Molecular dynamics simulations on europium nitrate complexes with neutral organophosphorus ligands. What governs the stoichiometry and extractability of the complex?

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Molecular dynamics simulations have been performed in water on europium nitrate complexes $Eu(NO_3)_3\mathbf{L}_m$ with three neutral organophosphorus extractants (**L** = tri-*n*-butylphosphate (TBP), triphenylphosphine oxide (TPPO) and carbamoylphosphine oxide (CMPO)) in order to determine which factors govern the experimental 1:3 stoichiometry in organic solution saturated with water. This stoichiometry was investigated by progressive saturation of the cation coordination sphere by **L**. Simulations without constraints lead to monodentate coordination of the NO_3^- anions to Eu^{3+}, and to stoichiometries higher than 1:3. When the NO_3^- ions are constrained to bind Eu^{3+} in a bidentate mode, complexes are stable up to 1:3 stoichiometry with **L** = TPPO and CMPO. From the 1:3 stoichiometry with bidentate nitrates, the interactions of the cation with water become repulsive, which facilitates the extraction from an aqueous to an organic phase. With TBP as ligand, 1:4 stoichiometry cannot be precluded, but formation of this complex appears to be kinetically more difficult than for the 1:3 complex.

Introduction

In the field of nuclear fuel reprocessing, there have been a number of studies devoted to the separation of long lived radioactive elements contained in high activity liquid waste after the PUREX process, in order to confine them to specific matrices for subsequent storage or repository, or to transmute them into short lived elements.[1] Neutral organophosphorus compounds, such as carbamoylphosphine oxides (CMPOs), phosphine oxides, or to a lesser extent trialkylphosphates (Fig. 1), are able to extract trivalent lanthanide and actinide nitrates from the acidic high activity solutions, but are unable to discriminate, however, between both families. These ligands can also be used in synergistic mixtures with soft donor molecules to achieve Ac(III)/Ln(III) separations in mildly acidic conditions.[2,3] Recently, a new family of "CMPO-like" calix[4]arenes was found to display a high extracting power and selectivity in the lanthanides series, and to separate Am(III) from some of the lanthanides (with the exception of La and Nd) from acidic solutions.[4,5]

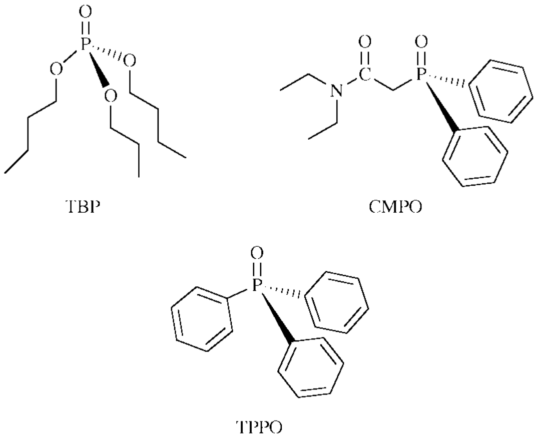


Fig. 1 Ligands studied.

In order to understand the extraction process, it is of importance to know the structure and stoichiometry of the $L_m(NO_3)_3$ organophosphorus complexes extracted in the organic phase. Hereafter, the stoichiometry will be noted 1:*m*, where *m* is the number of **L** extractant molecules per europium nitrate salt. This stoichiometry can be determined by solvent extraction experiments or spectroscopic investigations such as X-ray diffraction in the solid state or NMR in solution. Solvent extraction studies on Ac(III) or Ln(III) complexes with neutral organophosphorus extractants showed that their extracting power strongly depends on experimental conditions (aqueous phase acidity,[6,7] salinity,[8] or nature of the diluent in the organic phase[9]), whereas the stoichiometry of the complex was determined to be 1:3 in all these conditions.[8,10–12]

Spectroscopic studies in the liquid state are scarce, but ^{31}P NMR data have evidenced the 1:3 stoichiometry for TBP complexes in neat TBP[13] or for CMPO complexes in acetone-d_6.[14] In the solid state, the 1:3 stoichiometry was confirmed for $Eu(NO_3)_3$ complexes with TPPO,[15] but in the case of CMPOs, 1:2 and 1:3 complexes were characterized.[16,17] In these solid structures, the nitrates are bidentate, leading to a total coordination number (CN) of 9 or 10 for the lanthanide cations. To our knowledge, the bidentate coordination of nitrates in solution has only been characterized for TBP complexes in pure TBP[18–20] and recently in concentrated nitric acid solutions of lanthanide nitrates.[21] In diluted aqueous solution, the nitrate ions are dissociated and the CNs of the uncomplexed lanthanide cations range from 8 to 9[22–29] with a dynamic exchange between 8 and 9 in the middle of the series.[24]

Computer simulations can further describe the coordination sphere of the cation in its free and complexed states. The coordination complexes have been mainly studied by molecular mechanics and molecular dynamics (MD). Force field representations of the potential energy using covalent[30–33] or semi-covalent models,[34–38] developed to describe static structures with a well defined coordination sphere, are not adapted to describe dynamic exchanges of coordinated species (ligands,

Table 1 Non standard parameters for TPPO in AMBER force field

Bonds	K_r/kcal mol^{-1} Å^{-2}	r_{eq}/Å	
C–P	317.0	1.522	
Angles	K_θ/kcal mol^{-1} radian^{-2}	θ_{eq}/°	
O2–P–C	40.0	109.5	
C–P–C	40.0	109.50	
P–C–CA	85.0	120.00	
Dihedrals	V_n/2 kcal mol^{-1}	γ	n
X–P–C–X	0.00	0.00	3

solvent molecules, counterions). Thus, for the purpose of modeling the complexes in solution, ionic models, without covalent bonds around the cation, are preferred. Such simulations show that solvation may indeed play an important role in the ligand conformation[39] and in the nature and structure of complexes. Early MD studies of lanthanide complexes in water dealt with polyaminocarboxylate ligands.[40,41] Others performed on Eu^{3+} complexes with cryptand-222 in water[42] and acetonitrile[43,44] showed that the cation is not fully shielded by the ligand, but is coordinated to four solvent molecules. More recently, MD simulations of Eu^{3+} complexes with calixarenes bearing amide[45] or bipyridine units,[46,47] hemispherand,[48,49] or biscalix[4]arenes,[50] were reported in pure solvent phases, in relation to the luminescence properties of these complexes. In all these studies, the cation was assumed to be coordinated to one polydentate ligand, forming a 1 : 1 complex. To our knowledge, the question of stoichiometry had not been addressed so far by theoretical approaches with trivalent lanthanides, nor with less charged cations.

