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Inapplicability of the Antiperiplanar Lone Pair Hypothesis to C−P Bond Breaking and Formation in Some S−C−P$^+$ Systems

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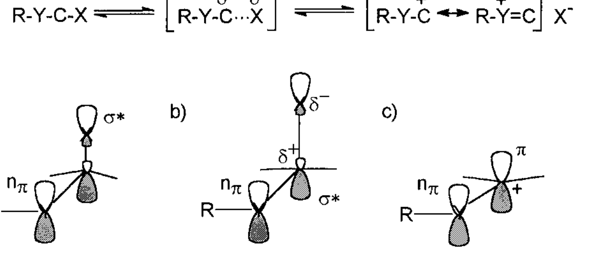
Both C(2)−P bond breaking and formation in the S−C−P$^+$ system do not occur according to the antiperiplanar lone pair hypothesis. Experiments using 2-phosphonio derivatives of 5-*tert*-butyl-1,3-dithiane and *cis*-4,6-dimethyl-1,3-dithiane are against the participation of higher-energy boat conformers as reactive intermediates. The results obtained support a possibility of conformational adjustment in the course of the reaction. Stereoelectronic control of the C(2)−P bond breaking and formation results from interplay of several factors. The role of the $n_S-\sigma^*_{C(2)-P}$ and $\sigma_{C(4,6)-S}-\sigma^*_{C(2)-P}$ hyperconjugation, as well as of the repulsive interactions between lone electron pairs π_S of endocyclic sulfur atoms and π-electrons of the phenyl ring(s) connected with phosphorus, is discussed.

Introduction

There are two main manifestations of the anomeric effect: energy and structure. As far as chemical reactions are concerned, such consequences are reflected in the rate of the C−X bond breaking as they depend on the conformation of the R−Y−C−X moiety. A pioneering observation in this area was done by Eliel and Nader[1] who showed the lack of reactivity of equatorial 2-alkoxy-1,3-dioxanes **1e** toward Grignard reagents, in contrast to axial derivatives **1a** (Scheme 1). Such a striking behavior has been called the *kinetic anomeric effect*.[2,3]

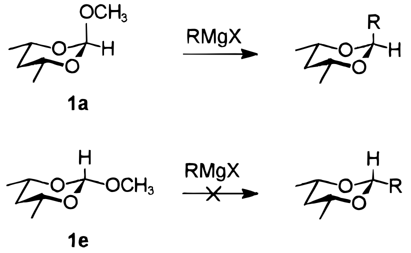
The kinetic anomeric effect is one of the most studied[4−13] and reviewed[3,14−19] phenomena in organic chemistry. Its explanation in terms of the theory of stereoelectronic control[14] is an extension of the interpretation of a ground-state behavior of molecules R−Y−C−X (**2**) based on $n_Y-\sigma^*_{C-X}$ negative hyperconjugation (see Figure 1a). Recently, a proposal to call this theory the *antiperiplanar lone pair hypothesis* (ALPH)was made,[16] since *stereoelectronic control* is far too general a term.



2 **3**

Figure 1. Negative hyperconjugation in (a) *og* conformer of R−Y−C−X, (b) transition state during heterolysis of the C−X bond, and (c) planar cation R−Y−C$^+$.

Scheme 1



Though the stabilizing role of the lone electron pair of oxygen atom (Figure 1c; Y = O) on the resulting cationic intermediate **3** has been supported both by experiment[20] and calculation,[21] the treatment of the ALPH as a dogma has been criticized from various standpoints which emphasize the importance of least motion effects[8,16] or destabilizing interactions.[22] Recently, Ratcliffe et al.[23] proposed that the hydrolysis (or formation) of glycosides **4** could take place in some cases by a synperiplanar rather than an antiperiplanar lone pair pathway (Figure 2). There is also a debate concerning the position of positively charged substituents X (e.g., $^+$OHR in the acid hydrolysis of glycosides **4**) in reactive species prior to the heterolysis of the C−$^+$OHR bond. In the opinion of

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[⊗] Abstract published in *Advance ACS Abstracts*, April 1, 1996.

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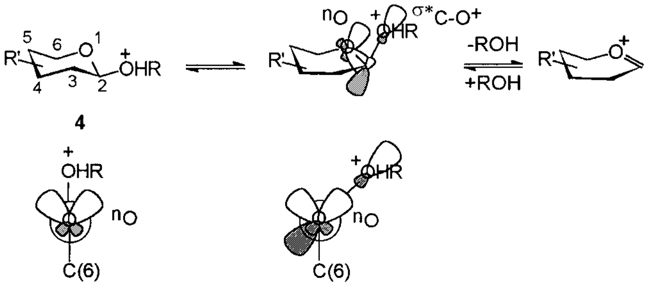


Figure 2. Synperiplanar pathway during the heterolysis of the equatorial C−O$^+$ bond in glycosides **4**.

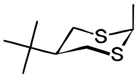
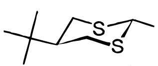
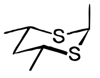
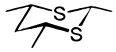
Sinnot,[16] due to the operation of the reverse anomeric effect, such substituents must acquire equatorial or pseudoequatorial position prior to the cleavage of the C−X bond in **5** (Scheme 2).

Recently, Caserio et al.[11] found an almost equal rate of formation of *cis*-4,6-dimethyl-1,3-dithian-2-yl cation (**6**) in the gas phase from the appropriate 2-methylthio derivatives **7** under FT-ICR conditions (Scheme 3). However, since phenomena occurring in a gas phase and in liquid can differ markedly,[24] the problem of applicability of ALPH, when second-row atoms are involved, remained unresolved.

In this paper we would like to show that the ALPH does not apply to C−P bond breaking and formation in some C−S−C−P$^+$ systems in solution. Since identifying even a few exceptions to the postulates of a hypothesis invalidates that hypothesis, this would be equivalent to an inapplicability of the ALPH in C−S−C−P$^+$ system.

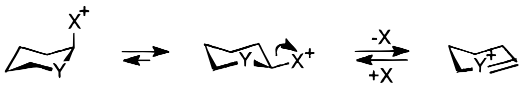
Results and Discussion

In the course of our work ten diastereomeric pairs of 2-phosphonio-1,3-dithianes **8**−**17** in the form of triflates and/or chlorides (e.g., **8a**-Cl, chloride; **8a**-Tfl, triflate) were studied.

