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pH determination of the acetate buffer solutions.

Apparatus. The separation and kinetic analysis of **1**, **2**, and **3** was carried out on an HPLC system consisting of a Micromeritics Model 725 autoinjector, Model 110A Altex pump, SP Model 770 spectrophotometric detector, and an SP 4000 computing integrator. The following RP-HPLC conditions provided a linear response throughout the range of 0.015–1.5 μg injected: column, Whatman Partisil 5 ODS 3 (25 × 0.4 cm, 5 μm); mobile phase, methanol–0.01 M phosphate buffer (pH 4)–tetrahydrofuran (47.5:40:12.5, v/v); flow rate, 1 mL/min; detection, 253 nm; typical retention times, **1**, 10.5 min; **2**, 14 min; **3**, 15.7 min; 3-methylene analogue of **1**, 8.6 min; 5-methylene analogue of **1**, 12.6 min. pHs were determined on a Radiometer PHM 64 pH meter and Model GK2401C combination electrode. Electron impact mass spectra were obtained on a Varian MAT 1125 or 311A direct inlet mass spectrometer.

Kinetics. In order to obtain pseudo-first-order kinetics, the buffer concentration ($\sim$0.01–0.15 M, μ = 0.15) was always maintained in excess over the anthryl ether concentration ($\sim$1.0 × 10^{-5} M). In a typical experiment, 5-mL aliquots of reaction solution containing a small amount (3.25 μg/mL) of the acetate salt of **1** were transferred to pretreated amber ampules, flame-sealed, and stored at 25, 40, 60, and 80 °C. At known time intervals, ampules were removed from the constant-temperature bath and refrigerated. Upon removal of the last sample, the stored samples were then all analyzed on the same day. Usually, 8–12 samples per kinetic run were collected, and the peak area integrations were converted to concentrations or percent remaining values by use of linear response calibration curves determined for solutions of known concentration of **1**, **2**, and **3**.

pK_a Determinations. The pK_a value for **1** was determined at 25 °C by the solubility–ionization method of Albert and Serjeant[46] using 0.001 M phosphate buffer with an ionic strength of 0.15 M (NaCl). pK_as at higher temperatures (40, 60, and 80 °C) were obtained from a four parameter (k_{H^+}, k_0, k_N, and K_a) fit[15] of the pH–rate profiles.

Product Identification. Large scale separation and collection of **2** and **3** was carried out by using the aforementioned HPLC method except that methanol–water–tetrahydrofuran (44:44:12, v/v) was used for the HPLC mobile phase. The positive identification of **2** and **3** was confirmed by comparison of the UV and electron impact mass spectra and HPLC retention times with authentic samples. Analysis of the amine reaction products derived from the side chain was carried out by quantitative preparation of the phenylthiourea derivative (by reaction of phenyl isothiocyanate and the amine[47]) and then HPLC detection using the same conditions as for **1**.

Isotopic Analysis. The deuterium or ^{18}O incorporation of the product, anthrone, was determined as follows: Approximately 1 mg of **1** was dissolved in either 500 μL of 0.15 M D^+/D_2O or $H^+/H_2{}^{18}O$, the samples were degassed under argon, and then they were stored at 40 °C for 4 days. Under these reaction conditions, anthrone precipitated slowly as needle-like crystals from the reaction solution. These crystals were filtered, washed with water, and analyzed by mass spectroscopy. Control experiments were carried out with both solubilized and suspended anthrone in D^+/D_2O or $H^+/H_2{}^{18}O$ to ensure that anthrone was not susceptible to isotopic exchange under the reaction conditions or that trace amounts of D_2O or $H_2{}^{18}O$ did not give erroneous mass spectral results. The deuterium or ^{18}O content of the anthrone was determined by comparison of the relative intensities of the $M - 1^+$, M^+, and $M + 1^+$ peaks (m/e 194 for anthrone). The experimental error on these single isotope determinations was estimated to be less than 2%.

Note Added in Proof: Incubation of **1** in tritiated $H^+/{}^3H_2O$ showed no radiolabeled remaining **1** when **1** was analyzed by radio-HPLC after approximately 1 half-life. This is further evidence for rate-determining proton transfer in this reaction.

