ARTICLE

OBC
www.rsc.org/obc

# $La^{3+}$-catalyzed methanolysis of *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate and *O*,*O*-diethyl *S*-phenyl phosphorothioate. Millions-fold acceleration of the destruction of V-agent simulants

**Josephine S. W. Tsang, Alexei A. Neverov and R. S. Brown***

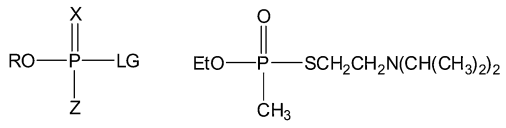
*Department of Chemistry, Queen's University, Kingston, Ontario, Canada K7L 3N6. E-mail: rsbrown@chem.queensu.ca; Tel: 613-533-2400; Fax: 613-533-6669*

***Received 6th August 2004, Accepted 27th September 2004***
***First published as an Advance Article on the web 1st November 2004***

The $La^{3+}$-catalyzed methanolysis of two phosphorothioate derivatives, *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate (**4a**) and *O*,*O*-diethyl *S*-phenyl phosphorothioate (**4b**) were studied as a function of $[La^{3+}]$ and ${}_s^spH$ in methanol solvent. In both cases the kinetics of catalyzed methanolysis maximize at ${}_s^spH$ 9.1 and a detailed analysis indicates that the dominant species responsible for catalysis are dimers formulated as $La^{3+}{}_2(^-OCH_3)_2$ and $La^{3+}{}_2(^-OCH_3)_4$. The catalysis is compared with that seen for the corresponding phosphate esters, namely paraoxon (**3a**) and *O*,*O*-diethyl phenyl phosphate (**3b**) for which $La^{3+}$ catalysis is slightly better and markedly worse than for **4a** and **4b** respectively. Overall, at ${}_s^spH$ 9.1, a 2 mmol $dm^{-3}$ solution of $La(OTf)_3$ with equimolar $NaOCH_3$ provides accelerations of $2.2 \times 10^8$-fold, $9.7 \times 10^6$-fold and $9.3 \times 10^6$-fold for methanolysis of **3a**, **4a** and **4b**, relative to the background reaction of methoxide reacting with the three substrates. In each case, the P-containing product of the reactions is exclusively diethyl methyl phosphate. Turnover experiments with 6-fold and 100-fold excesses of **4a** and **4b** respectively, methanolyzed in the presence of ~10 mmol $dm^{-3}$ $La^{3+}$ and equimolar $NaOCH_3$, indicate that the reactions are essentially complete within 103 s and 70 min respectively. The latter turnover experiment with **4b** corresponded to 100 turnovers in 70 min and an overall reaction $t_{1/2}$ of 8 min. A common mechanism of reaction is postulated for each of the substrates which involves Lewis acid coordination of one of the $La^{3+}$ to the P=O unit, followed by nucleophilic attack by the second $La^{3+}$-$^-OCH_3$.

## Introduction

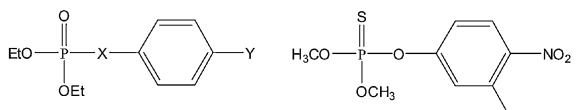
Neutral phosphorus triesters and phosphonate esters of general structure **1** are widely used as insecticides, acaricides[1,2] and in some cases chemical warfare (CW) agents.[3] In the latter category are included the phosphonofluoridate G-agents such as sarin (RO = $(CH_3)_2CHO$, X = O, Z = $CH_3$, LG = F) and the more deadly phosphonothioate esters VX (**2**, RO = $(CH_3CH_2O$, X = O, Z = $CH_3$, LG = $SCH_2CH_2N(CH(CH_3)_2)_2$) and Russian VX (RO = $(CH_3)_2CHCH_2O$, X = O, Z = $CH_3$, LG = $SCH_2CH_2N(Et)_2$), the latter materials being among the most effective neurotoxins due to their ability to inhibit the enzyme acetylcholinesterase.[4]




**1** **2**

Due to their toxicity and the attention drawn to them by the 1992 Chemical Weapons Convention Treaty,[5] which dictates timelines for the destruction of CW stockpiles by the signatory nations, considerable effort has been directed toward methods of facilitating the controlled decomposition of organophosphorus materials *via* hydrolysis[3], oxidation,[6] reaction with α-nucleophiles[7] (in some cases accompanied by oxidation[8,9]) and more exotic methods such as reduction with hydrated electrons.[10] Hydrolytic reactions under basic conditions, while seemingly attractive due to their simplicity, cannot be used effectively for destruction of V-agents, since the reaction of various simulants of these showed that the products comprise ~75–90% of the desired P–SR cleavage products ($R'OP(CH_3)(=O)(O^-) + {}^-SR$) and 10–25% of the undesired P–OEt cleavage products ($R'OH + {}^-OP(CH_3)(=O)(SR)$). Unfortunately, due to the fact that these are anionic, the latter phosphonate esters are also extremely toxic but are resistant to further base-promoted hydrolysis. On the other hand, the methoxide reaction of these same VX simulants was shown to proceed with >90% P–SR cleavage, yielding a new neutral transesterified starting material which could be further methanolyzed.[9]

Some time ago we proposed an alternative strategy for the destruction of neutral organophosphate (phosphonate) esters, namely metal ion catalyzed methanolysis, and demonstrated[11] that 2 mmol $dm^{-3}$ $La^{3+}$, introduced into methanol solution as the triflate or perchlorate salt, was capable of accelerating the methanolysis of paraoxon (**3a**, sometimes considered a simuluant for G-agents) by $10^9$-fold relative to the background reaction at near-neutral ${}_s^spH$[12,13] and ambient temperature. Subsequently we showed that transition metal ions and certain complexes of these such as the 1,5,9-triazacyclododecane complexes of $Zn^{2+}$ or $Cu^{2+}$, as their monomethoxy forms ($\mathbf{L}:M^{2+}(^-OCH_3)$), were excellent catalysts for the methanolysis of **3a** and also of the P=S derivative, fenitrothion for which $La^{3+}$ is ineffective.[14]




**3a** X=O, Y=$NO_2$
**3b** X=O, Y=H
**4a** X=S, Y=$NO_2$
**4b** X=S, Y=H

While the methodologies disclosed in the above studies show promise in providing effective catalysts for the destruction of P=O and P=S pesticides and certain of the P=O phosphonate CW agents, it remains to be demonstrated that these can be used for the decomposition of P(=O)SR derivatives which can be taken as simulants for the V-agents. In what follows we report our findings concerning the $La^{3+}$-catalyzed methanolysis of two phosphorothioate V-agent simulants **4a** and **4b**, and compare the $La^{3+}$-catalyzed methanolysis of these with their oxygen containing counterparts paraoxon (**3a**) and its phenyl derivative **3b**.

DOI: 10.1039/b412132e

## Results

### Kinetics with $La^{3+}$

The pseudo-first order rate constants ($k_{obs}$) for $La^{3+}$-catalyzed methanolysis of $2.03 \times 10^{-5}$ mol dm$^{-3}$ **4a** or $7.75 \times 10^{-5}$ mol dm$^{-3}$ **4b** were determined spectrophotometrically in the presence of varying [La(OTf)$_3$] ($2 \times 10^{-5}$ to $1.6 \times 10^{-3}$ mol dm$^{-3}$) under buffered conditions at various $^{s}_{s}$pH values. As was the case in our previous study with paraoxon,[11] plots of $k_{obs}$ *vs.* [$La^{3+}$] were curved upward at low [$La^{3+}$] (<$2 \times 10^{-4}$ mol dm$^{-3}$) and linear at higher [$La^{3+}$] ($5 \times 10^{-4}$ to $2 \times 10^{-3}$ mol dm$^{-3}$), suggestive of a process where $La^{3+}$ dimers are involved in the catalysis. The slopes of the linear parts of the plots for the two substrates were taken as $k_2^{obs}$, the observed second order rate constant for the $La^{3+}{}_2$-catalyzed methanolysis, these values being compiled in Table 1 and Table 2.

