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An Exceptionally Reactive Phosphotriester

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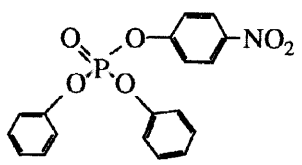
Abstract. The 1,8-naphthyl phosphotriester (**2**) is 1-2 orders of magnitude more reactive than the "standard" model phosphotriester (**1**) in phosphorolytic reactions with commonly employed nucleophilic phosphorolytic "decontamination" reagents.

Interest in the efficient chemical destruction of nerve agents and other toxic phosphorus ester derivatives remains strong,[2] with attention focused on peroxides,[3] iodosocarboxylates,[4] metallomicelles,[5] enzymes,[6] and antibodies[7] as hydrolytic catalysts. The extreme toxicity of the phosphorus nerve agents (sarin, soman, VX)[2] mandates that most laboratory research employ models or *simulants* in place of the actual compounds. Since its introduction in 1969, *p*-nitrophenyl diphenylphosphate (PNPDPP, **1**) has become the unofficial standard simulant for phosphotriester hydrolytic reactions.[4a,5a,8,9] Its widespread use allows ready comparison of kinetic data obtained with many different nucleophiles under widely varying reaction conditions, an activity essential to the development of effective decontamination reagents.



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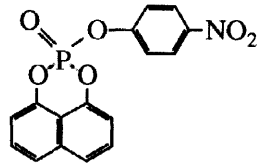

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Our ongoing concern with nerve agent decontamination and phosphotriester hydrolysis,[4,5a] led us to consider the effects of simple structural "mutations" on the reactivity of PNPDPP; for example, "fusion" of the phenyl residues of **1** into a naphthyl moiety, as in *p*-nitrophenyl 1,8-naphthyl phosphate, **2** (PNPNP). Here, we report that PNPNP is 1-2 orders of magnitude more reactive than PNPDPP toward 8 of the nucleophilic systems previously deployed in phosphorolytic reactions. Its enhanced sensitivity toward nucleophilic attack should secure its place as a valuable simulant in phosphorolytic decontamination chemistry.

PNPNP was prepared in 70% yield from 1,8-naphthalene diol[10] by reaction with an equimolar quantity of *p*-nitrophenyl phosphorodichloridate (Aldrich) and excess Et_3N in dry ether. Recrystallization from CH_2Cl_2 afforded **2** as a light yellow solid, mp 108-110 °C, which gave an appropriate NMR spectrum, elemental analysis, and X-ray crystal structure.[11] In order to compare the reactivities of **1** and **2**, phosphorolyses were carried out with a number of aqueous nucleophilic reagents. These included: (1) hydroxide ion in pH 9 buffer; (2) hydroxide ion in micellar cetyltrimethylammonium chloride (CTACl) at pH 8;

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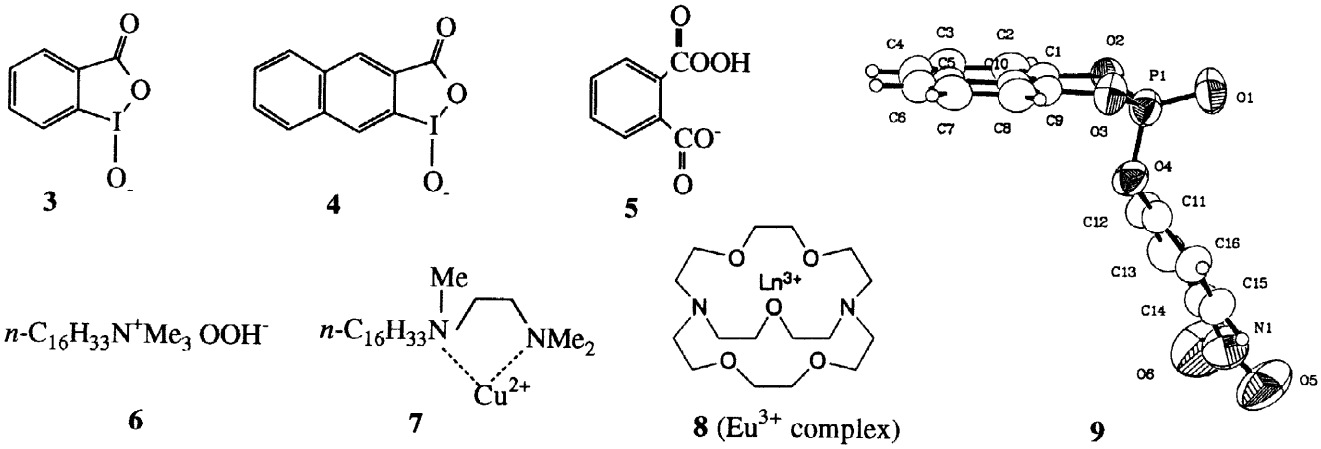