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Anionic Phosphorus as a Nucleophile. An Anion Chain Arbuzov Mechanism

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The reaction of the anion of dineopentyl phosphonate with alkyl iodides is kinetically second order and yields the P-alkylated dineopentyl alkylphosphonate. This supports, as previously suggested, a simple S_N2 mechanism for the reaction. Rate constants in sulfolane are reported. Trimethyl phosphate and phosphonate esters also alkylate this nucleophile. When dimethyl phosphonate dissolved in tetrahydrofuran or in benzene is treated with solid sodium hydride at room temperature, the initially formed anion is virtually quantitatively alkylated by remaining neutral ester before it can react with sodium hydride, yielding monomethyl phosphonate anion and dimethyl methylphosphonate. This major side reaction is less important with diethyl phosphonate and is not detected with the neopentyl ester. It does not occur with butyllithium as the base or with sodium hydride at −78 °C in either THF or benzene as the solvent. This fast reaction appears to be a surface reaction. The anion of diphenylphosphinite is similarly alkylated by methyl diphenylphosphinite, yielding methyldiphenylphosphine oxide and regenerating the anion, thus constituting a new anionic chain mechanism for the Arbuzov reaction.

The reaction of the anion of diethyl phosphonate with alkyl halides with the formation of a new carbon–phosphorus bond is of considerable synthetic value[1] and is known as the Michaelis–Becker reaction.[2] The anion was made by the ionization of the PH bond by a very strong base, such as an alkyllithium. Only a little work on the mechanism of this reaction has been done. A rough kinetic study[3] agreed with the suggestion[4] that it is a simple S_N2

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(1) A recent example is: Kaegi, H.; Chew, E.; Chien, P. *J. Labelled Compd. Radiopharm.* **1980**, *17*, 745.

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reaction. Here we explore the rates of reaction of these phosphonate ions as nucleophiles and also characterize an interesting side reaction.

Results and Discussion

Following some word-of-mouth advice on the preparation of the phosphonate anion, and substituting the dimethyl ester for the diethyl ester and using sodium hydride as the base, we found that none of the desired anion was present, as shown by the ^1H NMR spectrum when hydrogen evolution ceased. This showed a complexity best described as a mixture; one component showed the characteristically large J_{PH} of hundreds of Hertz, but the J_{PH} was not quite the same as that of the starting dimethyl phosphonate (**2a**). The ratio of methoxy protons to this PH proton was 3:1, leading to the structure $CH_3OPHO_2^-$. With this assignment, the other component was recognizable as dimethyl methylphosphonate, by comparison with the spectrum of an authentic sample. Furthermore, when the reaction mixture was quenched with D_2O, there was no change in the proton NMR, showing that there was no phosphorus-centered anion before quenching. These observations are explained by reaction 1, with R = CH_3. It is an alkylation on phosphorus of the anion **1a** by the neutral ester **2a**.

$$\underset{\mathbf{1}}{(RO)_2PO^-} + \underset{\mathbf{2}}{(RO)_2PHO} \rightarrow \underset{\mathbf{4}}{(RO)_2RPO} + \underset{\mathbf{3}}{ROPHO_2^-} \quad (1)$$

a, R = Me; **b**, R = Et;
c, R = 2,2-dimethylpropyl (neopentyl)

The absence of change when the reaction mixture was worked up with D_2O now shows in the context of eq 1 that the methyl phosphonate anion (**3a**) does not readily exchange even in the strongly alkaline solution resulting from this process. The contrast between this very slow exchange and the rather rapid one of neutral diethyl phosphonate[5] (**2b**) is attributable to the negative charge on **3**. The rapid alkylation of the dialkyl phosphonate anion **1a**, shown by the absence of any products except **3a** and **4a**, suggested that **1** might be a very powerful nucleophile. A reactivity perhaps well beyond that expected from its basicity, given by the recently determined $K_a = 2.5 \times 10^{-15}$ for **2b**,[6] was suggested. This anion is potentially nucleophilic at both P and O. It is therefore an α effect nucleophile,[7] and unusually high nucleophilic reactivity is at least conceivable. The supposition that reaction 1 is in fact a simple S_N2 is confirmed by the observation that **2b** shows less of this side reaction and dineopentyl phosphonate (**2c**), in contrast to **2a**, is quantitatively converted to its anion (**1c**) by sodium hydride in benzene. Much of the following work to study the nucleophilic properties of these dialkyl phosphonate anions is done with this neopentyl ester to avoid reaction 1.

