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## Lead(II) and Bismuth(III) Complexes of the Polyazacycloalkane-*N*-acetic Acids nota, dota, and teta†

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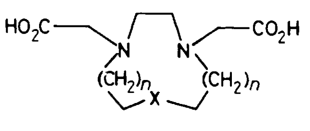
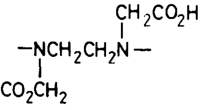
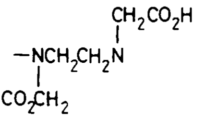
Lead(II) and bismuth(III) complexes of nota, dota, and teta were synthesized and their kinetic properties were investigated to show that the dota complexes are the most inert over the pH range 4—12 and 1—10 for lead and bismuth, respectively.

Of the radionuclides with physical properties most suited for use with monoclonal antibody in nuclear medicine for tumour imaging or therapy,[1,2] few are more available or desirable than $^{203}Pb$ and $^{212}Pb$.‡ The 279 keV γ-emission of $^{203}Pb$ ($t_{1/2}$ 52.1 h) is ideal for single photon emission computed tomography (SPECT)[3] while $^{212}Pb$ ($t_{1/2}$ 10.6 h) could serve as a source for its highly cytotoxic α-emitting daughter, $^{212}Bi$ ($t_{1/2}$ 1 h).[4—6] That no clinical studies have yet been possible is due entirely to the lability of known lead complexes. In contrast, despite their less than optimal decay characteristics, extensive use has been made of complexes of the radionuclide $^{111}In$ in radioimmunoimaging[7—9] and, recently, $^{90}Y$ for radioimmunotherapy.[10] These radionuclides do form inert complexes with acyclic polyamine polycarboxylate ligands such as dtpa.[11]



| | *n* | X | Compound |
|---|---|---|---|
| (1) | 1 | $-NCH_2CO_2H$ | $H_3$nota |
| (2) | 1 |  $-N(CH_2CO_2H)CH_2CH_2N(CH_2CO_2H)-$ | $H_4$dota |
| (3) | 2 |  $-N(CH_2CO_2H)CH_2CH_2N(CH_2CO_2H)$ | $H_4$teta |
| (1a-3a) | | | $Pb^{II}$ complexes of (1)-(3) |
| (1b-3b) | | | $Bi^{III}$ complexes of (1)-(3) |

In the hope of providing inert chelates of $Pb^{II}$ and $Bi^{III}$, we prepared and investigated the kinetic properties of their nota (**1**), dota (**2**), and teta (**3**) complexes.† Literature equilibrium formation constant measurements[12—15] indicated that each ligand co-ordinated to divalent metal ions with unusual stability. Here we report that $Pb^{II}(dota)^{2-}$ is inert to dissociation at pH 4—12, and $Bi^{III}(dota)^-$ is shown to be inert in acid except in concentrated HCl or above pH 10.

Microcrystalline samples of complexes of dota with $Pb^{II}$ (**2a**) or $Bi^{III}$ (**2b**) were prepared by heating the aqueous nitrate salts at 80 °C with stoicheiometric quantities of ligand with slow addition of NaOH until pH 10. Neutralization with base and addition of ethanol precipitated the complex. After purification by elution from Chelex 100 ion exchange resin with water as eluant, evaporation and precipitation with ethanol yielded the desired product, $Na_2[Pb(dota)]$. $2H_2O$ or $Na[Bi(dota)]$.-$H_2O$. Samples were analysed by microanalytical data and were characterized by $^1H$ n.m.r. and by $^{252}Cf$ plasma desorption mass spectroscopy (PDMS).§

Alternatively, each of the complexes (**1a**—**3a**) and (**1b**—**3b**) may be formed *in situ* by mixing a 5% excess of the ligand with respect to the nitrate salt and raising the pH of the mixture very slowly to 9. The complex formed was filtered through a

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† Abbreviations used: $H_3$nota = 1,4,7-triazacyclononane-*N*,*N*′,*N*″-triacetic acid, $H_4$dota = 1,4,7,10-tetra-azacyclododecane-N,*N*′,*N*″,*N*‴-tetra-acetic acid; $H_4$teta = 1,4,8,11-tetra-azacyclotetradecanetetra-acetic acid.

‡ $^{203}Pb$ is a byproduct of $^{201}Tl$, the largest selling radionuclide. $^{212}Pb$ is a natural product as well as a byproduct of $^{232}U$ production.

§ $^1H$ n.m.r. for (**2a**) (500 MHz, $D_2O$, pD 8) 3.76 (s, 4H), 3.41 (s, 4H), 3.31 (s, 4H), 3.15 (s, 4H), 2.80 (s, 4H), for (**2b**) (500 MHz, $D_2O$, pD 7.5) 4.28 (s, 4H), 3.45 (s, 16H), 3.28 (s, 4H). $^{252}Cf$ PDMS for (**2a**) (positive ions, methanol spray): *m/z* 677.2 [(**2a**) + $3Na^+$], 655.2 [(**2a**) + $H^+$ + $2Na^+$], 515.2 [(**2**) + 5 $Na^+$]. For (**2b**) (positive ions, methanol spray): *m/z* 648.1 [(**2b**) + $K^+$], 550.4 [(**2b**) − $CH_2COO^-$ + $H^+$], 463.6 [(**2**) + $K^+$ + $Na^+$ − $H^+$].

