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PHOSPHORUS-31 NUCLEAR MAGNETIC RESONANCE STUDIES OF CYCLIC DERIVATIVES OF PHOSPHORUS OXY-ACIDS[1]

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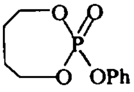
Abstract—Phosphorus-31 chemical shift data (δ ppm from 85% phosphoric acid) are reported for a series of 5- and 6-membered cyclic phosphites, phosphorochloridates, phosphates, phosphonates and phosphinates. Chemical shift differences between the cyclic and acyclic analogues in each of the series of phosphoryl compounds are $\Delta\delta_{5-a} \simeq -16$ ppm and $\Delta\delta_{6-a} \simeq +8$ ppm, while the phosphites have values of +3 and +9 respectively. The similar values of $\Delta\delta_{6-a}$ for all of the series, varying from two endocyclic P—O to two P—C bonds, indicates that a σ-bonding effect, steric in origin, is responsible for the shielding at phosphorus. The negative value of $\Delta\delta_{5-a}$ for the phosphoryl compounds indicates a significant deshielding at phosphorus on formation of the 5-membered ring. It is suggested that this results from "stereoelectronic" effects whose origins depend on the electronegativities of the ring-atoms bonded to phosphorus and which may well be related to the observed enchanced hydrolysis rates for P—O bond cleavage in 5-membered phosphoryl compounds containing an endocyclic P—O bond.

THE problem of rate enhancement in the acid and base catalyzed hydrolysis of 5-membered cyclic phosphorus esters over the acyclic and 6-membered analogues[2-6] has resulted in continuing interest in these compounds.[7-13] We now report details of a ^{31}PMR study of a comprehensive series of cyclic derivatives of phosphorus oxy-acids. The results enable us to probe further the nature of the ring-size chemical shift effects previously noted[1,14] and to relate this phenomenon to the chemical reactivity of these compounds.

RESULTS

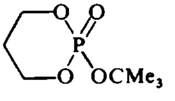
The ^{31}P chemical shift values for the individual compounds prepared are listed in Tables 1–4. The values for the phosphate and phosphite esters have been published previously,[1c] except for the following:

I§



+3·7
(CCl$_4$ solution)

II



+12·5

Mean chemical shift values for all of the series of compounds prepared in this work, as well as data from other sources, are listed in Table 5.

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DISCUSSION

(A) *The nature of the ring-size effect upon* ^{31}P *chemical shifts*

For each series of cyclic phosphoryl compounds studied the chemical shifts decrease in the order 6-membered > acyclic > 5-membered (Tables 1–4).[1] It is unlikely that changes in the shielding at phosphorus are due to changes in the P=O bond, since significant changes in the IR absorption frequency for this bond are not observed with changes in ring size for any of the classes of compounds studied.[1, 14]

Chemical shift differences in each of the series of phosphoryl compounds are $\Delta\delta_{5-a} \simeq -15$ to -19 and $\Delta\delta_{6-a} \simeq +7$ to $+11$ ppm (Table 5). The similar values for such a range of compound types varying from two P—O to two P—O endocyclic bonds, including the phostonates[5] as well as the cyclic phosphonates (Table 5), indicates no simple dependence of ^{31}P chemical shifts on variations in d_π–p_π bonding with ring size as previously had been tentatively suggested.[1, 24]

The theory of ^{31}P chemical shifts developed by VanWazer *et al.*[25, 26] divides the differences on substitution, $\Delta\delta$, into three parts,

