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111. Morio Ikehara, Tohru Ueda, and Kyoichi A. Watanabe : Debenzylation Reaction of Benzylphosphoric Acid Esters.

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The importance of obtaining appropriate phosphorylating agents has been very much stimulated by the recognition of the immense biological significance of compounds containing phosphate group such as nucleotides, phosphatides, sugar phosphates, and other phosphates. The development in the synthetic chemistry of this field in the last decade is remarkable, but the reaction mechanism involving even a single phosphoric ester has been little studied until recently on account of complexity of the problem.

One of the most difficult problems both for organic and physical chemists lies in the fact that ortho- or pyrophosphoric acid has three or four dissociable acid groups, and therefore, when a simple phosphoric ester is to be synthesized without protection of the acid groups, which should not be involved in the reaction course, the product obtained is often a complex mixture and a good yield is little promised.

Phenyl[1,2] and benzyl[3] derivatives are employed by many investigators as the easily accessible and detachable protecting groups. Among them, benzyl group is more convenient in many cases, since it is readily removed by palladium-catalyzed hydrogenation,[3] under the condition no aromatic double bond is affected. Furthermore, in the case of a full ester of phosphoric acid, it also regenerates an acidic group by treatment with amines,[4,5] inorganic salts,[6~9] substances bearing phenolic hydroxyl groups,[10] and by catalytic hydrogenation in the presence of amines.[11]

It is often desirable to remove the protecting groups arbitrarily in the course of chemical syntheses of biologically interesting phosphoric esters. Thus, study on selective debenzylation becomes of importance.

Not only the application to chemical synthesis, but also the interest in physical organic chemistry led to investigation of the mechanism of debenzylation reaction with sodium iodide. In the initial experiments, several tribenzyl phosphates containing dif-

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1) P. Brigl, H. Müller : Chem. Ber., **72**, 2121(1939).
2) J.G. Moffatt, H.G. Khorana : J. Am. Chem. Soc., **79**, 3741(1957); W.R. Chambers, J.G. Moffatt, H.G. Khorana : *Ibid.*, **79**, 3747(1957); A.R. Turner, H.G. Khorana : *Ibid.*, **81**, 4651(1959).
3) F.R. Atherton, T.H. Openshaw, A.R. Todd : J. Chem. Soc., **1945**, 382.
4) V.M. Clark, A.R. Todd : *Ibid.*, **1950**, 2623.
5) J. Baddiley, V.M. Clark, J.J. Michalski, A.R. Todd : *Ibid.*, **1945**, 815.
6) I. Dilaris, L. Zervas : J. Am. Chem. Soc., **77**, 5354(1955).
7) *Idem* : Chem. Ber., **89**, 925(1956).
8) V.M. Clark, A.R. Todd : J. Chem. Soc., **1950**, 2050; S.S.H. Christie, D.T. Elmore, G.W. Kenner, A.R. Todd, F.J. Weymouth : *Ibid.*, **1953**, 2947.
9) R.J.W. Cremlyn, G.W. Kenner, J. Mather, A.R. Todd : *Ibid.*, **1958**, 528.
10) G.W. Kenner, J. Mather : *Ibid.*, **1956**, 3524.
11) V.M. Clark, G.W. Kirby, A.R. Todd : *Ibid.*, **1958**, 3039.

ferent *para*-substituents were prepared and the effect of their substituent on the reaction with sodium iodide in boiling acetone was examined through elementary analyses and yield of the reaction products obtained.

As will be discussed later, since the evidence was quite inconsistent with the facts which had been reported already by other workers,[9] further study was made to clarify this disagreement. The investigation was done kinetically on the alcoholic moiety on the one hand, and on the acid moiety on the other hand. A satisfactory conclusion was obtained to illustrate the divergency.

Experimental

I. Large-scale Experiments: Syntheses of Tribenzyl Phosphates bearing Two Different *para*-Substituents—A mixture of *para*-substituted benzyl halide (0.025 mole) and silver bis(*para*-substituted benzyl) phosphate (0.025 mole) in dry $CHCl_3$ (50 cc.) was heated under reflux for 6 or 8 hr., light being excluded. The solution was filtered from silver halide and further quantities of the product were extracted with hot $CHCl_3$ and Me_2CO (20 cc. each). The combined filtrate and extracts was washed with dil. Na_2CO_3 solution (60 cc.) and water (2×60 cc.), dried over anhyd. Na_2SO_4, and evaporated to dryness under reduced pressure. The residue thus obtained was recrystallized.

