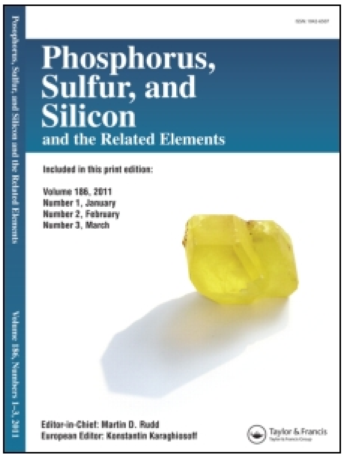
This article was downloaded by:
On: *28 January 2011*
Access details: *Access Details: Free Access*
Publisher *Taylor & Francis*
Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Synthesis of Stable Spirooxyphosphoranes - Potential Promoters of Catalytic Antibodies

Osnat Nir; Mati Fridkin; Yoffi Segall

To cite this Article Nir, Osnat , Fridkin, Mati and Segall, Yoffi(1996) 'Synthesis of Stable Spirooxyphosphoranes - Potential Promoters of Catalytic Antibodies', Phosphorus, Sulfur, and Silicon and the Related Elements, 109: 1, 241 — 244

To link to this Article: DOI: 10.1080/10426509608545135

URL: http://dx.doi.org/10.1080/10426509608545135

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: http://www.informaworld.com/terms-and-conditions-of-access.pdf

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

Phosphorus, Sulfur, and Silicon, 1996, Vols. 109–110, pp. 241–244
Reprints available directly from the publisher
Photocopying permitted by license only

Synthesis of Stable Spirooxyphosphoranes - Potential Promoters of Catalytic Antibodies

Osnat Nir*, Mati Fridkin# and Yoffi Segall*
Department of Organic Chemistry, *Israel Institute for Biological Research, P.O.Box 19, Ness-Ziona, 74100, Israel and #The Weizman Institute of Science, Rehovoth, 76100

Abstract Bis-[*ortho*-carboxyaryl]- and bis[*ortho*-amidoaryl]methylphosphine oxides, in acidic medium, spontaneously cyclodehydrate to give trigonal bipyramidal (TBP) spirodioxy- and azoxyphosphoranes, respectively. Regioselectivity with a few nucleophiles and electrophiles, unexpectedly, accompany some of their reactions. Their structural similarity to pentacoordinate intermediates, obtained on the hydrolysis of organophosphorus (OP) poisons, and their stability at the physiological pH, renders them, as transition state analogs (TSA), useful promoters of catalytic antibodies.

Key Words Dioxyphosphoranes, azoxyphosphoranes, transition state analogs, trigonal bipyramids, regioselective reactions, catalytic antibodies.

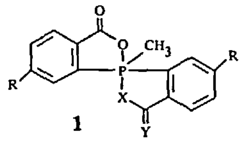
INTRODUCTION

The concept of inducing monoclonal antibodies (Ab) that catalyze hydrolysis reactions, has its roots in pioneering reports published by Schultz[1-2] . Designing TSA's intuitively requires the inclusion, in the hapten, of electronic and structural aspects residing in the actual substrate[3] . Recently, it was demonstrated that mice, immunized with a protein conjugate of a TBP TSA, produced Ab that enhanced the hydrolysis of phosphonates, including soman[4]. Pentacoordinate P-hydroxyphosphoranes, postulated to be intermediates or transition states in non-enzymic or enzymic hydrolysis reactions of tetracoordinate phosphorus[5] , are usually unstable[6] . Modelling such a TBP structure, for mimicking transition states of OP poisons (sarin, soman), requires the challenging synthesis of pentavalent hydroxyphosphoranes that would be stable in aqueous environment. Efficient Ab, produced by that route, are expected to compete with AChE on its deactivation by OP toxicants and significantly enhance their rate of hydrolysis.

RESULTS AND DISCUSSION

Synthesis

In attempting to prepare dioxyphosphoranes and incorporate functional groups comprised in OP poisons, we synthesized compounds **1** (scheme 1). Stable oxyphosphoranes **1** were obtained on spontaneous cyclodehydration of ortho-carboxyarylmethylphosphine oxides **2**, in acid, as outlined in scheme 2 for phosphorane **3**.



