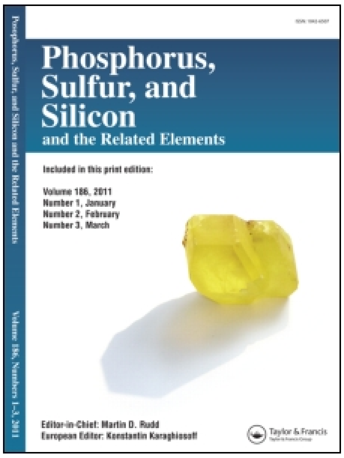

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

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To cite this Article Graczyk, Piotr P. and Mikolajczyk, Marian(1993) 'OPERATION OF THE GENERALIZED ANOMERIC EFFECT IN SOME 2-PHOSPHONIO-1,3-DITHIANES. STRIKING DIFFERENCE BETWEEN S-C-P AND O-C-N SYSTEMS', Phosphorus, Sulfur, and Silicon and the Related Elements, 78: 1, 313 — 316

To link to this Article: DOI: 10.1080/10426509308032447

URL: http://dx.doi.org/10.1080/10426509308032447

Phosphorus, Sulfur, and Silicon, 1993, Vol. 78, pp. 313–316
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Communication

OPERATION OF THE GENERALIZED ANOMERIC EFFECT IN SOME 2-PHOSPHONIO-1,3-DITHIANES. STRIKING DIFFERENCE BETWEEN S—C—P$^+$ AND O—C—N$^+$ SYSTEMS

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(Received October 9, 1992)

Both equilibration of diastereoisomeric 2-phosphonio-1,3-dithianes and NMR studies on conformationally labile models reveal the operation of the generalized anomeric effect in S—C—P$^+$ system. This finding is in a sharp contrast with O—C—N$^+$ systems, for which the reverse anomeric effect has been postulated.

Key words: Reverse anomeric effect; phosphonium salts; negative hyperconjugation.

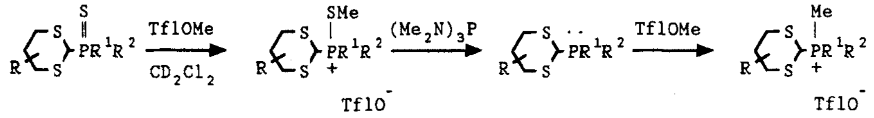
The term "reverse anomeric effect" was introduced in 1965 by Lemieux and Morgan[1] to describe additional tendency of a substituent bearing positive charge to occupy the equatorial position at the anomeric carbon of the pyranose ring. This effect was postulated for alkoxycarbonyl (X = COOR),[2,3] carbamoyl (X = $CONH_2$)[4], pyridinium,[1,5–7] and imidazolium[5] groups in O—C—X systems. The operation of the reverse anomeric effect was also suggested[2] for chloromethyl (CH_2Cl) and bromomethyl (CH_2Br) groups connected with the anomeric carbon atom of the 1,3-dioxane ring. The enhanced equatorial preference of the positively charged substituents has been attributed[8,9] to electrostatic destabilization of the axial position of a substituent. Electrostatic explanation seems to be in line with the observed reversed dependence of axial preference on solvent polarity, i.e. more polar solvents, where intramolecular electrostatic interactions are relieved, could increase the population of axial conformers, and that α-glucopyranosylimidazoles in water (very polar solvent) do not change conformation on protonation.[6]

In the course of our studies[10,11] on the conformation of S—C—P systems and the origin of S—C—P anomeric interactions we became interested in conformational behavior of phosphonium salts containing S—C—P$^+$ fragment, which are related to O—C—N$^+$ systems exhibiting the reverse anomeric effect. We expected that the latter effect could also be operative for second-row atoms, if the electrostatic explanation is correct. Our preliminary results[11] on 2-triphenylphosphonio-1,3-dithianes were seemingly consistent with the operation of the reverse anomeric effect although the equatorial preference of the Ph_3P^+ group was extremely low ($\Delta G^\circ_{293} = -1.35$ kJ/mol).

