Abnormal Behavior in the Reaction of Trialkyl Phosphite Esters with *N*-Haloimides

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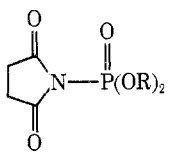
Characteristic of *N*-haloimides is the electropositive nature of halogen (X) induced by the strong electron-withdrawing polarization of the N-X bonds. Prior investigators have reported that phosphite esters react with *N*-haloimides *via* nucleophilic attack at halogen (X = Cl, Br), followed by collapse of the resultant phosphonium ion intermediate to normal Michaelis–Arbusov product, which bears an *N*-dialkylphosphonyl radical. For those esters, $P(OR)_3$, where R = *n*-alkyl but larger than methyl, the observation of normal Arbusov product produced in near-quantitative yield has been confirmed. However, when R = methyl or alkyl branched at the α carbon, the Arbusov product is observed as a minor component. N-Methylation and β elimination, respectively, are observed as the major processes. Further, minor deoxygenation by the branched alkyl systems and enhanced alkylation where R = CH_3 are processes influenced by the reaction's mode of addition. Extended mechanistic interpretations to rationalize these results are presented in terms of internal rotations within the initially formed intermediate followed by ancillary processes.

As part of a project to assess flame-retardant ability of a wide variety of phosphorus-containing compounds, syntheses of several *N*-(dialkylphosphonyl)succinimides (**1**) were attempted. In accordance with existent procedures,[1-3] whereby a trialkyl phosphite ester reacts with an *N*-haloimide, the desired compounds were obtained in good to excellent yields where R is *n*-alkyl (*e.g.*, C_2H_5, *n*-C_4H_9) or alkyl branched beyond the α carbon (*i*-C_4H_9). However, when R is methyl (CH_3) or alkyl branched at the α carbon (*i.e.*, oxygen-bearing carbon in phosphite ester, *e.g.*, *i*-C_3H_7, *sec*-C_4H_9, *t*-C_4H_9), Arbusov product (**1**)[4,5] is produced in low yield. The major products consist



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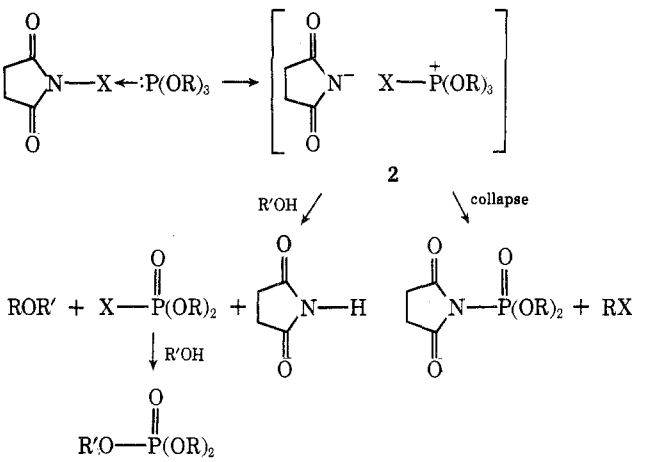
of *N*-methylsuccinimide and dimethyl phosphorohalidate, and succinimide and dialkyl phosphorohalidate for R = CH_3 and R = α-branched alkyl, respectively. Results are summarized in Table I.

By virtue of the polarizability of the N-X bond (Scheme I) nucleophilic attack on *N*-halosuccinimide by a phosphite ester has been proposed to occur at halogen in lieu of nitrogen.[1,6,7]

Characterization of the product mix from conducting the reaction in the presence of a proton source (ROH) offers convincing support for the intermediacy of the ion pair **2**.[1] In view of this mechanism, a consideration of the data in Table I notes definitive 1:1 ratios existing for Arbusov product and alkyl halide and for succinimide (*N*-methyl for R = CH_3) and dialkyl phosphorohalidate, $(RO)_2P(=O)X$. The former product ratio is expected on the basis of the established mechanism for the Arbusov reaction, but the latter correlation can be drawn only if an additional R group can be accounted for in those cases where R $\neq$ CH_3. More careful investigation employing low-temperature trapping and an additional phosphite ester bearing an alkyl radical of lower volatility revealed the complemental component existing as an olefin. Relative ratios of pertinent products to the correlation being discussed are listed in Table II. Mechanistically, the following extension (Scheme II) to the original scheme proposed by McEwen, *et al.*, is consistent with the observed results.