In this paper, we report a MD study, *in vacuo* and in water solution, of $Eu(NO_3)_3\mathbf{L}_m$ complexes with **L** = tri-*n*-butylphosphate (TBP), triphenylphosphine oxide (TPPO) and a carbamoylphosphine oxide (CMPO). We chose these ligands as representative neutral organophosphorus extractants and the Eu^{3+} cation due to its average size in the lanthanide series. We studied, in particular, the coordination properties, structure and stoichiometry of the $Eu(NO_3)_3\mathbf{L}_m$ complexes. Our main goal was to determine on what criteria it is possible to find the experimental 1 : 3 stoichiometry in the solvent phase. This was achieved by simulating $Eu(NO_3)_3\mathbf{L}_m$ complexes, where the number of ligands **L** was gradually increased, until dissociation occurred.

For each stoichiometry, nitrates were simulated with mono or bidentate coordination to the cation, as their coordination mode is unclear from experiment. We notice that previous MD simulations of the uranyl nitrate salt in water led to a bis-monodentate coordination of the anions; while in solid state structures, the latter are bound in a bidentate mode.[51] The *in vacuo* simulations were first performed to determine the cation coordination and steric hindrance in the complexes in the absence of competing interactions with the solvent. The complexes which remained bound *in vacuo* were then simulated in water, to investigate their stability in solution. Based on the corresponding hydration patterns of the complexed cation, a criterion of cation extractability and stoichiometry of the complex was established. The stability of complexes in water is of importance as the latter are suspected to be generated in the aqueous phase or at the interface before extraction.[52]

In addition, in the case of TBP complexes, potential of mean force (PMF) energy profiles of ligand dissociation have been calculated in order to determine why the $Eu(NO_3)_3(TBP)_4$ complex, found stable in water from the simulations, was not experimentally observed. Similarly, the status of nitrate counterions (inner *vs.* outer sphere coordination to Eu^{3+}) has been addressed by calculating the PMF dissociation profile of one nitrate anion from the $Eu(NO_3)_3(TBP)_3$ complex.

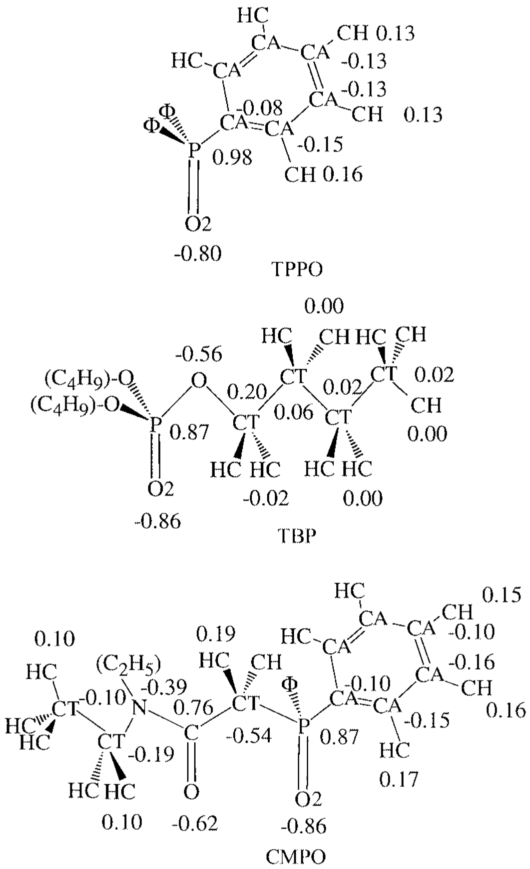


Fig. 2 Atomic charges and AMBER atom types used for simulations.

Simulation protocols

All calculations were carried out on an Origin 200 R10000 SGI computer with the AMBER 4.1 software,[53] using the all-atom force field defined in the PARM91.DAT file, and the following representation of the potential energy shown in eqn. (1).[54]

$$E_{\mathrm{pot}} = \sum_{\mathrm{bonds}} K_r(r - r_{\mathrm{eq}})^2 + \sum_{\mathrm{angles}} K_\theta(\theta - \theta_{\mathrm{eq}})^2 + \sum_{dihedrals} \frac{V_n}{2}(1 + \cos(n\varphi - \eta)) + \sum_{i<j}\left[\varepsilon_{ij}\left(\left(\frac{R^*}{R_{ij}}\right)^{12} - \left(\frac{R^*}{R_{ij}}\right)^{6}\right)\right] + \sum_{i<j}\left[\frac{q_i q_j}{\varepsilon R_{ij}}\right] + \sum_{\mathrm{H\text{–}bonds}}\left[\varepsilon_{ij}\left(\left(\frac{R^*}{R_{ij}}\right)^{12} - \left(\frac{R^*}{R_{ij}}\right)^{10}\right)\right] \quad (1)$$

The bonds and bond angles are treated as harmonic springs, and a torsional term is associated with the dihedral angles. Interactions between atoms separated by at least three bonds are described within a pairwise additive scheme by a 1-6-12 potential. Non standard parameters for TPPO are listed in Table 1, the other ones are taken from the following references: CMPO,[55] NO_3^- counter-ion,[56] Eu^{3+} cation (R^* = 1.6 Å, ε = 0.05 kcal mol^{-1}).[42] Charges for the **L** ligands (Fig. 2) were fitted from the electrostatic molecular potential calculated with the MNDO semiempirical method implemented in SPARTAN.[57] No scaling factor was used for 1–4 non-bonded interactions. The solvents were represented by the TIP3P model for water[58] and by the OPLS model for chloroform.[59,60] Each chemical entity (Eu^{3+}, NO_3^-, **L**, H_2O) was defined as a residue.

The initial structures of the complexes with intimate ion pairs were built independently, with all the ligands coordinated to the cation, and bidentate nitrates. In the simulations with constrained nitrates, two $d(O_{NO3}–Eu)$ distances were set at 2.27 Å with a force constant $K_R = 20$ kcal mol^{-1}.

The complexes were first energy minimized with 1000 steps of steepest descent *in vacuo*. Then MD simulations were performed at constant temperature (300 K) and energy for 500 ps with a 1 fs time step and a 100 Å residue-based cut-off.

All simulations in solution started with complexes minimized at the end of the MD run *in vacuo*, and immersed in a TIP3P cubic box, removing water molecules within 2 Å of the solute. The size of all solvent boxes was 35 × 35 × 35 Å^3 and the number of water molecules ranged between 1100 and 1250. After energy minimization, these systems were simulated for at least 250 ps of MD at a constant pressure of 1 atm and a 12 Å cut-off under 3D periodic boundary conditions, at a temperature of 300 K, using a time step of 1 fs in conjunction with the SHAKE procedure to constrain bonds involving hydrogen atoms.

In the simulations of the complexes in water with the nitrates initially dissociated, 5 ps of MD run were first performed with the BELLY option, freezing the solute. Then, the regular MD run was performed for 1 ns.

