Metal-Ion Catalysis

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Catalytic Decomposition of Simulants for Chemical Warfare V Agents: Highly Efficient Catalysis of the Methanolysis of Phosphonothioate Esters**

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Among the most noxious materials made by man are the organophosphorus chemical-warfare materials, such as the phosphonofluoridate G agents soman (**1**) and sarin (**2**) and the phosphonothioate V agents, such as VX (**3**).[2] The latter is particularly toxic[3] because it is N-protonated at physiological pH and is therefore well accommodated by the acetylcholine esterase active site, which it inhibits through irreversible phosphonyl transfer to an essential serine hydroxy group. Numerous strategies for destroying such materials are available especially with hydrolysis and oxidation.[2,4] Base hydrolysis of V agents and some simulants of these give products that comprise approximately 75–90 % of the desired P–SR cleavage products (R′OP(CH$_3$)(=O)(O$^-$) + $^-$SR) and

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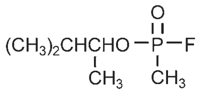
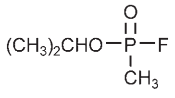
Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.


$(CH_3)_2CHCH(CH_3)O-P(=O)(CH_3)-F$

1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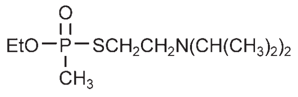
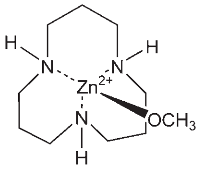
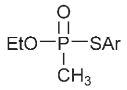
2

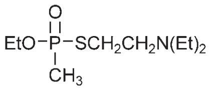

$EtO-P(=O)(CH_3)-SCH_2CH_2N(CH(CH_3)_2)_2$

3


[Zn(OCH$_3$)(**4**)]$^+$


$EtO-P(=O)(CH_3)-SAr$

5a Ar = 3,5-dichlorophenyl
b Ar = 4-chlorophenyl
c Ar = 4-fluorophenyl
d Ar = phenyl
e Ar = 4-methoxyphenyl


$EtO-P(=O)(CH_3)-SCH_2CH_2N(Et)_2$

6

10–25 % of the undesired P–OEt cleavage products (R′OH + $^-OP(CH_3)(=O)(SR)$).[5,6] The latter are anionic and resist further base-promoted hydrolysis but nevertheless are extremely toxic. However, the methoxide reaction of these same VX simulants was shown to proceed with > 93 % P–SR cleavage and yield (the other 7 %) a new, neutral transesterified methoxylated starting material, which subsequently can be methanolyzed to benign products.[6,7]

Recently, we reported the methanolysis of phosphate and phosphorothioate triesters[8] as well as a series of aryloxy methylphosphonate esters[9] catalyzed by La^{3+} and the complex [Zn(OCH$_3$)(**4**)]$^+$. Each is capable of very large accelerations of the methanolysis process at ambient temperature and essentially neutral ^s_spH values[10] in methanol. Herein, we report that both metal-containing systems are extremely effective in promoting the methanolysis of phosphonothioates **5a–e**, the only identifiable product being the corresponding *O*-ethyl *O*-methyl methylphosphonate. Based on the results, we predict that the corresponding –SCH$_2$CH$_2$NEt$_2$ derivative **6**, a very close analogue of VX, should be catalytically methanolyzed with a $t_{1/2}$ value of < 1 s at ^s_spH 9.1 in the presence of 1 mM of La^{3+}-containing catalyst at 25 °C.

The second-order rate constants for the methanolysis of **5a–e** promoted by methoxide, La^{3+}, and [Zn(OCH$_3$)(**4**)]$^+$ are given in Table 1, the latter two systems being buffered at ^s_spH 9.1 in methanol. The kinetic data for each substrate were determined in duplicate under pseudo first-order conditions of excess catalyst relative to substrate at ≥ 5 equivalents [metal catalyst] and 3 equivalents [methoxide]. The k_2^{catalyst} values in Table 1 were obtained as the gradients of the plots of k_{obs} versus [catalyst]. The Brønsted plots shown in Figure 1 for the $\log k_2^{\text{catalyst}}$ constants versus the experimentally determined $^s_sK_a$ values of the corresponding thiophenols give straight lines described by Equations (1)–(3). The gradients of

