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Dependence of ^{31}P Chemical Shifts on Oxygen–Phosphorus–Oxygen Bond Angles in Phosphate Esters

Sir:

We propose an empirical correlation between phosphate ^{31}P chemical shifts and O–P–O bond angles. That some such bond angle relationship probably exists for cyclic phosphate esters has been recognized,[1-3] but a direct bond angle relationship for all classes of phosphate esters has not been established.

Any successful theory must accommodate several apparently conflicting pieces of data. (1) The ^{31}P chemical shift of phosphates is generally insensitive to the chemical identity (R or H) of the group bonded to the phosphate oxygen. (2) The chemical shift is sometimes sensitive to the ionization state of the acid. (3) Association of divalent metal ions[4] and hydrogen bonding donors[5,6] has little effect on the ^{31}P chemical shift other than that explained by a shift in the p*K*. (4) Cyclic five-membered ring phosphate esters are shifted downfield from their acyclic counterparts by 15–20 ppm while cyclic six-membered ring esters are shifted *upfield* by 2–11 ppm from their acyclic analogs.

Several authors have attempted to create a unified theoretical foundation for ^{31}P chemical shifts in all classes of phosphorus compounds.[3,7-9] In one of the more successful theoretical approaches, Van Wazer and Letcher,[3,10] using quantum-mechanical calculations, demonstrate that three factors appear to dominate the ^{31}P chemical shift: electronegativity differences in the P–X bond, changes in the π-electron overlap, and changes in the σ-bond angle.

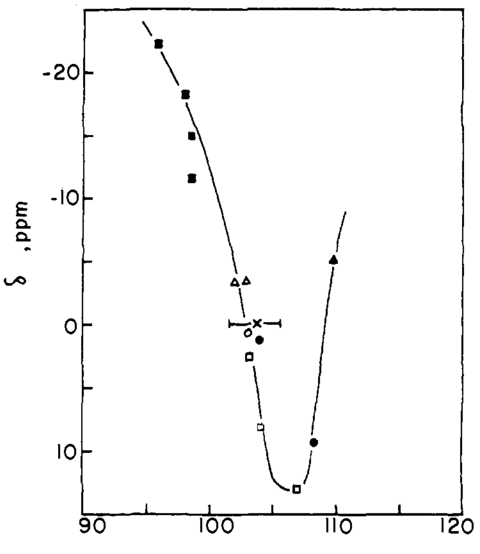

Figure 1. ^{31}P chemical shift of phosphate esters *vs.* O–P–O bond angle (■, five-membered cyclic esters; △, monoester dianions; ×, monoester monoanions; ○, acyclic diester monoanions; ●, acyclic diester free acids; □, six-membered cyclic esters; ▲, Li_3PO_4). Solid line has no theoretical significance.

For phosphoryl compounds Van Wazer concludes that changes in the σ-bond angles make a negligible contribution to the ^{31}P chemical shift,[10] with electronegativity effects apparently predominating.[3] Purdela claims establishing a correlation between X–P–X bond angles and chemical shifts for a wide variety of phosphoryl compounds, however, admitting that the correlation is poor.[9] Westheimer[1] and others[2] have argued that the O–P–O ring angle must play some role in ^{31}P chemical shifts on the basis of cyclic ester shifts, which is inconsistent with Van Wazer's theory. A change in dπ–pπ bonding resulting from bond angle changes was suggested as an explanation for these shifts. Recently Blackburn,[2] compiling all of the known cyclic ester chemical shifts, concluded that these ring shifts must arise from a "complex stereoelectronic effect" not explicable by present theory.

In Table I we have compiled nearly all of the X-ray crystallographic data on phosphates for which a ^{31}P chemical shift is known. The reported O–P–O bond angle shown in Table I is generally that between two phosphate oxygens which are either protonated or esterified. In triesters and monoester dianions they represent the cyclic or(for noncyclic esters) the smallest O–P–O bond angle in the structure.

A plot of ^{31}P chemical shift *vs.* O–P–O bond angle is shown in Figure 1 and demonstrates that a quite simple empirical correlation may be drawn relating the chemical shifts and bond angles of phosphate esters. (We make no claim for applicability of this correlation to other classes of phosphoryl compounds.) Although bond angles in the solid state may significantly differ from those in solution due to crystal packing forces, a simple Gillespie–Nyholm[11] analysis of electron pair repulsions in the phosphates would suggest that these solid-state angles do reflect the expected distortions from tetrahedral symmetry.