The PMF calculations started from the structures equilibrated after 250 ps of MD in water. They were performed as a function of the $d(O_P–Eu)$ or $d(N–Eu)$ distances, ranging respectively from $d_0 = 2$ and 2.4 Å (starting position: $\lambda = 1$) and $d_1 = 7$ and 9 Å (final position: $\lambda = 0$), considering $d_\lambda = \lambda d_1 + (1 - \lambda)d_0$. The space between d_0 and d_1 was divided into 140 windows, corresponding to an increment Δd of 0.05 Å. At each window, the difference of free energy between the states λ and $\lambda + \Delta\lambda$ ("forward calculation") and between the states λ and $\lambda - \Delta\lambda$ ("backward calculation") was calculated by eqn. (2),

$$\Delta G_{\lambda_i} = G_{\lambda_{i+1}} - G_{\lambda_i} = -RT\ln\left\langle \exp - \frac{U\lambda_{i+1} - U\lambda_i}{RT} \right\rangle_{\lambda_i} \quad (2)$$

where R is the molar gas constant and T is the absolute temperature. $\langle\rangle_{\lambda_i}$ stands for the ensemble average at the state λ_i where u_{λ_i} is the potential energy. At each window, 0.5 ps of equilibration were followed by 4.5 ps of data collection and averaging for all systems.

The MD trajectories, saved every picosecond, were visualised by the MD/DRAW software[61] and analysed by the MDS software.[62] Unless otherwise specified, the structural and energy values reported in tables and text are averages calculated on the last 100 ps of MD. The average interaction energies were calculated between each ligand **L** and nitrate, the cation and the solvent.

Results and discussion

$Eu(NO_3)_3$ in water

MD simulations were first performed on the free salt in water, in order to gain insight into the first coordination sphere of Eu^{3+} in the absence of ligand. During the 500 ps of MD run on $Eu(NO_3)_3$, the successive dissociation of the three nitrates was observed at 35, 265 and 300 ps, with water molecules filling the cation coordination sphere. For each species, the average coordination number, CN, was 8.5 with a dynamic exchange between CN = 8 (square based antiprism geometry) and CN = 9 (tricapped trigonal prism geometry), in agreement with experimental data.[24] The dissociation of nitrates resulted in a gain in hydration energy for all the species, leading to a total interaction energy ranging from −1349 ± 12 kcal mol^{-1} for $Eu(NO_3)_3$ in intimate pairs, to −1759 ± 17 kcal mol^{-1} for the dissociated salt. Dissociation of the salt in pure water (salt concentration about 4×10^{-2} M) is consistent with EXAFS data in nitric acid 0.1 M, where only water molecules were observed in the first coordination sphere of Eu^{3+}.[21] Nevertheless, in a more concentrated solution, EXAFS showed that nitrates are in the inner sphere, coordinated in a bidentate mode to the cation. Thus, in order to model the structure of the complex in concentrated conditions, we simulated the salt with bidentate nitrates by means of two $d(O_{NO_3}–Eu)$ constrained distances per nitrate. In that case, the coordination number was CN = 9, with three water molecules in the first coordination sphere, and no more dynamical exchange with bulk water.

Determination of the stoichiometry of $Eu(NO_3)_3L_m$ complexes by MD simulations *in vacuo*

To test if it was possible to retrieve by computer simulations the 1 : 3 stoichiometry, the coordination sphere of Eu^{3+} was first progressively saturated by the ligands **L** *in vacuo* (Scheme 1) until one of the ligands dissociated.

$$Eu(NO_3)_3 + L \longrightarrow Eu(NO_3)_3L$$

$$Eu(NO_3)_3L_{n-1} + L \longrightarrow Eu(NO_3)_3L_n$$

Scheme 1 Process of saturation of Eu^{3+} coordination sphere.

In a first set of simulations, the initially bidentate nitrates were free of motion during the MD run. $Eu(NO_3)_3\mathbf{L}_m$ complexes were stable up to $m = 5$ for **L** = TBP and $m = 4$ for **L** = TPPO and CMPO (Fig. 3). Beyond these values, one of the ligands **L** dissociated, due to steric hindrance. The coordination mode of the nitrates, which remained bidentate for 1 : 1 and 1 : 2 stoichiometries, whatever the ligand **L**, became monodentate when increasing the number of **L** ligands. CMPO complexes were built either monodentate (only P=O coordination to the cation) or bidentate. In the first case, the CMPO in the 1 : 1 complex became bidentate, but such evolution was not observed for the higher stoichiometries. In the second case, the dissociation of one and two carbonyl groups was observed respectively in the 1 : 3 and 1 : 4 stoichiometries.

The main energy and structural results are given in Table 2. When increasing the stoichiometry, the distances between the cation and the ligands increased due to steric hindrance and the interaction energies decreased.

A second set of simulations was performed with the nitrates constrained to be bidentately coordinated to the cation. In that case, the $Eu(NO_3)_3\mathbf{L}_m$ complexes remained bound up to 1 : 4 for **L** = TBP and 1 : 3 for **L** = TPPO and CMPO. In the $Eu(NO_3)_3$-$CMPO_3$ complex, the carbonyl groups were not coordinated to the cation whatever the starting structure. Interaction energies (Table 3) follow the same trend as with unconstrained nitrates, but decrease less when the number of **L** ligands increases.

Stability in water of $Eu(NO_3)_3L_m$ complexes

The final stable structures generated after 500 ps of MD *in vacuo* were used as starting points for the simulations in water in order to investigate the role of this solvent on their stabilities and structures.

Whatever the stoichiometry and the protocol used to simulate the nitrates, all **L** ligands remained associated to the cation and the same distances were observed between the cation and the phosphoryl or nitrate ligands. The average distance $d(O_P–Eu)$ was 2.13 ± 0.05 Å for TBP and TPPO, and 2.09 ± 0.04 Å for CMPO, while the distance $d(O_C–Eu)$ was respectively 2.3 ± 0.3 Å and 6.15 ± 0.1 Å for bidentate and monodentate CMPO.

Unconstrained nitrates turned monodentate with an average distance $d(O_{NO_3}–Eu)$ of about 2.22 ± 0.07 Å. This enhanced their interactions with water. The interaction energy between the different species within the complexes did not change with the stoichiometry, except for the 1 : 1 stoichiometry where a higher NO_3^-/NO_3^- repulsion was observed (Table 4), comparable to the value calculated for the free salt in water, before dissociation of the ion pairs. The cation coordination sphere was completed by water molecules, leading to a total coordin-

Table 2 $Eu(NO_3)_3\mathbf{L}_m$ *in vacuo* with unconstrained nitrates: average interaction energies, selected distances, and their fluctuations