Ring	Substituent				
	$\overset{\text{SMe}}{\overset{+\vert}{\text{PPh}_2}}$	$\overset{+}{\text{P}}\text{Ph}_3$	$\overset{+}{\text{P}}\text{Ph}_2\text{Me}$	$\overset{+}{\text{P}}\text{PhMe}_2$	$\overset{+}{\text{P}}\text{Me}_3$
	**8a**	**10a**	**12a**	**14a**	**16a**
	**8e**	**10e**	**12e**	**14e**	**16e**
	**9a**	**11a**	**13a**	**15a**	**17a**
	**9e**	**11e**	**13e**	**15e**	**17e**

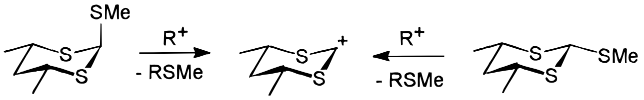
C−P Bond Breaking. Recently, we found[25] that the mechanism of a spontaneous epimerization of 2-((methylthio)phosphonio)-1,3-dithianes **8** consists of the heterolytic cleavage of the C(2)−P bond and the formation of relatively stable[26,27] 1,3-dithian-2-yl cation **18** and diphenylmethyl thiophosphinite (**19**, Scheme 4). In principle, if the transition state is not very late, compound **8e** should react exclusively via the appropriate twist-boat (**8e**-TB) conformer, in order to fulfill the requirements

Scheme 2

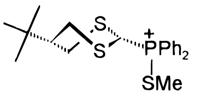


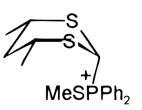
5a **5e**

Scheme 3



trans-**7** **6** *cis*-**7**





8e-TB **9e**-SB

of the ALPH,[14a] i.e., to place one lone electron pair of endocyclic sulfur in an antiperiplanar position to the C(2)−P bond being broken. By the same token, compound **9e** must acquire a stiff-boat (**9e**-SB) conformation[28] prior to the heterolysis of the C(2)−P bond. Let us find the relationship between free energies of activation for the heterolysis of the C(2)−P bond in the reactive higher-energy conformers (TB and SB) of **8e** and **9e**, i.e., $\Delta G^{\ddagger}_{TB} = G_{\mathbf{8}g} - G_{\mathbf{8}c}$ and $\Delta G^{\ddagger}_{SB} = G_{\mathbf{9}g} - G_{\mathbf{9}c}$, respectively (see Scheme 4; compound number included in subscripts $_{\mathbf{8}}$ or $_{\mathbf{9}}$, letters in subscript denote the level of G). Let us assume that G_e level lies sufficiently below G_g, as it is usually done.[14b,30] In general, for **8** (see Scheme 4)

$$(G_{\mathbf{8}b} - G_{\mathbf{8}a}) + (G_{\mathbf{8}f} - G_{\mathbf{8}b}) + (G_{\mathbf{8}g} - G_{\mathbf{8}f}) = (G_{\mathbf{8}g} - G_{\mathbf{8}c}) + (G_{\mathbf{8}c} - G_{\mathbf{8}a}) \quad (1)$$

where $G_{\mathbf{8}b} - G_{\mathbf{8}a}$ is the free energy difference between **8a** and **8e**, easily accessible from the equilibrium constant for epimerization of **8a** and **8e** (it is equal to 0.18 ± 0.22 kJ/mol (see Table 1)[32]), $G_{\mathbf{8}f} - G_{\mathbf{8}b}$ is the free energy of activation for the heterolysis of the C(2)−P bond in **8a** (in further discussion denoted as $\Delta G^{\ddagger}_{\mathbf{8}}$), $G_{\mathbf{8}g} - G_{\mathbf{8}f}$ is the free energy difference between barriers to equatorial and axial C(2)−P bond formation from **18** and **19** (this value was estimated independently from the starting ratio of products formed in the reaction between **19** and 5-*tert*-butyl-2-chloro-1,3-dithiane (**20**, see below) as $C_{\mathbf{8}}$),[33] $G_{\mathbf{8}g} - G_{\mathbf{8}c}$ is the free energy barrier $\Delta G^{\ddagger}_{TB}$ for the heterolysis of the C(2)−P bond in the **8e**-TB conformer,

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[28] Higher-energy (boat) conformations of 5-*tert*-butyl-1,3-dithiane and *cis*-4,6-dimethyl-1,3-dithiane derivatives must be different.[29]

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[30] Free energy barrier $\Delta G^{\ddagger} = G_e - G_a$ to ring inversion in 1,3-dithianes is on the order of 40 kJ/mol;[31] free energy of activation $\Delta G^{\ddagger} = G_{\mathbf{8}g} - G_{\mathbf{8}a}$ corresponding to rate constant $k = 5.64 \times 10^{-3}$ min^{-1} (see Table 1) for epimerization of **8e** is on the order of 100 kJ/mol.

[31] Friebolin, H.; Schmid, H. G.; Kabuss, S.; Faisst, W. *Org. Magn. Reson.* **1969**, *1*, 67.

[32] Mikolajczyk, M.; Graczyk, P. P. *J. Org. Chem.* **1995**, *60*, 5190−5208.

[33] $C_{\mathbf{8}}$ cannot be calculated directly because of the deviation of coefficients κ and n from 1 and the deviation of the system from Curtin−Hammett/Winstein−Holness approximation;[34] $k = \kappa k_B h^{-1} T^n exp(-\Delta G^{\ddagger} R^{-1} T^{-1})$, where κ is the transmission coefficient; k is the rate constant, k_B is the Boltzmann constant, h is Planck's constant, T is temperature, and $\Delta G^{\ddagger}$ is the free energy of activation (= C_1).

[34] Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

Table 1. Experimental $k_{a(0)}$, $k_{b(0)}$, and $\epsilon k_{c(0)}$ (see eqs 13−15) and Average k_a and k_b [min^{-1}] Rate Constants, Average Square of Difference S_{av} between Integrals Found Experimentally and Calculated, Equilibrium Constants K, and Free Energy Differences $\Delta G°_{293}$ [kJ/mol] for Spontaneous Epimerization of 8-TflO and 9-TflO

compd	$k_{a(0)} \times 10^3$	$k_a \times 10^3$	$k_{b(0)} \times 10^4$	$k_b \times 10^4$	$\epsilon k_{c(0)} \times 10^2$	$S_{av} \times 10^4$	K^a	$\Delta G°_{293}{}^a$
8	5.71	6.09 ± 0.47	52.9	56.4 ± 4.3	4.93	2.11	1.08 ± 0.09	−0.18 ± 0.22
	5.81		53.8		3.74	9.76		
	6.75		62.5		3.39	2.61		
9	4.77	4.75 ± 0.27	9.82	9.78 ± 0.56	2.75	10.76	4.86 ± 0.28	−3.85 ± 0.14
	4.40		9.06		2.62	9.06		
	5.08		10.46		2.94	7.33		