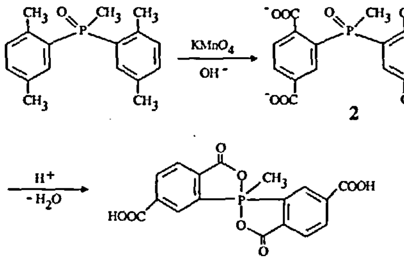
1

$X = O, NH, N\text{-}CH_3$
$Y = O, 2H, 2CH_3$
$R = COOH, COOCH_3, COCl, CONH_2$
$CONHCH_3, CH_2OH, C(CH_3)_2OH$

Scheme 1. Spirooxy- and azoxyphosphoranes

Structure and reactivity

The geometry around the phosphorus atom was directly elucidated using ^{31}P NMR spectroscopy. Thus, the chemical shifts of tetrahedral phosphine oxide analogs of **2** (δ ^{31}P ~ +25ppm) significantly shifted upfield ($\Delta\delta$= ~ 75ppm) on conversion to **3**. Likewise, the coupling constant for the P- CH_3 in phosphine oxides **2** (J=13Hz), is considerably higher in phosphoranes (J=17Hz), indicating an equatorial preference for the orientation of the P-methyl in the TBP structure **3**. Being the most electronegative atoms, the two oxygens take preference in occupying the diaxial position[7]. On dissolving in aqueous base (pH 9), phosphorane **3** reverts to phosphine oxide **2**. Surprisingly, on attempted esterification, in refluxing CH_3OH, diacid-phosphorane **3** quantitatively yields tetraester **4** rather than diester **5** (scheme 3), providing a unique way for synthesis of **4**.

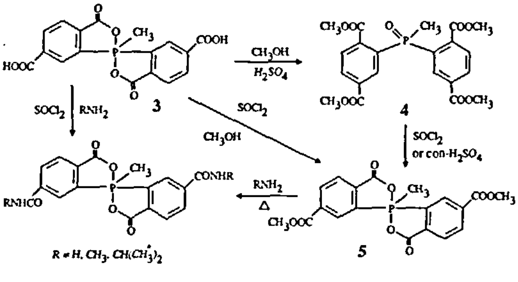


3, δ ^{31}P = -51.9 ppm ($J_{P\text{-}H}$ = 17.1Hz)

Scheme 2. Preparation of a P-methyldioxyphosphorane

Thus, an alternative route for the synthesis of diester-phosphorane **5** is refluxing diacid **3** in $SOCl_2$, followed by methanolysis (scheme 3). Unexpectedly, refluxing tetraester **4** in $SOCl_2$, or dissolving in concentrated H_2SO_4, regioselectively leads to phosphorane **5** while the other two arylesters at meta-position to phosphorus, remain intact.

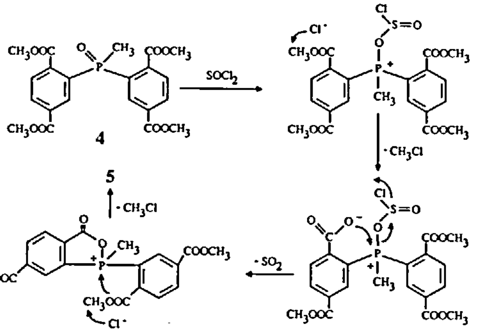
A suggested mechanism is depicted in scheme 4, indicating that regioselectivity is achieved on initial electrophilic thionyl chloride attack at the phosphoryl oxygen, followed by loss of CH_3Cl from within the reaction cage. A similar mechanism was postulated for the $COCl_2$ chlorination of an ^{18}O-alkyl labelled phosphinate ester, whereupon labelling was retained in the ultimate product as ^{18}O=P[8].



Scheme 3. Esterification and amidation reactions for phosphorane 3

Enhanced reactivity towards phosphorus ester

Most intriguing is the reaction of diester-phosphorane **5** with CH_3MgBr. Even with considerable large excess of the reagent (8 or 14 fold), the only product isolated was phosphorane 1 {X=O, Y=2CH_3, R=C$(CH_3)_2$OH} with one ester group remaining intact. With 4-fold excess of the reagent, reaction preferably takes place at the phosphorus ester with an ultimate product resulting from reaction at a single ester group. Regioselectivity was also demonstrated with $LiAlH_4$ reduction of phosphorane 5. Thus, only phosphorane 1 (X=O, Y=2H, R=$COOCH_3$) was isolated with two fold excess of the reagent.



Scheme 4. Regioselective chlorination of 4 leading to diester-phosphorane 5

Azoxyphosphoranes

Tetraamidate 6, in trifluoroacetic acid (TFA), exclusively leads to azoxyphosphorane 7, suggesting a reaction route outlined in scheme 5.