$$\Delta\delta = C\Delta\chi OR - k\Delta n_\pi + A\Delta\alpha$$

where, $\Delta\chi OR$ is the difference in the Pauling electronegativity, Δn_π is the change in π-electron overlap, $\Delta\alpha$ is the σ-bond angle change and C, k and A are constants. For the phosphites A was calculated to be 21 and for the phosphates $A < 0{\cdot}1$. Since both the phosphites and phosphates give a similar value of $\Delta\delta_{6-a} \simeq +10$ ppm on formation of the 6-membered ring, it appears possible that the value of constant A varies from compound to compound within a group. The argument[25] from the chemical shifts of the caged compounds V and VI[27] (Table 6) that since $\Delta\delta_{c-a}$ VI > V then $A_{P(OR)_3} \gg A_{OP(OR)_3}$ does not appear valid since for the very similar compounds VII and VIII[27] the opposite holds and $\Delta\delta_{c-a}$ VII > VIII. Thus, while it would seem to be justified to neglect π-bond differences and, to a large extent, electronegativity differences in a homologous substitution series, the exact nature of the steric effect involved in determining ^{31}P chemical shifts does not appear to be simply explicable in terms of a group constant and an angular change.

In the case of phosphites, there appears to be little doubt that the changes in chemical shift can be attributed primarily to changes in bond angles.[25] In contrast, the origin of variations in the chemical shifts for phosphoryl compounds depends on the electronegativity of the remaining three ligand atoms. It is this factor which determines the relative contributions of bond angle, electronegativity, and π-bonding effects to chemical shift changes. The extensive investigations of VanWazer into this problem[26] permit a tentative analysis of the chemical shifts observed for the different classes of phosphoryl compounds under discussion.

The contribution of phosphorus p-orbital occupation to the chemical shift in species OPZ_3 is markedly dependent on the ZPZ bond angle in the case of carbon ($Z = C$, Pauling electronegativity 2·5) but is almost independent of this feature for oxygen compounds ($Z = O$, Pauling electronegativity 3·55).[28] From this analysis, the $\Delta\delta$ between phospholanes and phosphorinanes and for tetramethylene and pentamethylene cyclic phosphoniono-compounds results from changes in the CPC bond angle and is predicted to have a magnitude of 20–30 ppm.

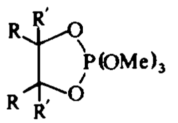
In contrast, for $OP(OR)_3$ systems there should be essentially no variation in chemical shift as a result of changes in the OPO bond angle *per se*. Thus the observed variations must result either from changes in the total occupation of the phosphorus d_π orbitals, perhaps induced by bond-angle alteration (a subject which still lacks proper theoretical attention), or from changes in σ-bond polarity. Presumably, mixed systems of $OP(OR)_nR'_{3-n}$ type will exhibit a variation in chemical shift which is some hybrid of these effects.

In contrast to our earlier tentative conclusion[1c] such changes would mean a *higher* occupation of d_π orbitals on phosphorus for 5-membered rings than for acyclic or 6-membered compounds.[29] Hence the consistent and significant deshielding of the 5-membered oxy-phosphoryl compounds must arise from a complex stereo–electronic effect.

There is considerable steric strain in certain 5-membered cyclic phosphates. Thus, the heat of hydrolysis of methyl ethylene phosphate exceeds that for dimethyl hydroxyethyl phosphate by 7–9 kcal/mole.[30] However, Hammes *et al.* have shown that for cytidine-2′,3′ phosphate there is essentially no thermodynamic ring strain.[31] The cyclic $\widehat{OPO}$ bond angle in structures determined by X-ray crystallography are all smaller (methyl ethylene phosphate,[7] 98·1°; methyl pinacol phosphate,[8] 98·4°; methyl acetoinenediol cyclophosphate,[29] 98·5°) than the expected tetrahedral angle (109°), and larger than the ideal pentagonal ring angle (i.e. $\widehat{OPO} = 540° - (2 \times 120°) - (2 \times 109°) \simeq 82°$). Calculations based on minimisation of bond angle and eclipsing strain in methyl ethylene phosphate, starting from known acyclic values, have given results[10] consistent with the known structure[7] though the effect of dihedral angle changes on the calculated results was small.[10]

MO calculations of the charge and energy distributions resulting from p–d orbital interactions in cyclic phosphates have also indicated an increased positive charge at phosphorus with increase in ring strain for the 5-membered ring compounds.[11,12] However, as has been pointed out from physical analysis above, the stereo-electronic ring-strain effect producing the observed deshielding at phosphorus need not be primarily a d-orbital effect.

