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Base-Catalyzed Hydrolysis of 1,2,2-Trimethylpropyl Methylphosphonofluoridate—An Examination of the Saturation Effect

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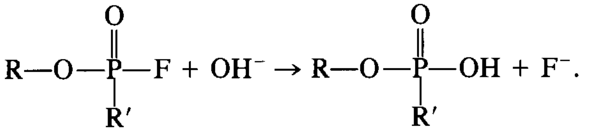
The kinetics of the hydrolysis of 1,2-2-trimethylpropyl methylphosphonofluoridate (soman) was measured from 1 to 80 × 10^{-5} M hydroxide-ion concentration. No apparent "saturation effect" could be positively identified such as was reported by Martell for the hydrolysis of isopropyl methylphosphonofluoridate (sarin). The second-order rate coefficient for soman was 10.0 ± 0.03 M^{-1} s^{-1} at 25.0°C over this pH range. © 1988 Academic Press, Inc.

INTRODUCTION

Organophosphonofluoridates are potent neurotoxins (*1*). The mechanism of nucleophilic substitution of such compounds is of interest in order to elucidate how the enzymes such as acetylcholinesterases are inactivated as well as how intoxication can be treated.

The base-catalyzed hydrolysis, Eq. [1], is generally thought to proceed by nucleophilic attack at the phosphorus ($S_N2(P)$) (*2*):



$$R{-}O{-}\overset{\overset{O}{\|}}{\underset{\underset{R'}{|}}{P}}{-}F + OH^- \rightarrow R{-}O{-}\overset{\overset{O}{\|}}{\underset{\underset{R'}{|}}{P}}{-}OH + F^-. \qquad [1]$$

The observed rate coefficient, k_{obs}, for this mechanism then takes the simple form

$$k_{obs} = k_1 + k_2 [OH^-], \qquad [2]$$

where k_1 represents nucleophilic attack by water.

In fact, as Jencks (*3*) observed, any deviation of k_{obs} from Eq. [2] is direct evidence for the formation of an intermediate which would discount the simple $S_N2(P)$ mechanism. Thus, testing the pH dependence of k_{obs} can be a conclusive test of the mechanism.

Martell (*4*) reported that the k_{obs} of isopropyl methylphosphonofluoridate (sarin)

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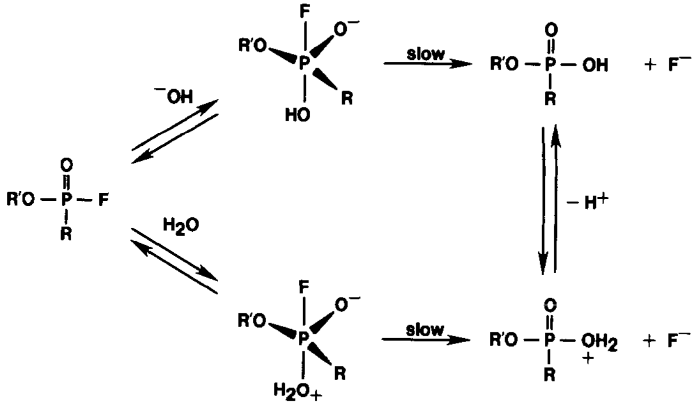

FIG. 1. Martell's mechanism for hydrolysis of organophosphonofluoridates.

failed to obey Eq. [2]; the hydrolysis rate leveled off at the upper end of the pH range studied. Martell suggested a mechanism consisting of the formation of intermediates as depicted in Fig. 1. Contrary to other studies which claimed that sarin hydrolysis was represented adequately by Eq. [2], Martell's mechanism and/or "saturation effect" was treated as an anomaly (*2*). For Martell's mechanism, the pH dependence of k_{obs} takes the form

$$k_{\text{obs}} = \frac{a + b\,[\text{OH}^-]}{1 + c\,[\text{OH}^-]}. \qquad [3]$$

We used a nonlinear least-squares computer method to fit Martell's k_{obs} vs (OH^-) data to Eq. [3] at 0.3 and 25°C. The results are shown in Table 1. Finite values of c, $(2.4 \pm 0.5) \times 10^5\ \text{M}^{-1}$ at 0.3°C and $(8 \pm 2) \times 10^{-5}\ \text{M}^{-1}$ at 25°C, were obtained, confirming the saturation effect.

In view of the important implication of pH dependence regarding the mechanism of nucleophilic substituion, we elected to do a careful study with an analog of sarin, 1,2,2-trimethylpropyl methylphosphonofluoridate (soman). There are no kinetic data available on the pH dependence of soman hydrolysis, particularly in the absence of buffers, so these data should prove useful in their own right.

TABLE 1

Illustration of the Saturation Effect for Sarin Hydrolysis[a]

	0.3°C	25.0°C
$a \times 10^5\ (\text{s}^{-1})$	2.1 ± 0.9[b]	3.3 ± 0.7
$b\ (\text{M}^{-1}\ \text{s}^{-1})$	4.8 ± 0.3	27.5 ± 1.5
$c \times 10^{-5}\ (\text{M})$	2.4 ± 0.5	8 ± 2

[a] Data are taken from Ref. (*4*) and fitted to Eq. [3].

[b] Error is sample standard deviation.

