Reactions of Phosphonic Acid Esters with Nucleophiles. Part IV.[1] Hydrazines and Hydroxylamines with *p*-Nitrophenyl Methylphosphonate

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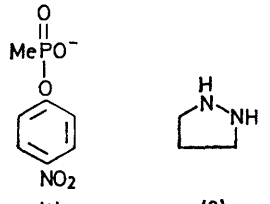
A steric argument accounts for the orders of reactivity of two parallel series of hydrazines and hydroxylamines with *p*-nitrophenyl methylphosphonates. The α effect is not especially important. The unusually high reactivity of hydroxylamine may reflect *O*-attack for this species. In some cases hydrogen bonding to the phosphoryl oxygen atom in the transition state is a possibility. The results agree with prevailing theories on the forces which control nucleophilic substitution at a tetrahedral phosphorus atom.

REACTIONS of amines with tetrahedral organophosphorus substrates are believed to be governed primarily by the basicity and steric effects of the nucleophiles.[1a,2] Another factor known to be important is the α effect.[3]

In earlier papers of this series we have reported kinetic data for the reactions of various nucleophiles with the monoanion of *p*-nitrophenyl methylphosphonate (1) (*p*-NPMP). We now present results of a study of the reactions of this anion with hydrazine, hydroxylamine, and seven of their dialkyl derivatives. These nine nucleophiles fall into two families, within each of which proton basicity varies only slightly. Thus, we could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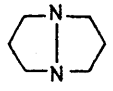
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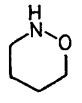
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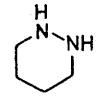
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evaluate our results in terms of a comparison between steric effects and the α effects which were anticipated.

EXPERIMENTAL

Materials.—Synthesis and characterization of the substrate have been described.[4] Pyrazolidine (2) oxalate,† perhydropyrazolo[1,2-*a*]pyrazole (3), 1,2-oxazolidine (4) hydrochloride, and tetrahydro-1,2-oxazine (5) hydrochloride were synthesized by reported methods.[5] I.r., n.m.r., and mass spectra (data obtainable on request) confirmed the assigned structures. Hexahydropyridazine (6) monohydrochloride was a gift.‡ All other reagents used were commercially available and purified by the usual techniques. The acid salts were synthesized or purchased for ease of handling. The kinetically-active free bases were liberated in the solvent, water, by addition of sodium hydroxide (1 equiv.).

Kinetics.—Reactions were carried out in 3-ml glass-stoppered cuvettes in the thermostatted cell compartment of a Cary 15 recording u.v.–visible spectrophotometer. Second-order rate constants were calculated from pseudo-zero-order plots of absorbance *vs.* time at 400 nm (ε 1·82 × 10^4 for *p*-nitrophenoxide ion). Some of these constants are not completely reproducible. This problem was most evident for the slower reactions, in which significant product formation could be attributed to hydrolysis of the substrate. These variations appear to be non-systematic and we believe they are not due to deviations from second-order kinetics. Phosphate buffers were used except where noted. Rate constants were corrected for product formation due to ester hydrolysis.

RESULTS

The stoicheiometry, rate law, and mechanism of this reaction have been given for the amines previously investigated.[1a] Our data indicate that the process investigated here is similar [reaction (1)].

$$p\text{-NPMP} + \text{nucleophile} \longrightarrow \text{MePO}_2\text{–nucleophile} + p\text{-nitrophenoxide} \quad (1)$$

Figure 1 is a typical pseudo-zero-order plot of absorbance *vs.* time. Table 1 gives the kinetic data; rate constants have not been statistically corrected. The constancy of second-order rate coefficients over varying reagent concentration affirms the rate law (2). Further-

$$v = k_2[p\text{-NPMP}][\text{nucleophile}] \quad (2)$$

† We found evidence for the air-oxidation of pyrazolidine to 1-pyrazoline. The saturated compound was isolable as its oxalate salt.

