# Synthesis of Charged and Uncharged Complexes of Gadolinium and Yttrium with Cyclic Polyazaphosphinic Acid Ligands for *in vivo* Applications

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The synthesis of 18 new macrocyclic complexing agents incorporating phosphinic acid (and carboxylic acid) groups is reported, based on the 1,4,7,10-tetraazacyclododecane ring. Through selective functionalisation of one ring nitrogen or by changing the nature of the P-substituent, anionic, neutral and cationic complexes of yttrium and gadolinium may be prepared of varying lipophilicity. Diamagnetic complexes have been characterised by $^{1}H$, $^{31}P$ and $^{89}Y$ NMR spectroscopy, and the rate of uptake of $^{90}Y$ of selected ligands compared. The kinetics of dissociation of nine gadolinium complexes has been measured in the pH range 1–2 using $^{153}Gd$-labelled complexes. Charge-neutral complexes dissociate more slowly than their anionic analogues, and the phosphinate complexes, although slightly less stable than their carboxylate analogues, are nevertheless sufficiently kinetically inert for *in vivo* applications.

The common theme which has unified our recent studies of the behaviour of metal complexes and their conjugates *in vivo* is that the complexes should be kinetically inert with respect to acid- or cation-promoted dissociation pathways.[1] This has been apparent in the development of antibody conjugates radiolabelled with copper,[2] indium or gallium,[3] and yttrium[4] ($^{90}Y$, $\beta^-$, $t_{\frac{1}{2}}$ 64 h) for effective tumour targeting. In radioimmunotherapy with $^{90}Y$-labelled conjugates, the need for high kinetic stability is particularly acute. Premature decomplexation of $^{90}Y$ (mediated by acid catalysis and/or cation assisted pathways),[5] severely limits the dose which may be administered of this therapeutic isotope due to localisation of $^{90}Y$ in the bone/bone-marrow resulting in, for example, myelosuppression.[1] A similar limitation in the amount of complex which can be administered is encountered in the use of paramagnetic gadolinium complexes which are used in magnetic resonance imaging (MRI) as contrast agents.[6] The aquo-gadolinium ion is also bone-seeking and toxic (in animals) ($LD_{50}$ in mice/rats of 0.38 mmol $kg^{-1}$) and is given to a patient in the form of a stable complex (e.g. $[Gd.DTPA]^{2-}$ or $[Gd.DOTA]^-$, where typically a solution containing 6–8 g of the complex is injected). The object of current research in this area is to devise methods of targeting the paramagnetic complex to selected tissues, and a first step in this direction has been the discovery that gadolinium complexes of certain analogues of DTPA (*e.g.* BOPTA[7] and EOBDTPA)[8] clear *via* the biliary system rather than the renal system. Although DTPA-based ligands are widely used for this purpose, they are *not* totally kinetically inert *in vivo*, and the gadolinium complex (and to a greater extent $^{90}Y$ complexes) dissociates measurably resulting in deposition of gadolinium (or $^{90}Y$) in the liver and skeleton.[9]‡ It is generally accepted that the complexes of Gd and Y with macrocyclic ligands are more kinetically stable *in vivo* than DTPA-based ligands, and should therefore avert any long term (*i.e.* chronic, rather than acute) toxicity problems.

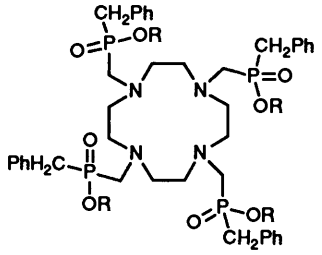
With this in mind, we have been studying the properties of a series of azaphosphinic acid macrocyclic ligands[10] based on the tetraazacyclododecane (12-$N_4$) skeleton which is found in DOTA. An intrinsic advantage of the $>NCH_2PRO_2H$ moiety (over $CH_2CO_2H$) is that structural variation is readily achieved at the P–R group, allowing for example easy linkage to a protein and control over ligand and complex lipophilicity. A series of charged (anionic and cationic) and neutral yttrium and gadolinium complexes has been prepared, with the objective of defining the structural and electrostatic features which determine the *in vivo* biodistribution. The synthesis and complexation behaviour of these ligands is reported herein, while the biodistribution results are being described elsewhere.[9] A preliminary account of some of this work has appeared.[11,12]

## Results and Discussion

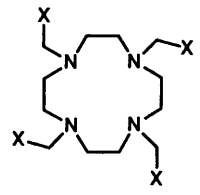
*Ligand Syntheses.*—The synthesis of the symmetrically substituted tetraphosphinic acid derivatives, **1–3**, followed the methods described in our earlier reports.[11–13] Condensation of paraformaldehyde and tetraazacyclododecane in dry tetrahydrofuran led to successive formation of the imine which was trapped by the appropriately substituted dialkoxyphosphine, $RP(OR')_2$ to yield, after an Arbuzov rearrangement, the tetraphosphinate esters, **1a–3a**. Acid hydrolysis (6 mol $dm^{-3}$ HCl, 110 °C) yielded the aminophosphinic acid, usually as the dihydrochloride salt, although the benzylphosphinic acid **1a** could be recrystallised from methanol to yield the zwitterion. In the case of the methylphosphinate reaction, the trisubstituted derivative **4** was also isolated in moderate yield, following chromatographic separation of the tetraester. This allows, in principle, the synthesis of a wider range of tribasic phosphinate ligands wherein the eighth coordination site can be varied by alkylation of the unique secondary amine in **4**. Clearly many different functional groups can be introduced at this stage, but in order to ligate effectively to the bound polarising trivalent cation, an amide carbonyl group is most appropriate, and offers further flexibility in respect of variation of the substituents at nitrogen (*e.g.* for linkage, or introduction of additional lipophilic groups). Reaction of **4** with *N*-methyl-2-bromoethanamide (DMF, $K_2CO_3$), **5**, gave the monoamide **6a** (63%) which was hydrolysed (KOH, $H_2O$) to the triphosphinic acid **6b** at room temperature. A limitation of this strategy is the poor yield (24%) of the triphosphinate **4**, which is itself simply an intermediate in the synthesis of the tetraphosphinates. A more

† *Present address:* MRC Radiobiology Unit, Chilton, Didcot, OX11 0RD.

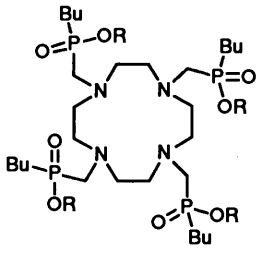
‡ Similar conclusions are being drawn for Gd complexes: P. Wedeking, K. Kumar and M. F. Tweedle, *Magn. Reson. Imag.*, 1992, **10**, 641; W. P. Cacheris, S. C. Quay and S. M. Rocklage, *Magn. Reson. Imag.*, 1990, **8**, 467.



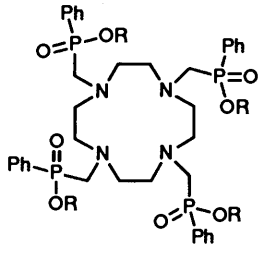
**1a** R = Et
**1b** R = H



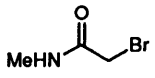
**1c** X = $CO_2H$ (DOTA)
**1d** X = $PMeO_2H$



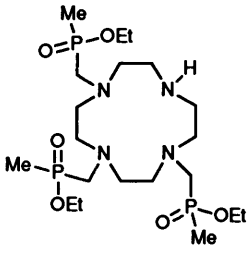
**2a** R = Et
**2b** R = H



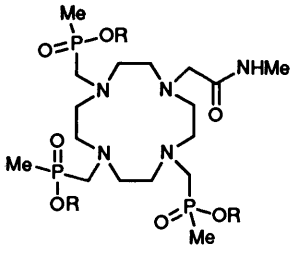
**3a** R = Et
**3b** R = H



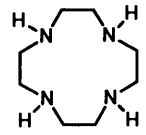
**5**

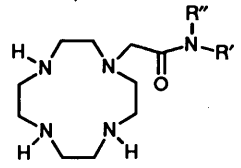


**4**

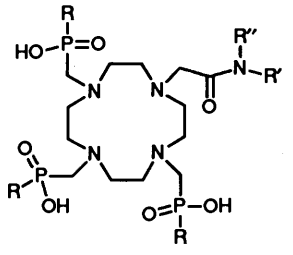


**6a** R = Et
**6b** R = H





**7a** R′ = R″ = Me
**8a** R′ = R″ = Bu
**9a** R′ = R″ = $CH_2Ph$
**10a** R′ = H, R″ = Me
**20** R′ = R″ = $Bu^i$



**6b** R = Me, R′ = H, R″ = Me
**7c** R = Me, R′ = R″ = Me
**8c** R = Me, R′ = R″ = Bu
**9c** R = Me, R′ = R″ = $CH_2Ph$
**10c** R = Bu, R′ = H, R″ = Me
**11c** R = Ph, R′ = R″ = Me
**21** R = Me, R′ = R″ = $Bu^i$

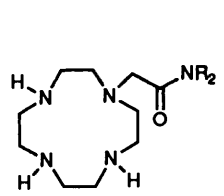
**Scheme 1** *Reagents and conditions:* i, $Mo(CO)_6$, $Bu_2O$; ii, $BrCH_2CONR'R''$, DMF; iii, HCl, $H_2O$, air; iv, $RP(OMe)_2$, THF, $(CHO)_n$; v, $OH^-$

effective route involves monoalkylation of the starting tetraazacyclododecane (12-$N_4$) followed by introduction of the desired alkylphosphinate residues.

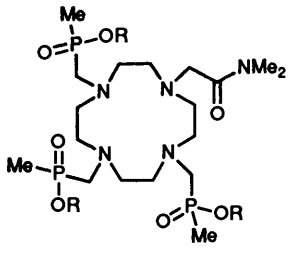
Following the report of the use of the octahedral chromium tricarbonyl complex of tetraazacyclododecane[14] as a protecting group for three of the ring nitrogens in 12-$N_4$, we have used the related molybdenum complex in a parallel manner. Reaction of tetraazacyclododecane with molybdenum hexacarbonyl in dibutyl ether results in formation of the bright yellow molybdenum tricarbonyl complex. This was suspended in dimethylformamide and the appropriate α-bromoamide added. Decomplexation of the molybdenum moiety in aqueous acid allowed the isolation of the monoalkylated amine (Scheme 1). Yields varied from 78 to 87%, and the conversion of the monosubstituted derivatives **7a**–**12a** to the various phosphinate esters and acids, **7b**–**12b** and **7c**–**12c** proceeded readily. Selective hydrolysis of the amide-triesters may be undertaken either using base (aq. KOH, 20 °C) or acid (HBr–AcOH–PhOH) to leave the amide intact.

In order to prepare yttrium and gadolinium complexes that bore a net positive charge, a set of ligands was synthesised with a pendant alkylammonium or tetraalkylammonium functional group. In the latter case reaction of the [12-$N_4$–$Mo(CO)_3$] complex, **18**, with the cationic α-bromoamide, **14**, yielded the monoamide **13a** which was converted into the triester **13b** ($K_2CO_3$/$BrCH_2CO_2Et$/DMF) and hence the triacid **13c**. The primary alkylammonium esters and acids **25**–**29** were prepared in a similar manner (Scheme 2), using the *p*-methoxybenzenesulfonyl group as the amine protecting group. This is readily removed with HBr–AcOH–PhOH. The triacids **26** and **29** were easily isolated as their tri-hydrobromide salts from the crude reaction mixture, following addition of diethyl ether.

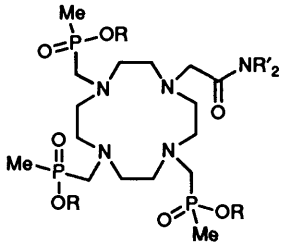
It is particularly notable that the compounds **26** and **29** are



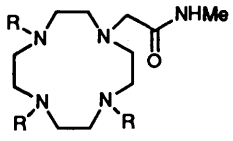
**7a** R = Me
**8a** R = Bu
**9a** R = $CH_2Ph$



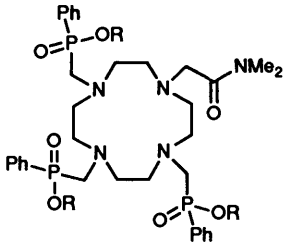
**7b** R = Et
**7c** R = H



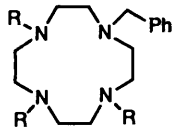
**8b** R = Et, R' = Bu
**8c** R = H, R' = Bu
**9b** R = Et, R' = $CH_2Ph$
**9c** R = H, R' = $CH_2Ph$



**10a** R = H
**10b** R = $CH_2PBuO_2Et$
**10c** R = $CH_2PBuO_2H$



**11b** R = Me
**11c** R = H



**12a** R = H
**12b** R = $CH_2PMeO_2Et$
**12c** R = $CH_2PMeO_2H$

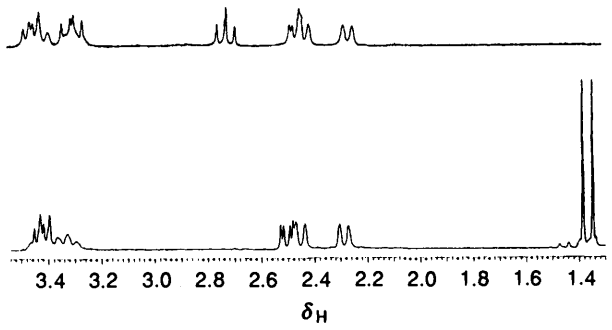
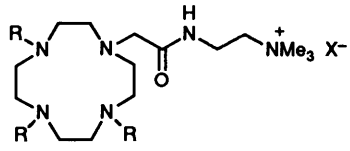
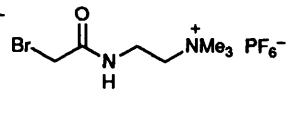



**Fig. 1** $^1H$ NMR spectra ($D_2O$; pD = 5.5, 293 K; 400 MHz) of $[Y\cdot\mathbf{1b}]^-$ and $[Y\cdot\mathbf{1d}]^-$ (lower)



**13a** R = H, X = OH
**13b** R = $CH_2CO_2Et$, X = Cl
**13c** R = $CH_2CO_2H$, X = Cl



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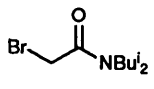
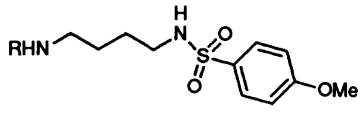
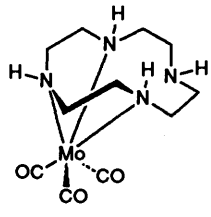


**15**



**16** R = H
**17** R = $COCH_2Br$



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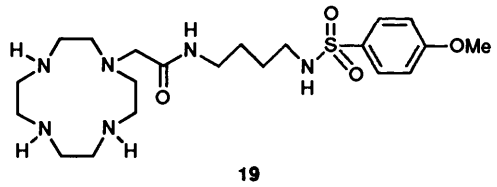

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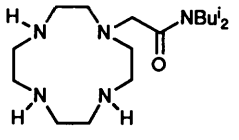

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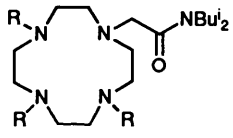


**21** R = $CH_2PMeO_2Et$
**22** R = $CH_2PMeO_2H$
**23** R = $CH_2CO_2Et$
**24** R = $CH_2CO_2H$

readily prepared in good yield (*e.g.* 63% for **26a**) in a *short* (three overall steps) synthetic sequence from the readily available tetraazacyclododecane (12-$N_4$) and the easily prepared α-bromoamide, **17**. These ligands are achiral bifunctional complexing agents and the pendant primary amine group may be transformed into an active ester or maleimide for protein conjugation.[15] Such a versatile synthetic route should be compared with the more lengthy synthetic methods reported earlier, involving preparation of enantiopure C-functionalised 12-$N_4$-based complexing agents[4,16,17] or of racemic N-functionalised analogues.[17]

*Complex Characterisation.*—Reaction of $Y_2O_3$ or $Gd_2O_3$ with an equimolar amount of the tetrabasic ligands **1b**–**3b** (pH 2–2.5, 80 °C, 12 h) gives rise to an intermediate N-bound complex (as observed by $^1H$ NMR spectroscopy) which is rapidly converted (presumably with concomitant proton loss) to the octadentate complex at pH ≥ 5.5. In each case, one major (≥90%) diastereoisomer may be observed by $^{31}P$ or $^1H$ NMR spectroscopy (on binding to a Y or Gd, a new stereogenic centre is created at each phosphorus) and in the $^{31}P$ NMR spectrum, coupling to the bound yttrium ($^{89}Y$, $I = \frac{1}{2}$, 100%; $^2J$ = 5 Hz) was observed. Representative $^1H$ NMR spectra are given in Fig. 1 for $[Y\cdot\mathbf{1b}]^-$ and $[Y\cdot\mathbf{1d}]^-$ and assignments were made with the aid of $^1H$–$^1H$ and $^{31}P$–$^1H$ COSY spectra. For each complex four of the ring protons are shifted to lower frequency (at *ca.* 2.3 ppm) and they are coupled to a multiplet centred at *ca.* 3.45 ppm. The other ring protons (as an AA'BB' multiplet) resonate as two multiplets centred at 2.45 and 3.30 ppm. For the benzylphosphinate complex, the diastereotopic benzyl methylene protons resonate as an ABX (X = $^{31}P$) system at 2.7 and 3.3 ppm. For both complexes the $NCH_2P$

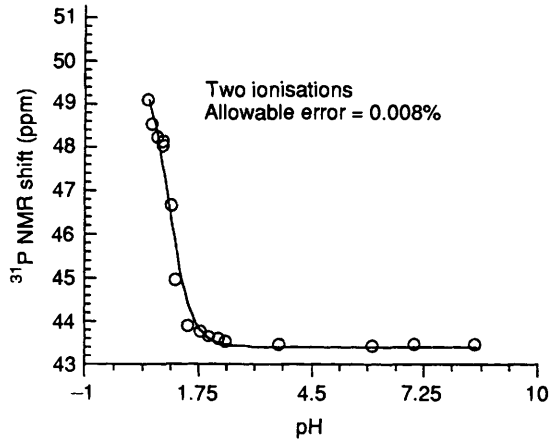
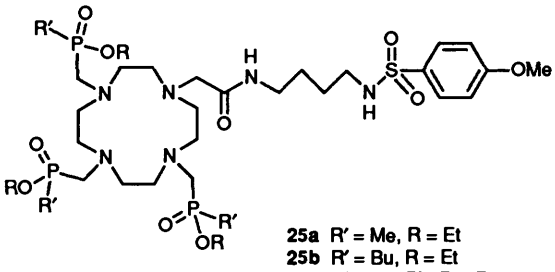
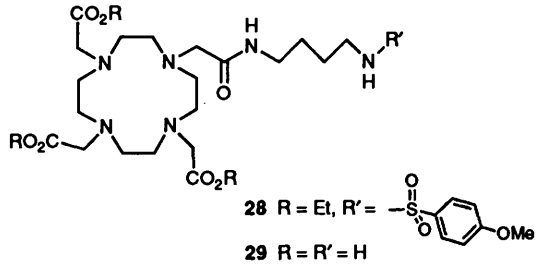



**Fig. 2** Variation of $\delta_P$ with pH (293 K, $H_2O$), in $[Y\cdot\mathbf{1b}]^-$ showing the agreement between observed (○) and calculated (—) values. The calculations assume that there are two closely spaced protonations ($pK_1$ = 1.28, $pK_2$ = 1.15). Details of the model used (including a comparison with a single protonation step) are given in the Appendix.



