Me-3,2-HOPO) is of low acute toxicity.[8] The toxicological findings can be summarized, as follows: Mice injected i.p. with 1000 μmol. kg^{-1} (two equal fractions 8 h apart or 10 equal fractions daily for 10 d, 10 to 20 mice per group) all survived the 10 to 20 d observation period; weight gain was normal; kidneys and livers were normal weight and appearance at autopsy; blood urea N was nearly the same as for saline-injected controls.

DISCUSSION

TREN-(Me-3,2-HOPO) forms transportable complexes *in vivo* with actinide ions in all four principal oxidation states. As judged by the small actinide residues in kidneys (kidney actinide was less than controls in all procedures), actinide-TREN-(Me-3,2-HOPO) complexes are stable at physiological pH. Speciation calculations, which indicate deprotonation of all three Me-3,2-HOPO groups and formation of a stable hexadentate Pu(IV)-(Me-3,2-HOPO) complex over the pH range 4.8 to 8, suggest that TREN-(Me-3,2-HOPO) should be effective for mobilizing Pu deposited in the lung.

Polydentate CAM(C) or CAM(S) ligands do not complex Am(III) stably at physiological pH.[13] However, stable Am(III) complexes form readily at pH 7.4 with the more acidic HOPO groups, probably because the Am(III) ion need not deprotonate HOPO before binding. The crystal structure of the chemically analogous Gd(III)-TREN-(Me-3,2-HOPO) predicts that actinide(III) ions will form complexes of similar structure and stability in the physiological pH range.[15]

Significant reductions in body Np and U and kidney U were achieved with TREN-(Me-3,2-HOPO). Skeletal deposits of Np and U were apparantely inaccessible to the ligand, but 65 and 55%, respectively, of Np or U still circulating or loosely

bound in soft tissue was eliminated in excess of control excretion. Both Np(V) and U(VI) (NpO_2^+ and UO_2^{2+}, respectively) are linear dioxo cations, O=M=O, that bind bidentate anions equatorially in the plane perpendicular to the oxo oxygens. Complexes of U(VI) with bidentate anions are relatively stable, and the U(VI) complexes formed *in vivo* with the bidentate HOPO group are also expected to be equatorial. The lower charge on the NpO_2^+ ion leads to weaker and less stable complexes with bidentate anions than those formed by U(VI), however, Np(IV) complexes are as stable as those of Pu(IV). The biological evidence suggests that some of the injected Np(V) was reduced to Np(IV) at physiological pH in the presence of sufficient concentrations of high affinity biological or therapeutic ligands: (a) Skeleton and liver Np deposits at 24 h greatly exceeded those of U(VI) and resembled the distribution pattern of Pu(IV); (b) Np was stably bound by TREN-(Me-3,2-HOPO); (c) A larger fraction of accessible Np than of U(VI) was chelated by TREN-(Me-3,2-HOPO), and excretion of the chelated Np was predominantly fecal, resembling the excretory pattern of the Pu (IV) complex. The mechanism of stable Np chelation is likely to be ligand-facilitated reduction of Np(V) to Np(IV), because Np(IV) forms complexes many orders of magnitude more stable than those of Np(V).[16,17]

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Table I. Reduction of intravenously injected $^{238}Pu(IV)$ in body and tissues of mice by TREN-(Me-3,2-HOPO) compared with 3,4,3-LI(1,2-HOPO) and $CaNa_3$-DTPA.[a,b]

