Heterocycles from Trifluoromethanesulfonamide: Formation and Structure

Bagrat A. Shainyan* and Vladimir I. Meshcheryakov

A.E. Favorsky Irkutsk Institute of Chemistry Siberian Division of Russian Academy of Sciences, 1 Favorsky Street 664033, Irkutsk, Russia

Abstract: Sulfonamides are capable of condensing with different carbonyl compounds to form heterocycles. Among other sulfonamides, trifluoromethanesulfonamide is of special interest because of its highest NH-acidity though until recently nothing has been known of its condensation with carbonyl compounds. The focus of the present review is made on reactions of oxymethylation and amidomethylation of sulfonamides and, especially, trifluoromethanesulfonamide, the structure and stereodynamic behavior of the heterocycles formed as well as on specific and often unique stereoelectronic interactions in their molecules.

1. INTRODUCTION

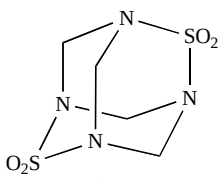
Condensation reactions leading to various heterocycles represent a vast and very important class of organic reactions. Among them, condensation of carboxamides and sulfamides with formaldehyde is of special interest as resulting in many potentially biologically active compounds containing different pharmacophore groups. Formaldehyde, as the simplest aldehyde, enters condensation reactions with various organic compounds. Among the most known are its reactions with acetylene (Favorsky reaction), alkenes (Prince reaction), nitroalkenes (Henry reaction), phenols (Lederer-Manasse reaction), aldehydes and ketones (Tollens reaction), ketons and amines (Mannich reaction), amines and formic acid (Eschweiler-Clarke reaction). It also reacts with NH_2-active compounds with formation of heterocycles, e.g., primary amines react with formaldehyde to afford symmetric 1,3,5-trialkyltriazinanes [1]. Carboxamides and alkyl(aryl)sulfonamides also form the products of oxymethylation with formaldehyde [2]. These products can further react with the next molecule(s) of the starting amide to form linear or cyclic derivatives. Thus, the reaction of alkyl- and arylsulfonamides with trioxane (as a source of formaldehyde) was reported to lead to N-sulfonylsubstituted 1,3,5-dioxazinanes, 1,3,5-oxadiazinanes and 1,3,5-triazinanes [3].

As distinct from organylsulfonamides RSO_2NH_2 forming heterocycles with the RSO_2 group in the side chain of the heterocycle, derivatives of sulfamide itself, $RR'NSO_2NRR'$, form a large variety of heterocycles with the endocyclic sulfonyl group [4].

The basicity of nitrogen in trifluoromethanesulfonamide $CF_3SO_2NH_2$ (triflamide) is lower than in other sulfonamides and it does not react even with highly electrophilic chloral molecule which gives adducts with carboxamides and sulfonamides without special activation [5]. Therefore, *a priori* it was not obvious whether it would give the products of oxymethylation even in conc. sulfuric acid, that is, under strongly electrophilic conditions.

2. REACTIONS OF SULFONAMIDES WITH FORMALDEHYDE

Sulfamide $H_2NSO_2NH_2$ itself reacts with formaldehyde or its sources like trioxane, paraformaldehyde, etc. with formation of different cage heterocycles **1–3** [6-10].



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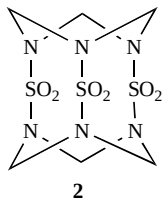

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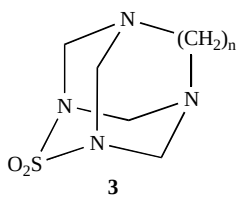

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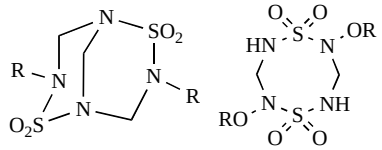
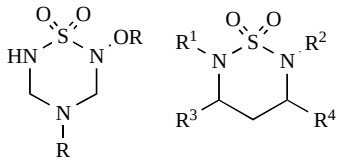
The heterocyclic analog of adamantane **1** is formed by condensation of two molecules of sulfamide with four molecules of formaldehyde in conc. hydrochloric or trifluoroacetic acid (40°C, 6 h), or in 60% sulfuric acid. The molecule has D_{2d} symmetry with all protons equivalent and its ^{1}H NMR spectrum contains one singlet [7]. More complex structure **2** is formed by condensation of three molecules of sulfamide with six molecules of formaldehyde under more severe conditions, that is, in conc. sulfuric acid or in trifluoroacetic acid at 82°C for 72 h. As follows from the dependence of the yield of **1** and **2** on the reaction time and temperature, the latter compound is formed from **1** upon heating and/or using more concentrated acid. The molecule has D_{3h} symmetry with firmly fixed axial and equatorial protons in the six equivalent methylene groups and shows two doublets in the ^{1}H NMR spectrum (given in the earlier work [7] as four signals) with $^2J_{HH}$ 15.4 Hz. When ammonia or ethylenediamine is introduced into the reaction mixture, cage compounds **3** (n = 1 or 2) are formed [10].

