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Conformational Analysis of 2-(Diphenylphosphinoyl)-tetrahydrothiopyran: Lack of Additivity of the S-C-P Anomeric Effect[†]

Mario Ordóñez and Eusebio Juaristi*

Departamento de Química, Centro de Investigación y de Estudios Avanzados
del Instituto Politécnico Nacional, Apartado Postal 14-740,
07000 México, D.F., México.

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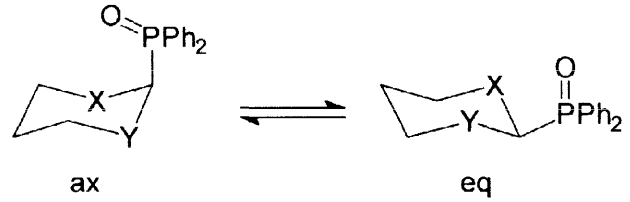
Abstract. The conformational preference of the diphenylphosphinoyl group at the alpha position in the thiane ring was estimated by low temperature NMR, $\Delta G^{\circ}_{173K} = +\ 0.46 \pm 0.11$ kcal/mol, and at 50°C, via chemical equilibration of anancomeric models, $\Delta G^{\circ}_{323K} = -\ 0.26 \pm 0.10$ kcal/mol. These thermodynamic data allowed the estimation of the enthalpic and entropic contributions to the axial $\rightleftharpoons$ equatorial conformational equilibrium of 2-(diphenylphosphinoyl)thiane, $\Delta H^{\circ} = +\ 1.29 \pm 0.12$ kcal/mol, and $\Delta S^{\circ} = +\ 4.8 \pm 0.7$ cal/K·mol. Comparison of the enthalpic S-C-P(O) anomeric effect in the thiane and 1,3-dithiane systems, 2.68 versus 3.39 kcal/mol, respectively, leads to the conclusion that no additivity of the S-C-P(O) anomeric effect takes place.

INTRODUCTION

The appearance of several recent reviews dealing with the origin and consequences of the anomeric effect provides evidence of the continuous attention given to this important conformational effect.[1] In this respect, the conformational behavior of 2-(diphenylphosphinoyl)-1,3-dithiane (**1**, Figure 1) has been extensively studied during the last fifteen years, owing in part to its importance regarding the existence of second- and lower-row anomeric interactions.[2]

Figure 1:



1, X = Y = S; **2**, X = CH$_2$, Y = S; **10**, X = Y = CH$_2$

[†] Dedicated to Professor William E. McEwen on the occasion of his 75th birthday.

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From the substantial predominance of **1**-ax at equilibrium, $K = 0.2$; $\Delta G^\circ_{298K} = +1.0$ kcal/mol, the magnitude of the anomeric effect in **1** could be estimated at 2.64 kcal/mol.[3] Nevertheless, dithiane **1** contains *two* S-C-P segments, and one relevant question is whether the anomeric interaction in each segment is worth one half of the total anomeric effect, i.e. ca. 1.34 kcal/mol.

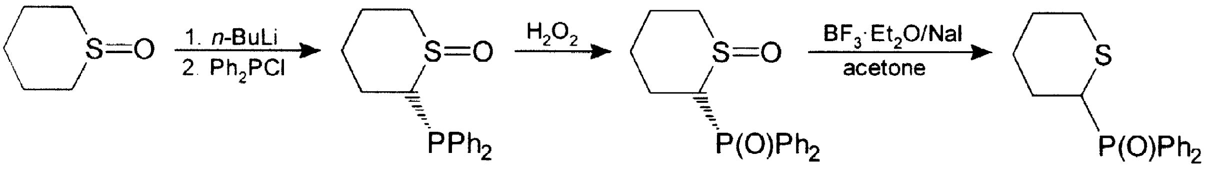
The aim of this work was to determine the extent of the anomeric effect in the tetrahydrothiopyran (thiane) analogue **2** (Figure 1), in order to ascertain whether or not it amounts to half the anomeric effect encountered in dithiane **1**.

RESULTS AND DISCUSSION

Preparation of 2-Diphenylphosphinoyltetrahydrothiopyran (2).

According to the procedure of Vedejs, *et al.*,[2a,4] thiane oxide **3** was metallated with *n*-butyllithium in dry THF at -78°C, and then treated with chlorodiphenylphosphine to give the desired phosphine, *trans*-**4** in 82 % yield (Scheme 1). Oxidation of *trans*-**4** with 3 % aqueous H_2O_2 at ambient temperature[4] afforded the corresponding phosphine oxide, *trans*-**5**, in 86 % yield (Scheme 1). Finally, the method described by Palumbo, *et al.*,[5] ($BF_3 \cdot Et_2O$/NaI) was employed in order to reduce sulfoxide *trans*-**5** to 2-diphenylphosphinoyltetrahydrothiopyran (**2**) in good yield (Scheme 1).