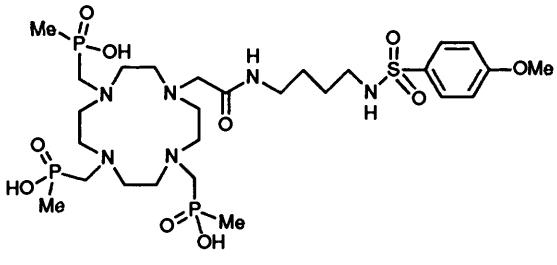
**25a** R′ = Me, R = Et
**25b** R′ = Bu, R = Et
**25c** R′ = $CH_2Ph$, R = Et

**26a** R′ = Me, R = H
**26b** R′ = Bu, R = H
**26c** R′ = $CH_2Ph$, R = H



**28** R = Et, R′ =

**29** R = R′ = H



**27**

protons resonate as similar ABX multiplets at *ca.* 2.45 and 3.4 ppm.

In the case of $[Y\cdot\mathbf{1b}]^-$, evidence for the minor diastereoisomer is most apparent in the appearance of a minor doublet to higher frequency of the major resonance for the P-methyl doublet at *ca.* 1.4 ppm. It is very likely that in each case, the P-alkyl substituent is disposed away from the $N_4$-ring, so that the major diastereoisomer observed comprises a 50:50 mixture of the enantiomeric (*RRRR*) and (*SSSS*) complexes,* each of which is of a defined helicity. Both $[Y\cdot\mathbf{1b}]^-$ and $[Y\cdot\mathbf{1d}]^-$ exhibited relatively little variation in their $^1$H NMR spectra ($D_2O$) in the temperature range 5–75 °C. This may be contrasted with the behaviour of $[Y\cdot DOTA]^-$ in which pronounced fluxional behaviour was observed ($T_c$ = 325 K), in a similar manner to that reported for the lanthanide complexes of DOTA.[19,20] This dynamic process observed with DOTA complexes was initially considered to be an 'ethylene inversion' of the rigid five-membered-ring chelates (NCCN–Y). It is now established[20] to arise from a 'concerted sliding motion' of the four oxygen donor atoms on the surface of the lanthanide (or Y) ion (*via* a prismatic transition state structure), with the conformation of the macrocyclic ring being conserved (*i.e.* rigid).

**Table 1** $^{89}$Y Chemical shift data for macrocyclic complexes[a]

| Complex | $\delta_Y$ |
|---|---|
| $[Y\cdot\mathbf{1c}]^-$ | +111.8 |
| $[Y\cdot EDTA]^-$ | +123.5 |
| $[Y\cdot DTPA]^-$ [c] | +81.6 |
| $[Y\cdot\mathbf{1d}]^-$ [b] | +156.8 |
| $[Y\cdot\mathbf{1b}]^-$ [b] | +152.8 |
| $[Y\cdot\mathbf{8c}]^-$ | +168.3 |
| $[Y\cdot\mathbf{24}]^-$ | +111.3 |
| $[Y\cdot\mathbf{27}]^-$ | +152.0 |

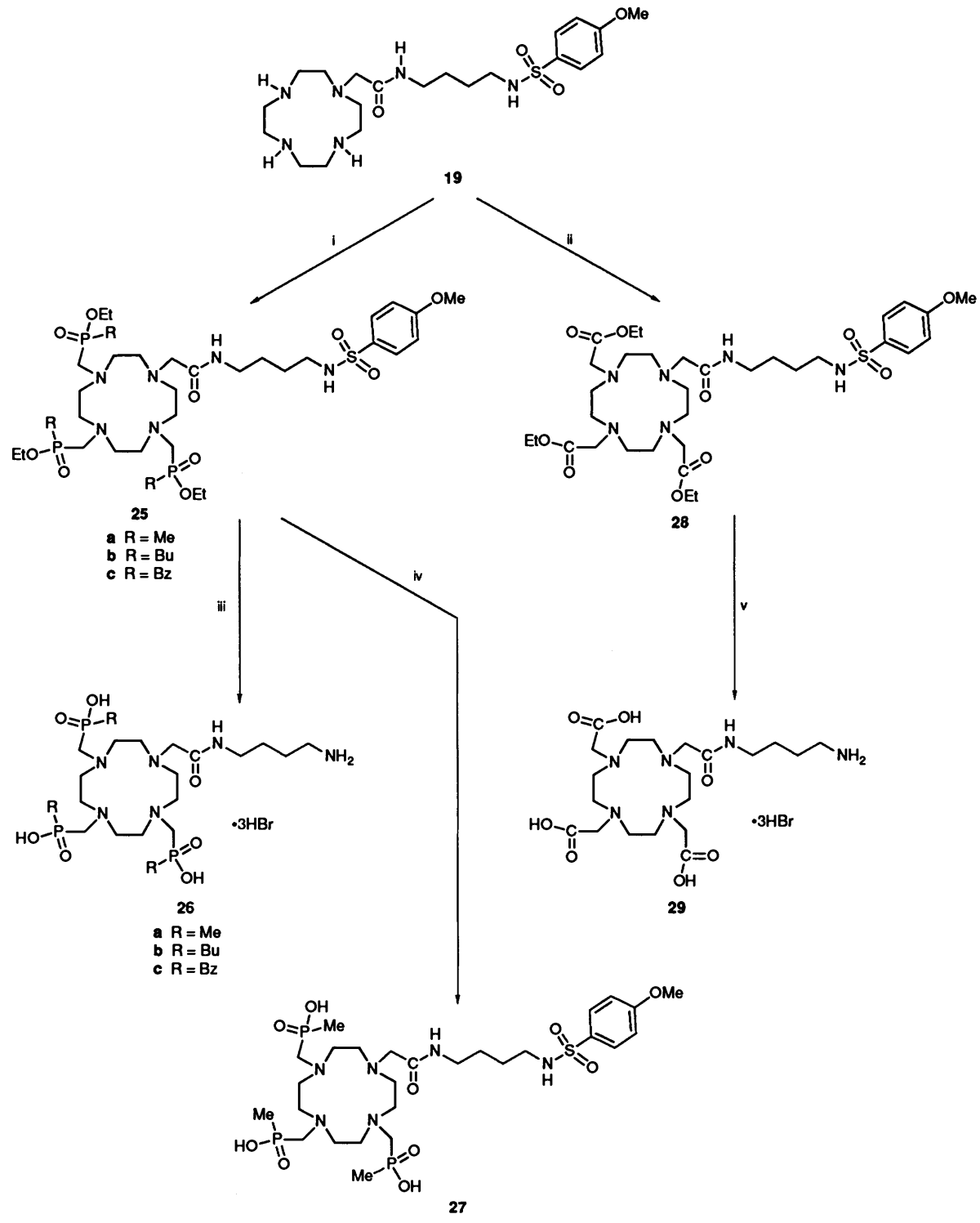
[a] In $H_2O$ (pH 6.5); [complex] *ca.* 0.15 mol $dm^{-3}$; $T$ = 23 °C; shifts relative to 1 mol $dm^{-3}$ Y $Cl_3$ ($\delta$ = 0). Values obtained were the same (±0.1 ppm) in $H_2O$ and $D_2O$. [b] Observed as a quintet with $J_{YP}$ = 5 Hz. [c] The yttrium complex of the dibenzyl-amide derivative of DTPA gave an $^{89}$Y NMR shift of +80.6 ppm.

In the $^{31}$P NMR spectrum of $[Y\cdot\mathbf{1b}]^-$, no variation of $\delta_P$ with pH was discerned in the pH range 2–11. Under more acidic conditions, the observed shift increased, displaying a quite marked 'end-point' at around pH 1.1 (Fig. 2). The inflection around pH 1.1 was fitted (using a simple curve-fitting procedure)[21] to two closely separated protonation steps. Whilst this fitting procedure does not unequivocally reproduce the observation variation, it does suggest that successive protonation of $[Y\cdot\mathbf{1b}]^-$ is likely over a narrow pH range.

In the preparation of the charge neutral yttrium and gadolinium complexes of the tribasic ligands (*e.g.* with **8c**–**10c**, **27** and **24**), purification was effected by column chromatography on neutral alumina. Again, a single major diastereoisomer was observed in the $^{31}$P NMR spectra of each of the diamagnetic chiral complexes. In $[Y\cdot\mathbf{8c}]$, for example, three closely spaced yttrium-coupled doublets were observed in the $^{31}$P NMR spectrum, one for each non-equivalent phosphorus atom ($\delta_P$ = 44.45, 43.8 and 43.2; $J_{YP}$ = 5 Hz). Assignment of the $^1$H NMR spectrum of $[Y\cdot\mathbf{8c}]$ (shown as the $^{31}$P decoupled spectrum in Fig. 3), was made with the aid of 2D $^1$H–$^1$H and $^{31}$P–$^1$H COSY experiments. The $NCH_2CON$ protons resonate as a simple 'AB' pair of doublets ($^3J$ = 16.5 Hz) to higher frequency of all other resonances. The P-coupled methyl groups are non-equivalent, and the diastereotopic methylene protons in the $NCH_2P$ groups are highly anisochronous (resonating as two 3 H multiplets at 2.68 and *ca.* 3.58 ppm).

For each yttrium complex, the $^{89}$Y NMR spectrum was acquired within 8 h (24.5 MHz, $H_2O$), without the addition of a relaxation agent, typically using 0.3 mol $dm^{-3}$ solutions. A 90° pulse with a 30 s delay was used, in order to minimise the

* In the case of $[Y\cdot\mathbf{1b}]^-$, a preliminary crystal structure analysis has confirmed this supposition and also shows that the yttrium is in a square antiprismatic arrangement and there is *no* yttrium-bound water molecule.[18]




**Scheme 2** *Reagents and conditions:* i, $RP(OEt)_2$, $(H_2CO)_n$, THF, 100 °C, 18 h; ii, $BrCH_2CO_2Et$, $K_2CO_3$, EtOH, 80 °C, 18 h; iii, HBr, AcOH, PhOH, 100 °C, 2 days; iv, KOH(aq), room temp., 18 h; v, HBr, AcOH, PhOH, 100 °C, 2 days

problems associated with the long relaxation times encountered in $^{89}Y$ NMR.[22] Chemical shift data are collated in Table 1 and, while there is no clear trend in $\delta_Y$ in respect of the number of bound nitrogen or oxygen atoms, certain general features can be distinguished. The phosphinate complexes resonate to higher frequency (*ca.* 40 ppm) of their carboxylate analogues, and the anionic and charge neutral complexes give very similar shifts (*cf.* $[Y\cdot\mathbf{1c}]^-$ *vs.* [Y·**24**] and $[Y\cdot DTPA]^{2-}$ *vs.* the neutral dibenzylamide analogues, Table 1). Notwithstanding the known and substantial solvent isotope effect (4.3 ppm $H_2O$ *vs.* $D_2O$) for the $^{89}Y$ shift of the aquo-ion, no difference in $^{89}Y$ shift was observed for $[Y\cdot\mathbf{1b}]^-$, $[Y\cdot\mathbf{1c}]^-$ or even $[Y\cdot EDTA]^-$ on changing from $H_2O$ to $D_2O$. This lack of variation precluded any conclusions being made about the solvation state of the bound yttrium ion.

*Kinetics of Association and Dissociation.*—A key feature in the development of radioimmunotherapy is the requirement that the bifunctional complexing agent should undergo efficient and rapid radiolabelling, under ambient conditions of pH and temperature, without significant non-specific labelling of the protein. Working at concentrations of the macrocyclic ligand

**Table 2** % $^{90}Y$ Uptake by charged and uncharged ligands[a]

| | Ligand | | | | | |
|---|---|---|---|---|---|---|
| *t*/min | **1c** | **1d** ($N_4P_4Me_4$) | **6b** ($N_4P_3CH_2CONHMe$) | **8c** ($N_4P_3CONBu_2$) | **26a** [$N_4P_3(CH_2)_4NH_3^+$] | **29** [$N_4C_3(CH_2)_4NH_3^+$] |
| 1 | 54.4 | 8.8 | 2.0 | 5.9 | 17.4 | 3.4 |
| 2 | 80.5 | 18.3 | 4.1 | 12.0 | 36.2 | 8.9 |
| 5 | 98.5 | 55.2 | 12.6 | 35.2 | 78.5 | 23.6 |
| 10 | 99.7 | 85.3 | 24.7 | 61.1 | 90.2 | 42.8 |
| 15 | | | 35.8 | 78.7 | 97.4 | 59.9 |
| 20 | | 92.6 | 45.4 | 86.8 | | 67.6 |
| 30 | | 93.4 | 58.4 | 90.2 | | 81.3 |
| 60 | | | 79.8 | | | 91.8 |

[a] [Ligand] 5 μmol $dm^{-3}$; pH 6.5; $T$ = 37 °C; 0.2 mol $dm^{-3}$ $NH_4OAc$.

that mirror the effective concentration of complexing agent on a conjugated antibody (5 μmol $dm^{-3}$, 37 °C, pH 6.5, $NH_4OAc$ 'buffer'), the rates of $^{90}Y$ uptake by various ligands have been compared (Table 2). Using $^{90}Y$ of the highest purity available,* the forward rate of $^{90}Y$ binding was measured by sampling the incubation at a fixed time interval, scavenging any 'free' yttrium with an excess of DTPA. The neutral or monoanionic complexes of the ligand screened elute much more quickly than $[Y{\cdot}DTPA]^{2-}$ on an anion-exchange HPLC column allowing separation and quantitation (*via* counting the activity with a radiometric detector). All of the ligands with the exception of **6b**, gave a radiolabelling yield of ⩾90% within 60 min, and the binding of $^{90}Y$ by **1c** (DOTA), **1d** and **26a** was particularly rapid.

The rates of dissociation of $^{90}Y$ from its complexes with **1d** and **1c** were compared using methods reported earlier.[5] As is evident from the data in Table 3, the yttrium complex of **1d** is less kinetically stable than that of DOTA, **1c**, although it shows a less steep dependence on pH. Similar behaviour is shown with the gadolinium complexes, which are generally *less* sensitive to acid-catalysed dissociation than their yttrium analogues. In the complexes of DOTA the yttrium complex is 5–6 times more labile than the gadolinium analogue at a given pH, whereas with the phosphinate complexes of **1d** this difference is less marked and the rate difference is only a factor of 2–3. It is particularly notable that the charge-neutral complexes of yttrium and gadolinium (*e.g.* with **8c–10c**) are more kinetically stable at a given pH than their anionic analogues, and exhibit a reduced dependence of rate with pH (*e.g.* [Gd·**9c**]: $t_{\frac{1}{2}}$ (pH 1.0) = 44.9 h, *cf.* $t_{\frac{1}{2}}$ (pH 2.0) = 194 h). Furthermore, the gadolinium complex with ligand **8c** is more stable with respect to dissociation at pH 1 than [Gd·DOTA] itself. Such kinetic stability may accord with a reduced tendency of the neutral complexes to protonate, to form the more labile protonated species.[5]

The dissociation of [$^{90}Y$·**1d**] (Fig. 4), has been examined in

* $^{90}Y$ was purchased from Amersham, and is relatively free from competing metal ions (as deduced by ICP-mass spectrometry) such as $Zn^{2+}$, $Cu^{2+}$, $Ni^{2+}$ and $Ca^{2+}$. Such cationic impurities may severely limit the radiolabelling yield which can be achieved at low concentrations of these macrocyclic ligands.