Scheme I



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Scheme II

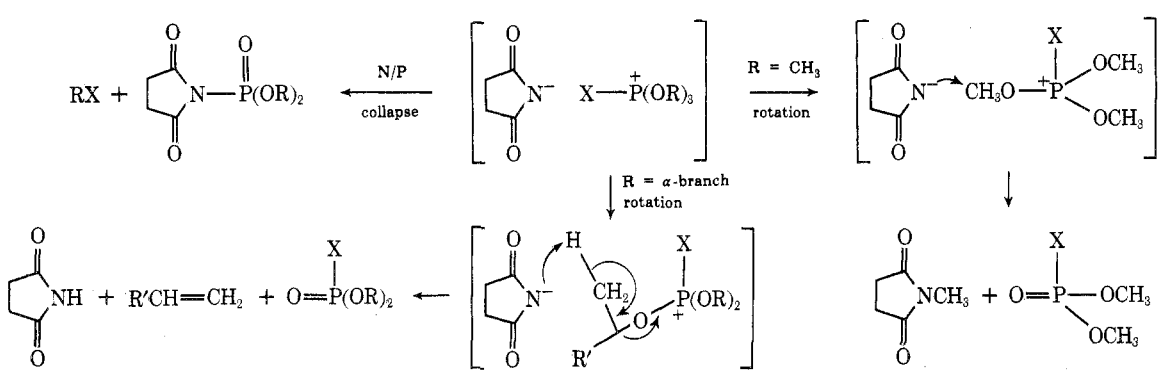
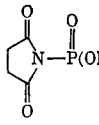
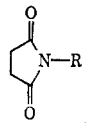
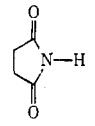
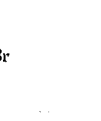


Table I
Product Distribution from the Reaction of Trialkyl Phosphites [$P(OR)_3$] with *N*-Bromosuccinimide (NBS)[a]

R	Reactants, mol[b]		Products, mol				
	NBS[c]	$P(OR)_3$				RBr	
CH_3	0.10	0.10	0.044	0.046		>0.04	0.049
	(0.10)	(0.20)[d]	(0.027)	(0.065)		(>0.02)	(0.061)
	0.10	0.20	0.043	0.053		>0.04	0.045
C_2H_5	0.10	0.10	0.092		<0.01	0.093	<0.01
	(0.10)	(0.10)	(0.081)		(0.01)	(0.075)	(0.01)
n-C_4H_9	0.10	0.10	0.095		0.00	0.089	0.00
	(0.10)	(0.10)	(0.083)		(0.015)	(0.080)	(0.012)
i-C_4H_9	0.10	0.10	0.091		0.00	0.086	0.00
	(0.10)	(0.10)	(0.078)		(0.018)	(>0.07)	(0.015)
sec-C_4H_9	0.10	0.10	0.033		0.064	0.029	0.066
	(0.10)	(0.10)	(0.022)		(0.060)	(0.020)	(0.063)
t-C_4H_9	0.10	0.10			0.096		0.091
i-C_3H_7	0.10	0.10	0.056		0.041	0.050	0.040
	(0.10)	(0.10)	(0.037)		(0.048)	(>0.03)	(0.045)

[a] All runs were conducted in CS_2 at 1 *M* concentrations under nitrogen at 0–5°. [b] Numbers in parentheses refer to inverse addition, *i.e.*, addition of *N*-haloimide to phosphite ester. [c] The reaction with *N*-chlorosuccinimide gave close to identical results. [d] Excess required to effect total conversion.