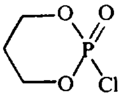
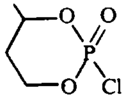
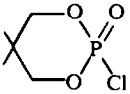
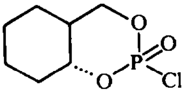
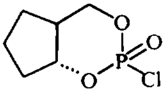
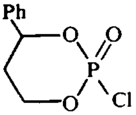
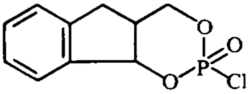
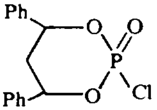
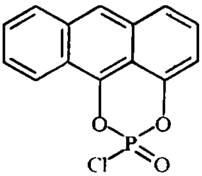
It is of interest to compare the chemical shift differences of the phosphates with those of the pentaalkoxyphosphoranes and other pentavalent species (Table 5). The value of $\Delta\delta_{5-a}$ deduced by comparison of $P(OEt)_5$[33] with compounds of the type (III) ($\delta \simeq +50$ ppm)[34] is -21. Furthermore, cyclisation in the series $P(OPh)_5$ results in $\Delta\delta_{5-a}$ of $-24{\cdot}8$ for the first ring and an additional $-31{\cdot}0$ for the second ring formed.[31]

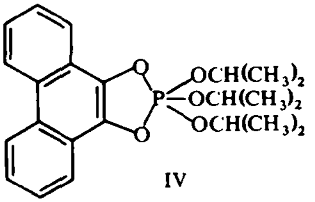


III: R, R′ = alkyl

Since the endocyclic $\widehat{OPO}$ angle of 89·3° in the crystalline phenanthrenequinone triisopropyl adduct IV[34] is very close to the value of 90° expected for the sp^3d hydrid, one might expect no significant deshielding due to angular distortion on formation of a 5-membered ring in pentaalkoxyphosphoranes. However, it has been pointed out that the pentaalkoxyphosphoranes are more (thermodynamically) stable when they have a 5-membered ring (including an unsaturated system), and this has been attributed to greatly reduced steric crowding[34] which could be expected to result in a relative deshielding at phosphorus.

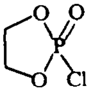
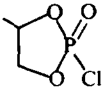
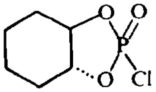
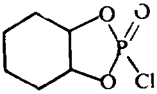
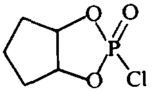
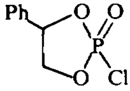
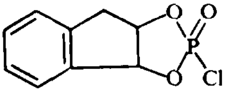
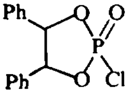
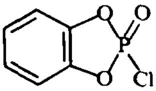
Table 1. ^{31}P Chemical shifts of 6-membered cyclic phosphorochloridates

	Solvent	δ
	Benzene	+ 2·8
	Neat liquid	+ 3·5
	CHCl$_3$	+ 5·7
	Dioxane	+ 4·5
	Dioxane/CHCl$_3$	+ 3·5
	Dioxane	+ 4·9
	CHCl$_3$	+ 4·9
	CHCl$_3$ Dioxane Benzene	+ 3·1 + 4·4 + 4·5
	Dioxane	+ 14·1



It is also noteworthy that the 7-membered ring compound I has a chemical shift very similar to the acyclic compound $OP(OC_4H_9)_2(OC_6H_5)$ ($\delta \simeq 4$).[35]

TABLE 2. ^{31}P CHEMICAL SHIFTS OF 5-MEMBERED CYCLIC PHOSPHOROCHLORIDATES

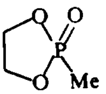
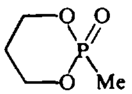
	Solvent	δ
	Neat liquid	−22·8
	Neat liquid	−22·4
	Dioxane	−17·7
	Dioxane	−21·1
	Dioxane	−22·4
	Dioxane	−19·4
	Dioxane	−19·8
	Dioxane	−14·5
	Benzene	−18·4*

* Provided by W. J. Haslam.