Previously we have determined from titration data that $La^{3+}$, at concentrations between $5 \times 10^{-4}$ mol dm$^{-3}$ and $5 \times 10^{-3}$ mol dm$^{-3}$, exists as a dimer associated with 1–5 methoxides depending upon the $^{s}_{s}$pH of the solution.[11,15] From the formation constants for these, defined as in eqn. (1) and eqn. (2), one can compute[16] the speciation diagram for the dimers as a function of $^{s}_{s}$pH which is shown in Fig. 1 and Fig. 2: superimposed on these diagrams are the respective $k_2^{obs}$ rate constants for methanolysis of the two phosphorothioates (from Table 1 and Table 2) in such a way that it becomes clear that some, but not all, of the dimeric species are responsible for the observed catalysis. Following the approach we used before,[11] the $k_2^{obs}$ data are fitted as a linear combination of individual rate constants (eqn. (3)) where $k_2^{2:1}$, $k_2^{2:2}$...$k_2^{2:n}$ are the second order rate constants for the methanolysis of **4a** and **4b** promoted by the various dimeric forms containing 1, 2...*n* methoxides. Given in Table 3 are the best-fit rate constants for the methanolysis of paraoxon (**3a**) and the phosphorothioates **4a** and **4b**. Shown in Fig. 3 and Fig. 4 are the computed fits of the kinetic $k_2^{obs}$ data as a function of $^{s}_{s}$pH based on the contributions of the various dimers (shown by the dotted lines) as well as the sums of these contributing to the overall observed profile.

**Table 1** Observed second order rate constants for $La^{3+}$-catalyzed methanolysis of *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate (**4a**) at various $^{s}_{s}$pH values, $T = 25$ °C

| $^{s}_{s}$pH | $k_2^{obs}$/dm$^3$ mol$^{-1}$ s$^{-1}$[a] |
|---|---|
| 6.50 | 0.76 ± 0.04 |
| 7.14 | 1.6 ± 0.08 |
| 7.86 | 8.3 ± 0.8 |
| 8.68 | 11.1 ± 0.5 |
| 9.08 | 12.4 ± 0.3 |
| 9.80 | 9.1 ± 0.7 |
| 10.70 | 6.7 ± 0.2 |

[a] $k_2^{obs}$ determined from the slope of the $k_{obs}$ *vs.* [$La^{3+}$]$_{total}$ plots at $5 \times 10^{-4}$ mol dm$^{-3}$ ≤ [$La^{3+}$] ≤ $1.6 \times 10^{-3}$ mol dm$^{-3}$ at each $^{s}_{s}$pH.

**Table 2** Observed second order rate constants for $La^{3+}$-catalyzed methanolysis of *O*,*O*-diethyl *S*-phenyl phosphorothioate (**4b**) at various $^{s}_{s}$pH values, $T = 25$ °C

| $^{s}_{s}$pH | $k_2^{obs}$/dm$^3$ mol$^{-1}$ s$^{-1}$[a] |
|---|---|
| 7.20 | 0.076 ± 0.004 |
| 7.76 | 0.16 ± 0.01 |
| 8.20 | 0.34 ± 0.01 |
| 9.10 | 0.48 ± 0.03 |
| 9.69 | 0.38 ± 0.03 |
| 10.73 | 0.30 ± 0.01 |

[a] $k_2^{obs}$ determined from slope of the $k_{obs}$ *vs.* [$La^{3+}$]$_{total}$ plots at $5 \times 10^{-4}$ mol dm$^{-3}$ ≤ [$La^{3+}$] ≤ $1.5 \times 10^{-3}$ mol dm$^{-3}$ at each $^{s}_{s}$pH.

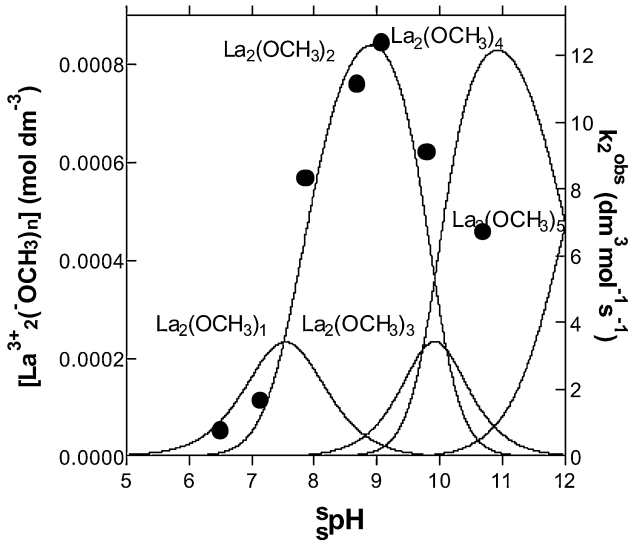



**Fig. 1** Plots of the speciation for $La^{3+}$ dimers as a function of $^{s}_{s}$pH as computed for [$La^{3+}$]$_{total} = 2 \times 10^{-3}$ mol dm$^{-3}$ from fits of potentiometric titration data to the models given in eqn. (1) and eqn. (2). Superimposed on the plots are the $k_2^{obs}$ data for the $La^{3+}$-catalyzed methanolysis of *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate (**4a**) from Table 1.

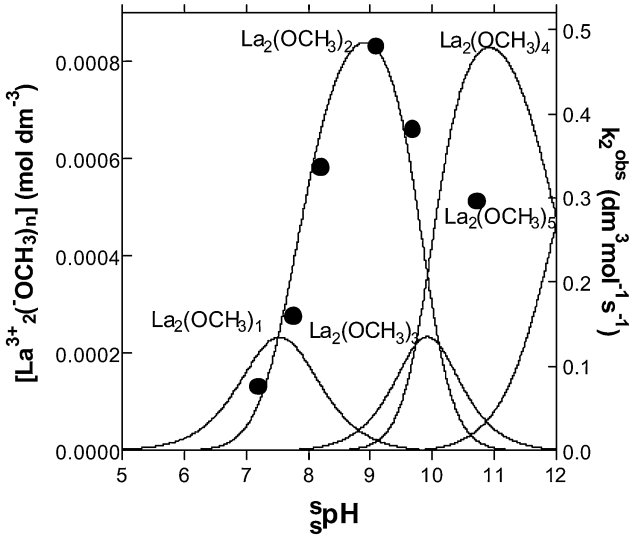



**Fig. 2** Plots of the speciation for $La^{3+}$ dimers as a function of $^{s}_{s}$pH as computed for [$La^{3+}$]$_{total} = 2 \times 10^{-3}$ mol dm$^{-3}$ from fits of potentiometric titration data to the models given in eqn. (1) and eqn. (2). Superimposed on the plots are the $k_2^{obs}$ data for the $La^{3+}$-catalyzed methanolysis of *O*,*O*-diethyl *S*-phenyl phosphorothioate (**4b**) from Table 2.