In this communication we would like to report the results of our studies on the conformation of 2-phosphonio-1,3-dithianes **1–8**, including four pairs of the diastereoisomeric compounds (*cis*- and *trans*-**3**, **4**, **7**, and **8**). The compounds under investigation were synthesized from the appropriate thiophosphoryl compounds **9**–**16** using alkylation-desulfurization-alkylation sequence worked out in our laboratory[12,13] (Scheme 1). Owing to a spontaneous epimerization of the diastereoisomeric diphenylmethylthiophosphonium salts **19**–**20**[14,15] we optimized their synthesis to ensure high conversion of a substrate **11**–**12** and sufficient diastereoisomeric purity of the resulting salts **19**–**20**.[16] The diastereoisomeric purity of **3**, **4**, **7**, and **8** corresponded to that of **19**, **20**, **23**, and **24**, respectively, and was high enough to confirm their structure via ^{1}H and ^{13}C NMR spectra,[17] and to perform their base-catalyzed (triethylamine or diisopropylethylamine) epimerization. The appropriate equilibrium constants K (ax ⇄ eq) and free energy differences ΔG°_{293} are collected in Table I. For the conformationally labile salts **1**, **2**, **5**, and **6** the position of conformational equilibrium was calculated using the weighted average method,[19] γ-effects in ^{13}C NMR spectra as a conformational probe, and 5-*t*-butyl-1,3-dithiane derivatives (**3** and **7**) as reference systems.

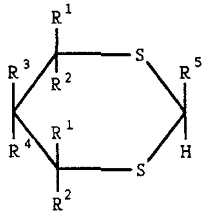
It is clearly seen from the data in Table I that the axial preference predominates in **3** and **5**–**8** ($K < 1$, $\Delta G^\circ > 0$) indicating unequivocally the operation of the generalized anomeric effect for Ph_2PMe^+ and $PhPMe_2^+$ groups attached to the C(2) atom of the 1,3-dithiane ring. This finding is especially interesting from the point of view widely accepted in chemical literature[20–22] that there is only quantitative difference between first- and second-row atoms in the magnitude of anomeric interactions. Therefore, it seems improbable that completely different effects operate in O—C—N$^+$ and S—C—P$^+$ systems.

It must be noted that spectral properties of the phosphonium salts investigated here support hyperconjugative ($n_S - \sigma^*_{C-P}$) origin of the observed anomeric effect. In particular, coupling constant $^1J_{C(2)-P}$ through the equatorial C(2)—P bond is always larger than that through the axial one by 3.3–11.6 Hz, in accord with the



R^1-R^2-Ph	9-12	17-20	25-28	1-4
R^1-Ph R^2-Me	13-16	21-24	29-32	5-8

SCHEME 1.



R^1	R^2	R^3	R^4	R^5= $^+$PPh$_2$Me	$^+$PPhMe$_2$
H	H	H	H	1	5
H	H	Me	Me	2	6
H	H	tBu	H	*cis*-3	*cis*-7
H	H	H	tBu	*trans*-3	*trans*-7
H	Me	H	H	*trans*-4	*trans*-8
Me	H	H	H	*cis*-4	*cis*-8

SCHEME 1'

TABLE I

Equilibrium constants *K* and free energy differences ΔG° for *ax* $\rightleftharpoons$ *eq* equilibrium in 2-phosphonio-1,3-dithianes **1–8** (CD_2Cl_2, 293 K)

Compound	K	ΔG° [kJ/mol]	Compound	K	ΔG° [kJ/mol]
1	2.38	−2.13	**5**	0.69	0.91
2	1.57	−1.11	**6**	0.52	1.61
3	0.831 ± 0.084	0.45 ± 0.26	**7**	0.340 ± 0.019	2.63 ± 0.14
4	2.12 ± 0.12	−1.83 ± 0.14	**8**	0.579 ± 0.057	1.33 ± 0.22

weakening of the latter due to $n_S - \sigma^*_{C-P}$ negative hyperconjugation.[23] The second mechanism responsible for the anomeric effect in S—C—P$^+$ system, which could be taken into account stems from the destabilizing interactions between π-electrons of the phenyl ring(s) connected with the equatorial phosphorus and lone electron pairs of endocyclic sulfur atoms.[10,11]

