



# Development of metal-ion containing catalysts for the decomposition of phosphorothioate esters <sup>☆</sup>

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## ARTICLE INFO

### Article history:

Received 4 January 2012

Received in revised form 8 February 2012

Accepted 11 February 2012

Available online 21 February 2012

### Keywords:

Phosphorothioate

Phosphate

Triester

Diester

Hydrolysis

Methanolysis

## ABSTRACT

The widespread use of phosphorothioate esters as agricultural pesticides, chemical weapons and mechanistic probes in enzymology has sparked interest in the reactivity of these thio-substituted analogues of phosphate esters. In this brief account, we summarize the recent developments in our understanding of the mechanisms of hydrolysis (and solvolysis in methanol) of phosphorothioates containing a sulfur atom in the bridging and/or non-bridging position. A small number of highly efficient catalytic systems containing the metal ions La(III), Pd(II), Cu(II) and Zn(II) have been developed to promote the degradation of the various classes of phosphorothioate esters. The mechanisms of the base promoted solvolytic reactions in water and methanol and those of the metal catalyzed cleavage are presented, as well as a discussion of the energetics of the catalytic processes and other salient features. The aim of this review is to provide the reader with a contemporary physical organic description of phosphorothioate ester cleavage. This article is part of a Special Issue entitled: Chemistry and mechanism of phosphatases, diesterases and triesterases.

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## 1. Introduction

Phosphorothioate esters such as the aryl-containing species **1** (Chart 1) comprise analogues of phosphate esters in which one or more of the oxygen atoms in a non-bridging position have been substituted with sulfur. Several of the neutral members of this class such as *O,O*-dimethyl *O*-(3-methyl-4-nitrophenyl) phosphorothioate (**2**) and parathion (*O,O*-diethyl *O*-4-nitrophenyl phosphorothioate (**3**) are important in agriculture where they have seen widespread use as pesticides [1]. Species containing one or more sulfurs in the bridging positions, such as VX (**4**) and Russian VX (**5**), are also termed phosphorothioates. These compounds are powerful acetylcholine esterase inhibitors and have seen use as organophosphorus nerve agents [2].

Phosphorothioate diesters (**1b**) and monoesters (**1c**) have been employed as mechanistic probes for enzyme catalyzed phosphoryl transfer reactions to deduce transition state structure [3] and sites of metal ion coordination [4]. Phosphorothioate modification of synthetic oligonucleotides provides an increased stability toward nucleases [5] giving useful applications in molecular biology [6].

Examples of naturally occurring phosphorothioate DNA linkages have been identified [7].

Several reviews of the reactions of phosphates exist [8], but less attention has been directed toward the related chemistry of phosphorothioates; the state of knowledge up to 2005 with particular reference to physical organic chemistry has been summarized [9,10]. This brief account summarizes some of the more recent results concerning the phosphorothioyl group transfer between oxyanions as in the hydrolysis and transesterification reactions. In addition, we will summarize the most recent work on solvolytic alcoholysis reactions, particularly those reporting mechanistic studies of small molecules which are promoted by metal ions in solution.

## 2. Features of the reactions of phosphorothioates with S in non-bridging position

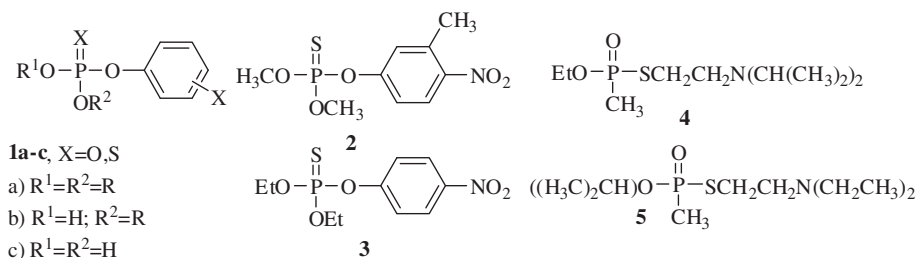
A pictorial representation of the bond-forming, bond-breaking processes occurring in various concerted phosphoryl/phosphorothioyl transfer reactions that phosphate and phosphorothioate mono-, di- and triesters (**1a–c**) undergo [10] is presented in the More-O'Ferrall-Jencks diagram in Fig. 1. Purcell and Hengge have reported the activation parameters for the hydrolysis of *p*-nitrophenyl substituted phosphate and phosphorothioate pairs (**1a,b,c**; X = O,S) which are reproduced in Table 1 [9a]. The general feature of note is that the hydrolysis of each phosphorothioate has a higher  $\Delta H^\ddagger$  than its corresponding phosphate by 4–6 kcal/mol, and has more favorable (more positive)  $\Delta S^\ddagger$ . The net effect on the kinetics of reaction is termed the 'thio effect' which is