Scheme 1



3 *trans*-**4** (82 %) *trans*-**5** (86 %) **2** (86 %)

Cis- and trans-2-(Diphenylphosphinoyl)-4-t-butyltetrahydrothiopyran (cis- and trans-9).

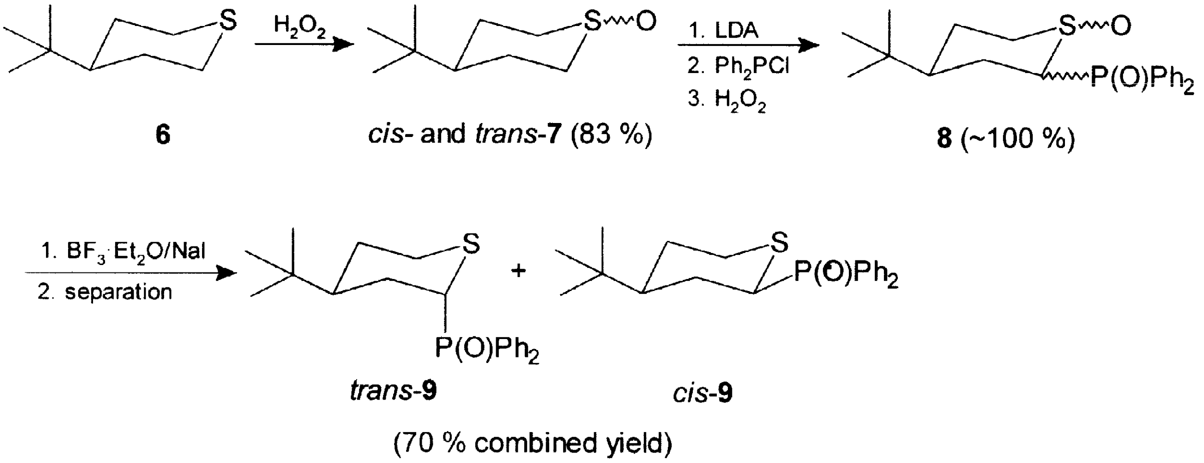
The conformationally fixed (anancomeric[6]) derivatives of thiane *S*-oxide **3** were used to synthesize *cis*- and *trans*-**9**, the anancomeric models for axial and equatorial phosphinoyl derivatives **2** (Scheme 2). The oxidation of 4-*t*-butyltetrahydrothiopyran (**6**) with H_2O_2 according to the method of Johnson[7] afforded a 35:65 mixture of conformationally fixed *cis*- and *trans*-**7**, respectively.[8] (Scheme 2). The mixture of diastereomeric sulfoxides *cis*- and *trans*-**7** was metallated with LDA in dry THF at -78°C, and then treated with chlorodiphenylphosphine to give the mixture of phosphines, which was oxidized with 3% aqueous H_2O_2 at room temperature to afford the corresponding mixture of phosphine oxides **8** in quantitative yield. Finally, the method of Palumbo, *et al.*,[5] ($BF_3.Et_2O$/NaI) was employed in order to reduce the mixture of sulfoxides to *cis*- and *trans*-2-(diphenylphosphinoyl)-4-*t*-butyltetrahydrothiopyran (*cis*- and *trans*-**9**) in good yield (Scheme 2).

Conformational Analysis

Conformational Preference of the α-Diphenylphosphinoyl Group in Thiane (2-ax $\rightleftharpoons$ 2-eq).

The equilibrium constant for the **2**-ax $\rightleftharpoons$ **2**-eq conformational process (Figure 1) was measured from integrations of ^{31}P NMR spectra (109.5 MHz) in THF-d_8 at temperatures below the coalescence temperature. At 183 K; $K = 0.20$, and $\Delta G^\circ_{183K} = +0.59$ kcal/mol. Similar values were obtained at 173 K; $K = 0.27$ and $\Delta G^\circ_{173K} = +0.46$ kcal/mol.

