Acta Chemica Scandinavica B 32 (1978) 269—273

Spontaneous Decomposition of 2-(*N*,*N*-Dimethylamino)ethyl Phosphates in Polar Solvents

P. ANTTI MANNINEN

Department of Chemistry, University of Helsinki, SF-00100 Helsinki 10, Finland

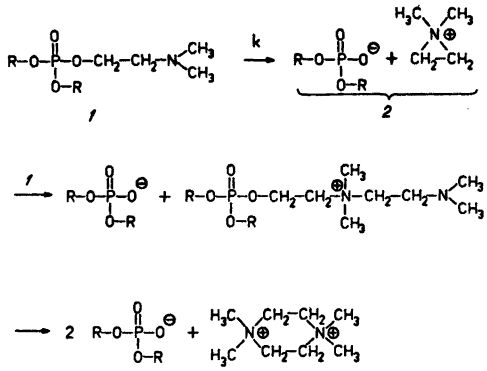
The spontaneous transformation of the dimethyl, diethyl and diisopropyl derivatives of the title compounds to their tetraalkylpiperazinium salts was investigated in water and ethanol at different temperatures. The rate of the decomposition decreases in the order: Me > Et > Pr^i. The effect of solvent polarity is pronounced: The rate is about 25 times as great in water as in ethanol. A linear correlation is found between the logarithms of the rate constants and the σ^{ph} substituent parameters. The kinetic data and activation parameters are presented and discussed. Dimethyl 2-(*N*,*N*-dimethylamino)ethyl phosphate was found to differ from the other two phosphates in giving methyl 2-(*N*,*N*,*N*-trimethylammonio)ethyl phosphate in pure form and in concentrated solutions.

This is the first of a series of papers intended to clarify factors affecting the reactions and properties of organic phosphates and organophosphorus compounds containing 2-(*N*,*N*-dimethylamino)ethyl or 2-(*N*,*N*,*N*-trimethylammonio)ethyl groups.

In pure form and in solutions, certain 2-substituted alkylamines are known to decompose spontaneously to heterocyclic amines or to 1,1,4,4-tetraalkylpiperazinium salts *via* the aziridinium cation.[1,2] Diethyl 2-(*N*,*N*-diethylamino)ethyl phosphate and its thio and thiono derivatives decompose and react with nucleophiles through the same intermediate cation.[3,4] The synthesis of diphenyl 2-(*N*,*N*-dimethylamino)ethyl phosphate is not favoured, and the product tends to be the 1,1,4,4-tetramethylpiperazinium salt of diphenyl phosphate.[5]

In this work the dimethyl, diethyl and diisopropyl 2-(*N*,*N*-dimethylamino)ethyl phosphates have been prepared and their spontaneous decomposition has been investigated in order to examine the effect of different substituents and reaction conditions on the reaction rates and to study the stability of phosphates of this type. These phosphates are suitable starting compounds for the preparation of 2-(*N*,*N*,*N*-trimethylammonio)ethyl phosphates and the ability to evaluate their stability beforehand is useful.

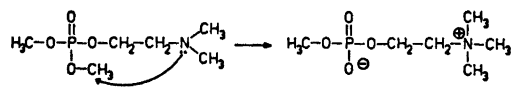
The reaction studied here has been assumed to resemble the reactions mentioned above [1-4] and can be described as in Scheme 1.



Scheme 1.