[a] From ref 32.

and $G_{8c} - G_{8a}$ is the free energy difference between chair and TB conformer of **8e** (it is equal to 7.63 ± 0.09 kJ/mol[29] minus the anomeric effect ΔG_{AE8} present[4] in the **8e**-TB conformer (one *sc* arrangement of the C−S−C−P system)). Hence

$$0.18 + \Delta G^{\ddagger}_{8} + C_{8} = \Delta G^{\ddagger}_{TB} + 7.63 - \Delta G_{AE8} \quad (2)$$

By the same token for **9**:

$$(G_{9b} - G_{9a}) + (G_{9f} - G_{9b}) + (G_{9g} - G_{9f}) = (G_{9g} - G_{9c}) + (G_{9c} - G_{9a}) \quad (3)$$

where $G_{9b} - G_{9a}$ is equal to 3.85 ± 0.14 kJ/mol (see Table 1),[32] $G_{9f} - G_{9b}$ is the free energy of activation for the heterolysis of the C(2)−P bond in **9a** (in further discussion denoted as $\Delta G^{\ddagger}_{9}$), $G_{9g} - G_{9f}$has been determined independently from the starting ratio of products in the reaction between **19** and 2-chloro-*cis*-4,6-dimethyl-1,3-dithiane (**21**) as C_9 kJ/mol (see below), $G_{9g} - G_{9c}$ is the free energy barrier $\Delta G^{\ddagger}_{SB}$ for the heterolysis of the C(2)−P bond in the **9e**-SB conformer, and $G_{9c} - G_{9a}$ is the free energy difference between chair and SB conformers of **9e** (it is equal to 11.40 ± 0.09 kJ/mol[29] minus the anomeric effect ΔG_{AE9} present in the **9e**-SB conformer (two *sc* arrangements of the C−S−C−P system; note, therefore, that ΔG_{AE9} must be larger than ΔG_{AE8})).

Therefore

$$3.85 + \Delta G^{\ddagger}_{9} + C_{9} = \Delta G^{\ddagger}_{SB} + 11.40 - \Delta G_{AE9} \quad (4)$$

Subtraction of eq 4 from eq 2 gives

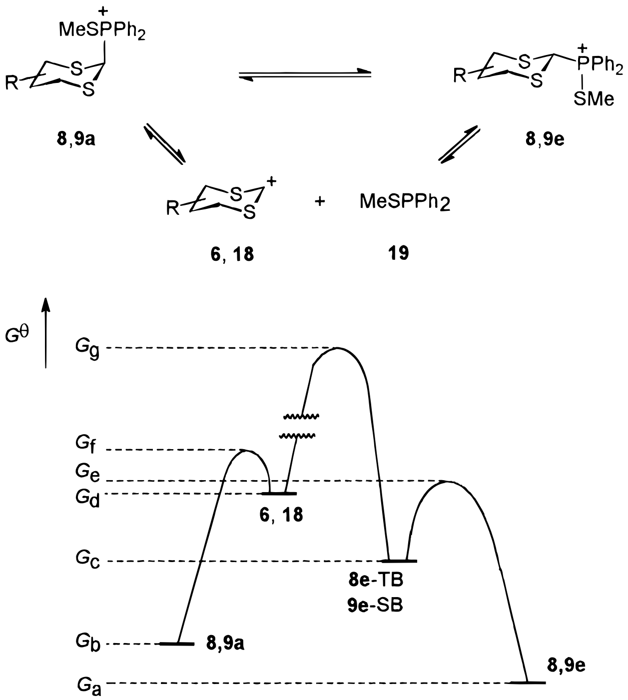
$$0.18 - 3.85 + \Delta G^{\ddagger}_{8} - \Delta G^{\ddagger}_{9} + C_{8} - C_{9} = \Delta G^{\ddagger}_{TB} - \Delta G^{\ddagger}_{SB} + 7.63 - 11.4 - \Delta G_{AE8} + \Delta G_{AE9} \quad (5)$$

Because of the chemical similarity of **8** and **9** and identical starting ratio of products in the reaction between **19** and 2-chloro-1,3-dithianes **20** and **21**, we assume $C_8 = C_9$. Hence

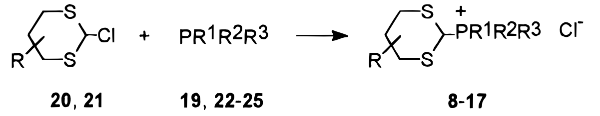
$$\Delta G^{\ddagger}_{SB} - \Delta G^{\ddagger}_{TB} = -0.10 + \Delta G^{\ddagger}_{9} - \Delta G^{\ddagger}_{8} - \Delta G_{AE8} + \Delta G_{AE9} \quad (6)$$

The difference $\Delta G^{\ddagger}_{9} - \Delta G^{\ddagger}_{8}$ was determined[35] from the relation between the appropriate rate constants for the epimerization of **9a** and **8a** (Table 1) as 0.60 kJ/mol. Since $\Delta G_{AE8} < \Delta G_{AE9}$, the free energy barrier $\Delta G^{\ddagger}_{SB}$ must be higher than $\Delta G^{\ddagger}_{TB}$ by more than 0.5 kJ/mol or at least (taking into account all the assumptions) must be comparable. This result is in disagreement with the requirements of ALPH, according to which two lone electron pairs antiperiplanar to a bond being broken (as in SB conformer of **9e**) are expected[3a,14c,d] to diminish the appropriate free energy barrier much more effectively than one lone electron pair (as in the TB conformer of **8e**).

Scheme 4



Scheme 5



C−P Bond Formation. The results of the kinetically controlled reaction between 2-chloro-1,3-dithianes **20** and **21** and phosphines **19** and **22**−**25** (Scheme 5, for **22**−**25** taken from ref 32) are presented in Table 2. Because products containing the axial C(2)−P bonds are clearly preferred, the formation of **8**−**11** seems to occur according to ALPH. However, the most striking example is provided by compounds **14** and **15**, where both isomers are formed in almost equal amounts. The latter reaction (between **21** and **24**) occurs, most probably, via an S_N1 mechanism,[36] because the reaction between undoubtedly ionic[41] *cis*-4,6-dimethyl-1,3-dithian-2-yl hexachloroanti-

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(35) Since $G_g - G_f$ (see Scheme 4) is the same for **8a** and **9a** ($C_8 = C_9$) and rate constants for epimerization of both substances (k_{8a} and k_{9a}, respectively; see Table 1) are close, the deviation from Curtin−Hammett/Winstein−Holness approximation[34] for **8a** and **9a** is the same. Therefore, and keeping in mind that $G_g - G_f$ is the same for **8a** and **9a**, the relationship between the rate constants (k_{8a} and k_{9a}) is determined by the difference between $\Delta G^{\ddagger}_{9}$ and $\Delta G^{\ddagger}_{8}$; $k_{9a}/k_{8a} = exp[-(\Delta G^{\ddagger}_{9} - \Delta G^{\ddagger}_{8})/RT]$, assuming equality of the transmission coefficients κ. Hence, $\Delta G^{\ddagger}_{9} - \Delta G^{\ddagger}_{8} = 0.60$ kJ/mol.