Benzyl bis(*p*-nitrobenzyl)phosphate (I) separated from EtOH as pale yellow leaflets, m.p. 66~67.5°; yield, 38%. *Anal.* Calcd. for $C_{21}H_{19}O_8N_2P$: C, 55.1; H, 4.2; N, 6.1. Found: C, 55.6; H, 4.2; N, 5.9.

Benzyl bis(*p*-bromobenzyl)phosphate (II) crystallized from $CHCl_3$-light petroleum (b.p. 80~100°) as white needles, m.p. 76~77.5°; yield, 48~52%. *Anal.* Calcd. for $C_{21}H_{19}O_4Br_2P$: C, 48.0; H, 3.6. Found: C, 47.8; H, 3.8.

p-Bromobenzyl bis(*p*-nitrobenzyl)phosphate (III) separated from EtOH as slightly greenish yellow needles, m.p. 92°; yield, 65%. *Anal.* Calcd. for $C_{21}H_{18}O_8N_2BrP$: C, 47.0; H, 3.3; N, 5.2. Found: C, 47.1; H, 3.5, N, 4.9.

p-Bromobenzyl dibenzylphosphate (IV) recrystallized from $CHCl_3$-petr. ether as white needles, m.p. 46°; yield, 41%. *Anal.* Calcd. for $C_{21}H_{20}O_4BrP$: C, 56.5; H, 4.5. Found: C, 56.4; H, 4.6.

p-Nitrobenzyl bis(*p*-bromobenzyl)phosphate (V) separated from EtOH as white needles, m.p. 92~93°; yield, 57%. *Anal.* Calcd. for $C_{21}H_{18}O_6NBrP$: C, 44.1; H, 3.2; N, 2.5. Found: C, 44.4; H, 3.5; N, 2.6.

Debenzylation of the Triesters—A solution of tribenzyl phosphate (0.01 mole) and NaI (0.011 mole) in Me_2CO (20 cc.) was boiled under reflux on a water bath for 30 min. Precipitation of the anhyd. sodium salt of dibenzyl phosphate began within the first few min. After the mixture was kept standing for several hr. in an ice-box, the salt was collected and washed with Me_2CO. Yield, 87~93%.

Sodium salt was dissolved in a minimum amount of water and acidified with conc. HCl. The results of elementary analyses of the products are given in Table I.

TABLE I.

Material	Analyses (%) of debenzylated phosphates			Ratio of products			
				Yield (%)		Molar ratio	
	C	H	N				
(I)	46.03	3.50	7.11	(VI) 93±10 84±16	(VII) 7±10 16±16$^{b)}$	(VI) 92±11	(VII) 8±11$^{a)}$
(II)	39.32	3.01		(VIII) 76±14	(IX) 24±14	(VIII) 72±14	(IX) 28±14
(III)	44.07	3.60	5.13	(VI) 64±13 53±2	(X) 36±13 47±2$^{b)}$	(VI) 66±13	(X) 34±13$^{a)}$
(IV)	49.00	4.49		(IX) 85±3	(XI) 15±3	(IX) 82±3	(XI) 18±3
(V)	40.24	3.15	1.91	(X) 55±6 57±7	(VIII) 45±6 43±7$^{b)}$	(X) 54±15	(VIII) 46±15$^{a)}$

a) based on C *b*) based on N

The crude acid which separated was subjected to purification by dissolving it again in a minimum amount of dil. Na_2CO_3 solution, boiled with charcoal, filtered, and precipitated by acidification. The phosphoric acid obtained was recrystallized repeatedly from EtOH.

The acid from benzyl bis(*p*-bromobenzyl)phosphate (II), after five recrystallizations from EtOH, formed white needles, m.p. 156°, and showed no depression in m.p. on admixture with the authentic sample of bis(*p*-bromobenzyl)hydrogenphosphate. Yield, 47%, on the basis of the sodium salt.