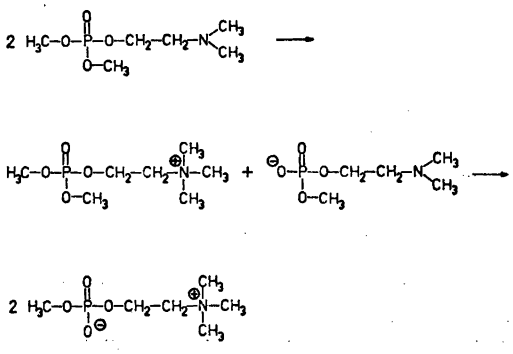
RESULTS AND DISCUSSION

Decomposition of the investigated compounds in dilute solutions yielded, as expected, the respective 1,1,4,4-tetramethylpiperazinium salts. However, the dimethyl derivative gave a different type of product when decomposing in pure form and in concentrated solutions (above 1 M). ^{1}H NMR and ^{13}C NMR spectroscopy



Scheme 2.

showed the product to be identical with authentic methyl 2-(*N*,*N*,*N*-trimethylammonio)ethyl phosphate (Scheme 2). The decomposition of dimethyl 2-(*N*,*N*-dimethylamino)ethyl phosphate in concentrated deuterium oxide solution was followed by ^{1}H NMR spectroscopy at 309 K. Several peaks appeared and disappeared in the course of the reaction. One transient doublet at δ 3.86 could be assigned to dimethyl 2-(*N*,*N*,*N*-trimethylammonio)ethyl phosphate cation through comparison with the spectrum of dimethyl 2-(*N*,*N*,*N*-trimethylammonio)ethyl bromide phosphate. Another transient peak was detected at δ 2.30 and was probably due to a new *N*,*N*-dimethyl group. The effect of the different concentrations and the appearance of intermediate products in the course of the reaction indicated that the decomposition of the dimethyl derivative in pure form and in concentrated solutions is not a direct intramolecular substitution (Scheme 2). The formation of methyl 2-(*N*,*N*,*N*-trimethylammonio)ethyl phosphate can be explained by the bimolecular reaction of two starting molecules and further reaction of the products so formed, as represented in Scheme 3. Direct intramolecular substitution is not favoured, perhaps due to the seven-membered ring, which should form in the transition state.



Scheme 3.

All reactions studied in dilute solutions followed first order kinetics, which can be explained by supposing that the formation of the 1,1-dimethylaziridinium cation (the first step in Scheme 1) is the rate-determining step of the reaction, and that the other steps are much faster. Thus, when the 1,1-dimethylaziridinium cation is formed, it reacts immediately with another molecule of the starting material. Rate constants can be calculated in the usual manner from the equation

$$C = C_0 e^{-2kt} \quad (1)$$

where C is the concentration of the starting material at time t, C_0 is the initial concentration and k is the rate constant. In one instance the thiosulfate ion was used as a nucleophilic agent reacting fast with aziridinium cations.[3] The rate equation in this case is

$$C = C_0 e^{-kt}.$$

The calculated rate constants are shown in Table 1. The Arrhenius parameters E_a and log A have been calculated in the usual manner and values of the parameters are listed in Table 2.

The hydrolysis of the present phosphates is so slow that hydrolysis products could not be detected among the reaction products by NMR spectroscopy. Only negligible amounts of methyl 2-(*N*,*N*,*N*-trimethylammonio)ethyl phosphate was found to form in dilute solutions from the dimethyl derivative.

Rate constants, activation parameters and their standard errors were calculated by computer with a least squares fitting procedure.

It can be seen from Table 1 that the reaction rate does not change when the thiosulfate ion is used as the nucleophilic agent instead of the decomposing phosphate itself. This confirms that the first step in the reaction (Scheme 1) is rate-determining.

Relative rate constants in water are almost independent of the temperature, and are as follows: $k(\mathrm{Pr^i}):k(\mathrm{Et}):k(\mathrm{Me}) \approx 1:2.5:5$. The effect of solvent is more pronounced: k(ethanol):k(water) $\approx 1:(20-30)$ depending on the compound and temperature.

In water the enthalpies of activation (Table 2) increase when the alkyl groups are changed from methyl to ethyl and from ethyl to isopropyl. Entropies of activation increase slightly too, which probably means that the diisopropyl derivative is somewhat sterically crowded in

Table 1. Rate constants for dialkyl 2-(*N*,*N*-dimethylamino)ethyl phosphates, $(RO)_2P(O)OCH_2CH_2N(CH_3)_2$.