$$La^{3+}{}_2(^{-}OCH_3)_n \rightleftharpoons 2La^{3+} + n^{-}OCH_3 \quad (1)$$

$$^{s}_{s}K_n = [La^{3+}{}_2(^{-}OCH_3)_n]/[La^{3+}]^2[^{-}OCH_3]^n \quad (2)$$

$$k_2^{obs} = (k_2^{2:1}[La^{3+}{}_2(^{-}OCH_3)_1] + k_2^{2:2}[La^{3+}{}_2(^{-}OCH_3)_2] + k_2^{2:n}[La^{3+}{}_2(^{-}OCH_3)_n])/[La(OTf)_3]_t \quad (3)$$

### Kinetics with mixed metal ions

$La^{3+}{}_2(^{-}OCH_3)_n$ dimers facilitate the methanolysis of both paraoxon and *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate, but this system is incapable of providing appreciable acceleration to the methanolysis of the P=S derivative fenitrothion (**5**), although certain $Cu^{2+}$:$^{-}OCH_3$ complexes are very effective for this reaction.[14] Thus it was of interest to see whether a mixed metal ion system comprising $Cu^{2+}$ and $La^{3+}$ might afford cooperative activity for the methanolysis of any of these substrates. Given in Table 4 are the conditional pseudo-first order rate constants for three sets of experiments where

**Table 3** Best fit second order rate constants for $La^{3+}{}_2$ dimers catalyzing the methanolysis of phosphorus triester substrates, $T = 25\ ^\circ C$ [a]

| Substrate | $La^{3+}{}_2(^-OCH_3)_n$ species | $k_2^{2:n}$/dm$^3$ mol$^{-1}$ s$^{-1}$ |
|---|---|---|
| Paraoxon[b] **3a** | $La^{3+}{}_2(^-OCH_3)_1$ | $k_2^{2:1} = 15.8 \pm 2.9$ |
| | $La^{3+}{}_2(^-OCH_3)_2$ | $k_2^{2:2} = 51.1 \pm 1.1$ |
| | $La^{3+}{}_2(^-OCH_3)_3$ | $k_2^{2:3} = 35.6 \pm 6.5$ |
| | $La^{3+}{}_2(^-OCH_3)_4$ | $k_2^{2:4} = 49.7 \pm 1.4$ |
| *O*,*O*-Diethyl *S*-(*p*-nitrophenyl) phosphorothioate[c] **4a** | $La^{3+}{}_2(^-OCH_3)_1$ | $k_2^{2:1} = 11.6 \pm 5.3$ |
| | $La^{3+}{}_2(^-OCH_3)_2$ | $k_2^{2:2} = 28.4 \pm 1.2$ |
| | $La^{3+}{}_2(^-OCH_3)_4$ | $k_2^{2:4} = 16.1 \pm 1.6$ |
| *O*,*O*-Diethyl *S*-phenyl phosphorothioate[d] **4b** | $La^{3+}{}_2(^-OCH_3)_2$ | $k_2^{2:2} = 1.10 \pm 0.01$ |
| | $La^{3+}{}_2(^-OCH_3)_4$ | $k_2^{2:4} = 0.71 \pm 0.08$ |

[a] Obtained by fitting the $k_2^{obs}$ second order rate constants to eqn. (3) using the speciation of $La^{3+}{}_2(^-OCH_3)_n$ computed from fits of the $La^{3+}$ titration data to the models given in eqn. (1) and eqn. (2). Note the $k_2^{2:n}$ values are for the dimer, and so incorporate a factor of 2 relative to the $k_2^{obs}$ values in Table 1 and Table 2, which refer to $La^{3+}$ monomer. [b] Second order rate constant for methoxide attack on paraoxon $k_2^{OCH_3} = 0.011$ dm$^3$ mol$^{-1}$ s$^{-1}$. [c] Second order rate constant for methoxide attack on **4a**, at 25 °C, $k_2^{OCH_3} = 0.12$ dm$^3$ mol$^{-1}$ s$^{-1}$. [d] Second order rate constant for methoxide attack on **4b**, at 25 °C, $k_2^{OCH_3} = 0.0048$ dm$^3$ mol$^{-1}$ s$^{-1}$.

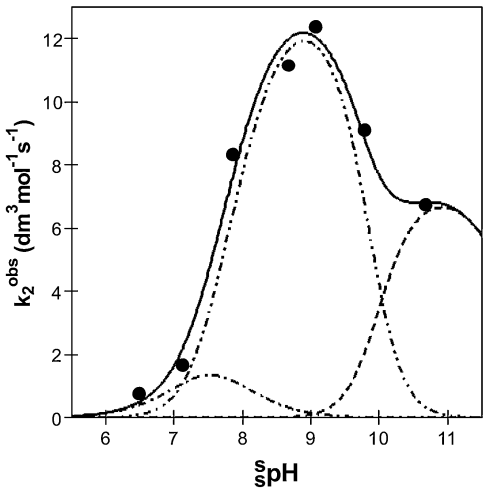



**Fig. 3** Plot of the predicted $k_2^{obs}$ *vs.* rate profile for $La^{3+}$-catalyzed methanolysis of **4a** (solid line) based on the kinetic contributions of (left to right) $La^{3+}{}_2(^-OCH_3)_1$, $La^{3+}{}_2(^-OCH_3)_2$, and $La^{3+}{}_2(^-OCH_3)_4$, computed from the $k_2^{2:1}$, $k_2^{2:2}$ and $k_2^{2:4}$ rate constants (Table 3), and their speciation shown in Fig. 1. Filled circles (●) are experimental $k_2^{obs}$ rate constants from Table 1.

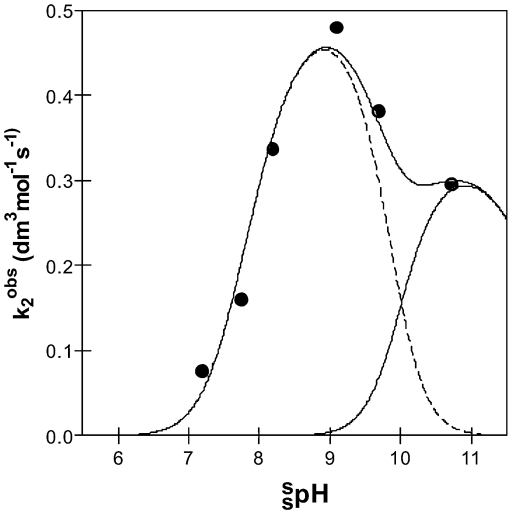



**Fig. 4** Plot of the predicted $k_2^{obs}$ *vs.* $_s^s$pH rate profile for $La^{3+}$-catalyzed methanolysis of **4b** (solid line) based on the kinetic contributions (left to right) of $La^{3+}{}_2(^-OCH_3)_2$ and $La^{3+}{}_2(^-OCH_3)_4$, computed from the best fit $k_2^{2:2}$ and $k_2^{2:4}$ rate constants given in Table 3, and the $La^{3+}{}_2(^-OCH_3)_n$ speciation shown in Fig. 2. Filled circles (●) are experimental $k_2^{obs}$ rate constants from Table 2.

1 mmol dm$^{-3}$ $Cu^{2+}$ in the presence of equimolar methoxide and the ligand 1,5,9-triazacyclododecane, 1 mmol dm$^{-3}$ $La^{3+}$ in the presence of equimolar methoxide, and a mixed system comprising 1 mmol each of $Cu^{2+}$ and ligand, $La^{3+}$, as well as 2 mmol dm$^{-3}$ methoxide, were allowed to react with the three phosphate substrates. The data in this table indicate that the rate constants of the mixed metal systems are slightly less than, but comparable to, those obtained with the individual metal ions, and that there is no cooperative interaction between the $Cu^{2+}$ and $La^{3+}$-systems.