(B) *Relation of the deshielding at phosphorus to the reactivity of 5-membered cyclic compounds*

It is well known that 5-membered cyclic phosphates are thermodynamically less stable[30] and much more rapidly hydrolysed in acid or base than the acyclic or 6-membered phosphates[2–4] or the 5-membered cyclic phosphites.[24] Since of the P^{III} and P^{IV} compounds studied only the 5-membered cyclic phosphoryl compounds exhibit significant relative deshielding at phosphorus, there appears to be a *prima facie* correlation between these two phenomena. The observed deshielding at phosphorus can be related to a more positive phosphorus atom or to a more basic O atom and the presence of the ring is likely to reduce steric hindrance to solvent attack on phosphorus. Thus, electronic and steric factors would be expected to combine to produce greater susceptibility to nucleophilic attack.

TABLE 3. ^{31}P CHEMICAL SHIFTS OF PHOSPHONATES

	δ		δ
	−49		−25

Such an analysis suggests that the origin of hydrolytic reactivity of 5-membered cyclic phosphates and their acyclic and 6-membered relatives is to be found entirely in the energy differences between the ground state, as observed by ^{31}PMR, and the transition state, for which the pentaoxyphosphoranes provide good models.

However, the limited chemical shift data available for cyclic pentaoxyphosphoranes shows a similar trend of deshielding at phosphorus on contraction of a 6- to a 5-membered ring (Table 5). Application of VanWazer's theoretical analysis of chemical shifts in $P(OR)_5$ compounds[26] to this situation leads to the conclusion that there is greater d_π orbital occupation at phosphorus in the 5-membered ring oxyphosphoranes to the extent of some 0·2 electron. So this situation is close to that observed in the ground state for $OP(OR)_3$ systems.

Clearly, there are here two conflicting ideas. Either differences in d_π bonding in 5- and 6-membered ring phosphate esters are irrelevant to their hydrolytic behaviour or, alternatively, the pentacovalent oxyphosphoranes are in some respects less similar to the transition state than to the ground state in the hydrolytic process.

The success of pentaoxyphosphoranes as models for such transition states has largely hinged on their characteristics with respect to pseudorotation[36]—a hypothesis which has been most successful in rationalising isotope exchange phenomena,[3] product ratio distributions in phosphate ester hydrolysis,[4] and the lack of hydrolytic reactivity observed in other select phosphoryl compounds.[37, 38] This has directed attention away from the fact that acyclic phosphate esters, for which there appear no obvious origins of strain barriers to pseudorotation, hydrolyse as slowly as do 6-membered cyclic phosphate esters; also, hydrolytic retention of 5-membered rings is observed.[3] It is, therefore, pertinent to indicate that the *relief* of ring strain in going

TABLE 4. ^{31}P CHEMICAL SHIFTS OF PHOSPHINATES

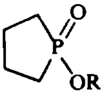
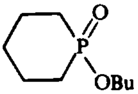
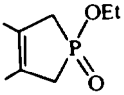
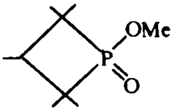
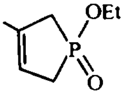
		δ		δ
	R = Et R = Bu	−70 −75		−45
		−63 ± 1 ppm (CCl$_4$ solution)		−52 (CCl$_4$ solution)
		−67 ± 2 ppm		

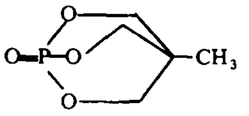
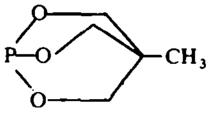
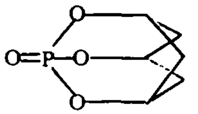
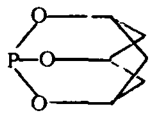
TABLE 5. ^{31}P CHEMICAL SHIFTS OF CYCLIC DERIVATIVES OF PHOSPHORUS OXY-ACIDS