Scheme 2



The substantial predominance of the axial conformer **2**-ax contrasts strongly with the large predominance of equatorial (diphenylphosphinoyl)cyclohexane **10**-eq[9] (ΔG°_{300K} = - 2.74 kcal/mol, Figure 1), and is an additional manifestation of the strong anomeric effect in S-C-P segments.[2,3,10]

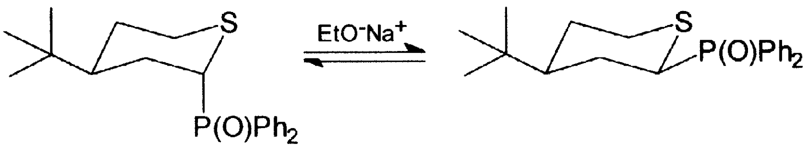
When one expresses the magnitude of the anomeric effect as the difference of ΔG° between (diphenylphosphinoyl)cyclohexane and the heterocycle of interest,[11] the anomeric effect operative in 2-(diphenylphosphinoyl)tetrahydrothiopyran (**2**) is estimated at + 0.53 - (-2.74) = 3.27 kcal/mol. A well recognized discrepancy in evaluating the anomeric effect in this way[12] is that the steric requirement of a group at the 2-position is significantly smaller (because of the longer C-S bonds) than the steric requirement in cyclohexane. Indeed, taking a *t*-butyl group as a model for the diphenylphosphinoyl group (but unable to act as an acceptor component in an anomeric interaction) molecular mechanics calculations show that the ΔG°(2-*t*-butyl) in tetrahydrothiopyran is about 71 % of ΔG°(*t*-butyl) in cyclohexane.[13] Thus, the anomeric effect in **2** can be estimated as 0.46 + (0.71 x 2.74) = 2.40 kcal/mol.[14]

By comparison of the anomeric effect in tetrahydrothiopyran **2** (*one* S-C-P segment; anomeric effect worth *ca.* 2.40 kcal/mol) with that in 2-(diphenylphosphinoyl)-1,3-dithiane **1** (*two* S-C-P segments; anomeric effect worth *ca.* 2.64 kcal/mol[3]) one may conclude that there exists a "saturation" of the effect.[15]

Chemical Equilibration of Anancomeric cis- and trans-2-(Diphenylphosphinoyl)-4-t-butyltetrahydrothiopyran (cis-9 $\rightleftharpoons$ trans-9).

Quantitative determination of the conformational free energy difference of the α-diphenylphosphinoyl group in thiane **2** was also accomplished by chemical equilibration of *cis*- and *trans*-**9** under ethanolic sodium ethoxide catalysis at 50°C (Figure 2). Equilibrium was reached from both sides and integration of the *t*-butyl signals in ^1H NMR spectra, as well as ^{31}P NMR signals, afforded a 60:40 *cis*-**9**:*trans*-**9** ratio; i.e., K = 1.5 and ΔG°_{323K} = - 0.26 ± 0.10 kcal/mol (Figure 2).

Figure 2:



trans-**9** *cis*-**9**

In order to evaluate the magnitude of the anomeric effect in this equilibrium it was again important to compare with the *A*-value of the diphenylphosphinoyl group,[9] correcting for the structural differences between the cyclohexane and thiane rings as described above. Thus, the magnitude of the anomeric effect is estimated as -0.26 + (0.71 x 2.74) = 1.69 kcal/mol

Enthalpic Anomeric Effect in α-(Diphenylphosphinoyl)tetrahydrothiopyran.

The substantial difference in $\Delta G°$ values at T = 173 K ($\Delta G°$ = + 0.46 ± 0.11 kcal/mol, Figure 2) and T = 323 K ($\Delta G°$ = -0.26 ± 0.10 kcal/mol, Figure 2) suggests a sizeable entropy effect. Indeed, the above temperature dependence corresponds to $\Delta S°$ = + 4.8 ± 0.7 cal/K·mol and $\Delta H°$ = + 1.29 ± 0.12 kcal/mol.

In this respect, Booth, *et al.*,[16] have stressed that in studies of the anomeric effect it is the $\Delta H°$ values, rather than the $T\Delta S°$-dependent $\Delta G°$ values, that correlate with the steric, polar and/or stereoelectronic origins of relevance. In the system under examination, the present results confirm the existence of a large *enthalpic* S-C-P(O) anomeric effect in **2**: $\Delta H°$(**2**-ax $\rightleftharpoons$ **2**-eq) - $\Delta H°$(**10**-ax $\rightleftharpoons$ **10**-eq) = + 1.29 - (0.71 x -1.96) = 2.68 kcal/mol. This enthalpy term favoring axial over equatorial 2-(diphenylphosphinoyl)thiane overcomes the entropic contribution (the equatorial conformer being of higher entropy[17]) at low temperature, ΔG^{o}_{173K} = + 0.46 kcal/mol, but not at ambient or higher temperature, ΔG^{o}_{323K} = - 0.26 kcal/mol, when the $T\Delta S°$ term becomes dominant.

