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HYDROLYSIS OF CYANOHYDRIN ESTERS

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Abstract: The kinetics of the base hydrolyses of a series of α-cyano thiophosphate esters are presented. A classic Hammett sigma-rho analysis showed these hydrolyses to be bimolecular in nature.

INTRODUCTION

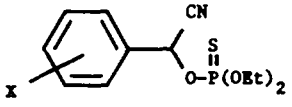
Simple phosphate and carboxylate ester hydrolyses have been extensively studied,[1] with the associated kinetics and mechanisms being generally well understood. Cyanohydrin-derived phosphate and carboxylate ester solvolyses, however, have not been studied nearly as thoroughly and form the basis for a number of recent studies.[2-6] Through the use of PTC techniques, interesting α-cyano-substituted thiophosphate and carboxylate esters have been synthesized. The α-cyano thiophosphate esters have shown insecticidal activity in initial screening tests. In this application, the hydrolytic stability of a subject compound is of critical importance. To investigate this problem, a series of α-cyano thiophosphate esters were synthesized and purified, and their relative rates of hydrolyses, under basic conditions were measured. Results were compared to those obtained with a control ester (no cyano group). A similar series of α-cyano carboxylate esters are currently being compared to their non-cyano counterparts under basic hydrolysis conditions.

RESULTS AND DISCUSSIONS

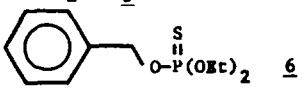
α-Cyano Thiophosphates

1. Syntheses and Purification

The following α-cyano thiophosphates were synthesized from the appropriate aldehyde and diethylthiophosphoryl chloride in the presence of a catalytic amount of base.[7] As a control compound the benzyl ester 6 derived from the diethyl chlorothiophosphate was also prepared.



X = p-CH_3O 1
p-CH_3 2
H 3
p-Cl 4
m-NO_2 5



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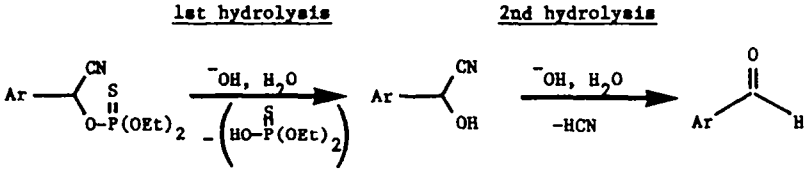
Synthetic and purification details for all of these thiophosphates are described in the experimental section.

2. Basic Hydrolyses

These studies were run at ambient (23-27 C) temperatures in a mixed solvent system of dioxane/water (3:1 by volume) using KOH ($\sim 10^{-2}$ to 10^{-1} M) as base and ester concentrations of 1 to 5 X 10^{-2}M. The base concentration was always at least 2 1/2 times that of the ester. The rate of ester hydrolysis was followed by titration with dilute acid solution (HCl) in the presence of an indicator, generally methyl red or methyl orange.

Table I contains the kinetic results obtained for the hydrolyses of compounds 1-6. A number of salient points should be made concerning these results. First, all of the esters α-cyano substituted and the control, exhibit clean second order kinetics. [8] This is what is expected for the general case of phosphate ester hydrolysis under basic conditions. Second, there are two distinct, sequential hydrolyses occuring in the presence of the cyano group, but only one in the case of the control ester. This is exactly what is to be expected upon consideration of the probable reaction sequence shown in Scheme I.[9]

Scheme I



Here the second hydrolysis is that of the cyanohydrin formed in the first hydrolysis step, a well-known reaction of cyanohydrins under basic conditions. In the case of the control compound 6 which does not contain a cyano group, the product of the first hydrolysis is benzyl alcohol which is unreactive under the described conditions. Thus only a single hydrolysis is observed for 6. The third point is the effect of the aryl substituent upon the reaction rate. As the electron withdrawing power of the sutstituent increases, so does the hydrolysis rate. Note also that this is true for both the first and second hydrolyses. Table I gives the rate constants for both hydrolysis steps for compounds 1-6. The most important result here is the difference between compounds 3 and 6, with and without a cyano group, respectively. Compound 3 hydrolyses ca 100 times faster than 6. Clearly, the presence of the cyano group significantly accelerates the hydrolysis rate. This is not surprising in view of the stabilizing effect the cyano group has upon an anionic transition state or product.