Substituted sulfamides H_2NSO_2NHR do not give cage structures but rather form bicyclic derivatives **4** [11]. When R = OR', dimeric products of cyclocondensation with formaldehyde **5** are formed, whereas in the three-component amidomethylation reaction with formaldehyde and amines 1,2,4,6-thiatriazines **6** were obtained [12]. Similar heterocycles with other substituents at the nitrogen atoms were described in [4]. With β-dicarbonyl compounds or their isoelectronic analogs like β-chlorovinyl ketones, substituted sulfamides react to afford heterocyclic products of condensation, 1,2,6-thiadiazine-1,1-dioxides **7** [13-16].



4 **5**



6 **7**

Practically, before our studies on oxymethylation and amidomethylation of triflamide, the only work which described the reaction of organylsulfonamides RSO_2NH_2 with formaldehyde was a short communication [3] where the authors reported the formation of six-membered heterocycles **8–10** as shown in Scheme **1**. Neither other heterocycles nor linear products of condensation were detected.

Noteworthy in relation to further discussion is the work of Borowski and Haas [17] who reported the formation of different heterocycles by condensation of nonoxidized analogs of triflamide, trifluoromethanesulfenamide CF_3SNH_2 and chlorodifluoromethanesulfenamide $ClCF_2SNH_2$, with formaldehyde in conc. sulfuric acid, as depicted in Scheme **2**.

*Address correspondence to this author at the A.E. Favorsky Irkutsk Institute of Chemistry Siberian Division of Russian Academy of Sciences, 1 Favorsky Street 664033, Irkutsk, Russia; Tel: +3952-511-425; Fax: +3952-419-346: E-mail: bagrat@irioch.irk.ru

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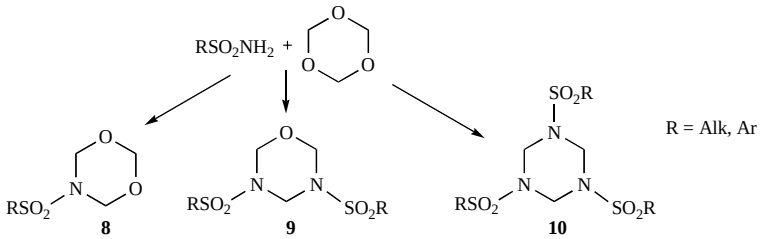
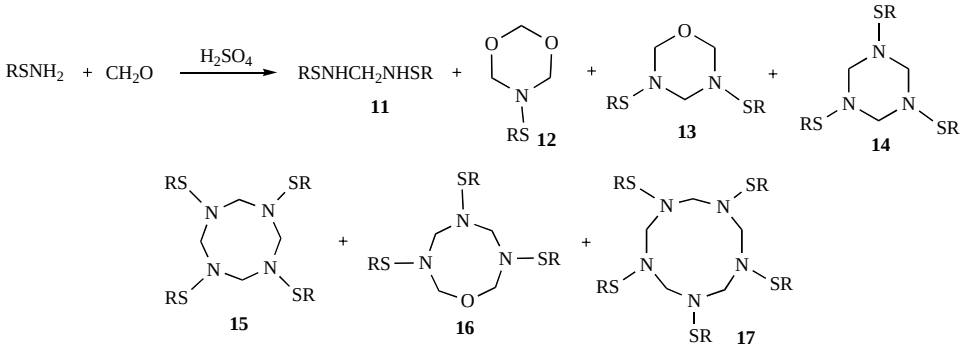


Scheme 1.