Further support for the correlation that we have drawn here is derived from the "anomalous" shifts of the cyclic *vs.* acyclic monoanions and free acids. In the acyclic phosphate

Table I. ^{31}P Chemical Shifts and O–P–O Bond Angles in Phosphate Esters

Compound	$\delta_{^{31}P}{}^{a}$ (ppm)	O–P–O angles^{b} (deg)
	Five-Membered Cyclic Phosphates	
2′,3′-Cyclic cytidine monophosphate (pH2–4)	-20.3^{c}	95.7^{d}, 96.0^{d}
Methyl ethylene phosphate	-18.2^{e}	98.1^{f}
Methyl pinacol phosphate	-15^{g}	98.4^{h}
Methyl acetoinenediol cyclophosphate	-11.5^{i}	98.5^{j}
	Monoesters (dianionic)	
Calcium 5′-thymidine monophosphate	-3.4^{k}	102^{l}
Barium 5′-uridine monophosphate	-3.6^{m}	103^{n}
	Monoesters (monoanionic)	
3′-Cytidine monophosphate	0.0^{o}	101.5^{p} (orthorhombic) 104.3^{q} (monoclinic)
3′-Adenosine monophosphate	0^{t}	103.4^{r}
5′-Adenosine monophosphate	0^{t}	105.7^{s}
2-Aminoethanol phosphate	0^{t}	103.9^{u}
1-Naphthyl phosphate	0^{t}	104.4^{v}, 105.2^{v}
	Acyclic Diesters (monoanionic)	
dG-3′,5′-C (pH5–8)	$+0.5^{w}$	103^{x}
U-3′,5′-A		100.3^{y}, 102.3^{y}
	$>0^{t}$	100.6^{z}, $104.6^{y,z}$
U-5′,2′-A	0^{t}	103^{aa}
Barium diethyl phosphate	$+0.5$ to -3.8^{jj}	103.5^{bb}
$H_2PO_4^-$	-0.4^{hh}	103.8^{cc}
	Acyclic Diesters (free acid)	
Dibenzyl phosphate	$+1.1^{dd}$	104^{ee}
Bis(*p*-chlorophenyl)phosphate	$+9.4^{ff}$	$108.1\ (106.5)^{gg}$
	Cyclic Six-Membered Ring (diester monoanion)	
3′,5′-Cyclic uridine	$+2.6^{hh}$	102.7, 103.5^{ii}
	Triesters	
Triphenyl phosphate	$+17.3$ to $+18.6^{jj}$	96.6, 104, 104^{kk}
Phenyl trimethylene phosphate	$+13^{jj}$	$107\ (102)^{mm}$
$CH_3C(CH_2O)_3PO$	$+8^{jj}$	104^{ll}
	Others	
Li_3PO_4	-5 to -6^{jj}	109.7^{nn}