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TABLE 1

Data on reactions of nucleophiles with *p*-NPMP

Nucleophile	*t*/°C	pK_A (25°)	pH [a]	*I* [b]	[Nucleophile]/mol l^{-1}	10^3[*p*-NPMP]/mol l^{-1}	10$^4k_2$/l mol^{-1} min^{-1}
MeNH·OMe	60·0	4·75	8·00	0·65	0·257	1·79	*ca.* 0·04 [c]
(4)	60·0	5·05	8·75	0·60	0·0562	1·79	2·88
	60·0		9·00	0·60	0·0562	1·79	3·00
	60·0		9·05	0·40	0·0562	1·79	2·92
	60·0		9·00	0·60	0·0562	1·79	2·89
	30·0		8·00	0·65	0·245	1·79	0·14
	30·0		8·00	0·33	0·122	3·58	0·12
	30·0		8·00	0·65	0·245	1·79	0·13
	30·0		8·00	0·49	0·183	2·69	0·11
(5)	60·0	5·20	8·35	0·67	0·253	1·60	1·10
	60·0		8·10	0·67	0·253	1·60	1·11
	60·0		8·10	0·80	0·303	0·958	1·15
	30·0		8·40	0·67	0·253	1·60	0·091
	30·0		8·20	0·67	0·253	1·60	0·087
	30·0		8·15	0·50	0·190	2·39	0·074
	30·0		8·30	0·67	0·253	1·60	0·075
	30·0		8·20	0·50	0·190	2·39	0·063
NH_2·OH	60·0	5·97 [d]	7·10	0·03	0·1	0·2	33 [e]
	60·0		8·30	0·67	0·239	1·60	39·5
	60·0		8·30	0·67	0·239	1·60	39·0
	60·0		8·30	0·67	0·239	1·60	38·5
	30·0		8·20	0·67	0·239	1·60	3·51
	30·0		8·20	0·67	0·239	1·60	3·56
	30·0		8·70	0·80	0·287	0·958	3·76
NH_2·NH_2	60·0	8·07	9·67—10·3	0·05—0·1	0·074—0·185	0·940	38·4
	60·0		9·60 [f]	0·05	0·289	1·60	39·1
	30·0		9·60	0·05	0·289	1·60	2·42
	30·0		9·75	0·05	0·289	1·60	2·42
	30·0		9·60	0·05	0·289	1·60	2·42
MeNH·NHMe	60·0	7·52 [d]	9·95	0·5	0·197	1·10	4·02
	60·0		9·90	0·5	0·100	1·10	4·00
	60·0		10·00	0·5	0·0985	1·05	3·55
	30·0		9·20	0·51	0·137	1·79	0·135
	30·0		10·05	0·59	0·293	1·79	0·164
	30·0		9·80	0·5	0·103	1·05	0·136
(2)	60·0	7·6	9·50	0·61	0·0333	1·79	39·0
	60·0		9·50	0·61	0·0667	1·79	39·2
	60·8		9·70	0·61	0·0333	1·79	44·0
	60·8		9·70	0·61	0·0667	1·79	44·2
	60·0		9·80 [g]	*ca.* 0·6	0·0333	1·90	39·5 [h]
	60·0		10·15 [g]	*ca.* 0·6	0·0667	1·90	36·6 [h]
	30·0		9·90	0·61	0·0667	1·79	3·34
	30·0		9·91	0·61	0·0667	1·79	3·50
	30·0		9·48	0·80	0·133	1·79	2·91
(6)	60·0	7·7	9·38	0·61	0·0667	1·79	13·0
	60·0		9·48	0·61	0·034	1·79	14·2
	60·0		10·30	0·61	0·0667	1·79	12·8
	60·0		10·30	0·61	0·0333	1·79	15·0
	30·0		9·90	0·61	0·133	1·79	0·750
	30·0		9·90	0·61	0·133	1·79	0·745
(3)	60·8	8·0 [i]	10·40	0·6	0·392	1·79	2·31
	60·8		10·40	0·6	0·392	1·79	2·35
	60·8		10·30	0·6	0·292	1·79	2·31
	30·0		10·25	0·6	0·380	1·79	0·0860
	30·0		10·25	0·6	0·292	1·79	0·0680

[a] pH Established by phosphate buffers in the concentration range 0·2—0·3M, except where noted. [b] Ionic strength. [c] This value is the best estimate of this rather unreactive nucleophile. The uncertainty is due to the preponderance of hydrolysis taking place in its presence. [d] P. A. S. Smith, 'The Chemistry of Open-Chain Organic Nitrogen Compounds,' Benjamin, New York, 1966, p. 3. [e] There appears to be a small effect of ionic strength or pH here. The value 39·0 was used in calculating activation parameters, since this value was obtained under kinetic conditions identical to those of the reactions at 30°. [f] pH Established by 0·16M-boric acid–NaOH buffer. [g] Apparent pH, since reaction was in D_2O. [h] In D_2O. [i] Contained 10^{-4}M-ethylenediaminetetra-acetic acid. [j] Ref. 5*a*.

more, no dependence of rate on pH is observed, at least in the limited ranges employed.