The acid from *p*-bromobenzyl dibenzylphosphate (IV) gave white needles after repeated recrystallization, m.p. 91°. *Anal.* Calcd. for $C_{14}H_{14}O_4BrP$ (Benzyl *p*-bromobenzylhydrogenphosphate) : C, 47.2; H, 3.9. Found : C, 47.4; H, 4.1.

Attempts to purify other acids by further recrystallization were unsuccessful.

II. Kinetic Studies : Materials—MeCOEt and $CHCl_3$ were purified by the method of Bramly[12] and Budde,[12] respectively. NaI was commercially available reagent grade and used without further purification. Phosphoric esters used were prepared and purified as follows (Table II) :

para-Substituted Benzyl Diphenylphosphate—A mixture of *para*-substituted benzyl halide (1 mole), silver diphenylphosphate (1 mole), and dry $CHCl_3$ was heated under reflux with vigorous stirring during 12 hr., in the dark. The solution was filtered from silver halide and the filtrate was washed with dil. Na_2CO_3 solution and water, dried over anhyd. Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was recrystallized. Further quantity of the same compounds was obtained by extraction of the crude silver halide with hot $CHCl_3$.

Benzyl diphenylphosphate (XII) separated from hexane as white needles, m.p. 48° (Kenner and Mather prepared it by the reaction of diphenyl phosphorochloridate and benzyl alcohol in pyridine and reported m.p. 48°). Yield, 85%. *Anal.* Calcd. for $C_{19}H_{17}O_4P$: C, 67.2; H, 5.0. Found : C, 67.5; H, 5.0.

p-Nitrobenzyl diphenylphosphate (XIII) recrystallized from EtOH-hexane as pale yellowish green leaflets, m.p. 55°; yield, 92%. *Anal.* Calcd. for $C_{19}H_{16}O_6NP$: C, 59.4; H, 4.2; N, 3.8. Found : C, 59.2; H, 4.2; N, 3.8.

p-Bromobenzyl diphenylphosphate (XIV) separated from EtOH-hexane as white needles, m.p. 62°; yield, 89%. *Anal.* Calcd. for $C_{19}H_{16}O_4BrP$: C, 54.6; H, 3.8. Found : C, 54.5; H, 3.8.

p-Methylbenzyl diphenylphosphate (XV) i) A mixture of *p*-methylbenzyl chloride (prepared by reaction between *p*-methylbenzyl alcohol and $SOCl_2$) (5.8 g., 1 mole), silver diphenylphosphate (16.0 g., 1 mole), and $CHCl_3$ (75 cc.) was heated under reflux with mechanical stirring for 12 hr., and treated as usual. $CHCl_3$ was removed, and the resulting oil was distilled in high vacuum (0.01 mm., 120°). The residue was purified by dissolving it in benzene and passing over an alumina column. The first eluted fraction was evaporated to dryness. The residue melted at 60~61°, depressed on admixture with *p*-methylbenzyl alcohol, and contained no phosphorus. This was recrystallized from hexane to white plates, m.p. 62~62.5° (Zeltner and Tarassow[13] reported m.p. 61.5~62.5°). *Anal.* Calcd. for $C_{16}H_{18}O$ (Bis-*p*-methylbenzyl) : C, 85.0; H, 8.0. Found : C, 84.6; H, 8.0. Yield, 500 mg.

From the slowly eluted fraction, an oil was obtained which crystallized from $CHCl_3$-hexane to white needles containing phosphorus, m.p. 51°; yield, 500 mg., 3.5%. *Anal.* Calcd. for $C_{20}H_{19}O_4P$: C, 67.8; H, 5.4. Found : C, 66.5; H, 4.9.

ii) A mixture of *p*-methylbenzyl alcohol (5.9 g., 0.05 mole), metallic Na (1.2 g., 0.05 mole), and Et_2O (50 cc.) was heated under reflux with vigorous stirring during 8 hr. and cooled to −10°. To the cold suspension of sodium *p*-methylbenzyloxide diphenyl phosphorochloridate (13.5 g., 0.05 mole) was added dropwise with mechanical stirring. NaCl formed was removed by centrifugation. Et_2O layer was treated as usual and the product obtained was chromatographed as in (i). Firsts ubstance obtained had no phosphorus, and separated from hexane as white needles, m.p. 79°; yield, 20 mg. (Moritz and Wolffenstein[14] recorded m.p. 82°). *Anal.* Calcd. for $C_{16}H_{18}$ (bis-*p*-methylbenzyl) : C, 91.6; H, 8.4. Found : C, 91.0; H, 8.1.