For the system where R is simple alkyl but not methyl, ion-pair collapse is the favored process due to facile attack of nitrogen on phosphorus. Where R is methyl, sterically unencumbered attack on methyl by the nucleophilic succinimidyl anion apparently competes favorably with ion-pair collapse. Note is made further that formation of a stable pentavalent phosphorus component provides driving force for this process. In the case where R is α-branched alkyl, the succinimidyl anion performs primarily as a proton-abstracting base. Here again, driving force is provided by the formation of a phosphorus double bond oxygen producing stable pentacovalent phosphorous. This latter ability is clearly dependent on the degree of steric inhibition to attack on phosphorus. An examination of Dreiding models for the system where R = cyclohexyl demonstrates decided secondary interactions of the approaching succinimidyl moiety with ring protons that are not present in the acyclic radicals. These added steric requirements apparently contribute appreciably to almost exclusive olefin formation in this system.[8] Similar mechanistic rationale has been proposed by Harpp and Orwig for the desulfurization–alkylation reaction of sulfenimides with tris(dimethylamino)phosphine.[9]

Alternative to the E2-elimination process is the possibility of initial dissociation *via* an E1 mechanism, followed by loss of a proton to succinimidyl anion. Precedent for this pathway is found in the Arbusov reactions of certain phosphite esters with alkyl halides where halide attack on the intermediate phosphonium ion (3) alkoxy group is hindered.[10,11] No facility for dissociative behavior exists for primary alkyl groups such that the S_N2 mechanism depicted for R = CH_3 seems likely.

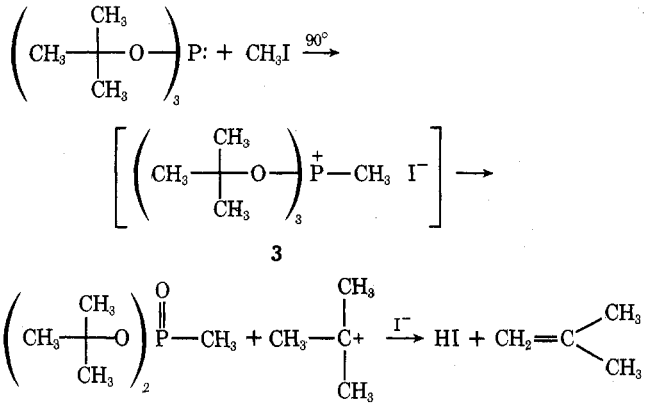


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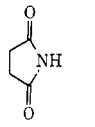
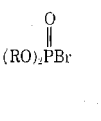
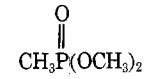
Table II
Ratio of Non-Arbusov Products

R			Olefin
sec-C_4H_9	1.0	1.0	Butenes[a] 0.9
t-C_4H_9	1.0	1.0	Isobutene[a] 1.0
	1.0	1.0	Cyclohexene 1.0

[a] Isolated and characterized as dibromides from bubbling into Br_2–CCl_4. [b] This distribution comprised *ca.* 85–90% of the product mix. A small (5–8%) quantity of Arbusov product was observed.

As indicated in Table I, experiments conducted wherein inverse addition of *N*-haloimide to the phosphite ester was made gave somewhat higher yields of products from competing processes at the expense of Arbusov product. An influential effect by phosphite ester in excess is apparent. This is borne out most dramatically for R = CH_3. When trimethyl phosphite (TMP) was employed as solvent (50-fold excess), minimal Arbusov product was produced, an 80% yield of *N*-methylsuccinimide was isolated, and copious dimethyl methylphosphonate (4) was observed. When conditions of high dilution (0.1 *M*) in an inert solvent ($CHCl_3$) were employed where 1 equiv of TMP was added to *N*-bromosuccinimide, the Arbusov product has been observed in as high as 70% yield. The following mechanistic refinement (Scheme III) is consistent with these observations.



