Rate Studies of Cyclic Phosphinates, Phosphonates and Phosphates

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The rates of alkaline hydrolysis of five- and six-membered cyclic ethylphosphinates, ethylphosphonates, and ethylphosphates are studied.

The rate of alkaline hydrolysis of the five-membered cyclic ethylphosphinate is of the same order of magnitude as the rate of hydrolysis of the corresponding six-membered and open chain ethylphosphinates. The hydrolysis of these phosphoryl esters therefore differs sharply from the alkaline cleavage of corresponding cyclic phosphonium compounds, where the nucleophilic displacement on phosphorus in the five-membered phospholan ring is approximately 1300 times more rapid than the displacements on phosphorus in six-membered ring and open chain analogs. The reactivity differences between corresponding phosphoryl and phosphonium compounds are discussed.

Some times ago we reported [1] that, although the rings are preserved during hydrolysis, methyl phenyl phosphonium salts containing the phosphorus atom in a five-membered phospholan ring were decomposed by hydroxyl ions approximately 1300 times more rapidly than the six-membered phosphorinan ring compounds and open chain analogs:

Scheme A
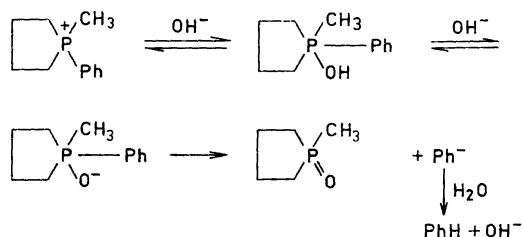
Studies of the temperature dependence showed that the high rate of the above phospholan compound was due to a high frequency factor, whereas

the activation energies were nearly equal for the phospholan, phosphorinan, and open chain compounds.

The kinetics of the alkaline hydrolysis of the phosphonium salts follow a third order rate law in accordance with the occurrence of a pentacovalent intermediate (scheme A). In the present study we have investigated the rates of alkaline hydrolysis of different esters of phosphoric, phosphonic, and phosphinic acids where the phosphorus atom is incorporated in five-, six-, and seven-membered rings. With respect to five-membered cyclic esters of phosphonic and phosphoric acids, Westheimer et al.[2-4] have shown that these are hydrolyzed 10^5-10^8 times as rapidly as corresponding six-membered cyclic esters and open chain analogs. No studies of five-membered cyclic phosphinates have so far been reported.* From previous investigations by several workers [5-10] it is generally agreed that the collision complex formed during alkaline hydrolysis of phosphoryl esters has the character of a transition state rather than an intermediate. The rate scheme for the hydrolysis of the phospholan ester should therefore be:
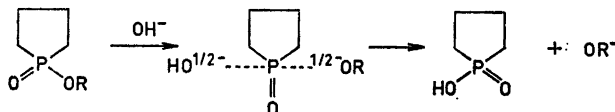
Scheme B

A point of special interest in this context is the comparison of the rates of nucleophilic displacement on phosphorus in five-membered and six-membered phospholan and phosphorinan esters with the earlier evaluated rates for nucleophilic displacement on phosphorus in corresponding phosphonium compounds. The assumed pentacovalent intermediate during alkaline hydrolysis of the latter compounds might require a more precise trigonal bipyramidal configuration than the loosely bonded S_N2P transition state indicated in the hydrolysis of phosphoryl esters.

EXPERIMENTAL

The cyclic phosphonate esters (I, II, and III, Table 1) were synthesized according to the method of Garner.[11] The esters have the following specifications: I: b.p.$_{10}$ 128°, n_D^{20} 1.4498 (reported:[11] b.p.$_2$ 106°, n_D^{20} 1.4497). (Found: C 39.53; H 7.59; E 151.0. Calc. for $C_5H_{11}O_3P$: 39.93; H 7.33; E 150.1). II: b.p.$_{10}$ 130°, n_D^{20} 1.4585 (reported:[11] b.p.$_2$ 100°). (Found: C 43.53; H 7.89; E 165.3. Calc. for $C_6H_{13}O_3P$: C 43.80; H 7.93; E 164.1). III. b.p.$_{10}$ 106°, n_D^{20} 1.4609. (Found: C 47.01; H 8.39. Calc. for $C_7H_{15}O_3P$: C 47.18; H 8.42). Gas-chromatographic analysis of I, II, and III showed the purity to be greater than 99%.

