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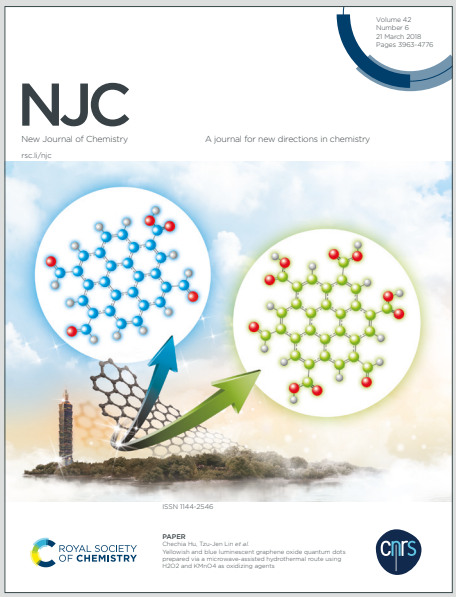

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Medium sized cyclic bis(anisylphosphonothioyl)disulfanes and the corresponding related cyclic sulfanes - structure and the most characteristic reactions

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ABSTRACT

Cyclic 8-, 9-, 10-, and 12-membered *bis*(anisylphosphonothioyl)disulfanes were synthesized. Next, structurally related 7 – 9-membered *cis* and *trans* sulfanes were isolated as a result of sulfur atom extrusion from parent cyclic disulfanes. Results of desulfurization of disulfanes with the use of triphenylphosphine have been compared to results obtained for desulfurization of the respective *bis*(anisylphosphodithioates) with the aim of 2-chloro-*N*-methylpyridinium iodide. Cyclic disulfanes predominantly provide *trans*-sulfanes and expansion of their ring size causes a *cis*/*trans* isomer ratio of cyclic sulfanes to increase. On the other hand *bis*(anisylphosphodithioates) give mainly *cis*-sulfanes and the *cis*/*trans* isomer ratio is greater than 3:1. Mechanistic and stereochemical aspects of cyclic disulfanes desulfurization have been presented to elucidate the above mentioned findings. Although it was suggested by calculation that *cis*-sulfanes are more thermodynamically stable than the respective *trans* isomers, the cyclisation is kinetically controlled reaction, which results in the predominance of *trans*-sulfanes in the case of *trans*-disulfane desulfurization.

Disulfanes exhibit thermal and solvolytic stability (except wet DMSO). A characteristic persistent deep-blue coloration of methanolic ammonia solutions is an unusual feature of cyclic disulfanes. Mechanism of their ammonolysis have been studied and have been compared to the respective reaction performed on acyclic disulfanes. Ammonia solution of an acyclic disulfane is colourless and contains phosphosulfenamide and dithiophosphate while the respective mixture of cyclic disulfane consists thiophosphonoamide-phosphonodithioate, *O*-methyl thiophosphonate–phosphonodithioate and deep-blue sulfur-ammonia species.

The detailed X-ray structural analysis was performed for all *trans*-disulfanes and *cis*- and *trans*-sulfanes. They were compared to each other and their acyclic or cyclic known analogs that comprise common subunits. 8-, 9-, 10-, and 12-membered disulfanes exist as *trans* isomers exclusively, both in the solid state and in solution. They are significantly more stable than their hypothetical *cis* isomers as shown by DFT calculations. The PSSP torsion angle of cyclic disulfanes lies in a range 94-125^{o}, increasing with the ring size. These values are greater than a typical torsion found for the respective non-cyclic disulfanes. The greater stability of *cis*-sulfanes was confirmed by calculation and can be ascribed mainly to the characteristic anisyl-anisyl stackings. Special attention was paid to the importance and the role of weak hydrogen bonds (CH...O/S) in conformational stabilization and intermolecular interactions. The conformation of cyclic disulfanes and cyclic sulfanes found in the crystalline state is also preserved in the solution (variable temperature NMR). A Karplus relationship has been established between the dihedral angles and vicinal H-P coupling constants for all disulfanes and sulfanes. The effect of solvent on ^{1}H NMR chemical shifts (ASIS) has been determined and associated with dipole moments of sulfanes.

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1. INTRODUCTION

Simple acyclic *bis*(dialkylphosphorothioyl)disulfanes $(RO)_2P(S)SSP(S)(OR)_2$ find use in the industry as sulfur donors and as fast accelerators for natural and synthetic rubbers vulcanization [1], as efficient sulfurization agents for oligo(nucleoside phosphorothioates) synthesis [2] as well as ligands forming stable complexes with a plethora of metal ions in coordination chemistry. [3] Due to synthetic difficulties, literature on respective phosphonodithioates $R(RO)PS_2$ chemistry is not as comprehensive as it is the case with their analogues, *i.e.* phosphorodithioates $(RO)_2PS_2$ and phosphinodithioates R_2PS_2. However, diverse applications of phosphonodithioates $R(RO)PS_2$ in the lubricant industry (multifunctional additives), the mining industry (agents for flotation and ore extraction), agriculture (pesticide derivatives), as potential antibacterial agents are highly valued. [4] Being efficient bidentate chelating agents *bis*(phosphonodithioic) acids are particularly interesting in this respect since they form much more stable complexes with metal ions than monodentate phosphonodithioic acids RP(OR)SSH. [5,6] On the other hand, related acyclic *bis*(phosphothioyl)sulfanes are a rare and unexplored class of phosphorus-sulfur organic compounds. In the past they were used occasionally as fungicides. [7]

Conformational and stereochemical analysis of phosphorus heterocycles having more than six members is still relatively unexplored. More than a decade ago, we used the reaction between Lawesson's reagent (LR) and diols/diphenols for the efficient synthesis of *bis*(anisylphosphonodithioic) acid **1** derivatives and among them the unique 8-, 9-, and 10-membered cyclic disulfanes **2a** and **2b**. [8] It seems to be evident that a high-yielded formation of our medium-sized heterocycles without

oligomeric by-products was connected with their fixed structure containing the most preferred a *zig-zag* motif of the SPSSPS unit. A similar procedure has been applied recently by Van Zyl's group for successful synthesis of the related cyclic *bis*(ferrocenylphosphonothioyl)disulfanes **2 (2e** as an example**)**. [9] Therefore, *P*-ferrocenyl instead *P*-anisyl containing heterocycles were obtained in the reaction between ferrocenyl analog of Lawesson's reagent (FcLR) and 1,2-diols (ethylene glycol, *trans*-1,2-cyclohexanediol, and pentaerythritol) followed by subsequent oxidation. Next, they were characterized by ^{1}H, ^{31}P NMR, single-crystal X-ray analysis and their electrochemical properties were investigated using cyclic voltammetry. Unfortunately, cyclic voltammetry was used only to test the reversibility of the ferrocenium-ferrocene and not disulfide-thiol redox couple. Previously, Woollins [10] prepared analogous eight-, nine-, and ten-membered diselenides starting from the selenium analog of LR ("Woollin's reagent") following a similar protocol. Quite recently, he has elaborated and applied one-pot procedure for obtaining 8- to 10-membered cyclic disulfanes using FcLR. [11]

The constitution of cyclic medium-sized *bis*(anisylphosphonothioyl)disulfanes **2a** and **2b** was confirmed earlier by means of spectroscopic methods (^{1}H and ^{31}P NMR). [8] We have already presented the preliminary results on crystal structure of 8- and 10-membered disulfanes **2a** and **2d** with comparison to the structure of their ferrocenyl analogues. [12] So far, there is no comparative study of the crystal structure of cyclic disulfanes and their structure in solution. Similarly, the effect of ring size on the basic structural parameters of cyclic disulfanes **2** has not been investigated. Their conformation in solid state as well in solution is not yet completely understood. In addition, the chemistry of cyclic *bis*(phosphonothioyl)disulfanes **2** is still not fully explored, albeit some of our previous experimental results confirm their similar behaviour to acyclic disulfanes.[13] For example, we have shown that 9-membered *bis*(anisylphosphonothioyl)disulfane **2b** undergoes nucleophilic substitution exclusively at the phosphorus atom when it reacts with sodium *N*-methyl benzohydroxamate. We have proved that the reaction proceeds with the inversion of the configuration at phosphorus and the resulting unstable >P(S)SS^{-} anion rapidly loses its sulfur atom *in statu nascendi* at a rate faster than the rate of its trapping by methyl iodide. On the other hand, we have observed that the sterically more demanded sodium *N*-*tert*-butyl benzohydroxamate already results in the reduction of disulfane **2b** giving, among others, the respective benzamide, as Lawesson's reagent does. [14] Next, we affirmed that sodium diethyl malonate attack preferably a soft sulfur atom of the disulfide bridge of **2b** giving the respective 2-phosphonothioylsulfenyl malonates [15] , i.e. behave as other simple carbanions against acyclic disulfanes **2**. [16] Our research on the reactivity of cyclic *bis*(phosphothioyl)disulfanes **2** described above suggests that their behavior with respect to other nucleophilic reagents should be consistent with the HSAB theory.

It is well known that disulfanes, including diorganyl RSSR, can be desulfurized to the respective sulfanes using P(III) reagents. However, it would be important and interesting to verify whether such a transformation performed on cyclic *bis*(phosphonothioyl) disulfanes **2** will lead to cyclic sulfanes **3** (as a result of intramolecular reaction) or to polysulfanes (as a result of intermolecular ring opening).

The results of previous works dealing with the formation of cyclic sulfanes **3** are given in Scheme 1 and 2. So far, only few cyclic cyclic *bis*(anisylphosphonothioyl)sulfanes **3** have been isolated. In the reaction between ethylene glycol and 1-aryl-1,3-propanediols with LR in boiling acetonitrile where the respective 5-membered 2-anisyl-1,3,2-dioxaphospholane 2-sulfide **4a** and and 6-membered 2-anisyl-1,3,2-dioxaphosphorinane 2-sulfide were principal heterocycles, traces of 7-membered **3a** (6%) and 8-membered sulfanes (3-6%) were obtained. [17,18] Unfortunately, due to limited spectroscopic data (a low resolution ^{1}H NMR spectrum) the stereochemistry of cyclic sulfane **3a** was not further assigned. Herein, our structural studies (based on comparison of ^{1}H and ^{31}P NMR spectra as well as melting point of both authentic isomers of **3a**) confirm unequivocally that Shabana [14] obtained merely *trans*-**3a** (see section 2.7). On the other hand, NMR spectra reported by Hue [15] proved to be insufficient to give unambiguously the geometry of 8-membered sulfanes using our spectroscopic data.

A similar condensation of *bis*(methylphosphonodithioic) acids derivated from 1,2-, 1,3- and 1,4-diols leading to related cyclic sulfanes **3** (with *P*-methyl instead of *P*-anisyl substituents) was described by Pudovik. [19] As a result 7- and 8-membered sulfanes **3** were obtained albeit in very low yields (25 and 7%, respectively) and characterized (IR, NMR). The largest 9-membered sulfane, namely 2,4-dimethyl-1,5,3,2,4-dioxathiadiphosphonane 2,4-disulfide, was not detected due to its alleged rapid oligomerization. Because apparently a mixture of *cis* and *trans* isomer was formed in the above mentioned reaction conditions, Pudovik had to isolate only one isomer of 7-membered 2,4-dimethyl-1,5,3,2,4-dioxathiadiphosphepane 2,4-disulfide. Unfortunately, also in that case, the data we have obtained below does not allow us to determine which of the isomer was actually isolated. Almost twice the smaller value of the geminal P-P coupling constant ($^{2}J_{PP}$ = 7.5 Hz vs 13.0 Hz for *trans*-**3a** as we report below) may indicate that the key effect on coupling in cyclic sulfanes **3** may, however, be the size of the *P*-substituent.

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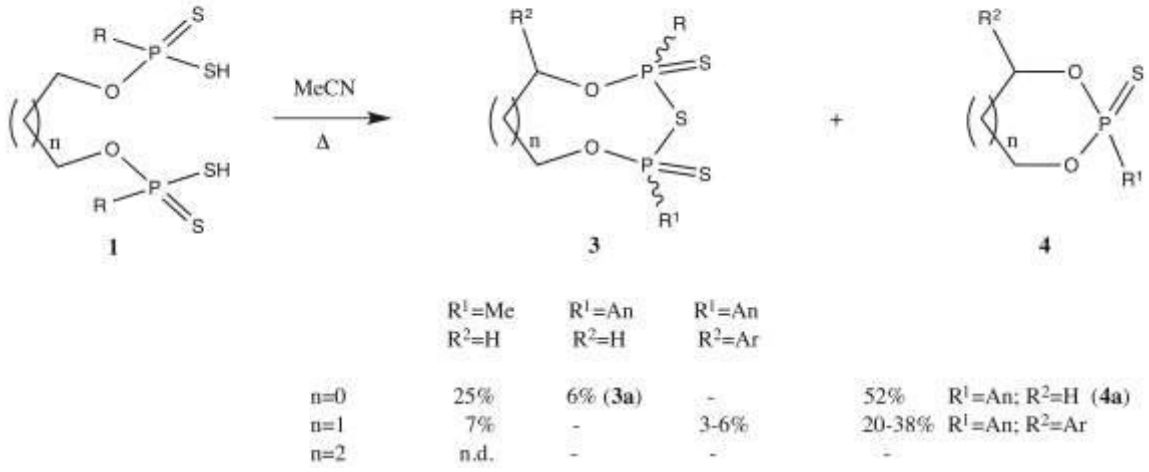
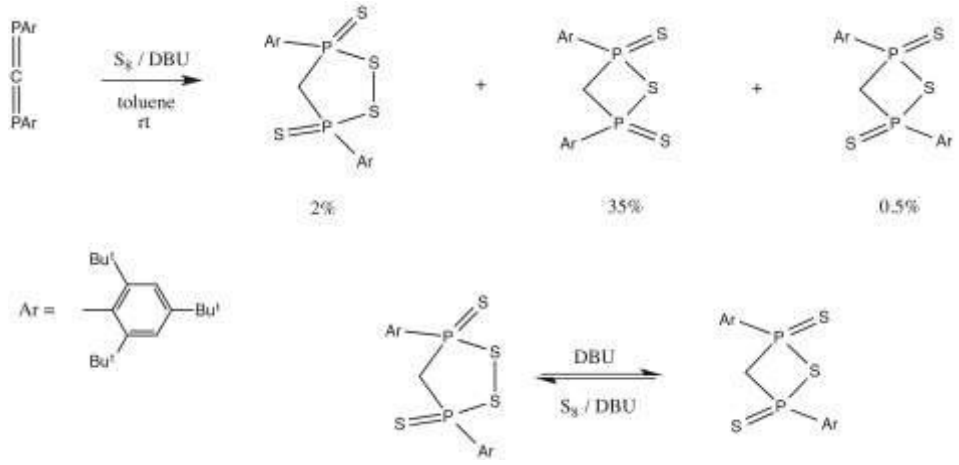


Scheme 1 Cyclic 7- and 8-membered *bis*(phosphonothioyl)sulfanes **3** of unknown geometry formed as by-products from the corresponding *bis*-phosphonodithioic acids **1**. [17-19]

It seems also interesting to note, that in 1991 a Japanese group obtained a mixture of stable, sterically protected small ring analogous heterocycles. [20] Sulfurization of diphosphalene ArP=C=PAr (Ar = 2,4,6-$Bu^t_3C_6H_2$) with elemental sulfur afforded the respective *cis*- and *trans* isomers of 4-membered sulfanes accompanied by *trans* 5-membered disulfane (Scheme 2). Next, every compound was isolated, characterized, and their crystal structure was successfully solved. It was found that the corresponding *cis*-sulfane was the main product of ArP=C=PAr sulfurization. Additionally, desulfurization of *trans*-3,5-*bis*(2,4,6-tri*tert*butylphenyl)-[1,2,3,5]dithiadiphospholane 3,5-disulfide yielded *trans*-2,4-*bis*(2,4,6-tri*tert*butylphenyl)-[1,2,4]thiadiphosphetane 2,4-disulfide sulfane (and *vice versa*). No information was provided about the reaction mechanism or diagnostic $^3J_{PP}$ and $^2J_{PP}$ coupling constant values in this report.