$Eu(NO_3)_3\mathbf{L}_m$		Distances/Å		Interaction energy/kcal mol^{-1}			
L	*m*	$d(O_P–Eu)$	$d(O_C–Eu)$	NO_3^-/NO_3^-	L/NO_3^- [a]	L/Eu^{3+}	NO_3^-/Eu^{3+}
TBP	1	2.08 ± 0.04	—	79 ± 4	19 ± 3	−147 ± 6	−381 ± 4
	2	2.10 ± 0.04	—	80 ± 3	18 ± 2	−146 ± 5	−377 ± 13
	3	2.12 ± 0.04	—	75 ± 4	19 ± 3	−144 ± 5	−365 ± 13
	4	2.13 ± 0.04	—	67 ± 4	16 ± 3	−144 ± 5	−339 ± 16
	5	2.16 ± 0.05	—	62 ± 3	15 ± 2	−145 ± 6	−321 ± 6
TPPO	1	2.07 ± 0.04	—	79 ± 4	19 ± 2	−153 ± 4	−381 ± 4
	2	2.10 ± 0.04	—	81 ± 3	18 ± 2	−150 ± 4	−377 ± 4
	3	2.11 ± 0.04	—	73 ± 4	18 ± 3	−149 ± 4	−358 ± 17
	4	2.14 ± 0.05	—	64 ± 4	15 ± 2	−146 ± 4	−328 ± 8
CMPO bidentate	1	2.07 ± 0.04	2.20 ± 0.06	80 ± 2	38 ± 3	−284 ± 5	−377 ± 4
	2	2.08 ± 0.04	2.26 ± 0.07	67 ± 2	33 ± 3	−280 ± 6	−341 ± 4
	3	2.10 ± 0.04	2.50 ± 0.19	61 ± 2	28 ± 3	−265 ± 11	−315 ± 5
CMPO monodentate	1	2.07 ± 0.04	2.22 ± 0.22	80 ± 2	38 ± 3	−284 ± 5	−377 ± 4
	2	2.06 ± 0.03	6.11 ± 0.13	77 ± 4	24 ± 4	−183 ± 5	−375 ± 5
	3	2.07 ± 0.03	6.11 ± 0.12	71 ± 3	20 ± 3	−181 ± 5	−352 ± 12
	4	2.11 ± 0.04	6.26 ± 0.10	64 ± 2	18 ± 2	−179 ± 5	−321 ± 5

[a] Average interaction energy per nitrate.

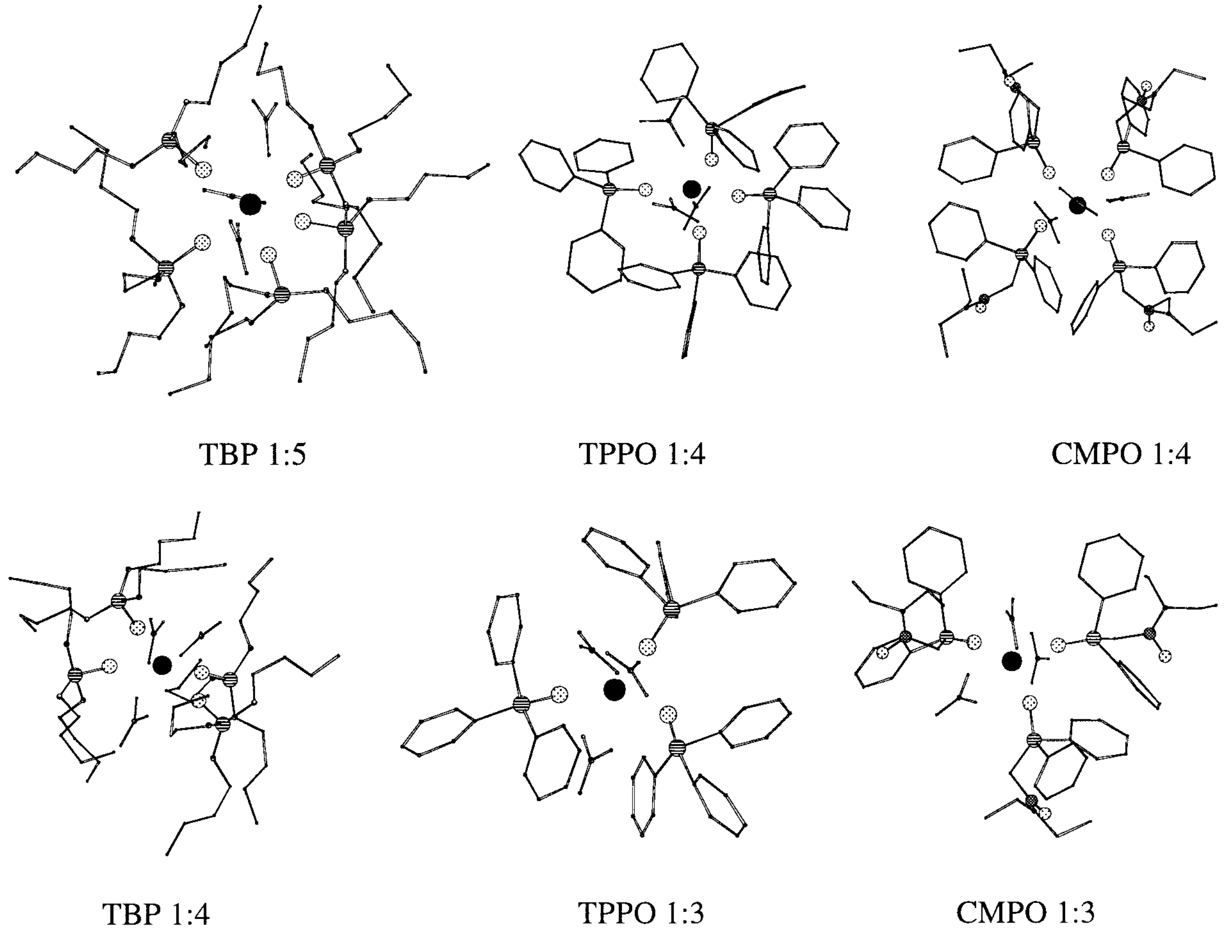


Fig. 3 $Eu(NO_3)_3\mathbf{L}_m$ complexes at saturation after 500 ps of MD *in vacuo*. *Top*: models with uncontrained nitrates. *Bottom*: models with bidentate constrained nitrates.

ation number between 8 and 9. According to the radial distribution functions, there are between four and five water molecules coordinated to the cation in the 1 : 1 complexes of TBP, TOPO and monodentate CMPO.