RESULTS AND DISCUSSION

The rate coefficient, k_{obs}, was determined by fitting added titrant concentration at time t, $[B]_t$, to

$$[B]_t = [B]_\infty + ([B]_0 - [B]_\infty)\exp(-k_{\mathrm{obs}}t), \qquad [4]$$

where $[B]_0$ and $[B]_\infty$ are the added titrant at times zero and infinity, respectively (*5*). Best-fit values of k_{obs}, $[B]_0$, and $[B]_\infty$ were obtained for each run. Only runs with sample standard deviation of each parameter less than 5% as computed by the program were accepted. Swain recently discussed the importance for determining best-fit values at time infinity (*6*). Therefore, in addition to the above constraint, results from runs were rejected when the experimental $[B]_\infty$ did not agree with the best-fit value. Observed first-order rate constants were measured at hydroxide ion concentrations ranging from 1.0 to 60 × 10^{-5} M (pH 9.0 to 10.8) as shown in Table 2. Five replicates were taken at the largest hydroxide ion concentration of 60.2 × 10^{-5} M in order to see if the k_{obs} vs pH was nonlinear. A plot of k_{obs} vs hydroxide ion concentration is presented in Fig. 2.

The rate coefficients in Table 2 were then fit to Eq. [3] to see if the value of c was finite, which would establish nonlinear dependence on pH, but the results showed that both c and a are not finite. The calculations were redone with c set equal to 0 which showed that a (corresponding to k_1 in Eq. [2]) was still 0. Finally, the calculations were repeated with both a and c set equal to 0, which gave a value of b of 10.0 ± 0.3 $\mathrm{M}^{-1}\ \mathrm{s}^{-1}$ (corresponding to k_2 in Eq. [2]). It is unclear why soman did not have finite values of a and c. There seems to be no reason to question Martell's rate coefficients, particularly since a finite value of c was detected at two temperatures. Possibly the geometry of the alkoxy group affects c. Thus, less hindered groups such as methyl or ethyl may show the saturation more readily. Nonetheless, Martell's data alone question assignment of simple S_N2(P) for nucleophilic substitutions of these compounds.

We also noted that individual kinetic runs gave excellent fits to Eq. [4], which means that the four stereoisomers of soman hydrolyze equally fast. The stereo-

TABLE 2

Rate Coefficients for Soman Hydrolysis at 25.0°C

$[\mathrm{OH}^-] \times 10^4$ (M)	$k_{\mathrm{obs}}{}^{a} \times 10^4$ (s^{-1})
0.11	0.90 ± 0.11 (2)
0.398	5.46 ± 1.4 (2)
0.602	5.91 (1)
2.00	17.6 ± 0.7 (2)
3.98	40.7 (1)
5.00	54.0 ± 0.9 (2)
6.02	57.1 ± 2.2 (5)

[a] Errors in k_{obs} are the maximum deviations from the mean; numbers of runs are indicated in the parentheses.

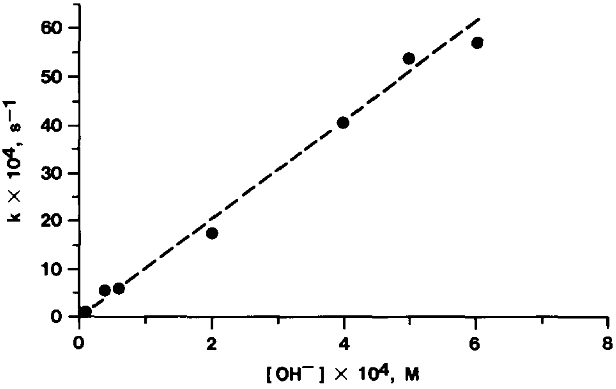

FIG. 2. pH dependence of soman hydrolysis.

isomers differ markedly in their reactivities toward enzymes (7). Note, too, that soman, unlike sarin, did not have a finite value of k_1.

EXPERIMENTAL

1,2,2-Trimethylpropyl methylphosphonofluoridate (soman) was from our own supply. Soman is *extremely toxic* and particularly difficult to treat. This compound should only be used in specialized facilities with medical treatment readily available. Ethanol solutions of soman were checked for purity by gas chromatography (GC) and fresh solutions were found to be at least 96% pure. Other chemicals were reagent grade.

Kinetic runs were conducted at SRI, Int., on a computer-controlled pH stat that serves the dual function of maintaining the pH and monitoring the reaction by titration of the acid produced in the hydrolysis reaction. The electrodes are "Ross" combination pH electrodes (Orion Research Model 8102) with pH resolution of 0.002 unit.

Kinetic studies were performed in jacketed, sealed, glass reaction vessels of 250- and 50-ml volumes, respectively, equipped with magnetic stirring bar, septa covered injection port, o-ring sealed electrode, and gas inlet/outlet. Inert atmosphere is maintained by slow purging of the head space with nitrogen. The temperature was maintained ±0.1°C by circulating coolant (water/ethylene glycol) through the water jacket from a Haake Model FE circulating constant-temperature bath.

Stock solutions of soman were prepared by dissolving soman in ethanol in a 1- or 2-ml volumetric flask. The reaction flask is filled with the appropriate volume of degassed, deionized water with the pH adjusted to the appropriate starting point and thermostated at 25.0°C. The ionic strength was adjusted to 0.10 M with potassium perchlorate. The final concentration of soman was 4.48×10^{-4} or 1.01×10^{-6} M in solutions containing about 1% (by volume) ethanol.

CONCLUSIONS

1. Martell's data for the hydrolysis of Sarin demonstrate nonlinear dependence on pH at two temperatures.

2. No "saturation effect" could be positively identified for soman hydrolysis. At 25°C, the rate law for soman hydrolysis is first order in hydroxide ion and soman concentrations with a second-order rate coefficient of 10.0 ± 0.03 $\text{M}^{-1}\ \text{s}^{-1}$. No hydroxide-independent path was detected.

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