### Turnover experiment with *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate (4a)

The $^{31}$P NMR spectrum of a methanol solution containing 20% $D_4$-methanol, buffered at $_s^s$pH 8.89 with half-neutralized *N*-ethyl morpholine (80 mmol dm$^{-3}$ in *N*-ethyl morpholine) and containing 30 mmol dm$^{-3}$ *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate exhibited a single peak at $\delta$ 22.39 ppm. The solution was then inoculated with 10 μmol dm$^{-3}$ of a stock solution of $La(OTf)_3$ containing equimolar sodium methoxide such that the final concentration of $La^{3+}$ was 9.8 mmol dm$^{-3}$.

**Table 4** Conditional pseudo-first order rate constants and half-times for the methanolysis of paraoxon, fenitrothion and *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate in the presence of various catalytic systems

| System | $k_{obs}$/s$^{-1}$ ($t_{1/2}$ for **3a**/s) | $k_{obs}$/s$^{-1}$ ($t_{1/2}$ for **4a**/s) | $k_{obs}$/s$^{-1}$ ($t_{1/2}$ for **5**/s) |
|---|---|---|---|
| $La^{3+}(^-OCH_3)$ alone[a], 1 mmol dm$^{-3}$ | $1.75 \times 10^{-2}$ (40)[b] | $9.6 \times 10^{-3}$ (72) | n.o. |
| $Cu^{2+}(OCH_3)$:1,5,9-triazacyclododecane alone[c], 1 mmol dm$^{-3}$ | $2.76 \times 10^{-3}$ (250)[d] | $8.3 \times 10^{-2}$ (8)[d] | $12.2 \times 10^{-3}$ (57)[e] |
| 1 mmol dm$^{-3}$ each of $Cu^{2+}$, $La^{3+}$, 1,5,9-triazacyclododecane and 2 eq. $NaOCH_3$[f] | $1.1 \times 10^{-2}$ (63) | $4.9 \times 10^{-2}$ (14) | $9.7 \times 10^{-3}$ (71) |

[a] Formulated as 1 mmol dm$^{-3}$ in each of $La(OTf)_3$ and $NaOCH_3$, measured $_s^s$pH = 9.03, [substrate] = $5 \times 10^{-5}$ mol dm$^{-3}$; n.o means $La^{3+}$-catalyzed reaction not observed for fenitrothion. [b] Data from ref. 11. [c] Formulated as 1 mmol dm$^{-3}$ in each of $Cu(OTf)_2$, ligand and $NaOCH_3$, measured $_s^s$pH = 8.75, [substrate] = $5 \times 10^{-5}$ mol dm$^{-3}$. [d] $k_2^{obs}$ values for the reaction of $Cu^{2+}(OCH_3)$:1,5,9-triazacyclododecane with **3a** and **4a** are 2.76 and 83 dm$^3$ mol$^{-1}$ s$^{-1}$ respectively. [e] Data from ref. 14*a*. [f] Formulated as 1 mmol dm$^{-3}$ in each of $La(OTf)_3$ and $NaOCH_3$, and 1 mmol dm$^{-3}$ in each of $Cu(OTf)_2$, ligand and $NaOCH_3$, measured $_s^s$pH = 8.5 ± 0.5 for the three substrates, [substrate] = $4 \times 10^{-5}$ mol dm$^{-3}$.

The $^{31}$P NMR spectrum, obtained 103 s after the addition of the $La^{3+}$, indicated complete disappearance of the phosphorothioate signal and the appearance of a new signal at $\delta$ 0.76 ppm, attributed to the phosphate reaction product, diethyl methyl phosphate. The result is consistent with a 6-fold turnover within the time of measurement.

### Turnover experiment with *O*,*O*-diethyl *S*-phenyl phosphorothioate (4b)

The $^{31}$P NMR spectrum of a $^{s}$pH 8.81 methanol solution containing 20% $D_4$-methanol buffered with 70 mmol dm$^{-3}$ *N*-ethyl morpholine and 73.7 mg of *O*,*O*-diethyl-*S*-phenyl phosphorothioate **4b** showed a single signal at $\delta$ 24.85 ppm. After the addition of a stock solution of $La^{3+}$ and sodium methoxide, the concentration of **3b** was 430 mmol dm$^{-3}$, while the concentrations of $La^{3+}$ and methoxide were 8.5 mmol dm$^{-3}$. The $^{31}$P NMR spectrum was monitored every 6 min and indicated almost complete disappearance of the phosphorothioate signal after 70 min and the appearance of a new signal at $\delta$ 0.76 ppm, attributed to diethyl methyl phosphate; see Fig. 5. This result is consistent with a 100-fold turnover within the time of measurement.

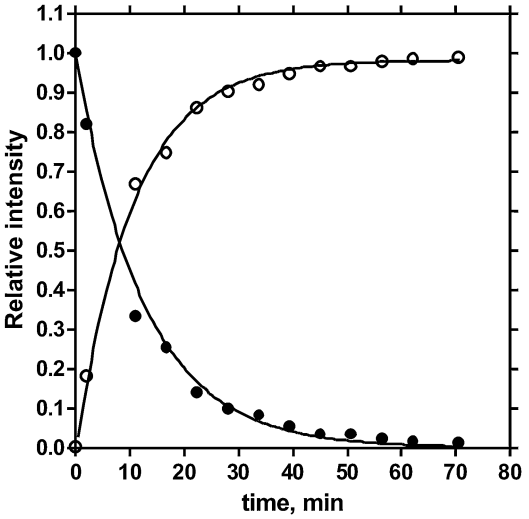
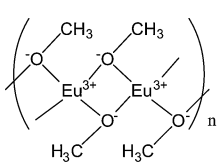


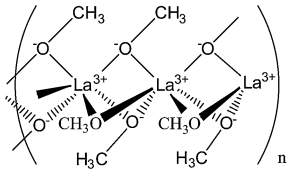

**Fig. 5** A turnover experiment for the methanolysis of **4b** in the presence of 8.5 mmol dm$^3$ La(OTf)$_3$ in a 0.08 mol dm$^{-3}$ *N*-ethyl morpholine buffered solution ($^{s}$pH = 8.8) monitored by $^{31}$P NMR. Filled circles (●), disappearance of $\delta$ 24.85 ppm signal corresponding to **4b**; open circles (○), appearance of $\delta$ 0.76 ppm signal corresponding to methyl diethyl phosphate product.

## Discussion

The methodologies for determining the kinetics of the $La^{3+}$-catalyzed methanolysis of the of the two phosphorothioate esters (**4a,b**) as a function of [$La^{3+}$] and $^{s}$pH, and speciation analysis are analogous to those that we reported earlier for the catalyzed methanolysis of paraoxon,[11] and so the results of the two studies can be compared directly. All the present data are explained *via* the involvement of catalytically active $La^{3+}$ dimers having associated methoxides, the number of which increases as a function of $^{s}$pH. However, in the present study, plots of the $k_{obs}$ of the catalyzed methanolysis of **4a** *vs.* [$La^{3+}$] at $^{s}$pH values greater than 10 reveal a significant plateau, as exemplified in Fig. 6. This behaviour is suggestive of the formation of oligomers, as was observed in a related study of the $Eu^{3+}$-catalyzed methanolysis of carboxylate esters,[17] and apparently is related to additional methoxides binding to the metal ion at higher $^{s}$pH values to form a network of $M^{3+}$ ions held together by methoxy bridges in repeating units such as **5**. The plateau in the $k_{obs}$ *vs.* [$La^{3+}$] plots observed in this study does not become apparent until $^{s}$pH values at which the speciation diagram indicates that significant amounts of $La^{3+}{}_2(^{-}OCH_3)_3$ and $La^{3+}{}_2(^{-}OCH_3)_4$ exist in solution, so it seems likely that the additional methoxides attach to the $La^{3+}{}_2(^{-}OCH_3)_2$ dimers to create higher order aggregates such as **6**, the $La^{3+}$ ions being connected by three or more bridging methoxides.