The cyclic phosphinate esters (IV and V, Table 1) were synthesized as described by Helferich and Aufderhaar.[12] The esters have the following specifications: IV: b.p.$_{10}$ 108°, n_D^{20} 1.4620 (reported:[13] b.p.$_{10}$ 108°, n_D^{20} 1.4615). (Found: C 48.33; H 8.80; E 148.7. Calc. for $C_6H_{13}O_2P$: C 48.65; H 8.84; E 148.1). V: b.p.$_{10}$ 109°, n_D^{20} 1.4489. (Found: C 52.02; H 7.30; E 163.8. Calc. for $C_7H_{15}O_2P$: C 51.86; H 7.34; E 162.1). Gas-chromatographic purity of IV and V > 99 %.

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* After this paper was accepted for publication a hydrolytic study of cyclic phosphinates has been published by Westheimer and coworkers.[26]

The esters IV and V were hydrolyzed by refluxing for 12 h with 50 ml concentrated hydrochloric acid. The acids obtained by evaporating the solutions to dryness were recrystallized from benzene/hexane. They had the following melting points: Acid from IV: m.p. 55° (reported:[12] m.p. 53—54.5°). Acid from V: m.p. 129° (reported:[14] m.p. 128—129°).

Ethyl diethylphosphinate (VI) was made by the method of Razumov *et al.*[15] The ester had the following specifications: b.p.$_{10}$ 88—89°, n_D^{20} 1.4321 (reported:[15] b.p.$_{14}$ 91—92°, n_D^{20} 1.4301). Gas-chromatographic purity > 99 %.

Kinetic measurements were performed in water as well as in water-alcohol mixtures using an ordinary back titration method. The hydrolysis of the esters was followed to approximately 75 % of completion, and eight or nine separate determinations of the ester concentration were performed at various time intervals. The average error of the calculated rate constants is estimated to ± 1 %. The reaction temperature was kept constant within ± 0.01°C.

RESULT AND DISCUSSION

Rate data together with activation parameters for the hydrolysis of the various esters are recorded in Table 1. Due to the insolubility of the ethylphosphinates in water, the hydrolysis of these esters were performed in alcohol-water mixtures. Their rate are therefore not strictly comparable with the rates of the phosphonate and phosphate esters. Usually the rates of hydrolysis of phosphorus esters are 20—30 % higher in 50 % alcohol-water mixture than in water.[16] The most characteristic features of the rate data in Table 1 are:

1. In the five-membered phospholan series there is an enormous increase in rate from the phospholan (IV) to the oxaphospholan (I) ester, and also a strong increase from the oxaphospholan (I) to the dioxaphospholan (VIII) ester. The latter two esters hydrolyse exclusively by ring cleavage, and the result is therefore in agreement with earlier findings of Westheimer *et al.*[2-4]

2. The greatest contribution to the 5×10^5 rate increase from the phospholan (IV) to the oxaphospholan (I) comes from the 18.4 e.u. greater activation entropy of the latter ester. This entropy difference corresponds to a rate factor of 10^4. The 2.4 kcal difference in activation energy of the same esters contributes only a rate factor of approximately 50.

3. The higher rates of hydrolysis of five-membered ring compounds relative to six-membered ring compounds and open chain analogs are observed only for the oxa- and dioxaphospholan esters, *i.e.* for phospholans containing oxygen atoms in the five-membered phospholan ring. The alkaline hydrolysis of phospholan esters therefore differs sharply from that of phosphonium compounds containing the phosphorus atom in a phospholan ring, where a 1300 times rate increase over the phosphorinan and open chain analogs was observed.[1]

4. The ethylphosphonate containing the phosphorus atom in a seven-membered ring (III) is hydrolyzed 25 times slower than the corresponding six-membered ring ester. The lower rate is chiefly an entropy effect. It is not limited to phosphonate esters since semi-quantitative rate data of Khorona *et al.*[17] show that also the seven-membered cyclic phosphate ester is considerably more stable than the corresponding six-membered ester.