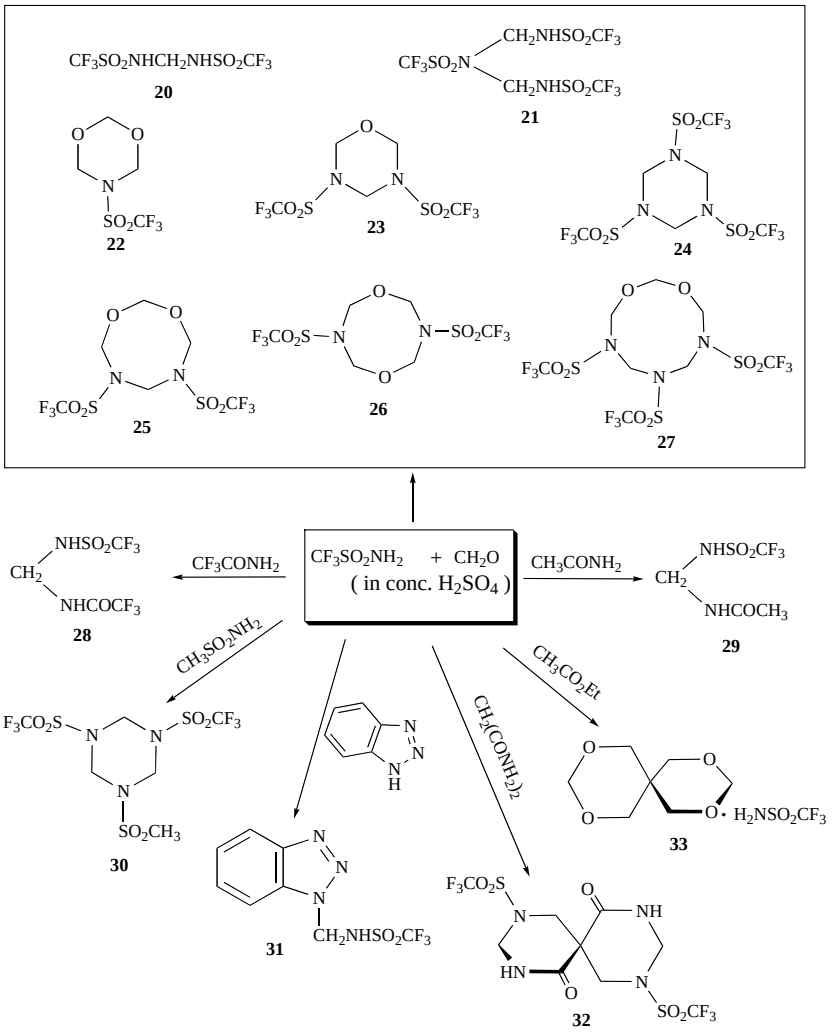


Scheme 2.

2.1. Cascade Transformations of Triflamide in the Reaction with Formaldehyde

We have found that triflamide **18** reacts with paraformaldehyde in the presence of conc. H_2SO_4 leading, depending on the reaction conditions, to a variety of open-chain and heterocyclic products of condensation (Scheme **3**) [18-21].

Their formation is launched by addition of triflamide to the molecule of formaldehyde activated by protonation to oxymethyl cation



Scheme 3.

$^{+}CH_2OH$ and formation of the methylol derivative $CF_3SO_2NHCH_2OH$ **19**. Subsequent stepwise condensation with triflamide and formaldehyde as meticulously described in [18] results in the whole banch of the open-chain and cyclic products presented in Scheme **3**. We failed to isolate individual compound **19**, yet, its formation is beyond doubt since in the one-pot reaction of triflamide, paraformaldehyde and acetonitrile in 85% H_3PO_4 or in the reaction of triflamide, paraformaldehyde and acetamide in conc. sulfuric acid the product of cross condensation, N-[(trifluoromethylsulfonyl) aminomethyl]acetamide is formed in 65% yield.

$$CF_3SO_2NH_2 + CH_2O + CH_3CN \text{ (or } CH_3CONH_2) \xrightarrow{[H^+]} CF_3SO_2NHCH_2NHCOCH_3 \quad (1)$$

Apparently, the reaction includes an intermediate formation of **19** which acts as an amidomethylating agent in the subsequent Tschernіac-Einhorn reaction with triflamide. The open-chain products **20** and **21** are soluble in the hexane–ether mixture and can be separated from the insoluble cyclic products. The latter were further separated by column chromatography. Note again, that no such open-chain products were detected in the reaction of alkyl- or arylsulfonamides with formaldehyde [3].

As to large heterocycles, the formation of an analog of the eight-membered cycle **18** was reported in the literature by the reaction of 1,3-dinitro-1,3-diazapropane $O_2NNHCH_2NHNO_2$ with paraformaldehyde in ethyl acetate in the presence of sulfuric acid [21].

The composition of the reaction mixture and the ratio of the products strongly depend on the reaction conditions. Thus, for **18**:formaldehyde = 2:1 at room temperature, when triflamide is not dissloved in sulfuric acid but rather forms a suspension, the open-chain product **20** and the cyclic product **23** are mainly formed. Upon heating to 40°C, triflamide is practically completely dissolved and the branched product of condensation **21** is formed along with compounds **20** and **23**. Amide **21** becomes the only open-chain product when the ratio **18**:formaldehyde is equal to 4:3 and the reaction is carried out for 4 h at 40°C and another 20 h at room temperature. In this case, after separation of the insoluble in hexane–ether small amount of the cyclic product **23**, compound **21** was separated in pure form. With the same ratio of the reagents (4:3) and heating to 60-70°C the symmetric triazinane derivative **24** is formed.

In the ^1H NMR spectrum of **20** two signals of equal intensity are observed: a triplet of the methylene group at 4.7 ppm and a broaden NH triplet at 7.8 ppm. Under the conditions of fast exchange (in the presence of traces of acid) the NH group signal becomes very wide and the CH_2 triplet degenerates into a singlet. The proton spectrum of amide **21** also contains a broaden NH triplet in the same region (7.8 ppm) but the signal of the CH_2 group splits to a doublet and is twice as intensive as the NH signal. In the ^{13}C NMR spectrum of **21**, apart from the CH_2 signal, shifted by ~5 ppm downfield with respect to **20**, two quartets of the CF_3 groups in the ratio of 1:2 are present at ~120 ppm, the lower field signal belonging to the CF_3SO_2NH and the higher field signal belonging to two CF_3SO_2N groups.

Methylene groups in the cyclic compounds **22–24** at room temperature give singlet signals, but upon cooling they are splitted (as well as the signals in the ^{13}C and ^{19}F NMR spectra) to show an interesting dynamic behavior and the presence of rotamers (vide infra).