The magnitude of the enthalpic S-C-P(O) anomeric effect found in 2-(diphenylphosphinoyl)thiane **2** is significantly larger than half of that determined in 2-(diphenylphosphinoyl)-1,3-dithiane **1**: 2.68 kcal/mol and ½(3.39 kcal/mol), respectively. This result is contrary to expectation if additivity of the conformational effect was operative; i.e., the enthalpic anomeric effect in **1** would be anticipated as twice that observed in **2**, 2 x 2.68 = 5.36 kcal/mol.

EXPERIMENTAL SECTION

General. Flasks, stirring bars, and hypodermic needles used for the generation and reaction of organolithiums were dried for *ca.* 12 h at 120°C and allowed to cool in a dessicator over anhydrous $CaSO_4$. Anhydrous solvents were obtained by distillation from benzophenone ketyl.[18] The *n*-butyllithium employed was titrated according to the method of Juaristi, *et al.*[19]

TLC: Merck-DC-F_{254} plates; detection by UV light. Flash column chromatography:[20] Merck silica gel (0.040-0.063 nm). Melting points: Mel-Temp apparatus; not corrected. ^1H RMN spectra: JEOL PMX-60 (60 MHz), JEOL GSX-270 (270 MHz) and JEOL Eclipse (400 MHz) spectrometers. ^{13}C NMR spectra: JEOL FX-90Q (22.50 MHz), JEOL GSX-270 (67.8 MHz) and JEOL Eclipse (100 MHz). ^{31}P NMR spectra: JEOL GSX-270 (109.25 MHz) and JEOL Eclipse (161.83 MHz). Chemical shifts (δ) in ppm downfield from internal TMS reference (^1H and ^{13}C NMR spectra) and external H_3PO_4 reference (^{31}P NMR spectra); the coupling constants (J) are given in Hz.

2-(Diphenylphosphinoyl)tetrahydrothiopyran (2). To a cooled (-78°C) of tetrahydrothiopyran *S*-oxide 0.47 g (4.0 mmol) in dry THF (30-mL) was added 2.63 mL (0.25 g, 3.9 mmol) of *n*-butyllithium 2.5 M in hexane. The resulting solution was stirred at -78°C for 15 min and then was added dropwise via cannula to 2 mL (2.45 g, 11 mmol) of chlorodiphenylphosphine in dry THF (15 mL) at -78°C, with a nitrogen atmosphere throughout. The reaction mixture was stirred at -78°C for 2 h and at room temperature for 1 h, before quenching with 5.0 mL of saturated aqueous NH_4Cl and then 5 mL of water, and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated in a rotary evaporator. The crude product was purified by flash chromatography (ethyl acetate/hexane, 9:1) to give 987 mg (82 % yield) of the *trans*-2-(diphenylphosphinyl)-tetrahydrothiopyran *S*-oxide as a white solid, mp 110-111.5°C (lit.[4] mp 110-111°C). To a solution of the diphenylphosphinyl derivative (200 mg, 0.66 mmol) in acetone (15 mL) was added dropwise a solution of 3 % aqueous H_2O_2 (26.8 mg, 0.79 mmol). The reaction mixture was stirred at room temperature for 2 h, then extracted with CH_2Cl_2 (2 x 25 mL). The organic layers were washed with saturated aqueous NaCl solution (50 mL), dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate) to give 181 mg (86.1 % yield) of the *trans*-2-(diphenylphosphinoyl)-tetrahydrothiopyran *S*-oxide as a white solid, mp 189°C (lit.[4] mp 179-181°C). Finally, a magnetically-stirred solution of the *trans*-2-(diphenylphosphinoyl)tetrahydrothiopyran *S*-oxide (300 mg, 1.1 mmol) and sodium iodide (840 mg, 5.6 mmol) in anhydrous acetone (100 mL) was cooled in an ice bath, and freshly destilled boron trifluoride etherate (0.7 mL, 5.6 mmol) was added drowise. The reaction mixture was stirred at 0°C for 30 min, then poured into water (20 mL) and extracted with ether (3 x 25 mL). The combined organic extracts were washed with 5 N aqueous sodium thiosulfate (25 mL), water (25 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The crude product was purified by flash chromatography (ethyl acetate/hexane, 8:2) affording **2** (186 mg, 86 % yield) as a white solid, mp 171.5-172°C (lit.[4] mp 159-162°C).