Scheme 2 Examples of stable small ring heterocycles of containing P-S-P and P-S-S-P linkages. [20]

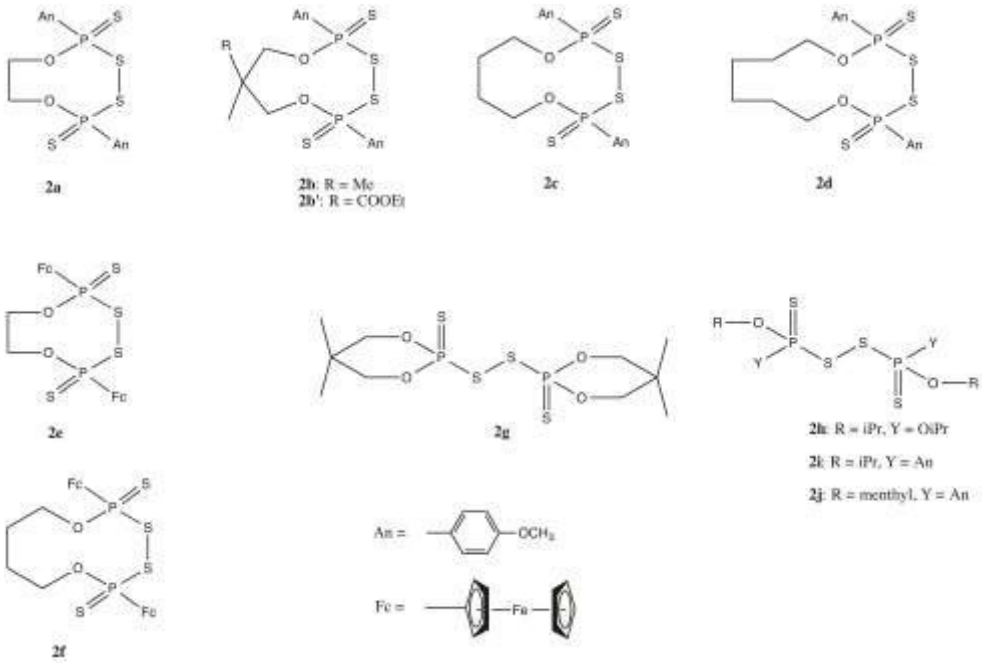
The experimental results on small and medium-sized cyclic *bis*(phosphothioyl)sulfanes described above confirm our below-stated statements (see *infra*) that *cis*-sulfanes **3** can be generally more thermodynamically stable than their opposite isomers, and that mainly *trans*-sulfanes **3** are formed from small rings of *trans*-disulfanes **2**.

2. RESULTS AND DISCUSSION

2.1 Synthesis of cyclic disulfanes 2 and sulfanes 3

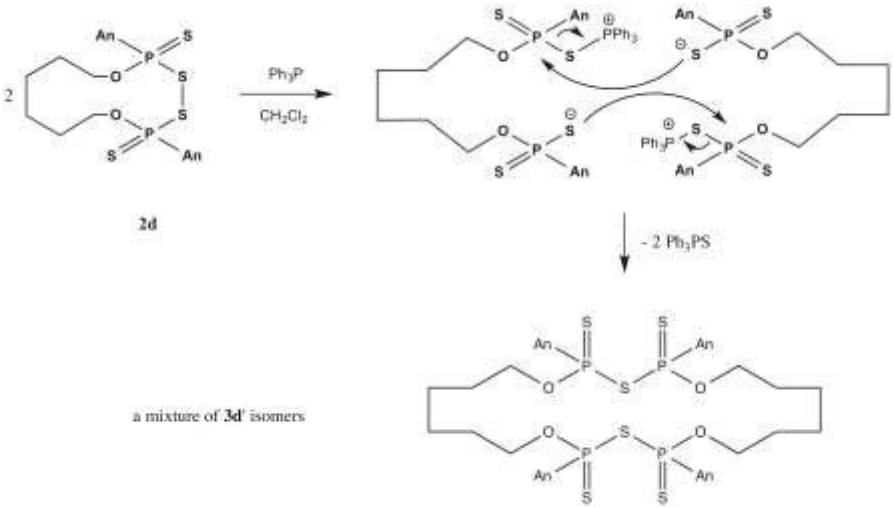
New cyclic 9-membered **2b'** containing ethoxycarbonyl moiety (as suitable starting material for further functionalization or tethering, 85% yield) and 12-membered **2d** (18% yield) as well as previously studied 8-membered **2a**, 9-membered **2b** and 10-

membered **2c** disulfanes have been obtained using our modified procedure [8] without isolation of di-*tert*-butylammonium *bis*(anisylphosphodithioates) **1 x 2 Bu^{t}NH$_2$** precursors (Scheme 3). Also, larger *i.e.* 14-, 16- and 20-membered disulfanes **2** synthesis has been essayed, but without success. In this case, complex mixtures of respective oxidation products of *bis*-phosphonoditioates **1** were tentatively attributed to cyclic disulfane macrocyclic oligomers (based on ^{31}P NMR analysis; see Figure S27).



Scheme 3 Structures of cyclic anisyl disulfanes **2a-d** under the study and related known cyclic and acyclic disulfanes **2e-2i** that have been used for a comparison study.

Next, cyclic disulfanes **2a-2d** have been treated with triphenylphosphine in acetonitrile – dichloromethane (1:1 v/v) and the corresponding cyclic sulfanes **3a-3d** as a mixture of *cis*/*trans* stereoisomers were formed quantitatively as a result of the S-S bond splitting and desulfurization. Just a few minutes after **2a-2c** and triphenylphosphine dissolution, the recorded ^{31}P NMR spectra mixtures consisted only three signals of both isomers of cyclic sulfanes **3a-3c** and triphenylphosphine sulfide (δ_P 43 ppm) (Figure 1 a-c). The presence of two additional broad phosphorus peaks in the spectrum of the **2d**–Ph_3P mixture (Figure 1d) probably indicates the formation of 22-membered dimeric *bis*sulfane **3d'** as a mixture of isomers (Scheme 4).

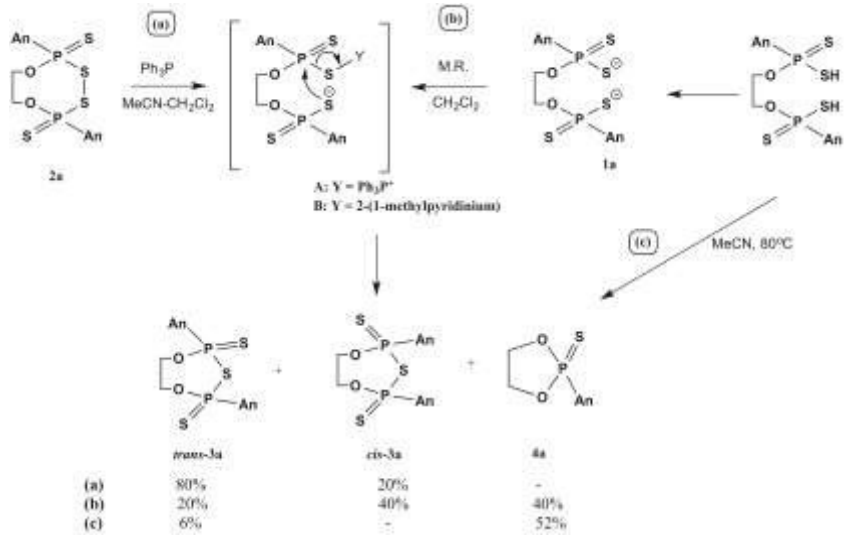


Scheme 4 Postulated intermolecular dimerization of Ph_3P-activated disulfane **2d** leading to *bis*sulfane **3d'**.

To obtain cyclic sulfanes **3a-c** we also used another method developed for the first time by Kato. [7] In this way, treating the appropriate di-*tert*-butylammonium salts of **1** with Mukaiyama's condensation agent (M.R.) afforded both isomers of **3a** and **3b**. As a result **3b** isomers were separated but a slight dominance of the *cis* over the *trans* isomer was noted. Also, the reaction leading to **3a** starting from ethylene glycol derivative **1a** gave even more significant predominance of *cis*-**3a** over *trans*-**3a**.

However, in that case the reaction mixture consisted up to 40% of 5-membered phospholane **4a** (see below) as a by-product (a 40:20:40 *cis*-**3a**:*trans*-**3a**:**4a** ratio).

All routes to cyclic sulfanes **3** under the study are presented in Scheme 5. The mechanism of these interesting desulfurization–cyclisation reactions, and their stereoselectivity is discussed below. Next, the *cis* and *trans* isomers of cyclic sulfanes **3a**-**3c** obtained according to above mentioned procedures were successfully separated chromatographically and their careful crystallization gave good quality crystals to perform X-ray crystallography for solving their structure. Unfortunately, attempts to isolate **3d** isomers were unsuccessful.



Scheme 5 Synthetic routes to cyclic sulfanes **3** of which **3a** is an exceptional example: (a) from disulfane **2a** using Ph_3P (method A), (b) from *bis*(phosphonodithioate) **1a** using Mukaiyama's reagent (Method B), (c) sulfane **3a** as a side product during dithio acid **1a** condensation, leading exclusively to **4a** according to Shabana [17] and Pudovik [19] works.

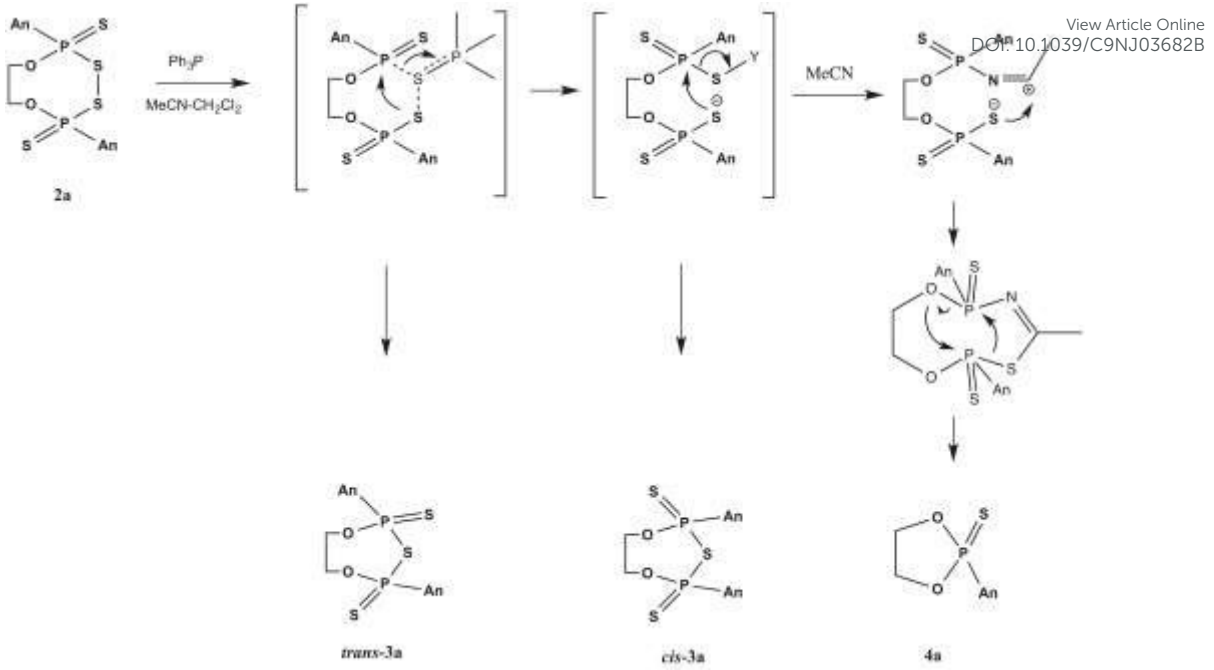
2.2. Mechanism of desulfurization of cyclic disulfanes 2 with triphenylphosphine

The reaction of open-chain *bis*(phosphoyl)disulfanes with P(III) compounds, including phosphines, has been already described [21] and spectroscopic properties of acyclic *bis*(phosphorothioyl) sulfanes **3** as desulfurization products were studied by Grossman. [22] Perlikowska et al [23] used such a transformation for preparation of optically enriched phosphine sulfides and phosphine oxides, where three acyclic enantiomerically pure *bis*(phosphorothioyl)disulfanes **2** were used as sulfur atom donors. Unfortunately, the fate of PSP sulfanes **3**, which were by-products of this reaction, was not followed and the sulfides **3** themselves were not isolated or characterized.

Based on a generally accepted mechanism described for related acyclic *bis*(phosphinoyl)disulfanes **2 (e.g. 2g)** [24], it was assumed that at the crucial step of the reaction phosphonium intermediate arises immediately (even at -100 ^{o}C) after the nucleophilic attack of phosphine on one bridged sulfur atom. In the next step, nucleophilic phosphodithioate (a leaving group) attacks phosphonium salt giving phosphine sulfide and trithioanhydride sulfane **3** (see Scheme 6).

The intriguing results of our preliminary experiments using cyclic disulfanes **2** indicated that their behavior towards phosphines may be slightly different. We suspected the special role of liberated nucleophilic anisylphosphonodithioate on the course of the reaction due to its proximity. Therefore, we decided to investigate in detail the mechanism of the extrusion of sulfur from **2**.

Since the phosphodithioic acids **1** salts (liberated in the reaction) are not optically active as they are a hybrid of two energetically equivalent resonance structures, the desulfurization reaction carried out on one disulfane **2** diastereomer should give an equal mixture of two sulfane diastereomers, *cis*-**3** and *trans*-**3**. The question remains why the *cis*/*trans* isomer ratio of sulfanes **3** never reaches unity and why its value increases nearly proportionally with increasing ring size of disulfane **2**.



Scheme 6 Proposed mechanism of desulfurization-cyclisation of cyclic disulfanes **2** (in which **2a** is an exceptional example) as a special case of the more general desulfurization mechanism supplemented with the postulated specific contribution of acetonitrile in the formation of cyclic five-membered phospholane **4a**.

Therefore, the problem associated with the desulfurization mechanism of our cyclic disulfanes **2** in its stereochemical aspect remains unresolved due to the lack of strong stereochemical proof. It was not known whether the reaction runs *via* pentacoordinated trigonal bipyramidal phosphorus and whether its mechanism is concerted or stepwise. If both isomers of **3** are formed in unequal amounts and their mutual interconversion is not possible then there is a need to reconsider the unquestioned mandatory reaction mechanism and propose a different reaction pathway.