Then an oil that eluted was crystallized from $CHCl_3$-hexane to white needles, m.p. and mixed m.p. 51°; yield, 350 mg.

Attempts to purify by further recrystallization led to decomposition of the material, and diphenyl hydrogenphosphate was recovered.

Kinetics of Phosphates—Runs were followed colorimetrically with a Shimadzu spectrophotometer. Good second-order rate coefficients were obtained in each case, and observed and calculated infinity values agreed closely with each other.

The following details are typical of experiments in which the rate of production of sodium diphenylphosphate was determined. To each of the aliquot (2.5 cc.) of MeCOEt solution of phosphoric triesters ($0.04M$) in stoppered glass tubes placed in a thermostat an aliquot of NaI in MeCOEt (2.5 cc., $0.04M$) was added. At appropriate times, an aliquot was taken out, added to distilled water (100 cc.) to stop the reaction, and the resulting benzyl iodides and unchanged triesters were extracted twice with $CHCl_3$ (50 cc. each, shaken for 30 sec., and aqueous layer separated by centrifugation at 2000

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12) J. A. Riddick, E. E. Toops, Jr. : "Technique of Organic Chemistry," Vol. VII, 381 and 411(1955). Interscience Publishers Inc., New York.

13) J. Zeltner, B. Tarassow : Ber., **43**, 941(1910).

14) C. Moritz, R. Wolffenstein : *Ibid.*, **32**, 2531(1899).

r.p.m., for 2 min.). The aqueous layer was kept at 20° for 3 hr. and its optical density was measured in the usual way. Since all the reactions were of second order and the intensity of ultraviolet absorption in the phosphate estimation was found to obey the Beer's law, second-order rate coefficients were calculated from the formula $k=D_t/D_\infty(D_\infty-D_t)t$, where D_t and D_∞ are the optical densities of the solutions, taken at time t and complete reaction, respectively. An aliquot taken at zero time was used as the reference. The results are given in Tables II and III.

Table II. Rate Coefficient

No.	Time (sec.)	(XII)		(XIII)		(XIV)		(XV)	
		k_1	k_2	k_1	k_2	k_1	k_2	k_1	k_2
1	300	3.25×10^{-6}	5.36×10^{-4}	1.12×10^{-4}	1.06×10^{-3}	10.09×10^{-5}	8.20×10^{-4}		
2	600	7.63×10^{-5}	3.29×10^{-4}	1.07×10^{-4}	1.01×10^{-3}	8.27×10^{-5}	8.44×10^{-4}		
3	1200	7.16×10^{-5}	3.17×10^{-4}	0.97×10^{-4}	1.02×10^{-8}	5.36×10^{-5}	8.10×10^{-4}		2.95×10^{-5}
4	2400	5.03×10^{-5}	3.09×10^{-4}	1.01×10^{-4}	0.92×10^{-3}	8.23×10^{-5}	8.10×10^{-4}	6.27×10^{-6}	3.02×10^{-5}
5	4800		3.39×10^{-4}	1.07×10^{-4}	0.90×10^{-3}	9.85×10^{-5}	7.97×10^{-4}	6.30×10^{-6}	3.04×10^{-5}
6	7200	5.98×10^{-5}	3.83×10^{-4}	1.02×10^{-4}	1.03×10^{-8}	9.51×10^{-5}	8.42×10^{-4}	6.25×10^{-6}	2.96×10^{-5}
7	10800	5.94×10^{-5}	3.13×10^{-4}	1.15×10^{-4}	1.19×10^{-3}	9.61×10^{-5}	11.2×10^{-4}	6.24×10^{-6}	3.04×10^{-5}
8	14400	6.16×10^{-5}	3.01×10^{-4}			8.87×10^{-5}	9.35×10^{-4}	6.27×10^{-6}	3.11×10^{-5}
9	18000	6.16×10^{-5}		1.27×10^{-4}		10.2×10^{-5}			
10	27000	5.97×10^{-5}		1.58×10^{-4}		9.89×10^{-5}			