Table 2. Results of the reaction^{a} between 2-chloro-1,3-dithianes 20, 21 and phosphines 19, 22–25 (for 22–25 based on data in Ref.32)

product	yield^{b} [%]	ratio^{c} **a**:**e**	product	yield^{b} [%]	ratio^{c} **a**:**e**
8^{d}	*e*	93:7^{f}	**9**^{d}	*e*	93:7^{f}
10	89	89:11	**11**	78	90:10
12	74	69:31	**13**	82	67:33
14	96	56:44	**15**	95	52:48
14^{g}	88	58:42			
16^{g}	95	70:30	**17**	82	67:33

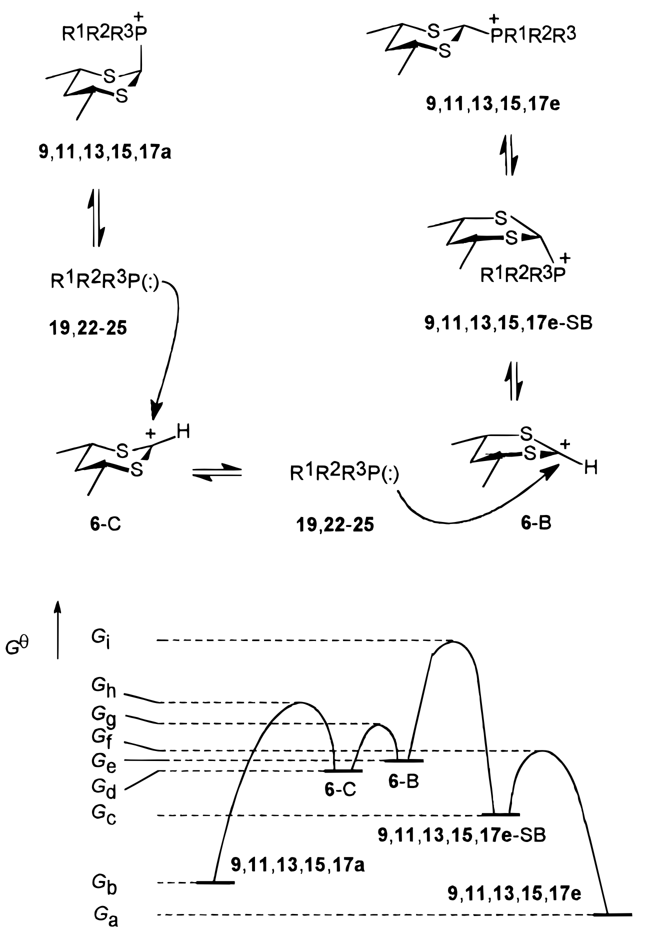
[a] Reaction carried out in benzene solution at 293 K, except as otherwise stated. [b] Isolated. [c] Based on integration in ^{31}P NMR spectra. [d] Reaction carried out in a 5 mm o.d. NMR sample tube in $CDCl_3$ solution and followed by ^{31}P NMR spectra. [e] Not determined. [f] Obtained via extrapolation of ratio of integrals to time t = 0. [g] Reaction carried out at 273 K.

monate (**26**) and phosphine **24** affords **15e**-$SbCl_6$ and **15a**-$SbCl_6$ in a similar ratio, i.e. 55:45, respectively.

If the relevant transition state is not very early, compound **15e** cannot be—following the ALPH principle—formed via the reaction of the appropriate 1,3-dithian-2-yl cation **6** in its chair conformation **6**-C (Scheme 6), since there is no lone pair antiperiplanar to the C–P bond to be formed. The ALPH explanation could be based on the participation of a higher energy boat-like conformer **6**-B, where two such pairs are available.[42] The appropriate free energy diagram is included in Scheme 6.

According to the Curtin–Hammett principle the ratio of products **e**:**a** is controlled by the difference in free energies of the respective transition states,[34] i.e., $G_i - G_h$. Since **15e** and **15a** are formed in almost equal amounts, G_i should be equal to G_h. However, while the transition state leading to **15a** is chair-like, the corresponding transition state responsible for the formation of **15e**-SB must be stiff-boat-like (according to ALPH), and therefore must be strongly destabilized.[14e] Hence, G_i should be higher than G_h, in disagreement with the Curtin–Hammett principle. Since the latter principle is based on mathematical formalism,[34] it seems to be more reasonable to assume inapplicability of ALPH in this case.

Scheme 6



Analogous reasoning can also be performed for 5-*tert*-butyl-1,3-dithiane derivatives. Interestingly, the ratio of products practically does not depend on the chlorodithiane (**20** *vs* **21**) used but is connected with a type of the applied phosphine. This observation seems to disagree with ALPH, too. Different transition states (corresponding to G_i)—twist-boat-like for the reactions with **20** and stiff-boat-like for **21**—should result in different energies G_i (Scheme 6) and consequently in different content of products with equatorial phosphorus. This is not observed.

In our opinion the ALPH does not apply to both the C–P bond breaking and formation in the S–C–P$^+$ system. These processes are controlled by several factors, *which as a whole* could be responsible for the stereoelectronic control of the reactions under investigation. The following factors should be, in our opinion, taken into account.

1. $n_S-\sigma^*_{C-P}$ Negative Hyperconjugation. This hyperconjugative interaction, according to the ALPH, is operative only for derivatives with axial (or pseudoaxial) C–P bonds. While this can be true for the ground-state phenomena, a situation in a transition state could be, in our opinion, quite different. Figure 3 shows possible steps during the heterolysis of the equatorial C–P bond. With the lengthening of this bond, the C(2) atom becomes more and more planar (on going from "a" to "e") and the $n_S-\sigma^*_{C-P}$ hyperconjugative stabilization increases.[43] Finally, when phosphorus is far enough away, the σ^*_{C-P} orbital is transformed into an empty π orbital of the sp^2

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[36] The chlorine atom connected with the C(2) atom of the 1,3-dithiane ring exhibits a strong preference for the axial position.[26] If the reaction occurred via an S_N2 pathway without epimerization, products containing equatorial phosphorus would be preferred, in contrast to what is observed for **8**–**11**. However, this chlorine atom is very labile[26] and the epimerization occurs via the stage of the 1,3-dithian-2-yl cation, a very reactive species.[27,37] It must be added that Sugawara et al.[38] postulated an S_N1 mechanism for benzenethiolysis of 2-(benzoyloxy)-1,3,5-trithiane derivatives. An analogous possibility of an S_N1 mechanism was considered Caserio et al.[11] for the reaction between 2-(dimethylsulfonio)-*cis*-4,6-dimethyl-1,3-dithiane and sodium methanethiolate. An attack of a nucleophile on a carboxonium ion was considered to be a general pathway of substitution in reactive α-halogeno ethers.[39,40]

[37] Houben-Weyl. *Methoden der organischen Chemie*; G. Thieme: Stuttgart, 1985; Vol. E11, part 2, p 1472 ff, and references therein.