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**Chart 1.** Chemical structures of various neutral phosphorothioates.

represented as  $k^O/k^S$  which, at 298 K, is 12.6 for the hydrolysis of **1a**, X = O/**1a**, X = S, 3.3 for hydrolysis of **1b**, X = O/**1b**, X = S, and 0.13 for the hydrolysis of the dianions of **1c**, X = O/**1c**, X = S. These are small numbers in the case of the solvent mediated reactions and, given the differences in the  $\Delta H^\ddagger$  for phosphates and their corresponding phosphorothioates, are expected to vary with temperature, possibly becoming inverted depending on which side of the isokinetic temperature the reactions are studied.

### 2.1. Solvolysis of diesters and monoesters (**1b/1c**)

The hydrolysis of phosphorothioate monoester dianions **1c**, X = S, R<sub>1</sub> = R<sub>2</sub> = (−) with aryloxy leaving groups is thought to proceed by a highly dissociative (D<sub>N</sub> + A<sub>N</sub>) mechanism involving formation of a metaphosphorothioate intermediate (O<sub>2</sub>PS<sup>−</sup>, bottom right corner of Fig. 1). This proposal is consistent with: 1) the large negative  $\beta^{\text{Lg}}$  of −1.1 determined for the hydrolysis of aryl phosphorothioate dianions; 2) the large positive entropy of activation ( $\Delta S^\ddagger$  of +29 cal/mol/K) for reaction of 4-nitrophenyl phosphorothioate dianion; and 3) the racemization observed in the hydrolysis of chiral 4-nitrophenyl [<sup>16</sup>O,<sup>18</sup>O]phosphorothioate [9a,11,12]. Heavy atom kinetic isotope effects indicate that the leaving group has undergone significant P–OAr cleavage and bears nearly a full negative charge at the transition state for hydrolysis of 4-nitrophenyl phosphorothioate dianion [13]. The hydrolytic mechanisms of phosphorothioate diesters (**1b**) have not been as extensively investigated to date. Nonetheless, kinetic isotope effects indicate that the transition state for hydrolysis of the diester, *O*-ethyl *O*-4-nitrophenyl phosphorothioate (**1b**, X = S, R<sub>1</sub> = Et, R<sub>2</sub> = (−)), involves less P–OAr bond cleavage relative to the monoester but more than the triester [13].

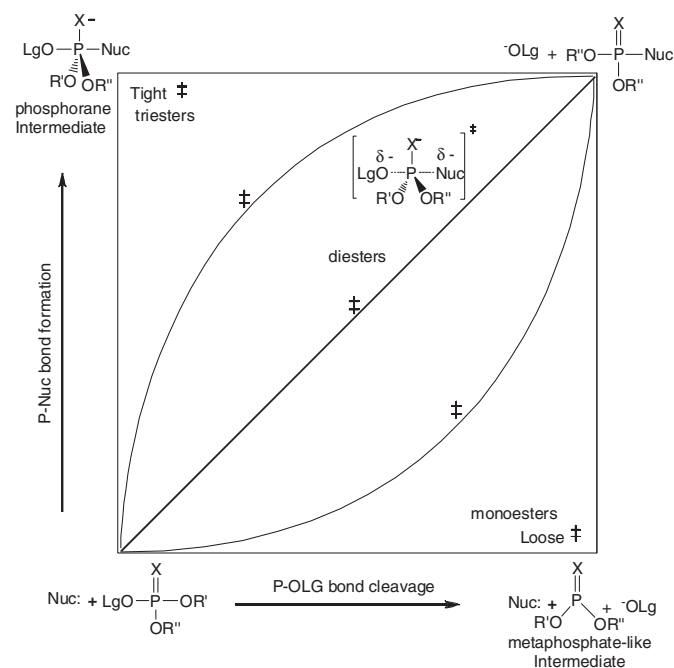
### 2.2. Solvolysis of *O,O*-dialkyl *O*-aryl phosphorothioates (**1a**)