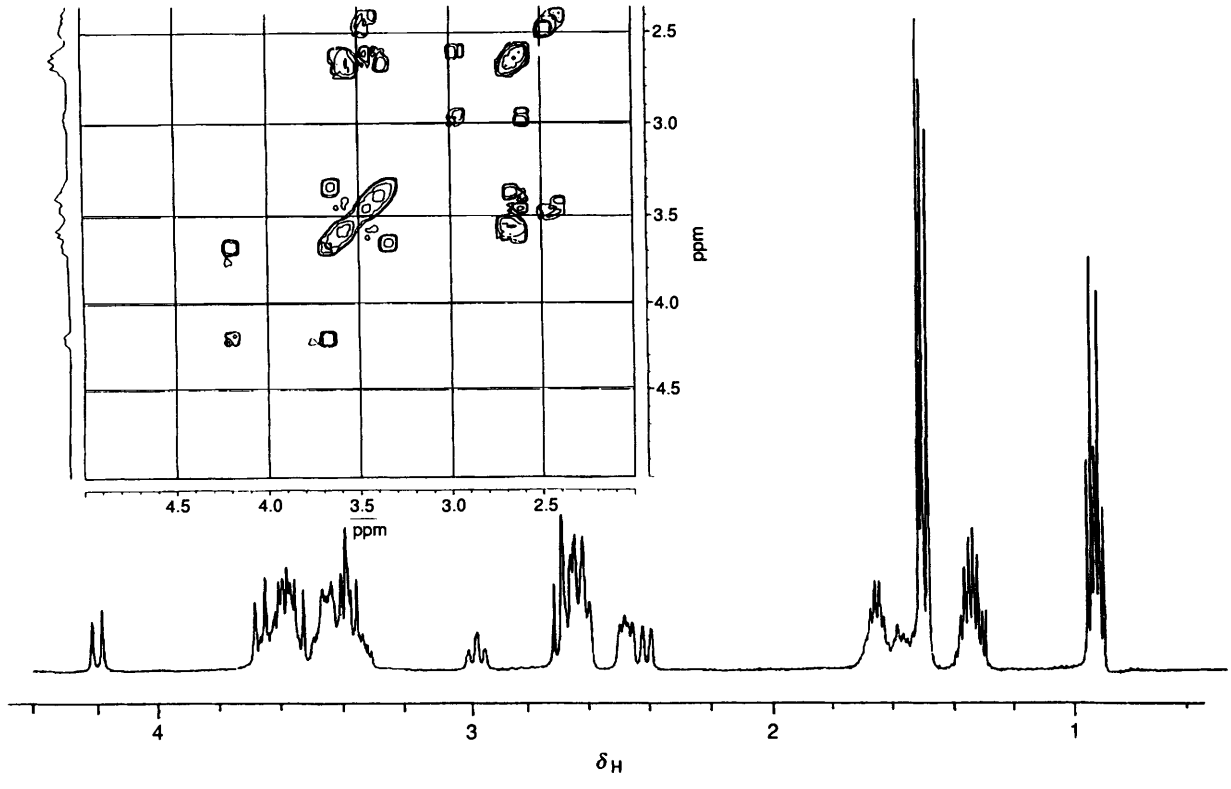



**Fig. 3** $^{31}P$ Decoupled $^1H$ NMR spectra of $[Y{\cdot}\mathbf{8c}]^-$ (293 K; 500 MHz; $D_2O$) and its partial $^1H$–$^1H$ COSY spectrum

**Table 3** Kinetics of dissociation of $^{90}Y$ and $^{153}Gd$ complexes (310 K)*

| Complex | pH | $k_{obs}/10^{-6}$ s$^{-1}$ (sd in parentheses) | $t_{\frac{1}{2}}$/h |
|---|---|---|---|
| [Y·DOTA]$^-$ | 1.0 | 15.0 (0.5) | 12.8 |
| | 1.5 | 1.88 (0.03) | 102 |
| | 2.0 | 0.33 (0.01) | 583 |
| [Y·**1d**]$^-$ | 1.0 | 21.0 (0.5) | 9.17 |
| | 1.5 | 9.6 (0.2) | 20.1 |
| | 2.0 | 3.1 (0.1) | 62.1 |
| [Gd·DOTA]$^-$ | 1.0 | 3.2 (0.03) | 60.2 |
| | 1.5 | 0.9 (0.004) | 214 |
| | 2.0 | 0.05 (0.005) | 3929 |
| [Gd·**1d**]$^-$ | 1.0 | 10.4 (0.1) | 18.5 |
| | 1.5 | 4.6 (0.03) | 41.6 |
| | 2.0 | 1.1 (0.03) | 171 |
| [Gd·**1b**]$^-$ | 1.0 | 23.9 (2) | 8.1 |
| | 1.5 | 9.1 (0.9) | 21.1 |
| | 2.0 | 2.8 (0.14) | 69.0 |
| [Gd·**2b**]$^-$ | 1.0 | 36.9 (0.6) | 5.2 |
| | 1.5 | 20.1 (0.3) | 9.6 |
| | 2.0 | 7.08 (0.1) | 27.2 |
| [Gd·**3b**]$^-$ | 1.0 | 77.7 (0.6) | 2.5 |
| | 1.5 | 36.4 (0.3) | 5.3 |
| | 2.0 | 14.7 (0.02) | 13.1 |
| [Gd·**9c**] | 1.0 | 4.3 (0.08) | 44.9 |
| | 1.5 | 1.6 (0.09) | 118 |
| | 2.0 | 1.0 (0.06) | 192 |
| [Gd·**8c**] | 1.0 | 1.3 (0.02) | 153 |
| | 1.5 | 0.49 (0.02) | 389 |
| | 2.0 | 0.20 (0.02) | 943 |
| [Gd·**10c**] | 1.0 | 4.1 (0.09) | 47 |
| | 1.5 | 1.5 (0.04) | 127 |
| | 2.0 | 0.45 (0.02) | 427 |

*Note added in proof. The $^{90}Y$ complex of **9c** is considerably more stable kinetically, than [Y·DOTA]$^-$: $t_{\frac{1}{2}}$ = 145 h (pH 1), 379 h (pH 1.5) and 989 h (pH 2).

more detail.† The effect on the rate of varying the ionic strength of the medium was examined. The observed rate at pH 1.05, *decreased* in an approximately linear manner as the ionic strength was increased (using $NMe_4NO_3$) from 0.1 to 1.0 mol dm$^{-3}$ ($k_{obs}$ decreasing from 2.1 × 10$^{-5}$ to 0.6 × 10$^{-5}$ s$^{-1}$). Given that this is unlikely to reflect the interaction of two oppositely charged ions in the rate-limiting step ($H_3O^+$ must surely interact with a cationic or neutral protonated yttrium species),[5] the results may simply be related to the perturbation of the equilibrium constant for successive protonation. As $I$ increases, the formation of the more highly charged species will be favoured (*e.g.* in $H_3O^+ + [YLH_2]^+ \rightleftharpoons [YLH_3]^{2+} + H_2O$, the equilibrium shifts to the right as $I$ is increased).

In addition, the effect on the rate of dissociation of [Y·**1b**]$^-$ of adding a divalent cation was examined using $Ca^{2+}$ as the additive. Relatively large concentrations of added calcium were required in order to increase significantly the rate of dissociation ($k_{obs}$ increased by a factor of four as [Ca] went from 0.1 to 1.0 mol dm$^{-3}$). However, these results clearly show that added

† The rate data for the dependence on $I$ and [$Ca^{2+}$] were obtained using $^{31}P$ NMR spectroscopy, measuring the disappearance of the $^{31}P$ resonance at $\delta_P$ 47.4 (pH 1.05) due to the complex. Good agreement was obtained, in control experiments, with the rates determined using the radiolabelled complex.

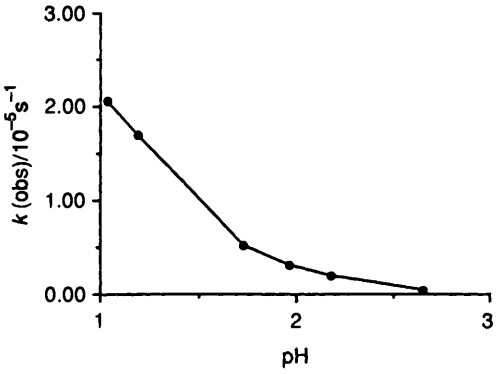



**Fig. 4** Rate of dissociation of [Y·**1b**]$^-$ (310 K; $I$ = 0.1) as a function of pH

cations can cause an effect on the dissociation rate, although the acid-catalysed pathway is likely to dominate *in vivo*, where the relative concentrations of free $Ca^{2+}$ and free $Zn^{2+}$ are low (*e.g.* 1.26 mmol dm$^{-3}$ $Ca^{2+}$, 10$^{-5}$ mol dm$^{-3}$ $Zn^{2+}$ in serum).

## Conclusions

It is slowly becoming generally accepted that the more reliable guide to predicting the stability of metal complexes *in vivo* is to examine the rate of dissociation at low pH *rather* than consider the relative magnitude of equilibrium stability constants.‡[1,4,9,25] Correlation of the rates of dissociation measured in this work, with the biodistribution data for the $^{153}Gd$-radiolabelled (and certain $^{90}Y$-labelled) complexes discussed here and reported elsewhere[9] is good. As discussed elsewhere,[9] the *in vivo* behaviour of charged and uncharged gadolinium complexes follows a simple rule. Anionic lipophilic complexes excrete predominantly *via* the biliary system, whereas the neutral and cationic complexes prepared herein are excreted *via* the renal route. Such a simple structure–activity relationship, whilst hinted at by earlier work[6,7,8] has not been reported previously.

It is clear that the gadolinium complex of **1b** is an attractive candidate as an MRI imaging agent. It is quite stable *in vivo* (no deposition of $^{153}Gd$ in the liver or bone was noted after 7 days),[9] is easily synthesised and purified, and clears with high specificity *via* the biliary system, permitting selective imaging of the liver/bile-duct/gall bladder, and in particular the intestinal tract.[24]

The short synthesis of the bifunctional complexing agents **26a** and **29** (multigram quantities have been prepared within 8 days by this route) their efficient radiolabelling by $^{90}Y$, and the ease of conjugation to a protein or other targeting vehicle also bodes well for their use in selective tumour targeting, for example, in a conjugate with a humanised monoclonal antibody fragment.

Finally the versatility of macrocyclic azaphosphinic acids as complexing agents for *in vivo* usage has been clearly demonstrated, with the ease of substitution and functionalisation at nitrogen and phosphorus aiding considerably the design of complexes with specific properties.

## Experimental

Column chromatography was carried out using neutral

‡ For [Gd·**1d**]$^-$, the 1:1 formation constant (298 K, $I$ = 0.1) is 19.8, compared to 25.6 for [Gd·DOTA]$^-$ and 22.4 for [Gd·DTPA]$^{2-}$ measured under the same conditions.[23] It is well-established that [Gd·DTPA]$^{2-}$ is considerably *less* stable *in vivo* than either [Gd·**1d**]$^-$ or [Gd·DOTA]$^-$ as evidenced by the slow release of Gd and deposition in the bone and liver.[9]

**Table 4** Typical data set for kinetic run

| | Concentration/mol dm$^{-3}$ | | | | |
|---|---|---|---|---|---|
| *t*/min | Run1 | Run 2 | Run 3 | Run 4 | Mean |
| 20 | 0.940 | 0.945 | 0.944 | 0.936 | 0.941 |
| 40 | 0.903 | 0.911 | 0.896 | 0.898 | 0.898 |
| 60 | 0.875 | 0.873 | 0.881 | 0.870 | 0.875 |
| 80 | 0.857 | 0.863 | 0.854 | 0.863 | 0.859 |
| 110 | 0.838 | 0.837 | 0.818 | 0.827 | 0.830 |
| 140 | 0.792 | 0.789 | 0.788 | 0.788 | 0.789 |
| 170 | 0.781 | 0.762 | 0.766 | 0.756 | 0.766 |
| 260 | 0.682 | 0.681 | 0.685 | 0.683 | 0.683 |
| 320 | 0.647 | 0.642 | 0.665 | 0.640 | 0.648 |
| 480 | 0.598 | 0.592 | 0.599 | 0.589 | 0.595 |

alumina (Merck Art 1077) which had previously been treated with EtOAc. Analytical and semi-preparative HPLC was performed with a Varian Vista 5500/Polychrome 9060 instrument fitted with either cation exchange ('Synchropak' CM 300), anion exchange ('Synchropak' AX 100) or reverse phase columns ('Spherisorb' 5 ODS2). Flow rates of 1.4 and 4.0 cm$^3$ min$^{-1}$ were used for analytical and semi-preparative columns respectively. Column and gradient elution conditions were as follows: cation exchange, $t$ = 0 min, 80% $H_2O$, 0% aq. $NH_4OAc$ (1.0 mol dm$^{-3}$, pH 5.6), 20% MeCN; $t$ = 5 min, 60% $H_2O$, 20% aq. $NH_4OAc$, 20% MeCN; $t$ = 10 min, 0% $H_2O$, 80% aq. $NH_4OAc$, 20% MeCN. For anion exchange: $t$ = 0 min, 70% $H_2O$, 10% aq. $NH_4OAc$, 20% MeCN; $t$ = 20 min, 0% $H_2O$, 80% aq. $NH_4OAc$, 20% MeCN. For reverse phase: $t$ = 0 min, 95% $H_2O$, 0% aq. $NH_4OAc$, 5% MeCN; $t$ = 20 min, 5% $H_2O$ (0.1% trifluoroacetic acid), 0% $NH_4OAc$, 95% MeCN (0.1% trifluoroacetic acid). Solvents used were dried from an appropriate drying agent, and water was purified by the Milli Q system. IR spectra were recorded with a Perkin-Elmer 577 spectrometer, $^1H$, $^{13}C$ and $^{31}P$ NMR spectra were obtained with a Bruker AC 250 operating at 250.13, 62.90 and 101.1 MHz, respectively. $^{89}Y$ NMR spectra were recorded on a Bruker AM500 operating at 24.5 MHz (using a 30 s pulse delay, and 0.3 mol dm$^{-3}$ solutions). All coupling constants are in Hz. Mass spectra were recorded with a VG 7070E spectrometer operating in CI, DCI or FAB modes with DCI samples presented as dilute MeOH solutions and ammonia as the impingent gas. *m*-Nitrobenzyl alcohol or glycerol were used as the matrix for FAB analyses. Reactions involving molybdenum tricarbonyl intermediates were carried out under an atmosphere of dry argon.

*Kinetics of Dissociation.*—The methods used to monitor the rate of gadolinium (and yttrium) dissociation from the complexes at 310 K as a function of pH were the same as those described earlier.[5] Values quoted for the observed rate of dissociation represent the mean value of three or four separate determinations. A typical data set is given in Table 4, for the dissociation of [$^{90}$Y·**1d**]$^-$ at pH 1.0, giving the concentration of the intact complex ($t$ = 0; 1) as a function of time (min) for four independent experiments, for each of which a correction due to the decaying activity of the $^{90}Y$ has been made (*n.b.* this correction was not applied for $^{153}$Gd labelled complexes: $t_{\frac{1}{2}}$ $^{90}Y$ = 64 h; $t_{\frac{1}{2}}$ $^{153}Gd$ = 242 days). Values of $k_{obs}$ (s$^{-1}$) and $t_{\frac{1}{2}}$ are given in Table 3.

*Kinetics of Association.*—Incubations were effected at 310 K at pH 6.5 (0.2 mol dm$^{-3}$ $NH_4OAc$) with a ligand concentration of 5 μmol dm$^{-3}$. Typically, a 1 mm$^3$ aliquot (67 μCi) of high quality $^{90}Y$ (Amersham) was added to a solution containing: (*a*) 25 mm$^3$ of a 50 μmol dm$^{-3}$ solution of the ligand; (*b*) 125 mm$^3$ of an 0.4 mol dm$^{-3}$ solution of $NH_4OAc$; (*c*) 99 μmol dm$^{-3}$ of MilliQ water. A 10 mm$^3$ sample was removed at various time intervals up to 1 h, and was added to a solution containing DTPA in excess (5 mm$^3$ of 500 μmol dm$^{-3}$) and 85 mm$^3$ of 0.15 mol dm$^{-3}$ $NH_4OAc$ (pH 6.8). Under these conditions any dissociated $^{90}Y$ is immediately scavenged by the DTPA, and the remaining bound $^{90}Y$ has been shown in control experiments to be stable with respect to transcomplexation by DTPA, in the pH range 5–6.5, over a 24 h period, at least.