The increase in the number of **L** ligands around the cation leads to a decrease in the number of water molecules directly coordinated to Eu^{3+} and important changes in the interaction energy between the cation and water, ranging from highly attractive values (about −350 kcal mol^{-1}) to highly repulsive ones (about +100 kcal mol^{-1}) when reaching the saturation of the first coordination sphere by **L** ligands, and no more water molecules in contact with the cation (Table 5). This analysis strongly suggests that the stoichiometry of extracted complexes is not solely governed by steric hindrance and cation–ligand interactions, but also by interactions between the cation and water. Thus, *the coordination mode of the nitrates critically*

Table 3 Eu(NO_3)$_3$**L**$_m$ *in vacuo* with constrained nitrates: average interaction energies and their fluctuations

Eu(NO_3)$_3$**L**$_m$		Interaction energy/kcal mol^{-1}			
L	*m*	NO_3^-/NO_3^- [a]	L/NO_3^- [b]	L/Eu^{3+} [c]	NO_3^-/Eu^{3+} [a]
TBP	1	78 ± 4	19 ± 3	−149 ± 6	−380 ± 3
	2	80 ± 3	18 ± 2	−146 ± 5	−376 ± 4
	3	77 ± 3	19 ± 2	−142 ± 5	−370 ± 5
	4	74 ± 3	20 ± 3	−141 ± 6	−361 ± 7
TPPO	1	79 ± 4	19 ± 2	−152 ± 4	−379 ± 4
	2	80 ± 3	18 ± 2	−149 ± 4	−376 ± 4
	3	77 ± 3	20 ± 3	−147 ± 4	−370 ± 5
CMPO bidentate	1	79 ± 4	38 ± 3	−284 ± 5	−377 ± 4
	2[d]	77 ± 2	40 ± 3	−278 ± 5	−370 ± 5
			23 ± 3	−183 ± 7	
CMPO monodentate	1	79 ± 4	23 ± 3	−189 ± 6	−379 ± 4
	2	77 ± 4	24 ± 4	−183 ± 6	−375 ± 4
	3	76 ± 3	23 ± 3	−178 ± 5	−367 ± 6

[a] Average interaction energy per NO_3^-. [b] Average interaction energy per L ligand and NO_3^-. [c] Average per L ligand. [d] Upper line: bidentate CMPO, lower line: one monodentate CMPO due to the decomplexation of one carbonyl group during the MD run.

Table 4 Eu(NO_3)$_3$**L**$_m$ in water with unconstrained nitrates: average interaction energies and their fluctuations

	Interaction energy[a]/kcal mol^{-1}					
				NO_3^-/NO_3^-		
Eu(NO_3)$_3$**L**$_m$ **L**	L/L	L/NO_3^-	L/Eu^{3+}	1 : 1	higher	NO_3^-/Eu^{3+}
TBP	9 ± 2	17 ± 3	−151 ± 6	78 ± 9	64 ± 4	−320 ± 9
TPPO	4 ± 1	15 ± 3	−148 ± 4	76 ± 8	66 ± 5	−325 ± 13
CMPO bidentate	28 ± 2	30 ± 4	−272 ± 12	77 ± 8	63 ± 3	−319 ± 5
CMPO monodentate	10 ± 1	19 ± 3	−185 ± 5	72 ± 8	64 ± 3	−319 ± 7

[a] Averages independent of the stoichiometry with the exception of the NO_3^-/NO_3^- interaction where the 1 : 1 stoichiometry is presented separately.

Table 5 Eu(NO_3)$_3$**L**$_m$ in water: average interaction energies (and their fluctuations) with water

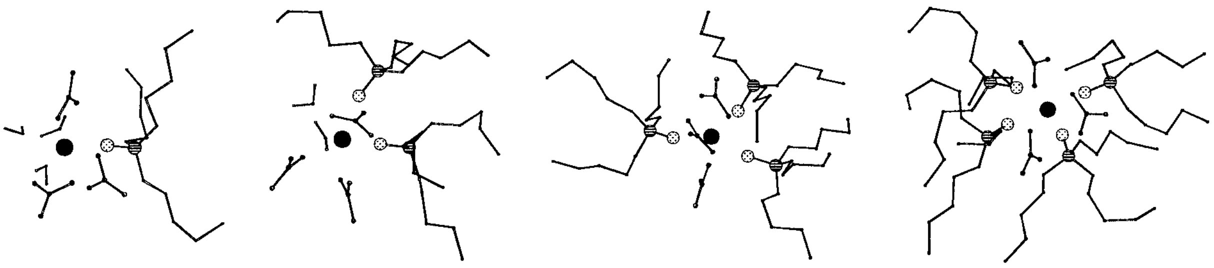
Eu(NO)$_3$**L**$_m$		Simulation with free nitrates			Simulation with constraints on nitrates		
L	*m*	NO_3^-/water	Eu^{3+}/water	L/water	NO_3^-/water	Eu^{3+}/water	L/water
TBP	1	−51 ± 16	−379 ± 37	8 ± 6	−17 ± 11	−186 ± 42	−11 ± 5
	2	−37 ± 11	−232 ± 49	−5 ± 5	−53 ± 11	−68 ± 32	−13 ± 5
	3	−51 ± 12	−98 ± 50	−11 ± 5	−62 ± 10	110 ± 23	−26 ± 4
	4	−63 ± 11	19 ± 41	−16 ± 5	−74 ± 10	138 ± 21	−27 ± 4
	5	−78 ± 11	112 ± 18	−23 ± 4	—	—	—
TPPO	1	−47 ± 18	−374 ± 47	−3 ± 7	−26 ± 9	−142 ± 22	−27 ± 5
	2	−37 ± 11	−222 ± 51	−17 ± 5	−40 ± 10	−11 ± 21	−32 ± 4
	3	−59 ± 11	36 ± 41	−29 ± 6	−62 ± 9	113 ± 21	−37 ± 4
	4	−72 ± 9	99 ± 17	−29 ± 4	—	—	—
CMPO bidentate	1	−61 ± 14	−270 ± 40	−10 ± 7	−46 ± 10	−17 ± 23	−48 ± 6
	2	−66 ± 10	1 ± 21	−38 ± 7	−78 ± 10	156 ± 21	−66 ± 6[a] −74 ± 7
	3	−82 ± 11	128 ± 20	−50 ± 7	—	—	—
CMPO monodentate	1	−41 ± 15	−346 ± 26	−11 ± 8	−24 ± 10	−194 ± 23	−35 ± 6
	2	−43 ± 11	−192 ± 40	−23 ± 8	−51 ± 10	19 ± 25	−47 ± 6
	3	−58 ± 11	−59 ± 41	−31 ± 7	−69 ± 9	140 ± 20	−52 ± 6
	4	−73 ± 10	118 ± 17	−44 ± 6	—	—	—

[a] Upper line: bidentate CMPO, lower line: one monodentate CMPO.

determines the solvent content of the first coordination sphere of the cation.