The ^1H NMR spectrum of the eight-membered heterocycle **25** at room temperature shows three singlets at 3.7 (NCH_2O), 4.0 (NCH_2N) and 4.7 (OCH_2O) ppm in the ratio of 2:1:1, and the corresponding signals at 69.9, 64.0 and 94.8 ppm in the ^{13}C NMR spectrum. Its isomer **26** has two broaden singlets at 5.0 and 5.5 ppm in the ^1H NMR spectrum at room temperature and the only methylene group signal in the ^{13}C NMR spectrum. The assignment of the signals was made by the use of the 2D{^1H–^{13}C} HETCOR spectrum. The low-temperature dynamic ^1H and ^{19}F NMR study for the latter compound showed the presence of two conformers in the ratio of ~6:1 (Fig. **1**) [22]. The major conformer has two nonequivalent trifluoromethyl groups whereas in the minor conformer they are equivalent.

Among the diversity of possible conformers for **26**, the most stable for eight-membered rings are the *boat-chair* conformers [23]. B3LYP/6-311G(d,p) calculations showed the 3,7-*boat-chair* conformer with nonequivalent CF_3 groups **26a** to be the global minimum on the potential energy surface [22]. Note, that most stable conform-

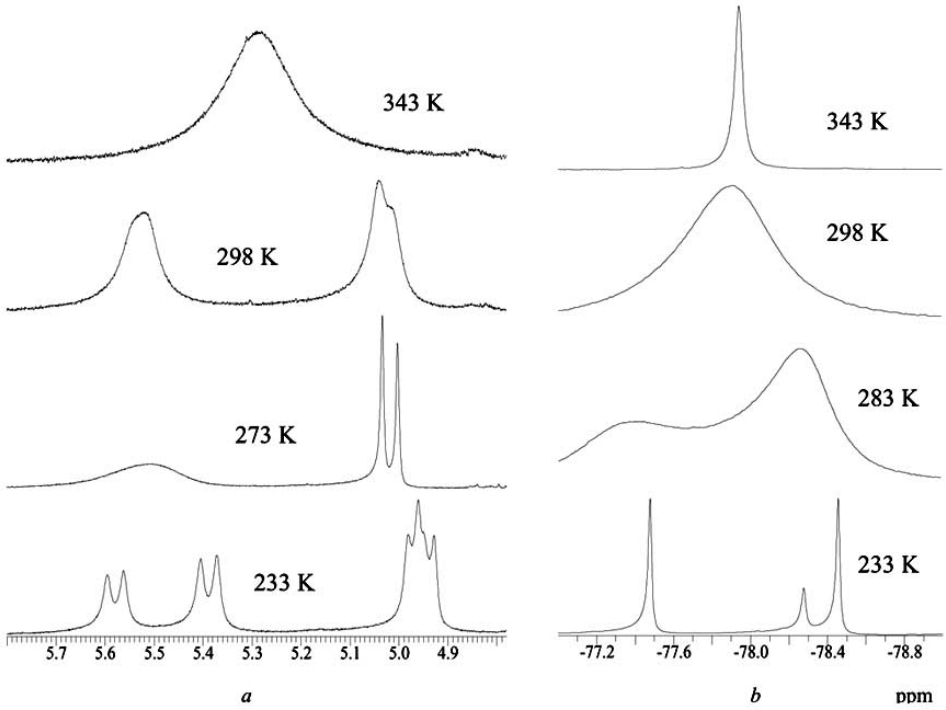
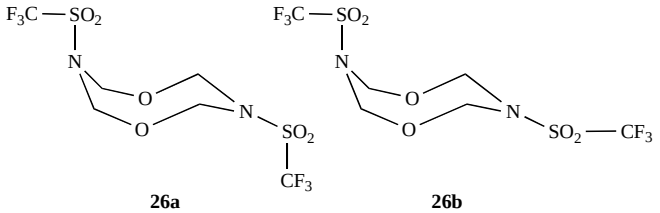


Fig. (1). Temperature dependence of ^1H NMR (*a*) and ^{19}F NMR (*b*) spectra of 3,7-bis(trifluoromethylsulfonyl)-1,5,3,7-dioxadiazocane **26** in CD_3CN.

ers of the six-membered heterocycles **22–24** also have differently oriented CF_3 groups (vide infra).



26a **26b**

Conformer **26b** is calculated to be 0.83 kcal/mol higher in energy; this energy difference exactly coincides with that determined from the experimental ratio of the intensities of the corresponding signals in their ^{19}F NMR spectra [22].

Characteristic chemical shifts of the NCH_2O, NCH_2N and OCH_2O groups in the ^1H and ^{13}C NMR spectra of the studied heterocycles and the relative intensity of the signals allowed us to ascribe compound **27** the structure of the ten-membered heterocycle with two NCH_2O (3.8 ppm), two NCH_2N (4.1 ppm) and one OCH_2O (4.8 ppm) group. The corresponding carbon atoms in the ^{13}C NMR spectrum of the same relative intensity resonate at 69.5, 63.5 and 94.8 ppm, respectively.