Ligand and treatment mode	Percent of injected $^{238}Pu \pm SD$[c,d]						
	Skeleton	Liver	Kidneys	Residual soft tissue	Total body	Urine	Feces and GI contents
Injection ip at 1 h							
TREN-(Me-3,2-HOPO)[a]	8.1 ± 1.3 [e]	3.8 ± 0.8	1.1	1.4 ± 0.7	14 ± 2.2[e]	30	55
TREN-(Me-3,2-HOPO)	11 ± 0.9	4.4 ± 1.2	0.5	2.3 ± 0.6	18 ± 1.8	30	52
3,4-LI(1,2-HOPO)	9.9 ± 3.6	18 ± 4.8[f]	0.6	5.8 ± 1.3[f]	34 ± 9.2[f]	7.9	58
3,4,3-LI(1,2-HOPO)	7.5 ± 0.7[g]	8.9 ±1.7[f]	0.2	1.6 ± 0.6	18 ± 1.7	24	57
$CaNa_3$-DTPA	12 ± 2.2	17 ± 3.7[f]	1.1	3.5 ± 1.6	33 ± 6.3[f]	62	5.5
Injection ip at 24 h							
TREN-(Me-3,2-HOPO)	36 ± 5.2	32 ± 6.6	0.6	5.7 ± 1.0	74 ± 1.2	11	14
3,4,3-LI(1,2-HOPO)	20 ± 3.2[g]	28 ± 8.9	0.6	4.9 ± 1.0	54 ± 7.6[g]	8.4	37
$CaNa_3$-DTPA	27 ± 5.3	45 ± 6.9[f]	0.9	5.6 ± 0.8	79 ± 3.1[f]	12	9.3
Gastric intubation at 3 min							
TREN-(Me-3,2-HOPO)	15 ± 4.4	9.0 ± 4.5	0.7	2.4 ± 1.2	27 ± 9.0	31	42
3,4,3-LI(1,2-HOPO)	12 ± 2.4	11 ± 4.9	0.1	1.3 ± 0.7	24 ± 7.7	26	51
$CaNa_3$-DTPA	35 ± 2.7[f]	45 ± 2.4[f]	1.1	4.1 ± 0.7	85 ± 1.8[f]	9.5	5.0
Pu-injected controls							
Kill at 24 h (fed)	31 ± 7.4	50 ± 8.0	1.8	8.0 ± 2.3	91 ± 6.1	4.2	4.8
Kill at 24 h (fasted)	39 ± 7.7	44 ± 2.4	1.7	6.1 ± 1.0	90 ± 2.6	5.1	4.5
Kill at 48 h	29 ± 7.0	48 ± 7.7	0.8	8.1 ± 2.5	86 ± 4.6	7.2	6.9

(a) 30 $\mu mol.kg^{-1}$ of ligand except for first entry, 100 $\mu mol\ kg^{-1}$ of TREN-(Me-3,2-HOPO).

(b) All ligand treatments significantly reduced Pu in body and tissues compared with appropriate controls, except for orally administered $CaNa_3DTPA$ (t-test, $p \leq 0.01$) [14].

(c) Groups of five mice except: TREN-(Me-3,2-HOPO) ip at 1 h, 10; $CaNa_3$-DTPA ip at 1 h, 15; fed 24 h controls, 140; fasted 24 h controls, 15; 48 h controls, 10. Results are expressed at percent of injected ^{238}Pu (%ID) normalized to 100% material recovery, discrepancies are due to rounding.

(d) Standard deviation, $SD = [\Sigma dev^2(n-1)^{-1}]^{1/2}$. Kidneys and excreta were pooled for each five-mouse group.

(e) Significantly improved Pu reduction than for mice given 30 $\mu mol\ kg^{-1}$ of TREN-(Me-3,2-HOPO).

(f) Significantly poorer Pu reduction than for mice given TREN-(Me-3,2-HOPO) in same protocol.

(g) Significantly improved Pu reduction than for mice given TREN-(Me-3,2-HOPO) in same protocol

Table II. Reduction of intravenously injected $^{241}Am(III)$, $^{237}Np(V)$, or $^{232, 234, 235}U(VI)$ in body and tissues of mice by TREN-(Me-3,2-HOPO) compared with $CaNa_3$-DTPA.[a]

Percent of injected actinide ± SD[b,c]

Ligand, actinide	Skeleton	Liver	Kidneys	Residual soft tissue	Total body	Urine	Feces and GI contents
Am(III)							
TREN-(Me-3,2-HOPO)	8.1 ± 1.6[d]	1.0 ± 0.6[d,e]	0.2	1.6 ± 0.6[d]	11 ± 1.4[d,e]	51	38
$CaNa_3$-DTPA	8.5 ± 0.9[d]	13 ± 1.5[d]	0.4	1.9 ± 0.3[d]	24 ± 1.3[d]	68	8.0
Am controls, kill 24 h	27 ± 5.3	50 ± 5.3	1.2	5.7 ± 0.7	84 ± 3.7	14	2.6
Np(V)							
TREN-(Me-3,2-HOPO)	34 ± 4.5	3.8 ± 5.7[d,e]	1.0	3.1 ± 1.1	42 ± 11[d,e]	40	17
$CaNa_3$-DTPA	40 ± 4.4	14 ± 5.7	1.3	3.5 ± 0.9	58 ± 8.0	40	1.5
Np controls, kill 24 h	37 ± 5.1	14 ± 2.3	1.7	5.8 ± 2.3	59 ± 4.1	<41> [f]	
U(VI)							
TREN-(Me-3,2-HOPO)	16 ± 2.4	0.6 ± 0.3	9.4 ± 6.0[d,e]	1.6 ± 0.3	27 ± 8.5[d,e]	70	2.3
$CaNa_3$-DTPA	19 ± 3.0	1.0 --	17 ± 2.8	2.2 ± 0.1	38 ± 0.7	<62> [f]	
U controls, kill 24 h	17 ± 2.5	1.4 --	19 ± 6.9	2.8 ± 0.5	40 ± 7.8	<60> [f]	