Samples were analysed by anion-exchange HPLC [Hichrom AX300 or Poros Q/M (Perceptive Biosystems): eluent 0.15 mol dm$^{-3}$ $NH_4OAc$ pH 6.8 run at 2 cm$^3$ per min. The [$^{90}$Y·DTPA]$^{2-}$ elutes under these conditions at *ca.* 3 min, and the monoanionic (or neutral) complexes elute at *ca.* 1 min, as detected (and counted) by a Beckman 170 radioisotope detector. Longer retention times may be achieved by increasing the % of acetonitrile added.

### *Ligand Synthesis*

*Tetraethyl* 1,4,7,10-*Tetraazacyclododecane*-1,4,7,10-*tetrayltetramethylenetetra*(*benzylphosphinate*) **1a**.—1,4,7,10-Tetraazacyclododecane (1 g, 5.8 × 10$^{-3}$ mol) was stirred in dry THF (50 cm$^3$) under an argon atmosphere. To this was added paraformaldehyde (0.9 g, 29 × 10$^{-3}$ mol) and benzyldiethoxyphosphine (6 g, 29 × 10$^{-3}$ mol). The mixture was heated under reflux over molecular sieves for about 18 h to give a cloudy solution. The solution was filtered and the solvent was evaporated under vacuum. The product was purified using alumina column chromatography (gradient elution from dichloromethane to 2% ethanol–dichloromethane, $R_f$ product = 0.7, 5% ethanol–dichloromethane) to yield a colourless oil (2.5 g, 45%); $\delta_H(CDCl_3)$ 1.15 (12 H, t, $OCH_2CH_2CH_3$), 2.86 (20 H, br, m $NCH_2CH_2$ and $NCH_2$), 3.16 (8 H, m, $PCH_2Ar$) and 7.25 (20 H, m, Ar); $\delta_P\{^1H\}(CDCl_3)$ 48.9 (s); $\delta_C(CDCl_3)$ 17.17 (d, $^3J$ 5.5, $CH_2CH_3$), 36.4 (d, $^1J$ 81, $PCH_2$), 53.8 (d, $^1J$ 99, $PCH_2N$), 53.86, 53.99, 54.11 and 54.37 (s, $NCH_2$), 61.19 (d, $^2J$ 7, $OCH_2CH_3$) and 127.15, 127.2, 128.97 and 130.34 (d, $^2J_{PC}$ 10, Ar); *m*/*z* (DCI) 956 (100%, M$^+$).

1,4,7,10-*Tetraazacyclododecane*-1,4,7,10-*tetrayltetramethylenetetra*(*benzylphosphinic Acid*) **1b**.—The tetrabenzyl tetraester **1a** (2.5 g, 2.6 mmol) was treated with 50 cm$^3$ of hydrochloric acid (6 mol dm$^{-3}$) and the solution was heated under reflux for 18 h to give a clear solution. After cooling, the product precipitated from the solution at pH 1.5–2.0 as the zwitterion, and was recrystallised from methanol to yield a colourless crystalline solid, m.p. >200 °C (1.8 g, 80%); $\delta_H(D_2O)$ 2.9 (32 H, br m, $NCH_2$) and 7.15 (20 H, br m, Ar); $\delta_P(D_2O$; pD = 1.831; *m*/*z* (DCI) 844 (100, M$^+$) (Found: C, 52.1; H, 7.2; N, 6.0. $C_{40}H_{56}N_4O_8P_4{\cdot}4H_2O$ requires C, 52.4; H, 6.99; N, 6.11%).

*Tetraethyl* 1,4,7,10-*Tetraazacyclododecane*-1,4,7,10-*tetrayltetramethylenetetra*(*butylphosphinate*) **2a**.—The title compound was prepared using a method similar to that of the benzyl analogue using 1,4,7,10-tetraazacyclododecane (0.34 g, 1.9 × 10$^{-3}$ mol), butyldiethoxyphosphine (1.3 g, 9.7 × 10$^{-3}$ mol) and paraformaldehyde (0.7 g, 9.7 × 10$^{-3}$ mol). The product was purified using alumina column chromatography (gradient elution from dichloromethane to 5% ethanol–dichloromethane, $R_f$ = 0.7, 10% ethanol–dichloromethane) to yield a colourless oil (0.7 g, 46%); $\delta_H(CDCl_3)$ 0.97 (12 H, t, $^3J$ 7.5, $CH_2C$), 1.24 (12 H, t, $CH_2C$), 1.35 (8 H, dt, $CH_2C$), 1.50 (8 H, m, $CH_2C$), 1.70 (8 H, br m, $CH_2P$), 2.6–2.95 (24 H, br m, $CH_2N$ ring) and 4.01 (8 H, dq, $CH_2O$); $\delta_P(CDCl_3)$ 53.8 (s); $\delta_C(CDCl_3)$ 12.7 ($CH_2CH_3$), 15.8 (d, $^2J$ 5, $OCH_2CH_3$), 22.85 ($CH_2CH_3$), 23.06 (d, $J_{PC}$ 15, $PCH_2CH_2$), 26.46 (d, $^1J_{PC}$ 87, $PCH_2CH_2$), 52.38 (d,

$^1J_{PC}$ 104, $NCH_2P$), 53.2 (br, $CH_2N$ ring) and 59.1 (d, $^2J$ 5, $OCH_2CH_3$); *m/z* (DCI) 820 (100, $M^+$).

1,4,7,10-*Tetraazacyclododecane*-1,4,7,10-*tetrayltetramethylenetetra*(*butylphosphinic Acid*) **2b**.—The ester **2a** (0.41 g, 0.5 mmol) was treated with hydrochloric acid (6 mol $dm^{-3}$, 50 $cm^3$) and the solution was heated at 100 °C for 18 h to give a clear solution. The solvent was evaporated under vacuum to give the dihydrochloride salt as a glassy colourless solid, m.p. > 200 °C which was characterised as the title compound; $\delta_H(CD_3OD)$ 0.97 (12 H, t, $^3J$ 7.5, $CH_2CH_3$), 1.4–1.7 (16 H, m, $CH_2C$), 1.95 (8 H, dt, $CH_2CH_2P$) and 3.4–3.8 (24 H, br m, $CH_2N$); $\delta_P$-($CD_3OD$) 46.83 (s); $\delta_C(CD_3OD)$ 13.95 (s, $CH_3$), 24.13 (d, $^3J$ 2.5), 24.87 (d, $^2J$ 8), 29.6 (d, $^1J$ 96, $CH_2P$) and 52.4, 52.9 (s, $CH_2N$) (Found: C, 38.6; H, 8.8; N, 6.2. $C_{28}H_{66}Cl_2N_4P_4O_8 \cdot 4H_2O$ requires: C, 39.0; H, 8.59; N, 6.50%).

*Tetramethyl* 1,4,7,10-*Tetraazacyclododecane*-1,4,7,10-*tetrayltetramethylenetetra*(*phenylphosphinate*) **3a**.—The title compound was synthesised using a method similar to that used for the benzyl analogue using 1,4,7,10-tetraazacyclododecane (0.5 g, 2.9 × $10^{-3}$ mol) and phenyldimethoxyphosphine (2.5 g, 14.5 × $10^{-3}$ mol) and paraformaldehyde (0.45 g, 14.5 × $10^{-3}$ mol). The product was purified using alumina column chromatography (gradient elution from dichloromethane to 2% methanol–dichloromethane, $R_f$ = 0.63, 10% methanol–dichloromethane) to yield a colourless solid (1.4 g, 57%); $\delta_H(CDCl_3)$ 2.42 (16 H, br m, $CH_2C$), 2.9 (8 H, br m, $NCH_2P$), 3.56 (12 H, d + d + d + d, $POCH_2$ isomers), 7.4 (12 H, m, Ar) and 7.75 (8 H, m, *ortho* Ar); $\delta_P\{^1H\}(CDCl_3)$ 41.5 (s); *m/z* (DCI) 844 (100, $M^+$).

1,4,7,10-*Tetraazacyclododecane*-1,4,7,10-*tetrayltetramethylenetetra*(*phenylphosphinic Acid*) **3b**.—The title compound was isolated as a colourless glassy solid which could be recrystallised from water as the zwitterion, m.p. > 200 °C as described for the butyl analogue; $\delta_H(D_2O$; pD = 10) 2.06 (16 H, m, $CH_2N$), 2.26 (8 H, br, $CH_2N$), 7.25 (12 H, m, Ar), 7.46 (8 H, m, *ortho* Ar); $\delta_P\{^1H\}(D_2O$; pD = 14), 28.0; $\delta_C(D_2O$; pD = 14) 49.6 (d, $^1J$ 98, $NCH_2P$), 56.0 (br, ring $CH_2N$) 128.3 (br, ArCH) and 130.9, 137.1 (d, $^1J$ 118, CP) (Found: C, 48.3; H, 6.75; N, 6.6. $C_{36}H_{48}N_4P_4O_8 \cdot 5H_2O$ requires: C, 48.6; H, 6.53; N, 6.31%).

*Triethyl* 1,4,7,10-*Tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*) **4**.—1,4,7,10-Tetraazacyclododecane (1 g, 5.8 × $10^{-3}$ mol) was stirred in dry THF (50 $cm^3$) under an argon atmosphere. To this was added paraformaldehyde (0.6 g, 19.2 × $10^{-3}$ mol) and methyldiethoxyphosphine (2.6 g, 19.2 × $10^{-3}$ mol). The mixture was heated under reflux over molecular sieves for about 18 h to give a cloudy solution. The solution was filtered and the solvent was evaporated under vacuum. The product was separated from the tetraester using alumina column chromatography (gradient elution from dichloromethane to 4% methanol–dichloromethane, $R_f$ product = 0.28, 5% methanol–dichloromethane) to yield a colourless oil (0.74 g, 24%); $\delta_H(CDCl_3)$ 1.4 (9 H, t, $OCH_2CH_3$), 1.53 (9 H, d, $PCH_3$), 2.8 (22 H, br, m, $CH_2CH_2$ and $NCH_2$), 4.1 (6 H, m, $OCH_2$); $\delta_P\{^1H\}(CDCl_3)$ 51.4, 51.5 and 51.6; *m/z* (DCI) 533 (100, $M^+ + 1$), 425 [89, $M^+ - P(O)(OC_2H_5)(CH_3)$] (Found: $M^+ + 1$, 533.2793. $C_{20}H_{47}N_4O_6P_3$ requires *M*, 532.2708).

2-*Bromo*-N-*methylethanamide* **5**.—Methylamine hydrochloride (13.5 g, 0.2 mol) was added to a stirred solution of 1,2-dichloroethane (150 $cm^3$) and sodium hydroxide (16 g, in 25 $cm^3$ of water). The mixture was cooled to −10 °C using an ice–salt–ethanol bath. Bromoacetyl bromide (31.5 g, 0.2 mol) in 1,2-dichloromethane (25 $cm^3$) was added to the solution at a rate at which the temperature of the solution was kept below −10 °C. After the addition, the mixture was warmed to room temperature, the organic layer was separated, dried with magnesium sulfate and the solvent was evaporated under vacuum to give a pale brown solid. The product was isolated as white crystals by sublimation (25 °C, 0.05 mmHg); $\delta_H(CDCl_3)$, 2.87 (3 H, d, $HNCH_3$), 3.9 (2 H, s, $BrCH_2$) and 6.6 (1 H, br s, HN); *m/z* (CI) 152 ($M^+ + 1$) and 151 ($M^+$) (Found: C, 23.6; H, 4.0; N, 9.15. $C_3H_6BrNO$ requires C, 23.7; H, 3.95; N, 9.21%).

*Triethyl* 10-(*Methylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*) **6a**.—The triester **4** (0.1 g, 1.8 × $10^{-4}$ mol) and potassium carbonate (0.03 g, 1.8 × $10^{-4}$ mol) were stirred in anhydrous dimethylformamide (5 $cm^3$) under an argon atmosphere. To this was added 2-bromo-*N*-methylethanamide (0.03 g, 1.8 × $10^{-4}$ mol) and the mixture was heated at 80 °C for about 16 h to give a cloudy solution. The solvent was evaporated and the residue mass was redissolved in dichloromethane and filtered to give a clear solution. The solvent was evaporated and the crude product was purified using alumina column chromatography to yield a colourless oil (68 mg, 63%) (gradient elution from dichloromethane to 2% methanol–dichloromethane, $R_f$ = 0.6, 10% methanol–dichloromethane); $\delta_H(CDCl_3)$ 1.31 (9 H, t, $^3J$ 7.5, $CH_2CH_3$), 1.5 (9 H, d, $^2J$ 12.5, $PCH_3$), 2.85 (27 H, br, m, $CH_2CH_2$, $NCH_2$ and $NCH_3$), 4.06 (6 H, dt $POCH_2$) and 8.2 (1 H, br s, NH); $\delta_P\{^1H\}(CDCl_3)$ 52.1, 52.3 and 52.4; *m/z* (DCI) 604 (100, $M^+ + 1$) and 533 [12.5, $M^+ - CH_2C(O)NHMe$]. A satisfactory microanalysis could not be obtained for this product.

10-(*Methylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinic Acid*) **6b**.—The monoamide triester **6a** (0.05 g, 5.9 × $10^{-4}$ mol) was treated with potassium deuteroxide in deuterium oxide and the $^1H$ NMR spectrum of the reaction mixture comprised resonances corresponding to ethanol and the hydrolysed product; $\delta_H(D_2O)$ 1.2 (9 H, d, $PCH_3$) and 2.66 (27 H, br, m, $CH_2CH_2$, $NCH_2$ and $NCH_3$); $\delta_P\{^1H\}(D_2O)$ 39.3, 39.4, 39.5; *m/z* (FAB) 520 (100, $M^+ + 1$) (Found: $M^+$, 520.210. $C_{17}H_{35}N_5O_7P_3$ requires *M*, 519.215).

1-(*Dimethylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane* **7a**.—1,4,7,10-Tetraazacyclododecane (0.32 g, 1.8 × $10^{-3}$ mol) and molybdenum hexacarbonyl (0.5 g, 1.8 × $10^{-3}$ mol) in dibutyl ether (20 $cm^3$) were heated at reflux temperature, under argon for 2 h to give a bright yellow precipitate. The yellow precipitate was filtered under argon and dried under vacuum. The yellow 1,4,7,10-tetraazacyclododecane–molybdenum tricarbonyl complex (0.62 g, 1.7 × $10^{-3}$ mol) and fine mesh anhydrous potassium carbonate (excess) were taken into degassed dry dimethylformamide (10 $cm^3$) and heated to 80 °C under an argon atmosphere. To this was added 2-bromo-*N*,*N*-dimethylethanamide (0.3 g, 1.7 × $10^{-3}$ mol) and heating was continued for another 1.5 h. The solvent was distilled off under vacuum. The residue was taken up in hydrochloric acid solution (10%, v/v). The resulting acidic solution was oxidised in air for about 1.8 h. The pH of the solution was raised to 14 with potassium hydroxide pellets with cooling. Molybdenum residues were filtered off to give a clear solution. The product was extracted into chloroform (4 × 50 $cm^3$) and the solvent was evaporated off to give a pale yellow oil (0.37 g, 78%); $\delta_H(CDCl_3)$ 2.57 (6 H, br m, $NCH_2$), 2.66 (2 H, s, $NCH_2$), 2.77 (8 H, br m, $NCH_2$), 2.90 (3 H, s, $NCH_3$), 3.00 (3 H, s, $NCH_3$) and 3.41 (2 H, s, $NCH_2CO$); $\delta_C(CDCl_3)$ 35.1, 36.5 (s, $NCH_3$) 45.1, 45.7, 45.88, 46.86, 51.8 (s, $NCH_2$ ring) and 56.9 (s, $NCH_2C{=}O$), 170.3 (s, C=O); *m/z* (DCI) 257 (100, $M^+$) (Found: $M^+$, 257.2209. $C_{12}H_{27}N_5O$ requires *M*, 257.2216).

*Triethyl* 10-(*Dimethylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*) **7b**.—Methyldiethoxyphosphine (1.14 g, $8.34 \times 10^{-3}$ mol) followed immediately by paraformaldehyde (0.62 g, $8.34 \times 10^{-3}$ mol) were added to anhydrous tetrahydrofuran (50 $cm^3$) containing the monosubstituted cycle **7a** (0.65 g, $2.5 \times 10^{-3}$ mol) at 100 °C under an argon atmosphere. The solution was heated at reflux temperature for 18 h over 4Å molecular sieves. Excess paraformaldehyde was filtered off and the solvent was removed under vacuum to yield a pale yellow oil. The product (0.8 g, 51%) was isolated following alumina column chromatography as a mixture of stereoisomers (gradient elution from dichloromethane to 3% ethanol–dichloromethane, $R_f$ = 0.55, 10% ethanol–dichloromethane); $\delta_H(CDCl_3)$ 1.25 (9 H, t, $^3J$ 4, $OCH_2CH_3$), 1.47 (9 H, d, $^2J$ 8, $PCH_3$), 2.15 (3 H, s, $NCH_3$), 2.21 (3 H, s, $NCH_3$), 2.5–3.1 (24 H, br m, $NCH_2$ ring, $NCH_2P$, $NCH_2CO$), 4.0 (6 H, dt, $OCH_2CH_3$); $\delta_P\{^1H\}(CDCl_3)$ 52.5, 52.8 and 53.2; $\delta_C(CDCl_3)$ 13.0 (d, $^1J$ 90, $PCH_3$), 16.3 (d, $^3J$ 5.8, $OCH_2CH_3$), 34.9, 36.3 (s + s, $NCH_3$), 51.9 (d, $J_{PC}$ 104, $NCH_2P$), 53.5, 53.7, 53.9, 54.6, 54.7 ($CH_2N$, ring), 57.1 (s, $CH_2NCO$), 59.8 (d, $^3J$ 5.6, $OCH_2CH_3$) and 171.3 (CO); *m/z* (DCI) 618 ($M^+ + 1$, 100) (Found: $M^+ + 1$, 617.3249. $C_{24}H_{54}N_5O_7P_3$ requires $M + 1$, 617.3236).