Haake and Westheimer [3] assume that during acid hydrolysis of 2-hydroxy-2-oxy-1,3,2-dioxaphospholan either a trigonal bipyramidal transition state, or

Table 1. Rate constants and activation parameters for the alkaline hydrolysis of cyclic and open chain phosphinates, phosphonates and phosphates.

| Compound	Solvent	Rate constant, l mole⁻¹ sec⁻¹ × 10⁴					E kcal/mole	log A	ΔS^*
		30°	40°	50°	60°	70°			
(IV)	50 % alcoholwater	—	—	1.18	2.24	4.22	14.1±0.5	5.60	−35.0
(V)	80 % alcoholwater	—	—	0.300	0.568	1.08	14.2±0.5	5.17	−37.0
(VI)	50 % alcoholwater	—	—	0.730	1.39	2.63	14.3±0.5	5.53	−35.2
(I)	Water	19250 (0°C)	51250 (13°C)	5.4×10⁵ (calc.)	—	—	11.7± 1	9.64	−16.6
(II)	»	—	13.6	26.2	50.3	—	13.7±0.5	6.65	−30.3
(III)	»	—	—	1.096	2.109	4.056	14.0±0.2	5.46	−35.7
(VII)	»	0.407	0.872	1.72	—	—	14.0±0.5	5.76	−34.2
(VIII)	»	—	—	∼10⁷	—	—	—	—	—
(IX)	»	—	18.1	36.0	68.7	125	13.8	6.87	−29.3
(X)	»	12.8 (0.1°C)	48.9 (15°C)	74.1 (20°C)	163 (30°C)	—	14.0	8.30	−22.5
(XI)	»	—	0.249	0.520	1.042	2.00	14.8	5.75	−34.4
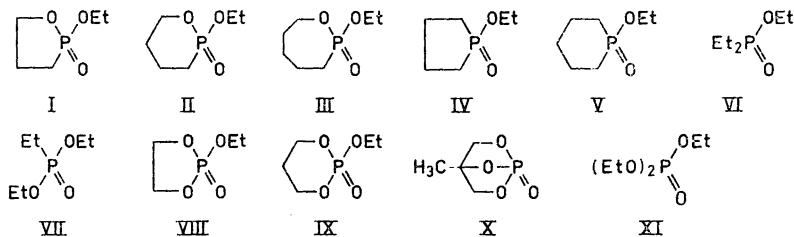
a tetragonal pyramidal one, is operative. Recent X-ray analysis [18] of a penta-oxy-phosphoran containing the phosphorus atom in a 1,3,2-dioxaphospholan ring has shown that the phosphorus atom is at the centre of a nearly perfect trigonal bipyramid, with one of the ring oxygen atoms in apical position, the other in equatorial position. The apical P—O bond is 0.16 Å longer than the equatorial one. A similar configuration therefore seems highly reasonable for the transition state or the intermediate formed in acid hydrolysis of quaternary phospholans:
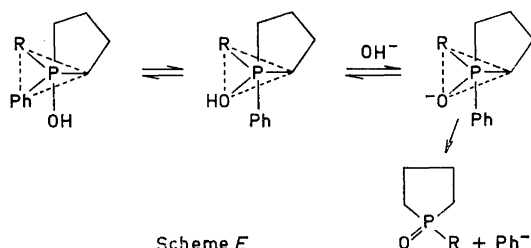
Scheme C
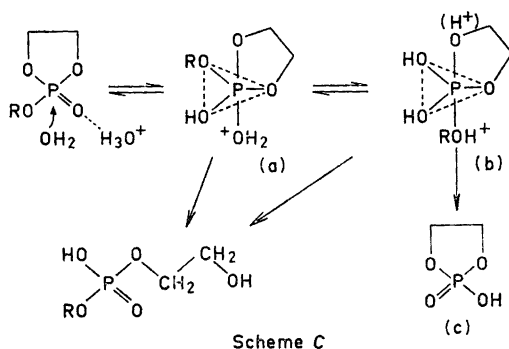
The intermediate (a) would explain the observed preferential breaking of the labile ring P—O bond in apical position during hydrolysis. But the isolation of some ring preserved product (c) in acid hydrolysis,[19] indicates that the intermediate may be sufficiently long-lived to allow for redistribution of its bonds, to form a new intermediate (b) with the alkoxy group in apical position. Depending upon the position of the proton, intermediate (b) can give rise to a ring cleavage product or a ring preserved product.