(a)(

(a) Ligands (30 $\mu mol.kg^{-1}$) i.p at 3 to 5 min after actinide i.v.; kill at 24 h.

(b) Groups of five mice except: TREN-(Me-3,2-HOPO) ip at 3 min after ^{241}Am, 10; 24 h Am, Np, or U controls, 10. Results are expressed as percent of injected actinide (%ID) normalized to 100% material recovery, discrepancies are due to rounding.

(c) Standard deviation, $SD = [\Sigma dev^2(n - 1)^{-1}]^{1/2}$. Kidneys of Am- and Np-injected mice, livers of some U-injected groups, and all excreta were pooled for each five-mouse group.

(d) Significantly less actinide than appropriate controls (t-test, $p \leq 0.01$) [14].

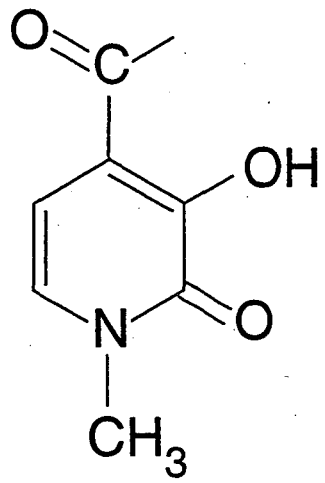
(e) Significantly improved actinide reduction than for mice given $CaNa_3$-DTPA in same protocol.

(f) Combined excreta.

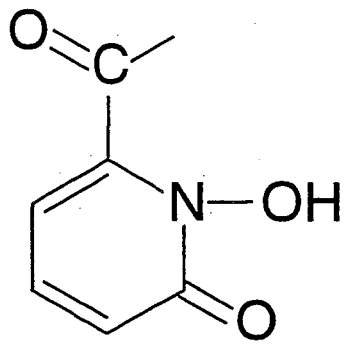
FIGURE LEGENDS

Figure 1. Molecular structure of Me-3,2-HOPO and 1,2-HOPO hydroxypyridinone isomers, TREN-(Me-3,2-HOPO), and 3,4,3-LI(1,2-HOPO).

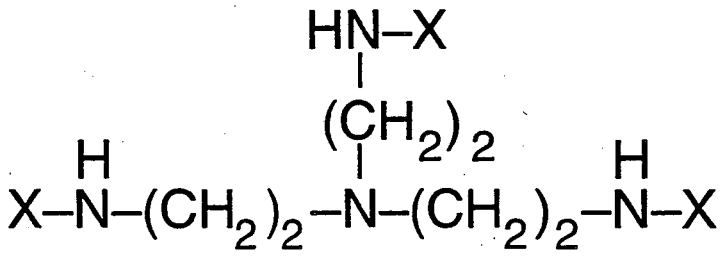
Figure 2. Dosage-effectiveness in mice of TREN-(Me-3,2-HOPO) compared with 3,4,3-LI(1,2-HOPO) and $CaNa_3$-DTPA[3].