$$\log k_2^{\text{OMe}} = (6.39 \pm 1.12) - (0.65 \pm 0.10)\ ^s_s\text{p}K_a^{\text{HSAr}} \quad r^2 = 0.930 \tag{1}$$

$$\log k_2^{\text{4:Zn(OMe)}} = (7.89 \pm 0.41) - (0.66 \pm 0.04)\ ^s_s\text{p}K_a^{\text{HSAr}} \quad r^2 = 0.990 \tag{2}$$

$$\log k_2^{\text{La}} = (10.51 \pm 0.10) - (0.75 \pm 0.01)\ ^s_s\text{p}K_a^{\text{HSAr}} \quad r^2 = 0.999 \tag{3}$$

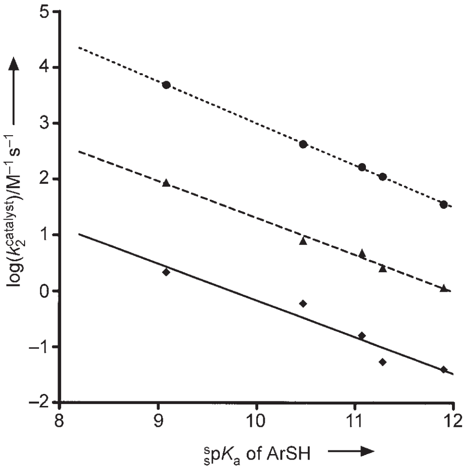


Figure 1. Brønsted plots for $\log k_2^{\text{catalyst}}$ versus the ^s_spK_a of aryl thiol; ●, [{La^{3+}($^-$OCH$_3$)}$_2$]; ▲, [Zn(OCH$_3$)(**4**)]$^+$; ◆, $^-$OCH$_3$.

Table 1: Second-order rate constants for the methanolysis of phosphonates **5a–e** catalyzed by methoxide, [{La^{3+}($^-$OCH$_3$)}$_2$], and [Zn(OCH$_3$)(**4**)]$^+$ in methanol at T = 25 °C.

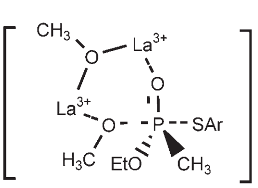
Phosphonothioate	^s_spK_a of thiol (methanol)[a]	k_2^{OMe} [M^{-1} s^{-1}]	$k_2^{\text{4:Zn(OMe)}}$ [M^{-1} s^{-1}][b]	k_2^{La} [M^{-1} s^{-1}][c]
5a	9.08 ± 0.04	2.17 ± 0.03 (1.96±0.03)[d]	95.2 ± 1.4 (75.7±4.6)[d]	(4.84±0.09) × 10^3
5b	10.47 ± 0.01	0.60 ± 0.01	7.85 ± 0.25	(4.25±0.12) × 10^2
5c	11.07 ± 0.03	0.16 ± 0.01	4.83 ± 0.11	(1.64±0.07) × 10^2
5d	11.28 ± 0.14	0.054 ± 0.002	2.60 ± 0.06	(1.10±0.02) × 10^2
5e	11.98 ± 0.08	0.040 ± 0.006	1.16 ± 0.03	(3.55±0.17) × 10^1
6	9.54 ± 0.04	[e]	38.02 ± 0.04[f]	(2.06 ±0.09) × 10^3 [f]