2.2. Three-Component Condensation Reactions of Triflamide, Formaldehyde and Other Amides

The abovementioned reaction (1) represents an example of three-component condensation reactions of triflamide, formaldehyde and a carboxamide. Another example is a similar reaction with trifluoroacetamide leading to the product of cross-condensation **28** (Scheme **3**). We have also studied three-component reactions of triflamide and formaldehyde with benzotriazole, methanesulfonamide $CH_3SO_2NH_2$ and malonamide $CH_2(CONH_2)_2$ as a third component.

In order to compare sulfonamides and carboxamides in oxymethylation reaction we have performed the reaction of trifluoroacetamide with paraformaldehyde in conc. sulfuric acid. Unlike the reaction of triflamide with paraformaldehyde, trifluoroacetamide does not form any cyclic products; the only product identified in the reaction mixture was methylenebis(trifluoroacetamide) **34** which was isolated in 68% yield:

$$CF_3SO_2NH_2 + CH_2O \xrightarrow{H_2SO_4} CF_3CONHCH_2NHCOCF_3 \quad (2)$$

34

An attempt to cyclize the individual compound **34** by its reaction with paraformaldehyde in conc. sulfuric acid lead only to N-hydroxymethyl(trifluoroacetamide) **35** as a result of protolytic cleavage of the CH_2–N bond with the formation of trifluoroacetamide and $CF_3CONHCH_2^+$ cation. Oxymethylation of the former and hydroxylation of the latter give the same final product **35**. This product is formed in low yield (conversion after 3 h is ~50%) but is easily separated from the unreacted starting material by sublimation.

$$CF_3CONHCH_2NHCOCF_3 + CH_2O \xrightarrow{H_2SO_4} CF_3CONHCH_2OH \quad (3)$$

34 **35**

Since compound **35** is known to be a good amidomethylating reagent [24–29], we tried to use it as such in the reaction with triflamide. According to the NMR data, the following mixture of the products was formed after 50% conversion, the product of cross-condensation **36** being the major component [20]:

$$CF_3SO_2NH_2 + CF_3CONHCH_2OH \xrightarrow{H_2SO_4} \mathbf{20} + \mathbf{34} + CF_3SO_2NHCH_2NHCOCF_3 \quad (4)$$

36

The three-component reaction of 1*H*-benzotriazole, sulfonamides and aldehydes is known to give rise to 1-[(organylsulfamido)alkylidene]benzotriazoles [29]. For example, in one-pot reaction of methanesulfonamide, formaldehyde and 1*H*-benzotriazole, or, in a stepwise manner, by condensation of methanesulfonamide with the independently prepared 1-oxymethylbenzotriazole 1-(methylsulfonylamidomethyl)benzotriazole is formed [29]. Triflamide enters similar reaction with 1-oxymethylbenzotriazole giving rise to the product of mixed condensation **31** (Scheme **3**).

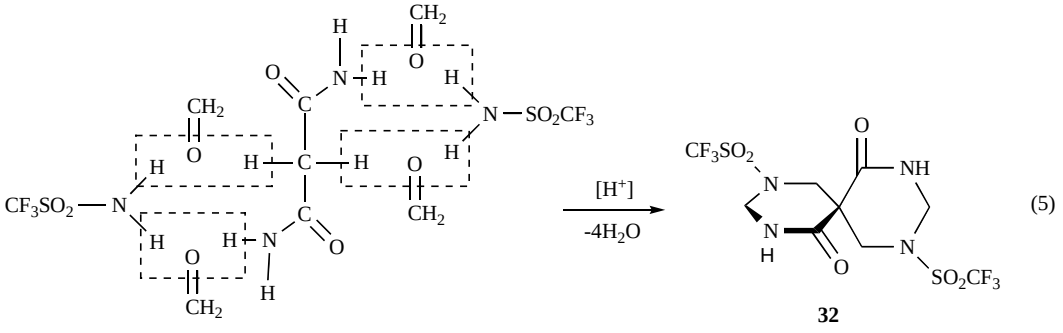
The process can also be performed as one-pot three-component reaction of benzotriazole, paraformaldehyde and triflamide. As other N-substituted triflamides, compound **31** is a strong NH-acid, its pK_a in methanol is equal to 11.08, that coincides with pK_a for triflamide itself in the same solvent (11.06 [30]).

The cyclic product of cross-condensation of two sulfonamides, 1-methylsulfonyl-3,5-bis(trifluoromethylsulfonyl)-1,3,5-triazinane **30**, close analog of compound **24**, is formed as a minor product along with compound **20** in the reaction of equimolar mixture of triflamide and methanesulfonamide with paraformaldehyde in conc. sulfuric acid (Scheme **3**). The ratio of products **20** and **30** prior to separation is ~5:1. Compound **20** was washed out from the product mixture by treatment with ether:hexane 2:1 and after its separation the individual target product **30** was isolated by column chromatography. As other six-membered heterocycles **22–24**, compound **30** demonstrates the presence of rotamers and interesting stereoelectronic effects by low-temperature dynamic NMR (vide infra).