At first, quantitative analysis of reaction mixtures of cyclic disulfanes **2a, 2b** and **2c** and Ph_3P (by means of ^{31}P NMR) was carried out. Next, a much more reliable quantitative analysis based on integration of all signals in ^{1}H NMR spectra followed by chromatographic isolation of both isomers of **3** was done. All three approaches used showed that the populations of diastereomers of **3** can be accurately estimated both by ^{31}P NMR and ^{1}H NMR techniques. In this way, we have found that only the desulfurization of the largest 10- and 12-membered disulfanes (**2c** and **2d**) yields both diastereoisomers of the corresponding sulfanes **3** in almost equal amounts (see Figure 1). On the other hand, in the case of desulfurization of disulfane **2a** and **2b**, the corresponding *cis*/*trans* isomer ratio was 0.24 and 0.50. Thus, if triphenylphosphine mediated desulfurization of **2a** provides four times more of *trans*-**3a**, it may mean that the key rate-determining step proceeds in an S_Ni-like manner with retention of configuration at the phosphorus atom. On the other hand, a dissociative $S_N1(P)$ mechanism should be excluded because it would have to supply equal amounts of *cis*- and *trans*-**3a** (vide infra).

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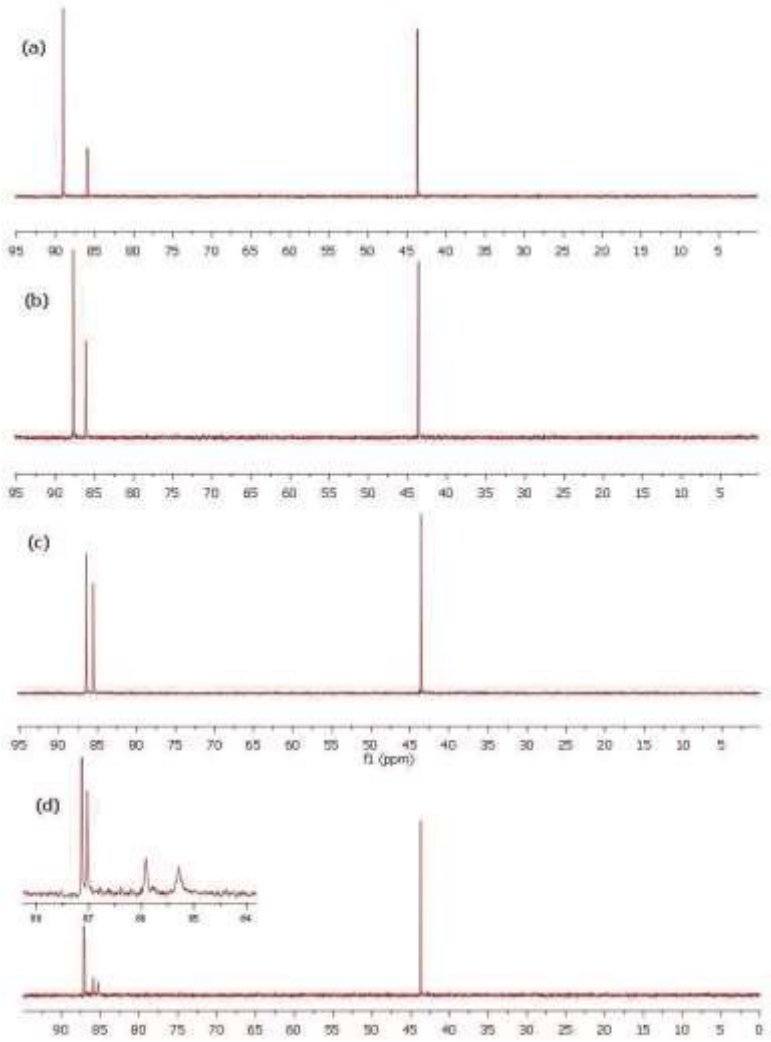


Fig. 1 202 MHz ^{31}P NMR spectra of reaction mixtures of disulfanes **2a-2d** with Ph_3P showing the presence of *cis* and *trans* isomers of cyclic sulfanes (a) **3a**, (b) **3b**, (c) **3c**, and (d) **3d** (δ_P 87.0 and 87.1 ppm). Additional broad signals of dimeric 22-membered *bis*sulfane isomers **3d'** (δ_P 85.3 and 85.9 ppm) accompanying both **3d** isomers (d). The peak at δ_P 43 ppm corresponds to the signal of triphenylphosphine sulfide which is the only by-product of the desulfurization.

Thus, the above mentioned results indicate that the electrophilic phosphorus atom and the nucleophilic dithiophosphonodithioate anion >P(S)S$^-$ being generated from *trans*-disulfane **2** begin to move away gradually from each other since the moment of the S-S bond heterolysis during the desulfurization. Since the likelihood of finding of two ends of the bifunctional chain decreases with increasing the length of the chain, it is obvious that in the case of **2d** desulfurization the spacing between both reactive ends reaches the maximum. Therefore, the open-chain intermediate derived from **2d** has much more time to preorganization, because its cyclisation is the slowest step of the reaction. As a result, populations of *cis* and *trans* isomer are nearly equal for **2d** as well as for **2c**. Besides, in the case of twelve-membered **2d** the probability of reactive centers contact is so low that the probability of intermolecular dimerization also increases (see Scheme 4). At least two of three above postulated and described desulfurization steps (*i.e.*: the S-S bond splitting, preorganization and cyclisation) have different rates for different ring sized disulfanes **2**. Because it is well known that the S-S bond cleavage is the fastest process during disulfane **2** desulfurization, the rate of cyclisation and the preorganization step dependent on it should affect the isomeric distribution. Thus, there is a correlation between the *cis*/*trans* ratio and the size of cyclic disulfane **2** ring.

To prove that the cyclisation rate affects the *cis*/*trans* isomer ratio, we decided to slow it down by lowering the pH of the reaction medium. We have found that the addition of 2,4-dinitrobenzoic acid to a mixture of **2a** and Ph_3P causes a slight increasing of the *cis*/*trans* isomer ratio of **3a** (from 0.26 to 0.31) apparently due to a reverse protonation of phosphodithioate anion that is formed in the first stage of the reaction (Figure S26). This result strongly suggests that cyclisation step rate determinates the *cis*/*trans* ratio of cyclic sulfanes **3** during cyclic disulfanes **2** desulfurization.

On the other hand, we have found that desulfurization-condensation experiments performed on *bis*-anisylphosphonodithioic acids **1** salts with the aim of Mukaiyama's reagent give the preference of *cis* isomers of **3a** and **3b** (the *cis/trans* ratio: 2.0 and 3.8, respectively, see Figure 2). Almost two-fold increase in the *cis*/*trans* isomer ratio for **3b** compared to **3a** is most likely caused by the formation of 5-membered **4a** in a competitive reaction during **1a** desulfurization. Certainly in that case the direct precursors of cyclic sulfanes **3** are fully preorganized because they have been formed from acyclic **1** rather than cyclic **2** starting materials. Additionally, the lower reactivity of 2-(anisylphosphonothioylsulfenyl)-1-methylpyridinium chlorides in relation to (anisylphosphonothioylsulfenyl) triphenylphosphonium salts (both are the reactive intermediates and direct precursors of **3)** could have a significant influence on the preferential formation of the *cis* isomers in the process of *bis*dithiophosphonic acids **1** salts desulfurization. Evidently, the results of experiment performed on *bis*dithiophosphonic acids **1** salts are proof that *cis*-**3** isomers are more thermodynamically stable than their *trans* isomers. This statement will be further supported by DFT calculations (see below).

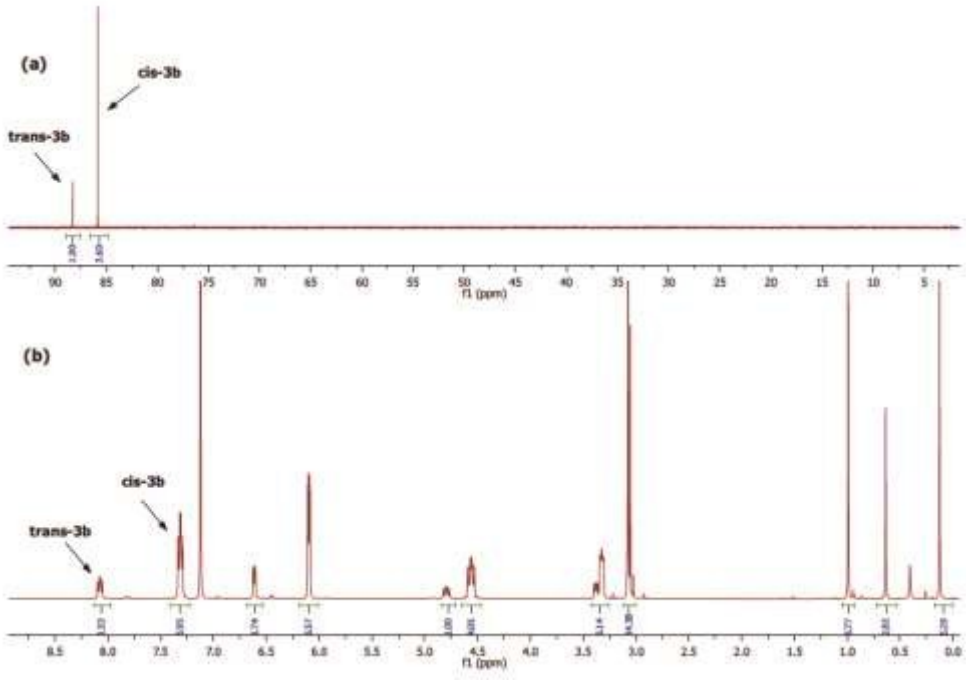


Fig. 2 ^{31}P (a) and ^{1}H (b) NMR spectrum of the reaction mixture of **1b** and M.R. in C_6D_6 after chromatographic separation from two byproducts, namely, 1-methylpyridine-2-thione and *tert*-butylammonium iodide.

It was also necessary to explain the mechanism of the formation of a 5-membered by-product **4a** that accompanied the 7-membered sulfane **3a** isomers. It was found that when we performed the desulfurization of **2a** using Ph_3P in pure acetonitrile comparative amounts of *cis*-**3a**, 5-membered phospholane **4a** and thioacetamide were formed next to the main product *i.e.* *trans*-**3a** (55%) (see Scheme 5). On the other hand, desulfurization of **1a** salt in pure CH_2Cl_2 gave 40% of **4a**. Therefore, acetonitrile (as a competitive nucleophile) taking part in a reversible exchange with the thiotriphenylphosphonium cation (in method a), and to a larger extent the already formed preorganized intermediate with remote reactive end groups (in method b) are both responsible for the side-product (*i.e.*, **4a**) formation during sulfane **3** synthesis trials.

2.3 Cyclic disulfanes 2 stability and decomposition

Among cyclic disulfanes **2a**-**2d**, disulfane **2b** seems to be the most stable. After 10 years of storage of its samples, there was no characteristic unpleasant sulfur-like odour of decomposition products and its melting point did not change. Detailed analysis of the recorded ^{1}H NMR spectra did not show any conformational changes, *trans*-*cis* isomerization, ring destruction or oxidation of 9-membered disulfane **2b** for a broad temperature range. **2b** stays intact in dichloroetylene at 90 ^{o}C for 3 hrs as well as in nitrobenzene-d_5 solution at 190 ^{o}C for 0.5 h. The polymerization processes start only above 200 ^{o}C and are initiated by homolytic scission of the disulfide bridge (see: Figure S24 and 25).

Ring strain energy calculations (the 6-311G* basis set with MN12SX functional) based on hypothetical hydrogenolysis of cyclic disulfanes **2** revealed that both **2c** and **2b** are the most stable and have a stability advantage of 1.2 and 4.4 kcal/mol over **2a** and **2d**, respectively. It should be stressed that the calculated stability order of R10 ~ R9 > R8 >> R12 for cyclic disulfanes **2** is inverse than that for medium-sized cycloalkanes (R12 > R8 > R9 ~ R10) and the respective energy differences are twice smaller (Table 1).

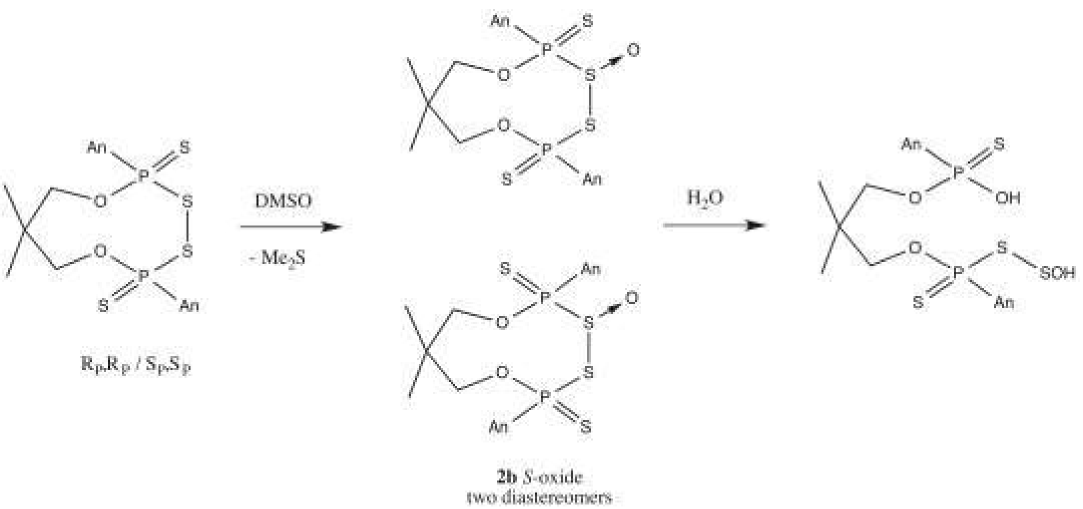
It is known that in medium-sized carbocycles an additional stress occurs due to the presence of transannular hydrogen atoms pointed inwards (so-called transannular strain). On the other hand, the atomic radius of phosphorus and sulfur atoms present in cyclic disulfanes **2** causes that the length of bonds between them and thus the "ring surface" increases. Thus, in consequence, also distances the transannular hydrogen atoms from each other. Inspection of the data in Table S8 leads to the conclusion that transannular hydrogens causes unfavorable H-H repulsive interactions only in the case of both isomers of the largest 12-membered disulfane **2d**, where the corresponding pairs of transannular hydrogens are placed on the same side of the ring. Disulfane **2a** is free of transannular hydrogens and in other disulfanes **2** that contain one or two transannular hydrogens, they approach the sulfur ring atoms and can rather form attractive intramolecular H-bonds.

Table 1 Relative (in kcal/mol) energies of cyclic disulfanes **2** (MN12SX/6-311*/PCM) and the respective cycloalkanes (E. V. Anslyn and D. A. Dougherty, Modern Physical Organic Chemistry, University Science Books, Sausalito, 2006, p. 108).