A summary of rates and activation parameters for the reactions of *p*-NPMP with hydrazines and hydroxylamines is given in Table 2. Figure 2 is the appropriate Brönsted plot, constructed by superimposing values obtained from Table 2 on the correlation line of a plot of data already published.[1a] Only hydroxylamine shows an appreciable α effect, which is demonstrated by the positive Brönsted deviation. However, this compound is alone among those shown in that attack by nitrogen on the phosphorus atom is not the only conceivable mode of reaction. Possibly hydroxylamine attacks *via* the oxygen atom. (A product study of the reaction, although desirable from the point of view of identification of the site of attack, would have been very difficult because of the small quantities available. However attack at either site would be consistent with the steric argument which is advanced below to explain the reactivities.) It is noteworthy that for both the hydrazine and hydroxylamine series, reactivity orders are the same in terms of structure: that is to say, for both families, the order of reactivity is parent compound ⩾ five-membered ring analogue > six-membered ring analogue > dimethyl derivative.

TABLE 2

A summary of data for displacements by hydrazines and hydroxylamines on *p*-NPMP

Nucleophile	pK_A (25°)	t/°C	k_2/l mol^{-1} min^{-1} ± s [a]	E_a/kcal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
NH_2·NH_2	8·07	60·0	3·88 ± 0·03 × 10^{-3}	18·6	−24
		30·0	2·42 ± 0·00 × 10^{-4}		
MeNH·NHMe	7·52	60·0	3·86 ± 0·27 × 10^{-4}	21·8	−19
		30·0	1·45 ± 0·16 × 10^{-5}		
(2)	7·6	60·0	3·86 ± 0·13 × 10^{-3}	16·8	−29
		30·0	3·25 ± 0·31 × 10^{-4}		
(6)	7·7	60·0	1·38 ± 0·10 × 10^{-3}	19·4	−24
		30·0	7·48 ± 0·02 × 10^{-5}		
(3)	8·0	60·8	2·32 ± 0·02 × 10^{-4}	22·8	−19
		30·0	7·70 ± 0·90 × 10^{-6}		
NH_2·OH	5·97	60·0	3·90 ± 0·05 × 10^{-3}	15·9	−32
		30·0	3·61 ± 0·13 × 10^{-4}		
MeNH·OMe	4·75	60·0	*ca.* 4 × 10^{-6}		
(4)	5·05	60·0	2·92 ± 0·05 × 10^{-4}	21·1	−22
		30·0	1·25 ± 0·13 × 10^{-5}		
(5)	5·20	60·0	1·12 ± 0·02 × 10^{-4}	17·4	−35
		30·0	7·8 ± 1·1 × 10^{-6}		

[a] s = Standard deviation = $\left[\frac{\sum_{i=1}^{N}(x_i - \bar{x})^2}{N-1}\right]^{\frac{1}{2}}$ where $\bar{x}$ is the arithmetic mean over N determinations.

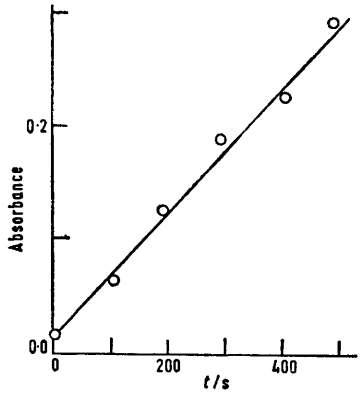

FIGURE 1 A pseudo-zero-order plot of absorbance of *p*-phenoxide ion at 400 nm *vs.* time; [substrate] 1·60 × 10^{-3}M; [hydrazine] 0·289M 60°; pH 9·6; I 0·05