An unexpected result was obtained in the three-component condensation reaction of malonamide and triflamide with paraformaldehyde. A high-melting product isolated in 25% yield from the reaction mixture showed in the ^1H NMR spectrum a singlet of NH proton at 8.8 ppm and two AB quartets at 4.0 and 4.8 ppm, and in the ^{13}C NMR spectrum – the signal of an amide group at 165 ppm, a CF_3 quartet at 119 ppm, two signals of the CH_2 groups in the range 50-56 ppm, and a *quarternary carbon* signal at ~25 ppm. In the IR spectrum an absorption band of the C=O group at 1680 cm^{-1} is observed, which is higher than the values for open-chain amides. These data suggest the formation of a cyclic structure containing C(O)NH and CF_3SO_2N fragments in the ring. Finally the structure was established by X-ray analysis. The product turned out to be 4,10-bis(trifluoromethylsulfonyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,7-dione **32**, apparently formed as a result of the three-component heterocyclization with participation of both the amide groups of malonamide and its active methylene group as shown in reaction (5).

Interatomic distances and bond angles in compound **32** (Fig. **2**) correspond to normal values. Both spiro-linked heterocycles have *chair* conformation. In the C1-C2-C3-N1-N2 ring C1,C2,C3 and N2 atoms are coplanar, N1 and C4 deviate from this plane to opposite directions by 0.66 and 0.12 Å, respectively; in the second ring the C1, C6, C7 and N3 atoms are coplanar, and N4 and C5 deviate to opposite directions by 0.26 and 0.66 Å, respectively.

As said above, the result of condensation of triflamide with paraformaldehyde strongly depends on the reaction conditions. One of the most remarkable manifestations was found when the reaction was carried out in ethyl acetate in the presence of conc. sulfuric acid. Under mild conditions (20°C, 6 h), 5-trifluoromethylsulfonyl-1,3-dioxazinane **22** was found to be the major product. Under more severe conditions (80°C, 3 h) a 1:1 complex of triflamide with 2,4,8,10-tetraoxospiro[5,5]undecane **33** was prepared and isolated by column chromatography. Its structure was proved by the presence in the ^1H NMR spectrum the signals of NH_2, CCH_2O and OCH_2O groups in the ratio of 2:4:8, and in the ^{13}C NMR spectrum the signals of CF_3, CCO, OCO and a quarternary carbon. Finally, the structure was proved by X-ray analysis (Fig. **3**).



(5)

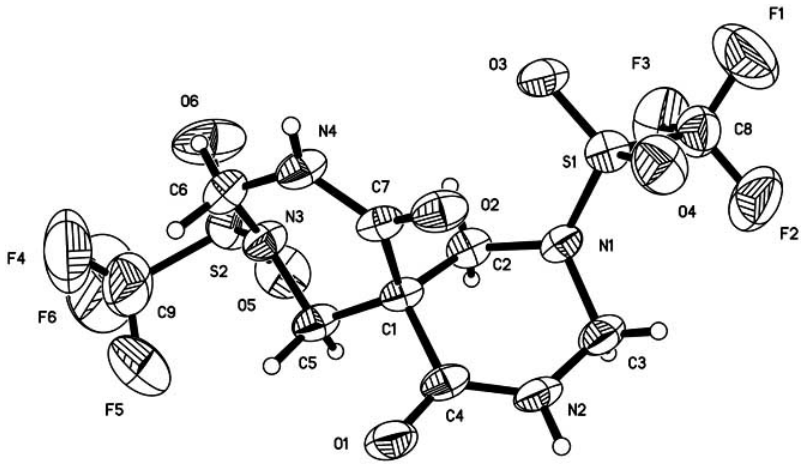


Fig. (2). ORTEP view of 4,10-bis(trifluoromethylsulfonyl)-2,4,8,10-tetraazaspiro[5.5]undecane-1,7-dione **32**.

The formation of the spirocyclic complex **33** is absolutely unexpected since no reagents contain a quarternary carbon atom. We suggest that complex **33** is formed by cyclization of pentaerythritol with formaldehyde. Pentaerythritol, in turn, is formed (by analogy with the industrial method of its manufacturing by the reaction of formaldehyde with acetaldehyde) as a result of triple aldol condensation of formaldehyde to the activated methyl group of ethyl acetate followed by reduction of the ester group in the intermediate ethyl ester of 3-hydroxy-2,2-bis(hydroxymethyl)propionic acid and oxidation of formaldehyde according to the general reaction presented in equation (6).