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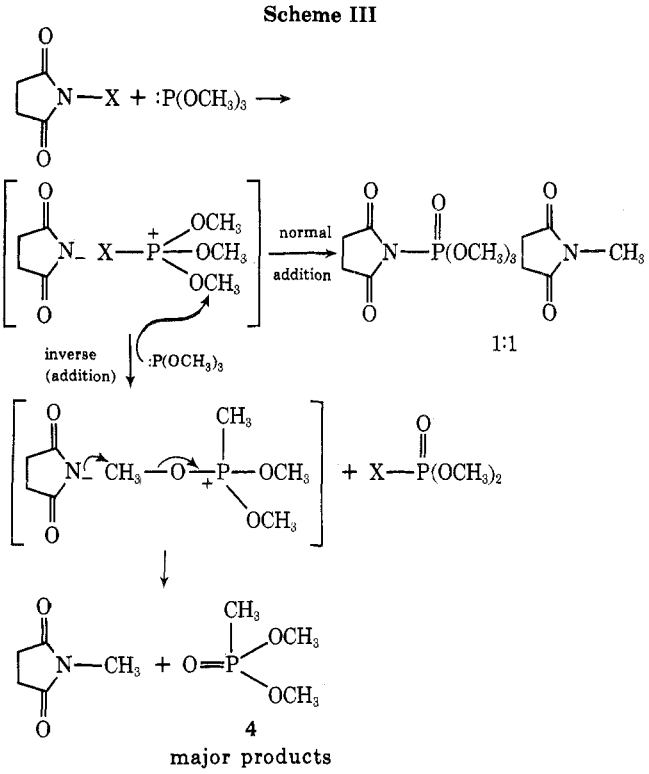
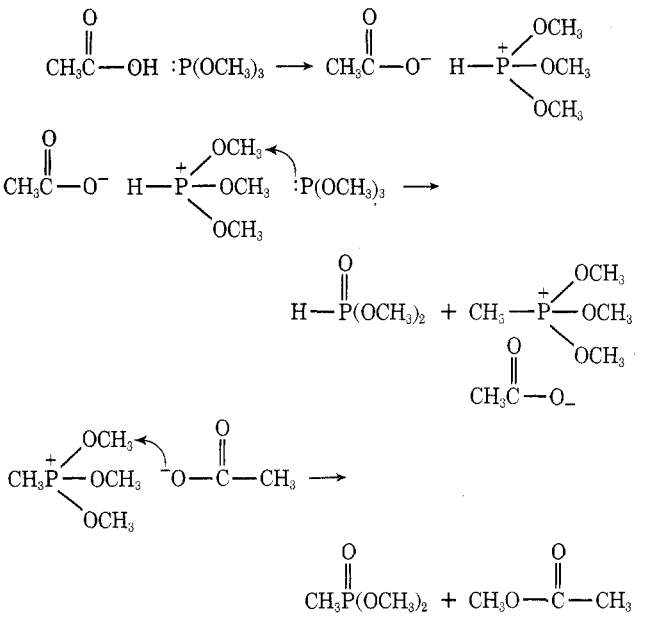
The depicted dealkylation–alkylation sequence has support from an independent study wherein alkyl dialkyl phosphonate ester is observed as a side product in deoxy-

Scheme III



genation reactions by phosphite esters.[12] Further, a similar mechanism has been proposed for the rearrangement of TMP to dimethyl methylphosphonate (4) when reaction is carried out with acetic acid.[13] Little, if any, alkylation–dealkylation behavior is thought to be operative for the higher alkyl phosphites owing to steric considerations and the failure to detect the respective dialkyl alkylphosphonate esters.



Small quantities of trialkyl phosphate (5–10%) were isolated from all experiments in which the inverse mode of addition was utilized. This component is attributed to minor deoxygenation of the succinimidyl moiety. Note is made that this process is dominant for cyclic anhydrides.[12]

Further investigation of this reaction in this laboratory will proceed in the direction of isolating and further characterizing a stable intermediate (1). Reactivity with alkylating and acylating agents and other chemistry will be explored.

Experimental Section

Materials. *N*-Bromosuccinimide (mp 181–183°) and *N*-chlorosuccinimide (mp 147–149°) were purchased from Matheson Coleman and Bell. Methyl, ethyl, and isopropyl trialkyl phosphite esters were purchased from Aldrich Chemical Co., Inc., and were fractionally distilled through a 12-in. glass helices column several times before use. The preparation of *tert*-butyl,[11] *n*-butyl, isobutyl, *sec*-butyl, and cyclohexyl[14] trialkyl phosphites was according to known procedures. All reaction solvents were dried over sodium and distilled directly into the reaction flask.

Instruments. All nmr spectra were recorded on Varian Models T-60 and HA-100 MHz spectrometers. Ir spectra were obtained on a Perkin-Elmer Model 337 spectrophotometer. All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. For quantification of product distributions, gas–liquid chromatography on a Hewlett-Packard 402 high efficiency gas chromatograph employing 4 ft × 6 mm o.d. × 3 mm i.d. columns was used. Two column systems of 20% SE-30/80–100 mesh Chromosorb W and Carbowax 20M were used for the determination. (See Analyses section.)