**5**




**6**

Since the extent of oligomerization must be dependent on the [$La^{3+}$]$_{total}$, a possible approach to obtain the $k_2^{obs}$ values for $La^{3+}{}_2$-catalyzed methanolysis at the higher $^{s}$pH values would be to determine the slope of the $k_{obs}$ *vs.* [$La^{3+}$] relationship at very low [$La^{3+}$], which we have done. It also seems possible that a strong complexing agent such as 18-crown-6 might break apart the putative oligomers and stabilize either monomeric forms or dimeric forms. Shown in Fig. 6 as the open squares are the $k_{obs}$ data obtained in the presence of equimolar 18-crown-6 which indicate that a linear dependence on [$La^{3+}$] is achieved in the presence of the complexing agent. Interestingly, the gradients of the lines obtained in the absence (initial gradient determined at [$La^{3+}$] $\leq 2 \times 10^{-4}$ mol dm$^{-3}$) and presence of the ligand are nicely coincident, suggesting that the $La^{3+}$-catalytic species in both cases is not significantly perturbed by the presence of the encapsulating 18-crown-6. Thus, the $k_2^{obs}$ values reported at $^{s}$pH values >10 in Table 1 and Table 2 are those based on the initial slope or that determined in the presence of complexing agent.[18]

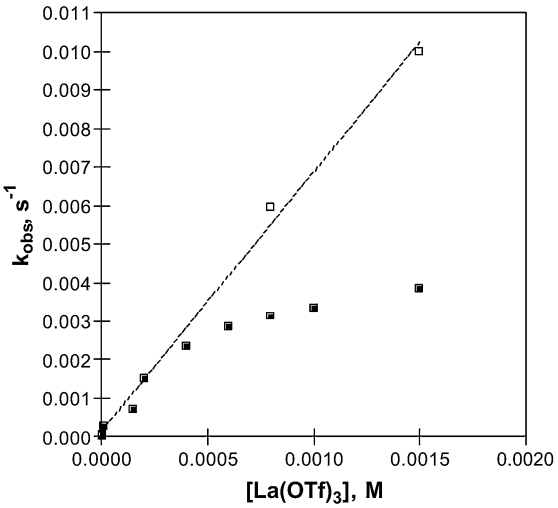
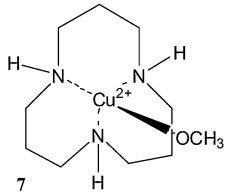



**Fig. 6** A plot of $k_{obs}$ *vs.* [La(OTf)$_3$] for the methanolysis of *O*,*O*-diethyl *S*-(*p*-nitrophenyl) phosphorothioate (**4a**) at $^{s}$pH 10.71 (triethylamine buffer). Filled squares (■), no added 18-crown-6; open squares (□), added equimolar 18-crown-6.

Fitting of the $k_2^{obs}$ values to the expression in eqn. (3) provides the individual rate constants $k_2^{2:n}$ for the various dimers with 1 to *n* associated methoxides promoting the methanolysis of **4a** and **4b**, these being given in Table 3 along with the recomputed[18] values for **3a**. In each case the most active forms from $^{s}$pH 7.5–10.5 (which surrounds the neutral $^{s}$pH region of 8.4) are the dimers containing 2 and 4 methoxides, bearing in mind that the activity depends both upon species concentration and the $k_2^{2:n}$ rate constant. For **3a**, **4a** and **4b** the activity is maximal at $^{s}$pH 9.1, with at least 95% of the activity being attributable to $La^{3+}{}_2(^{-}OCH_3)_2$. It is instructive to compare the $k_2^{2:2}$ rate constants with those for attack of methoxide ($k_2^{OCH_3}$), given in the footnotes of Table 3, the ratios ($k_2^{2:2}/k_2^{OCH_3}$) being 4645,

236 and 229 for **3a**, **4a** and **4b** respectively. In the case of **3b**, where reaction with methoxide is slow ($k_2^{OCH_3} = 1.4 \times 10^{-4}$ dm$^3$ mmol$^{-1}$ s$^{-1}$), a lower limit for the $k_2^{2:2}/k_2^{OCH_3}$ ratio is approximately[19] 25. The data in Table 4 indicate that the $Cu^{2+}$ complex **7** is slightly more effective for the phosphorothioate derivative than the phosphate derivative since the $k_2^{7}/k_2^{OCH_3}$ values for **3a** and **4a** are 250 and 691 respectively. The fact that all these metal ion catalyzed reactions have rate constants larger than those for attack of free methoxide, even though the latter is a far more basic nucleophile, must reflect a dual role for the metal ions in these systems, acting both as a Lewis acid and deliverer of a coordinated nucleophile.[14a]



**7**

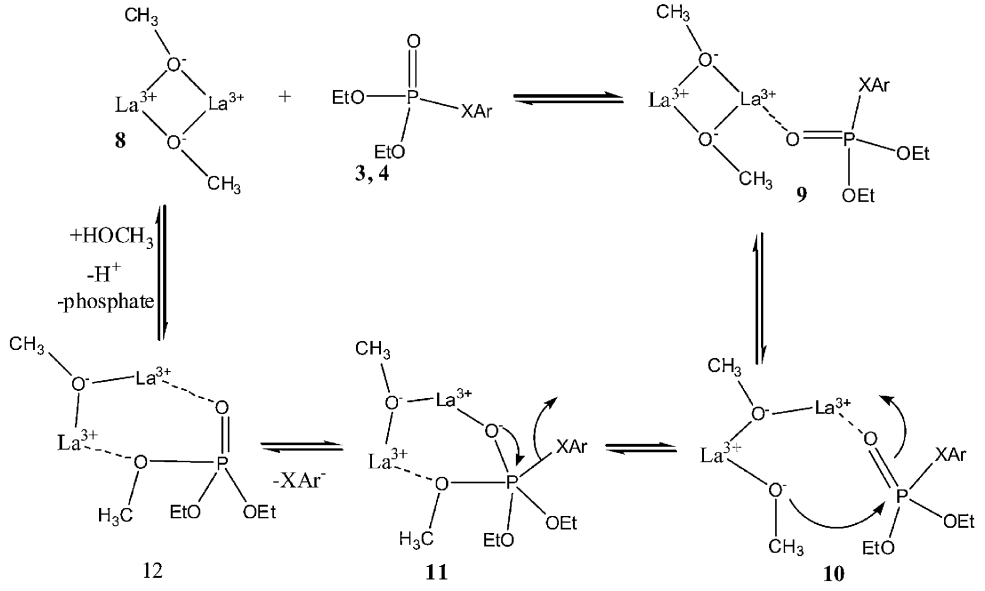
The catalysis afforded by the $La^{3+}$ system for the methanolysis of **3a**, **4a** and **4b** at $_s^s$pH 9.1 is extremely good. A 2 mmol dm$^{-3}$ solution of $La^{3+}$ at that $_s^s$pH, forming a 1 mmol dm$^{-3}$ solution of dimer, accelerates the methanolysis of these three substrates by $2.2 \times 10^8$-fold, $9.7 \times 10^6$-fold and $9.3 \times 10^6$-fold respectively, relative to the background reaction.[20] While not as precisely determined, the acceleration afforded for the same system to the methanolysis of **3b** is ~$1.1 \times 10^6$-fold. The **L**:$Cu^{2+}$($^-OCH_3$) system is slightly better for the methanolysis of **4a**, the catalysis at $_s^s$pH 9.1 afforded by 2 mmol dm$^{-3}$ **7** being $6.5 \times 10^7$-fold relative to the background.