The rates of reaction of dineopentyl phosphonate anion (**1c**) with methyl iodide and with ethyl iodide were followed in sulfolane solution by measuring the remaining iodine spectrophotometrically after treating an aliquot with a measured excess amount of iodine. The alkyl iodide was in considerable excess so the reaction followed a first-order course; a plot of the pseudo-first-order rate constant vs. the alkyl iodide concentration was linear and passed through the origin. The slope gave the second-order constant. The product of the alkylation was identified by its single-line ^{31}P NMR spectrum of expected chemical shift. Since the anion was made from dineopentyl phosphonate by treatment with an equivalent of sodium neopentoxide, the solution is not wholly aprotic; it contains a little neopentyl alcohol. We do not expect a major retardation from this, however, since the nucleophile may not be strongly hydrogen bonded. Rates were also measured by phosphorus NMR in the solvent dineopentyl phosphonate for the reaction of the anion with ethyl iodide and with trimethyl phosphate. The study of these slower reactions required higher concentrations than were practical in sulfolane, which is also not very base stable for long times, thus the choice of this rather unusual solvent. The rate of reaction of ethyl iodide was remeasured in this solvent to allow an estimate of the solvent effect. The analysis was not able to measure the extent of any reaction of the alkylating agent with the alkoxide ion, although the alkylation of the anion **1c** was complete, as shown by the phosphorus NMR. The results of these experiments are given in Table I.

Table I. Second-Order Rate Constants for Alkylation of Dienopentyl Phosphonate Anions (1c) by RX at 30 °C

RX	solvent	k, M^{-1} s^{-1} (±5%)[a]
CH_3I	sulfolane	5.3
C_2H_5I	sulfolane	8.7×10^{-2}
C_2H_5I	**2c**	4.0×10^{-4}
$(CH_3O)_3PO$	**2c**	3.0×10^{-4}

[a] The errors are estimated by the quality of the fit to the integrated rate equation, by the fit of the plot of the pseudo-first-order rate constants vs. alkyl iodide concentration to a straight line through the origin, and by the reproducibility. It is nevertheless a rough estimate. The first two entries are probably better than shown; the second two, using the NMR analysis, may be somewhat worse.

The table contains no great surprises. Methyl iodide reacts about 60 times as fast as ethyl iodide, a reasonable ratio.[8] In the rather unfamiliar solvent dineopentyl phosphonate, the reaction is about 200 times slower than in sulfolane, perhaps suggesting an interaction of modest magnitude of the salt with the solvent, which is also suggested by the higher solubility. There is no symmetrical hydrogen bond linking two phosphonate anions, nor is there rapid proton exchange between the anion and the neutral ester, because two compounds had clearly distinct ^{31}P chemical shifts in the solution of **1c** in **2c**, with no conspicuous broadening. In dineopentyl phosphonate solution, trimethyl phosphate is a little slower as an alkylating agent than ethyl iodide. The phosphorus anion **1** is therefore a good nucleophile but not an exceptionally powerful one. We can estimate for the reaction of the phenoxide ion with methyl iodide a rate constant in sulfolane of 4 M^{-1} s^{-1}, using the relative rates of the *p*-nitrophenoxide and the phenoxide and the measured rates of the *p*-nitrophenoxide (at 42 °C).[9,10] Thus, the phosphonate anion is hardly better as a nucleophile than phenoxide and reacts with methyl iodide far more slowly than does the thiophenoxide ion ($k = 5.7 \times 10^4$ at 42 °C).[10] There is no substantial special reactivity either as an α

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[9] Lewis, E. S.; Vanderpool, S. *J. Am. Chem. Soc.* **1977**, *99*, 1946.