[a] Experimental values from 2 mM solutions titrated in methanol according to procedures in ref. [10]. [b] Catalyst was prepared in situ by adding 1 equivalent of each of Zn(OTf)$_2$ and the triaza ligand along with 0.5 equivalents of tetrabutylammonium hydroxide in methanol to self-buffer the solution at ^s_spH 9.1 as the ^s_spK_a of [Zn^{2+}(HOMe)(**4**)] is 9.1;[8,11] the kinetics were determined in duplicate at 5 [catalyst] concentrations ranging from 0.4 to 2.0 mM. [c] Catalyst was prepared in situ by adding a stock solution of La(OTf)$_3$ in methanol to a 17 mM *N*-ethylmorpholine with perchloric acid in a 4:1 ratio to buffer the solution at ^s_spH 9.1; the kinetics were determined in duplicate at 5 [La^{3+}]$_{\text{total}}$ concentrations ranging from 0.4 to 2.4 mM. [d] In [D$_1$]methanol. [e] Number predicted to be approximately 2 × 10^{-3} M^{-1} s^{-1} under highly basic conditions based on comparison with data for VX and *O*-ethyl *S*-ethyl methylphosphonothioate given in ref. [6]. [f] Predicted k_2^{catalyst} value computed using Equations (2) and (3).

the lines are all substantially negative and suggest extensive cleavage of the P–SAr bond in the transition state (TS) for the reaction. The reactions of methoxide and $[\mathrm{Zn(OCH_3)}(\mathbf{4})]^+$ with **5a** exhibit solvent kinetic isotope effects of $k_H/k_D = 1.11 \pm 0.03$ and 1.26 ± 0.10, respectively; these low values are most consistent with nucleophilic rather than general base-promoted methanolysis.[11]

A turnover experiment was conducted in solution with methanol, the concentrations were 3.62 mM for **5a** and 0.36 mM for $\mathrm{La(OTf)_3}$ (Tf = trifluoromethylsulfonyl) buffered with *N*-ethyl morpholine at ${}^{s}_{s}$pH 9.1, in which the dominant catalytically active form in solution was probably the bis(methoxy)-bridged dimer $[\{\mathrm{La^{3+}}(^{-}\mathrm{OCH_3})\}_2]$, which we had shown earlier makes a contribution of >90 % toward the catalysis of phosphate ester methanolysis at that ${}^{s}_{s}$pH value.[8a,b] None of the starting material, which has a ^{31}P NMR signal at $\delta = 50.37$ ppm, was evident within the five minutes required to obtain the spectrum: only a single peak at $\delta = 30.6$ ppm, which corresponds to *O*-ethyl *O*-methyl methylphosphonate, was observed. These data indicate that the catalyst performs at least 20 turnovers in that time, although it is probably far more active than is revealed by this NMR technique.[12]

Several pieces of information allow us to propose a mechanism for the metal-catalyzed reactions of **5a–e** that appears to be a common one for the neutral phosphate, phosphorothioate, and phosphonate esters.[8,9,11] As both metal systems are more active than methoxide for a given substrate (≈30–40-fold for $[\mathrm{Zn(OCH_3)}(\mathbf{4})]^+$ and ≈1000-fold for $[\{\mathrm{La^{3+}}(^{-}\mathrm{OCH_3})\}_2]$), the mechanism likely involves a dual role for the metal ion as a Lewis acid activator of a transiently bound substrate followed by intramolecular nucleophilic delivery of a metal-coordinated methoxide. The skie data and Brønsted slopes with large negative values are consistent with associative mechanisms via TS structures **7** and **8**, in which nucleophilic delivery of the methoxide species is coupled with a concerted departure of the leaving group. In the case of $[\{\mathrm{La^{3+}}(^{-}\mathrm{OCH_3})\}_2]$, we envision that a methoxide species bridged between two electropositive $\mathrm{La^{3+}}$ ions is not nucleophilic enough to attack the bound substrate, so one of the $\mathrm{O{-}La^{3+}}$ bonds is broken in the TS to reveal a bifunctional catalyst containing both the Lewis acid and nucleophilic $\mathrm{La^{3+}}$-coordinated methoxide. The $\mathrm{Zn^{2+}}$ ion in **8** is five-coordinate, and the intramolecular delivery is accomplished through a direct four-membered TS.