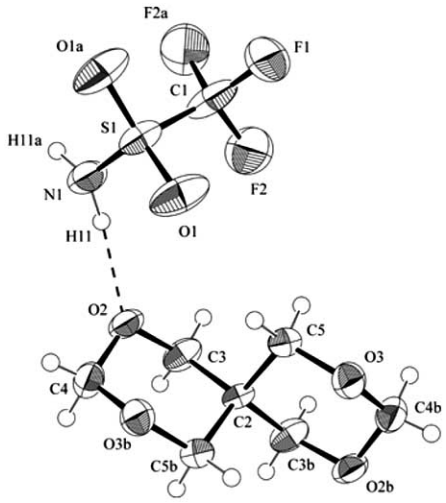
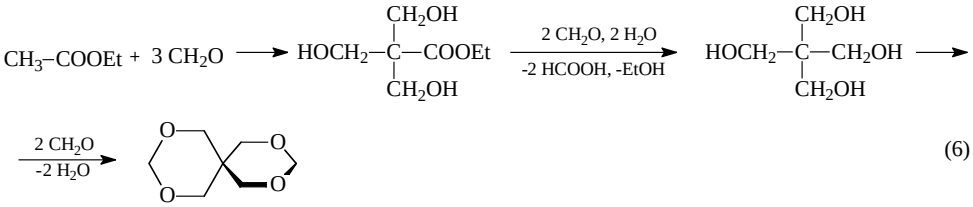


Fig. (3). X-ray structure of the complex of triflamide with 2,4,8,10-tetraoxospiro[5,5]undecane **33**.

To check this hypothesis, we performed the reaction of paraformaldehyde with ethyl acetate in the excess of the latter with gradual addition of conc. sulfuric acid and keeping the reaction mixture for 24h at room temperature with subsequent heating to 80°C during 7h. Samples were taken periodically from the reaction mixture for NMR analysis after usual water–ethyl acetate treatment. The main signals in the NMR spectra are those of 2,4,8,10-tetraoxospiro[5,5]undecane, singlets at 3.7 and 4.7 ppm in the 2:1 ratio in the proton spectrum, and signals at 71 and 95 ppm also in the 2:1 ratio as well as the quarternary carbon signal at 34.4 ppm in the ^{13}C NMR spectrum. To the best of our knowledge, reaction (6) is the first example of reduction of ester group COOR to alcohol group CH_2OH under the action of formaldehyde.



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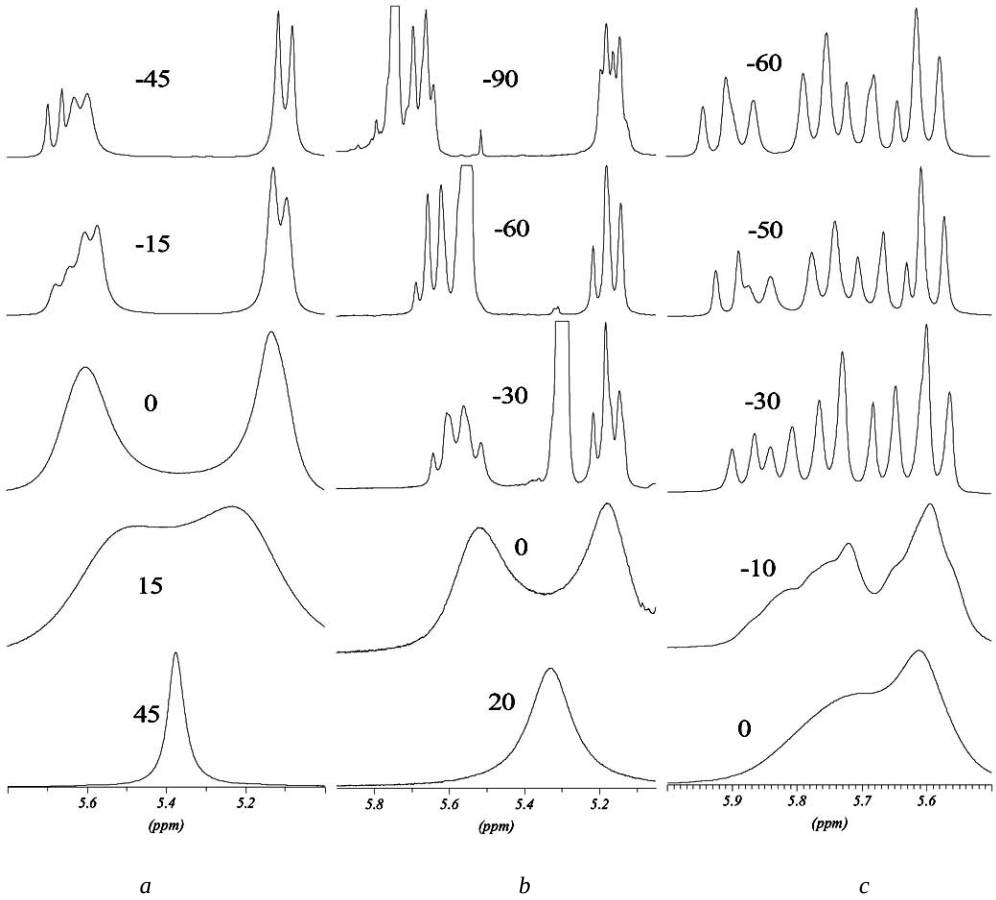

Fig. (4). Temperature dependence of the ^{1}H NMR spectra of 1,3,5-tris(trifluoromethylsulfonyl)-1,3,5-triazinane **24** in CD_3CN(left), CH_3OH (center), and $(CD_3)_2CO$ (right).