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Table II. H_2 and CH_4 Yields in Deprotonation of $(RO)_2PHO$ under Various Conditions

base	solvent	temp, °C	R	% yield
NaH	THF[a]	67	neopentyl	95
NaH	benzene	25	neopentyl	97
NaH	benzene	25	ethyl	58
NaH	benzene	25	methyl	53
LiMe	benzene	25	neopentyl	99
LiMe	benzene	25	ethyl	95
LiMe	benzene	25	methyl	106
NaH	THF	−78	ethyl	98
NaH	THF	−78	methyl	96
NaH	THF	25	neopentyl	101
NaH	THF	25	ethyl	78
NaH	THF	25	methyl	48

[a] THF = tetrahydrofuran.

effect nucleophile or as a soft nucleophile. In this connection, we should note that the success of the Marcus equation in treating methyl transfer rates[11] suggests that neither hard–soft effects nor α effects are expected to be important as special transition state stabilizing effects.

The question then remains why reaction 1 occurs so easily when we expect that dimethyl phosphonate will methylate more slowly than trimethyl phosphate, which has the higher oxidation state as well as half again as many equivalent methyl groups. Furthermore, the fact that reaction 1 has not been observed before as a major side reaction in a common synthetic process also is strange. The answer is that the conditions under which we observed reaction 1 are specialized, and the reaction is not usually nearly so fast. Table II shows the yield of the conjugate acid of the strong base (either NaH or LiMe in our cases) used for the initial ionization of the neutral phosphonate, which is reduced by the destruction of this reagent by reaction 1. Thus, a quantitative occurrence of reaction 1 will give only a 50% yield of H_2 or CH_4, and absence of reaction 1 will give a 100% yield based onthe dialkyl phosphonate.

It is now clear that the occurrence of reaction 1 is limited to the use of sodium hydride as a base at higher temperatures; it is then serious for the methyl ester, less so for the ethyl ester (the common Michaelis–Becker reagent), and undetected with the neopentyl ester. Since the phosphonate esters are not unusually potent alkylating agents in homogeneous solution, the observed fast reaction 1 must occur at the sodium hydride surface, possibly by electrophilic activation of the neutral ester.

Nevertheless, the occurrence of reaction 1 and the significant methylating power of trimethyl phosphate in Table I suggested that a new ionic chain mechanism for the Arbuzov reaction might be found, carried by nucleophilic anions such as **3**. Such a chain can only persist if the starting trivalent ester is a better alkylating agent than the higher oxidation state product **4**. This seems unlikely except for the cases for which the product is hardly an alkylating agent at all. This will be the case when the groups on phosphorus are not simple primary alkoxy groups. We therefore chose to study the possible conversion of methyl diphenylphosphinite to methyldiphenylphosphine oxide, catalyzed by the sodium salt of diphenylphosphinate, eq 2.

$$(Ph)_2POMe + (Ph)_2PO^- \rightarrow (Ph)_2MePO + (Ph)_2PO^- \quad (2)$$

The reaction was too slow to follow easily in sulfolane at temperatures where this solvent is reasonably stable. It was therefore studied in solution of dimethyl sulfone at 122 °C, both by an iodometric method and by ^{31}P NMR. Reaction 2 indeed does occur under these conditions, with a rate constant of $1.68 \times 10^{-2}\ M^{-1}\ s^{-1}$. Thus, to the usual "textbook" mechanism, involving attack of iodide ion on the intermediate alkoxyphosphonium ion,[12] the "autocatalytic" reaction[12,13] (a cationic chain mechanism), and some free-radical mechanisms,[14] we must now add this anionic chain mechanism, with the reservation that, because in most cases the product is likely to be a more powerful alkylating agent than the starting material, it is very unlikely to have much generality. This richness of mechanisms arises from the considerable exothermicity, for example, for the rearrangement of trimethyl phosphite, $\Delta H° = -24$ kcal/mol.[15]