The three main modes of nucleophilic cleavage for phosphorothioate triesters (**1a**, X = S) are illustrated in Scheme 1 for the decomposition of fenitrothion (**2**) in basic ethanol. Nucleophilic attack of ethoxide on the

aryl group of **2** leading to C–O bond cleavage competes with attack on the phosphorus and fission of the P–OAr bond. The rate constants for these two processes are similar in ethanol ( $k_2 \approx 6 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$  at 25 °C) affording near equal amounts of the C–O and P–O bond cleavage products [14]. Selectivity for the P–O bond cleavage products is higher in methanol [15] at 93:7 and essentially quantitative in water [16]. A minor amount of product, (~5%) from nucleophilic aromatic substitution, is obtained in ethanol but this process does not generally compete significantly with the other two modes of cleavage.

### 2.3. Mechanistic details of P–OAr fission from triesters

Linear free energy relationships for the transfer of the *O,O*-dimethyl phosphorothioyl (S=P(OCH<sub>3</sub>)<sub>2</sub>) group between aryloxy anions in water are consistent with a concerted process involving simultaneous bond formation with the incoming nucleophile and bond rupture of the nucleofuge [17,18]. A charge map for the symmetrical reaction between the weak nucleophile, 2,4,5-trichlorophenoxide, and *O,O*-dimethyl *O*-2,4,5-trichlorophenyl phosphorothioate in water is shown in Scheme 2 [18]. On the basis of the experimental evidence, the activated complex is described as slightly loose, where bond cleavage has progressed to the extent of 61% defined in terms of the Leffler parameter,  $\alpha$ , which relates the extent of bond cleavage or formation by comparing the Brønsted  $\beta^{\text{Lg}}$  for the TS to the  $\beta^{\text{Eq}}$  for equilibrium



**Fig. 1.** A More-O'Ferrall-Jencks diagram showing bond forming and bond cleaving axes, and the types of transition structures for nucleophilic substitution of the mono-, di-, and triesters of phosphates (X = O) and phosphorothioates (X = S).

**Table 1**

Activation parameters for the aqueous cleavage of the *p*-nitrophenyl derivatives of phosphate and phosphorothioate esters **1a,b,c**; X = O,S at 312 K under basic conditions.<sup>a</sup>

Substrate	$\Delta G^\ddagger$ (kcal/mol)	$\Delta H^\ddagger$ (kcal/mol)	$\Delta S^\ddagger$ (cal/mol/K)
<i>Monoester dianion</i>			
<b>1c</b> , R <sub>1</sub> = R <sub>2</sub> = (−), X = O	29.5	30.6	+3.5
<b>1c</b> , R <sub>1</sub> = R <sub>2</sub> = (−), X = S	27.9 ± 1.0	37.0 ± 1.0	+29 ± 3
<i>Diester, monoanion</i>			
<b>1b</b> , R <sub>1</sub> = Et; R <sub>2</sub> = (−), X = O	27.4 ± 0.5	14.91 ± 0.06	−36.3 ± 0.1
<b>1b</b> , R <sub>1</sub> = Et; R <sub>2</sub> = (−), X = S	27.9 ± 0.4	18.5 ± 0.1	−26.9 ± 0.3
<i>Triester</i>			
<b>1a</b> , R <sub>1</sub> = R <sub>2</sub> = Et, X = O	20.0 ± 0.3	12.69 ± 0.03	−24.81 ± 0.05
<b>1a</b> , R <sub>1</sub> = R <sub>2</sub> = Et, X = S	21.5 ± 0.2	16.43 ± 0.08	−17.3 ± 0.1

<sup>a</sup> Data reproduced from ref. [9a].

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