[38] Sugawara, T.; Iwamura, H.; Ôki, M. *Tetrahedron Lett.* **1975**, *11*, 879.

[39] Jonas, J.; Kratochvil, M.; Mikula, J.; Pichler, J. *Collect. Czech. Chem. Commun.* **1971**, *36*, 202.

[40] Box, V. G. S. *Heterocycles* **1984**, *22*, 891.

[41] Hartke, K.; Akgun, E. *Chem. Ber.* **1979**, *112*, 2436 and references therein.

[42] The assumption of the existence of two distinguishable conformers of **6** is convenient but not necessary. Further considerations concerning the relation between the relevant free energies of transition states (G_i and G_h; Scheme 6) for the formation of **8a** and **8e** are also valid if there is only one reactive form of **6** (i.e., there is no difference between **6**-C and **6**-B).

[43] According to Box[44] the hyperconjugation may intervene significantly only after the C–P bond has been deformed beyond its "elastic limit".

[44] Box, V. G. S. *Heterocycles* **1991**, *32*, 795.

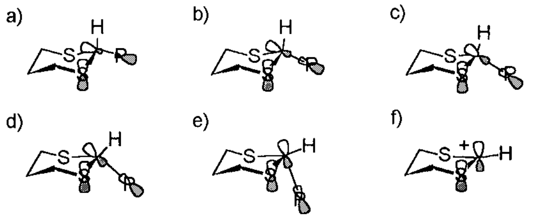
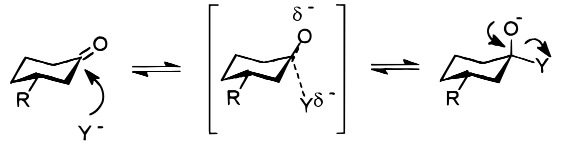


Figure 3. Conformational adjustment during the heterolysis of the equatorial C−P bond in 2-P-substituted 1,3-dithianes.

Scheme 7



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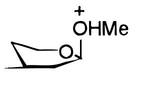
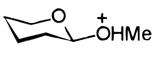
carbon, which is situated adequately to overlap with lone electron pair(s) of endocyclic sulfur atom(s). This process, during which the H(2) hydrogen and nuclei of the S−C−S part of the ring change their mutual position, is called "conformational adjustment". However, it must be stressed that while conformational changes are accompanied by crossing an energetic barrier, this process is similar to vibrational movement of a ring and would correspond to monotonic movement through a potential energy surface toward the transition state. Analogous structural adjustment (in a reverse direction) has been considered[45,46] for an equatorial attack of a nucleophile at 3-substituted cyclohexanones **27**, as shown in Scheme 7.

This idea is strongly supported by an ab initio study[47] of a transition state in the hydrolysis of 2-methoxytetrahydropyrans. The authors[47] found that on going to the transition state the conformation of the possible reactive intermediates (protonated 2-methoxytetrahydropyrans) undergoes a change analogous to that shown in Figure 3. In particular, the C−OMe bond breaking occurs concurrently with ring flattening.[47] The appropriate transition state for the protonated β-glycoside **28** was found to be ^{4}E-*endo* sofa, which is close to the transition state "e" (Figure 3).[48] Hence, this process is always fast enough to follow the heterolysis of a bond. The influence of the conformational adjustment on energy of the transition state is, therefore, dependent on its character and increases for systems where it is late. This would account for the observed[16] inapplicability of the ALPH for such systems. Moreover, it fits the observations of Kirby's group, who in a series of papers[4−7] showed that the degree of "stereoelectronic control" decreases with more late character of the transition state. The importance of the character of the transition state for the stereochemical outcome of a reaction was also appreciated by Deslongchamps' group.[12,13] Nevertheless, they still maintain the existence of boat-type compounds as the reactive intermediates.



28 ^{4}E sofa

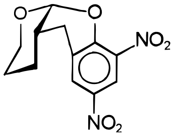


28 $^{4}C_1$ chair

The idea of the conformational adjustment could explain the observed lack of stereoselectivity for the C(2)−OR bond breaking in ortho esters in a gas phase[24] (in a solution the axial bond is much more easily cleaved than the equatorial one[14d]). In contrast to the situation in a solution, both the substrate (large ion) and the products (neutral molecule and ion) resulting from the heterolysis are not solvated. The lack of solvation results in much a higher increase of energy of products (which are smaller species) than of the substrate. According to the Hammond's postulate, this would result in a much later transition state in a gas phase, a much more effective conformational adjustment, and the disappearance of the stereoselectivity implied by ALPH. By the same token, solvent dependence of the reactions of cyclic ortho esters[50] could be explained.

Late transition states are accompanied by significant secondary H/D isotope effects.[4] This seems also to be the case for the heterolysis of the C(2)−P bond in **8a** and **8e** (and most probably in **9**), where H/D isotope effects are 1.14 and 1.29, respectively. Hence, if, for example, situation "e" (Figure 3) corresponds to the transition state for **8e**, it will be stabilized in the same manner as during the heterolysis of the axial C−P bond. If both transition states were of the same energy, the difference in the rate of the heterolysis would arise from the difference in ground-state energies of isomers.

Analogous treatment of the C−P bond formation, according to the principle of microscopic reversibility, shows that both isomers, being formed in a comparable amount, could arise from chair-like transition states. Moreover, the same ratio of isomers formed from **20** and **21** could be easily explained, as it is not connected with the participation of particular twist-boat-like and stiff-boat-like transition states.



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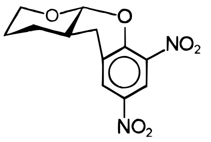

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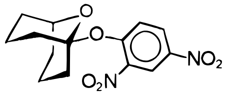

31

The possibility of the conformational adjustment, though recognized by others,[4−8,15,17,51] has not been accepted, so far. In particular, this possibility was studied by Kirby's group[4−7] on the basis of a solvolysis of some acetals containing aryloxy groups connected to the anomeric carbon atom. In our opinion, their studies provide no evidence to reject (with one exception—see below) the possibility of the conformational adjustment. They strongly support the dependence of the degree of "stereoelectronic control" on a character of the transition

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(45) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540.