## Mechanism of the catalyzed reaction

All evidence points to a common mechanism for the catalysis exhibited by the $La^{3+}{}_2(^-OCH_3)_n$ system acting on paraoxon and the phosphorothioate substrates we have investigated, which is illustrated in Scheme 1 using the $La^{3+}$ dimer containing two methoxides, **8**. Given the well-known coordinating ability of trialkyl phosphates to lanthanides and actinides,[21] it is difficult to envision any mechanism that does not involve a pre-equilibrium binding of the P=O of the substrate to **8** to form the transient complex **9**. The $La^{3+}$ system shows no propensity to promote the methanolysis of the P=S derivative fenitrothion, presumably due to the fact this ion is considered 'hard' in the Pearson 'hard–soft' sense[22] although complex **7** containing the softer $Cu^{2+}$ ion is an effective catalyst. Because the methoxide in **9** is bound between two electropositive $La^{3+}$ ions, it is unlikely that it is sufficiently nucleophilic to attack a coordinated, but still relatively inert, phosphate.[23] Thus we propose that one of the methoxide–$La^{3+}$ bonds is transiently cleaved, as in **10**, to reveal a $La^{3+}$-coordinated O=P adjacent to a metal-bound methoxide nucleophile, the attack of which creates the five-coordinate phosphorane intermediate **11**, which is stabilized by coordination to $La^{3+}$. Turnover to reform **8** is accomplished by breakdown of the 5-coordinate intermediate followed by methanol addition to the complex, deprotonation and release of the transiently bound trialkoxy phosphate ester product, although the exact sequence of these steps is not clear at present. We assume the mechanism of the $La^{3+}$ dimer with four associated methoxides is closely similar, also involving binding of the substrate followed by an internal attack of a metal coordinated nucleophile.

It is important to note that the $La^{3+}$ dimer system is truly catalytic for the methanolysis of these phosphorothioates and also for the previously studied **3a**. Turnover experiments with **4a** indicate that at least a 6-fold excess of substrate can be methanolyzed by 10 mmol dm$^{-3}$ La(OTf)$_3$ under buffered conditions at $_s^s$pH 8.8 without destruction of the catalyst. In the case of **4a**, the substrate was consumed within the time taken to determine the $^{31}$P NMR spectrum (103 s). A turnover experiment with 0.43 mol dm$^{-3}$ of the more slowly reacting **4b** was undertaken with 8.5 mmol dm$^{-3}$ La(OTf)$_3$ under buffered conditions at $_s^s$pH 8.8. Continuous monitoring of the spectrum as a function of time gave a pseudo-first order rate constant of $0.087 \pm 0.01$ min$^{-1}$, corresponding to a $t_{1/2}$ of roughly 8 min and 100 turnovers after 70 min. This is particularly noteworthy since the solution composition in the latter experiment was 10% **4b** by volume , and excellent first order kinetics were exhibited over the 100 turnovers, indicating the catalyst does not lose its integrity under these conditions. By way of comparison, the $CH_3O^-$ reaction at $_s^s$pH 8.8 has a half-time of 18 years and 457 years for reaction with **4a** and **4b** respectively. With both substrates the exclusive products are diethyl methyl phosphate and the arylthiol formed by breakdown of the presumed 5-coordinate phosphorus intermediate.

There are some interesting preliminary observations which set the $La^{3+}$-catalyzed methanolysis of the phosphorus esters **3a,b** and **4a,b** apart from the $La^{3+}$-catalyzed methanolysis of the corresponding carboxylate esters.[24] The second order



**Scheme 1** (Methanols of solvation omitted for clarity).

rate constants for $La^{3+}{}_2(^{-}OCH_3)_2$-catalyzed methanolysis of *p*-nitrophenyl acetate and phenyl acetate are very similar, at 77.2 and 58.6 $dm^3\ mol^{-1}\ s^{-1}$, while those for methanolysis of **3a** and **3b** are 51 and $\sim 3.5 \times 10^{-3}$ $dm^3\ mol^{-1}\ s^{-1}$. In the case of the sulfur derivatives **4a** and **4b**, the rate constants are 28.4 and 1.1 $dm^3\ mol^{-1}\ s^{-1}$. This reflects a large sensitivity to the nature of the aryloxy leaving group in the case of the phosphate, less sensitivity for the phosphorothioates and virtually no sensitivity in the case of the aryl esters. For the carboxylate aryl esters we rationalized the insensitivity by a mechanism which involves rate-limiting formation of a metal coordinated intermediate, and a counterbalancing of the substituent effect on the pre-equilibrium binding and nucleophilic attack step.[24b] In the case of $La^{3+}$ catalysis of the phosphate methanolysis, the data justify a mechanistic proposal where there are at least two main modes of action, namely Lewis acid activation and delivery of the coordinated nucleophile, and using the same general arguments that we used for the caraboxylate esters, there should be a counterbalancing of the effects of substituent on these two steps. Almost certainly the hard $La^{3+}$ cannot be involved in assisting, by coordination, the departure of the arylthiol group. The case is less settled for $La^{3+}$ assistance of departure of the harder aryloxy leaving groups, and the large sensitivity to the leaving group change from *p*-nitrophenoxy to phenoxy may be indicative of a rate-limiting breakdown of the phosphorane intermediate.

Inspection of the Table 4 data indicates that the $k_2{}^{obs}$ ratio for $La^{3+}$ catalysis of paraoxon (**3a**) and its thio derivative (**4a**) is $\sim$2 (17.5/9.6), favouring the phosphate, while that for catalysis by the softer metal containing complex **7** is $\sim$0.03 (2.76/83) suggesting that the latter complex is far better at methanolyzing the phosphorothioates. These data may suggest that for the softer metal ions there are three modes of catalysis operating, namely Lewis acid activation, delivery of nucleophile, and possible electrophilic assistance of the departure of the thiol leaving group. Future work from these laboratories is aimed at investigating the structure/activity relationships for metal-catalyzed methanolysis of aryl phosphates and phosphorothioates.

## Experimental

### Materials

Methanol (99.8% anhydrous), sodium methoxide (0.5 M solution in methanol), $La(OTf)_3$, benzenethiol and *p*-nitrobenzenethiol (89% pure, 11% 1,2-bis(*p*-nitrophenyl)disulfide) were purchased from Aldrich and used without any further purification. $HClO_4$ (70% aqueous solution) was purchased from BDH.

Phosphorothioates **4a** and **4b** were synthesized in low yield by a slight modification of the reported procedure[25] from the corresponding thiol (1 eq.), DBU (1.1 eq.) and diethyl chlorophosphate (1 eq.) in THF at ambient temperature under an inert atmosphere. Fenitrothion was a gift from Professor Erwin Buncel of this department, and paraoxon was obtained from Aldrich. **Caution:** phosphorothionates **4a,b**, paraoxon (**3a**) and fenitrothion are all acetylcholinesterase inhibitors, with the latter two having oral $LD_{50}$ values of 1.8 and 250 mg $kg^{-1}$ respectively in rats.[26]

### Methods

$^1H$ NMR spectra were determined at 400 MHz and referenced to the $CD_2H$ peak of $D_4$-methanol appearing at $\delta$ 3.31.