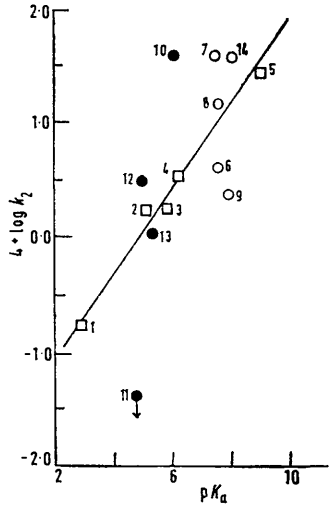

FIGURE 2 Brönsted plot for amines reacting with *p*-NPMP at 60° (pK_A values at 25°). Arrow indicates reaction rate is equal or less than the rate in sodium hydroxide–water at the pH employed. Squares, substituted pyridines (data from ref. 1a); open circles, hydrazines; and filled circles, hydroxylamines. 1, 3-chloropyridine; 2, pyridine; 3, 3-picoline; 4, 4-picoline; 5, 4-aminopyridine; 6, 1,2-dimethylhydrazine; 7, pyrazolidine; 8, hexahydropyridazine; 9, perhydropyrazolo[1,2-*a*]pyrazole; 10, hydroxylamine; 11, *NO*-dimethylhydroxylamine; 12, 1,2-oxazolidine; 13, tetrahydro-1,2-oxazine; and 14, hydrazine

All of the hydrazine compounds fall within a basicity range of 0·6 pK_A units, and the four hydroxylamines fall in a range of only 1·25 units.

The activation parameters show that reactivities are governed primarily by changes in E_a (with one exception, the tetrahydro-1,2-oxazine, where the E_a value is more uncertain).

DISCUSSION

Order of Observed Reactivities.—The fact that both families react in the same order from a structural point of view suggests a steric explanation. The government of rates by changes in E_a strengthens the argument. The parent compounds are least hindered and react fastest. Models show that the 3- and 5-axial hydrogen atoms can hinder approach of the six-membered ring to the phosphorus atom, while such interaction is missing in the five-membered rings. The dimethyl compounds are least reactive, since their most stable conformations have the methyl groups *anti*. (An i.r. study [6] has confirmed this for *NO*-dimethylhydroxylamine.) In order to react, the *anti*-methyl group must 'bend back' into a *syn*-conformation. This bending back process is not necessary for five- and six-membered rings, in which the alkyl groups have to be *cis*.

Magnitudes of Reactivity Ratios.—Relative to 1,2-dimethylhydrazine, the hydrazines have relative rates of: hydrazine, 10; pyrazolidine, 10; hexahydropyridazine, 3·6. Relative to *NO*-dimethylhydroxylamine, the hydroxylamines have the ratios: hydroxylamine, 975; 1,2-oxazolidine, 73; tetrahydro-1,2-oxazine, 28. Thus, all four hydrazines have rates within a single power of ten, while hydroxylamine is nearly 10^3 times more reactive than its dimethyl derivative.

Particularly noteworthy is that hydrazine and its five-membered ring analogue are equally reactive, whereas hydroxylamine is over 13 times as reactive as its five-membered ring analogue. As we have already stated, these ratios do not reflect widely varying basicities; furthermore, steric factors are essentially parallel as shown by the similar *orders* of reactivity. The unusually high value for hydroxylamine may be due to *O*-attack, either through hydroxylamine or through the zwitterion $NH_3^+O^-$.[7] (We feel that none of the other compounds studied can reasonably attack *via* the oxygen atom, as proton loss from hydroxylamine in the transition state can prevent the otherwise improbable formation of positive charge on the oxygen.)

A real possibility is hydrogen bonding [3a] in the transition state (Figure 3).

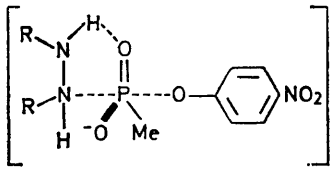

FIGURE 3 $S_N2(P)$ Transition state for attack by a biphilic hydrazine *

* A biphilic reagent is one which utilizes more than one reaction site in its attack on a substrate. It contrasts with an ambident reagent in that the latter does not use both its potential reaction sites in the transition state.

If hydrogen bonding is operative, a solvent isotope effect, k_{H_2O}/k_{D_2O}, greater than unity is often observed. For pyrazolidine the value equals 1·0. However, the lack of an isotope effect is not definitive evidence against a hydrogen-bonding mechanism. In addition Goodman and Glaser [8] have found 'that those α nucleophiles which show an enhanced nucleophilicity . . . are capable of a biphilic (electrophilic–nucleophilic) interaction with the carbonyl group of an oxazolone.' Earlier results showed that methyl substitition decreases the α effects of hydrazines reacting with *p*-nitrophenyl acetate.[9]

The α Effect.—Other than hydroxylamine (*vide supra*), only hydrazine and pyrazolidine show small α effects with *p*-NPMP. Therefore, we feel we have no evidence that contributes to a clarification of the α effect in a general context.

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[1/1383 *Received*, 5*th August*, 1971]

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