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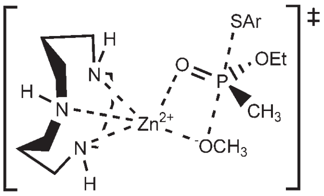

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It is of interest to utilize the present correlations to predict the rates of the reactions for a substrate containing an $\mathrm{(R)_2NCH_2CH_2S{-}}$ group which would be a close analogy of VX without having to handle such a dangerous material. Titration of (*N*,*N*-diethylamino)ethanethiol in methanol gives two macroscopic ${}^{s}_{s}$pK_a values of 9.54 ± 0.04 and 13.3 ± 0.07, the low value for the thiol is due to the zwitterionic stabilization of the thiolate anion by the internal ammonium group [Eq. (4)].

$$\mathrm{HS(CH_2)_2\overset{+}{N}(Et)_2H} \xrightleftharpoons{{}^{s}_{s}\mathrm{p}K_a\ 9.54} {}^{-}\mathrm{S(CH_2)_2\overset{+}{N}(Et)_2H} \xrightleftharpoons{{}^{s}_{s}\mathrm{p}K_a\ 13.3} {}^{-}\mathrm{S(CH_2)_2N(Et)_2} \qquad (4)$$

The fact that putative phosphonothioate **6** would be substantially N-protonated in methanol[13] at ${}^{s}_{s}$pH 9.1, the value at which the metal-catalyzed reactions are run, makes the thiolate in $\mathrm{EtO(CH_3)P({=}O)SCH_2CH_2N^+(Et)_2H}$ a much better leaving group than if the amino group were deprotonated, as it would be under the highly basic conditions required to effect the methoxide reaction in a reasonable time. By analogy, lyoxide-catalyzed decomposition of the related V agents also suffers from this leaving-group retardation at high pH values and proceeds much more slowly[14] than if the decomposition could be done at neutral pH, the value at which the amine is protonated, as is the case with our metal systems. The predicted k_2^{catalyst} values computed with Equations (2) and (3)[15] are given in Table 1 and suggest that a solution of 1 mM $[\mathrm{Zn(OCH_3)}(\mathbf{4})]^+$ or $[\{\mathrm{La^{3+}}(^{-}\mathrm{OCH_3})\}_2]$ should methanolyze **6** with respective $t_{1/2}$ values of 18 and 0.33 s.

We have described a highly efficient, truly catalytic methodology for the decomposition of phosphonothioates to benign products based on metal-catalyzed methanolysis under essentially neutral conditions. The Brønsted correlation of a well-defined series of simulants allows prediction of the reactivity of more deadly substrates by simple determination of the ${}^{s}_{s}$pK_a values of the thiol leaving group. The results indicate this approach could be attractive for the decomposition of the real V agents which will not suffer from the known problems of base-catalyzed hydrolysis under highly basic conditions. One can envision that anchoring metal-binding ligands to solid supports may provide effective heterogeneous methods for organophosphate decomposition by alcoholysis, a project under current investigation.

Experimental Section

Caution: all the phosphonothioates are potentially serious neurotoxins and should be handled with extreme care.

All the phosphonothioates were prepared by the following general route from methylphosphonic dichloride via (*S*)-aryl methylphosphonochloridate. Thiophenol (5 mmol) was added to a solution of methylphosphonic dichloride (5 mmol) in dry THF (10 mL) under nitrogen. The mixture was cooled in an ice bath and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 5 mmol, neat) was added dropwise. The reaction mixture was allowed to stir in an ice bath for 30 min and at room temperature for 24 h. Following this period, $\mathrm{Na_2CO_3}$ (1 g) in ethanol (10 mL) was added to the reaction mixture, which was stirred under $\mathrm{N_2}$ for 30 minutes. The reaction mixture was filtered, the volatiles removed, and the crude product purified by flash chromatography on silica gel using a Biotage SP1 purification system with ethyl acetate/hexanes (1:1) as the eluent. The non-optimized yields of the isolated products were approximately 20 %. The physical data for **5a–e** are given in the Supporting Information.

Kinetic data for the methanolysis of **5a**–**e** were obtained by UV/Vis methods, as described earlier for phosphates, phosphorothioates, and phosphonates.[8,9,11] The reactions were run under pseudo first-order conditions of excess catalyst in duplicate with a substrate concentration of 0.2 mM. Pseudo first-order rate constants were evaluated by fitting traces of the absorbance versus time to a standard exponential, and the second-order rate constants were evaluated as the gradients of the plots of k_{obs} versus [catalyst].