Compd	**R8**	**R9**	**R10**	**R12**
disulfane **2**	-1.63	-0.42	0	-4.43
cycloalkane	-5.6	-8.5	-8.3	0

As can be clearly seen, cyclic *bis*(phosphothioyl)disulfanes **2** are much more thermally stable than dialkyl, diaryl, and especially dithiocarbamoyldisulfanes (thiurams). Since the later ones are used in vulcanization processes as sulfur donors and ultra-accelerators (the vulcanization initiation temperature in the range of 70-150 ^{o}C), there is a need to discover and study appropriate organic disulfanes, which decompose in a controlled manner in the range of 200-300 ^{o}C. Thanks to the generation of thiyl radicals, they are effective halogen-free flame retardants in various polymer compositions. [25] Thus, exceptional thermal durability is a very valuable property of cyclic disulfanes **2** that can also be potentially promising reagents or additives used in polymer industry.

Some of the cyclic disulfanes **2** under the study exhibit improved hydrolytic stability compared to their acyclic analogs. And so, **2b** preserves intact crystal structure after a few months of storage in an open vessel, while acyclic **2i** shows substantial deterioration after just a few days. On the other hand, we have noticed that disulfane **2b** is rapidly decomposed in DMSO-d_6 solutions due to oxidation and subsequent hydrolysis. On ^{31}P NMR spectrum of **2b** solution in DMSO-d_6 within a few minutes at 80 ^{o}C there appear additional well-resolved multipletes (Figure S28). Their splitting patterns and integration correspond, with all probability, to both diastereomers of **2b** *S*-oxide (48%) in a 1:1 ratio. Unfortunately, all attempts to isolate **2b** *S*-oxide were unsuccessful probably due to its higher polarity and susceptibility to further hydrolysis. **2b** *S*-oxide hydrolysis starts already in a NMR tube and is caused by the presence of residual water in standard DMSO-d_6. As a result, originally colourless solution of the starting disulfane **2b** turns pale yellow and opaque due to precipitation of elemental sulfur, and there is also a strong odour of dimethylsulfane. At this stage of **2b** deterioration, ^{31}P NMR analysis showed the presence of an additional signal (δ_P = 84 ppm) from the endproduct of **2b** *S*-oxides hydrolysis containing the >P(S)OH fragment (Scheme 7). Although a similar redox reaction between simple diorganyl disulfanes RSSR and DMSO is already described in literature, there are no reports on the analogous reaction for *bis*(phosphoryl)disulfanes **2**.



Scheme 7 Proposed mechanism of cyclic disulfane **2b** decomposition caused by wet DMSO.

2.4 Cyclic disulfanes 2 ammonolysis

It turned out that the most intriguing and characteristic reaction of cyclic disulfanes **2** is their ammonolysis, which can be performed in liquid ammonia at -33 °C as well as in methanolic ammonia solutions at ambient temperature. Unlike their open-chain acyclic analogs **2h** and **2i**, all cyclic disulfanes **2a**-**2d** under the study give deep-blue solutions immediately after their dissolution in ammonia. In both cases, different ammonolysis products are also formed. At first, we decided to investigate acyclic disulfane **2h** reactivity toward ammonia using ^{31}P NMR. Based on NMR analysis we have confirmed that *bis*(diisopropylphosphorothioyl)disulfane **2h** treated with a saturated methanolic ammonia in excess gives a colourless solution of the respective sulfenamide $(iPrO)_2P(S)SNH_2$ **5h** (δ_P = 81.3 ppm, *ca* 90%) which is the only product of the nucleophilic substitution on the bridged sulfur atom of **2h** after 1h at room temperature. Later the sulphenamide **5h** slow-rate decomposition reactions start leading after two weeks to the formation of a stable end-product, namely ammonium diisopropylphosphorothioylthioate **1h** (δ_P = 109.1 ppm, >95%) (Figure 3).

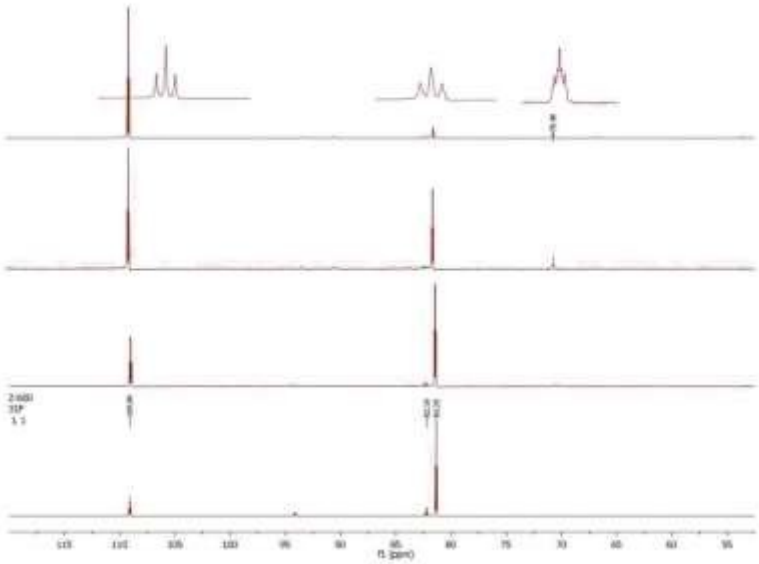


Fig. 3 $\{^1H\}$ ^{31}P NMR spectra of $[(iPrO)_2P(S)S]_2$ **2h** in 10 M methanolic NH_3 recorded after 16 h, 48 h, 3 days and 2 weeks (from a bottom to a top) showing slow decomposition of $(iPrO)_2P(S)SNH_2$ **5h** δ_P = 81.3 ppm (t, J = 11.5 Hz) into $(iPrO)_2P(S)S^-NH_4^+$ **1h** δ_P = 109.1 ppm (t, J = 13.2 Hz). Minor signals at 82.21 ppm (t, J = 12.4 Hz) and 70.40 ppm (tt, J_1 = 11.1 and J_2 = 4 Hz) correspond to unreacted starting material **2h** and amide $(iPrO)_2P(S)NH_2$ **6h**, respectively.

As was mentioned above, cyclic disulfanes **2** dissolved in saturated methanolic ammonia give solutions with a long-lasting deep-blue coloration (the color last over two months in a screw vial). EPR experiments performed with these blue solutions did not reveal any signal of radicals and the UV-Vis absorption peak position (λ_{max} = 563 nm, ε = 6528) was constant for all disulfanes **2a**-**2d**. Therefore, we assumed that one type of "NS" species that is formed is responsible for the deep-blue coloration. [26] As the concentration of ammonia decreases due to evaporation from a semi-open UV cuvette, the color loses its intensity and eventually disappears (Figure 4).

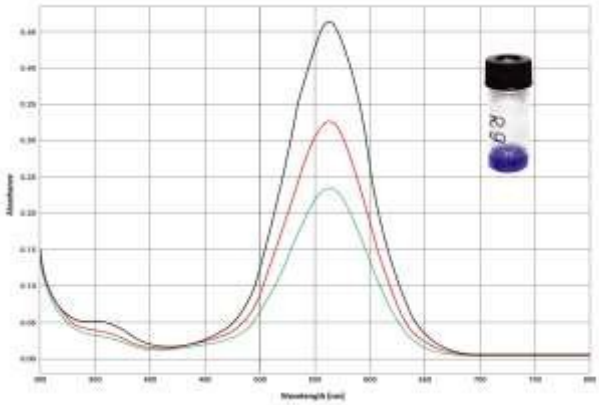


Fig. 4 UV spectrum of 7.2 x 10^{-5} M solution of **2b** in 10 M methanolic NH_3 recorded in open cuvette showing a decay of absorbance in time (2 min → 45 min).

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The recorded ^{31}P NMR spectrum of the deep-blue **2b** ammonia-methanolic solution confirmed that the main ammonolysis product **6b** has the same structure as the sulfane **3b** ammonolysis product and posses two functional groups, i.e. >P(S)NH_2 (δ = 77.2 ppm) and >P (S)S^- (δ = 105.3 ppm) (Figure 5).

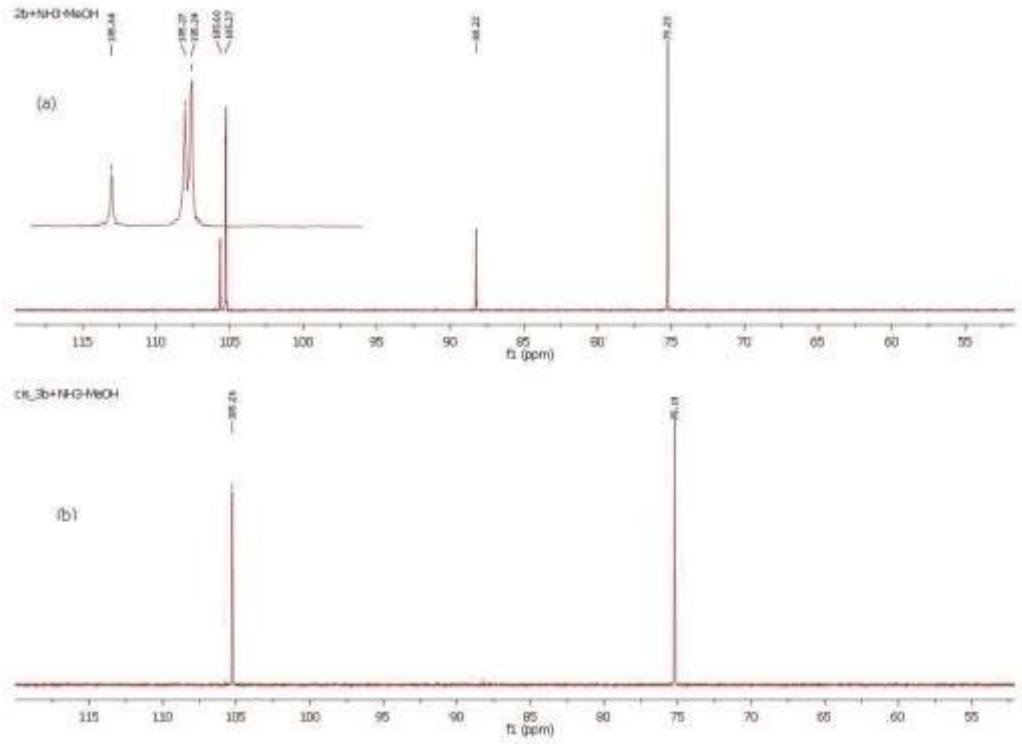


Fig. 5 202 MHz ^{31}P NMR spectra of the reaction mixture between methanolic ammonia in excess and (a) disulfane **2b** and (b) sulfane *cis*-**3b** recorded 1 h after the reactants were mixed.

Thus, at first sight, ammonia behaves as previously tested hydroxamates attacking preferably the hard phosphorus atom of cyclic disulfane **2** to release the phosphodisulfane anion >P(S)SS^-. [13] However, it should be stressed that such a statement would be totally contrary to our results of ammonolysis experiments on disulfane **2h** (vide supra) and to Khaskin [27] results. Khaskin claimed that the corresponding phosphorothioyl sulfenamides **5** >P(S)SNH_2 alone are products of acyclic *bis*(phosphorothioyl) disulfanes **2** ammonolysis and that ammonia prefers a soft sulfur atom of the disulfide bridge in disulfanes **2**. It is worth mentioning Michalski's results [28] here, who noted that related primary phosphoryl sulfenamides >P(O)SNH_2 are labile and decompose quickly to give phosphoramides >P(O)NH_2 and elemental sulfur. Apparently, phoshorothioyl sulfenamides **5** are much more stable than the respective phosphoryl sulfenamides.

A more careful analysis of the ^{31}P NMR spectrum of the deep-blue solution of **2b** in methanolic ammonia after 1 h showed that the formation of phosphorothioyl sulfenamide >P(S)SNH_2 **5b** as an intermediate should not be excluded. Besides the amide **6b**, the presence of small amounts of the the respective methyl ester **7b** and diammonium salt of **1b**, *i.e.* the product of reduction of the starting disulfane **2b** was corroborated by doping of authentic samples into the reaction mixture. The yields of individual disulfane **2** ammonolysis products were estimated based on the intensity of the phosphodithioate residue signal for **6b** (57%), **7b** (18%) and **1b** (25%) (Figure 6).

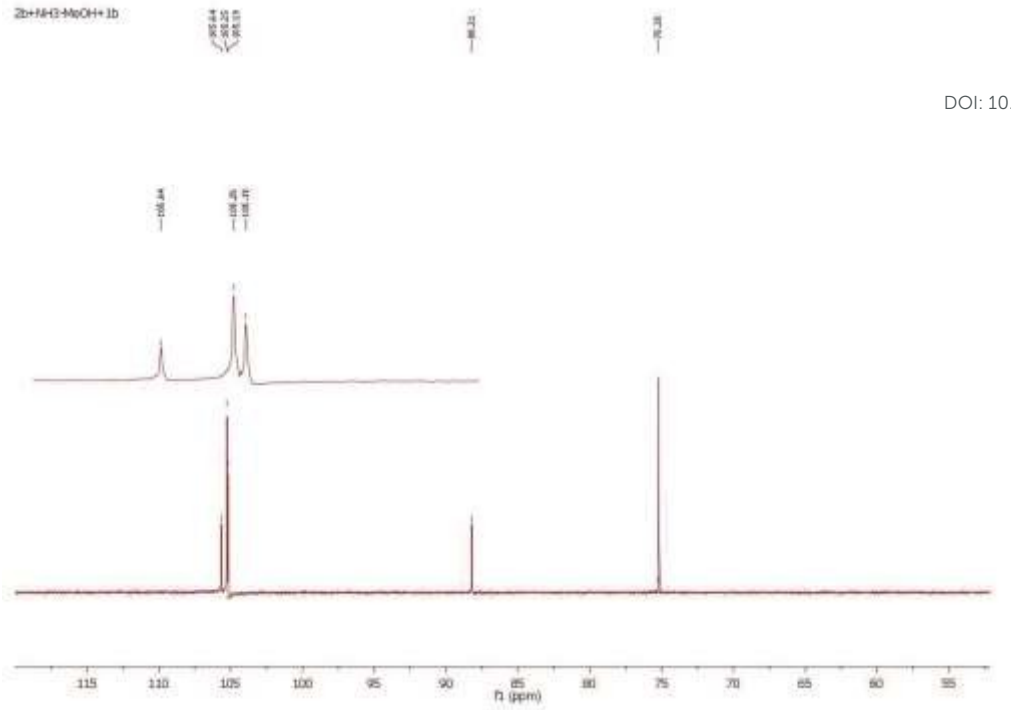
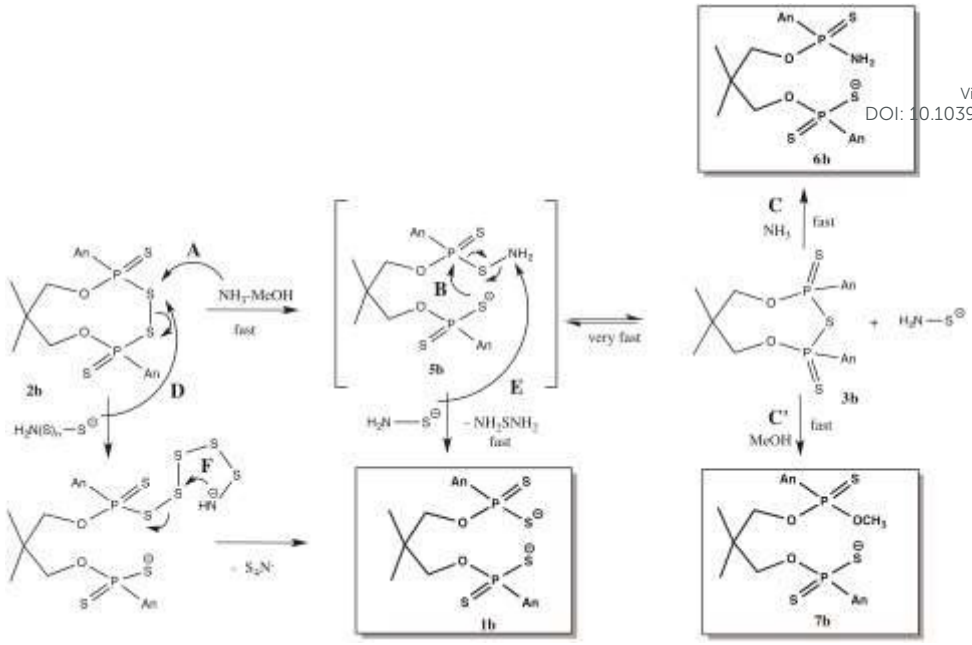


Fig. 6 ^{31}P NMR spectrum of a solution of disulfane **2b** in 10 M methanolic ammonia recorded after 1 h and enriched with **1b**. The presence of diammonium dithioate **1b** $(CH_3)_2C[CH_2OP(S)(An)SH]_2 \cdot 2\ NH_3$ (δ_P = 105.25 ppm) was thus confirmed. The presence of amide ammonium thioate $NH_2P(S)(An)POCH_2C(CH_3)_2CH_2OP(S)(An)SH \cdot NH_3$ **6b** (δ_P = 75.3 ppm and δ_P = 105.19 ppm) and methyl ester ammonium thioate $NH_3 \cdot CH_3OP(S)(An)OCH_2C(CH_3)_2CH_2OP(S)(An)SH \cdot NH_3$ **7b** (δ_P = 83.0 ppm and δ_P = 105.64 ppm) was also unequivocally verified by doping of authentic samples.