(46) Coxon, J. M.; McDonald, D. Q. *Tetrahedron* **1992**, *48*, 3353.

(47) Andrews, C. W.; Fraser-Reid, B.; Bowen, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 8293.

(48) Surprisingly, the ground-state conformation of the protonated β-glycoside **28** was found[47] to be ^{4}E sofa, by ca. 25 kJ/mol more stable than the appropriate $^{4}C_1$ chair. This result stands in flat contradiction to the idea of the reverse anomeric effect,[3b,19,49] according to which positively charged substituents are expected to exhibit a strong preference to the equatorial position in the pyranose ring ($^{4}C_1$ chair should be the most stable). For a more exhaustive discussion see ref 50.

(49) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.

(50) Croteau, A.; Bailey, W. F. *Abstracts of Papers*, 178th National Meeting of the American Chemical Society, Washington, DC, Sept 1979; American Chemical Society: Washington, DC, Org 105.

(51) Ahmad, M.; Bergstrom, R. G.; Cashen, M. J.; Chiang, Y.; Kresge, A. J.; McClelland, R. A.; Powell, M. F. *J. Am. Chem. Soc.* **1979**, *101*, 2669.

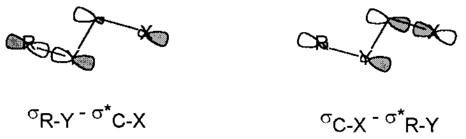

Figure 4. Involvement of σ-orbitals of R–Y and C–X bonds in (a) σ_{R-Y}–σ^*_{C-X} and (b) σ_{C-X}–σ^*_{R-Y} hyperconjugations.

state.[4] A very small difference (ca. 4.2-fold) between the rate of spontaneous hydrolysis of two (dinitrophenyl)-tetrahydropyranyl acetals **29** and **30**, with the leaving group in **30** fixed equatorial by the trans-ring junction,[5] is not consistent with the ALPH.[52] The possibility of the conformational adjustment was indeed excluded by Kirby et al.[7] in bicyclic acetal **31**. However, this system was designed especially for this purpose, and the structural restrictions in **31** are not present in other acetals studied by them. In particular, there is no convincing reason to explain all failures of the ALPH by the participation of higher-energy intermediates (boat conformations). In our opinion, the involvement of two possible pathways—the first with conformational adjustment and the second via higher-energy intermediates—could be estimated if the energies of the appropriate transition states [e.g., corresponding to G_g (Scheme 4) and "e" (Figure 3)] were known (Curtin–Hammett/Winstein–Holness principle[34]). So far, nobody has considered such a possibility.

The discussed problem of the applicability of the ALPH is the problem of the relative magnitude of hyperconjugative interactions in appropriate transition states and the character of the latter. It must also be added that conformational adjustment is not limited to cyclic compounds, as has recently been discussed by us.[19]

2. **$\sigma_{C(4,6)-S}$–$\sigma^*_{C(2)-P}$ and $\sigma_{C(2)-P}$–$\sigma^*_{C(4,6)-S}$ Hyperconjugations.** The importance of the n_Y–σ^*_{C-X} negative hyperconjugation for the stabilization of the relevant transition state is well-recognized now (vide supra). However, it is, in our opinion, of considerable concern that the donor abilities of σ-orbitals of R–Y and C–X bonds in σ_{R-Y}–σ^*_{C-X} and σ_{C-X}–σ^*_{R-Y} hyperconjugation, respectively (Figure 4), in the *ap* conformer of the R–Y–C–X system are usually overlooked, despite theoretical,[53] spectroscopic[54] (for Y = S), and X-ray crystallographic (for Y = O[55,56] and Si[56,57]) support. While these donor abilities are of rather small importance for Y = O, their role for second-row atoms is much greater. In 1987 Anet and Kopelevich showed,[58] for example, that the stretching frequencies of the axial and equatorial C(2)-D bonds in a 1,3-dithiane ring are equal and that there is no isotope effect on the corresponding conformational equilibrium. Recent *ab initio* studies by Wolfe and Kim[59] on $CH_2(XH)_2$ (X = O, S) systems revealed the main factors responsible for such behavior, with the hyperconjugation involving σ_{S-H} orbitals as donors as one of them (the σ_{S-H} orbitals in $CH_2(XH)_2$ correspond to the $\sigma_{C(4,6)-S}$ orbitals in 1,3-dithiane).

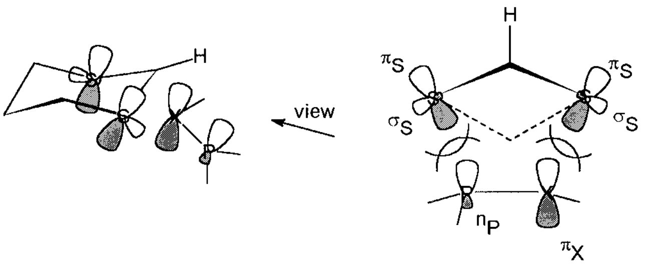

Figure 5. Repulsive interactions during equatorial approach of phosphine to 1,3-dithianyl cation.

Hence, if the donor abilities of the $\sigma_{C(4,6)-S}$ orbitals in 1,3-dithiane can influence its ground-state energy, it seems quite possible that they may influence the energy of 2-P-substituted 1,3-dithiane derivatives during the heterolysis of the equatorial C(2)–P bond. It seems also possible that if the transition state is not very late, the $\sigma_{C(4,6)-S}$–$\sigma^*_{C(2)-P}$ interaction may facilitate initial heterolysis of the C–P bond, prior to the subsequent effective conformational adjustment.[60]

3. Overlap Repulsion. It must be noted that the importance of hyperconjugative interactions for ground-state behavior of molecules is not universally accepted. In the opinion of Box[22,63] and Tvaroška and Bleha,[17] a source of ground-state preferences can be found rather in destabilizing interactions in the antiperiplanar (*ap*) form of the C–O–C–O systems. Hence, if they exist and if they can decrease in the transition state, they could influence the stereochemical course of a reaction.