The turnover experiment was conducted with 3.62 mM **5a** in 0.6 mL of methanol buffered with 17 mM *N*-ethylmorpholine and perchloric acid in a 4:1 ratio to achieve a $^{s}_{s}$pH value of 9.1. La(OTf)$_3$ and tetrabutylammonium hydroxide were added to this reaction mixture so that the final concentration of each was 0.36 mM and 0.09 mL of [D$_1$]methanol. The reaction was followed using ^{31}P NMR spectroscopic analysis on a 400-MHz machine.

Titrations were performed in duplicate on 2 mM solutions of thiol in methanol under nitrogen at 25 °C using standardized 20 mM NaOCH$_3$ as the titrant. The $^{s}_{s}$pK_a values were obtained by fitting the titration data using the program Hyperquad 2000 (version 2.1 NT).[16]

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[1] The content of the information discussed herein does not necessarily reflect the position or the policy of the federal government of the United States of America, and no official endorsement should be inferred.

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

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[5] N. B. Munro, S. S. Talmage, G. D. Griffin, L. C. Waters, A. P. Watson, J. F. King, V. Hauschild, *Environ. Health Perspect.* **1999**, *107*, 933.

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[7] Yang et al. also showed[5] that the HOO$^-$ ion reacts with phosphoniothioates to give exclusive P–S cleavage, although these reactions are not catalytic and are carried out under alkaline conditions.

[8] a) J. S. Tsang, A. A. Neverov, R. S. Brown, *J. Am. Chem. Soc.* **2003**, *125*, 7602; b) T. Liu, A. A. Neverov, J. S. W. Tsang, R. S. Brown, *Org. Biomol. Chem.* **2005**, *3*, 1525; c) J. S. W. Tsang, A. A. Neverov, R. S. Brown, *Org. Biomol. Chem.* **2004**, *2*, 3457; d) W. Desloges, A. A. Neverov, R. S. Brown, *Inorg. Chem.* **2004**, *43*, 6752.

[9] R. E. Lewis, A. A. Neverov, R. S. Brown, *Org. Biomol. Chem.* **2005**, *3*, 4082.

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[11] C. Maxwell, A. A. Neverov, R. S. Brown, *Org. Biomol. Chem.* **2005**, *3*, 4329.

[12] In actuality, the turnover experiment for the La^{3+}-catalyzed methanolysis of **5a** must be essentially complete early in the NMR experiment because if it were not the summation of the 256 scans over five minutes would have revealed the presence of starting material in the first few scans.

[13] A referee rightly points out that the ammonium ion in **6** does not have the zwitterionic stabilization of $^{-}$SCH$_2$CH$_2$N$^+$(H)Et$_2$, so the $^{s}_{s}$pK_a value will not be as high as 13.3; while true, we note that the $^{s}_{s}$pK_a value of triethylamine is 10.78, thus indicating that the nitrogen atom in **6** will still be substantially protonated at $^{s}_{s}$pH 9.1.

[14] The methoxide-promoted methanolysis of VX and *O*-ethyl *S*-ethyl methylphosphonothioate at 22 °C and 0.25–0.3 M concentrations of base have k_2 values of 1.85×10^{-3} and 1.70×10^{-3} M^{-1} s^{-1}[5], which is similar to that expected for **6** under highly basic conditions; however, the methoxide reaction on **6** at any $^{s}_{s}$pH value at which the nitrogen atom is protonated is computed by Equation (1) to be 1000-fold faster at 1.28 ± 0.10 M^{-1} s^{-1}.

[15] The predicted rate constants assume that the Brønsted relationships of Equations (2) and (3), which are derived for aryl thiols, are followed by a primary alkyl thiol. Previous studies indicate that methanolysis and hydrolysis of carboxylate esters bearing aryloxy groups are up to tenfold less reactive than those bearing primary alkoxyl groups, presumably because of steric effects; see: a) N. E. Sunderland, A. A. Neverov, R. S. Brown, *Org. Biomol. Chem.* **2005**, *3*, 65; b) J. F. Kirsch, W. P. Jencks *J. Am. Chem. Soc.* **1964**, *86*, 837.

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