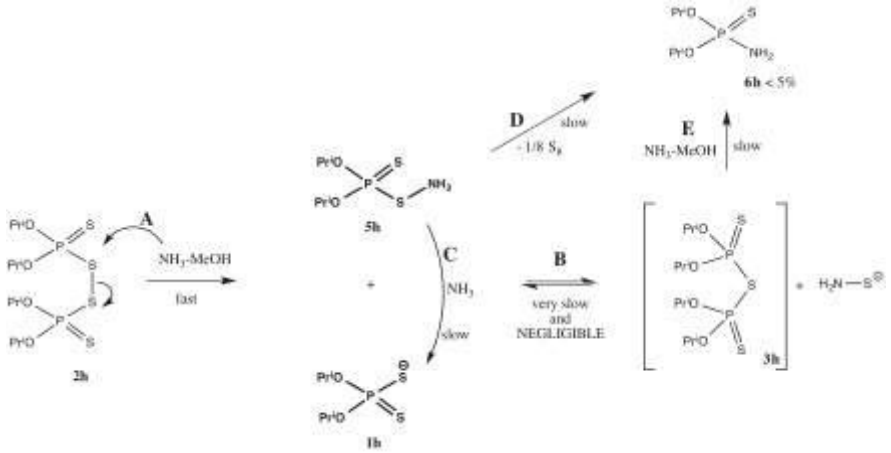
On the other hand, we have found that **2b** stays intact in triethylamine methanolic solution for three days, but it reacts with it smoothly in the presence of DBU (1 equiv) yielding exclusively the methanolysis product **7b** (δ_{P1} = 88.2 ppm, δ_{P2} = 105.6 ppm). Because ammonia is much weaker base than triethylamine, we have concluded that the mechanism of disulfane **2b** to **7b** conversion in methanolic ammonia is not direct and must be more complex. At first, we postulate that the reaction proceeds *via* the formation of reactive sulfenamide $>P(S)SNH_2$ **5b**, which is prone to intermolecular nucleophilic substitution at phosphorus atom by neighbouring phosphodithiolate group yielding cyclic sulfane **3b**. Next, a reactive ring of sulfane **3b** (formally cyclic anisylphosphodithioic acid anhydride) undergoes a fast opening in methanolic ammonia to give the respective phosphorothioamide **6b** and traces of methyl ester **7b**. As stated above, the same main product **6b** was formed when pure sulfane *cis*-**3b** was subjected to the action of ammonia in methanol. More accurate inspection of the recorded ^{31}P NMR spectrum (see Figure 8) showed that trace amounts of the respective methyl ester salt **7b** were also formed (<2%) from **3b**. The formation of **6b** and **7b** directly from sulfenamide **5b** is excluded as sulfenamide $(iPrO)_2P(S)SNH_2$ **5h** described above did not undergo either ammonolysis or methanolysis under the same reaction conditions.

In summary, the formation of **6b** as the main product of cyclic disulfane **2** ammonolysis is the result of three consecutive steps, namely, the nucleophilic attack of ammonia at the bridged sulfur atom of **2b** (A), the cyclisation to trithioanhydride **3b** (B) and finally ammonolysis/methanolysis of **3b** (C/C'). Methyl ester **7b** is formed from cyclic **3b** and its yield depends on the concentration of methanol (i.e. decreases significantly when freshly saturated methanolic ammonia is used). We believe that the appearance of **1b** among the reaction products is the result of the reduction of sulfenamide $>P(S)SNH_2$ **5b** (route E) or disulfane **2b** (route D-F), which occurs with the participation of ammonium salt of thiohydroxylamine NH_2SNH_4. Ammonia alone can not effectively reduce sulfenamide **5b**, because a similar process on a simple sulfenamide **5h** carried out under the same conditions takes place very slowly within two weeks (vide supra). On the other hand, it is well known that the trivalent nitrogen atom in hydroxylamine derivatives is characterized as a fairly soft base center in terms of the HSAB principle. Thus, ammonium sulfenamide NH_2SNH_4 as a supernucleophile and a soft base is able to replace **1b (**a very good leaving group) on sulfenamide **5b** nitrogen atom or even cause starting disulfane **2b** ring opening. The proposed sequence of reaction steps D-E-F can be repeated to furnish a more complex NS species such as blue S_4N^- (Scheme 8).



Scheme 8 Postulated transformations of cyclic disulfane **2b** in methanolic ammonia leading to three organic end-products: thiophosphonoamido-phosphonodithioate **6b**, *O*-methylthiophosphonato-phosphonodithioate **7b** and **1b**, accompanied by S_4N anion, which is probably responsible for a characteristic deep-blue-coloration.

The above reported experimental results also strongly suggest that analogous intermolecular contribution of **1h** to the formation of acyclic trithioanhydride **3h** has an inconspicuous effect on splitting of the respective sulfenylamide >P(S)SNH_2 **5h** considering ammonolysis as a whole process. The lack of a characteristic deep-blue coloration of acyclic disulfides (e.g. **2h**) ammonia solutions is caused by very low concentration or even the absence of any colored SN species. Therefore, we confirmed simultaneously a plausible mechanism of specific cyclic disulfanes **2** ammonolysis (see Scheme 8) and a significant stability of simple sulfenamides (e.g **5h**) those stay intact in the presence of ammonia in excess (Scheme 9).



Scheme 9 A proposed mechanism for the transformation of acyclic disulfide **2h** in methanolic ammonia solution.

2.5. Crystal structure of cyclic disulfanes 2

The geometry and conformations of the main ring of cyclic disulfanes **2** and especially of its PSSP unit have been determined and tested using a combination of X-ray crystallographic analysis and NMR spectroscopy (see section 2.7).

All cyclic disulfanes **2** are formed from the respective *bis*-anisylphosphonodithioates **1** as *trans* isomers and exist solely as *trans* isomers. It is well known that the *zig-zag* geometry of P_2S_4 unit is the most common in acyclic disulfanes **2**. [29] It was

imposed by cyclisation and obviously provides an extra stabilization for the *trans*-geometry of disulfanes **2**. That special shape of SPSSPS motif must be much more attractive than π–π interactions in hypothetical *cis*-**2**. Anisyl-anisyl stackings were observed in both polymorphs of acyclic t*rans*-disulfane **2i** (R=iPr; intercentroid distances = 3.725 and 3.828 A, interplanar angles = 10.6 and 18.2°) [28], but not in *trans*-disulfane **2j** (R = L-menthyl) [11]. It follows that these types of interactions can exist among acyclic disulfanes **2** where rotation around the S-S bond is free and alkoxy substituents do not provide (as in **2j**) more favorable van der-Waals attractive forces. Indeed, the predicted free energy difference were 3-5 kcal/mol more favorable for cyclic *trans*-**2** are of that for cyclic *cis*-**2**.

It should be added that acyclic disulfanes **2** are usually formed as mixtures of two diastereomers, as was observed, *inter alia*, by Woollins. [29] After oxidation of the corresponding anisylphosphonodithioate **1i**, the presence of both (R_P,S_P)/(S_P,R_P) and (R_P,R_P)/(S_P,S_P) stereoisomers of **2i** were confirmed and two polymorphs of the other one in the crystal were characterized. We postulate that both Woollins's stereoisomers are solely *trans*-disulfanes, but one contains anisyls arranged in π-stackings and the second has *trans*-oriented anisyls. As we will explain below, the diagnostic effect of anisyls π-π interactions is a significant deshielding of *ortho*-protons as well as C-1' carbons that is observed in NMR spectra of cyclic disulfanes **2**. This tendency can also be found in the spectroscopic description of Woollins' disulfanes. [29] In addition to the larger distance separating both anisyl rings in linear disulfane **2i**, an additional feature that differentiates their mutual position is that they are arranged convergently in **2i** but divergently in hypothetical cyclic *cis*-**2** as well as in *cis*-**3** sulfanes (see below).

All crystal structures of cyclic disulfanes **2**, except **2d**, have fixed geometry of both rotable methoxyl groups. In **2a**, **2b**, **2b'** methoxyls are *anti*-oriented and in **2c** *syn*-oriented. For **2d** where both polymorphs were isolated independently, energy calculations showed insignificant preference of *anti*-**2d** ($\Delta G^0_{syn\text{-}anti}$ = 0.05 kcal/mol, ΔH^0 = -0.14 kcal/mol). Apparently for smaller rings (8 - 10-membered) optimal packing of molecules requires a suitable (*syn* or *anti*) methoxyl orientation, while in the case of the largest 12-membered ring of **2d** allows the existence of two forms slightly differing in packing efficiency in their crystals. Since methoxyl pairs of all tested cyclic disulfanes **2** were involved in the formation of weak hydrogen bonds in crystal state (both as donors and acceptors), their mutual arrangement certainly affects the strength of intermolecular interactions.

A specific structural feature of acyclic chairlike thiophosphates such as **2g** is their preference for a conformation with axial P=S substituent due to stabilizing anomeric effect. [30] For our disulfanes **2a**-**2d** this preference is not observable at all. As was mentioned above, both the anisyl and the P=S adopt usually intermediate, inclinal positions. For *syn*-**2d** only anisyl groups (not P=S) prefers to be in a pure axial orientation and in the case of **2b** (closely related to **2g**) also anisyl shows greater tendency to choose an axial than equatorial position (RC-P-C angle of 67° vs RC-P=S angle of 51°). Undoubtedly, the preference of the axial position by the anisyl groups, which are much steric bulkier than sulfur atom (A-values: 3 vs 1.3, respectively), is connected with a more energetically favorable anomeric stabilization with an aromatic ring participation. The shielding of C-1 atoms in anisyls expressed by observed lower ^{13}C chemical shift values for **2b** and **2d** (Δδ = 1 ppm) is an indirect proof for this statement.

We expected that the lengths of P-S and S-S bonds in disulfanes **2a**-**2d** may be important in explaining the observed differences in their reactivity toward nucleophilic reagents, including their hydrolytic stability. However, both bonds only slightly increase in length with increasing size of the disulfane **2a**-**2d** ring (by 0.016 and 0.08 A, respectively). In addition, the dependence of the S-S bond length on the PSSP torsion angle, as established by Potrzebowski [31] for acyclic *bis*[phosphoro(thio)yl]disulfanes, is not met. For this relationship, similar in the course of the curve to the appropriate dependence for diorganyl disulfanes RSSR [32], there is a minimum at the torsion angle PSSP 90°, which explains the particular stability of *bis*(phosphothioyl)disulfanes **2** (e.g. **2g**) with this structure. Significant discrepancies occurring for disulfanes **2a** and **2b**, for which the S-S bond lengths are longer than anticipated by about 0.04 Å, presume that such a relationship does not exist for cyclic disulfanes **2a**-**2d**, where it is not the PSSP torsion angle but the ring closure defines the S-S bond distance.
A lack of correlation was also noted for relating Raman stretching frequencies of S-S bonds to their respective S-S bond distances and PSSP torsion angles in our disulfanes **2** (484, 476 and 482 cm^{-1} for **2a-c** respectively; Figure S32-36). However, according to the literature, these relationships are rare, because too many structural factors affect the frequency of stretching vibrations of S-S bonds in disulfanes. [33]

Thus, the the above-mentioned exceptional hydrolytic stability of **2b** as compared to other cyclic **2** under the study can be mostly due to steric protection (branching at β-carbon; **2b** is a neopentyl ester) and/or so-called the *gem*-dimethyl effect. [34]

Similarly, we did not notice remarkable differences in the P=S bond length for disulfanes **2** under the study. We found that none of their individual molecular parameters significantly affect the P=S bond length. These values are similar to those given by Woollins [28] for linear disulfane **2i**.

The complete structural parameters of all cyclic disulfanes **2** are listed in Tables S3 and S7.

Crystal Packing and intermolecular interactions of Cyclic Disulfanes 2

Non-classical hydrogen bonds in disulfanes **2**. For cyclic disulfanes **2a** and **2c** weak hydrogen bonding of the C—H…O or C—H…S type were found and were already described in our previous work.[12] Detailed parameters of hydrogen bonding for the other disulfanes **2** are presented in Table S6. No significant intramolecular hydrogen bonds were found. Since O-atoms from the macrocycle are not involved as acceptors in the hydrogen bonding the conformation of the ring is not influenced by this effect (unlike for described earlier **2a** and **2c**). Two C—H…O interactions can be noted in **2b** and *syn*-**2d mono**, where hydrogen bond donor is aromatic C-H bond from anisyl group (**2b**) or methoxy C-H bond (*syn*-**2d mono**) and the acceptor is O-atom from methoxy anisyl residue in both cases. Hydrogen bonds of the C—H…S type are formed mainly with P=S type of sulfur acceptors with the only exception of bonding to S2 in **2b'** which is also weak regarding the angle *D*—H···*A* of only 125°.

Among disulfanes **2** studied, the most interesting crystal packing motif has **2b'**. Molecules of **2b'** are connected to each other using week non-classical H-bonds: C6—H6C… $O3^{i}$ (see Table S6) and centrosymmetric cyclic motif C15—H15…S3 thus forming infinite rods spreading along the **a** axis. Bonding of the rods is accomplished by π – π stackings mentioned below (Figure 7).