Present work		δ ppm from 85% H$_3$PO$_4$ δ 5-memb.	δ acyclic	(R = alkyl) δ 6-memb.	$\Delta\delta_{5-a}$	$\Delta\delta_{6-a}$
Phosphite P(OR)$_3$		−135 ± 2	−138 ± 2	−127 ± 3	+3	+9
Phosphate OP(OR)$_3$		−15 ± 2	+0·5 ± 1·5	+8 ± 1	−15	+8
Phosphonates						
RP(O)(OR′)$_2$ (R acyclic)		−49	−33	−25	−16	+8
Phosphinates*						
R$_2$P(O)OR		−72 ± 2	−53	−45	−19	+8
Phosphorochloridates						
(RO)$_2$POCl		−19 ± 3	−3	+4 ± 1	−16	+7
Other work	Ref.					
Phosphorochloridites						
(RO)$_2$PCl	14	−167	−164	−153	−3	+11
Phostonate RP(O)(OR′)$_2$						
(R cyclic)	5	−49	−35	−23	−14	+12
Penta-alkoxy phosphorus P(OR)$_5$	33, 34	+50 ± 2	+71	+70	−21	−1
Fluorophosphorus R$_2$PF$_3$	40	−30	−6		−24	
Phosphonium salts						
R$_2$P$^+$(CH$_2$R)$_2$	26, 28	−45	−26	−22	−19	−4
Spiropenta-alkoxy phosphorus	41	+30	+49	+53	−19	+4

* In an independent study Dennis[39] found a value of −24 for $\Delta\delta_{5-a}$.

from 5-membered cyclic phosphate to a strainless pentacovalent intermediate may account for some but *does not account for all of the rate enhancement.* The discrepancy between the measured ring strain in methyl ethylene phosphate (5·5 kcal M^{-1})[24] and the observed rate enhancement of hydrolysis relative to trimethyl phosphate shows that the cyclic transition state is more stable than the acyclic one by some 2–3′ kcal M^{-1}. Moreover, the observation[31] that not all 5-membered phosphate esters possess this measure of ring strain implies that this may be a minimum value for the *stabilisation* of the hydrolytic transition state through the presence of a 5-membered ring.

TABLE 6

		δ	Δ_{c-a}
V[27]		+8	+1
VI[27]		−92	+45
VII[27]		+10	+9
VIII[27]		−137	0

This discussion of the present situation leads to no firm conclusion. But it appears distinctly possible that the electronic deshielding of phosphorus revealed by the ^{31}PMR technique may still indicate the origin of the unusual reactivity of cyclic phosphate esters. It undoubtedly points to the need for a better understanding of the transition state for their hydrolyses.

Acknowledgements--We thank Professor Lord Todd for his initial interest in and support of this work, E. A. Dennis for a copy of his thesis, and J. R. VanWazer and G. C. K. Roberts for helpful discussions.

EXPERIMENTAL

Triethyl, trimethyl and diethyl phosphites were obtained from Albright and Wilson, and were distilled before use.

Detailed descriptions of the preparations of the many compounds studied in the course of this work will be found in refs 1 *a* and *b*. Cyclic alkyl phosphites were synthesised by modifications of the methods of

Oswald[15] and Wadsworth and Emmons.[16] The corresponding cyclic alkyl phosphates were prepared from these by oxidation.[17] Thymidine-3′,5′ cyclic phosphate was prepared by the method of Khorana[18] and cytidine-2′,3′ cyclic phosphate by that of Michelson.[19] In each case treatment with ethereal diazomethane gave the respective methyl ester. The cyclic phosphonates were synthesised from methyl phosphonodichloridate and a diol.[20] The cyclic phosphinates[21] and phosphorochloridates[22,23] were prepared by modifications of published methods.

Satisfactory elemental analyses were routinely obtained for the compounds synthesised[1] (Tables 1–4). Several techniques were used to characterise the products, including IR, UV and PMR spectroscopy and paper, thin-layer and gas-liquid chromatography. The physical properties of the compounds are described elsewhere.[1]

^{31}PMR spectra were recorded using a Varian 4300B spectrometer operating at 16·2 MHz, using 10 mm samples. Chemical shifts are given in ppm relative to 85% phosphoric acid in capillary inserts to the external reference. The reproducibility was ±1 ppm.

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