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Catalytic Micellar Nucleophilic Hydrolysis of Phosphotriesters

D.K Tyagi[1] and Suman Mandrwal[2]

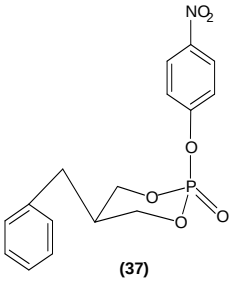
[1,2]Department of Chemistry M.M.(P.G) College ModiNagar U.P.201204 India
E-mail: [2]suman_mandrwal_18@yahoo.com

Abstract—*Phosphate esters and anhydrides dominate the living world. The genetic materials DNA and RNA are phosphodiesters. Most of the coenzymes are esters of phosphoric or pyrophosphoric acid. The principal reservoirs of biochemical energy [adenosine triphophate (ATP), creatine phosph In conjuction with the biological methods for the destruction of such phosphorus neurotoxins, as sarin, soman, paraoxon, and parathion, which have focused on phosphotriesterase[12], antibodies have also been designed and generated to catalyze phosphorolytic reactions.*

Keywords*: phosphotriesters*

1. INTRODUCTION

In conjuction with the biological methods for the destruction of such phosphorus neurotoxins, as sarin, soman, paraoxon, and parathion, which have focused on phosphotriesterase[1], antibodies have also been designed and generated to catalyze phosphorolytic reactions.



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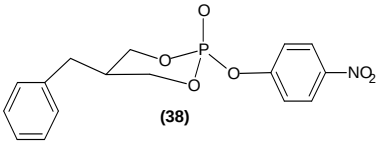


(38)

It is important to note that these two diasteromeric dialkyl p–nitrophenyl phosphotriesters, **37** and **38**, are related to paraoxon, **34**. Among the many nucleophiles surveyed for phosphorolysis activity, o–iodosobenzoate, **14**, stands out as a potent catalyst for the catalytic cleavage of neurotoxin simultants[2] at moderate pH in micellar solution

2. EXPERIMENTAL PROCEDURE:

General method: M.P. are uncorrected.

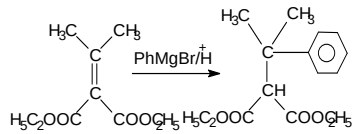
NMR:NMR were determined on a varian 200 MHz Instrument

PH METER: fisher module 320 digital Ph meter(calomel electrode) was used to adjust ph of solution.

Material Used: all materials were used as comercialy available.

Preparation of diastereomeric phosphotriesters, **37** and **38**

The synthesis of diastereomeric phosphate trimesters, **37** and **38** is outlined in Scheme 7.[3]



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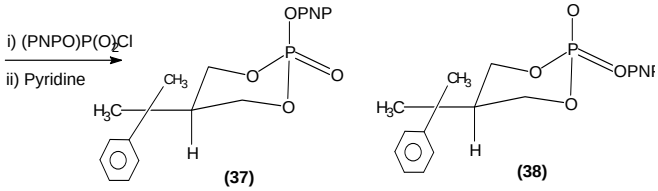


(37) (38)

Synthesis of diastereomeric phosphate triesters and various nucleophiles Diastereomeric phosphotriesters, 37 and 38.[3]

To a solution of 5 g of diethyl isopropylidine malonate, **42** (25 mmol), in 50 ml of dry THF, was slowly added phenyl magnesium bromide (37.5 ml, 1.0 M in THF) at 0°C (see Scheme 7). The reaction mixture was kept at 0°C for ~30 min., and then heated to reflux for 30 min. After cooling to 0°C, excess PhMgBr was quenched by the addition of saturated aqueous ammonium NH_4Cl chloride solution until the evolution of H_2 gas ceased. The product 43 was extracted from the aqueous solution with ethyl acetate 3 times (3 × 30 ml), and the combined extract was dried over Na_2SO_4 for 5 min. After removing the drying agent and the solvent the product was purified by chromatography over a 400 mesh silica gel column, using 8% ethyl acetate in hexane as the eluent.

3. RESULT AND DISCUSSION

Kinetic studies

Pseudo–first–order rate constants, k_Ψ, were determined for the cleavage of two diastereomeric substrates **(37** and **38)** using different nucleophiles, by monitoring the appearance of p–nitrophenoxide ion at 400 nm.: Table 7 presents the rate constants for the cleavage of these two diastereomeric phosphotriesters with various nucleophiles.