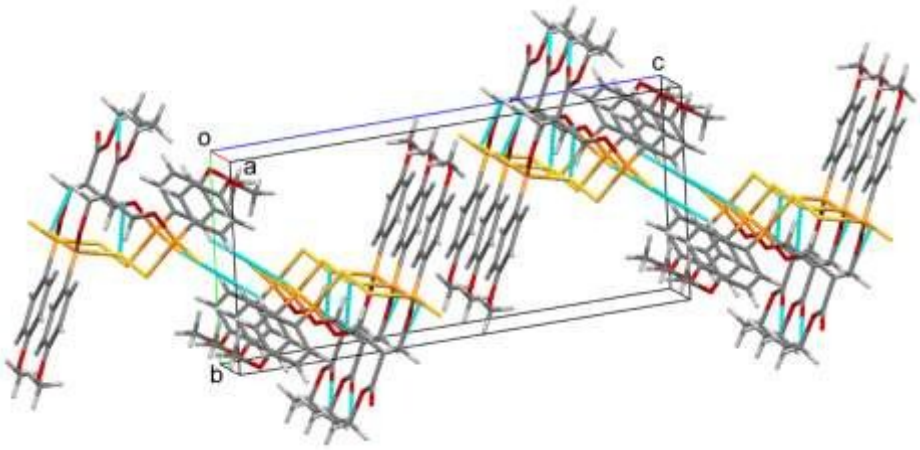


Fig. 7 Crystal packing of **2b'**. Parallel stacking of anisyl rings are readily visible in the middle of the unit cell.

Stacking interactions in disulfanes **2**. Minimal distances found between centroids of potentially stacking aromatic rings (anisyl groups) are listed in the table 2 and are rather long indicating minor role of stacking for intermolecular interactions. All data are based on calculations performed by PLATON program (A. L. Spek, *Acta Cryst*., 2015, **C71**, 9-18.)

Table 2

	2a [Ref. 10]	**2b**	**2b'**	**2c** [Ref.10]	*anti*-**2d mono**	*syn*-**2d tri**
Minimal distance between ring centroids, Å	5.0956(3)	5.0185(5)	4.4434(7) and 4.5143(7)	4.9213(4)	4.3778(8)	4.9208(6)

Interaction between rings	Insignificant	Insignificant	C20-C25 and its equivalent (1-x,1-y,1-z); C10-C15 and equiv. (2-x,2-y,-z)	Insignificant	C10-C15 and its equiv. (1/2-x,1/2-y,-z)	Insignificant

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2.6. Crystal structure of cyclic sulfanes 3 and theoretical calculations

It has been proved by experiments, that cyclic sulfanes **3** derived from disulfanes **2** can exist both as *cis* and *trans* isomers. It is important to note that every *cis* isomer of cyclic sulfides **3** have a higher melting point than its opposite isomer. Of course, this feature may be related to their higher polarity (lower R_f values observed on silica gel TLC plates). However, the inverse correlation between the melting temperature difference (Δmp) and the difference in retention coefficients (ΔR_f) is much more characteristic (for **3a** isomers, Δmp is the lowest, while ΔR_f is the highest).
On the other hand, it was found that none of the higher-melting crystals *cis*-**3** is significantly denser (only *cis*-**3c** has about 5% higher density), nor does not contain more strongly bound molecules compared to the crystals of the opposite isomer. It has been proved by a standard calculation performed on sulfanes **3** involving their crystal data. Thus obtained lattice energy values are significantly lower for trans isomers of **3a** and **3b**, but only slightly lower for trans isomer of **3c** (see Table 3).
In the first approximation, the much larger dipole moment of each *cis* **3** isomer is caused by the presence of both polar P=S groups directed by negative poles in the same direction, and the difference of the dipole moment values between the *cis* isomers ($\Delta\mu_D$) by the angle of the P=S vectors. However, the estimation of the $\Delta\mu_D$ of each cyclic sulfane **3** (as the sum of the individual P=S bond vectors) on this basis leads to the opposite conclusion that the $\Delta\mu_D$ increases with the expansion of the sulfane **3** ring.
Fortunately, respective total dipole moments calculated for the optimized structures in DCM solutions are much more reliable. Both dipole moments and differences for the isomer dipole moments $\Delta\mu_D$ of **3** explain sufficiently their retention behaviour on TLC plates. The dipole moment increases for *trans* isomers and decreases for *cis* isomers with sulfane **3** ring enlarging. Thus, $\Delta\mu_D$ values decreases also from **3a** to **3c** reflecting a characteristic retention on silica of every isomer (μ_D: 9.77 D, 1.87, 8.75, 5.01, 9.81, and 6.42 D for *cis*-**3a**, *trans*-**3a**, *cis*-**3b**, *trans*-**3b**, *cis*-**3c**, and *trans*-**3c**, respectively).

Performed calculations showed also that all *cis*-**3** sulfanes are thermodynamically more stable than *trans-ones* . Such a statement supported by experiments (vide supra) is not common in literature, because *cis* isomers are usually less stable than *trans* ones mainly due to steric hindrance. The structure of *cis*-**3** sulfanes is similar only to the structure of hypothetical *cis*-1,3-diaryl-1,3-dimethylcyclohexanes, which, according to calculations exist only in the conformations with diaxial aromatic rings in the π-stacked orientation. [35] The π-stacking system in *cis*-**3** sulfanes, however, more closely resembles the structure of the 6-membered thiophosphine oxide trimer *cyclo*-$(AnsPOS)_3$, where two of the three anisyl rings assume a parallel orientation (intercentroid distance = 3.695 Å; interplanar angle = 8.7°). [36] In both described above examples, the 1,3-diaxial adverse effect is usually beneficial due to the participation of aryl groups in it.

As was expected, a relative energy difference $\Delta G_{cis\text{-}trans}$ diminishes with sulfane **3** ring size (Table 3). This trend can be explained only by the energy differences among the *trans*-isomers, because the key geometric parameters of the mutual orientation of the approximately coplanar anisyl rings in *cis* sulfanes **3** are not significantly different from each other (for *cis*-**3a**, *cis*-**3b** and *cis*-**3c** the intercentroid distance is 3.637, 3.694, 3.528 Å and the interplanar angle is 4.1, 11.6, 2.3°, respectively). As a reminder, the parent cyclic disulfanes **2** exist only as *trans* isomers, which results to a large extent from the greater distance of *P*-anisyl rings in the hypothetical *cis* isomers caused by the presence of the disulfide bridge (see above). Some relevant structural differences between the *cis* and *trans* isomers are detailed below when discussing the ^1H and ^{13}C NMR spectra of sulfanes **3**. As has been mentioned above, the highest observed difference in relative energy for sulfane **3a** isomers (-1.57 kcal/mol) is not reflected in a desulfurization experiment where 4-fold more *trans*-**3a** is formed. Obviously, this is caused by the fact that desulfurization of cyclic disulfanes **2** is an irreversible reaction under kinetic control.

Table 3 Calculated relative energies for hypothetical *cis*-disulfanes **2** and actual *cis*-sulfanes **3** in kcal/mol.

	$\Delta G_{cis\text{-}trans}$	$\Delta H^0_{cis\text{-}trans}$	% *cis*	$\Delta E_{latt\ cis\text{-}trans}$*
2a	4.77		0.03	-
2b	5.40		0.01	-
2c	-1.14		(87.5)	-
2d	3.46		0.27	-

3a	-1.57	-2.08	93.6	6.8
3b	-1.14	-5.15	87.5	5.8
3c	-1.13	-3.48	87.3	1.5

(*) $\Delta E_{latt\ cis\text{-}trans}$ were referenced to computed intermolecular potentials from crystal data using Mercury 3.8.

Regarding the indication of transannular hydrogens effect on the stability of sulfanes **3**, the analysis of the data from Table S8 shows that every cyclic sulfane **3** possess one or two transannular hydrogens. However, none of these causes unfavorable H-H repulsive interactions, but rather forms attractive intramolecular H-bonds with the participation of the bridged sulfur atom, especially for *cis*-**3a** and *trans*-**3b**. Therefore, the formation of transannular CH...S bonds can also be beneficial and responsible for the exceptional stability all *cis*-**3** beside attractive π-π stackings.

The complete structural parameters of all cyclic disulfanes **3** are listed in Tables S4 and S7.

Analysis of the Crystal Packing and Intermolecular Interactions in cyclic Sulfanes 3

Stacking interactions in sulfanes **3.** The shortest distances between centroids of potentially stacking aromatic rings (anisyl groups) are listed in the Table S5 and are generally much shorter than for disulfanes **2**, indicating the importance of stacking in interactions among investigated sulfanes **3**. It is expected for *cis* isomers to form parallel orientation of anisyl rings inside the molecule and it is indeed so. The table indicates the number of molecules in the asymmetric unit *Z'* to present the situation properly. Nevertheless, also for *trans*-configuration intermolecular π – π stacking is observed in the cases of *trans*-**3a** and *trans*-**3b**.

Intermolecular H-bonds forms both CH...S as CH...O systems. Among them one can found some strong bonds concerning the corresponding distances of <2.9 Å and <2.5 Å, respectively. Detailed parameters of hydrogen bonding are presented in Table S7.

2.7. Solution state structure of cyclic disulfanes 2 and sulfanes 3

As previously suggested based on standard NMR spectra, [8] cyclic disulfane **2a** and **2b** rings are fairly rigid in solution. Analysis of variable temperature ^{1}H and ^{31}P NMR spectra carried out as a part of this work fully confirmed the earlier statement. All proton multiplets and phosphorus signals remain unchanged at higher temperatures (up to 185 ^{o}C) in anhydrous solvents (Figure S24 and S25). At low-temperatures (up to -80 ^{o}C) proton and phosphorus signals remain sharp too, but slight changes in the position of CH_{eq}, CH_{ortho} and OCH_3 proton signals (**2b**: Δδ = +0.04, +0.06, and -0.02 ppm) as well as more noticeable shielded phosphorus resonances (Δδ = -0.6 and -0.9 ppm for **2a** and **2b**, respectively) were observed (Figure S23). On the other hand, the finding that the **2a** and **2b** phosphorus chemical shift values (δ_P) decrease proportionally with the temperature agrees with the general theory of dishielding. [37]

We also sustain our previous statement [8] that axial *alpha*-protons are more deshielded than their equatorial counterparts (see below) in cyclic disulfanes **2a-c** (**2d** is the exception) and also in all cyclic sulfanes **3**. This fact was confirmed by comparing the HCOP torsion angles found in the crystal state with the observed $^{3}J_{HCOP}$ coupling constants (see below). At first glance, this extraordinary deshielding of axial protons seems to contradict the general shielding theory arguing that in cycloalkanes (due to the C-C bond anisotropy) and also in heterocycloalkanes (due to the *n*-σ* delocalization) axial protons resonate rather at higher fields than equatorial ones. [38] We postulate that the proximity of the P=S groups (anisyls are significantly distant), their magnetic anisotropy and dispersion interactions, are the main factors that enhances deshielding of axial protons in cyclic disulfanes **2**. Additional proof for this statement we have found in disulfane **2** and sulfane **3** crystal state, where the respective P=S…H_{ax} distances are shorter as compared to P=S…H_{eq} ones (see above). Another, but not less important reason for the shifting of axial proton signals to lower field (especially for some sulfanes **3)**, is the possibility of forming CH...S intramolecular hydrogen bonds with the participation of transannular inward-pointed hydrogens and ring sulfur atom (see Table S8). According to the literature, systems where intramolecular CH...S hydrogen bonds play a key role in stabilization are rare.[39]

The increase in conformational freedom of disulfane **2c** and especially of 12-membered **2d** is evidenced by, among others, a much smaller difference in the chemical shifts of their axial and equatorial protons $\Delta\delta_{Hax\text{-}Heq}$ (see Figure S29). For disulfane **2d**, assigning ^{1}H NMR signals to axial and equatorial protons becomes ambiguous due to existence of a mixture of conformers in dynamic equilibrium as in the case of acyclic disulfane **2g** containing 6-membered dioxaphosphorinane rings. [40] For **2g**, the observed difference in chemical shifts of geminal protons ($\Delta\delta_{Hgeminal}$ = 0.37 ppm) was also small and additionally, both $^{3}J_{HCOP}$ coupling constants were strongly dependent on the temperature ($\Delta^{3}J_{HA\text{-}P}$ = -3.5 Hz and $\Delta^{3}J_{HB\text{-}P}$ = +3.5 Hz in the range of -50 ^{o}C to rt), which clearly indicates a rapid inversion of chair conformations.

Despite the fact that ^{1}H and ^{31}P NMR measurements carried out at low temperatures (up to -80°C) did not show any dynamic behavior, which should result in line broadening or changing the coupling constants for **2a** and **2b**, small ring pseudolibrations should not be excluded. Based on the observed consistency of the $^{3}J_{HCOP}$ coupling constants in the range of negative temperatures, we assume that the respective HCOP torsion angles of disulfanes **2a**, **2b** and **2b'** in solutions undergo only minor changes and their values can be arithmetic averages of the respective angles measured in the crystal state. A comprehensive study of relationship of $^{3}J_{HCOP}$ coupling constants with the HCOP torsion in acyclic disulfanes **2** in the range 70-180^{o} was reported by Potrzebowski. [31] Currently, we decided to determine the Karplus relationship [41] for cyclic disulfanes **2** (ϕ_{HCOP} 1 - 143^{o}), for cyclic sulfanes **3** (ϕ_{HCOP} 1 - 165^{o}) and **4a** (Figure 8) with a much wider range of appropriate torsion angles. Therefore, the torsion angles for axial and equatorial *alpha*-protons were taken from X-ray data (Tables S3 and S4) and were averaged, and coupling constants values from the respective ^{1}H NMR spectra. It should be stressed that for larger rings (10- and 12-membered), one should expect greater deviations from thus determined Karplus dependance.

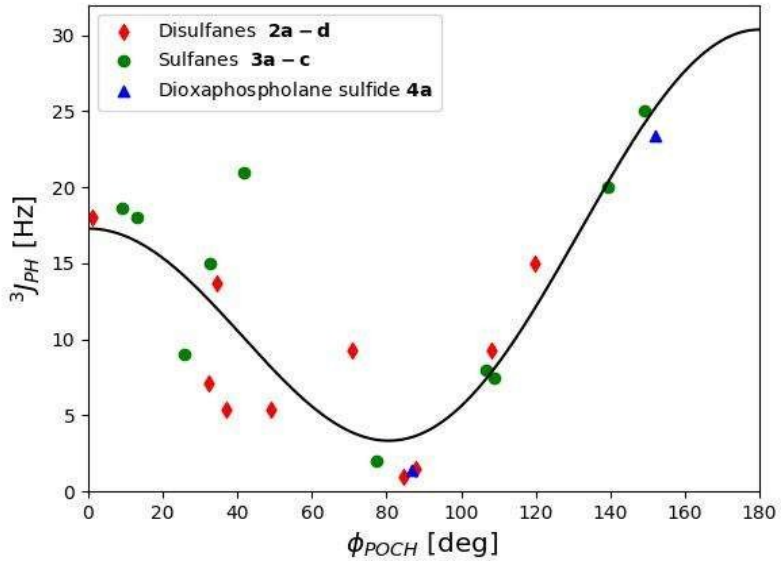

Fig. 8 Karplus dependance ($^{3}J_{POCH}$ = 9.98 cos 2 □ - 6.54 cos □ + 13.85) for cyclic disulfanes **2**, sulfanes **3** (for data see table S4 and S5) and phospholane **4a** (CCDC 1948450).