There is an even greater increase in the rate of the first hydrolysis step (≃700 X's) in going from the electron-donating methoxy group to the strongly electron-withdrawing nitro substiuent on the aryl ring. Again this is due to the stabilizing influence of an electron withdrawing group (NO_2, Cl) upon the incipient anionic intermediate. Clearly, electron donation has the opposite effect accounting for the retarded rates observed for the methyl and methoxy substituted esters relative to the unsubstituted aryl ester. The last comparison worthy of mention from Table I is that between the rates of the first and second hydrolyses. In general the rate difference is a factor of ca. 100, the second rate being the slower one.

Figure 1 presents the Hammett sigma-rho plot[10] associated with the data of Table I for the first hydrolysis of esters 1-6. The rho value determined by the slope of this plot is ρ=2.90. A positive rho value of this magnitude is expected for a bimolecular

reaction as shown in equation (2):[11]

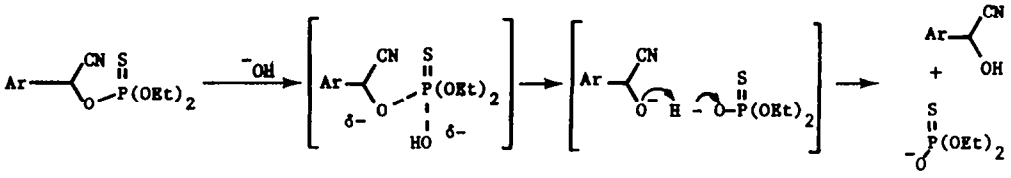


Figure 1 has a similar plot for the second hydrolysis for which ρ=2.30. A similar (E2?) type of bimolecular mechanism can be postulated here.

SUMMARY AND CONCLUSIONS

The presence of an α-cyano group in thiophosphates destabilizes the molecule toward basic hydrolysis. The observed hydrolyses probably proceed by a classical bimolecular mechanism and are accelerated by electron withdrawing ring substituents and decelerated by electron donating substituents. Two sequential hydrolyses are observed when a α-cyano group is present. The first is the hydrolysis of the ester functionality while the second involves decomposition of the cyanohydrin formed as a product of the first hydrolysis into an aldehyde and HCN.

EXPERIMENTAL

Materials: p-Dioxane was obtained from Fisher Scientific Co. All of the starting aldehydes, thiophosphoryl chlorides, and benzyl alcohol were obtained from Aldrich Chemical Co.. The α-cyanothiophosphates 1-5 were synthesized using the general procedure which follows: 0.04 moles of aldehyde and 0.04 moles of diethylthiophosphoryl chloride were stirred in 50 ml of CH_2Cl_2 in the presence of catalytic amounts of 4-dimethylaminopyridine and tetrabutyl ammonium chloride at 25° . A solution of 3g NaCN in 25 ml of H_2O was added with vigorous stirring, and left to stir overnight. The CH_2Cl_2 layer was washed with saturated $NaHSO_3$ and 10% $NaHCO_3$, dried over $MgSO_4$ and then filtered. Upon removing the CH_2Cl_2 in vacuo a light yellow to brown oil remained. This was then chromatographed on silica gel with hexane/ethyl acetate (0 to 40% EtOAc), yielding a yellow oil. After purification the esters 1-5 give the following proton nmr spectra with the α-proton being characteristic at δ6.35 ppm (all in CCl_4 with TMS as internal standard):

1: δ1.00-1.50 ppm (m, 6H, methyl), δ3.75-4.35 (m, 4H, methylene), δ3.80 (s, 3H, methyl), δ 6.12 (d, 1H, methine, J=7Hz), δ6.8-7.6 (2 doublets, 4H, aromatic). 2: δ 1.05-1.55 (m, 6H, methyl), δ3.65 - 4.35 (m, 4H, methylene), δ 2.40 (s, 3H, methyl), δ 6.10 (d, 1H, 7=Hz), δ 7.05-7.5 (2 doublets, 4H, aromatic). 3: δ 1.1-1.6 (m, 6H, methyl), δ 3.7-4.6 (m, 4H, methylene), δ 6.15 (d, 1H, methine, J=7Hz), δ 7.4-7.6 (m, 5H, aromatic). 4: δ 1.0-1.5 (m, 6H, methyl), δ 3.75-4.35 (m, 4H, methylene), δ 6.15 (d, 1H, methine, J=7Hz), δ 7.25-7.55 (2 doublets, 4H, aromatic). 5: δ 1.15-1.55 (m, 6H, methyl), δ 3.9-4.5 (m, 4H, methylene), δ 6.35 (d, 1H, methine, J=7Hz), δ 7.5-8.5 (m, 4H, aromatic.