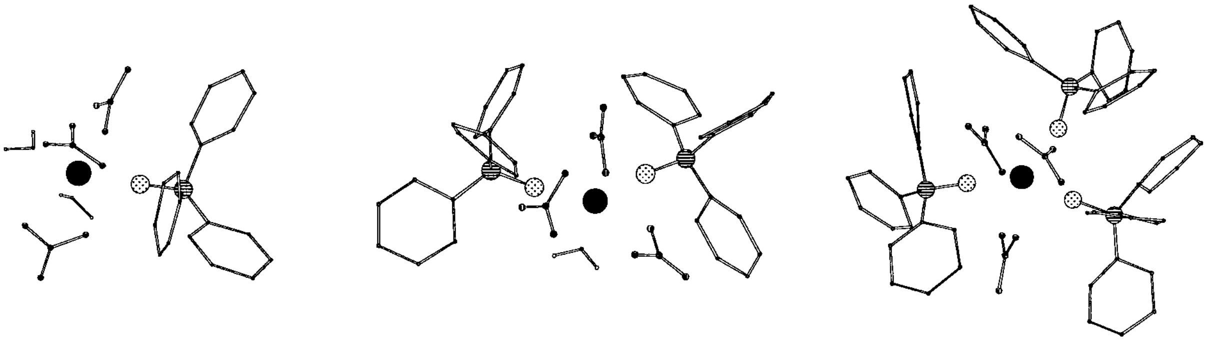
The complexes with constrained nitrates interact much less with water than the complexes with free nitrates, due to an important decrease of the Eu^{3+} contribution which becomes highly repulsive from the 1 : 3 stoichiometry. Water molecules are found in the first coordination sphere only for the 1 : 1 and 1 : 2 stoichiometries. In the 1 : 3 complexes, no cation hydration is observed after 1 ns of simulation (Fig. 4).

Assisted extraction of trivalent cations requires the formation of an hydrophobic complex which has to display therefore weak, or repulsive interactions with the water phase. In practice, the water activity of the aqueous phase is lowered by salting-out agents which facilitate the extraction. From the



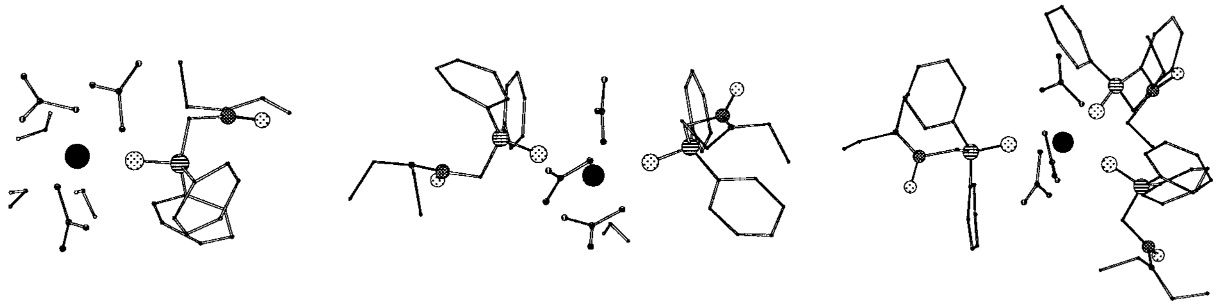
1:1 1:2 1:3 1:4

TBP



1:1 1:2 1:3

TPPO



1:1 1:2 1:3

CMPO monodentate

Fig. 4 $Eu(NO_3)_3L_m$ complexes with bidentate nitrates after 250 ps of MD in water.

present simulations in pure water with the three organophosphorus ligands, several observations can be made. (i) To recover the experimental 1 : 3 stoichiometries in solution, nitrate counterions must be modelled with a bidentate coordination to the cation, which corresponds to their coordination mode in most solid state structures and in concentrated solutions. (ii) From these 1 : 3 stoichiometries, the interactions between cation and water become highly repulsive. (iii) The 1 : 3 complexes obtained are "anhydrous" which is in agreement with experimental IR data on $Eu(NO_3)_3(TBP)_3$ complexes in the organic phase.[11,20] (iv) For TBP ligands, the 1 : 3 complex is hydrophobic enough to be extracted towards the organic phase, but the 1 : 4 complex remains bound *in vacuo* and in water. To our knowledge, this stoichiometry has never been observed so far by spectroscopy, so one can wonder whether this bound state corresponds to a real thermodynamic equilibrium or to a metastable, kinetically trapped species. This question is investigated in the next section *via* PMF calculations.

PMF dissociation profile of one TBP from $Eu(NO_3)_3(TBP)_{3\text{ or }4}$ complexes

According to experimental data, trivalent lanthanide complexes with TBP adopt the 1 : 3 stoichiometry.[8,10–11] However, 1 : 4 complexes have also been proposed for light lanthanides, in order to account for extraction isotherms.[63,64] As our simulations show that the complex $Eu(NO_3)_3(TBP)_4$ remains bound *in vacuo* and in water, we decided to calculate the dissociation energy profile of one TBP from 1 : 3 and 1 : 4 complexes in water, to determine whether there is an energy barrier to the formation of the 1 : 4 species. The starting structures of these simulations are those of the complexes equilibrated after 250 ps of MD in water with bidentate nitrates.

Both energy profiles (Figs. 5 and 6) have common features: the energy minimum corresponds to the intimate pair at $d(O_P\text{–}Eu) = 2.1$ Å, then the free energy increases up to $d(O_P\text{–}Eu) = 3.5$ Å. The well depth, of 38 kcal mol^{-1} for the 1 : 3 complex and 20 kcal mol^{-1} for the 1 : 4 complex, show that these complexes are very stable. The main differences concern the energy profiles beyond 3.5 Å. For the 1 : 3 complex, it corresponds to a plateau. Along the dissociation pathway, the coordination number of Eu^{3+} is constant and equal to 9, due to coordination of one water molecule when TBP is decomplexed, as in the 1 : 2 complex simulated previously, and there is no significant reorganization of the ligands around the cation. The 1 : 3 complex thus forms easily from the 1 : 2 one. On the contrary, for the 1 : 4 complex, the dissociation energy profile decreases continuously beyond 3.5 Å. No water molecule

