Communications

Axial Preference of 2-[1,3]Dithianyldiphenylphosphine Oxide. A Strong S–C–P Anomeric Interaction†

Summary: Spectroscopic evidence indicates a *predominantly axial* conformation of 2-[1,3]dithianyldiphenylphosphine oxide. X-ray diffraction data confirm the axial orientation of the diphenylphosphinoyl substituent and, therefore, the existence of a strong S–C–P anomeric interaction.

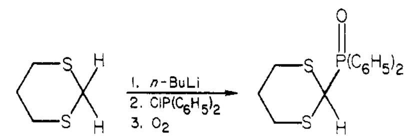
Sir: The tendency of an electronegative substituent to assume the axial rather than equatorial orientation at C(1) of a pyranoid ring has been termed "the anomeric effect" by Lemieux.[1] This conformational effect is not restricted to carbohydrate systems, and evidence for its existence in many heterocyclic systems has been recorded.[2] Although comparison of the anomeric interaction in X–C–Y systems, where X = O, S, F, Cl, Br, N, and Y = O, S, has been performed either theoretically[3] or experimentally,[4] there has been, to our knowledge, no evaluation of the S–C–P anomeric interaction.

In connection with current work,[5] we recently prepared the title dithiane (Scheme I). Assignment of its proton NMR spectrum[6] offers evidence of a very large (ca. 1.2 ppm) chemical shift difference between axial and equatorial protons at C(4,6). [By comparison, $\Delta\delta_{ax/eq}(H_{4,6})$ in 2-*tert*-butyl-1,3-dithiane[7] is ca. 0.09 ppm.] That the signals at 3.70 and 2.50 ppm correspond to the axial and equatorial protons, respectively, was confirmed by irradiation at 3.70 ppm causing the signals at 2.50 ppm to loose the gem coupling, since it collapsed into a triplet (J_{gauche} = 4.5 Hz). Similarly, irradiation at 2.05 ppm modified the signals at 3.70 and 2.50 ppm into an AB quartet (J_{gem} = 14.4 Hz).

These spectroscopic observations are evidence for a deshielding effect of a *predominantly axial* phosphoryl group on the syn-axial $H_{4,6}$ (Scheme II).

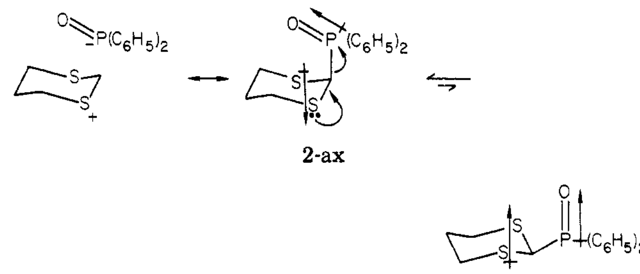
Support for this reasoning comes from the observation that the downfield shifting produced by the addition of $Eu(fod)_3$ is in the order $H_{4,6}$(axial) > H_2 > $H_{4,6}$(equatorial) > H_5. Observation of Dreiding models indicates that this result is only possible if one assumes the axial orientation

Scheme I



1 2

Scheme II



2-ax

2-eq

for the phosphoryl group, being the P–O bond above the dithianyl ring.[8]

We had, therefore, clear evidence for a strong anomeric interaction between two second-row elements: sulfur and phosphorus. This anomeric interaction is particularly interesting because in contrast with the reported examples of this conformational effect,[2] the axial substituent is fully bonded (there is no lone-electron pairs on Y), and the steric interactions with syn-axial hydrogens should be more important (compared with, for example, OR, SR, Cl, etc.).

Definitive evidence for the stereostructure of 2 was obtained by single-crystal X-ray diffraction. A crystal measuring approximately 0.15 × 0.25 × 0.60 mm was used to collect intensity data on a Nicolet R3m/E autodiffractometer system within the angular range 0.0° < 2θ < 116°, using monochromated Cu Kα radiation and the Nicolet standard data collection procedure.[9] Least-squares analysis of the setting angles of 25 reflections with a good distribution throughout reciprocal space provided the unit cell dimentions: a = 12.304 (2), b = 5.6311 (8), c = 22.826 (3) Å, β = 99.84 (1)°, V = 1558.3 Å^3 with Z = 4 and d_{calcd} = 1.366 g cm^{-1}. Systematic absences unambiguously indicated the monoclinic space group $P2_1/c$. Of the 2987 independent reflections measured, 983 had intensities less than 2.5σ (F_o) and were not used in the refinement. The remaining 2004 reflections were corrected for Lorentz and polarization effects and used to solve and refine the structure.

Positions of all non-hydrogen atoms were located by using the direct methods program available as part of the SHELXTL package.[10] These positions were refined to convergence with use of isotropic thermal parameters.

† Dedicated to Professor Ernest L. Eliel, on the occasion of his 60th birthday.