Experimental Section

Materials. Dimethyl phosphonate, diethyl phosphonate, trimethyl phosphate, methyl iodide, and ethyl iodide were all commercial materials distilled before use. Sulfolane (tetrahydrothiophene-1,1-dioxide) was purified as described earlier.[10] Methyl diphenylphosphinite was a commercial sample contaminated with about 3% of its rearrangement product, methyldiphenylphosphine oxide, which was not removed although allowance was made for it in the NMR kinetics. Dimethyl sulfone was recrystallized from water and dried before use. Dineopentyl phosphonate, bp 80 °C (4 torr), was prepared by the general method described by Kosolapoff and Maier.[16] Sodium diphenylphosphinite was prepared following Horner et al.[17] by fusion of triphenylphosphine oxide with sodium hydride. The identity of the salt was confirmed by alkylation with ethyl iodide to yield ethyldiphenylphosphine oxide, mp 124 °C (lit.[17] mp 125 °C). The identities of all phosphorus compounds, both reagents and products, were confirmed by the phosphorus chemical shifts, which agreed with the literature values for all compounds previously reported. The following new chemical shifts were also observed, all reported as ppm downfield from 85% H_3PO_4: dineopentyl phosphonate, δ −7.5 in $CDCl_3$; dineopentyl phosphonate anion, δ −250 in the neutral ester; dineopentyl methylphosphonate, δ −31.2 in $CDCl_3$; dineopentyl ethylphosphonate, δ −32.6 in $CDCl_3$.

Product Identification. The starting dimethyl phosphonate had in the proton NMR two doublets, one at δ 3.72, J = 12 Hz, and one at δ 6.68, J = 674 Hz. After 1 h of stirring of 0.10 mL of **2a** and 0.04 g of 60% sodium hydride in mineral oil in 30 mL of dry benzene, the mixture was frozen and the benzene removed under vacuum. Then 1 mL of water or D_2O was added and the NMR again taken. The spectrum consisted of a doublet at δ 6.65, J = 634 Hz, apparently associated with a doublet at δ 3.53, J = 9 Hz, assigned to the monomethyl phosphonate ion, the area of the second doublet amounted to about three times the area of the first doublet; and two doublets of a lesser product, identified as dimethyl methylphosphonate, at δ 3.57, J = 10.8 Hz, and δ 1.62, J = 17 Hz. The smaller amount of this product was accounted for by evaporative loss during the solvent removal. Significant methanol and protium contamination in the D_2O were also seen. Similar experiments on the diethyl phosphonate gave a still more complex spectrum, showing with H_2O workup two different protons bonded to phosphorus, indicating that reaction 1 occurred but was not quantitative. With the neopentyl ester **2c**, no reaction other than ionization and reprotonation was detected.

Kinetics. In sulfolane solution, advantage was taken of the facile oxidation of the anion by iodine. An aliquot of the solution was added to a constant measured excess of iodine, and the concentration of the remaining iodine was estimated by measuring the absorbance of the solution at 470 nm, extinction coefficient

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about 200 in sulfolane. The alkyl iodides were present in large excess, so pseudo-first-order rate constants were calculated from the slope of a plot of ln $(A_\infty - A_t)$ vs. time, and these divided by the alkyl iodide concentration gave the second-order constants. This same method was used for reaction 2, where both the anion and the starting phosphinite ester react rapidly with iodine, except that the solvent for the iodine and the measurement was potassium iodide in water. Again, the reaction followed a first-order course, because the anion is not consumed. Reactions in the phosphonate ester solvent could not be followed this way; instead, they were followed by observing the disappearance of the anion ^{31}P NMR absorption at -250 ppm from 85% H_3PO_4, using a JEOL FX90Q spectrometer. Reaction 2 was also followed this way, by using the decay of the phosphinite ester concentration. It gave a rate constant in reasonable agreement with the more precise iodine method.

Gas Evolution. The gas (H_2 or CH_4) was measured from a weighed sample of the three esters **2** with an excess of the base and solvent as described in Table II. The precision of measurement is about ±7%. Yields of hydrogen or methane were determined by displacing water with the gas at 1 atm and measuring the volume of the water. Since no water vapor pressure correction was applied, the yields may be as much as but not more than 5% too high. The rate of reaction with sodium hydride of the esters fell markedly in the sequence **2a**, **2b**, and **2c**.