[a] Chemical shift *vs.* 85% H_3PO_4. [b] Either R(H)O–P–OR(H) angle or smallest OPO angle. Error generally ±0.5°. [c] D. G. Gorenstein, A. M. Wyrwicz, and J. Bode, to be submitted. [d] C. L. Coulter, *J. Am. Chem. Soc.*, **95,** 570 (1973). [e] E. Dennis, Ph.D. Thesis, Harvard University, 1967; F. Ramirez, A. V. Patwardhan, H. J. Kugler, and C. P. Smith, *Tetrahedron Lett.*, 3053 (1966). [f] T. A. Steitz and W. N. Lipscomb, *J. Am. Chem. Soc.*, **87,** 2488 (1965); X. Chiu and W. N. Lipscomb, *ibid.*, **91,** 4150 (1969). [g] Estimated value. See ref 2. [h] M. G. Newton, J. R. Cox, Jr., and J. A. Bertrand, *J. Am. Chem. Soc.*, **88,** 1503 (1966). [i] F. Ramirez, O. P. Madan, and C. P. Smith; *J. Amer. Chem. Soc.*, **87,** 670 (1965). [j] D. Swank, C. N. Caughlan, F. Ramirez, O. P. Madan, and C. P. Smith, *J. Am. Chem. Soc.*, **89,** 6503 (1967). [k] Chemical shift for deoxy-5′-thymidine monophosphate. M. Mandel and J. W. Westley, *Nature (London)*, **203,** 302 (1964). [l] K. N. Trueblood, P. Horn, and V. Luzzati, *Acta Crystallogr.*, **14,** 965 (1961). [m] Chemical shift of 3′-uridine monophosphate (ref *c*). [n] E. Shefter and K. N. Trueblood, *Acta Crystallogr.*, **18,** 1067 (1965). [o] D. G. Gorenstein and A. M. Wyrwicz, to be submitted. [p] M. Sundaralingam, *J. Mol. Biol.*, **13,** 914 (1965). [q] C. E. Bugg and R. E. Marsh, *ibid.*, **25,** 67 (1967). [r] M. Sundaralingam, *Acta Crystallogr.*, **21,** 495 (1966). [s] J. Kraut and L. H. Jensen, *ibid.*, **16,** 79 (1963). [t] Estimated. [u] J. Kraut, *Acta Crystallogr.*, **14,** 1146 (1961), 106.2° for ROPOH angle. [v] C. Li and C. N. Caughlan, *ibid.*, **19,** 637 (1965). Two crystalline modifications, for RO–P–OH angle. [w] D. J. Patel, *Biochemistry*, **13,** 2388, 2396 (1974); chemical shift *vs.* 16% H_3PO_4. [x] R. O. Day, N. C. Seeman, J. M. Rosenberg, and A. Rich, *Proc. Nat. Acad. Sci. U. S.*, **70,** 849 (1973). [y] J. Rubin, T. Brennan, and M. Sundaralingam, *Biochemistry*, **11,** 3112 (1972); two crystalline forms. Larger angle for a folded structure is likely to be found in solution. [z] J. L. Sussman, N. C. Seeman, S. M. Kim, and H. M. Berman, *J. Mol. Biol.*, **66,** 403 (1972). [aa] E. Shefter, M. Barlow, R. A. Sparks, and K. N. Trueblood, *Acta Crystallogr.*, **25,** 895 (1969). [bb] Y. Kyogoku and Y. Iitaka, *ibid.*, **21,** 49 (1966). [cc] I. L. Karle and K. Britts, *ibid.*, **20,** 118 (1966). [dd] M. L. Nielsen, J. V. Pustinger, and J. Strobel, *J. Chem. Eng. Data*, **9,** 167 (1964). [ee] J. D. Dunitz and J. S. Rollett, *Acta Crystallogr.*, **9,** 327 (1956). [ff] Chemical shift for diphenyl ester (see ref *dd*). [gg] M. Calleri and J. C. Speakman, *Acta Crystallogr.*, **17,** 1097 (1964). ROPOH bond angle is 106.5°. [hh] Chemical shift of 3′,5′-cyclic adenosine monophosphate. Private communication, D. G. Gorenstein and A. M. Wyrwicz. [ii] C. Coulter, *Acta Crystallogr., Sect. B*, **25,** 2055 (1969). [jj] Referenced in Crutchfield, Dungan, Lechter, Mark, and Van Wazer, *Top. Phosphorus Chem.*, **5,** (1967). [kk] G. W. Svetich and C. N. Caughlan, *Acta Crystallogr.*, **19,** 645 (1965). Authors indicate asymmetry is due to packing forces. [ll] D. M. Nimrod, D. R. Fitzwater, and J. G. Verkade, *J. Am. Chem. Soc.*, **90,** 2780 (1968). [mm] H. J. Geise, *Recl. Trav. Chim. Pays-Bas*, **86,** 362 (1967). Small angle in parentheses PhO–P–O–ring. Other ring O to O-phenyl angle is 107°. [nn] J. Zemann, *Acta Crystallogr.*, **13,** 863 (1960).

esters little shift of the ^{31}P signal is observed upon ionization of the free acid. If electronegativity played an important role in these shifts, this would be a difficult result to rationalize. It is, however, consistent with our O–P–O bond angle hypothesis since in unstrained phosphate mono- and diesters the O–P–O bond angle is the same (*ca.* 103–104°) in both the free acid and monoanion, and therefore no shift is expected in the ^{31}P signal. Ionization of a second proton results in a significant reduction in the bond angle (to *ca.* 102°) and hence a downfield shift (*ca.* 4 ppm).

Most significantly, the monoanions of the five- and six-membered ring esters are shifted downfield by 2–10 ppm from the neutral cyclic esters. This must again be a ring angle effect since the O–P–O ring angle is smaller by *ca.* 2° in the monoanions.

If, indeed, a simple relationship exists between bond angles and ^{31}P chemical shifts, with other factors playing a minor role, then these shifts may in turn be used to define solution structures. For example, Patel[12] has recently noted a substantial downfield shift (1.7 ppm) of the diester phosphate signal in a Watson–Crick type d-pGpC dimer upon complexation with the DNA inhibitor, Actinomycin D. Jain and Sobell[13] have proposed a model for this complex based upon related crystallographic data which has the aromatic ring of the actinomycin intercalated between the stacked, base pairs of the dimer. In their model this requires an expansion of the O–P–O diester bond to *ca.* 113°. Although our correlation would suggest an O–P–O bond angle of 109–110°, qualitatively, these results are in agreement. It may be possible now to utilize ^{31}P nmr spectroscopy to define structures of more complex phosphate esters, particularly the biochemically important nucleotides, including possibly small tRNA's[14] and DNA fragments.