(3) iodosobenzoate (**3**, IBA)[4a,12] in micellar CTACl at pH 8; (4) iodosonaphthoate (**4**, INA)[4a,13] under the same conditions; (5) monoperoxyphthalate (**5**, MPP)[3b] in micellar CTACl at pH 8.5; (6) cetyltrimethylammonium hydroperoxide (**6**, CTAOOH)[3c] in micellar CTACl at pH 8; (7) the Cu^{2+} complex of *N*-hexadecyl-*N*,*N*',*N*'-trimethylethylene diamine (**7**, HTMED),[5a,e] in micellar $CTANO_3$ at pH 8; and (8) the Eu^{3+} (2.2.1) cryptate, **8**, at pH 8.[14] The kinetics of cleavage of **1** and **2** were followed spectrophotometrically, monitoring the appearance of *p*-nitrophenylate ion at 400 nm; rate constants were obtained from computer-generated correlations of log (A_∞-A_t) with time. Reactions were generally followed to >90% completion, and exhibited good first-order kinetics with reproducibilities of better than ±5%. Rate constants appear in Table 1.

The cleavages of PNPNP are uniformly 1-2 orders of magnitude faster than those of PNPDPP, and a normal reactivity/selectivity pattern obtains: kinetic discrimination between **2** and **1** is greatest for the least reactive nucleophiles (OH^-, CTAOOH), and least for the most reactive reagents (INA, IBA, MPP). The latter 3 reagents cleave micellar PNPNP with *exceptionally* large rate constants. Note also that PNPNP is cleaved 80-100 times more rapidly than PNPDPP by the metal-OH reagents, **7** and **8**.

Why are phosphorolyses of PNPNP so rapid? The mechanism of nucleophilic displacement at phosphorus(V) esters is complicated and controversial.[15] The reaction may proceed via a trigonal bipyramidal intermediate (TBP). If the TBP is sufficiently long-lived, substituent pseudorotation may occur. Alternatively, the TBP lifetime may be so short as to render the displacement effectively concerted. In the limit, the TBP

becomes a transition state rather than an intermediate, and the reaction is best described as $S_N2(P)$.[3a,15c,d]

Whether the reactions of PNPNP transit a short-lived TBP intermediate or a TBP $S_N2(P)$ transition state, the X-ray structure (**9**)[16] suggests that PNPNP is ideally suited for nucleophilic displacement. In particular, the 1,8-naphthylenedioxy unit is "tied back," so that, in contrast to PNPDPP with its 2 "floppy" phenoxy groups, nucleophilic access to P should be much less hindered. This may be a principal source of the kinetic advantage enjoyed by PNPNP.

Table 1. Kinetics of the Phosphorolytic Cleavages of PNPNP and PNPDPP

nucleophile	conditions[a]	k_ψ, s^{-1} PNPNP (**2**)	k_ψ, s^{-1} PNPDPP (**1**)	k_2/k_1
OH^-	0.02M Tris, 0.01 M KCl[b]	3.28×10^{-3}	2.91×10^{-5} [c]	113
OH^-	7 mM CTACl, 0.02 M $H_2PO_4^-$, 0.08 M NaCl	5.30×10^{-2}	2.48×10^{-4} [d]	214
IBA (**3**)	as above, 0.1 mM IBA	2.82	0.064[e]	44
INA (**4**)	as above, 0.1 mM INA	4.83	0.26[f]	18.6
MPP (**5**)	as above,[g] 0.3 mM MPP	3.33	0.024[h]	138
CTAOOH (**6**)	0.02 M Tris, [subst.] = 3×10^{-5} M.[i]	0.13	4.27×10^{-4} [j]	304
(Cu^{2+}) (**7**)	0.05 M HEPES, [$CTANO_3$] = 10 mM, [Cu^{2+}] = [HTMED] = 1mM[k]	0.20	2.50×10^{-3} *l*	80
(Eu^{3+}) (**8**)	0.01 M Tris, 0.1 M NaCl, 10% MeCN, [**8**] = 0.8 mM[k]	0.16	1.60×10^{-3} [m]	100