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Selective Substitutions of Imidoyl Halide in 2-Azanorbornenes[1]

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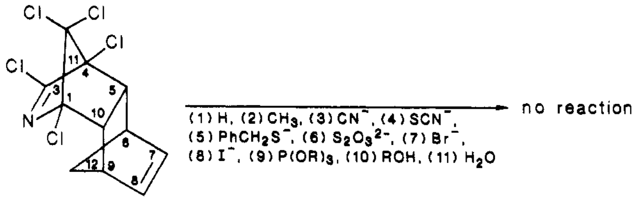
Cyclic imidoyl halides are assumed to undergo nucleophilic substitutions by way of addition-elimination. The imidoyl moiety in azaaldrin (1) has turned out to be a very sensitive substrate in determining the scope and limitation of the addition-elimination pathway of substitution. There was no reaction observed for 1 with 11 common nucleophiles: H, CH_3, CN, SCN, SCH_2Ph, $S_2O_3^{2-}$, Br^-, I^-, $P(OR)_3$, ROH, H_2O. This outcome was not changed by varying solvent or temperature or adding modifiers such as crown ether. However, successful substitutions of 1 and several homologues were obtained with piperidine, fluoride, thiophenolate, ethoxide, and hydroxide in alcohol. The observations are explained by applying Pearson's hard- and soft-base classification of the nucleophiles used. In general, those that are soft bases do not react with 1, while those that are hard *and* basic do. A mechanism is proposed that involves an early acid-base complex and a transition state stabilized by σ bonding to account for the selectivity of nucleophiles. The structure of the lactam derivative 6 is discussed in detail.

Nucleophilic substitution reactions of acyl halides, —C(X)=O, are well-known,[2] but not so for imidoyl halides, —C(X)=N—. Much of the present knowledge of the latter is based on the work of Hegarty,[3] Scott,[4] Rappoport,[5] and their co-workers. They studied reactions of mainly acyclic imidoyl halides and a few 6- and 5-membered cyclic derivatives with amines, fluoride, and alkoxides. As expected in analogy to the acyl halide, substitutions of imidoyl halide are shown to be either the S_N1 type, involving a nitrilium ion intermediate, or the addition-elimination reaction via a tetrahedral intermediate.[5] The predictive values of these pathways have not been shown beyond the few nucleophiles used.

As part of our continuing program to study polycyclic amines,[1] we have attempted to replace the imidoyl chloride group in azaaldrin (**1**) with other substituents. The imine double bond is part of a rigid norbornyl system; hence, the S_N1 pathway for replacing the C-3 chloro group is disallowed due to the geometric constraint. Thus, the success and failure of nucleophiles in reacting with **1** will determine the scope and limitation of the addition-elimination pathway in imidoyl halide substitution. We report herein the selective substitutions of **1** where 11 nucleophiles showed no reaction and 5 gave positive substitutions. Several homologues of **1** behaved similarly. These results are rationalized by applying Pearson's HSAB (hard and soft acid and base) principle.[6] Also discussed is the structure of the hydroxy-substituted product, which has been examined by X-ray and spectroscopic means.

Scheme I[a]



1

[a] Key: (1) NaH in THF, $LiAlH_4$, or $NaBH_4$ in diethyl ether; (2) CH_3MgX (X = Cl, I) in ether or THF; (3) KCN; (4) KSCN; (5) $PhCH_2SH$ and KOH; (6) $K_2S_2O_3$; (7) KBr; (8) KI; (9) $P(OR)_3$ (R = Me, Et); (10) EtOH; (11) 50% aqueous dioxane.

Results

The "no reactions" are summarized in Scheme I. For reactions 3-8, a 0.5 M solution of the nucleophilic reagent, which was about 10-fold excess of **1**, was used. Acetonitrile was the solvent except in reaction 5 where ethanol was employed. The trialkyl phosphite was applied either as a neat liquid or in toluene. Many variations of the no-reaction systems were tried in order to determine the lack of a reaction. Thus, KCN in CH_3OH was tried, but no reaction was detected even when it was kept in a sealed

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