(1) Lemieux, R. U.; Chu, N. J. "Abstracts of Papers", 133rd National Meeting of the American Chemical Society, San Francisco; American Chemical Society: Washington, DC, 1958; N-31.

(2) Eliel, E. L. *Acc. Chem. Res.* **1979**, *3*, 1–8. Eliel, E. L. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 739–750. Lemieux, R. U. *Pure Appl. Chem.* **1971**, *25*, 527–548.

(3) Wolfe, S.; Whangbo, M.-H.; Mitchell, D. J. *Carbohydr. Res.* **1979**, *69*, 1–26.

(4) Eliel, E. L.; Juaristi, E. "Anomeric Effect, Origin and Consequences"; American Chemical Society: Washington, DC, 1979; ACS Symp. Ser. No. 87, pp 95–106, and references cited therein.

(5) Juaristi, E.; Valle, L.; Mora, C. "Abstracts of Papers", 183rd National Meeting of the American Chemical Society, Las Vegas; American Chemical Society: Washington, DC, 1982; ORGN-69.

(6) Data for 2: mp 242–243 °C; ^{1}H NMR (90 MHz, $CDCl_3$; Me_4Si) δ 2.05 (m, 2 H), 2.5 (d of t, J_{gem} = 14.4 Hz, J_{gauche} = 4.5 Hz, 2 H), 3.7 (m, 2 H), 4.0 (d, $^2J_{P\text{-}C\text{-}H}$ = 6 Hz, 1 H), 7.3–8.0 (m, 10 H); ^{13}C NMR (25.2 MHz, $CDCl_3$; Me_4Si) δ 24.9 (s, $CH_2(CH_2S)_2$), 27.0 (s, 2 CH_2S); 37.5 (d, $^1J_{CP}$ = 69.6 Hz, SCHS), 128.3 (d, $^3J_{CP}$ = 12 Hz, meta C), 131.1 (d, $^2J_{CP}$ = 8.6 Hz, ortho C), 131.7 (d, $^4J_{CP}$ = 2.5 Hz, para C), 132.2 (d, $^1J_{CP}$ = 102 Hz, ipso C); MS, *m/e* 320 (M^+), 201 (M^+ – 119), 119 (M^+ – 201); IR 3080 (m), 2890 (s), 1445 (s), 1190 (vs) cm^{-1}. Anal. Calcd for $C_{16}H_{17}OPS_2$: C, 59.98; H, 5.35; P, 9.67; S, 20.01. Found: C, 60.16; H, 5.30; P, 9.56; S, 20.18.

(7) Prepared according to: Eliel, E. L.; Hutchins, R. O. *J. Am. Chem. Soc.* **1969**, *91*, 2703–2715.

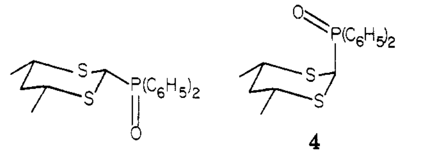
(8) It is reasonable to assume that complexation of 2 with $Eu(fod)_3$ takes place on the oxygen: Mosbo, J. A.; Verkade, J. G. *J. Am. Chem. Soc.* **1973**, *95*, 4659–4665. Burdett, J. L.; Burger, L. L. *Can. J. Chem.* **1966**, *44*, 111–118.

(9) Campana, C. F.; Shepard, D. F.; Litchman, W. M. *Inorg. Chem.* **1981**, *20*, 4039–4044.

(10) Sheldrick, G. M. "Nicolet SHELXTL Operations Manual"; Nicolet XRD Corp.: Cupertino, CA, 1981.

0022-3263/82/1947-5038$01.25/0

Scheme III



3 4

Idealized hydrogen positions were calculated and tied to the associated non-hydrogen positions through a riding model for the remainder of the refinement. Final refinement of 20 non-hydrogen atoms using anisotropic thermal parameters and 17 hydrogen atoms using isotropic thermal parameters gave residual values of $R_1 = 0.049$ and $R_2 = 0.067$ where $R_1 = \sum||F_o| - |F_c||/\sum|F_o|$ and $R_2 = [\sum\omega(|F_o| - |F_c|)^2/\sum\omega|F_o|^2]^{1/2}$.

A perspective view of the molecular structure is shown in Figure 1 (supplementary material). The heterocyclic six-membered ring exists in a chair conformation with the substituent at C(1) being axial. The plane containing S(1), S(2), C(2), and C(4) bisects that passing through C(2), C(3), and C(4) at 58.1° and the S(1), C(1), S(2) plane at 54.1°. The two latter planes are almost parallel, forming an angle of 4.1°. The oxygen atom is centered above the heterocyclic ring and the two phenyl ring planes bisect at 85.8°. Bond distances and bond angles (supplementary material) within the molecule are consistent with those expected from the molecular geometry.