R	Medium	$k/10^{-5}$ s^{-1} 313.2 K	323.2 K	333.2 K
CH_3	Water	5.69(3)	17.3(3)	52.5(7)
CH_2CH_3	Water	2.84(3)	8.89(3)	29.8(3)
$CH(CH_3)_2$	Water	1.05(3)	3.88(4)	12.0(1)
$CH(CH_3)_2$	Water ($+S_2O_3^{2-}$)		3.88(20)	–
CH_3	Ethanol	0.32(16)	0.845(20)	2.52(8)
CH_2CH_3	Ethanol	–	0.353(4)	–
$CH(CH_3)_2$	Ethanol	–	0.135(3)	–

Table 2. Thermodynamic parameters for the decomposition of dialkyl 2-(*N*,*N*-dimethylamino)-ethyl phosphates.

R	Medium	E_a/kJ mol^{-1}	log *A*	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1}
CH_3	Water	96.4(13)	11.8(2)	93.7(14)	−27.6(42)
CH_2CH_3	Water	101.9(33)	12.4(5)	99.2(35)	−15.8(101)
$CH(CH_3)_2$	Water	105.7(24)	12.7(4)	103.1(26)	−11.4(20)
CH_3	Ethanol	88.6(48)	9.3(8)	86.0(45)	−76.1(139)

Table 3. Relationship between log *k* and σ^{ph} parameters, $\log k = \log k_0 + \varrho\sum\sigma^{ph}$. $\sum\sigma^{ph}(OMe) = -0.24$, $(OEt) = -0.42$ and $(OPr^i) = -0.58$.[6]

Temp./K	Medium	ϱ^a	log k_0^a
313.2	Water	2.1(3)	−3.70(13)
323.2	Water	1.9(2)	−3.29(8)
333.2	Water	1.8(3)	−2.80(14)
323.2	Ethanol	2.3(1)	−4.50(6)

[a] k_0 is the rate constant for a hypothetical molecule $H_2P(O)OCH_2CH_2N(CH_3)_2$ and ϱ is the reaction parameter.

its initial state and the crowding is relieved in the intermediate. In the dimethyl derivative, the methyl groups are relatively free, both in the initial state and in the intermediate. In ethanol the entropy of activation of the dimethyl derivative is much more negative than in water because of the smaller polarity of ethanol.

The effects of substituents are mainly electronic since the relatively big phosphorus atom and distant reaction centre keep the steric effects small.[6] Substituent constants, σ^{ph}, which reflect the electronic effects of substituents on phosphorus in reactions not involving the phosphorus atom have been measured and calculated previously.[6] The relationship between the rate constants measured in this investigation and the σ^{ph} values [6] is presented in Table 3. The plot of log *k* against σ^{ph} shows a fair linear dependence.

EXPERIMENTAL

The dialkyl 2-(*N*,*N*-dimethylamino)ethyl phosphates were prepared from the corresponding dialkyl phosphorochloridates and sodium 2-(*N*,*N*-dimethylamino)ethoxide by

dropping the ethoxide into the equivalent amount of phosphorochloridate,[4] both in absolute ether. Dialkyl phosphorochloridates were prepared by the author according to the method in Ref. 7 and were purified by fractional distillation. The products in ether solution were purified by extraction first with dilute hydrochloric acid and then with dilute sodium hydroxide. The ether solution was washed with water and dried with magnesium sulfate. After evaporating the ether the product was eluted with an ether-pentane mixture 1:1 through an aluminium oxide column. The dimethyl derivative was not extracted because of its ready solubility in water. The eluent was removed in vacuum and the product was used immediately in the decomposition reaction.