Table 7: Kinetics of phosphorolytic cleavage of phosphate diastereomeric substrates (37 and 38)[4]

Reagent	Experimental conditions	kΨ (37), s–1	kΨ (38), s–1	k38/k37
Uncatalyzed60	pH 8.5, 50 mM Bicine, 30°C, 402 nm	4.62 × 10–7	1.46×10–6	3.16
Antibody60	pH 8.5, 50 mM Bicine, 30°C, 402 nm	1.68 × 10–4	3.08 × 10–5	0.183
0.02M Carb Bicarb buffer	No CTACl/pH 10	1.61×10–3	3.52×10–3	2.19
0.02M NaOH	No CTACl/pH 12	5.25×10–4	2.06×10–3	3.93
CTACl (pH 10)	0.02 M Carb–Bicarb buffer, [CTACl] = 1×10–3 M, 25–26°C, final [subs] = 1×10–5M	1.26 × 10–4	4.93 × 10–4	3.90
CTACl (pH 12)	0.02 M NaOH (no buffer), 25°C, [CTACl] = 1×10–3 M, final [subs]=1 ×10–5 M	1.83 × 10–2	8.94 × 10–2	4.87
IBA (14)	pH 8, 0.02 M NaH2PO4 (in 0.08 M NaCl), [CTACl]=1 × 10–3 M, 25–60°C, final [IBA]=1×10–4 M final [subs]=1×10–5M	1.21×10–4	3.84 × 10–4	3.18
INA (39)	Same as above	6.59 × 10–4	1.82 × 10–3	2.76
CTAOOH pH 8.0	Final [CTAOH] = 1.5×10–3 M, [H2O2] = 0.02 M CTAOOH (CTAOH+H2O2)	1.79 × 10–3	2.13×10–3	1.19
CTAOOH pH 9.0	Same as above	5.43 × 10–3	1.5 × 10–2	2.76
CTAOOH, pH 10.0	Same as above	4.19 × 10–2	7.75 × 10–2	1.85
Amidoxime (pH 10.0)	Final [Cat] =1×10–4 M, [Subs]= 1×10–5 M, [CTACl]=1×10–3M, 0.02 M Carb–Bicarb buffer, 25°C	1.67×10–4	4.17×10–4	2.50
Amidoxime (pH 12.0)	0.02 M NaOH, 25°C, other conditions as above	2.18 × 10–2	0.11	4.96

a) All k_Ψ are reported as an average of two runs; reproducibility, ± 4%.

X–Ray Structure Determination

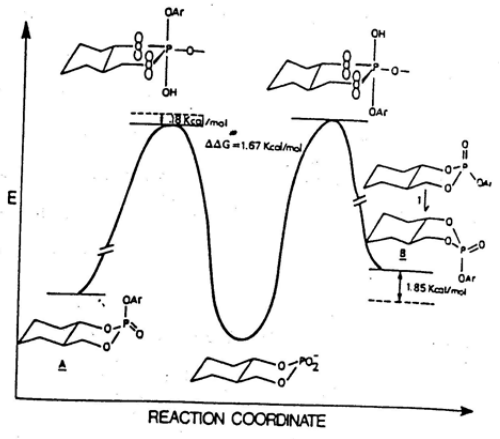
The crystal used for the X–ray data collection of 9–iodoso–10–phenanthroic acid w as a colourless prism of dimensions 0.025×0.10×0.20 mm^3, obtained from a supersaturated solution in DMSO.

Table 8: Crystal Data Summary for 9–Iodoso–10–phenanthroic Acid (38)

Crystal Data	
Empirical Formula:	C15H9IO2
Formula Weight:	364.10
Colour/Habit:	Colourless/plate
Crystal Dimensions:	0.200×0.100×0.025 mm
Crystal System:	Monoclinic
Space Grou:	C2
Unit Cell Dimensions (Å)	33.741, 5.277, 9.120 (a, b, c)
Unit Cell Volume:	1589.0(5) Å3
Calculated Density:	1.849 Mg/m3
Absorption Coefficient:	2.164 mm–1
F000 and Z	872.4
Data Collection	
Diffraction System Used:	CAD4
Radiation (type, wavelength):	MoKα, λ=0.71069 Å
Temperature:	295 K
Monochromator Type:	Graphite
ϕ Range:	2° to 23°
Index Ranges:	–36 ≤h≤36, 0≤k≤5, 0≤1≤10

4. CONCLUSION

In conclusion, the hapten choice in Lerner's work was not ideal–because it is tetravalent not pentavalent. By introducing proper structural features in hapten more reactive antibody could be produced that will have more reactivity and more diastereoselectivity. All the nucleophiles used in the present work are much more reactive than antibody.



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