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A novel catalytic approach to the chemical detoxification of P-ester nerve agents

Wendy Y. Mills, Rebecca M. Kissling and Michel R. Gagné*

Department of Chemistry CB#3290, University of North Carolina, Chapel Hill, NC 27599, USA. E-mail: mgagne@unc.edu

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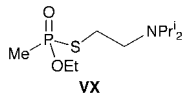
An effective method for the destruction of P-based nerve agent simulants using the ester interchange reaction is described; depolymerization of polycarbonate in the presence of aryl phosphinates and KOBu^t (5 mol%) leads to a net breakdown of the toxic constituents of the simulants while immobilizing each component as a polymer end group; the data suggest that application of this approach to the destruction of nerve agents such as VX may be fruitful.

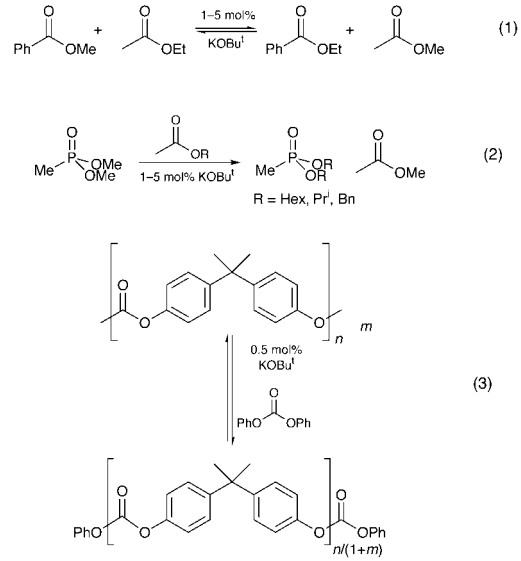
Chemical warfare agents such as VX [*S*-2-(diisopropylamino)-ethyl *O*-ethyl methylphosphonothioate] are polar organic liquids at ambient conditions.[1] Given the current stockpile of these agents (thousands of tons in the US alone), efficient and safe methods for their destruction present a scientifically challenging and important research problem. Currently, methods for their destruction rely on incineration or chemical neutralization. Each of these methods, however, have attendant disadvantages as they produce hazardous fumes or byproducts that may still be highly toxic. To address some of these issues, we have recently initiated experiments utilizing ester interchange to disassemble (*i.e.* detoxify) the key subunits of these agents, while simultaneously immobilizing them for subsequent safe disposal.



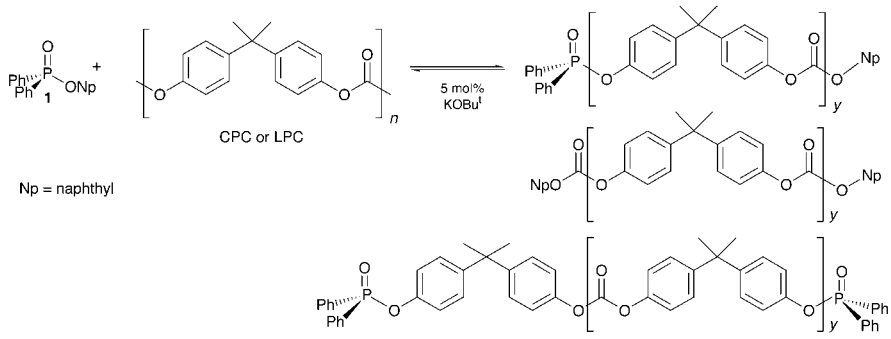
VX

We have previously reported that alkali-metal alkoxide clusters catalyze the ester interchange reaction under mild conditions and at high rates (up to 10^6 turnovers h^{-1}) [eqn. (1)].[2] As an extension of this original observation we have additionally demonstrated that (i) phosphonates are highly susceptible to ester interchange [eqn. (2)],[3] and (ii) diaryl carbonate (DAC) interchange can be used to depolymerize high molecular weight (MW) bisphenol A polycarbonate (PC) with subsequent control over polymer end groups [eqn. (3)].[4] The reaction rates for the former processes are also rapid and turnover frequencies as high as 1.5×10^6 h^{-1} have been measured. A key consideration in the successful application of this methodology is a matching of the pK_as for the two interchanging esters, *i.e.* the two ester leaving groups must be similarly competent.