General Procedure. All reactions were carried out in a 250-ml three-neck flask, equipped with a stirring bar/Mag-Mix stirrer, gas inlet tube, addition funnel, and gas evolution tube connected to a trap immersed in Dry Ice–acetone. Carbon disulfide (100 ml) was distilled from sodium into the preflamed reaction flask. *N*-Bromosuccinimide (0.1 mol) was suspended in the CS_2, the flask was immersed in an ice–water bath,[15] and agitiation was begun. After temperature equilibration (5–10 min) a slow stream of nitrogen was passed through the CS_2 suspension and the trialkyl phosphite (0.1 mol) was added neat over 10–15 min. When addition was complete, the system was allowed to warm to room temperature and stir for an additional 1 hr. During this period, Arbusov product and/or succinimide separated from the reaction medium. The flask contents were allowed to stand, the clear CS_2 solution was decanted, and the oily to solid residue was extracted with several portions of CS_2. The combined CS_2 solutions, trap contents, and CS_2-insoluble residue were analyzed according to the method under Analyses. *Note:* The inverse addition reactions were identical in every respect except that *N*-halosuccinimide was added as a solid to phosphite ester in CS_2 solution.

Analyses. Except for methyl bromide (bp 3.5°) which was isolated and determined from the tared Dry Ice–acetone trap, ethyl chloride and bromide, and isopropyl chloride, determined exclusively by nmr of CS_2 reaction medium, all alkyl halide yields were estimated by vpc comparison against benzene as an internal standard (column temperature 90°) coupled with ^1H nmr comparison of halide *vs.* remaining components. The dialkyl phosphorobromidates and -chloridates were quantified by vpc against naphthalene as an internal standard (column temperature 150–190°); identification of these last components was made on the basis of peak enhancement (vpc) with authentic materials prepared according to known methods.[16,17] Further identification was made by conversion of the halo phosphates to the respective dialkyl methyl phosphates. These latter materials were produced by treating the product mix from the CS_2 fraction with methanol. Nmr ($POCH_3$ doublet, 3.75 ppm, J = 12 Hz) and the vpc peak enhancement technique with authentic materials was definitive for these components.

All Michaelis–Arbusov products, *N*-(dialkylphosphonyl)succinimide, as well as succinimide, were isolated by exhaustive stripping of the reaction mix followed by column chromatography on silica gel; benzene–$CHCl_3$ was used as elution solvent. Identification was made on the basis of ^1H nmr and combustion analyses. Quantification was based on a proton nmr determination of the crude product, since some deterioration on the column was noted. Data pertinent to these latter materials are given below for each system.

***N*-(Dimethylphosphonyl)succinimide** was isolated from silica gel chromatography (44% N.A., 27% I.A.)[18] as a light yellow to amber viscous oil unstable to distillation: ir ν_{max} (film) 1750 (C=O), 1290, 1180, 1125, 1045, 850, 820, 780, 660, 550 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 2.82 (singlet, 4 H, succinimidyl ring), 3.93 (doublet, J = 12 Hz, 6 H, phosphorous ester methyls).

Anal. Calcd for $C_6H_{10}NO_5P$: C, 34.80; H, 4.84; P, 14.98; N, 6.77. Found: C, 34.68; H, 4.87; P, 14.76; N, 6.55.

N-Methylsuccinimide (46% N.A., 65% I.A.) was obtained from

this experiment as white, crystalline needles, mp 68–70° (lit.[19] mp 68–70°).

N-**(Diethylphosphonyl)succinimide.** This material separated from solution (92% N.A., 81% I.A.) during reaction as a white solid which was purified by recrystallization from methanol: mp 57–60° (lit.[2] mp 60–62°); ir ν_{max} (Nujol) 1730 (C=O), 1295, 1250, 1125, 1030, 815, 755, 665, 555 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 3.20 (triplet, J = 8 Hz, 6 H, CH_3's), 2.80 (singlet, 4 H, succinimidyl ring), 4.32 (quintet, J = 8 Hz, 4 H, ethyl CH_2's).