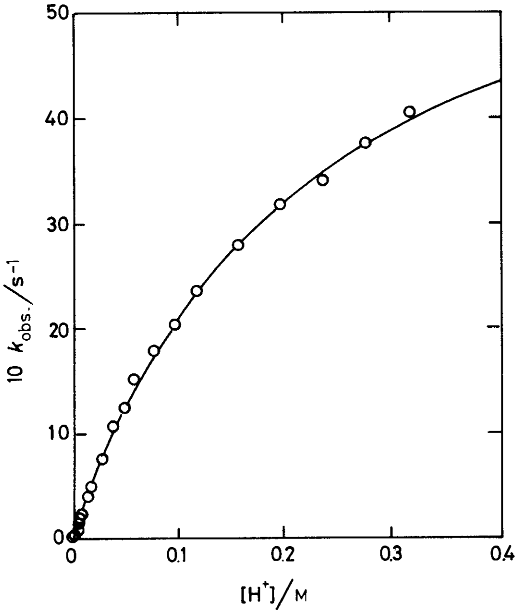

**Figure 1.** Pseudo-first-order rate constants as a function of acid concentration for the dissociation of Pb(Hdota)$^-$ at 25 °C and $\mu$ = 1.0 M. Solid line is the calculated line based on resolved rate constant [$k = (6.89 \pm 0.18) \times 10^{-4}\ s^{-1}$] and equilibrium constant [$K_H = (4.35 \pm 0.20)\ M^{-1}$].

0.45 μm filter to remove any M(OH)$_n$ formed. Formation of these complexes is stoicheiometric and easily observed by measurement of distinct u.v. absorption bands at 255, 257, and 270 nm with molar extinction coefficients of 7100, 10 000, and 6800 dm$^3$ mol$^{-1}$ cm$^{-1}$ for the lead complexes of (**1**), (**2**), and (**3**), respectively. Similarly, the complexes of (**1**), (**2**), and (**3**) with Bi$^{III}$ can be characterized by u.v. bands at 285, 305, and 323 nm with molar extinction coefficients of 6080, 6300, and 5400 dm$^3$ mol$^{-1}$ cm$^{-1}$, respectively.

When placed in 0.01 M perchloric acid, solutions of (**1a**) and (**3a**) decomposed during the mixing time of the two solutions, as shown by the complete disappearance of their u.v. absorptions. Conversely, a similar solution of (**2a**) shows an instantaneous small change (*ca.* 5—15%) in absorbance followed by a slow, time-dependent decrease to near zero, thus permitting measurements of acid-catalysed dissociation. No change at all in absorbance is detected for (**2b**) when maintained for a month in 1 M perchloric acid at 25 °C. Under similar conditions, (**1b**) was decomposed slowly, and (**3b**) instantaneously, to metal and protonated ligand.

A careful study of the acid dependence of the rapid absorbance decrease revealed the protonation of (**2a**) to form Pb(Hdota)$^-$, which subsequently dissociates to Pb$^{II}$ and protonated ligand. In Figure 1, a plot of pseudo-first-order rate constants for dissociation of Pb$^{II}$ (Hdota)$^-$ as a function of acid concentration is shown. From this study it is evident that Pb$^{II}$(dota)$^{2+}$ is the most inert complex of lead known so far in the literature.[16] Based on the estimated formation rate and equilibrium constants for this complex, one would predict a half-life for the dissociation of (**2a**) at pH 7 of greater than several years,[¶] long compared to half-lives of $^{203}$Pb and $^{212}$Pb. No absorbance change was observed for three months in the solutions of (**2a**) in the pH range of 4—9 in a well buffered medium.[††] Similarly, the very short half-life of $^{212}$Bi compared to the kinetic inertness of (**2b**) argues well for its use *in vivo*. Studies are underway to investigate whether the weak β transition from $^{212}$Pb to $^{212}$Bi compromises the integrity of dota complexes.[‡‡] Methods for linkages of lead and bismuth dota to immunoproteins are under investigation. The 1-(*p*-isothiocyanatobenzyl) derivative of dota has been synthesised.[17]

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[¶] It is assumed that the formation rate of (**2a**) is diffusion controlled and can be used to calculate the dissociation rate constant from the stability constant of (**2a**).[12] Alternatively, one can calculate $k_r$ from $k_{ex}$ for Pb$^{II}$(H$_2$O)$_n$ and $K_{os}$. A rough estimate for proton catalysed rate at pH 7.0 can also be made from conditional equilibrium constant and formation rate constant, $k_f$.

[††] Buffers used (pH in parentheses): acetate (3.80, 5.08), MES (5.94), MOPS (7.14), HEPES (8.10), and TRIS (8.80). Conditions used are [Pb(dota)] = $2.22 \times 10^{-5}$ M, [Buffer] = 0.050 M, $\mu$ = 1 M (NaClO$_4$).

[‡‡] We note that the maximum recoil energy of $^{212}$Bi upon formation from the maximum β-decay energy (568 keV) of $^{212}$Pb is 2.3 eV, which is less than the energy of one divalent metal–nitrogen co-ordinate covalent bond.