It should be stressed that phenomenological reverse anomeric effect is not supported by MO calculations. Wolfe *et al.*[20] postulated the reverse anomeric effect for CH_3CH_2XH (X = O,S) and NH_2CH_2OH compounds, however, after redefinition of this term on theoretical grounds. Hosie *et al.*[7] pointed out that this approach is wholly without experimental foundation just like the explanation of the reverse anomeric effect given by David *et al.*[25,31]

Some data from the chemical literature are also in striking disagreement with the concept of the reverse anomeric effect.

Tvaroška and Bleha[21] calculated that for $CH_3OCH_2NH_3^+$ cation conformer *sc* is less stable than *ap* (rotation about C—O bond) by 3.8 kJ/mol, not much more than in isoelectronic $CH_3OCH_2CH_3$ (3.1 kJ/mol). The expectations based on the reverse anomeric effect in $CH_3OCH_2NH_3^+$ suggest that this difference should have been much larger (several kJ/mol). The calculated value can be, perhaps, sufficiently explained as due to the increase of steric interactions in the *sc* form of the cation owing to shorter C—N versus C—C bond. Hence, there is no additional preference for *ap* arrangement in the cation.

Deslongchamps[26] suggested that the protonation of one of alkoxyl groups in acetal molecule affords alkyloxonium group (RO^+H, with positively charged oxygen, as it is required by the reverse anomeric effect) which is involved in classical $n_O - \sigma^*_{C-O^+}$ hyperconjugative interaction that may be solely reponsible for the generalized anomeric effect. This inconsistency was appreciated by Sinnot[27] and Box[28] in their review articles.

It must be noted that semiempirical MNDO calculations[29] of the conformation of various *N*-alkylpyridinium compounds containing O—C—N$^+$ system indicate the increased preference of ΔH = 13.8 kJ/mol for *og* (appropriate angle Θ = 106.1°) over *ap* conformation around C—O bond. The analogous angle in the crystal was found[29] to be 109.7°. This data is in disagreement with expectations based on observations of sugar derivatives where the reverse anomeric effect is manifested in enhanced preference of pyridinium group for *ap* arrangement in C—O—C—N$^+$ system.

Recently, Ratcliffe and Fraser-Reid[30] have shown that the formation of α-D-glucopyranosylacetonitrilium ions from the appropriate oxocarbenium ion and acetonitrile occurs highly stereoselectively. This result is in contrast to that predicted by the reverse anomeric effect, while applied to the stability of the appropriate transition state. On the other hand, such behavior agrees with the anticipation based on the $n_O - \sigma^*_{C—N^+}$ interaction.

Therefore, the operation of the reverse anomeric effect even in O—C—N$^+$ system seems to be not so general phenomenon, as it has been thought, so far. Since the S—C—P$^+$ system exhibits the generalized anomeric effect the scope and limitations of the reverse effect require, in our opinion, further studies.

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16. Time of alkylation of *cis*-**11** and *trans*-**12** was t = 40 min; for *trans*-**11** and *cis*-**12** t = 20 min. Degree of conversion: above 90%, content of undesired isomer in the synthesis of *cis*-**19**, *trans*-**20**, *trans*-**19**, and *cis*-**20**: less than 15, 7, 8, and 7%, respectively.
17. ^{1}H and ^{13}C NMR (300.13 MHz, CD_2Cl_2) spectra of **3**, **4**, **7**, and **8** are very close with respect to chemical shifts and coupling pattern of 1,3-dithiane ring nuclei to the spectra of their 2-triphenylphosphonio analogs.[11] In addition, spectral characteristic of triflate *trans*-**3** is almost identical with that of the relevant iodide, structure of which was confirmed by X-ray crystallography.[18]
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