***N*-(Diisopropylphosphonyl)succinimide** was obtained as a dark red oil from silica gel (56% N.A., 37% I.A.): ir ν_{max} (film) 1725 (C=O), 1280–1290, 1100–1140, 1000, 750, 650, 560 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 1.43 (doublet, J = 6 Hz, 12 H, isopropyl CH_3's), 2.80 (singlet, 4 H, succinimidyl ring), 4.85 (septet, J = 6 Hz, 2 H, isopropyl methines).

Anal. Calcd for $C_{10}H_{18}NO_5P$: C, 45.65; H, 6.85; N, 5.33; P, 11.78. Found: C, 45.57; H, 6.68; N, 4.96; P, 11.83.

N-**(Di-*n*-butylphosphonyl)succinimide.** This material was isolated from exhaustive stripping of product mix followed by recrystallization from chloroform. Melting point (45–47°) and spectral data were identical with those reported previously.[1]

N-**(Diisobutylphosphonyl)succinimide.** Solids (dark red) that separated from CS_2 solution during reaction at 5° were collected by suction filtration. Nmr (see below) indicated the crude material to be 90% of the title compound. Purification by recrystallization from ethyl ether (slow evaporation) yielded wheat-white needles: mp 94–97°; ir ν_{max} (Nujol) 1735 (C=O), 1275, 1130, 1030, 880, 820, 660, 545 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 0.98 (doublet, J = 6 Hz, 12 H, ester CH_3's), 2.0 (multiplet, broad, 2 H, butyl methine), 2.80 (singlet, 4 H, succinimidyl ring), 4.1 (doublet of doublets, J_{PCH_2} = 8 Hz, J_{CH_2CH} = 6 Hz, 4 H, $POCH_2$).

Anal. Calcd for $C_{12}H_{22}NO_5P$: C, 49.50; H, 7.56; N, 4.81; P, 10.65. Found: C, 49.36; H, 7.42; N, 4.54; P, 10.59.

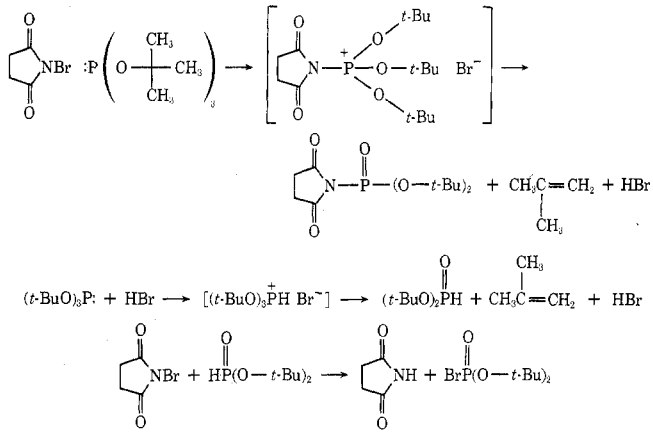
N-**(Di-*sec*-butylphosphonyl)succinimide.** This material was obtained from silica gel chromatography as a light red oil not analytically pure. Spectral evidence is offered as proof of structure: ir ν_{max} (film) 1740 (C=O), 1280, 1180, 1120, 1040, 815, 770, 660, 550 cm^{-1}; nmr δ_{TMS} ($CDCl_3$) 0.95 (triplet, J = 8 Hz, 6 H, γ methyls on butyl group), 1.30 (doublet, J = 6 Hz, 6 H, α methyls on butyl group), 1.65 (multiplet, 4 H, butyl methylenes), 2.80 (singlet, 4 H, succinimidyl ring), 4.45 (sextet, J = 6 Hz, OCH methines).

Acknowledgment. Appreciation is afforded Hooker Chemical Corp. for permission to conduct and publish this work under its auspices.

Registry No.—1 (R = CH_3), 39843-52-2; 1 (R = C_2H_5), 2737-05-5; 1 (R = *i*-C_3H_7), 50599-95-6; 1 (R = *i*-C_4H_9), 50599-96-7; 1 (R = *sec*-C_4H_9), 50599-97-8; $P(OR)_3$ (R = CH_3), 121-45-9; $P(OR)_3$ (R = C_2H_5), 122-52-1; $P(OR)_3$ (R = *n*-C_4H_9), 102-85-2; $P(OR)_3$ (R = *i*-C_4H_9), 1606-96-8; $P(OR)_3$ (R = *sec*-C_4H_9), 7504-61-2; $P(OR)_3$ (R = *t*-C_4H_9), 15205-62-6; $P(OR)_3$ (R = *i*-C_3H_7), 116-17-6; *N*-bromosuccinimide, 128-08-5; *N*-chlorosuccinimide, 128-09-6.