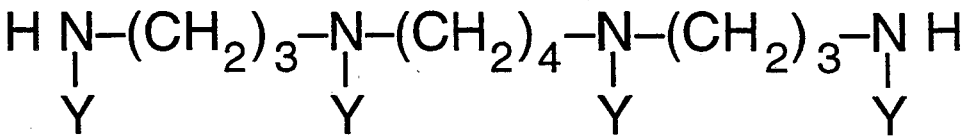
3,2-HOPO



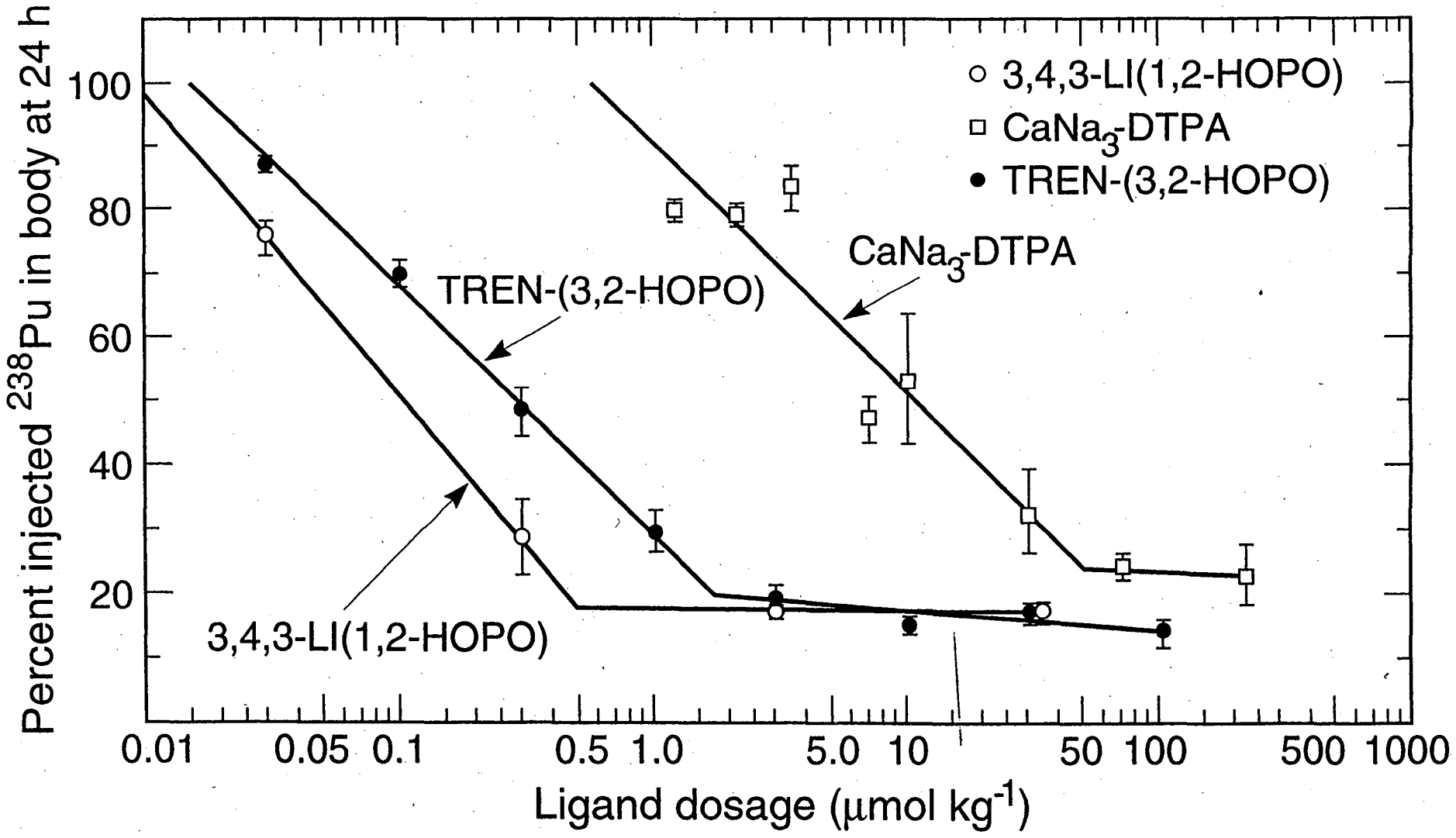
1,2-HOPO



TREN-(3,2-HOPO) X = 3,2-HOPO



3,4,3-LI(1,2-HOPO) Y = 1,2,-HOPO


Percent injected 238Pu in body at 24 h
100
80
60
40
20
0.01
0.05
0.1
0.5
1.0
5.0
10
50
100
500
1000
Ligand dosage (μmol kg-1)
3,4,3-LI(1,2-HOPO)
CaNa3-DTPA
TREN-(3,2-HOPO)
CaNa3-DTPA
TREN-(3,2-HOPO)
3,4,3-LI(1,2-HOPO)

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