Our data therefore suggest that, given a suitable interchange partner, VX should be capable of swapping its toxic amino thiolate side chain for a less toxic one. pK_a considerations indicate that thioesters (*e.g.* AcSEt) or aryl esters (*e.g.* AcOAr) should be suitable.[5] Since VX derivatives containing simple non-functionalized side chains like SEt are toxic and can be volatile, polymeric non-sulfur containing side chains might be ideal detoxification products from both a toxicity and volatility perspective. Therefore, in analogy to the depolymerization process, utilization of VX or a VX simulant as a breakdown agent for PC should effectively destroy the agent while immobilizing the toxic components as polymer end groups (Scheme 1). The additional entropic driving force associated with a polymer breakdown protocol should additionally maximize the chemical potential for P-ester destruction.



To test this hypothesis, two model VX simulants (naphthyl diphenylphosphinate **1** and phenyl diphenylphosphinate **2**) were each allowed to interchange with diphenyl carbonate (DPC) [eqn. (4)], cyclic PC (CPC)[6] and linear PC (LPC)[7] in the presence of 5 mol% KOBu^t as shown in Scheme 1. Some of the expected products from the reaction are also highlighted in Scheme 1. Under a dry argon atmosphere the desired phosphinates and carbonate were dissolved in THF and, after catalyst addition, were stirred for 30 min at room temperature. The polymer-based reactions were subsequently worked up by precipitation into a 10-fold excess of MeOH; the collected polymeric precipitates were then analyzed by GPC (Table 1) and ^{31}P NMR (*vide infra*). The amount of unreacted phosphinate in the filtrate was obtained by solvent removal and quantitative HPLC analysis (Table 1).[8] The relative amount of carbonate to phosphinate functional groups in the starting mixture was varied (10 : 1, 20 : 1 and 50 : 1) to determine its effect on simulant conversion. As expected, increasing ratios of carbonate drove the reactions forward, especially in the cases of CPC and LPC (entries 1–10). With ratios of 50 : 1, CPC and LPC reactions yielded residual amounts of **2** that were too low to accurately measure using our HPLC assay. Optimized breakdown conditions required 5 mol% of KOBu^t; lower catalyst loadings or the use of NaOBu^t or LiOBu^t gave inferior results. Most surprising were the attenuated changes in the residual phosphinate observed using DPC as the carbonate source. Longer reaction times before quenching indicated that the DPC breakdown experiments had not yet reached equilibrium (Table 1, entries 11–13). For example, quenching the reactions in entry 11 after 6 h led to 5.3% residual **1**.[9] The polymeric breakdown experiments apparently reach a final state more rapidly (< 30 min) than DPC-based protocols, as later quenching did not



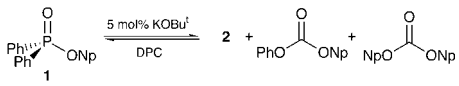
Scheme 1

Table 1 HPLC and GPC analysis data[a]

Entry	Carbonate	Phosphinate	Substrate ratio[b]	Unreacted[c] (%)	M_n[d]	M_w	PDI
1	CPC	**1**	10:1	5.3	2497	3541	1.42
2	CPC	**1**	20:1	2.1	3182	4982	1.57
3	CPC	**1**	50:1	0.95	3773	6313	1.67
4	CPC	**2**	10:1	6.2	2504	3553	1.42
5	CPC	**2**	20:1	1.1	2842	4254	1.50
6	LPC	**1**	10:1	5.3	2214	3353	1.52
7	LPC	**1**	20:1	2.4	2531	3922	1.55
8	LPC	**1**	50:1	0.9	2989	4959	1.66
9	LPC	**2**	10:1	5.3	2217	3166	1.43
10	LPC	**2**	20:1	1.4	2633	4102	1.56
11	DPC	**1**	10:1	6.8–8.3[e]	—	—	—
12	DPC	**1**	20:1	3.5–6.1[e]	—	—	—
13	DPC	**1**	50:1	3.1–4.9[e]	—	—	—