References and Notes

(1) A. K. Tsolis, W. E. McEwen, and C. A. WanderWerf, *Tetrahedron Lett.*, 3217 (1964).
(2) T. Mukaiyama, T. Obata, and O. Mitsunobu, *Bull. Chem. Soc. Jap.*, **38**, 1088, 1091 (1965).
(3) J. M. Desmarchelier and T. R. Fukuto, *J. Org. Chem.*, **37**, 4218 (1972).
(4) B. A. Arbusov, *Zh. Russ. Fiz. Khim. Obshch.*, **38**, 687 (1906).
(5) A. Michaelis and R. Kaehne, *Ber Deut. Chem. Ges.*, **31**, 1048 (1898).
(6) G. W. Kenner, A. R. Todd, and F. J. Weymouth, *J. Chem. Soc.*, 3675 (1952).
(7) A. J. Kirby and G. G. Warren, "The Organic Chemistry of Phosphorous," Elsevier, N. Y., 1967, pp 113–114.
(8) In compliance with a referee's comments concerning the following alternative scheme for sterically hindered phosphite esters, an additional experiment was conducted employing a fourfold excess of tri-*tert*-butyl phosphite and a stoichiometric amount of pyridine as an HBr acceptor. In keeping with the suggested alternative, an increase in the *N*-(di-*tert*-butylphosphonyl)succinimide component would be expected. Results from the cited experiment show no observable change in product distribution from that of the entry in Table I. As in the former experiment, no detectable dialkylphosphonylsuccinimide was found.



(9) D. N. Harpp and B. A. Orwig, *Tetrahedron Lett.*, 2691 (1970).
(10) G. M. Kosolapoff, *J. Amer. Chem. Soc.*, **74**, 4953 (1952).
(11) V. Mark and J. R. VanWazer, *J. Org. Chem.*, **29**, 1006 (1964).
(12) F. Ramirez, H. Yamanaka, and O. H. Basedon, *J. Amer. Chem. Soc.*, **83**, 173 (1961).
(13) P. A. Chopard, *Helv. Chim. Acta*, **50**, 1021 (1967).
(14) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).
(15) The tri-*tert*-butyl phosphite system required reflux (46°) to affect reaction and the cyclohexyl system was carried out at room temperature. Reaction time of 8–10 hr was necessary for 100% conversion in both systems.
(16) W. Gerrard and G. J. Jeacocke, *J. Chem. Soc.*, 3647 (1954).
(17) H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).
(18) N.A. implies addition of phosphite ester to the *N*-haloimide; I.A. implies addition of *N*-haloimide to phosphite ester.
(19) F. S. Spring and J. C. Woods, *J. Chem. Soc.*, 625 (1945).

Studies of Chemical Exchange by Nuclear Magnetic Resonance. IX. Rotation about the Amide Bond in *N,N*-Dimethylformamide[1,2]

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Activation parameters have been determined for rotation about the amide bond in pure *N,N*-dimethylformamide-d_1: E_a, 24.3 ± 0.2 kcal/mol; log A, 14.6 ± 0.1; ΔS^*, +6.3 ± 0.4 eu; ΔF^*_{298}, 21.8 kcal/mol. Kinetic data were obtained by total line shape analysis of the nmr spectra. The activation parameters are contrasted with previous values obtained using different techniques and a structure–reactivity correlation for amide rotation is discussed. These results are also compared with data for unsubstituted and *N*-methylformamide in an attempt to assess the importance of alkyl substitution on nitrogen on the C–N rotational barrier.

Rotation about the partial double bond of *N,N*-dimethylamides (1) has been extensively studied in part because these systems are the simplest models for the peptide bond in proteins.[1,3-10] Early studies gave inaccurate activation parameters for C–N rotation because approximate procedures were used to derive rate constants. Now