In the case of the reaction between Ph_3P (**22**) and **20** (or **21**), steric interactions between a large phosphine molecule and the 1,3-dithiane ring must not be so important. Otherwise, steric congestion during the axial approach would be prohibitive for the formation of the axial derivative. Hence, the C–P distance in the transition state should be rather long and the origin of the observed preference for the axial approach could not be connected exclusively with the n_S–σ^*_{C-P} interaction. On the other hand, repulsive interactions between lone electron pairs π_S of endocyclic sulfur atoms and π-electrons of the phenyl ring(s) as well as the lone electron pair on phosphorus can destabilize the equatorial approach of a phosphine molecule (see Figure 5). This is why Ph_3P prefers the axial attack. The preference for the axial approach should decrease with the decreasing number of phenyl rings, as is observed (see Table 2). For trimethylphosphine (**25**) the axial approach becomes again more preferred than for **24**, presumably due to more effective repulsions between π_S and the more localized lone electron pair on phosphorus in **25**.

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[52] Rate-determining steps for **29** and **30** must be the same because of a very close deuterium solvent isotope effect.

[53] Wolfe, S.; Pinto, M. B.; Varma, V.; Leung R. Y. N. *Can. J. Chem.* **1990**, *68*, 1051.

[54] Juaristi, E.; Cuevas, G. *Tetrahedron Lett.* **1992**, *33*, 1847.

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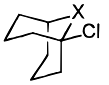
[57] White, J. M.; Robertson, G. B. *J. Org. Chem.* **1992**, *57*, 4638.

[58] Anet, F. A. L.; Kopelevich, M. *J. Chem. Soc., Chem. Commun.* **1987**, 595.

[59] Wolfe, S.; Kim, C.-K. *Can. J. Chem.* **1991**, *69*, 1408.

[60] Indeed, Meyer and Martin[61] showed an important fractional contribution of resonance stabilization by an α-heteroatomic substituent X of the resulting bridgehead cation resulting from the solvolysis of bicyclic chlorides **29**. Nevertheless, the overall rate of solvolysis was shown[62] to decrease in the series X = NMe, CH_2, O, S.



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[61] Meyer, W. P.; Martin, J. C. *J. Am. Chem. Soc.* **1976**, *98*, 1231.

[62] Krabbenhoft, H. O.; Wiseman, J. R.; Quinn, C. B. *J. Am. Chem. Soc.* **1974**, *96*, 258.

[63] Box, V. G. S. *Heterocycles* **1991**, *32*, 2023.

Interestingly, the largest preference for the axial approach is observed for Ph_2PSMe (**19**; 93:7, see Table 2). It has been argued (vide supra) that, in the sense of the C−P bond formation, the appropriate transition state is early. Hence, ALPH cannot be expected to account for the observed stereoselectivity. On the other hand, the interactions discussed now consitute a very good explanation, with lone electron pairs on MeS sulfur being involved in repulsions with lone electron pairs of endocyclic sulfur atoms.

Summary

Both C(2)−P bond breaking and formation in the $C-S-C-P^+$ system support the minor importance of the antiperiplanar lone pair hypothesis. Stereoelectronic control of these reactions results most probably from interplay of several factors of stabilizing and destabilizing character. Our results suggest a possibility of conformational adjustment during the reaction and are not consistent with participation of higher-energy boat intermediates. Because of rather long bond distances and easier conformational adjustment, as well as first-row−second-row difference in donor and acceptor properties, it seems possible that the ALPH in its pure form will be facing more difficulties when applied to reactions in which second-row atoms are involved.

Experimental Section

^1H NMR spectra of 0.5−0.8% solutions in appropriate deuterated solvent containing 0.1% of tetramethylsilane were recorded at 200.13 or 300.13 MHz on Bruker AC 200 and Bruker MSL 300 spectrometers, respectively. The ^{13}C NMR spectra of about 4% solutions in appropriate deuterated solvent containing 0.4% of tetramethylsilane were measured at 75.47 MHz on the Bruker MSL 300. The ^{31}P NMR spectra were measured on Bruker AC 200 and Bruker MSL 300 instruments at 81.0 and 121.49 MHz, respectively, with 85% H_3PO_4 as an external reference. All the spectra were taken at 293 K, and solutions were not degassed.

The following instrumental parameters for ^1H NMR spectra are typical: flip angle, 60−75°; SW (scan width), 9 ppm; number of scans, 100−400; TD (data size), 16K, AQ (acquisition time), 2.3−3.1 s. The sign of coupling constants was not determined.

Typical parameters for ^{13}C NMR spectra: flip angle, 60−75°; SW, 160 ppm; number of scans, 100−1000; TD, 16K, AQ, 0.67 s. The assignment of signals, if not straightforward, was based on DEPT technique.

All standard 16K FID's in the ^1H and ^{13}C NMR spectra were zero filled to 32K prior to the Fourier transformation.

In ^{31}P NMR spectra used for quantitative determination of the ratio of diastereomers after equilibration, the flip angle was 30−35° and relaxation delay was 5 s.

Methyl diphenylphosphinothioite (**19**),[64] *cis*-5-*tert*-butyl-2-(diphenylthiophosphinoyl)-1,3-dithiane (**30a**),[65−67] *trans*-5-*tert*-butyl-2-(diphenylthiophosphinoyl)-1,3-dithiane (**30e**),[65−67] *r*-2-(diphenylthiophosphinoyl)-*t*-4,*t*-6-dimethyl-1,3-dithiane (**31a**),[65−68] *r*-2-(diphenylthiophosphinoyl)-*t*-4,*t*-6-dimethyl-1,3-dithiane (**31e**),[65−68] 5-*tert*-butyl-1,3-dithiane (**32**),[67,69,70] and *cis*-4,6-dimethyl-1,3-dithiane (**33**)[67,69,70] were prepared acccording to known procedures. Other compounds if not described below were commercially available.

Determination of the Rate of Epimerization of 2-(Diphenyl(methylthio)phosphonio)-1,3-dithianes 8-TflO and 9-TflO. 2-(Diphenyl(methylthio)phosphonio)-1,3-dithianes **8**-TflO and **9**-TflO were prepared by alkylation[32] of the corresponding 2-thiophosphoryl analogs **30** and **31**, respectively, with methyl trifluoromethanesulfonate.