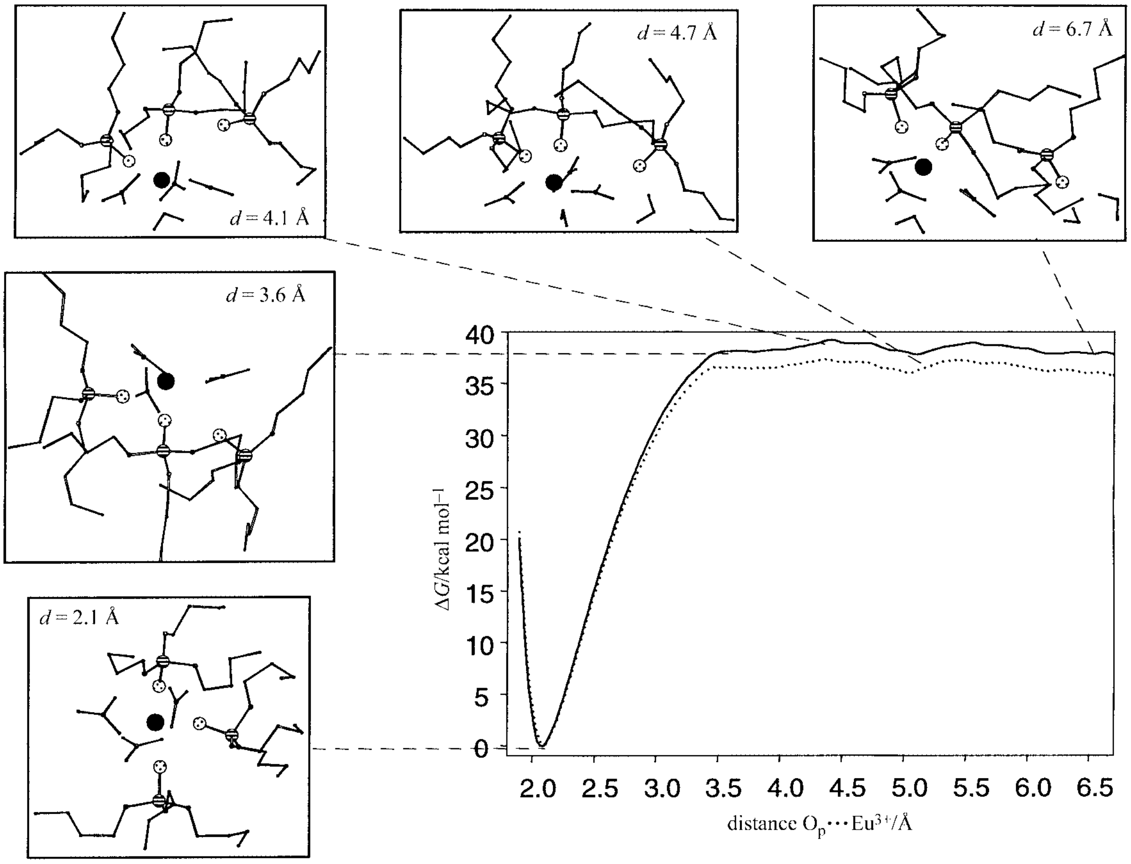


Fig. 5 PMF dissociation profile of one TBP from the $Eu(NO_3)_3(TBP)_3$ complex in water. Forwards (*full line*) and backwards (*dotted line*) cumulated ΔGs. Snapshots along the dissociation pathway.

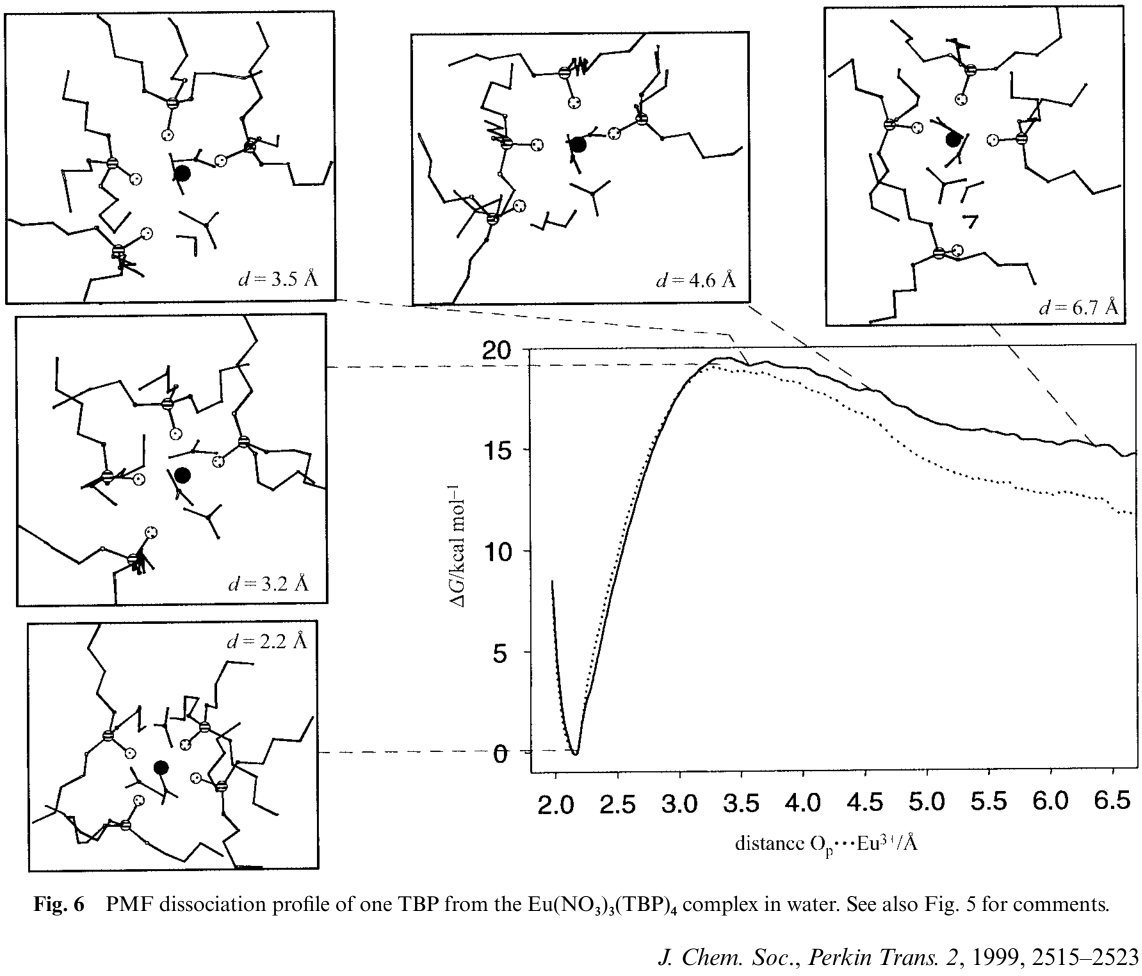


Fig. 6 PMF dissociation profile of one TBP from the $Eu(NO_3)_3(TBP)_4$ complex in water. See also Fig. 5 for comments.