[a]At 25 °C and pH 8.0, unless otherwise noted; [substrate] = 1×10^{-5} M. [b]pH 9.0. [c]Reference 9b. [d]k_ψ(max) at 1mM CTACl. [e]Reference 12, [CTACl] as in *d*. [f]References 4a,13, k_ψ(max) at 0.5 mM CTACl. [g]0.1 M KCl instead of NaCl, [substrate] = 3×10^{-5} M, pH 8.5. [h]Reference 3b, 1mM CTACl, pH 8.5. [i][H_2O_2] = 10 mM, [CTAOH] = 1.5 mM, [CTACl] = 5.5 mM, pH = 8.0. [j]Reference 3c. [k][substrate] = 4×10^{-5} M. *l*Reference 5a. [m]Reference 14.

Nucleophilic attack will convert PNPNP to a TBP in which the nucleophile and the *p*-nitrophenylate leaving group occupy apical positions, while oxygen (O_1) and the naphthalenedioxy group are equatorial, in keeping with TBP substituent rules.[3a,15b] The O_2-P_1-O_3 bond angle, which from the X-ray structure is 105.8° and unstrained[15b] in ground state PNPNP, will expand toward 120°, engendering strain.[17] Relative to acyclic PNPDPP, where such strain is absent, compensation for PNPNP may be found in the absence of non-bonded phenyl/phenyl interactions in the TBP,[18] which should be present for PNPDPP, but not for PNPNP, and thus another likely source of the latter's kinetic advantage.

One could also suggest that the TBP derived from PNPNP would hydrolyze with acceleration, compared to PNPDPP, due to stereoelectronic factors associated with antiperiplanar lone pairs that are "locked" into favorable positions on the oxygen atoms of the naphthalenedioxy moiety.[15c] The magnitude of this stereoelectronic effect, however, remains uncertain[15b,19] and may be quite small.

In conclusion, a simple structural "mutation" of the widely used phosphotriester substrate, PNPDPP, converts it to PNPNP, which is much more reactive toward a variety of standard "decontamination" nucleophiles. The readily prepared PNPNP should find many applications as an exceedingly sensitive substrate for synthetic and mechanistic phosphorolysis studies related to the problems of decontamination.[2]

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References and Notes

(1) Rutgers Undergraduate Research Fellow.

(2) Reviews: (a) Segues, B.; Perez, E., Rico-Lattes, I.; Riviere, M.; Lattes, A. *Bull. Soc. Chim. France* **1996**, *133*, 925. (b) Yang, Y-C. *Chem. Ind. (London)*, 1 May 1995, 334. (c) Yang, Y-C.; Baker, J.A; Ward, J.R *Chem. Rev.* **1992**, *92*, 1729. (d) Pearson, G. *Chem. Brit.* Oct. 1995, 782.

(3) (a) Yang, Y-C.; Berg, F.J.; Szafraniec, L.L.; Beaudry, W.T.; Bunton, C.A.; Kumar, A. *J. Chem. Soc. Perkin Trans. 2* **1997**, 607. (b) Bhattacharya, S.; Snehalatha, K. *J. Org. Chem.* **1997**, *62*, 2198. (c) Toullec, J.; Moukawim, M. *Chem. Commun.* **1996**, 221. (d) Bunton, C.A.; Foroudian, H.J. *Langmuir* **1993**, *9*, 2832. (e) Yang, Y-C.; Szafraniec, L.L.; Beaudry, W.T.; Bunton, C.A. *J. Org. Chem.* **1993**, *58*, 6964.

(4) (a) Moss, R.A.; Kotchevar, A.T.; Park, B.D.; Scrimin, P. *Langmuir* **1996**, *12*, 2200. (b) Moss, R.A.; Bose, S. *Tetrahedron Lett.* **1997**, *38*, 965. (c) Berg, F.J.; Moss, R.A.; Yang, Y-C.; Zhang, H. *Langmuir* **1995**, 11, 411. (d) Moss, R. A.; Bracken, K.; Emge, T.J. *J. Org. Chem.* **1995**, *60*, 7739.