10-(*Dimethylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinic Acid*) **7c**.—Compound **7b** (0.6 g, $9.7 \times 10^{-4}$ mol) was taken into a solution of potassium deuteroxide in deuterium oxide. The solution was stirred for 16 h at room temperature. The $^1H$ NMR spectrum of the solution was comprised of resonances corresponding to ethanol and the title product. The solution was neutralised using hydrochloric acid and the solvent was evaporated to dryness to give a quantitative yield of the title product; $\delta_H(D_2O$; pD = 5) 0.99 (6 H, d, $^2J$ 12.5, $PCH_3$), 1.02 (3 H, d, $^2J$ 12.5, $PCH_3$), 2.1–2.7 (24 H, br m, $NCH_2$ ring, $NCH_2CO$, $NCH_2P$), 2.67 (3 H, s, $NCH_3$) and 2.78 (3 H, s, $NCH_3$); $\delta_P(D_2O)$ 38.58, 38.76 and 39.06; *m/z* (FAB) 534 (100, $M^+$).

1-(*Dibutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane* **8a**.—Compound **8a** was synthesised using a method similar to that of compound **7a** using 1,4,7,10-tetraazacyclododecane (1 g, $5.8 \times 10^{-3}$ mol) and molybdenum hexacarbonyl (1.53 g, $5.8 \times 10^{-3}$ mol) in dibutyl ether (100 $cm^3$). The yellow molybdenum tricarbonyl complex and potassium carbonate (0.85 g, excess) were taken up in degassed anhydrous DMF (60 $cm^3$) and 2-bromo-*N*,*N*-dibutylethanamide (1.45 g, $5.8 \times 10^{-3}$ mol) was added. The product was isolated as a colourless oil (1.3 g, 86%); $\delta_H(CDCl_3)$ 0.7 (6 H, m, $CH_2CH_3$), 1.05 (4 H, m, $CH_2CH_2$), 1.30 (4 H, m, $CH_2CH_2$), 2.55 (16 H, m, $NCH_2$ ring), 3.0 [4 H, m, $N(CH_2)_2$] and 3.25 (2 H, $NCH_2CO$); *m/z* (DCI) 342 (100, $M^+ + 1$) (Found: $M^+ + 1$, 342.3149. $C_{18}H_{39}N_5O$ requires *M*, 341.3155).

*Triethyl* 10-(*Dibutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*) **8b**.—The title compound was synthesised using a method similar to that for **7b**, using **8a** (1.2 g, $3.5 \times 10^{-3}$ mol) and paraformaldehyde (0.42 g, $12.3 \times 10^{-3}$ mol) in anhydrous tetrahydrofuran (30 $cm^3$) which were heated to 100 °C and diethoxy(methyl)phosphine (1.68 g, $12.3 \times 10^{-3}$ mol) was added. The product was purified using alumina column chromatography (gradient elution from dichloromethane to 5% ethanol–dichloromethane, $R_f$ = 0.4, 10% ethanol–dichloromethane) and was isolated as a pale oil (1.1 g, 45%); $\delta_H(CDCl_3)$ 0.95 (6 H, m, $CH_2CH_3$), 1.21 (8 H, m, $CH_2CH_2$), 1.31 (9 H, t, $^3J$ 7.5, $OCH_2CH_3$), 1.54 (9 H, d, $^2J$ 15, $PCH_3$), 2.5–3.5 (24 H, br m, $NCH_2$ ring, $NCH_2P$, $NCH_2CO$), 3.66 [4 H, m, $N(CH_2)_2$] and 4.06 (6 H, dq + dq, $OCH_2CH_3$); $\delta_P\{^1H\}$-$(CDCl_3)$ 51.86, 51.73 and 51.62; *m/z* (Found: $M^+ + 1$, 702.4189. $C_{30}H_{66}N_5O_7P_3$ requires *M*, 701.4175).

10-(*Dibutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinic Acid*) **8c**.—The title compound was prepared using a method similar to that for compound **7c**; $\delta_H(D_2O$; pD = 5) 0.92 (6 H, t, $^3J$ 7.5, $CH_2CH_3$), 1.1–1.8 (17 H, br m, $CH_2CH_2$, PMe), 2.5–2.7 (4 H, br, $NCH_2$) and 3.51 (24 H, br, $NCH_2$ ring, $NCH_2CO$, $NCH_2P$); $\delta_P\{^1H\}(D_2O)$ 37.2, 37.5 and 37.9; *m/z* (FAB, glycerol) 619 (100, $M^+ + 2$).

1-(*Dibenzylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane* **9a**.—The title compound was synthesised using a method similar to that for compound **7a** using 1,4,7,10-tetraazacyclododecane (0.8 g, $4.7 \times 10^{-3}$ mmol), molybdenum hexacarbonyl (1.26 g, $4.76 \times 10^{-3}$ mmol), potassium carbonate (excess) and *N*,*N*-dibenzyl-2-bromoethanamide (1.0 g, $4.6 \times 10^{-3}$ mmol) and was isolated as a pale yellow oil (1.5 g, 78%); $\delta_H(CDCl_3)$ 2.5–2.8 (16 H, br m, $NCH_2$ ring), 3.75 (2 H, s, $NCH_2CO$), 4.41, 4.60 [2 H + 2 H, s + s, $N(CH_2)_2$], 7.3 (10 H, br m, Ar); *m/z* (DCI) 410 (100, $M^+ + 1$) (Found: $M^+ + 1$, 410.2846. $C_{24}H_{35}N_5O$ requires *M*, 409.2842).

*Triethyl* 10-(*Dibenzylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*) **9b**.—The title compound was synthesised using a similar method to that of the compound **7b** using the amine **9a** (1.0 g, $2.4 \times 10^{-3}$ mmol) paraformaldehyde (0.3 g $\times 10^{-3}$ mmol) and methyldiethoxyphosphine (1.24 g, $9.0 \times 10^{-3}$ mmol). The product was purified using alumina column chromatography (gradient elution from dichloromethane to 5% ethanol–dichloromethane, $R_f$ = 0.6, 10% ethanol–dichloromethane) and was isolated as a colourless oil (1 g, 55%); $\delta_H(CDCl_3)$ 1.29 (9 H, t, $^3J$ 7.5, $OCH_2CH_3$), 1.56 (9 H, d, $^2J$ 17, $PCH_3$), 2.5–3.2 (22 H, br m, $NCH_2$ ring, $NCH_2P$), 3.66 (2 H, s, $NCH_2CO$), 4.02 (6 H, dq, $POCH_2CH_3$) and 4.70, 4.80 [4 H, s, $N(CH_2)_2$]; $\delta_P\{^1H\}$-$(CDCl_3)$ 51.7, 51.8 and 52.0; *m/z* (DCI) 769 (100, $M^+$). A satisfactory microanalysis was not obtained for this product.

10-(*Dibenzylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinic Acid*) **9c**.—The title compound was prepared using a method similar to that for compound **7c**; $\delta_H(D_2O$; pD = 5) 1.07 (9 H, t, $^2J$ 14.5, $PCH_3$), 1.9–2.8 (24 H, br, $NCH_2$ ring, $NCH_2CO$ + $NCH_2P$), 4.1–4.4 [4 H, br, $N(CH_2)_2$] and 7.0 (10 H, br, Ar]; $\delta_P\{^1H\}(D_2O)$ 36.4, 36.5 and 36.6; *m/z* (FAB) 686 (100, $M^+ + 1$).

1-(*Methylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane* **10a**.—The title compound was synthesised using a method similar to that for **7a** using 1,4,7,10-tetraazacyclododecane (1 g, $5.8 \times 10^{-3}$ mol), molybdenum hexacarbonyl (1.54, $5.8 \times 10^{-3}$ mol), potassium carbonate (excess) and 2-bromo-*N*-methylethanamide (0.88 g, $5.8 \times 10^{-3}$ mol) to give a colourless oil (1.1 g, 84%); $\delta_H(CDCl_3)$ 2.58 (16 H, br m, $NCH_2$ ring), 2.73 (3 H, d, $^3J$ 5, $NCH_3$), 3.08 (2 H, s, $NCH_2CO$) and 7.70 (1 H, br s, NH); $\delta_C(CDCl_3)$ 35.5 ($NCH_3$), 45.2, 45.8, 46.0, 47.0 and 52.1 ($NCH_2$ ring), 57.8 ($CH_2CO$) and 171.2 (C=O); *m/z* (DCI) 244 (100, $M^+ + 1$) (Found: $M^+ + 1$, 244.2063. $C_{11}H_{25}N_5O$ requires *M*, 243.2059).

*Triethyl* 10-(*Methylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*butylphosphinate*) **10b**.—The title compound was prepared using a method similar to that for compound **7b** using the amine **10a** (0.4 g, $1.6 \times 10^{-3}$ mol), paraformaldehyde (0.15 g, $1.6 \times 10^{-3}$ mol) and butyldiethoxyphosphine (0.87 g, $4.9 \times 10^{-3}$ mol). The product (isolated as a mixture of diastereoisomers) was purified using

alumina column chromatography (gradient elution from dichloromethane to 2% ethanol–dichloromethane, $R_f$ = 0.2, 10% ethanol–dichloromethane) to yield a colourless oil (0.83 g, 68%); $\delta_H(CDCl_3)$ 0.89 (9 H, t, $^3J$ 7.2, $CH_2CH_3$), 1.26 (9 H, t, $^3J$ 7, $OCH_2CH_3$), 1.3–1.8 (18 H, m, $PCH_2CH_2CH_2$), 2.5–3.6 (27 H, br m, $NCH_2$ ring, $NCH_2P$, $NCH_2CO$, $NCH_3$), 4.1 (6 H, dq, $OCH_2CH_3$) and 8.3 (1 H, br s, NH); $\delta_P\{^1H\}(CDCl_3)$ 53.2, 53.3 and 53.8; $\delta_C(CDCl_3)$ 13.4 ($CCH_2CH_3$), 16.51 ($OCH_2CH_3$), 23.55, 23.58, 23.67, 23.82 and 25.81 ($CH_2C$), 27.5, 27.8 (d + d, $^1J$ 86, $CH_2P$), 52.8 (d, $^1J$ 100, $CH_2N$), 53.59, 53.69, 53.78, 53.96, 54.05, 54.78, 54.85, 54.89, 55.47 (ring $CH_2N$, NMe), 59.84 (d, $^2J$ 6, $CH_2O$) and 171.89 (s, C=O); *m/z* (DCI) 729 (100, $M^+$).

10-(*Methylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*butylphosphinic Acid*) **10c**.—The title compound was prepared using a method similar to that for compound **7c**; $\delta_H(D_2O$; pD = 5) 0.92 (9 H, t, $^3J$ 7.5, $CH_2CH_3$), 1.3–1.45 (6 H, br, $PCH_2$), 1.45–1.65 (12 H, br, $CH_2CH_3$) and 2.2–2.9 (27 H, br, $NCH_2$ ring, $NCH_2CO$, $NCH_2P$, $NCH_3$); $\delta_P\{^1H\}(D_2O)$ 45.8, 45.9 and 46.0; *m/z* (FAB) 645 (100, $M^+ + 1$).

*Trimethyl* 1-(*Dimethylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*phenylphosphinate*) **11b**.—The title compound was prepared using a method similar to that of compound **7b** using the amine **7a** (0.3 g, 1.16 × $10^{-3}$ mol), phenyldimethoxyphosphine (0.65 g, 3.5 × $10^{-3}$ mol) and paraformaldehyde (0.15 g, 3.5 × $10^{-3}$ mol). The product was purified using alumina column chromatography (gradient elution from dichloromethane to 2% methanol–dichloromethane, $R_f$ = 2.5, 10% methanol–dichloromethane) and yielded a colourless oil (0.6 g, 69%); $\delta_H(CDCl_3)$ 1.9–2.9 (24 H, br m, $NCH_2$ ring, $NCH_2P$, $NCH_2CO$), 2.8, 2.9 (6 H, s + s, $NCH_3$), 3.6 (6 H, dt, $OCH_2CH_3$), 7.5 (9 H, br m, Ar) and 7.8 (6 H, br m, *ortho* Ar); $\delta_P\{^1H\}(CDCl_3)$ 46.3; *m/z* (DCI) 762 (100, $M^+ + 1$) (Found: $M^+ + 1$, 762.3231. $C_{36}H_{54}N_5O_7P_3$ requires *M*, 761.3236).

10-(*Dimethylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*phenylphosphinic Acid*) **11c**.—The title compound was prepared using a method similar to that for compound **7c**; $\delta_H(D_2O$; pD = 5) 2.1–2.8 (22 H, br, $NCH_2$ ring, $NCH_2P$), 2.83 (2 H, br, $NCH_2CO$), 2.92 (3 H, s, $NCH_3$), 2.99 (3 H, s, $NCH_3$), 7.54 (9 H, br, Ar), 7.75 (6 H, br, *ortho* Ar); $\delta_P\{^1H\}(D_2O)$ 29.1, 29.6 (5, in ratio 1:2); $\delta_C(D_2O)$ 35.7, 36.6 [s + s, $N(CH_3)_2$], 48.8, 51.33, 54.25 (br, $NCH_2$ ring, $NCH_2P$, $NCH_2CO$), 128.3, 128.4, 130.7, 130.9, 131.3 and 138.5 (br, Ar) and 172.88 (CO); *m/z* (FAB) 720 ($M^+ + 1$), 678.

1-*Benzyl*-1,4,7,10-*tetraazacyclododecane* **12a**.—This compound was prepared using a method similar to that of compound **7a** using 1,4,7,10-tetraazacyclododecane (1 g, 5.8 × $10^{-3}$ mol), molybdenum hexacarbonyl (1.54 g, 5.8 × $10^{-3}$ mol), dibutyl ether (70 $cm^3$), benzyl chloride (0.74 g, 5.8 × $10^{-3}$ mol) and potassium carbonate (excess) to give a colourless solid, m.p. 78–79 °C (1.3 g, 86%); $\delta_H(CDCl_3)$ 2.1–2.5 (16 H, br m, $NCH_2$ ring), 3.25 (2 H, s, $NCH_2P$) and 6.95 (5 H, br m, Ar); $\delta_C(CDCl_3)$ 45.3, 46.6, 47.4 and 51.5 ($CH_2N$ ring) and 59.44 ($NCH_2Ph$), 127.2, 128.5, 129.1 and 139.1 (Ar); *m/z* (DCI) 263 (100, $M^+ + 1$) (Found: $M^+ + 1$, 263.2194. $C_{15}H_{26}N_4$ requires *M*, 262.2188).

*Triethyl* 10-*Benzyl*-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*) **12b**.—The ester **12b** was prepared using a method similar to that of compound **7b**, using the amine **12a** (1 g, 3.8 × $10^{-3}$ mol), diethoxy(methyl)phosphine (1.71 g, 12.5 × $10^{-3}$ mol) and paraformaldehyde (0.5 g, 12.5 × $10^{-3}$ mol). The product was purified using alumina column chromatography (gradient elution from dichloromethane to 2% ethanol–dichloromethane, $R_f$ = 0.4, 10% ethanol–dichloromethane) to yield a colourless oil (1.5 g, 65%); $\delta_H(CDCl_3)$ 1.19 (9 H, t, $^3J$ 6, $OCH_2CH_3$), 1.35 (9 H, d, $^2J$ 16, $PCH_3$), 2.4–3.0 (22 H, br m, $NCH_2$ ring, $NCH_2P$), 3.45 (2 H, s, $NCH_2Ar$), 3.92 (6 H, dt, $OCH_2CH_3$) and 7.2 (5 H, br m, Ar); $\delta_P\{^1H\}(CDCl_3)$ 52.9 and 53.1; $\delta_C(CDCl_3)$ 14.0 (d, $^1J$ 90, $PCH_3$), 17.12 (d, $^3J$ 6, $OCH_2CH_3$) 14.0 (d, $^1J$ 90, $PCH_3$), 17.12 (d, $^3J$ 6, $OCH_2CH_3$), 53.1, 53.8, 54.7, 54.8, 55.2, 56.4 and 56.5 ($NCH_2$ ring, $NCH_2P$), 60.5 (d, $^3J$ 5.5, $NCH_2Ar$), 127.3, 128.5, 129.8 and 139.4 (ArC) (Found: $M^+ + 1$, 623.3179. $C_{27}H_{53}N_4O_6P_3$ requires: *M*, 622.3178).