The control ester (no cyano group) 6 was synthesized by allowing benzyl alcohol (0.002 moles, 0.22 ml) to react with NaH (0.002 moles, 0.31 ml). 6 was purified by chromatography as described for esters 1-5) and gave the following pmr: δ 1.25 (m, 6H, methyl),δ4.02 (m, 4H, methylene),δ5.00 (d, 2H, J=7Hz),δ7.28 (aromatic)

EQUIPMENT

Proton magnetic resonance spectra were obtained on a Varian EM-390 pmr spectrometer. Gas chromatography analyses were carried out on a Hewlett-Packard Model 5710 Flame Ionization Gas Chromatograph fitted with a 50 m glass capillary column.

KINETIC DATA

The kinetic data were accumulated for the thiophosphates by the following general procedure: Using methyl red as indicator, a solution of KOH ($0.5-1.5 \times 10^{-1}$ M) in p-dioxane/water (3:1, v:v) was held at ambient (24-28°) temperature. This solution was added to enough ester to give a 1.5 to 5×10^{-2} M solution of ester, with the KOH being always in at least three fold excess over ester. Aliquots of this hydrolyzing ester

solution were periodically removed and titrated with dilute ($\simeq 10^{-3}$ - 10^{-2} M) HCl solution to the endpoint. Blanks of the KOH in p-dioxane/water solvent system were taken for t_o volumes. The data were then analyzed using classical second order rate equations and Hammett analyses.[8]

TABLE I

SECOND ORDER RATE CONSTANTS FOR THE BASIC HYDROLYSES[a] OF THIOPHOSPHATES 1-6

X =	Rate of 1st Hydrolysis	Rate of 2nd Hydrolysis
m-NO_2	7.0×10^{-1} $\pm$0.1 $M^{-1}s^{-1}$	8.2×10^{-3} $\pm$0.2 $M^{-1}s^{-1}$
p-Cl	2.1×10^{-2} $\pm$0.1 $M^{-1}s^{-1}$	3.2×10^{-4} $\pm$0.5 $M^{-1}s^{-1}$
H	3.5×10^{-3} $\pm$0.2 $M^{-1}s^{-1}$	2.5×10^{-4} $\pm$0.5 $M^{-1}s^{-1}$
p-CH_3	3.0×10^{-3} $\pm$0.2 $M^{-1}s^{-1}$	3.8×10^{-5} $\pm$0.6 $M^{-1}s^{-1}$
p-OCH_3	1.0×10^{-3} $\pm$0.2 $M^{-1}s^{-1}$	not observed
Ph, S, O-P(OEt$_2$)	4.0×10^{-5} $\pm$0.1 $M^{-1}s^{-1}$	not observed

[a] KOH ($0.5\text{-}1.5\times10^{-1}$M); Ester ($1.5\times10^{-2}$M) in dioxane/$H_2O$ (3:1 v:v); Titrated with HCl (10^{-3}-10^{-2}M).

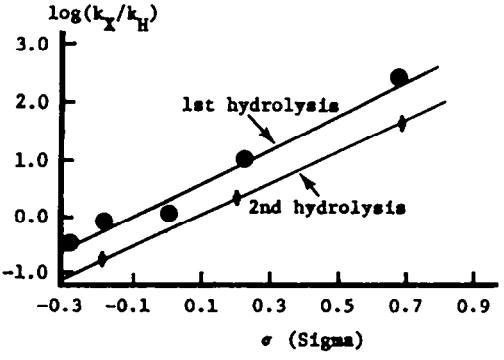


FIGURE 1 - HAMMETT SIGMA PLOT FOR THE HYDROLYSES OF 1 - 5

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8. For a discussion of the derivation of the kinetic equations, see C. D. Ritchie "Physical Organic Chemistry", Marcel Dekker, Inc., New York, 1975.
9. Nucleophilic attack upon the benzylic carbon is possible (see reference 1) but unusual.
10. Sigma values obtained from reference #7, p. 111. See also Ritchie, D. C.; Sager, W. F. ;Prog. Phys. Org. Chem 1964, 2, 323.
11. Equation 2 shows a concerted mechanism of hydrolysis. One involving the formation of a discreet intermediate is equally viable.