As already indicated above, the influence of the size of the disulfane **2** ring on the chemical shift of *ortho*-protons of anisyls is also observed (Figure S29). This effect can be related to the magnetic anisotropy and the electric field effects of the P=S group, which has a deshielding (+δ) region in the its plane. According to X-ray data the coplanarity of both residues occurs (the smallest SPCC angle of 4^{o}) only in disulfane **2a**. Therefore, **2a** has and should have the most strongly downfield shifted *ortho*-proton among all cyclic disulfanes **2** under the study. Thus, the position of the *ortho*-proton signal can be correlated with the torsion angles found in the disulfane **2a**-**2d** crystal state (see section 2.5). On the other hand, the ^{13}C NMR parameters of all cyclic disulfanes **2** (chemical shifts and coupling constants of the carbon atoms in the main ring as well as the anisyls to phosphorus) seem not to be influenced by their geometry or their ring size. However, the observable difference in chemical shifts of alpha-carbons (Δδ 3.3 ppm) and geminal coupling constants $^{2}J_{CP}$ (6.3 vs. 4.8 Hz despite a similar COP angle of about 120^{o}) between 10- and 12-membered **2c** and **2d** can be significant.

The ^{31}P chemical shifts range for all cyclic disulfanes **2a**-**2d** is rather narrow (88.0–90.0 ppm), and ring expansion results in a proportional increase in phosphorus chemical shift values. Thus, a linear correlation exists between the P...P distance and the δP value (4.334 Å, 4.483 Å, 4.615 Å and 4.695 Å , vs δP 88.0, 88.7, 89.2 and 90.0 ppm) for 2a, 2b, 2c, and 2d, respectively. It may be the result of the increase of the OPS angle from 107^{o} (for 8-membered **2a)** to 109.2^{o} (for 12-membered **2d**), because it is well known that any deviation from the angle of 107^{o} (ideal pentagon angle) causes phosphorus deshielding effect. [42] Another reason for phosphorus downfield shift may be the aforementioned loss of the coplanarity of the P=S group with the plane of the anisyl ring expressed by a gradual increase in the SPCC torsion from 4^{o} for **2a** to 37^{o} for **2d**. However, as we will show below, the lack of coplanarity exhibited in the anisylphosphonothioyl residues shown in the crystal is of no importance in the solutions of the compounds in question.

Comparison of ^{31}P chemical shifts of cyclic disulfanes **2a** and **2c** with chemical shifts of their ferrocenyl analogs **2e** and **2f** would allow to explain the effect of anisyl and ferrocenyl residue on the geometry of the main rings of 8- and 10-

membered disulfanes **2**. Appropriate ^{31}P increments of both aromatic *P*-substituents can be determined by comparing chemical shifts of the respective model compounds described in the literature, *i.e.*, anisylphosphonic acid (δ_P 19.5 ppm [43]) and ferrocenylphosphonic acid (δ_P 24.8 ppm [44]). Exactly the same difference in ^{31}P chemical shifts ($\Delta\delta_P$ = 5.3 ppm) was noted for 8-membered **2a** and **2e**. This may indicate the structural similarity of both compounds at least in the sphere of electronic and steric effects on their ^{31}P chemical shifts. The difference of phosphorus shifts $\Delta\delta_P$ for the corresponding 10-membered analogues **2c** and **2f** is already smaller and amounts to only 3.4 ppm. As shown by the data for ferrocenyl disulfanes (**2e** and **2f**) [9,11] and anisyl disulfanes **2a**-**2d** (current work) the change in phosphorus shifts at the size increase of the 8- to 10-membered ring is -0.7 and +1.2 ppm, respectively. Therefore, it seems that they are not significant enough to find out the particular impact of the structural differences of both classes of compounds. Thus, the aforementioned difference in phosphorus chemical shifts $\Delta\delta_P$, and in particular the difference in chemical shifts of axial and equatorial alpha protons ($\Delta\delta_{ax\text{-}eq}$ = 0.96 and 0.93 ppm, and 0.52 and 0.12 ppm, for the pair **2a** and **2e** and for the pair **2c** and **2f**, respectively) suggest close conformational similarity between **2a** and **2e**, but also large structural differences between **2c** and **2f** in solution. It turns out that key structural parameters describing the main ring conformation, *i.e*. CCCC, OCCC, POCC and PSSP torsion angles are surprisingly convergent within pairs **2a**-**2e** and **2c**-**2f**, and the only factor clearly distinguishing crystalline structures of these compounds is the coplanarity of P=S groups with planes of anisyl/ferrocenyl rings. The corresponding torsion angle is 3.8^o and 32.9^o for 8-membered analogues **2a** and **2e**, while for the 10-membered **2c** and **2f** the mean value is 31.6^o and 16.7^o. These data [12] confirm the above-mentioned suggestion that it is not the aromatic rings but exocyclic and bridge sulfur atoms that have the greatest influence on differentiation of chemical shifts of axial and equatorial protons. However, as far as the influence of CCPS torsion angles is concerned, it should be assumed that in the solution due to free rotation around the C_{aryl}-P bond the degree of coplanarity of the P=S and the OPS groups with aromatic rings is much larger than in the solid state, where the arrangement of aromatic rings in space depends mainly on their participation in intermolecular contacts.

Unsymmetrical from the point of view of magnetically and chemically inequivalent phosphorus atoms, disulfane **2b'** gives two distinct phosphorus resonances ($\Delta\delta_P$ = 1 ppm), which reveals the P-P vicinal coupling constant $^3J_{PP}$ of 4.2 Hz. Chemical and magnetic inequivalence of phosphorus atoms in **2b'**($\Delta\delta_P$ = 1 ppm) enabled the measurement of the P-P coupling constant directly from its proton-decoupled ^{31}P NMR spectrum. However, in the case of other symmetrical disulfanes **2a**-**2d**, determination of the indirect $^3J_{PP}$ coupling constant by observation of C-13 satellites required long acquisition times, because the ^{31}P main signal is about 1000 times more intense. It turned out that the value of thus determined $^3J_{PP}$ vicinal coupling constant decreases very slightly with increasing ring size (4.4, 4.2, 4.0 and 4.0 Hz for **2a**, **2b**, **2c** and **2d** respectively) despite the significant increase in the PSSP torsion angle observed in the crystal state (from 94^o to 125^o). It should be mentioned that in analogous open-chain disulfanes **2g** and **2h**, the vicinal coupling constants $^3J_{PP}$ have a slightly lower value (3 Hz and 0.7 Hz, respectively). It is generally accepted that in the solution all non-cyclic *bis*(phosphorothioyl) disulfanes such as **2g** and **2h** are in the conformation in which the PSSP torsion angle is about 90^o, regardless of the fact that for some of them in the crystal state this angle can be up to 180^o. [21] In non-cyclic disulfanes, rotation around the S-S bond is possible over the full range of angles (from 0 - 180^o), while in cyclic disulfanes **2a**-**2d** the change in the PSSP torsion angle is largely limited due to their ring stiffness and the presence of bulky groups on phosphorus atoms. Grossmann reported the dependence of the P-P vicinal coupling constant on the PCCP torsion angle in symmetrical *bis*-phosphonates. As expected, $^3J_{PP}$ assumes values close to 0 Hz for angles close to 90^o and reaches 30 Hz and 90 Hz for angles of 0^o and 180^o respectively. [45] Since cyclic disulfanes **2** must comply with the general Karplus equation and the values of the vicinal coupling constant $^3J_{PP}$ do not change despite the ring size change, we can speculate that their PSSP structural units tend to achieve the most optimal torsion in the solution. This has been verified by calculation. In the optimized structures of **2a**-**2d**, the PSSP torsion angle range is much narrower (99.5 - 114.6°) compared to that determined for their crystal structures. In the crystal and in the calculated structures, the corresponding PSSP torsion angles for 8- and 9-membered disulfanes **2a**, **2b** and **2b'** are the closest to the optimal value (94-105^o) and the values of the $^3J_{PP}$ coupling constants in the solution correspond to an angle of 95-100^o (according to the dependence given by Grossmann [45]). This indicates that the dominant conformations of these medium-sized disulfanes in the solution are very similar to those in the crystal, which adain confirms their conformational rigidity.

In the initial stages of the study, ^{31}P NMR spectra were recorded for disulfane **2** desulfurization solutions in the MeCN-C_6D_6 system, which contained *cis* and *trans* isomers of cyclic sulfanes **3** and triphenylphosphine sulfide as the by-product (see Figure 1). All *cis*-**3** isomers gave signals in a very narrow range (δ_P 85.85 ppm +/- 0.25 ppm) while phosphorus chemical shifts of *trans*-**3** isomers decreased proportionally as the ring expanded, differing by a maximum of 2.54 ppm. Thus, the largest ^{31}P chemical shift difference between the *cis* and *trans* isomers of **3** ($\Delta\delta_{Ptrans\text{-}cis}$) of 3.1 ppm was noted for the 7-membered sulfane **3a**. It should be added here that the position of the phosphorus signal of the *cis*-**3** isomers is more strongly dependent on the solvent used. In chloroform $\Delta\delta_{Ptrans\text{-}cis}$ are suppressed as compared to benzene solutions. For *cis*-**3b** phosphorus resonance is shifted upfield (-0.8 ppm) in benzene as compared to *trans*-**3b**. This so called aromatic solvent-induced shift (ASIS) effect found for individual sulfane **3** isomers as well as for sulfanes **3** of different ring size. This effect is more pronounced for *cis*-**3** phosphorus chemical shifts, because it is well known that benzene molecules interact stronger with more polar solute molecules (*cis*-isomers) at their local electron-deficient sites (*i.e* phosphorus atoms in **3**). The ASIS effect is notable also in ^{1}H NMR spectra although we found unexpectedly that selected protons of *cis* and *trans* isomers of **3b** are shielded to the same extent in benzene solution (Table 4). However, the most intriguing is the observed total lack of benzene influence on the chemical shifts of axial protons and aromatic *ortho*-protons with simultaneous significant shielding of equatorial protons, especially the meta (H_{meta}) and even the methoxyl (OCH_3) protons in both isomers of **3b**. According to the

ASIS theory H_{meta} and OCH3 chemical shifts should not be affected by solvent change, because they are near the negative pole of the respective dipole moments of **3** (see Figs S49-S54). Thus, it seems that the observed up-field shift of these protons indicates that some benzene molecules and the anisyl groups are arranged in the offset parallel $\pi - \pi$ stacking interactions with benzene molecules pointed toward methoxyls and can be caused by the hydrogen-like interaction between the OCH_3 group and pi-electrons of benzene rings. On the other hand, the presence of bulky anisyl and sulfur substituents results in the exclusion of space above and below the plane of the main ring for benzene molecules. Therefore, setting of the remaining benzene molecules perpendicular to the plane of the main heterocyclic ring of **3b** at its quaternary C-terminus reflects the shielding of its equatorial protons and both methyl group protons. The existence of such arrangement of interactions of molecules **3** with benzene molecules confirms the observed difference between two methyl groups for *cis*-**3b**, where the axial methyl protons are two times strongly shielded and they show an unusual upfield shift of -0.88 ppm (δ = 0.13 ppm) with respect to the signal recorded in chloroform.

It is interesting to note, that all measured H-H and H-P coupling constants for sulfanes **3** do not change when the solvent is changed from chloroform to benzene. Thus, the main ring conformation of cyclic sulfanes **3** is preserved in benzene solution.

Table 4 $\Delta\delta$(ASIS) for sulfide **3b** isomers.

	CH_3	OCH_3	H_{eq}	H_{ax}	H_{ortho}	H_{meta}
Cis-**3b**	-0.88 -0.46	-0.69	-0.51	+0.04	-0.03	-0.44
Trans-**3b**	-0.53	-0.82	-0.37	+0.02	+0.14	-0.37

$\Delta\delta(ASIS) = \delta_{C6D6} - \delta_{CDCl3}$

In chloroform, the ^{1}H chemical shift difference between aromatic protons for *cis* and *trans* sulfanes **3** is very characteristic, too. A close proximity and parallel orientation of both anisyl groups (see section 2.6) lead to significant diamagnetic shifts of *ortho* and *meta* proton resonances ($\Delta\delta_{Ho}$ = -0.51 - -0.59 ppm, $\Delta\delta_{Hm}$ = -0.20 - -0.45 ppm) in each *cis*-**3**. A similar tendency was observed by analyzing the aromatic ranges of the ^{13}C NMR spectra. C-1' carbons are shielded in **3b** and **3c** by 0.5 and 2.1 ppm, respectively, whereas they are surprisingly deshielded in *cis*-**3a** by 1.7 ppm. This fenomena can be explained by the fact that the C1'-C1'' distance in *cis*-**3a** is the largest (3.575 Å - no interaction between anisyls) and in *cis*-**3c** the smallest (3.444 Å - the strongest interaction between the anisyls). *Ortho*-carbons are more shielded than *meta*-ones (-1.0 to -1.2 ppm vs -0.2 to -0.5 ppm) in all sulfanes **3** as expected. Clearly, the *meta* protons and the *meta* carbons are farther away from each other than the atoms in the *ortho* positions, because the anisyl rings in the crystalline state are not ideally parallel but slightly divergent (the measured angle between the C1'-C4 'and C1' '- C-4' 'axes is 2-5^o) and, what is more important, they are flexible in solution.

The P-P geminal coupling constant value is characteristic and diagnostic feature of cyclic sulfane **3** isomers. It has a value of -21 Hz and of -14 Hz for *cis*-**3** and *trans*-**3**, respectively. The magnitude of $^2J_{PP}$ can be extracted from ^{31}P NMR spectra recorded after longer acquisition times, when ^{13}C satellites become observable as doublets, with a splitting that is equal to the $^2J_{PP}$ coupling (Figure S30). Reported by Grossmann [40] the $^2J_{PP}$ coupling have values of -9 and -19 Hz for acyclic *bis*(phosphorothioyl) sulfanes **3g** and **3h**, respectively. However, in the case of acyclic sulfanes, the free rotation around both P-S bonds causes that we do not deal with *cis*-*trans* isomerism. While in our cyclic sulfanes **3a**-**3c** the imaginary S=P…P=S torsion angle is strictly defined (in the range of 3.6 - 23.6^o and 155.4 - 176.5^o for *cis*-3 and *trans*-**3**, respectively) and clearly defines the *cis*-*trans* isomerism, for an acyclic sulfanes even in the crystalline state, there is an intermediate form (*e.g.* for the **3g**, the angle is 117^o). Geminal $^2J_{PP}$ is above 50% greater in *cis*-**3** than in *trans*-**3**. Unfortunately, we have not been able to relate the measured coupling constants to the corresponding differences in structural parameters or justify their magnitude by means of NBO analysis. There is no the PSP bond angle dependance of the $^2J_{PP}$ magnitude found, although every *trans*-**3** have slightly larger PSP bond angle than *cis*-**3** one (for **3c** isomers, the difference in the PSP angles is even 5.8^o; see section 2.6). On the other hand, small changes of P-S bonds lengths for both isomers of **3** can not determine the $^2J_{PP}$ magnitude, therefore other effects influencing $^2J_{PP}$ should be considered which make PP splitting more efficient for *cis*-**3**.