The purity of the phosphates was checked by ^{1}H NMR, ^{13}C NMR and IR spectroscopy. The NMR parameters are as follows:

Dimethyl 2-(N,N-dimethylamino)ethyl phosphate.

$$\overset{4}{(CH_3O)_2}\overset{3}{P(O)}\overset{2}{OCH_2}\overset{1}{CH_2N(CH_3)_2}$$

^{1}H NMR (60 MHz, $CDCl_3$): δ 2.28 (6 H, s), 2.59 (2 H, t), 3.77 (6 H, d), 4.10 (2 H, m). ^{13}C NMR (25.14 MHz, $CDCl_3$): δ 44.48 (C1, s), 52.92 (C4, d), 58.01 (C2, d), 64.52 (C3, d), J(C2,P) 6.6 Hz, J(C3,P) 6.1 Hz, J(C4,P) 5.9 Hz.

*Diethyl 2-(N,N-dimethylamino)*ethyl *phosphate.*

$$\overset{5}{(CH_3}\overset{4}{CH_2O)_2}\overset{3}{P(O)}\overset{2}{OCH_2}\overset{1}{CH_2N(CH_3)_2}$$

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.33 (6 H, t), 2.27 (6 H, s), 2.60 (2 H, t), 4.10 (2 H, m), 4.12 (4 H, m). ^{13}C NMR (25.14 MHz, $CDCl_3$): δ 15.11 (C5, d), 44.60 (C1, s), 58.01 (C2, d), 62.47 (C4, d), 64.02 (C3, d), J(C5,P) 6.6 Hz, J(C2,P) 6.8 Hz, J(C3,P) 5.9 Hz, J(C4,P) 5.9 Hz.

Diisopropyl 2-(N,N-dimethylamino)ethyl phosphate.

$$[\overset{5}{(CH_3)_2}\overset{4}{CHO}]_2\overset{3}{P(O)}\overset{2}{OCH_2}\overset{1}{CH_2N(CH_3)_2}$$

^{1}H NMR (60 MHz, $CDCl_3$): δ 1.33 (6 H, d), 2.28 (6 H, s), 2.60 (2 H, t), 4.08 (2 H, m), 4.63 (2 H, m). ^{13}C NMR (25.14 MHz, $CDCl_3$): δ 23.64 (C5, d), 45.70 (C1, s), 59.05 (C2, d), 65.16 (C3, d), 72.22 (C4, d), J(C5,P) 4.9 Hz, J(C2,P) 7.3 Hz, J(C3,P) 6.1 Hz, J(C4,P) 6.1 Hz.

The refractive indices were measured just after purification: Me, 1.4218; Et, 1.4205 (1.4220); Pr^i, 1.4176 (1.4215). Numbers in parentheses are from Ref. 8.

After complete decomposition of the studied phosphates, the solvent was removed in vacuum and the ^{1}H NMR spectra of the products were recorded:

1,1,4,4-Tetramethylpiperazinium bis(dimethyl phosphate). ^{1}H NMR (60 MHz, D_2O, ref. TMSP):* δ 3.42 (12 H, s), 3.58 (12 H, d), 3.98 (8 H, s).

1,1,4,4-Tetramethylpiperazinium bis(diethyl) phosphate).

^{1}H NMR (60 MHz, D_2O, ref. TMSP): δ 1.25 (12 H, t), 3.42 (12 H, s), 3.93 (8 H, m), 3.98 (8 H, s),

1,1,4,4-Tetramethylpiperazinium bis(diisopropyl phosphate). ^{1}H NMR (60 MHz, D_2O, ref. TMSP): δ 1.25 (24 H, d), 3.42 (12 H, s), 3.98 (8 H, s), 4.38 (4 H, m).