10-*Benzyl* 1,4,7,10-*Tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinic Acid*) **12c**.—The title compound was prepared using a method similar to that for compound **7c**; $\delta_H(D_2O$; pD = 5) 1.3 (6 H, d, $^2J$ 14, $PCH_3$), 1.34 (3 H, d, $^2J$ 14, $PCH_3$), 2.8–383 (16 H, br, $NCH_2$ ring), 3.52 (6 H, br, $NCH_2P$), 4.45 (2 H, s, $NCH_2Ph$) and 7.38 (5 H, br, Ar); $\delta_P\{^1H\}(D_2O)$ 37.9 and 50.7 (1:2); *m/z* (FAB) 540 (100, $M^+ + 2$) and 539 ($M^+ + 1$).

1-[2-(*Trimethylammonio*)*ethylcarbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane hydroxide* **13a**.—The amine **13a** was prepared using a method similar to that for compound **7a** using 1,4,7,10-tetraazacyclododecane (0.4 g, 2.32 × $10^{-3}$ mol), molybdenum hexacarbonyl (0.61 g, 2.32 × $10^{-3}$ mol), and the ammonium salt **14** (0.86 g, 2.32 × $10^{-3}$ mol). The oxidised acidic solution was treated with potassium hydroxide to adjust the pH to 14. The aqueous layer was washed with chloroform (2 × 30 $cm^3$) to remove the residual free amine. The molybdenum residues were filtered off from the aqueous solution and the solvent was removed to give a white residue. The residual solid was taken up in methanol (2 × 50 $cm^3$) and insoluble potassium chloride was filtered off. This process was repeated until no more potassium salts were deposited. The solvent was evaporated off to give a colourless solid (0.6 g, 78%); $\delta_H(CD_3OD)$ 2.6–3.0 (16 H, br m, $NCH_2$ ring), 3.40 [11 H, br s, $N(CH_3)_3$, $NCH_2CO$] and 3.83 (2 H, t, $^3J$ 7.5, $CH_2CH_3$); *m/z* (FAB) 315 ($M^+$) and 314 (100, $M^+ - 1$). A satisfactory microanalysis was not obtained for this product.

10-[2-(*Trimethylammonio*)*ethylcarbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltriacetate Chloride* **13b**.—The compound **13a** (as the hydroxide) was converted into chloride by stirring for 1 h with Amberlite IRC(I) anion exchange resin ($Cl^-$) in a 1:1 (v/v) methanol–water solution. The resin was filtered off and the solvent was removed to give a white solid. The chloride salt (0.2 g, 5.7 × $10^{-4}$ mol), ethyl bromoacetate (0.3 g, 1.83 × $10^{-3}$ mol) and potassium carbonate (0.22 g, 1.83 × $10^{-3}$ mol) were heated at reflux temperature for 18 h. The remaining white solid was filtered off. The solvent was removed and the product was purified using alumina column chromatography (gradient elution from 10% to 50% ethanol–dichloromethane, $R_f$ = 0.8, 70% ethanol–dichloromethane) to yield a glassy solid (0.2 g, 58%); $\delta_H(D_2O)$ 1.50 (9 H, t, $^3J$ 7.5, $OCH_2CH_3$), 1.5–3.3 (24 H, br m, $NCH_2$ ring, $NCH_2CO$), 3.19 [9 H, s, $N(CH_3)_3$], 3.50 (6 H, q, $^3J$ 7.5, $OCH_2CH_3$), 3.80 (2 H, br, $COCH_2$) and 4.40 (2 H, br, $CH_2CH_2$); *m/z* (FAB) 573 (100, $M^+$).

10-[2-(*Trimethylammonio*)*ethylcarbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*tri*(*acetic Acid*) *Chloride* **13c**.—The title compound was prepared using a method similar to that for compound **7c**; $\delta_H(D_2O$; pD = 5) 2.2–2.7 (16 H, br, $NCH_2$ ring), 2.8–3.0 (8 H, br, $NCH_2CO$), 3.08 [9 H, s, $N(CH_3)_3$] and 3.3–3.5 (4 H, br, $CH_2CH_2$); $\delta_C(D_2O)$ 34.88, 34.95 and 35.0 ($NMe_3$), 46.5–47.5 (br s, $CH_2$ ring, $NCH_2CO_2$, $NCH_2CON$),

53.9, 54.5 (s + s, $NCH_2CH_2$) and 176.5 (CO); *m/z* (FAB) 489.30 (100, $M^+$).

2-*Bromo*-N-(2-*trimethylammonioethyl*)*ethanamide Hexafluorophosphate* **14**.—A mixture of (2-aminoethyl)trimethylammonium chloride (1 g, $5.7 \times 10^{-3}$ mol) and sodium hydroxide (0.46 g, $1.5 \times 10^{-3}$ mol) in 1,2-dichloroethane (100 $cm^3$) was cooled to −10 °C using an ice–salt–ethanol bath. Bromoacetyl bromide (1.14 g, $5.7 \times 10^{-3}$ mmol) was added to the stirred reaction mixture (portion-wise) while maintaining the temperature below 0 °C. The reaction mixture was warmed to room temperature and the stirring was continued for another hour. The organic layer was separated, and the aqueous layer was neutralised and washed with 1,2-dichloroethane (2 × 15 $cm^3$). Ammonium hexafluorophosphate (excess) was added to the aqueous solution to give a white precipitate. The solid was separated, washed with water (twice) and dried to yield a colourless solid, m.p. >240 °C (1.2 g, 53%); $\delta_H$[$^2H_6$]acetone) 3.41 [9 H, s, $\overset{+}{N}(CH_3)_3$], 3.70 [2 H, $CH_2\overset{+}{N}(CH_3)_3$], 3.87 (2 H, dt, $NCH_2$), 3.94 (2 H, s, $BrCH_2C$) and 7.99 (1 H, br s, NH); $\delta_C$[$^2H_6$]acetone) 34.95 (s, $NCH_2$), 35.06 (s, $BrCH_2$), 53.97, 54.05 and 54.1 [s, $\overset{+}{N}(CH_3)_3$] and 65.41 [br s, $C H_2\overset{+}{N}(CH_3)_3$]; *m/z* (FAB) 224 (100, $M^+ + 1$) (Found: C, 22.8; H, 4.3; N, 7.5. $C_7H_{16}N_2BrF_6OP$ requires: C, 22.7; H, 4.33; N, 7.59%).

2-*Bromo*-N,N-*diisobutylethanamide* **15**.—To a solution of diisobutylamine hydrochloride (33.14 g, 0.20 mol) and sodium hydroxide (16 g, 0.4 mol in 20 $cm^3$ of water) in 1,2-dichloroethane (150 $cm^3$) was added a solution of bromoacetylbromide (40.4 g, 0.2 mol) in $C_2H_4Cl_2$ (25 $cm^3$) dropwise maintaining a temperature of approximately −10 °C by way of an ice–salt–ethanol bath. The solution was stirred at −10 °C for a further 1 h, allowed to warm to room temperature and stirred overnight. The organic phase was washed with NaOH (0.1 mol $dm^{-3}$, 2 × 25 $cm^3$), HCl (0.1 mol $dm^{-3}$, 2 × 25 $cm^3$), and water (3 × 25 $cm^3$), dried ($MgSO_4$), and the solvent evaporated off to yield a colourless viscous oil (36.03 g, 72%); $\nu_{max}/cm^{-1}$ 1655 [NC(O)]; $\delta_H(CDCl_3)$ 1.02 (6 H, d, *J* 6.6, $CH_3$), 1.08 (6 H, d, *J* 6.4, $CH_3$), 1.15 (2 H, m, *J* 7.0, CH), 2.32 (4 H, d, *J* 7.6, $NCH_2$) and 3.07 (2 H, s, $BrCH_2$); *m/z* (CI) 250 ($M^+$) (Found: C, 47.7; H, 8.2; N, 5.45. $C_{10}H_{20}BrNO$ requires: C, 48.0; H, 8.00; N, 5.60%).

N-(4-*Aminobutyl*)-4-*methoxybenzenesulfonamide* **16**.—4-Methoxybenzenesulfonyl chloride (7.62 g, 36.9 mmol) was added to a stirred solution of butane-1,4-diamine (22.46 g, 254.8 mmol) in dichloromethane (400 $cm^3$) over a period of 45 min. The solution was stirred under nitrogen overnight, filtered, the solvent removed under reduced pressure, and saturated aqueous potassium hydroxide added to raise the pH to ⩾13. The aqueous phase was extracted exhaustively with chloroform, the organic fractions combined, dried ($MgSO_4$) and the solvent removed under reduced pressure to yield a thick pale yellow oil (8.38 g, 88%) of the title compound; $\delta_H$(DMSO) 1.37 (2 H, p, *J* 6.8, $CH_2CH_2NH_2$), 1.39 (2 H, p, *J* 6.5, $CH_2CH_2NHSO_2$), 2.48 (2 H, t, *J* 6.5, $CH_2NH_2$), 2.72 (2 H, t, *J* 6.6, $CH_2NHSO_2$), 3.4–4.0 (3 H, br s, $NH_2$, NH), 3.84 (3 H, s, $CH_3O$), 7.12 (2 H, d, *J* 8.8, $CHCSO_2$) and 7.77 (2 H, d, *J* 9.1, $CHCOCH_3$); $\delta_C$(DMSO) 26.9 (1 C, $CH_2CH_2NH_2$), 30.7 (1 C, $CH_2CH_2NHSO_2$), 41.5 (1 C, $CH_2NH_2$), 42.8 (1 C, $CH_2NHSO_2$), 55.8 (1 C, $CH_3O$), 114.5 (2 C, $CHCSO_2$), 128.9 (2 C, $CHCOCH_3$), 132.6 (1 C, $CSO_2$) and 162.3 (1 C, $COCH_3$) (Found: $M^+$, 258.1031. $C_{11}H_{18}N_2O_3S$ requires *M*, 258.1038).

N-(4-*Bromoacetamidobutyl*)-4-*methoxybenzenesulfonamide* **17**.—To a solution of the monohydrochloride salt of **16** (8.38 g, 28.43 mmol) and sodium hydroxide (2.28 g, 57.00 mmol, in 6 $cm^3$ of water) in 1,2-dichloroethane (300 $cm^3$) was added bromoacetyl bromide (5.71 g, 28.28 mmol) in $C_2H_4Cl_2$ (100 $cm^3$) dropwise, maintaining a temperature of approximately −10 °C. The solution was stirred at −10 °C for a further 1 h, allowed to warm to room temperature, and stirred overnight. The organic phase was washed with NaOH (0.1 mol $dm^{-3}$, 2 × 25 $cm^3$), HCl (0.1 mol $dm^{-3}$, 2 × 25 $cm^3$), and water (3 × 25 $cm^3$) and dried ($MgSO_4$) and the solvent was evaporated off, to yield, on standing, a crude yellow solid (approx. 75%). The solid was shaken vigorously in hot toluene (100 $cm^3$), the cloudy solvent decanted off, cooled (0 °C), and any precipitated solids filtered off. These were washed with a small quantity of cold toluene, and dried *in vacuo*. The process was repeated until the solution no longer became cloudy on shaking with the crude solid residue. A colourless solid resulted, m.p. 76–77 °C (3.90 g, 36%) (Found: $M^+ + 1$, 379.0251. $C_{13}H_{19}BrN_2O_4S$ requires *M*, 378.0249; $\nu_{max}/cm^{-1}$ 1650 (CO) (Found: N, 7.4; C, 41.35; H, 5.05. $C_{13}H_{19}BrN_2O_4S$ requires: N, 7.39; C, 41.16; H, 5.05%); $\delta_H(CDCl_3)$ 1.48 (4 H, m, $CH_2CH_2$-$CH_2NH$), 2.84 [2 H, m, $CH_2NHC(O)$], 3.17 (2 H, m, $CH_2NHSO_2$), 3.69 (2 H, s, $CH_2Br$), 3.80 (3 H, s, $OCH_3$), 5.77 [1 H, t, C(O)NH], 6.92 (2 H, d, *J* 8.3, $CHCSO_2$), 7.07 (1 H, t, $SO_2NH$) and 7.74 (2 H, d, *J* 8.3, $CHCOCH_3$); $\delta_C(CDCl_3)$ 26.0 [1 C, $CH_2CH_2NHC(O)$], 26.2 (1 C, $CH_2CH_2NHSO_2$), 28.8 (1 C, $CH_2Br$), 39.2 [1 C, $CH_2NHC(O)$], 42.4 (1 C, $CH_2$-$NHSO_2$), 55.3 (1 C, $OCH_3$), 113.9 (2 C, $CHCSO_2$), 128.7 (2 C, $CHCO$), 130.9 (1 C, $CSO_2$), 162.4 (1 C, $COCH_3$) and 166.2 [1 C, C(O)].

*Molybdenum Tricarbonyl*-1,4,7,10-*tetraazacyclododecane Complex* **18**.—1,4,7,10-tetraazacyclododecane (1.64 g, 6.21 mmol), and molybdenum hexacarbonyl (1.64 g, 6.21 mmol) were refluxed in dibutyl ether under argon at 160 °C for 2 h, the bright yellow solids were filtered off under argon, and dried *in vacuo*, to give the title compound (2.08 g, 95%). This was used directly in the following reaction.

[4-(4-*Methoxyphenylsulfonamido*)*butylcarbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane* **19**.—To the molybdenum tricarbonyl–12-N-4 complex, **18** (3.55 g, 10.09 mmol) in degassed DMF (50 $cm^3$) under argon was added **17** (3.83 g, 10.09 mmol), and a slight excess of mesh potassium carbonate (1.79 g, 12.98 mmol) and the solution was heated for 1–2 h at 80 °C. The solvent was removed under reduced pressure ($10^{-2}$ mmHg), and the black residue taken up in 10% v/v HCl and left open to the air overnight. The pH was adjusted to 14 (KOH pellets) and the suspension filtered (to remove decomplexed molybdenum species), to give a yellow aqueous solution which was exhaustively extracted with dichloromethane. The organic fractions were combined and dried ($K_2CO_3$), and the solvent removed to give a pale yellow oil (4.13 g, 87%) (Found: $M^+ + 1$, 471.2681. $C_{21}H_{38}N_6O_4S$ requires: *M*, 470.2675); $\delta_H(CDCl_3)$ 1.42 (4 H, m, $CH_2CH_2NHSO_2$), 2.10–3.03 [23 H, m, $CH_2N$ ring, $CH_2NHC(O)$, NH ring, $NCH_2C(O)$], 3.12 (2 H, m, $CH_2NHSO_2$), 3.71 (3 H, s, $OCH_3$), 6.82 (2 H, d, *J* 8.8, $CHCSO_2$), 7.60 (2 H, d, *J* 8.8, $CHCOCH_3$) and 7.92 (1 H, t, $SO_2NH$); $\delta_C(CDCl_3)$ 26.0 (2 C, $CH_2CH_2CH_2NH$), 37.8 [1 C, $CH_2NHC(O)$], 42.0 (1 C, $CH_2NHSO_2$), 44.4 [2 C, $CH_2CH_2$-$NCH_2C(O)$], 46.0 [4 C, $CH_2CH_2NHCH_2CH_2NCH_2C(O)$], 52.5 [2 C, $CH_2NCH_2C(O)$], 55.1 (1 C, $OCH_3$), 58.2 [1 C, $NCH_2C(O)$], 113.5 (2 C, $CHCSO_2$), 128.3 (2 C, $CHCOCH_3$), 131.8 (1 C, $CSO_2$), 161.9 (1 C, $COCH_3$) and 171.2 [1 C, C(O)].

1-(*Diisobutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane* **20**.—Synthesis as for **19** using molybdenum tricarbonyl–12-N-4 complex (1.75 g, 4.97 mmol), 2-bromo-*N*,*N*-diisobutylethanamide (1.24 g, 4.97 mmol), and potassium carbonate (0.96 g, 6.94 mmol) to yield a colourless oil (1.43 g, 84%) (Found: $M^+ + 1$, 342.3170. $C_{18}H_{39}N_5O$ requires *M*, 341.3155); $\delta_H$-

($CDCl_3$) 0.73 (6 H, d, *J* 7.2, $CH_3$), 0.77 (6 H, d, *J* 7.0, $CH_3$), 1.82 (2 H, m, CH), 2.40–3.10 (23 H, m, $NCH_2$ ring, NH, $NCH_2CH$) and 3.40 [2 H, s, $NCH_2C(O)$]; $\delta_C$($CDCl_3$) 19.7 (2 C, $CH_3$), 19.8 (2 C, $CH_3$), 26.0 (1 C, CH), 27.3 (1 C, CH), 45.3, 45.4, 46.7, 51.6, 52.4, 54.2, 55.2 [11 C, $NCH_2$ ring, $NCH_2C(O)$, $NCH_2CH$] and 170.6 [1 C, C(O)N].