Scheme 5. Synthesis of azoxyphosphorane 7 from tetraamidate 6

The initial formation of a carboxyaryl, due to reaction with TFA, affords the first phospholane ring. Subsequent elimination of H_2O from the intermediate, leads to diamidophosphorane 7, expressing, again, a regioselecte reaction. The molecular asymmetry in azoxyphosphorane 7 (as opposed to dioxyphosphoranes) is reflected in its ^1H and ^{13}C NMR spectra (Fig.). The aryl protons show up as 6 non-equivalent protons(^1H), along with 4 non-equivalent carbonyls(^{13}C), of which, two are split (J=2.7Hz), due to their proximity to the phosphorus atom.

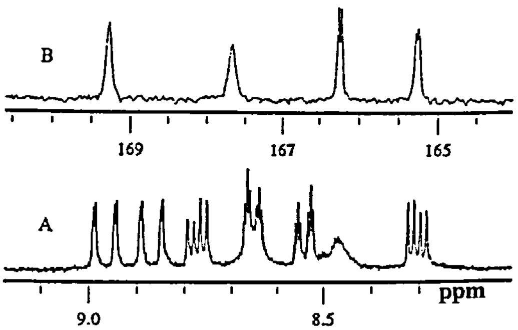


Fig. Partial ^1H aromatics (A) and ^{13}C carbonyls (B) NMR spectra of phosphorane 7.

Stability in aqueous solutions

The hydrolytic stability of the phosphoranes, at various pH values, was measured by monitoring their ^{31}P NMR spectra in aqueous solutions, comprising 10% DMSO as a cosolvent. All of the dioxyphosphoranes were stable and only converted to the corresponding phosphine oxides at pH > 8.5. Therefore, the spirodioxyphosphoranes are expected to be stable at the physiological pH. In that respect, the azoxyphosphoranes convert to the corresponding phosphine oxides at pH 7.4 and are, thus, unusable as haptens.

Summary

Spirodioxy- and azoxyphosphoranes were obtained on spontaneous conversion of tetrahedral phosphine oxides to TBP in acidic environment. Regioselective electrophilic and nucleophilic reactions were demonstrated on attempted synthesis of some of these phosphoranes. Enhanced reactivity at the ArCOOP moiety, rather than the other aryl ester moiety, was observed with certain nucleophiles. Excluding azoxyphosphoranes, the dioxyphosphoranes were found to be stable at the physiological pH. Although far from an assumed acyclic TBP intermediate structure and much bulkier, these cyclic phosphoranes are characterized by: a) a CH_3-P moiety and an O-alkyl fragment, both typical to most OP chemical warfare agents, b) stability at physiological conditions (excluding azoxyphosphoranes), and c) a functional group for further conjugation to a protein carrier. Therefore, these TBP compounds, as haptens, are potential candidates for the promotion of catalytic antibodies.

REFERENCES

1. S.J. Pollack, J.W. Jacobs and P.G. Schultz, *Science*, **234**, 1570 (1986).
2. R.A. Lerner, S.J. Benkovic and P.G. Schultz, *ibid*, **252**, 659 (1991).
3. L. Izadyar, A. Friboulet, M.H. Remy, A. Roseto and D. Thomas, *Proc. Natl. Acad. Sci.* USA, **90**, 8876 (1993).
4. A.A. Brimfield, D.E. Lenz, D.M. Maxwell and C.A. Broomfield, *Chem. -Biol. Interactions*, **87**, 95 (1993).
5. F.H. Westheimer, *Acc. Chem. Res.*, **1**, 70 (1968);
   R.F. Hudson and C. Brown, *ibid.*, **5**, 204 (1972).
6. Y. Segall and I. Granoth, *J. Am. Chem. Soc.*, **101**, 3687 (1979);
   I. Granoth and J.C. Martin, *ibid.*, **101**, 4618 (1979);
   A. Murillo, L.M. Chiquette, P.J. Nathan and R. Contreras, *Phosphorus, Sulfur and Silicon*, **53**, 87 (1990).
7. Y. Segall and I. Granoth, *J. Am. Chem. Soc.*, **100**, 5130 (1978).
8. A.J. Kirby and S.G. Warren, *The Organic Chemistry of Phosphorus*, Elsevier Publishing Company (1967), pp. 228.