As with cyclic disulfanes **2**, also for all cyclic sulfanes **3**, $^2J_{PC}$, $^3J_{PC}$, and $^4J_{PC}$ couplings were observed as false triplets or quintets, [46] indicating second-order effects (Figure S31).

Inspection of Table S1 shows that although calculated chemical shifts overestimate the ^{31}P chemical shifts by 10-15 ppm, they nevertheless agree with the observed trends of experimental values, so as such they can be useful for predicting chemical shifts for similar systems. Calculations supported also the general notion that geminal $^2J_{PP}$ in *cis*-**3** and *trans*-**3** are larger (3-5 times)

than the corresponding vicinal $^{3}J_{PP}$ for disulfanes **2**. Although they have comparable values, clearly all coupling constants in *cis*-**3** isomers are larger by about 1 Hz than those calculated for *trans*-**3**. The calculated values of $^{2}J_{PP}$ geminal coupling constants, however, are 2.5 - 3.3 times smaller than the experimental values.

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3. SUMMARIZED CONCLUSIONS AND OUTLOOK:

- Despite the facility of the formation of disulfane **2**/sulfane **3** medium rings, the proposed methods of their synthesis are limited to the preparation of seven to ten-membered heterocycles (12-membered **2d** was isolated in only 18% yield).

- Although cyclic sulfanes **3** can be efficiently obtained from disulfanes **2** or directly from *bis*-phosphonodithioates **1**, both desulfurization routes afford different *cis*/*trans* isomer ratio of sulfanes **3**. Desulfurization of disulfanes **2** gives predominance of *trans*-**3**, while *cis*-**3** are mainly formed from *bis*-anisylphosphonodithioates **1**.

- Observed *cis*/*trans* selectivity of cyclic sulfane **3** formation was explained on the base of the results of experiments on reaction mechanisms and also was confirmed by the respective calculations. The highest selectivity (*cis/trans* ratio 4:1) achieved for **1b** desulfurization can be explained by either *gem*-dimethyl effect or suppression of sulfane **3** formation by competitive cyclisation to 5-membered **4a**. On the other hand, the lowest selectivity (*cis/trans* ratio 1:4) during disulfane **2a** desulfurization is caused by their fixed *trans*-geometry and the shortest distance between the reactive ends.

- During the synthesis of 8-membered disulfanes (*e.g.* **2a**) and 7-membered sulfanes (*e.g.* **3a**) the use of acetonitrile alone or in a combination with DCM should be avoided. In both cases acetonitrile takes a part in a competitive reaction leading to the formation of a stable 5-membered phosphate **4a**.

- The most characteristic reaction of cyclic disulfanes **2** is their specific color ammonolysis. Thanks to the participation of the neighboring group, this reaction is very fast and provides a high concentration of deep-blue unstable by-product even in methanolic ammonia solutions. Generally, in their reactions with N- and P-nucleophiles all cyclic disulfanes **2** behave as their open-chain analogs, although their fixed SPSSPS structural motif responsible for the reactivity determines kinetics as well as specific stereochemical course of the S-S bond splitting reactions.

- It was confirmed that all cyclic disulfanes **2a-2d** have *trans* configurations. Calculations confirmed that hypothetical *cis*-**2** are much more energetic.

- Variable-temperature NMR spectra showed the outstanding thermal stability and conformational inertness of cyclic disulfanes **2a** and **2b**. Calculation of ring strain energy indicates the following stability order: **2c** > **2b** > **2a** >> **2d**. Exceptional hydrolytic stability of **2b** is mostly due to branching at β-carbon and/or so-called the *gem*-dimethyl effect.

- Unlike cyclic disulfanes **2**, all *cis*-**3** sulfides are more stable than *trans*-**3**. However, the difference in energy $\Delta E_{cis\text{-}trans}$ decreases with the increase in the size of the ring.

- The P-S single bond length ranges (2.091-2.117 Å, and 2.103-1.149 Å) and P=S double bonds (1.916-1.946 Å and 1.917-1.938 Å) are consistent with the typical values for the P(=S)S moiety, [47] for cyclic disulfanes **2** as well as for cyclic sulfanes **3**, respectively.

- The polar ethoxycarbonyl substituent is responsible for a better packing density (additional intermolecular week H-bonds) and a higher symmetry in disulfane **2b'** as compared to **2b**. The strength of intermolecular contacts in disulfanes **2** represented by P=S…H3COAr distances decreases in order: **2d** >> **2a** > **2b** ≅ **2c**.

- The Karplus-type dependance of the vicinal coupling constant on the dihedral angle is of particular importance in the stereochemistry of cyclic systems. All measured vicinal $^{3}J_{HCOP}$ coupling constants have been correlated with the respective average torsion angles for disulfanes **2** and sulfanes **3** under the study. Its allowed to find a suitable relationship that could be useful for determining the conformation of other medium-sized heterocyclic rings.

- ^{1}H- and ^{13}C-NMR spectra showed that solution state conformers closely resemble those present in the solid-state for 7 - 9 membered **2** and **3**. ^{31}P chemical shift increases proportionally with increasing ring size for cyclic disulfanes **2**. This phenomenon can be mainly correlated with the OPS bond angle value. As the size of the disulfane **2** ring increases, the conformational freedom increases especially for the 10- and 12-membered rings of **2c** and **2d**. The observed difference in chemical shifts of axial and equatorial alpha-protons and a range of the HCOP torsion angle corresponding to the observed $^{3}J_{HCOP}$ coupling constant are both a measure of the degree of conformational freedom of the heterocycles tested.

- An pronounced upfield shift for the aromatic protons of sulfanes **3** is a spectral evidence for the *cis* configuration and additionally it shows that face-to-face stacking of the anisyl rings in crystals of *cis*-**3a** are preserved in solution. There are also significant differences in $^{3}J_{PP}$ being ⅔ higher for *cis*-ones.

- Neither vicinal $^{3}J_{PP}$ value nor the S-S bond length is influenced by the PSSP torsion in cyclic disulfanes **2**. These findings do not agree with the corresponding relationships found in literature.

- Specific solute-solvent interactions were evidenced in NMR spectra of cyclic sulfanes **3** measured in benzene solutions. A significant negative ASIS effect for phosphorus in sulfanes **3** of different ring size as well as for H_{eq}, H_{meta}, OCH_3 and CH_3 protons of individual sulfane **3b** isomers was found. The ASIS effect is more pronounced for *cis*-**3** phosphorus chemical shifts, but selected protons of *cis* and *trans* isomers of **3** are shielded to the same extent. Obtained results reveal that some benzene molecules and the anisyl groups are arranged in the offset parallel $\pi - \pi$ stacking interactions with benzene molecules pointed toward methoxyls of **3b** and others perpendicular to the plane of the main heterocyclic ring at its quaternary C-terminus. The main ring conformation of cyclic sulfanes **3** is preserved in benzene solution, because coupling constants do not change with solvent.

- *Cis*-**3** are more polar than *trans* ones as expected. The largest difference in polarity (expressed as both $\Delta\mu_D$ and ΔR_f) is found in the **3a** isomers. It decreases with the increase in the size of the sulfane **3** ring. Calculated dipole moments are always directed to anisyl end(s) of the molecules. The magnitude of the dipole moment depends both on the spatial arrangement of the anisyl rings but also on the value of the CCPS torsion angle in sulfanes **3**. The smaller the CCPS torsion angle, the the higher value of the dipole moment. For *trans*-**3b** and *trans*-**3b** the negative pole of the dipole is directed towards the equatorial anisyl whose ring plane is more coplanar with the P=S group. *Trans*-**3a** has the lowest dipole moment, because both anisyls are pseudoequatorial and their vectors partly cancel each other out.

- *trans*-**3** cyclic sulfides have more deshielded phosphorus nuclei and their ^{31}P chemical shifts are much more differentiated (from 0.9 to 3.1 ppm for *trans*-**3c** and *trans*-**3a**, respectively) as compared to *cis*-**3** which have ^{31}P NMR chemical shifts in the narrow range of 0.5 ppm. Additionally, an upfield shift of aromatic carbons of *ca.* 1 ppm was observed that evidently confirms the existence of intramolecular face-to face interactions between anisyl rings in every *cis*-**3**.

- Medium-sized cyclic disulfanes **2** are redox active compounds. Unusual durability of disulfanes **2** and their reduction products, *bis*anizylophosphonothioates **1**, can ensure a high turnover number if someone use them in redox catalytic cycles.

- 9-Membered **2b'**, as containing ester functional group represents a relatively rare example of a redox-active cyclic disulfane that can be potentially used for grafting with a polymer matrix, tethering or conjugated with bioactive compounds or other carriers.

- Medium-sized cyclic disulfanes **2** and sulfanes **3** can not be used as monomers for anionic ROP polymerization due to preferred ring-closing reactions as well as negligible reactivity of the resulting PSS^- anion to the PSSP. The exception is 12-membered disulfane **2d** which undergoes desulfurization to give mainly macrocyclic oligomers. However, in this case it is necessary to further optimize the conditions of this process.

- The preliminary results of controlled thermolysis of disulfanes **2**, which gives polymeric *poly*(disulfanes), are promising and suggest that they can be useful in vulcanisation processes.

4. Experimental section

Synthesis of Disulfanes 2b' and 2d: To a stirred solution of the corresponding diol (1 mmol) in THF (5 mL) Lawesson Reagent (0.404 g, 1 mmol) was added in one portion at room temperature. After 15 min when the mixture became homogeneous, *tert*-butyl amine (0.21 mL, 2 mmol) was added dropwise and the clear solution was concentrated in vacuo. The residue was dissolved in ethyl acetate (15 mL) and a solution of iodine (0.254 g, 1 mmol in 10 ml of ethyl acetate) was added

dropwise with ice-cooling to reach a persistent brown coloration. Next, the solution was washed with a 2% aqueous $Na_2S_2O_3$ solution, water, and then with brine. The organic layer was dried with $MgSO_4$ and concentrated. The crude product was dissolved in chloroform (30 mL) and passed through a short pad of silica gel. After evaporation of the solvent, the solid precipitate was recrystallized to give the respective disulfane **2** as colorless crystals.

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Synthesis of Sulfanes 3a-c and phospholane 4a:

Using Ph_3P as desulfurization agent (Method A): To a stirred suspension of disulfane **2** (0.2 mmol) in 2 ml of acetonitrile-dichloromethane (1:1, v.v) triphenylphosphine (0.052 g, 0.2 mmol) was added in one portion at room temperature. The reaction mixture immediately becomes a clear and colorless solution. After the ^{31}P NMR spectrum of the reaction mixture had been recorded. Next solvents were evaporated from the filtrate and the solid residue was fractionated by silica gel column chromatography using hexane-ethyl acetate (7:3) or chloroform-hexane (1:1) as eluents.

Using Ph_3P as desulfurization agent (Method A) with the additive 2,4-dinitrobenzoic acid: To a stirred solution of disulfane **2a** (0.023 g, 0.05 mmol) in dichloromethane (1 ml, 1/1, v/v) 2,4-dinitrobenzoic acid (0.013 g, 0.065 mmol) and triphenylphosphine (0.013 g, 0.05 mmol) was added at room temperature. ^{31}P NMR analysis showed increasing of the *cis/trans* isomer ratio of **3a** from 0.26 to 0.31.

Via Mitsunobu coupling (Method B): Di-*tert*-butylammonium *O,O'*-(2,2-dimethylpropane-1,3-diyl) *bis*[(4-methoxyphenyl)phosphonodithioate **1b** (0.654 g, 1 mmol) was dissolved in dichloromethane (5 ml) and 2-chloro-*N*-methylpyridinium iodide (0.256 g, 1 mmol) was added. After 24 h at room temperature the homogeneous reaction mixture was evaporated and the remaining yellow solid was filtered through a short pad of silica with ethyl acetate eluent to remove tetrabutylammonium iodide and 1-methylpyridine-2-thione as byproducts. ^{31}P and ^{1}H NMR analysis showed the the *cis/trans* isomer ratio of **3b** was 3.8. Separation by silica gel column chromatography using hexane-ethyl acetate (7:3) gives, besides both isomers of **3b**, 0.075 g (30%) of phospholane **4a**.

Ammonolysis of disulfanes 2: Disulfane **2b** (0.01 g, 0.02 mmol) was added to 10 M NH_3 in methanol (0.7 ml, 7 mmol) with stirring (at the moment of **2b** dissolution, the solution turned deep-blue). Next, the resulting solution was subjected to ^{31}P NMR analysis at different intervals and, after appropriate dilution, UV spectra were recorded to study absorbance changes with time.

^{31}P NMR (crude reaction mixture after 5 min, 10% C_6D_6) 75.30 (100%) and 105.19 (80%) (**6b**), 83.0 (30%) and 105.64 (25%) (**7b**), 105.25 (70%) (**1b**).

UV (10 M NH_3 in MeOH): λ_{max} = 563 nm (log ε = 3.81).

Keywords: Phosphorus and Sulfur heterocycles, Medium-ring compounds, Conformation analysis, Stacking and π-π interactions, Reaction mechanisms, Nucleophilic substitution, Neighboring-group effects, Reduction, Solvolysis, Ring contraction, X-ray diffraction, Solid-state structures, NMR spectroscopy, Ab initio calculations

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Conflict of interest: The authors declare no conflict of interest.

†Electronic supplementary information (ESI) available: Disulfanes **2** and sulfanes **3** characterization data, supplementary Figures, Schemes, Tables, crystallography data including ORTEP views of all compounds and their NMR spectra.

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A Family of cyclic medium-sized disulfanes and related sulfanes was synthesized and characterized, followed by desulfurization and disulfane ammonolysis mechanisms

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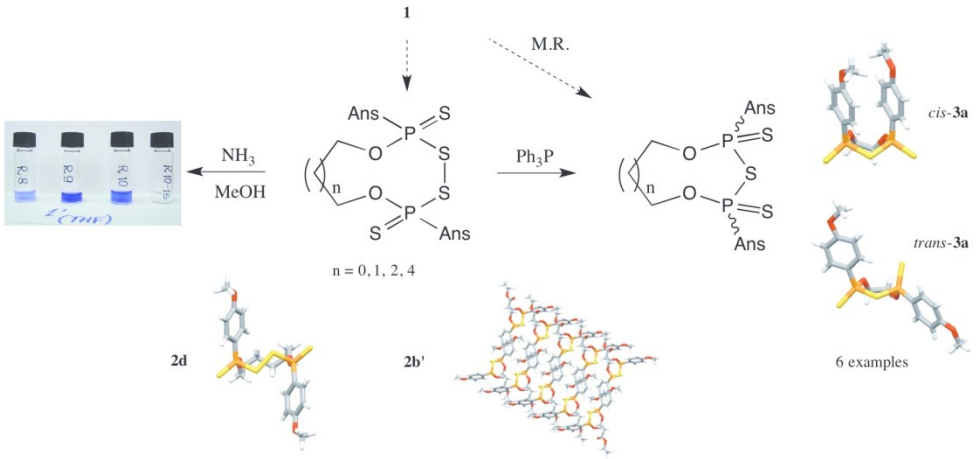

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