*Triethyl* 10-(*Diisobutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*) **21**.—Diethoxymethylphosphine (0.81 g, 5.95 mmol), followed immediately by paraformaldehyde (0.25 g, 8.32 mmol) were added to anhydrous THF (30 $cm^3$) containing **20** (0.50 g, 1.47 mmol) at 100 °C under nitrogen. The solution was heated to reflux for 18 h at 100 °C with azeotropic removal of water by 4 Å molecular sieves, followed by filtration (to remove excess paraformaldehyde) and evaporation of the solvent to yield a pale yellow oil. Purification by alumina column chromatography (gradient elution 0–3% methanol in dichloromethane) afforded the title compound (0.58 g, 56%) as a pale yellow oil (Found: $M^+ + 1$, 702.4210. $C_{30}H_{66}N_5O_7P_3$ requires *M*, 701.4175); $\delta_H$($CDCl_3$) 0.80 (6 H, d, *J* 6.5, $CH_3$), 0.86 (6 H, d, *J* 6.5, $CH_3$), 1.25 (9 H, t, $^3J$ 7.1, $CH_2CH_3$), 1.49 (9 H, d, $^1J$ 13.7, $PCH_3$), 1.91 (2 H, m, CH), 2.20–3.80 [28 H, m, $NCH_2$ ring, $NCH_2C(O)$, $NCH_2P$, $NCH_2CH$] and 4.01 (6 H, $POCH_2$); $\delta_C$($CDCl_3$) 13.6 (3 C, $^1J$ 90, $PCH_3$), 16.7 (3 C, $^3J$ 5.4, $OCH_2CH_3$), 20.0 (4 C, $CH_3$), 26.3, 27.6 (2 C, CH), 50–57 [14 C, br, $NCH_2$ ring, $NCH_2C(O)$, $NCH_2P$, $NH_2CH$], 60.1 (3 C, $^2J$ 6.1, $OCH_2$) and 170.5 [1 C, C(O)N]; $\delta_P$($CDCl_3$) 52.5 (br m).

10-(*Diisobutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinic Acid*) **22**.—An excess of 1 mol $dm^{-3}$ aqueous KOH solution was added to the phosphinate ester **21**, and the solution shaken to dissolve all of the compound. The solution was left overnight, the pH lowered to 5 by addition of acetic acid, and the solution passed down an $H^+$ cation-exchange resin column. The solvent was removed to yield the title compound as a clear pale yellow solid, m.p. > 220 °C; $\delta_H$($D_2O$; pD = 4) 0.55–0.85 (12 H, m, $CH_3$), 0.92–1.22 (9 H, m, $PCH_3$), 1.68–1.95 (2 H, m, CH), 2.25–3.50 (22 H, m, $NCH_2$ ring, $NCH_2P$), 2.92–3.17 (4 H, m, $NCH_2$/CH) and 3.17–3.35 [2 H, m, $CH_2C(O)N$]; $\delta_P$($D_2O$; pD = 4) 27.8, 26.6 (ratio 2:1) (Found: $M^+$, 618.330. $C_{24}H_{54}N_5O_7P_3$ requires *M*, 617.3236).

*Triethyl* 10-(*Diisobutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltriacetate* **23**.—To a stirred solution of **20** (0.15 g, 0.43 mmol) in anhydrous ethanol (10 $cm^3$) under nitrogen was added potassium carbonate (0.18 g, 1.33 mmol) and ethyl bromoacetate (0.21 g, 1.24 mmol), and the solution refluxed at 80 °C for 18 h. The solvent was evaporated off, the residue was taken up in dichloromethane and filtered (to remove KBr and excess $K_2CO_3$), and the filtrate was evaporated to yield a pale yellow oil which was purified by alumina column chromatography. (Gradient elution 0–5% methanol in dichloromethane) to yield the title compound, as a pale yellow oil (0.18 g, 68%) (Found: $M^+ + 1$, 600.47. $C_{30}H_{57}N_5O_7$ requires *M*, 599.43); $\delta_H$($CDCl_3$) 0.82 (6 H, d, *J* 6.6, $CH_3$), 0.89 (6 H, d, *J* 6.5, $CH_3$), 1.24 (6 H, t, *J* 7.1, $CH_2CH_3$), 1.25 (3 H, t, *J* 7.1, $CH_2CH_3$), 1.91 (2 H, m, CH), 2.15–3.90 [28 H, m, $NCH_2$ ring, $NCH_2C(O)N$, $NCH_2CH$, $NCH_2CO_2$] and 4.05–4.30 (6 H, m, $OCH_2$); $\delta_C$($CDCl_3$) 13.9 (1 C, $OCH_2CH_3$), 14.0 (2 C, $OCH_2CH_3$), 19.7 (2 C, $CH_3$), 19.9 (2 C, $CH_3$), 26.1 (1 C, CH), 27.2 (1 C, CH), 46–56 [14 C, br, $NCH_2$ ring, $NCH_2CO_2$, $NCH_2C(O)N$, $NCH_2CH$], 60.8 (2 C, $OCH_2$), 61.0 (1 C, $OCH_2$), 170.9 [1 C, C(O)N], 173.0 (2 C, $CO_2$) and 173.3 (1 C, $CO_2$).

10-(*Diisobutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltriacetic Acid* **24**.—Hydrolysis of the ester **23** to the carboxylic acid was brought about by dissolving it in an excess of 1 mol $dm^{-3}$ KOH solution (> three-fold excess) and leaving it for 18 h. Removal of the solvent yielded the acid and an excess of KOH which was removed by taking up the residues in ethanol (15 $cm^3$) and filtering off the insoluble KOH solid. This process was repeated five times. $\delta_H$($D_2O$; pD = 8) 0.76 (12 H, m, $CH_3$), 1.70–1.90 (2 H, m, CH), 2.00–3.23 [26 H, m, $NCH_2$ ring, $NCH_2CO_2$, $NCH_2CH$, $NCH_2C(O)N$] and 3.23–3.48 [2 H, br, $NCH_2C(O)$]; *m*/*z* (FAB) as for **24b**.

10-(*Diisobutylcarbamoylmethyl*)-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltriacetic Acid Trihydrobromide* **24b**.—To the phosphinate ester **24a** (120 mg, 0.20 mmol) was added an excess of phenol (120 mg) and 40% v/w HBr in glacial acetic acid (20 $cm^3$). The solution was heated at 100 °C for 2 days, an extra 15 $cm^3$ of HBr in glacial acetic acid being added after the first day, and the solution was allowed to cool to effect precipitation of the product. The reaction mixture was centrifuged, and the solvent decanted off, to leave a pale white/brown solid which was washed with cold glacial acetic acid (3 × 15 $cm^3$), and diethyl ether (3 × 15 $cm^3$), or until the washings were colourless). (All supernatants and washings were retained and combined.) The solid were taken up in water and filtered, the solvents evaporated off to yield a pale white solid. An equivalent volume of diethyl ether was added to the retained solvent and washings to yield further product, which was washed and filtered as before. The product was crystallised from ethanol–ether to yield a colourless solid, m.p. > 250 °C (65 mg, 43%); $\delta_H$($D_2O$; pD = 2), 0.82 (12 H, 2 × d, $CH_3$), 1.8–2.1 (2 H, m, CH) and 2.7–4.4 [28 H, m, $CH_2$ ring, $NCH_2CO_2$, $NCH_2C(O)N$, $NCH_2CH$] (Found: $M^+$, 516.3334. $C_{24}H_{45}N_5O_7$ requires *M*, 515.3319).

*Triethyl* 10-[4-(4-*Methoxyphenylsulfonamido*)*butylcarbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinate*) **25a**.—Synthesis as for **21** using diethoxymethylphosphine (1.12 g, 8.23 mmol), paraformaldehyde (0.28 g, 9.33 mmol) and **19** (0.97 g, 2.06 mmol). Yield (1.41 g, 82%), as a pale yellow oil (Found: $M^+ + 1$, 831.39. $C_{33}H_{65}N_6O_{10}P_3S$ requires *M*, 830.37); $\delta_H$($CDCl_3$) 1.24 (9 H, t + t, $^3J$ 6.6, $CH_2CH_3$), 1.47 (13 H, two d + m, $^2J$ 13.0, $CH_2CH_2CH_2NHSO_2$, $PCH_3$), 2.20–3.30 [28 H, m, $CH_2$ ring, $NCH_2P$, $NCH_2C(O)$, $CH_2NHSO_2$, $CH_2NHC(O)$], 3.79 (3 H, s, $OCH_3$), 4.00 (6 H, dq + dq, $^3J$ 6.8, $OCH_2$), 6.78 [1 H, t, C(O)NH], 6.88 (2 H, d, *J* 8.6, $CHSCO_2$), 7.72 (2 H, d, $CHCOCH_3$) and 7.91 (1 H, t, $NHSO_2$); $\delta_C$($CDCl_3$) 13.1 (3 C, $^1J$ 89, $PCH_3$), 15.9 (3 C, $^3J$ 5.6, $OCH_2CH_3$), 26.1, 25.9 (2 C, $CH_2CH_2CH_2NHSO_2$), 37.8 [1 C, $CH_2NHC(O)$], 41.8 (1 C, $CH_2NHSO_2$), 53.4–55.4 [12 C, br, $CH_2$ ring, $NCH_2P$, $NCH_2C(O)$], 54.8 (1 C, $OCH_3$), 59.4 (3 C, $^2J$ 6.7, $OCH_2$), 113.2 (2 C, $CHCSO_2$), 128.1 (2 C, $CHCOCH_3$), 131.7 (1 C, $CSO_2$), 161.6 (1 C, $COCH_3$), and 170.6 [1 C, C(O)]; $\delta_P$($CDCl_3$) 52.0, 52.2 (2:1).

*Triethyl* 10-[4-(4-*Methoxyphenylsulfonamido*)*butylcarbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*butylphosphinate*) **25b**.—As for **21** using **19** (0.21 g, 0.45 mmol), diethoxybutylphosphine (0.36 g, 2.02 mmol) and paraformaldehyde (0.08 g, 2.66 mmol). Yielded a pale yellow oil (331 mg, 78%) (Found: $M^+ + 1$, 957.499. $C_{42}H_{83}N_6O_{10}P_3S$ requires *M*, 956.510); $\delta_H$($CDCl_3$) 0.87 (9 H, t, $^3J$ 6.6, butyl $CH_3$), 1.26 (9 H, t, $OCH_2CH_3$), 1.32–1.68 (16 H, br m, $PCH_2CH_2CH_2$, $CH_2CH_2CH_2NHSO_2$), 1.68–1.80 (6 H, m, $PCH_2CH_2$), 2.32–3.42 [28 H, m, $NCH_2P$, $NCH_2$ ring, $CH_2NHSO_2$, $CH_2NHC(O)$, $NCH_2C(O)$], 3.81 (3 H, s, $OCH_3$), 4.03 (6 H, m, $OCH_2$) and 6.60 (1 H, s, $NHSO_2$); $\delta_P$($CDCl_3$) 54.5, 54.9 (2:1).

*Triethyl* 10-[4-(4-*Methoxyphenylsulfanamido*)*butylcarbamo-*

*ylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*benzylphosphinate*) **25c**.—As for **21**, using **19** (0.23 g, 0.49 mmol), diethoxybenzylphosphine (0.41 g, 1.93 mmol) and paraformaldehyde (0.08 g, 2.66 mmol). Yielded a pale yellow oil (298 mg, 58%); $\delta_H(CDCl_3)$ 1.00–1.32 (9 H, m, $OCH_2CH_3$), 1.32–1.56 (4 H, br m, $CH_2CH_2CH_2NHSO_2$), 2.00–2.98 [26 H, m, $NCH_2$ ring, $NCH_2P$, $NCH_2C(O)$, $CH_2NHC(O)$], 2.98–3.35 (8 H, m, $PCH_2C$, $CH_2NHSO_2$), 3.76 (3 H, d, $OCH_3$), 3.79–4.17 (6 H, m, $OCH_2$), 6.40–6.80 [2 H, br s, C(O)NH, $SO_2NH$], 6.86 (2 H, d, *J* 10, $CHCSO_2$), 7.05–7.40 (15 H, m, ArH) and 7.71 (2 H, d, $^3J$ 10, CHCOMe); $\delta_P(CDCl_3)$ 49.1, 49.7 (2:1) (Found: M + 1, 1059.465. $C_{51}H_{77}N_6O_{10}P_3S$ requires *M*, 1058.4635).

10-[(4-*Aminobutyl*)*carbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*methylphosphinic Acid*) *Trihydrobromide* **26a**.—Method as for **24b** using **25a** (160 mg, 0.19 mmol). The product was crystallised from ethanol–ether to yield a colourless solid (as the 3 HBr salt) (140 mg, 89%) (Found: $M^+ + 1$, 577.27. $C_{20}H_{47}N_6O_7P_3$ requires *M*, 576.27); $\delta_H(D_2O)$ 1.47 (9 H, d, $^2J$ 14.4, $PCH_3$), 1.60 (4 H, m, $CH_2CH_2CH_2NH_3^+$), 2.98 (2 H, t, $CH_2NH_3^+$), 3.05–3.75 [24 H, m, $CH_2$ ring, $NCH_2P$, $NCH_2C(O)$] and 4.00 [2 H, m, $CH_2NHC(O)$]; $\delta_C(D_2O)$ 16.9 (3 C, $^1J$ 89, $PCH_3$), 26.5, 27.5 [2 C, $CH_2CH_2NH_3^+$, $CH_2CH_2NHC(O)$], 41.3, 41.5 [2 C, $CH_2NH_3^+$, $CH_2NHC(O)$], 52–56 (11 C, $CH_2$ ring $NCH_2P$), 57.6 [1 C, $NCH_2C(O)$] and 167.8 [1 C, NHC(O)].

10-[(4-*Aminobutyl*)*carbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*butylphosphinic Acid*) *Trihydrobromide* **26b**.—Method as for **24b**, using **25b** (188 mg, 0.20 mmol). Yield (as the 3 HBr salt) (150 mg, 80%); $\delta_H(CD_3OD)$ 0.96 (9 H, t, $^3J$ 6.74, $CH_3$), 1.30–2.50 [22 H, m, $P(CH_2)_3$, $CH_2CH_2CH_2NH_3^+$], 2.90–4.50 [28 H, m, $CH_2$ ring, $NCH_2P$, $NCH_2C(O)$, $CH_2NH_3^+$, $CH_2NHC(O)$] (Found: $M^+ + 1$, 703.423. $C_{29}H_{65}N_6O_7P_3$ requires *M*, 702.413).

10-[(4-*Aminobutyl*)*carbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*(*benzylphosphinic Acid*)] *Trihydrobromide* **26c**.—Method as for **24b**, using **25c** (166 mg, 0.16 mmol). Yield (as the 3 HBr salt) (138 mg, 84%); $\delta_H(CD_3OD)$ 1.55–1.90 (4 H, br, $CH_2CH_2CH_2NH_3^+$), 2.70–4.10 [34 H, m, $CH_2NH_3^+$, $CH_2NHC(O)$, $NCH_2$ ring, $NCH_2P$, $NCH_2C(O)$, $PCH_2C$] and 7.20–7.55 (15 H, m, benzyl H) (Found: $M^+ + 1$, 805.370. $C_{38}H_{59}N_6O_7P_3$; *M*, requires 804.3658).

10-[4-(4-*Methoxyphenylsulfonamido*)*butylcarbamoylmethyl*]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltrimethylenetri*-(*methylphosphinic Acid*) **27**.—Hydrolysis of the methylphosphinate ester **25a** to the methylphosphinic acid was brought about as for **24a**; $\delta_H(D_2O)$ 0.82–1.09 (9 H, t + t, $PCH_3$), 1.15 (4 H, br s, $CH_2CH_2CH_2NHSO_2$), 1.90–2.70 [24 H, br, m, $CH_2N$ ring, $NCH_2P$, $NCH_2C(O)$], 2.87 [4 H, br s, $CH_2NHSO_2$, $CH_2NHC(O)$], 3.60 (3 H, s, $OCH_3$), 6.80 (2 H, d, $CHCSO_2$) and 7.43 (2 H, d, $CHCOCH_3$); $\delta_C(D_2O)$ 19.5 (2 C, $^1J$ 89, $PCH_3$), 19.8 (1 C, $^1J$ 88, $PCH_3$), 28.9 [1 C, $CH_2CH_2NHC(O)$], 31.1 (1 C, $CH_2CH_2NHSO_2$), 41.5 [1 C, $CH_2NHC(O)$], 47.4 (1 C, $CH_2NHSO_2$), 53.4–61.0 [12 C, $NCH_2$ ring, $NCH_2P$, $NCH_2C(O)$], 58.0 (1 C, $COCH_3$), 116.3 (1 C, $CHCSO_2$), 130.8 (1 C, $CHCOCH_3$), 137.9 (1 C, $CSO_2$), 163.0 (1 C, $COCH_3$) and 175.6 [1 C, C(O)NH] (Found: $M^+ + 1$, 747.280. $C_{27}H_{53}N_6O_{10}P_3S$ requires *M*, 746.2757; $\delta_P$(pH 14) 38.7, 39.2 (2:1).