The $CH_3OH_2^+$ concentration was determined using a Radiometer Vit 90 Autotitrator equipped with a Radiometer GK2322 combination (glass/calomel) electrode calibrated with Fisher Certified Standard aqueous buffers (pH = 4.00 and 10.00) as described in our recent papers.[11,14,15,17] Values of ${}_s^spH$ [12] were calculated by adding a correction constant of 2.24 to the experimental meter reading as reported by Bosch *et al.*[13]

### Kinetics

UV kinetics of methanolysis were monitored at 25 ± 0.5 °C by observing the rate of disappearance of $2.03 \times 10^{-5}$ mol $dm^{-3}$ **4a** at 280 nm using an OLIS®-modified Cary 17 UV-vis or Cary 100 Bio UV-vis spectrophotometers. The $[La(OTf)_3]$ was varied from $2 \times 10^{-6}$ to $1.5 \times 10^{-3}$ mol $dm^{-3}$. UV kinetics of methanolysis of **4b** and **3b** were monitored by observing the rate of appearance of thiophenolate at 242 nm at $[\mathbf{4b}] = 7.75 \times 10^{-5}$ mol $dm^{-3}$ or phenol at 278 nm at $[\mathbf{3b}] = 3.96 \times 10^{-4}$ mol $dm^{-3}$. The $[La(OTf)_3]$ was varied from $2 \times 10^{-4}$ to $1.5 \times 10^{-3}$ mol $dm^{-3}$. All reactions for were followed to at least three half-times except for the slow reactions of **3b**, where $t_{1/2} = 8000$ min, which were only followed for 3 days.

All kinetics were determined under buffered conditions. Buffers were prepared from *N*-methylimidazole (${}_s^sp K_a = 7.60$), *N*-ethyl morpholine (${}_s^sp K_a = 8.60$) and triethylamine (${}_s^sp K_a = 10.78$). Due to the fact that added counterions can ion-pair with $La^{3+}$ ions and affect its speciation in solution,[15] ionic strength was controlled through neutralization of the buffer. The total [buffer] varied between $1 \times 10^{-2}$ and $2 \times 10^{-2}$ mol $dm^{-3}$, and the buffers were partially neutralized with 70% $HClO_4$ to keep the $[ClO_4^-]$ at a low, but constant value of $5 \times 10^{-3}$ mol $dm^{-3}$, which leads to a reasonably constant ionic strength in solution. With $[La^{3+}] > 5 \times 10^{-4}$ mol $dm^{-3}$ at ${}_s^spH > 7.0$, the metal ion was partially neutralized by adding an appropriate amount of NaOMe to help control the ${}_s^spH$ at the desired value. ${}_s^spH$ measurements were performed before and after each experiment and in all cases the values were consistent to within 0.1 units.

The pseudo-first order rate constants ($k_{obs}$) were evaluated by fitting the absorbance *vs.* time traces to a standard exponential model. The second order rate constants for $La^{3+}$-catalyzed methanolysis ($k_2{}^{obs}$) were evaluated as the slopes of the linear parts of the $k_{obs}$ *vs.* $[La^{3+}]$ plots at each ${}_s^spH$.

### Turnover experiments

**4a.** To 4.9 $cm^3$ of anhydrous methanol at ambient temperature was added *N*-ethyl morpholine (0.0638 $cm^3$ or 57.7 mg) half-neutralized with 11.4 M $HClO_4$ (0.0215 $cm^3$), so that the final total buffer concentration was 0.1 mol $dm^{-3}$ in 4.95 $cm^3$ of solution. To 0.8 $cm^3$ of this buffer and 0.2 $cm^3$ deuturated methanol (added as an NMR lock signal) was added 8.8 mg of *O*,*O*-diethyl-*S*-(*p*-nitrophenyl) phosphorothioate. The measured ${}_s^spH$ of the methanol solution was 8.89. The $^{31}P$ NMR spectrum showed a single signal at $\delta$ 22.39 ppm. To the resulting mixture was added 0.010 $cm^3$ of a stock solution prepared by dissolving 16.4 mg $La(OTf)_3$ in 0.0569 $cm^3$ of a 0.5 mol $dm^{-3}$ solution of sodium methoxide in methanol. At this point, the concentration of phosphorothioate was 0.030 mol $dm^{-3}$ and that of $La(OTf)_3$ was 0.0098 mol $dm^{-3}$ and the measured ${}_s^spH$ of the methanol solution was 8.89. The $^{31}P$ NMR spectrum, obtained 103 s after the addition of lanthanum catalyst, indicated complete disappearance of the phosphorothiolate signal and the appearance of a new signal at $\delta$ 0.76 ppm, attributed to the phosphate reaction product, diethyl methyl phosphate.

**4b.** To 4.9 $cm^3$ of anhydrous methanol at ambient temperature was added *N*-ethyl morpholine (0.0638 $cm^3$ or 57.7 mg) half-neutralized with 11.4 M $HClO_4$ (0.0215 $cm^3$), so that the final total buffer concentration was 0.1 mol $dm^{-3}$ in 4.95 $cm^3$ of solution. To 0.5 $cm^3$ of this buffer and 0.1 $cm^3$ of deuturated methanol (added as an NMR lock signal) was added 73.7 mg (0.062 $cm^3$) of *O*,*O*-diethyl-*S*-phenyl phosphorothioate, which constitutes 10% by volume. The measured ${}_s^spH$ of the methanol solution was 8.8. The $^{31}P$ NMR spectrum showed a single signal at $\delta$ 24.85 ppm. To the resulting mixture was added 0.024 $cm^3$ of a stock solution prepared by dissolving 12.2 mg $La(OTf)_3$ in 0.084 $cm^3$ of a 0.25 M solution of sodium methoxide in methanol. At this point, the concentration of phosphorothioate was 0.43 mol $dm^{-3}$ and that of $La(OTf)_3$ and $NaOCH_3$ were

0.0085 and 0.0086 mol $dm^{-3}$, respectively. The reaction was continuously monitored using $^{31}P$ NMR with a spectrum being obtained every 6 min after the addition of lanthanum catalyst. The time course of the reaction is shown in Fig. 6. The $^{31}P$ NMR spectrum after 70 min indicated almost complete disappearance of the phosphorothioate signal (the residual signal shows the presence of 1.1% of the initial amount) and the appearance of a new signal at $\delta$ 0.76 ppm, attributed to the phosphate reaction product, diethyl methyl phosphate.

## Acknowledgements

The authors gratefully acknowledge the financial support of the Natural and Engineering Research Council of Canada, Queen's University and United States Department of the Army, Army Research Office, Grant No. W911NF-04-1-0057.[27] In addition, they thank Professor F. M. Raushel for information related to the synthesis of **4a** and **4b**.

## References

1 (*a*) A. Toy and E. N. Walsh, *Phosphorus Chemistry in Everyday Living* (2nd edn.), American Chemical Society, Washington, DC, 1987, ch. 18–20; (*b*) L. D. Quin, *A Guide to Organophosphorus Chemistry*, Wiley, New York, 2000; (*c*) M. A. Gallo and N. J. Lawryk, *Organic Phosphorus Pesticides. The Handbook of Pesticide Toxicology*, Academic Press, San Diego, CA, 1991; (*d*) P. J. Chernier, *Survey of Industrial Chemistry* (2nd edn.), VCH, New York, 1992, pp. 389–417.

2 K. A. Hassall, *The Biochemistry and Uses of Pesticides* (2nd edn.), VCH, Weinheim, 1990, pp. 269–275.

3 (*a*) Y.-C. Yang, J. A. Baker and J. R. Ward, *Chem. Rev.*, 1992, **92**, 1729; (*b*) Y.-C. Yang, *Acc. Chem. Res.*, 1999, **32**, 109; (*c*) Y.-C. Yang, *Chem. Ind. (London)*, 1995, 334.