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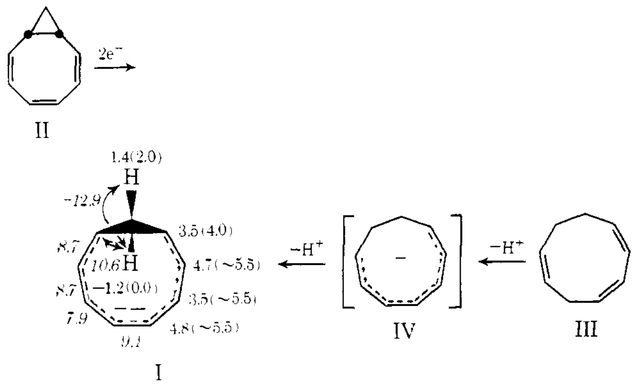
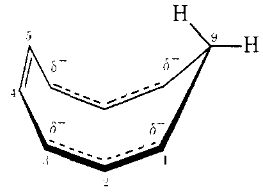
Homocyclooctatetraene Dianion: Preparation by Dimetalation; Geometry[1]

Sir:

The preparation of the title substance I by reduction of II with metallic potassium, and pmr shifts which supported the proposed structure, were reported in 1966.[2] We have found that I can readily be prepared as the dilithium salt by dimetalation of (*Z,Z,Z*)-1,3,6-cyclononatriene (III);[3] its proton–proton coupling constants help to reveal its geometry.

III is not metalated by *n*-butyllithium in THF, but in TMEDA III reacts to give a tan precipitate which is quite soluble in THF-d_8.[4] Quenching by addition to excess methanol at −78° gave back III in almost quantitative yield. Quenching with D_2O gave III containing by mass spectrometry 82.4% d_2, 12.8% d_1, and 4.8% d_0; pmr spectrometry showed this largely dideuterated material to be monodeuterated at C5 and also at either C8 or C9.[5] This is exactly the result expected from the quenching of I.





V

The ^1H nmr spectrum of this substance in THF-d_8 at 35° shows a ~1:1:1:1 quartet for 2 H at δ 4.8 (spacings 3.0, 2.5, and 3.0 Hz), a 1:2:1 triplet for 2 H at δ 4.7 (J = 8.7 Hz), a complex multiplet for 4 H at δ 3.5, and a doublet (J = 12.9 Hz) of triplets (J = 10.6 Hz) for 1 H at δ −1.2.[6] This is clearly not the ^1H nmr spectrum of the monoanion IV.[7] The shifts also differ considerably from those reported[2] for the dipotassium salt of the dianion I and given in δ units in parentheses on structure I. However, the dipotassium salt of I had very low solubility in THF and DME, and time averaging was used to obtain these shifts; no coupling constants were reported. Our pmr assignments for the much more soluble dilithium salt are shown on formula I (italicized numbers are coupling constants in hertz). They are supported by decoupling experiments: irradiation at δ 3.5 collapses the quartet at δ 4.8 and the triplet at δ 4.7 to singlets and the multiplet at δ −1.2 to a doublet; irradiation of a TMEDA-obscured proton at δ 1.4 reduces the multiplet at δ −1.2 to a triplet. The coupling constants J_{34} (=J_{56}) and J_{45} are not directly measurable from the spectrum, but were calculated by treating H3-H6 as an AA′XX′ system.[8] Using the position of a small line 10.4 Hz to the left of the center of the pattern for H4 and H5, the values shown for J_{45} and J_{34}(=J_{56}) were calculated, and in addition, J_{36} = 0 and J_{35} = J_{46} = +0.6 Hz. The small line was calculated and observed to be about 11% as intense as the largest line in the pattern.

These coupling constants provide further evidence regarding the geometry of this dianion. The −12.9 Hz (sign assumed) coupling between the methylene protons is much too large for geminal protons in a three-membered ring[9] and rules out norcaradiene-like structures. The angle-strainless boat conformation V, analogous to the conformation of cycloheptatriene (homobenzene) favored in the vapor state,[10] is excluded since J_{34} = 7.9 Hz, far larger than the value of 0–1 Hz expected for V.[11] The similarity of vicinal coupling constants J_{12}, J_{23}, J_{34}, and J_{45} suggests a similar degree of twist about the corresponding carbon–carbon bonds around the ring. Since these values are all slightly below the value anticipated for a structure with C1–C8 coplanar,[12] it is likely that C1–C8 are not coplanar, but instead some twist is present about each of the bonds in the ring.