Studies of the phosphoryl oxygen exchange of 2-hydroxy-2-oxy-1,3,2-dioxaphospholan in ^{18}O-enriched water,[3] have shown that under acidic condition the exchange proceeds with rate comparable to that of hydrolysis, which again points to formation of an intermediate. The non-exchange of phosphoryl oxygen as well as the exclusive formation of ring cleavage product under alkaline conditions, are probably due to a lower stability of the negatively charged pentacovalent intermediate, giving rise to a S_N2P displacement reaction only:

Scheme D
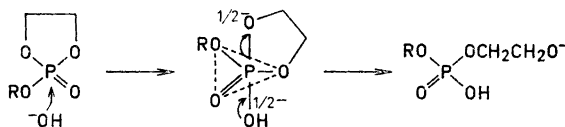
Steitz and Lipscomb [20] have recently shown that the O—P—O angle in the five-membered ring of 2-methoxy-2-oxy-1,3,2-dioxaphospholan is 99°, i.e. 10° less than the tetrahedral angle. An X-ray study performed at this institute [21] shows that the C—P—C angle in the phospholan ring of the phosphonium

iodide, $CH_2CH_2CH_2CH_2P^+(CH_3)Ph$ is $95 \pm 3°$. The reasonable assumption can be drawn from these bond angle data that the sp^3d-hybridized intermediate or transition state which the hydroxyl ion forms with pholan, oxaphospholan and dioxaphospholan esters as well as with the five-membered cyclic phosphonium cation, will have one of the α-pholan ring atoms (C or O) in equatorial position, the other (C or O) in apical position. When the phospholan ring contains an α-oxygen atom, this more electronegative atom will occupy the apical position in the transition state. According to this argument, in the transition state formed from the five-membered ethylphosphinate with no α-oxygen atoms in the ring (IV, Table 1) the leaving ethoxy group must occupy a more firmly bonding equatorial position, and no acceleration of the rate of hydrolysis would therefore be observed. The difference between the alkaline hydrolysis of the five-membered cyclic phosphinate ester and the corresponding five-membered cyclic phosphonium compound (scheme E) may be due principally to a different character of the collision complex, the latter compound forming a true pentacovalent intermediate. The leaving phenyl group which originally occupies an equatorial position in the sp^3d-hybridized intermediate may have time to exchange its position with the apical group and thus leave the intermediate through a favourable energy path:

Scheme E

With reference to rate scheme C it might be argued that the acid hydrolysis of the five-membered ethylphosphinate (IV) should show a rate increase relative to six-membered ring and open chain analogs since ^{18}O-exchange is usually observed in phosphoryl esters under acidic conditions,[3] which points to an intermediate during hydrolysis. However, data for hydrolysis in ^{18}O-enriched water of various phosphoryl esters seem to indicate C—O bond splitting.[3,22–24] We have performed some rate measurements of the acid catalysed hydrolysis of open chain and cyclic phosphinate esters. In 50 % ethanol-water mixture at 50°C the following rate data was obtained: $Et_2P(O)OEt$: 1.0×10^{-5} l mole^{-1} min^{-1}, $CH_2CH_2CH_2CH_2—P(O)OEt$: 1.2×10^{-5} l mole^{-1} min^{-1}. These very similar values are most probably due to preferential C—O bond rupture during hydrolysis. This assumption is strengthened by the fact that we have been unable to observe any ^{18}O-exchange in the phospholan ester and the corresponding phospholan oxide, $CH_2CH_2CH_2CH_2—P(O)CH_2CH_2CH_3$, in boiling acetonitrile containing 0.1 M

HCl and 0.2 M 87 % ^{18}O-enriched water. After 2 h in a pressure flask at 150°C exchange was observed for the pholan oxide.

The activation parameter data in Table 1 indicate that the different rates of hydrolysis of the various phosphoryl esters are chiefly due to different entropies of activation. The activation energy for the oxaphospholan (I) shows that the P—O bond in the phospholan ring may be approximately 2—2.5 kcal less stable than the P—O bond in the corresponding six- and seven-membered rings and open chain analogs. The assumption of Westheimer et al.[3,4] that the phospholan ring is strained seems therefore justified. The high rate of hydrolysis for this compound is, however, only partly due to release of strain during hydrolysis; the strongest effect is caused by a favourable entropy of activation. Both steric effects and solvation effects may contribute to this result.

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