General Procedure. To a solution of **30a** (39.3 mg, 0.10 mmol) or **31a** (37.0 mg, 0.10 mmol) in chloroform-*d* (1.0 mL) in a 5 mm o.d. NMR sample tube was added methyl trifluoromethanesulfonate (12 μL, 0.10 mmol) in one portion. The progress of alkylation and epimerization was determined on the basis of integration of signals of the *tert*-butyl group in **30a**, **8a** and **8e** (δ 0.865, 0.580 and 0.887 ppm, respectively) or H(2) doublets in **31a**, **9a**, and **9e** (δ 4.62, 5.90, and 6.68, respectively) in ^1H NMR (200.13 MHz) spectra at 293 K. The relative integrations I in three independent series of measurements as a function of time are collected in Tables 3, 4, and 5 (for **30a**, **8a** and **8e**; Supplementary Material) and Tables 6, 7, and 8 (for **31a**, **9a**, and **9e**, see supporting information). In order to establish the magnitude of epimerization rate constants, we assumed irreversible alkylation of **30a** and **31a** with rate constants k_{8c} and k_{9c}, respectively. The rates of epimerization of the resulting products were designated as k_{8a} and k_{8b} for **8a** and **8e**, respectively, and k_{9a} and k_{9b} for **9a** and **9e**, respectively. The appropriate rate expressions (for the sake of simplicity only for **8**) are given in eqs 7−9. Let us assume that concentrations are proportional to integrations as shown in eqs 10−12, where I_{30}, I_{8a}, and I_{8e} are relative integrations of NMR signals due to **30**, **8a**, and **8e**, respectively, and ϵ is a constant equal to 0.1 M (for $t = 0$ $I_{30} = 1$ and $[\mathbf{30}] = 0.1$ M). Therefore, the data were analyzed by means of the adjustment of the results obtained via numerical integration of eqs 13−15, using the method of Runge and Kutta ("Scientist" version 2.0, MicroMath, Inc.), to the results derived from experiment, assuming $k_a/k_b = K$, where K is the equilibrium constant determined via direct equilibration of both diastereomers of **8** and **9**. The best k values (shown in Table 1) correspond to the minimum of average square S_{av} of differences between ^1H NMR signal integrations observed and calculated. The calculated values of relative integration are collected in Tables 11−16 (supporting information).

$$\mathbf{30} + \mathrm{TflOMe} \xrightarrow{k_{8c}} \mathbf{8a} \underset{k_{8b}}{\overset{k_{8a}}{\rightleftharpoons}} \mathbf{8e}$$

$$\frac{d[\mathbf{30}]}{dt} = -k_{8c}[\mathbf{30}]^2 \tag{7}$$

$$\frac{d[\mathbf{8a}]}{dt} = k_{8c}[\mathbf{30}]^2 - k_{8a}[\mathbf{8a}] + k_{8b}[\mathbf{8e}] \tag{8}$$

$$\frac{d[\mathbf{8e}]}{dt} = k_{8a}[\mathbf{8a}] - k_{8b}[\mathbf{8e}] \tag{9}$$

$$[\mathbf{30}] = \epsilon I_{30} \tag{10}$$

$$[\mathbf{8a}] = \epsilon I_{8a} \tag{11}$$

$$[\mathbf{8e}] = \epsilon I_{8e} \tag{12}$$

$$\frac{dI_{30}}{dt} = -\epsilon k_{8c} {I_{30}}^2 \tag{13}$$

$$\frac{dI_{8a}}{dt} = \epsilon k_{8c} {I_{30}}^2 - k_{8a} I_{8a} + k_{8b} I_{8e} \tag{14}$$

$$\frac{dI_{8e}}{dt} = k_{8a} I_{8a} - k_{8b} I_{8e} \tag{15}$$

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[64] Giles, J. R. M.; Roberts, B. P. *J. Chem. Soc., Perkin Trans. 2* **1981**, 1211.

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General Procedure for the Reaction between 2-Chloro-1,3-dithianes 20 and 21 and Phosphine 19. The reaction was carried out in a 5 mm o.d. NMR sample tube. To a chloroform-*d* (0.9 mL) solution of 2-chloro-1,3-dithiane (**20** or **21**) which was prepared from the appropriate 1,3-dithiane (**32** or **33**, respectively, 0.10 mmol) and sulfuryl chloride (9 μL, 0.12 mmol) following the known procedure,[71] a 2.0 M chloroform-*d* solution of phosphine **19** (50 μL, 0.10 mmol) was added, and the course of the reaction was monitored by ^{31}P NMR (81.0 MHz). The relative intensities of signals δ 50.1 and 52.0 due[32] to **8a** and **8e**, respectively, as a function of time are collected in Table 9 (supporting information). The relative intensities of signals δ 51.2 and 51.4 due[32] to **9a** and **9e**, respectively as a function of time are presented in Table 10 (supporting information). The current ratios K_{cur} of intensities, which was assumed to be proportional to the ratio of concentrations of diastereomers, are also presented in the tables.

The initial ratio of diastereomeric products was found via extrapolation to $t = 0$, assuming that $K_{cur} = f(t)$ is a linear function of time t (this is justified for an initial period of reaction; otherwise *log K* should be used). The least-squares method applied to the data in Tables 9 and 10 (the first five points) afforded

$$K_{cur} = 7.05 \times 10^{-2} + (8.90 \times 10^{-3})t \qquad r = 0.994 \qquad \text{for } \mathbf{8}$$

$$K_{cur} = 7.05 \times 10^{-2} + (1.42 \times 10^{-2})t \qquad r = 0.994 \qquad \text{for } \mathbf{9}$$

where r is correlation coefficient.

Thus, the initial ratio of concentrations (K_{cur} for $t = 0$) for both reactions is 7.05×10^{-2}, which corresponds to 7:93 (see Table 2).

Studies on the Reaction between *cis*-4,6-Dimethyl-1,3-dithian-2-yl Hexachloroantimonate (26) and Dimethylphenylphosphine (24). <sen>The reaction was carried out under a nitrogen atmosphere. To a $CHCl_3$ (50 mL) solution of **21**, which was prepared from **32** (831 mg, 5.60 mmol) and SO_2Cl_2 (0.45 mL, 5.60 mmol) following the known procedure,[71] was added a 1.23 M $CHCl_3$ solution of $SbCl_5$ (4.5 μL, 5.54 mmol). The salmon suspension thus obtained was magnetically stirred for 1.5 h, and then phosphine **24** (1.5 mL, ca 10 mmol) was added in one portion. A dark solution was immediately formed, and after stirring for 6 h the ^{31}P NMR (81.0 MHz, $CDCl_3$) spectrum showed three singlets at δ 28.7, 28.9, and 59.1 ppm of relative integration 23.54:28.27:48.19, respectively. The two upfield signals at δ 28.7, 28.9 were attributed to **15a**-$SbCl_6$ and **15e**-$SbCl_6$ by analogy to **15a**-Cl and **15e**-Cl prepared from **21** and **24** (see Table 2), which resonate[32] at δ 29.40 and 29.54 ppm, respectively (at 121.49 MHz, in $CDCl_3$).

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Supporting Information Available: Tables 3−16 (14 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[71] Kruse, C. G. Ph.D. Thesis, University of Leiden, 1978.