4 The reported $LD_{50}$ for VX administered subcutaneously in rabbits is 15.4 μg $kg^{-1}$: J. J. Gordon and L. Leadbeater, *Toxicol. Appl. Pharmacol.*, 1977, **40**, 109.

5 *Conference on Disarmament. The Convention of the Development, Production, Stockpiling and Use of Chemical Weapons and on Their Destruction*, CD/1170, Geneva, August 1992 (see http://www.dfait-maeci.gc.ca/nndi-agency/cwc_1-en.asp) .

6 H. Morales-Rojas and R. A. Moss, *Chem. Rev.*, 2002, **102**, 2497, and references therein.

7 F. Terrier, E. Le Guével, A. P. Chatrousse, G. Moutiers and E. Buncel, *Chem. Commun.*, 2003, 600.

8 (*a*) G. W. Wagner and Y.-C. Yang, *Ind. Eng. Chem. Res.*, 2002, **41**, 1925; (*b*) T. Cassagne, H.-J. Cristau, G. Delmas, M. Desgranages, C. Lion, G. Magnaud, É. Torreilles and D. Virieux, *Heteroat. Chem.*, 2001, **12**, 485.

9 Y.-C. Yang, F. J. Berg, L. L. Szafraniec, W. T. Beaudry, C. A. Bunton and A. Kumar, *J. Chem. Soc., Perkin Trans. 2*, 1997, 607.

10 J. J. Kiddle and S. P. Mezyk, *J. Phys. Chem. B*, 2004, **108**, 9568.

11 J. S. W. Tsang, A. A. Neverov and R. S. Brown, *J. Am. Chem. Soc.*, 2003, **125**, 7602.

12 For the designation of pH in non-aqueous solvents we use the forms described by Bosch and co-workers[13] based on the recommendations of the IUPAC: *Compendium of Analytical Nomenclature. Definitive Rules* (3rd edn.), 1997, Blackwell, Oxford, UK, 1998. If the measuring electrode is calibrated with aqueous buffers and then the pH of an aqueous buffer solution is measured, the term ${}^{w}_{w}pH$ is used; if the electrode is calibrated in water and the 'pH' of the neat buffered methanol solution then measured, the term ${}^{s}_{w}pH$ is used; and if the latter reading is made, and the correction factor of 2.24 (in the case of methanol) is added, then the term ${}^{s}_{s}pH$ is used.

13 Given that the autoprotolysis constant of methanol is $10^{-16.77}$, neutral ${}^{s}_{s}pH$ in methanol is 8.4: E. Bosch, F. Rived, M. Rosés and J. Sales, *J. Chem. Soc., Perkin Trans. 2*, 1999, 1953.

14 (*a*) A. A. Neverov and R. S. Brown, *Org. Biomol. Chem.*, 2004, **2**, 2245; (*b*) W. Desloges, A. A. Neverov and R. S. Brown, *Inorg. Chem.*, 2004, **43**, 6752.

15 G. Gibson, A. A. Neverov and R. S. Brown, *Can. J. Chem.*, 2003, **81**, 495.

16 The potentiometric data were fitted using the computer program Hyperquad 2000 (version 2.1 NT): P. Gans, A. Sabatini and A. Vacca, *Talanta*, 1996, **43**, 1739.

17 A. A. Neverov, G. Gibson and R. S. Brown, *Inorg. Chem.*, 2003, **42**, 228.

18 In order to allow consistent comparison between these new data and our previously published paraoxon data[11] we reanalyzed the initial slopes for those $k_{obs}$ *vs.* $[La^{3+}]$plots determined at ${}^{s}_{s}pH > 10$, and have recomputed the various $k_2^{2:n}$ parameters in this study.

19 The complete ${}^{s}_{s}pH$/rate constant profile for $La^{3+}$-catalyzed methanolysis of diethyl phenyl phosphate **3b** is difficult to determine because the reactions are very slow. However, by initial rate measurements we have determined a $k_2^{obs}$ value at ${}^{s}_{s}pH$ 9.1 of $(1.7 \pm 0.4) \times 10^{-3}$ $dm^3$ $mol^{-1}$ $s^{-1}$. Since all the other phosphorus substrates show maximal catalytic activity at this ${}^{s}_{s}pH$, we assume a $k_2^{2:2}$ rate constant of $\sim 3.5 \times 10^{-3}$ $dm^3$ $mol^{-1}$ $s^{-1}$.

20 The background reaction is assumed to be entirely attributable to the methoxide-promoted reaction at ${}^{s}_{s}pH$ 9.1, the $[^{-}OCH_3]$ being $2.14 \times 10^{-8}$ mol $dm^{-3}$.

21 (*a*) J. Petrova, S. Momchilova, E. T. K. Haupt, J. Kopf and G. Eggers, *Phosphorus, Sulfur Silicon Relat. Elem.*, 2002, **177**, 1337; (*b*) D. R. Peterman, R. Fox and H. W. Rollins, 223rd ACS National Meeting, Orlando, FL, 7–11 April 2002, *Abstracts of papers*, NUCL-131; (*c*) J. R. Ferraro, A. W. Herlinger and R. Chiarizia, *Solvent Extr. Ion Exch.*, 1998, **16**, 775; (*d*) R. Du Preez and J. S. Preston, *S. Afr. J. Chem.*, 1986, **39**, 137; (*e*) D. F. Peppard, G. W. Mason, W. J. Driscoll and S. McCarty, *J. Inorg. Nucl. Chem.*, 1959, **12**, 141; (*f*) E. N. Lebedeva, M. G. Zaitseva, O. V. Galaktionova, L. V. Bystrov and S. S. Korovin, *Koord. Khim.*, 1981, **7**, 870, CAN 95:87058; (*g*) A. K. Pyartman, A. A. Kopyrin, E. A. Puzikov and K. B. Bogatov, *Zh. Neorg. Khim.*, 1996, **41**, 347, CAN 125:124905;; A. K. Pyartman, A. A. Kopyrin, E. A. Puzikov and K. B. Bogatov, *Zh. Neorg. Khim.*, 1996, **41**, 686, CAN 126:11927; (*h*) A. K. Pyartman, V. A. Keskinov, S. V. Kovalev and A. A. Kopyrin, *Radiochemistry (Transl. of Radiokhimiya)*, 1997, **39**, 142, CAN 127:210889; AN 1997:471873.

22 M. B. Smith and J. March, *Advanced Organic Chemistry* (5th edn.), Wiley Interscience, New York, 2001, pp. 338–342, and references therein.

23 (*a*) N. H. Williams, W. Cheung and J. Chin, *J. Am. Chem. Soc.*, 1998, **120**, 8079; (*b*) D. Wahnon, A.-M. Lebuis and J. Chin, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2412.

24 (*a*) A. A. Neverov, T. McDonald, G. Gibson and R. S. Brown, *Can. J. Chem.*, 2001, **79**, 1704; (*b*) A. A. Neverov, N. E. Sunderland and R. S. Brown, *Org. Biomol. Chem.*, 2004, DOI: 10.1039/b414763d.

25 S.-B. Hong and F. M. Raushel, *Biochemistry*, 1996, **35**, 10904.

26 *The Merck Index* (11th edn.), Merck & Co. Inc., Rahway, NJ, 1989.

27 The content of the information does not necessarily reflect the position or the policy of the federal government, and no official endorsement should be inferred.