(5) (a) Scrimin, P.; Ghirlanda, G.; Tecilla, P.; Moss, R.A. *Langmuir* **1996**, *12*, 6235. (b) Kimura, E; Hashimoto, H.; Koike, T. *J. Am. Chem. Soc.* **1996**, *118*, 10963. (c) Weijnen, J.G.J.; Engbersen, J.F.J. *Rec. Trav. Chim.* **1993**, *112*, 351. (d) Gellman, S.H.; Petter, R. ; Breslow, R. *J. Am. Chem. Soc.* **1986**, *108*, 2388. (e) Menger, F.M.; Gan, L.H.; Johnson, E.; Durst, H.D. *J. Am. Chem. Soc.* **1987**, *109*, 2800.

(6) Vanhooke, J.L.; Benning, M.W.; Raushel, F.M.; Holden, H.M. *Biochem.* **1996**, *35*, 6020. Benning, M.W.; Kuo, J.M.; Raushel, F.M.; Holden, H.M. *Ibid.* **1994**, *33*, 15001.

(7) Weiner, D.P.; Weimann, T.; Wolfe, M.M.; Wentworth, P., Jr.; Janda, K.D. *J. Am. Chem. Soc.* **1997**, *119*, 4088. Lavey, B.J.; Janda, K.D. *J. Org. Chem.* **1996**, *61*, 7633. Rosenblum, J.S.; Lo, L-C.; Li, T.; Janda, K.D.; Lerner, R.A. *Angew. Chem. Int. Ed. (Engl.)* **1995**, *34*, 2275.

(8) Bunton, C.A.; Robinson, L. *J. Org. Chem.* **1969**, *34*, 773.

(9) See: (a) Fendler, J.H.; Fendler, E.J. *Catalysis in Micellar and Macromolecular Systems;* Academic: New York, 1975, pp. 150-161. (b) Moss, R.A.; Ihara, Y. *J. Org. Chem.* **1983**, *48*, 588.

(10) The diol (mp 138 -140 °C) was obtained by basic cleavage of 1,8-naphthosultone: Erdmann, H. *Ann.* **1888**, *247*, 306.

(11) See below; details of the X-ray structure are available on request.

(12) Moss, R.A.; Alwis, K.W.; Shin, J-S. *J. Am. Chem. Soc.* **1984**, *106*, 2651.

(13) Moss, R.A.; Zhang, H.; Chatterjee, S.; Krogh-Jespersen, K. *Tetrahedron Lett.* **1993**, *34*, 1729.

(14) Oh, S.J.; Kyong, H.S.; Park, J.W. *Chem. Commun.* **1995**, 575.

(15) (a) A brief summary can be found in ref. 3a. (b) Thatcher, G.R.J.; Kluger, R. *Adv. Phys. Org. Chem.* **1989**, *25*, 99. (c) Ba-Saif, S.A.; Waring, M.A.; Williams, A. *J. Am. Chem. Soc.* **1990**, *112*, 8115. (d) Williams, A. *Adv. Phys. Org. Chem.* **1992**, *27*, 1. (e) Gorenstein, D.G.; Chang, A.; Yang, J-C. *Tetrahedron* **1987**, *43*, 469.

(16) The structure of **2** was determined by single crystal X-ray diffraction: space group $P2_1/c$; Mo Kα radiation, $\lambda = 0.71073$ Å; a = 8.795(1) Å, b = 13.024(2) Å, c = 26.279(3)Å, $\beta = 90.97(1)°$, z = 8; the final R(F) for 2486 observations with $I > 2\sigma > (I)$ was 0.038.

(17) Putative pseudorotation (if the TBP is an intermediate) of the naphthalenedioxy unit (from eqeq to apeq) would reduce the O_2-P_1-O_3 angle to 90°, also incurring strain.

(18) *Cf.*, Taylor, S.D.; Kluger, R. *J. Am. Chem. Soc.* **1992**, *114*, 3067.

(19) Wroblewski, A.E.; Verkade, J.G. *J. Am. Chem. Soc.* **1996**, *118*, 10168.