^{1}H NMR (270 MHz, $CDCl_3$) δ 1.35-1.50 (m, 1H), 1.65-2.05 (m, 4H), 2.12-2.30 (m, 1H), 2.57-2.70 (m, 1H), 2.80-2.93 (m, 1H), 3.50 (dt, J_{anti} = 9.9 Hz, $J_{H/P}$ = 6.6 Hz, J_{gauche} = 2.64 Hz, 1H), 7.44-7.59 (m, 6H), 7.78-7.96 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 25.2 (d, J = 8.8 Hz), 26.5, 29.3 (d, J = 5.5 Hz), 39.3 (d, J = 70.5 Hz), 128.4 (d, J = 15.4 Hz), 128.5 (d, J = 14.3 Hz), 131.3 (d, J = 8.8 Hz), 131.9 (d, J = 3.3 Hz). ^{31}P NMR (109.25 MHz, $CDCl_3$) δ 30.02.

***cis*- and *trans*-2-(Diphenylphosphinoyl)-4-*t*-butyltetrahydrothiopyran (*cis*- and *trans*-9).** The mixture of sulfoxides *cis*- and *trans*-**7** (3.36 g, 19.3 mmol)[7] was metallated with LDA and treated with 4.68 g (21.2 mmol) of chlorodiphenylphosphine according to the procedure described above for the preparation of **2**. Similar procedure for oxidation of the phosphinyl group and for the reduction of the sulfinyl group was subsequently used. The crude product was purified by flash chromatography (ethyl acetate/hexane, 3:2) to give 2 g (29.2 % yield) of the less polar isomer, identified as *trans*-**9** as a white solid with mp 213.5-215°C, and 2.8 g (40.8 % yield) of the more polar isomer, identified as *cis*-**9** as a white solid, 183-184°C.

cis-**9**

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.79 (s, 9H), 1.05-1.15 (m, 1H), 1.24-1.57 (m, 2H), 2.03-2.14 (m, 1H), 2.37-2.53 (m, 1H), 2.70-2.78 (m, 2H), 3.58 (dq, $J_{H/P}$ = 18.7 Hz, J_{anti} = 12.5 Hz, J_{gauche} = 2.6 Hz, 1H), 7.43-7.59 (m, 6H), 7.81-7.94 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 27.3, 27.8 (d, J = 2.2 Hz), 28.1, 30.9 (d, J = 8.8 Hz), 33.1, 42.0 (d, J = 70.5 Hz), 48.2 (d, J = 11.0 Hz), 128.3 (d, J = 14.3 Hz), 128.5 (d, J = 15.4 Hz), 131.4 (d, J = 8.8 Hz), 132.0 (d, J = 3.3 Hz). ^{31}P NMR (109.25 MHz, $CDCl_3$) δ 32.1.

Elemental analysis, Calcd. for $C_{21}H_{27}OPS$: C, 70.36; H, 7.59. Found: C, 70.17; H, 7.73.

trans-**9**

^{1}H NMR (270 MHz, $CDCl_3$) δ 0.67 (s, 9H), 1.24-1.42 (m, 1H), 1.54-1.92 (m, 2H), 2.08-2.24 (m, 2H), 2.39-2.53 (m, 1H), 3.39 (b, 1H), 3.62 (t, J = 12.5 Hz, 1H), 7.46 (s, 6H), 7.77-7.94 (m, 4H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 26.7, 27.2, 27.9, 28.4, 32.5, 35.3 (d, J = 70.5 Hz), 41.5, 128.3 (d, J = 11.0 Hz), 128.4 (d, J = 11.0 Hz), 130.9 (d, J = 8.8 Hz), 131.2 (d, J = 8.8 Hz). ^{31}P NMR (109.25 MHz, $CDCl_3$) δ 33.4.

Elemental analysis, Calcd. for $C_{21}H_{27}OPS$: C, 70.36; H, 7.59. Found: C, 70.65; H, 7.75.

Method of Equilibration of Diastereomers *cis*-9 $\rightleftharpoons$ *trans*-9. Equilibrium was approached from both sides; sodium ethoxide was the catalyst. For this purpose, 30-40 mg of the thiane was placed in a 5-mL ampule and dissolved in 4 mL of ethanolic sodium ethoxide. The ampule was sealed and immersed in a constant temperature bath (50°C) until equilibrium was reached. Quenching was effected by pouring the equilibrating solution into aqueous HCl. The thianes were then extracted with methylene chloride, dried over anhydrous Na_2SO_4, evaporated, and transferred into 5-mm NMR tubes for analysis.

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