[a] Catalyst loadings were at the 5 mol% level with respect to total carbonate and phosphinate functionalities; reactions were carried out in THF and were each quenched after 30 min. [b] Ratios refer to the relative quantities of carbonate and phosphinate functionalities. [c] Residual amounts of phosphinate reflect an average of at least two runs. [d] Corrections for the MW of PC utilized the universal calibration method (K_{PS} = 0.013, K_{PC} = 0.039, α_{PS} = 0.71 and α_{PC} = 0.70, see ref. 11 [e] Ranges reflect non-equilibrium ratios (see text).

affect the amount of residual **1**. While we are confident that 10:1 and possibly 20:1 polymer experiments reach a true equilibrium state,[10] we suspect that the 50:1 cases do not. Unfortunately the low phosphinate concentrations in the residues do not allow us to determine whether catalyst death occurs before a true equilibrium is reached. Clearly, low phosphinate concentrations can be achieved with these experimental conditions.



(4)

In addition to preparative protocols, *in situ* ^{31}P NMR experiments to monitor the transfer of the phosphorus-containing fragment from the simulant to the polymer were also undertaken. The naphthyl phosphinate **1** proved particularly useful in this regard as its conversion to product was readily observed by the 0.5–1 ppm upfield shift of its resonance upon substitution of an oligomeric substituent for ONp. The amount of unreacted phosphinate in these experiments closely matched those data obtained on preparative scales. ^{31}P NMR spectra of the precipitated polymers showed only a singlet shifted slightly upfield from the starting material. Spiking of these samples with either **1** or **2** confirmed that no starting material was present in the MeOH precipitate and that quantifying unreacted simulant in the filtrate is a valid protocol for assessing overall destruction.

In summary, by combining two separate methodologies, one for the synthesis of phosphonates and the other for the breakdown of polycarbonates, a potentially useful method for the destruction of toxic chemical warfare agents has been revealed. The salient features of this approach are the low levels of simulant remaining after reaction and the safe immobilization of the simulant constituents as polymer end groups.

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Notes and references

1 Y. C. Yang, *Acc. Chem. Res.*, 1999, **32**, 109; Y. C. Yang, J. A. Baker, and J. R. Ward, *Chem. Rev.*, 1992, **92**, 1729.
2 M. G. Stanton and M. R. Gagné, *J. Am. Chem. Soc.*, 1997, **119**, 5075; M. G. Stanton and M. R. Gagné, *J. Org. Chem.*, 1997, **62**, 8240.
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5 In DMSO, the pK_a of butanethiol and naphthol are 17.0 and that of phenol is 18.0, see: F. G. Bordwell, *Acc. Chem. Res.*, 1988, **21**, 456.
6 M_n = 852; DP = 3.4, PDI = 1.37. See: D. J. Brunelle, E. P. Boden and T. G. Shannon, *J. Am. Chem. Soc.*, 1990, **112**, 2399.
7 The linear PC was prepared by first dissolving it into THF, filtering it, precipitating it into an excess of MeOH, and finally drying *in vacuo* at 50 °C (M_n = 14 330; DP = 55; PDI = 1.99).
8 Chromatograms were obtained on a Hewlett-Packard 1100 LC instrument using a cyano-terminated silica gel column (LiChrosphere 100CN) for **1**, and a silica gel column (DYNAMAX 60A) for **2**. For **1**, filtrate samples were run at 1 ml min^{-1} in THF–hexanes (3:7 v/v) with a gradient elution of 0.5% THF min^{-1} for 10 min. For **2**, filtrate samples were run at 1 ml min^{-1} in THF–hexanes (45:55 v/v). A UV diode array detector was used for analysis.
9 As expected, no net reaction is observed with **2** and DPC.
10 Monitoring reactions *in situ* by ^{31}P NMR while sequentially adding aliquots of catalysts indicated that after reaching *ca.* 5% conversion (10:1 case), additional catalyst did not change the amount of unreacted phosphinate. Similar observations were noted for the 20:1 experiments.
11 M. Kurata and Y. Tsunashima, *Viscosity–Molecular Weight Relationships and Unperturbed Dimensions of Linear Chain Molecules*, in *Polymer Handbook*, 3rd edn., ed. J. Brandrup and E. H. Immergut, Wiley-Interscience, New York, 1989, ch. VII, pp. 1–60.

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