In an attempt to quantitate this conformational effect, the anancomeric derivatives 3 and 4 (Scheme III) were prepared,[11] and their proton NMR spectra were compared with that for 2. Most interestingly, the coupling constant of H_2 to phosphorus in 2, 3, and 4 varies considerably: 6, 15, and 4.2 Hz, respectively. On the assumption that $^2J_{H(2)/P}$ in the mobile dithiane (2) is the weighed average of those for the model diastereomers 3 and 4,[12] then $K = (J_{ax} - J)/(J - J_{eq}) = 5.0$, which affords $\Delta G° \simeq 1.0$ kcal/mol, for the free energy difference favoring 2-ax over 2-eq.

Most commonly, the anomeric effect has been rationalized in terms of stabilization by (1) dipole–dipole interaction[13] and (2) delocalization of the lone pair on the endocyclic heteroatom into the antiperiplanar (axial) adjacent polar bond[15] (Scheme II). So far, we have not found supporting evidence for either mechanism.[16] On the one hand, if dipole–dipole interactions were operative here, it would be expected that the contribution of 2-eq should increase with increasing dielectric constant of the medium.[18] However, little change was observed for the proton NMR spectra of 2 [e.g., fairly similar $\Delta\delta_{ax/eq}(H_{4,6})$] in solvents of different polarity[19] (Table I).

Table I. Solvent Effect on the Chemical Shift Difference ($\Delta\delta_{ax/eq}$) for the C(4,6) Methylene Protons

solvent	ϵ^a	$\Delta\delta$, ppm
$CDCl_3$	4.7	1.19
$CD_3CO_2D^b$	6.2	1.05
$CD_3COCD_3{}^b$	20.7	1.36
CD_3OD^b	32.6	0.94
DMF-d_7	36.7	1.22
CD_3CN	37.5	1.04

[a] Dielectric constant for protiated solvents. [b] Due to low solubility in this solvent, the measurement was performed by pulse FT NMR at 100.1 MHz, using a (PD, 180°, τ, 90°, AT)$_n$ sequence to eliminate the solvent signal.

On the other hand, n_S/σ^*_{C-P} interaction (Scheme II) in 2-ax should result in a shorter than normal sulfur–anomeric carbon bond and a longer than normal axial carbon–phosphorus bond.[15] This is not the case, though. Both the sulfur–anomeric carbon (1.809 ± 0.012 Å) and the carbon–phosphorus (1.825 ± 0.003 Å) bond distances appear normal.

Registry No. 1, 505-23-7; 2, 83476-36-2; 3, 83463-92-7; 4, 83509-98-2; $ClP(C_6H_5)_2$, 1079-66-9.

Supplementary Material Available: Listings of atomic coordinates, anisotropic thermal parameters for all non-hydrogen atoms, isotropic thermal parameters for hydrogen atoms, observed and calculated structure factors, bond distances and bond angles, and an ORTEP drawing (15 pages). Ordering information is given on any current masthead page.

(11) Full details with be published separately.

(12) Also, it has to be assumed that the methyl substituents at C(4,6) have a negligible effect on the value of the coupling constant between the nuclei at C(2).

(13) Edward, J. T. *Chem. Ind. (London)* 1955, 1102–1104. See also ref 14.

(14) Jeffrey, G. A.; Pople, J. A.; Radom, L. *Carbohydr. Res.* 1972, 25, 117–131.

(15) Romers, C.; Altona, C.; Buys, H. R.; Havinga, E. *Topics Stereochem.* 1969, 4, 39-97. See also ref 14.

(16) The mechanism responsible for this conformational effect should be worth ca. 2.25 kcal/mol; i.e., the sum of the axial preference of the phosphinoyl group (ca. 1.0 kcal/mol, see text) and the value of the steric repulsion present in the axial orientation (E_v = 1.25 kcal/mol; estimated from the structural data, by means of the Hill equation[17]).

(17) Hill, T. L. *J. Chem. Phys.* 1948, 16, 399–404.

(18) See, for example: Eliel, E. L.; Giza, C. A. *J. Org. Chem.* 1968, 33, 3754–3758.

(19) The possibility exists that alternative C(2)–P rotamers, which in relation to the dominant conformer are on steric and/or dipolar grounds slightly more destabilized and which may become only modestly populated over the polarity range studied, are responsible for the small variations observed in Table I.[20]

(20) We thank one of the reviewers for this suggestion.

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Deuterium Isotope Effects and the Mechanism of Kinetic Enolate Formation[1]

Summary: The reaction of lithium diisopropylamide with 2-methyl-3-pentanone in tetrahydrofuran at 0 °C occurs with a deuterium isotope effect of 5.1 at the 2-position but only of 0.9 at the 4-position, suggesting a mechanism of at least two steps in which the proton transfer need not always be the slow step.

Sir: We present evidence that the mechanism of kinetic enolate formation involves at least two steps and that the proton-transfer step is not always rate determining. By "kinetic enolate" we mean the product of irreversible attack

(1) This work was supported by the National Science Foundation.