*Triethyl* 10-[4-(4-*Methoxyphenylsulfonamido*)*butylcarbamoylmethyl*]-1,4,7-*tetraazacyclododecane*-1,4,7-*triyltriacetate* **28**.—As described using **19** (0.18 g, 0.38 mmol) potassium carbonate (0.19 g, 1.34 mmol) and ethyl bromoacetate (0.19 g, 1.14 mmol), to give the title compound, as a very pale yellow oil (0.16 g, 57%) (Found: $M^+$, 728.43. $C_{33}H_{56}N_6O_{10}$ requires *M*, 728.38; $\delta_H(CDCl_3)$ 1.23 (9 H, t, *J* 7.0, $OCH_2CH_3$), 1.54 (4 H, $CH_2CH_2CH_2NH$), 1.80–3.80 [28 H, m, $CH_2$ ring, $NCH_2CO_2$, $NCH_2C(O)N$, $CH_2NHSO_2$, $CH_2NHC(O)$], 3.84 (3 H, s, $OCH_3$), 4.0–4.3 (6 H, m, $OCH_2$), 6.2–6.6 [1 H, br s, NCH(O)], 6.97 (2 H, d, $CHCSO_2$), 7.84 (2 H, d, $CHCOCH_3$) and 8.23 (1 H, t, $SO_2NH_2$); $\delta_C(CDCl_3)$ 14.0 (3 C, $OCH_2CH_3$), 25.7, 26.3 (2 C, $CH_2CH_2CH_2NHSO_2$), 38.5 [1 C, $CH_2NHC(O)$], 42.6 (1 C, $CH_2NHSO_2$), 46.5–57.5 [12 C, $CH_2$ ring, $NCH_2CO_2$, $NCH_2C(O)N$], 55.4 (1 C, $OCH_3$), 61.0 (3 C, $OCH_2$), 113.8 (2 C, $CHCSO_2$), 129.0 (2 C, $CHCOCH_3$), 131.7 (1 C, $CSO_2$), 162.1 (1 C, $COCH_3$), 171.6 [1 C, C(O)N], 172.5 (1 C, $CO_2$), 173.0 (2 C, $CO_2$).

10-[(4-*Aminobutyl*)*carbamoylmethyl*)]-1,4,7,10-*tetraazacyclododecane*-1,4,7-*triyltriacetate* **29**.—Method as for the formation of **24b** using the ester **28** (144 mg, 0.20 mmol), to give the title compound as an off-white solid as its trihydrobromide salt, m.p. >210 °C (84 mg, 60%); $\delta_H(D_2O)$ 1.40–2.85 (4 H, m, $CH_2CH_2CH_2NH_3^+$), 2.96 (2 H, t, $CH_2NH_3^+$) and 2.50–4.25 [26 H, m, $CH_2$ ring, $NCH_2CO_2$, $NCH_2C(O)N$, $CH_2NHC(O)$] (Found: $M^+ + 1$, 472.261. $C_{20}H_{35}N_6O_7$ requires *M*, 471.257).

### *Synthesis of Yttrium and Gadolinium Complexes*

$H_3O^+[Y\cdot\mathbf{1b}]^-$.—Compound **1b** (0.2 g, 0.24 mmol) was dissolved in water (10 $cm^3$) (pH = 1.5). Yttrium oxide (0.026 g, 0.12 mmol) was added to the solution and heated to reflux for 18 h to give a white precipitate. The pH of the solution was raised to 6–7 and the solution boiled for 1 h, cooled and filtered through a 0.45 μm filter (Millipore). The water was removed under vacuum to give a white solid, which was recrystallised from water to give the complex as its oxonium salt (0.18 g, 80%); $\delta_H(D_2O)$ 2.26 (4 H, br d, *J* 12, $CH_2N$ ring, coupled to m at 3.46), 2.44 (4 H, dd, *J* 12), $NCH_2P$), 2.47 (4 H, d, *J* 16, ring $CH_2N$), 2.72 (4 H, dd, *J* 12.5, $PCH_2Ph$), 3.28 (4 H, d, *J* 16, $CH_2N$ ring), 3.31 (4 H, dd, *J* 12.5, $PCH_2Ph$), 3.43 (4 H, dd, *J* 12, $NCH_2P$) and 3.46 (4 H, br d, $CH_2N$ ring); $\delta_P(D_2O)$ 39.2 (d, $J_{YP}$ 5.5); $\delta_C(D_2O)$ 39.79 (d, *J* 89, $PCH_2$), 54.07, 54.34, 56.96 ($CH_2N$), 59.29 (d, *J* 94, $PCH_2N$), 128.9, 131.08, 133.31, 133.24, 135.9 and 136.11 (Ar); *m/z* (FAB) 931 (100, $M^+ + 2$) (Found: C, 47.2; H, 5.6; N, 5.35. $C_{40}H_{55}N_4O_9P_4Y\cdot 4H_2O$ requires C, 47.1; H, 6.81; N, 5.49%); $\delta_Y(D_2O) = +152.8$ (quintet, $J_{YP}$ 5 Hz).

$H_3O^+[Gd\cdot\mathbf{1b}]^-$.—The complex was prepared using a method similar to that for the related yttrium complex and was recrystallised from water and isolated as the oxonium salt; *m/z* (FAB) 999 (100, $M^+ + 1$) (Found: C, 44.4; H, 5.85; N, 5.0. $C_{40}H_{55}GdN_4O_9\cdot 4H_2O$ requires: C, 44.1; H, 5.79; N, 5.14%).

[Y·**24**].—To a sample of the carboxylic acid **24** (142 mg, 0.28 mmol) in 10 $cm^3$ of water at pH 2 (HCl) was added yttrium oxide (31 mg, 0.14 mmol). The solution was heated to reflux at 110 °C for 18 h after which the pH was raised to 6 (aqueous KOH) and the solution was heated to reflux for a further 45 min. After evaporation of the solvent, removal of any excess $Y_2O_3$ and ligand was effected by taking up the solid residues in methanol and filtering them through a 2-inch plug of alumina, using a large volume of methanol to ensure that all the complex had been washed through. However, fine alumina particles were also washed through, and these were removed by dissolving the products from the column in water and filtering through a 'Millipore' filter (0.45 μm) to yield, on evaporation of the water, a colourless solid, m.p. >200 °C (137 mg, 72%); $\delta_H(D_2O)$ 0.78 (6 H, d, *J* 6.9, $CH_3$), 0.82 (6 H, d, *J* 6.9, $CH_3$), 1.75–2.04 (2 H, m, CH) and 2.08–4.10 [28 H, m, $CH_2$ ring, $NCH_2CO_2$, $NCH_2$-

C(O)N, NC$H_2$CH]; $\delta_C(D_2O)$ 22.0, 22.2 (4 C, $CH_3$), 28.9, 29.7 (2 C, CH), 48.0, 48.1 (2 C, NC$H_2$CH), 55–60 (8 C, $CH_2$ ring), 64.5–66.5 [1 C, NC$H_2$C(O)N], 68.7 (3 C, NC$H_2CO_2$), 177.8 [1 C, C(O)N] and 183.0 (3 C, $CO_2$); $\delta_Y(D_2O)$ +111.3; $\nu_{max}$(Nujol)/cm$^{-1}$ 1607 (NCO; *cf.* 1640 for free ligand) (Found: M$^+$, 601.215. $C_{24}H_{42}N_5O_7Y$ requires: *M*, 601.214).

[Y·**27**].—Synthesis as described above, except for the use of **27** (289 mg, 0.39 mmol) and yttrium oxide (53 mg, 0.23 mmol), to give the complex as a colourless solid, m.p. >200 °C (367 mg, 85%); $\delta_H(D^2O)$ 1.24–1.60 [13 H, m, $PCH_3$, $(CH_2)_2CH_2$-$NHSO_2$], 2.19–2.93 (16 H, br m, $CH_2$ ring), 2.93–3.64 [12 H, br m, $CH_2NHC(O)$, $CH_2NHSO_2$, NC$H_2$P, NC$H_2$C(O)], 3.77 (3 H, s, $OCH_3$), 7.01 (2 H, d, *J* 8.6, $CHCSO_2$) and 7.68 (2 H, d, *J* 8.6, $CHCOCH_3$); $\delta_C(D_2O)$ 18.8 (3 C, $^1J$ 106, $PCH_3$), 26.1 [1 C, $CH_2CH_2NHC(O)$], 28.6 (1 C, $CH_2CH_2NHSO_2$), 42.4 [1 C, br, $CH_2NHC(O)$], 44.9 (1 C, $CH_2NHSO_2$), 51–62 [12 C, br, $CH_2$ ring, $NCH_2P$, $NCH_2C(O)$], 56.2 (1 C, $OCH_3$), 117.4 (2 C, $CHCSO_2$), 131.7 (2 C, $CHCOCH_3$), 132.8 (1 C, $CSO_2$), 165.3 (1 C, $COCH_3$) and 183.9 [1 C, C(O)NH]; $\delta_P(D_2O)$ 44.63, 43.13, 42.91 (ratio 1:1:1, $J_{YP}$ 5.1); $\delta_Y(H_2O)$ +151.9 (Found: M$^+$, 832.1601. $C_{27}H_{50}N_6O_{10}P_3SY$ requires *M*, 832.1580).

[Y·**8c**].—The ligand **8c** (0.25 g, 9.07 × 10$^{-4}$ mol) was dissolved in water (15 cm$^3$) and the pH was adjusted to 1.5–2.0 with dilute hydrochloric acid. Yttrium oxide (0.05 g, 2.03 × 10$^{-1}$) was added and the cloudy solution was heated to reflux to give a clear solution. The pH of the solution was raised to 7.0 with potassium hydroxide solution. The solution was filtered through 0.45 μm (Millipore) filters. The water was removed under reduced pressure and the product was purified by means of alumina column chromatography (10% methanol–dichloromethane, $R_f$ = 0.5), to yield a colourless solid, m.p. >200 °C (0.24 g, 85%); $\delta_H(D_2O)$ 0.76 (6 H, t + t, $^2J$ 4, $CH_2CH_3$), 1.18 (4 H, tq, $CH_2CH_2$), 1.31, 1.33, 1.34 (9 H, d + d + d, $PCH_3$, $J_{P-Me}$ 14.6), 1.50 (4 H, br m, $NCH_2CH_2$), 2.41 (1 H, d, *J* 13.5, CHN, coupled to m at *ca.* 3.45), 2.45 (2 H, dd, CHN ring, coupled to CHN protons in m, at *ca.* 3.45), 2.63 (3 H, br m, ring CHN), 2.69 (3 H, dd, NCHP), 2.97 (1 H, dd, CHN, coupled to ring proton at 2.63), 3.36 (1 H, m, ring $CH_aH_bN$), 3.39–3.50 (6 H, m, ring CHN), 3.58 (3 H, dd, CHP), 3.65 (1 H, m, $CH_aH_bN$ ring), 3.67 (1 H, d, *J* 16.5, CHNCO) and 4.20 (1 H, d, *J* 16.5, CHNCO); $\delta_P(D_2O)$, 43.16, 44.45, 43.8 (d + d + d, $^2J_{YP}$ 5.1 Hz); $\delta_C(D_2O)$ 15.94 (d, $^3J$ 9, $CH_2CH_3$), 18.6, 18.79, 18.84 (d + d + d, $J_{PC}$ 97), 22.34 (d, $^3J$ 7.5, $CH_2CH_3$), 31.7, 32.4 (s, $NCH_2CH_2$), 50.27, 50.99 (s, NCH) 51.71, 53.9, 54.06, 54.18, 54.3, 56.49, 56.74 (s, $NCH_2$ ring), 59.04 (d, $^2J_{PC}$ 95, $NCH_2P$), 60.41 (s, $NCH_2CO$) and 176.45 (s, C=O); *m/z* (FAB) 704 (100, M$^+$ + 1) (Found: C, 38.8; H, 7.8; N, 9.1. $C_{24}H_{51}N_5O_7P_3Y·2H_2O$ requires C, 38.91; H, 7.59; N, 9.27%).

The following complexes were prepared in an analogous manner.

[**8a**·Gd] (Found: M$^+$ + 1, 772.551. $C_{24}H_{51}GdN_5O_7P_3$ requires *M*, 771.550) (Found: C, 35.4; H, 7.0; N, 8.3. $C_{24}H_{51}$-$GdN_5O_7P_3·2H_2O$ requires C, 35.7; H, 6.81; N, 8.67%).

[**9c**·Gd] (Found: M$^+$ + 1, 841.195. $C_{30}H_{47}GdN_5O_7P_3$ requires *M*, 840.193) (Found: C, 40.0; H, 6.0; N, 7.5. $C_{30}H_{47}$-$GdN_5O_7P_3·3H_2O$ requires: C, 40.3; H, 5.93; N, 7.83%).

[**10c**·Gd] (Found: M$^+$ + 1, 801.250. $C_{26}H_{55}GdN_5O_7P_3$ requires *M*, 800.256) (Found: C, 37.0; H, 7.3; N, 8.05. $C_{26}H_{55}GdN_5O_7P_3·2H_2O$ requires: C, 37.3; H, 7.05; N, 8.37%).

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## Appendix

Fitting the curve in Fig. 2 ($\delta_P$ *vs.* pH for [Y·**1b**]$^-$)

(*a*) *One ionisation*:

$$\underset{\delta P_0}{[YL^-]} + H_3O^+ \rightleftharpoons \underset{\delta P_1}{[YLH]}$$

$$K_a = \frac{[YL^-][H_3O^+]}{[YLH]} \equiv \frac{[A^-][H^+]}{[HA]}$$

$$\delta P = \frac{[A^-]\delta P_0 + [HA]\delta P_1}{[A^-] + [HA]}$$

divide by $[H^+][A^-]$

$$= \frac{\frac{1}{[H^+]}\delta P_0 + \frac{1}{K_a}\delta P_1}{\frac{[A^-] + [HA]}{[H^+][A^-]}}$$

$$\frac{\frac{1}{[H^+]}\delta P_0 + \frac{1}{K_a}\delta P_1}{\frac{1}{[H^+]} + \frac{1}{K_a}}$$

$$pH = -\log[H^+] \rightarrow H^+ = 10^{-pH}$$

$$\therefore \delta P = \frac{10^{pH}\delta P_0 + \frac{1}{K_a}\delta P_1}{10^{pH} + \frac{1}{K_a}}$$

(*b*) *Two ionisations:*

$$[YL^-] + H_3O^+ \overset{K_a1}{\rightleftharpoons} [YLH] + H_3O^+ \overset{K_a2}{\rightleftharpoons} [YLH_2^+]$$

$$\underset{[A^-]}{\delta P_0} \qquad \underset{[HA]}{\delta P_1} \qquad \underset{[H_2A^+]}{\delta P_2}$$

$$\delta P = \frac{\delta P_0[A^-] + \delta P_1[HA] + \delta P_2[H_2A^+]}{[A^-] + [HA] + [H_2A^+]} \quad (1)$$

$$K_a1 = \frac{[YL^-][H^+]}{[YLH]} \quad K_a2 = \frac{[YLH][H^+]}{[YLH_2^+]}$$

$$K_a1 = \frac{[A^-][H^+]}{[HA]} \quad K_a2 = \frac{[HA][H^+]}{[H_2A^+]}$$

divide (1) across by $[A^-][HA][H^+]$:

$$\delta P = \frac{\delta P_0\left(\frac{1}{[HA][H^+]}\right) + \delta P_1\left(\frac{[HA]}{[HA][A^-][H^+]}\right) + \delta P_2\left(\frac{[H_2A^+]}{[HA][A^-][H^+]}\right)}{\frac{[A^-] + [HA] + [H_2A^+]}{[A^-][HA][H^+]}}$$

$$= \frac{\delta P_0\left(\frac{1}{[HA][H^+]}\right) + \delta P_1\left(\frac{1}{[HA]K_a1}\right) + \delta P_2\left(\frac{1}{[A^-]K_a2}\right)}{\frac{1}{[HA][H]} + \frac{1}{[A^-][H^+]} + \frac{[H_2A^+]}{[A^-][HA][H^+]}\frac{1}{K_a2}} \quad (2)$$

multiply (2) above and below by $[H^+][HA]$:

$$\delta P = \frac{\delta P_0 + \delta P_1(H^+/K_a1) + \delta P_2\left(\frac{[H^+][HA]}{[A^-][K_a2]}\right)}{1 + \frac{[HA]}{[A^-]} + \frac{[H^+][HA]}{[A^-]\cdot K_a2}} \quad (3)$$

divide (3) above and below by $[H^+]^2$:

$$\delta P = \frac{\delta P_0\left(\frac{1}{[H^+]^2}\right) + \delta P_1\left(\frac{1}{[H^+]\cdot[K_a1]}\right) + \delta P_2\left(\frac{1}{K_a1\cdot K_a2}\right)}{\frac{1}{[H^+]^2} + \left(\frac{1}{K_a1[H^+]}\right) + \left(\frac{1}{K_a1\cdot K_a2}\right)}$$

The best fit (0.008%) error for the expression based on one ionisation gave:

$$\delta P_0 = 43.24 \text{ ppm}; \frac{1}{K_a} = 5.78; \delta P_1 = 52.79; R = 0.979.$$

For two successive ionisations, the best fit (0.008% allowable error) gave:

$\delta P_0 = 43.398$; $\delta P_1 = 44.65$; $\delta P_2 = 50.43$; $pK_a1 = 1.277$; $pK_a2 = 1.155$. $R = 0.988$.

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