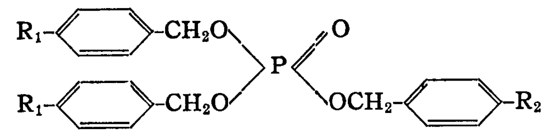
k_1 at 20°, k_2 at 35°

Table III. Rate Coefficient

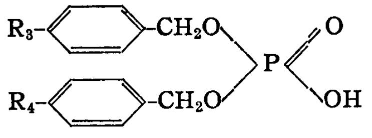
Phosphate	k_1	k_2	Phosphate	k_1	k_2
(XII)	6.15×10^{-5}	3.05×10^{-4}	(XIV)	9.50×10^{-5}	8.42×10^{-4}
(XIII)	1.00×10^{-4}	1.00×10^{-3}	(XV)	6.27×10^{-6}	3.13×10^{-5}

Results and Discussion

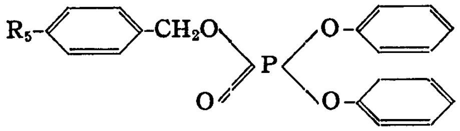
Considering the results of initial experiments (Table I), the activation of methylene group of benzyl moiety does not depend on the electron-attracting tendency of *para*-substituent groups, but it is mainly affected by the ease with which quinoid-type intermediates are formed[15] (Chart 2). Namely, S_N1 type reaction seemed to proceed against the expectations. Todd *et al.*[9] reported that iodide reacted faster than thiocyanate and that



(I) $R_1=NO_2$, $R_2=H$ (IV) $R_1=H$, $R_2=Br$
(II) $R_1=Br$, $R_2=H$ (V) $R_1=Br$, $R_2=NO_2$
(III) $R_1=NO_2$, $R_2=Br$



(VI) $R_3=R_4=NO_2$ (IX) $R_3=H$, $R_4=Br$
(VII) $R_3=H$, $R_4=NO_2$ (X) $R_3=NO_2$, $R_4=Br$
(VIII) $R_3=R_4=Br$ (XI) $R_3=R_4=H$



(XII) $R_5=H$ (XIV) $R_5=Br$
(XIII) $R_5=NO_2$ (XV) $R_5=CH_3$

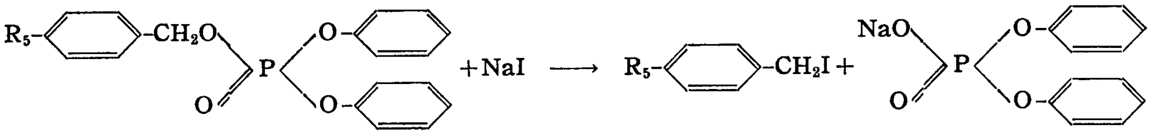


Chart 1.

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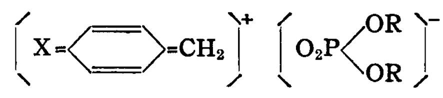
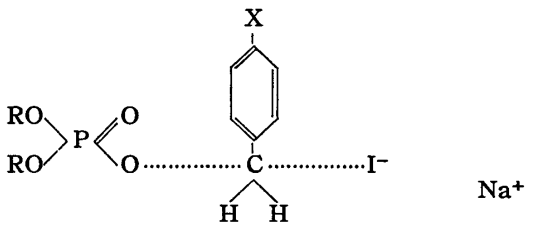
15) J. K. Kochi, G. S. Hammond : J. Am. Chem. Soc., 75, 3445(1953).



Quinoid-type intermediate



Transition state of S_N2 type reaction

Chart 2.

the reaction was favored by lowering the dielectric constant of the medium. Therefore, S_N2 reaction must be more reasonable.