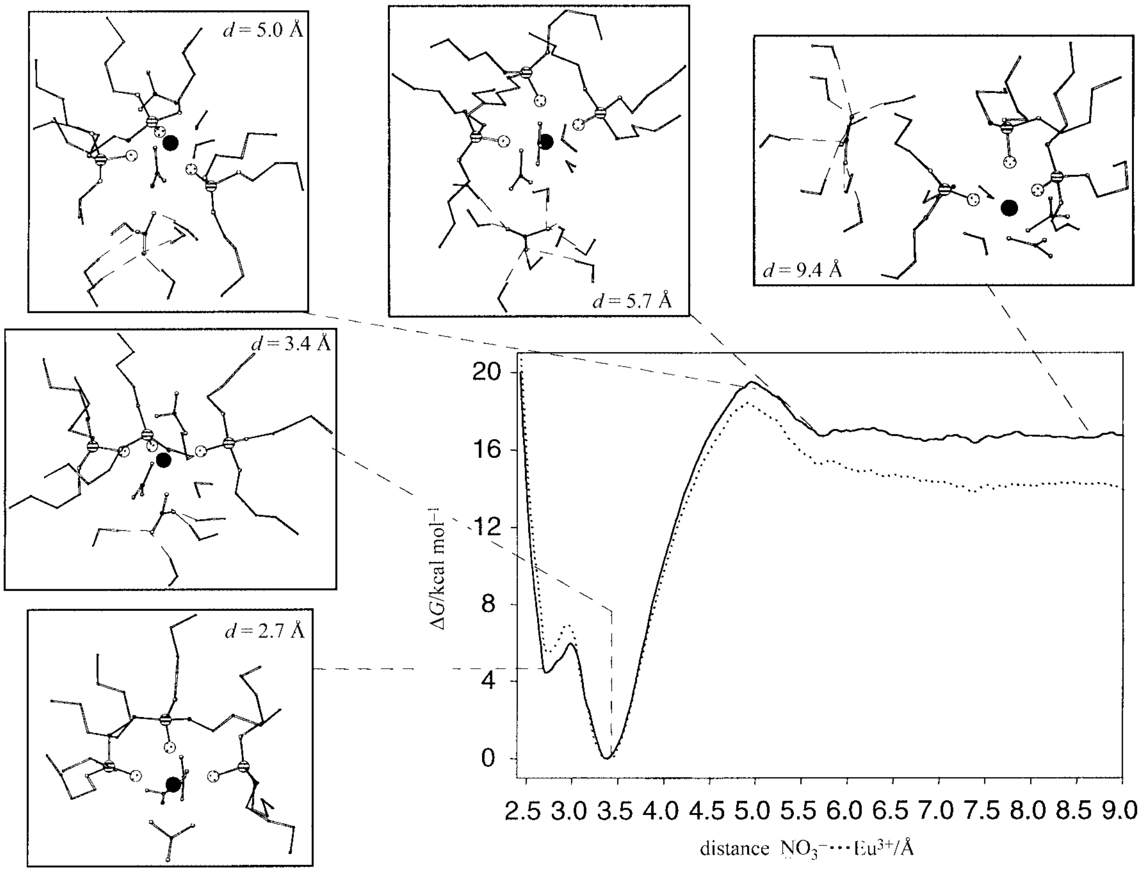


Fig. 7 PMF dissociation profile of one NO_3^- from the $Eu(NO_3)_3(TBP)_3$ complex in water. Snapshots along the dissociation pathway with selected water molecules H-bonded to the dissociating NO_3^-. See also Fig. 5 for comments.

replaces the dissociated ligand around the cation whose coordination number drops from 10 to 9. Thus, formation of the 1 : 4 complex from the 1 : 3 one requires an energy barrier of about 5 kcal mol^{-1}, and leads to a less common coordination of 10.

These PMF results cannot be quantitative, because of important approximations made in the calculations, imposed by computer time limitations. The first is the assumption of the same charge distribution in the uncomplexed and coordinated ligands, neglecting therefore the polarization and non-additive contributions to the non-covalent interactions. The second concerns the neglect of non-bonded interactions beyond the cut-off distance. These interactions are not constant along the PMF. Another critical parameter is the sampling time at each window, which may not be sufficient enough to allow for an adequate sampling of the all important configurations. However, interestingly, comparison of the energy profiles to form 1 : 3 *vs.* 1 : 4 complexes, calculated with the same approximations, shows that there is a barrier for 1 : 4 complexes only. This suggests that formation of the latter is kinetically less favoured, but cannot be precluded, as indicated above.[63]

Location and coordination of the nitrate counter-ions

The simulations discussed above started with nitrate counter-ions initially coordinated to the cation. In each case, at complex saturation, they remained coordinated and a phosphoryl ligand decomplexed. This behaviour may result from the choice of the starting structures. We therefore performed additional MD simulations on 1 : 3 complexes of TBP, TPPO and CMPO in water, starting with three solvent separated ion pairs, at a *d*(N–Eu) distance of 6 Å. In the case of TBP, the complex with one dissociated nitrate only was also modelled. In all cases, after 1 ns, no spontaneous association of nitrates to the cation was observed, the nitrates staying at 10 Å from Eu^{3+} in an outer sphere coordination. These results suggest that the formation of intimate ion pairs is prevented by some energy barrier between intimate and dissociated ion pairs.

This question was addressed by simulating the PMF profile of the dissociation of one nitrate from the $Eu(NO_3)_3(TBP)_3$ complex in water. We started with the structure of the complex after 250 ps of MD run in water, with three nitrates bidentately constrained. The dissociation profile was recorded with respect to the *d*(N–Eu) distance for one anion, keeping the two other anions bidentate. The resulting energy profile (Fig. 7) displays two deep minima, at *d*(N–Eu) = 2.8 and 3.4 Å, corresponding respectively to a bidentate and to a monodentate coordination of the nitrate to Eu^{3+}. The energy barrier corresponding to the bidentate-to-monodentate transformation is weak (1 kcal mol^{-1}), compared to the barrier for the reverse transformation (6 kcal mol^{-1}). This explains the spontaneous monodentate coordination of the nitrates, which is favoured by a better solvation of the anion and of the cation. According to the PMF curve, this complex is very stable, and energy of about 20 kcal mol^{-1} is needed to dissociate the counterion at *d*(N–Eu) over 5 Å. Between 5 and 5.6 Å, the energy first decreases and then stays constant. In the direction of the complexation of the third nitrate, we calculate an energy barrier of 3 kcal mol^{-1} between 5 and 5.6 Å. This corresponds to the partial dehydration of the approaching nitrate. The dehydration of Eu^{3+} (between 5 and 3.5 Å) corresponds to a downhill energy process with no barrier.

As pointed out above, these PMF results should be examined with caution. They however strongly suggest that the complex with nitrates in intimate pairs is thermodynamically more stable than the monodissociated system. What happens upon dissociation of the two other nitrates remains to be investigated.

Another feature not considered here is the effect of concentration, which also requires further study.

Conclusion

Based on MD simulations using a classical force field representation of the potential energy and a commonly used methodology, we explored the question of the stoichiometry of complexes in aqueous solution, taking europium nitrate with neutral organophosphorus ligands **L** (TBP, TPPO and CMPO) as a test case.

To retrieve from these simulations the experimental stoichiometries in solution, nitrate counter-ions must be coordinated bidentate to the cation. This observation is of interest, due to the difficulties in obtaining such data in the organic phase. With bidentate nitrates, from the 1 : 3 stoichiometry, we find that the first coordination sphere of the cation becomes free of water, in agreement with available experimental data in extraction systems, and that the interaction energy between the cation and bulk water becomes highly repulsive. Thus, we observe that the stoichiometry from which there is a repulsion between the cation and water corresponds to the stoichiometry of complexes actually extracted to the organic phase. In the particular case of TBP, the 1 : 3 complex is readily extractable, but the formation of a 1 : 4 complex cannot be precluded as a minor species.

MD simulations in water are thus able to give valuable insights on the structure and stoichiometry of complexes which can be extracted from an aqueous phase to an organic phase. Further simulations with these complexes at a liquid–liquid interface,[65] with higher concentrations of the extractant, will be reported in a following paper.

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