Pure dialkyl 2-(*N*,*N*-dimethylamino)ethyl phosphate was allowed to stand several days at room temperature. Unreacted starting material was removed by extraction with ether and ^{1}H NMR spectra were recorded. The products of the diethyl and diisopropyl derivatives were 1,1,4,4-tetramethylpiperazinium salts of the respective dialkyl phosphates. The ^{1}H and ^{13}C NMR spectra of the dimethyl derivative were the same as those of a known sample of methyl 2-(*N*,*N*,*N*-trimethylammonio)ethyl phosphate prepared from dimethyl 2-bromoethyl phosphate and trimethylamine.[9]

Methyl 2-(N,N,N-trimethylammonio)ethyl phosphate.

$$\overset{4}{CH_3O}\overset{-\ 3}{P(O)(O)}\overset{2\ +\ 1}{OCH_2CH_2N(CH_3)_2}$$

^{1}H NMR (60 MHz, D_2O, ref. TMSP): δ 3.24 (9 H, s), 3.60 (3 H, d), ~3.7 (2 H, m), ~4.3 (2 H, m), J(H4,P) 11 Hz. ^{13}C NMR (25.14 MHz, D_2O, ref. dioxane): δ 13.60 (C4, d), 12.62 (C1, t), 7.21 (C3, d), 0.63 (C2, m), J(C4,P) 5.5 Hz, J(C3,P) 4.9 Hz, J(C2,P) 7.9 Hz, J(C1, ^{14}N) 3.7 Hz, J(C2, ^{14}N) 3.7 Hz.

Dimethyl 2-(N,N,N-trimethylammonio)ethyl bromide phosphate was prepared from equivalent amounts of dimethyl 2-bromoethyl phosphate and trimethylamine in benzene. ^{1}H NMR of the crude product (60 MHz, D_2O, ref. TMSP): δ 3.26 (9 H, s), ~3.80 (2 H, m), 3.89 (6 H, d), ~4.63 (2 H, m), J(H_3C,P) 11 Hz.

The change in the concentration of the starting material was followed by determining the free amino group with 0.05 M hydrochloric acid and using neutral red as indicator. The addition of 0.5–0.7 g of the compound studied into 50 cm^3 of the thermostated solvent gave the concentration 0.04–0.06 M. Usually 7–8 samples of 5.0 cm^3 were taken and the concentration was followed until it had decreased to about half the initial value. The solvents used were distilled water and absolute ethanol, and the temperatures were 313.2 K, 323.2 K and 333.2 K.

When the thiosulfate ion was used as a nucleophile, its concentration was followed by titration with 0.05 M potassium iodate solution (standard method [10]). The initial concentration

* TMSP = sodium salt of 3-(trimethylsilyl)propanesulfonic acid

of the diisopropyl derivative was 0.0218 M and of the thiosulfate ion, 0.0520 M.

REFERENCES

1. Bartlett, P. D., Ross, S. D. and Swain, C. G. *J. Am. Chem. Soc. 69* (1947) 2971.
2. Geissman, T. A., Hochman, H. and Fukuto, T. R. *J. Am. Chem. Soc. 74* (1952) 3313.
3. Fukuto, T. R. and Stafford, E. M. *J. Am. Chem. Soc. 79* (1957) 6083.
4. Cadogan, J. I. G. and Thomas, L. C. *J. Chem. Soc.* (1960) 2248.
5. Durant, G. J., Turnbull, J. H. and Wilson, W. *Chem. Ind. London* (1958) 157.
6. Mastryukova, I. A. and Kabachnik, M. I. *Russ. Chem. Rev. 38* (1969) 795.
7. Sosnovsky, G. and Zaret, E. H. *J. Org. Chem. 34* (1969) 968.
8. Tammelin, L.-E. *Acta Chem. Scand. 11* (1957) 1340.
9. Chabrier de Lassauniere, P. E., Nguyen-Thanh-Thuong, Le Maitre, D. and Perat, M. *Fr.* 1,551,060 (27. 12. 1968); Ref. *Chem. Abstr. 72* (1970) 42777.
10. *Scott's Standard Methods of Chemical Analysis*, Furman, N. H., Ed., 5th Ed., Van Nostrand, Princeton 1939, Vol. I, p. 1211.

Received December 13, 1977.