Along this line, a more precise examination was made on the true activation caused by several kinds of *para*-substituent in benzyl groups. For this purpose, mono(*p*-substituted benzyl)diphenylphosphates were prepared by an improved method. Reaction of benzyl halide and silver diphenylphosphate in chloroform yielded a purer material and the yield was well reproducible except for *p*-methylbenzyl diphenylphosphate, because the reaction of silver diphenylphosphate and *p*-methylbenzyl bromide afforded bis-*p*-methylbenzyl in a good yield, irrespective of variation in reaction conditions and a trace of the material was obtained by using *p*-methylbenzyl chloride instead of bromide.

All the triesters liberate only the benzyl group by the attack of nucleophilic reagents. Sodium diphenylphosphate, which is expected as the product in kinetic run, obeyed the Beer's law strictly as shown in Fig. 5 at λ_{max} 261 mμ. Typical second-order plots of kt vs. time is given in Fig. 1, calculated by an equation mentioned in the Ex-

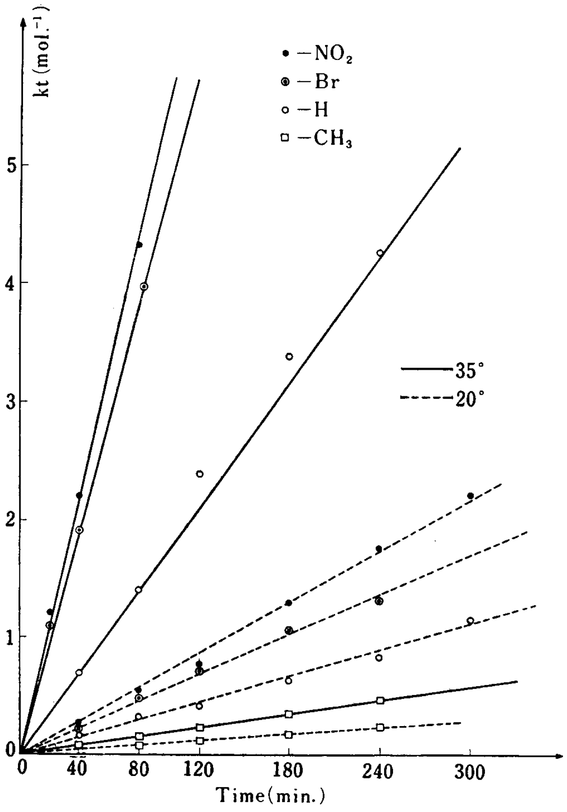
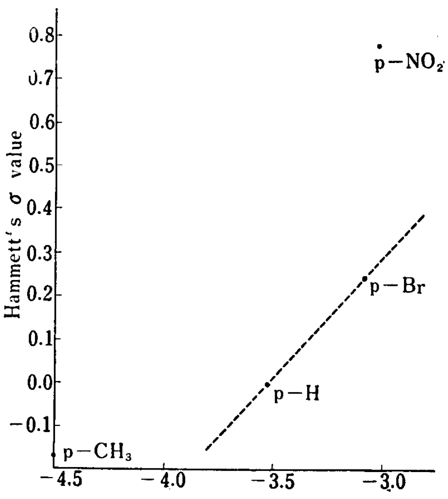
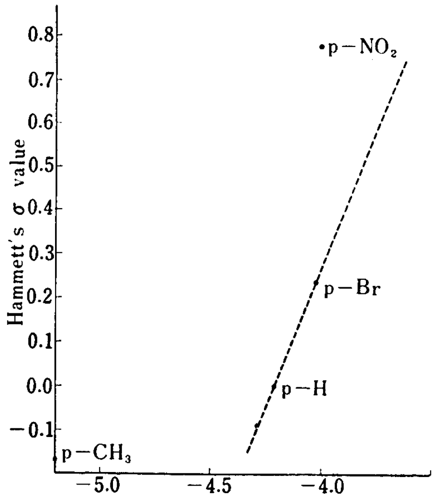


Fig. 1. Rate of Debenzylation



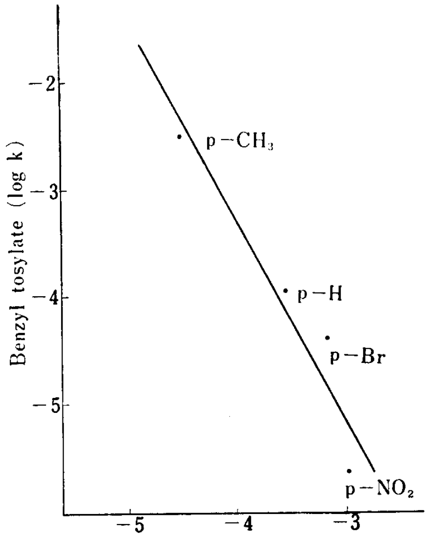
Benzyl Phosphate (log k_2)

Fig. 2.



Benzyl Phosphate (log k_1)

Fig. 3.



Benzyl Phosphate (log k)

Fig. 4.

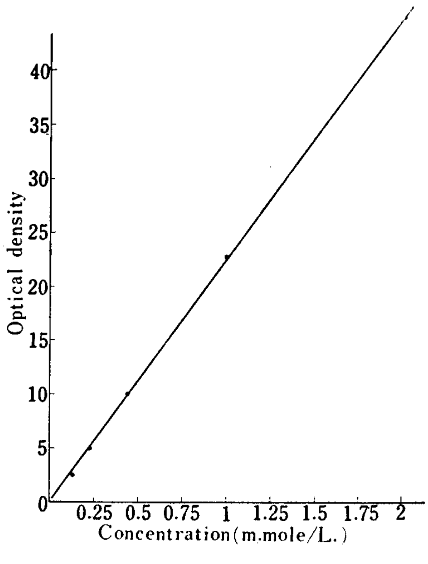


Fig. 5.

perimental part. Rate constants of four benzyl diphenylphosphates at 20° and 35° are summarized in Table III. The rate of the reaction increases in the order of *p*-methyl-, unsubstituted, *p*-bromo-, and *p*-nitro-benzyl derivatives. This result is explained by the tendency of electron attraction of *para*-substituents, which caused significant decrease in electron density of methylene carbon atom (Chart 2). Linear free energy relationship with Kochi's various *para*-substituted benzyl tosylates is shown in Fig. 4. Logarithms of rate constant vs. Hammett's σ value are arranged in the same direction, but not in a straight line (Figs. 2 and 3). This may indicate that the type of activation on methylene carbon atom should not be affected only by the polar effect of the *para*-substituents, but also by the resonance effect. In the case of *p*-methylbenzyl derivative, hyperconjugation effect must be quite important and this may cause deviation from the line through the points corresponding to unsubstituted and *p*-bromobenzyl derivatives (dotted lines). This may also explain the deviation of *p*-nitrobenzyl derivative. In this case the inclination to take a quinoid form is much easier and this makes the rate smaller as is seen in the case of the hyperconjugation of *p*-methylbenzyl derivative. Attempts have been made to separate the polar, steric, and resonance effects in reactivity.[16] Moreover, the effect of solvents and interaction between the reactants, especially sodium iodide and the *para*-substituent may not be negligible. Therefore, there are still unsolved problems to be studied in order to clarify the reaction mechanism, but as a whole, from the above evidences together with other facts, S_N2 mechanism for debenzylation of benzyl diphenylphosphates in methyl ethyl ketone in the presence of sodium iodide seems reasonable. Quite recently, Streitweiser and Wolfe[17] reported complete inversion of benzyl-*α-d* *p*-toluenesulfonate in solvolysis, which is well in accord with the above conclusion. Reaction of benzyl bis(*para*-substituted phenyl)phosphates in similar reaction will be reported later.

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Summary

Various *para*-substituted benzyl phosphates were subjected to debenzylation reaction with sodium iodide in acetone or methyl ethyl ketone. Reaction of *para*-substituted benzyl diphenylphosphates was investigated kinetically and relative easiness of debenzylation was found to be in the decreasing order of *p*-nitro-, *p*-bromo-, unsubstituted, and *p*-methyl-benzyl groups. Evidences for S_N2 mechanism are described.

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[16] R. W. Taft, Jr. : "Steric Effects in Organic Chemistry," 556(1956). Ed. by M. S. Newman, John Wiley & Sons, Inc., New York.

[17] A. Streitweiser, J. R. Wolfe : J. Am. Chem. Soc., **81**, 4912(1959).