We have found only one example of formation of complex of triflamide with a heterocyclic base, tetrahydro-N-(4*H*-1,2,4-triazol-4-yl)-2*H*-pyrane-2-imine, also of 1:1 composition, with hydrogen bonds between the triflamide protons and the N^1 and N^2 atoms of the triazole ring of the heterocycle 1.84–2.13 Å [31]. Interestingly, with less basic analog of this heterocycle, N-methyl-N-phenylhydrazone of tetrahydro-2*H*-pyran-2-one, triflamide does not form an adduct [31].

3. STRUCTURE AND STEREOELECTRONIC EFFECTS IN N-TRIFYL SUBSTITUTED AZINANES

3.1. Dynamic Behavior of N-trifyl Substituted Azinanes

As was said above, the six-membered heterocyclic products of condensation of triflamide with formaldehyde **22–24, 30** show an interesting behavior when studied by low-temperature multinuclear NMR specroscopy.

The ancestor of all these heterocycles, cyclohexane itself, prefer the *chair* conformation [32] unless specific intramolecular interactions stabilize more strained *twist* or *boat* conformers [33]. The substituents usually occupy the equatorial position [32], although there may be exceptions if the 1,3-*syn* interactions with the axial substituent are attractive (like in cyclic sulfoxides [34] or absent (like in 1,3-dialkyl-1,3-diazinanes [35] and 1,3,5-trialkyl-1,3,5-triazinanes [36, 37] with two alkyls equatorial and one axial).

The fully substituted symmetric 1,3,5-tris(trifluoromethylsulfonyl)-1,3,5-triazinane **24** showed in the ^{1}H NMR spectrum at room and higher temperatures a broaden singlet of the methylene protons at 5.35 ppm. On cooling, it decoalesces at 15°C into two signals of equal intensity, and at –15°C these signals decoalesce further (Fig. **4**, *a*). Similar behavior was observed in methanol and acetone (Fig. **4**, *b* and *c*, respectively).

Thus, compound **24** demonstrates two dynamic processes. The first one is ring inversion, while the second one, by analogy with 1,3,5-trialkyl-1,3,5-triazinanes [36, 37] could be inversion at the nitrogen atom provided that the latter is pyramidal. However, as shown by NMR and X-ray studies ([38] and refs. therein) the nitrogen atom in sulfonamides is planar. The B3LYP/6-311G(d,p) calculations revealed two conformational minima for **24**. The lower lying minimum has C_S symmetry with one CF_3 group (at N1) directed inward the cycle (Fig. **5**, **24a**). The second minimum lies 2.12 kcal/mol higher and has C_{3v} symmetry with all three trifyl groups identical and directed outward (Fig. **5**, **24b**). All nitrogen atoms in **24** are virtually planar, the sum of the bond angles at nitrogen is close to 360° in both rotamers. Therefore, no inversion on nitrogen in **24** can occur and the second dynamic process must be internal rotation about the N–S bond.

Detailed analysis of the low-temperature ^{1}H, ^{13}C, ^{15}N, ^{19}F NMR spectra of **24** performed in [39, 40] allowed to determine the ratio of rotamers **24a**:**24b** equal to 4:1. The calculated ΔE value of 1.44 kcal/mol in favor of **24a** is consistent with the experiment [40].

The energy barriers $\Delta G^{\neq}$ for the ring inversion and the restricted rotation of the trifyl group in acetonitrile solution are equal to 13.5 and 13.0 kcal/mol, respectively. 1,3,5-Trimethyl-1,3,5-triazinane has the barrier of the ring inversion of 12.8 kcal/mol [36]. Chair-to-chair inversion of **24a** or **24b** places two or three CF_3SO_2 groups in the inward position, which is sterically impossible and compels them to turn outward. Thus, the necessity for additional movement of atoms

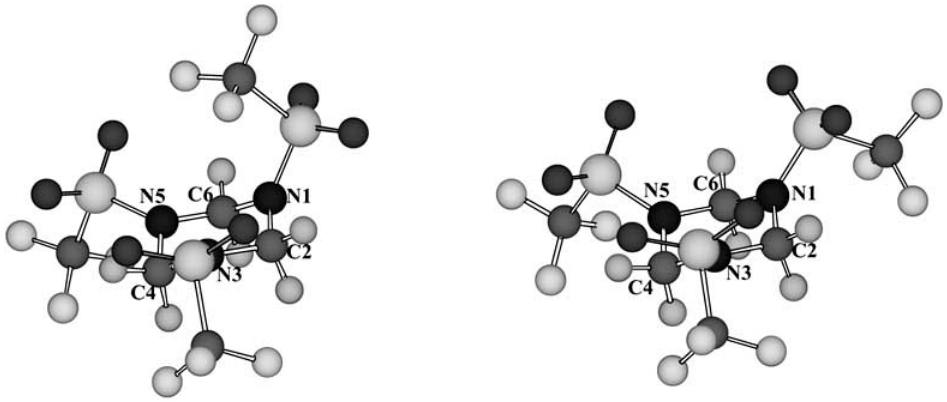

Fig. (5). The inward **24a** and outward **24b** rotamers of 1,3,5-tris(trifluoromethylsulfonyl)-1,3,5-triazinane **24**.

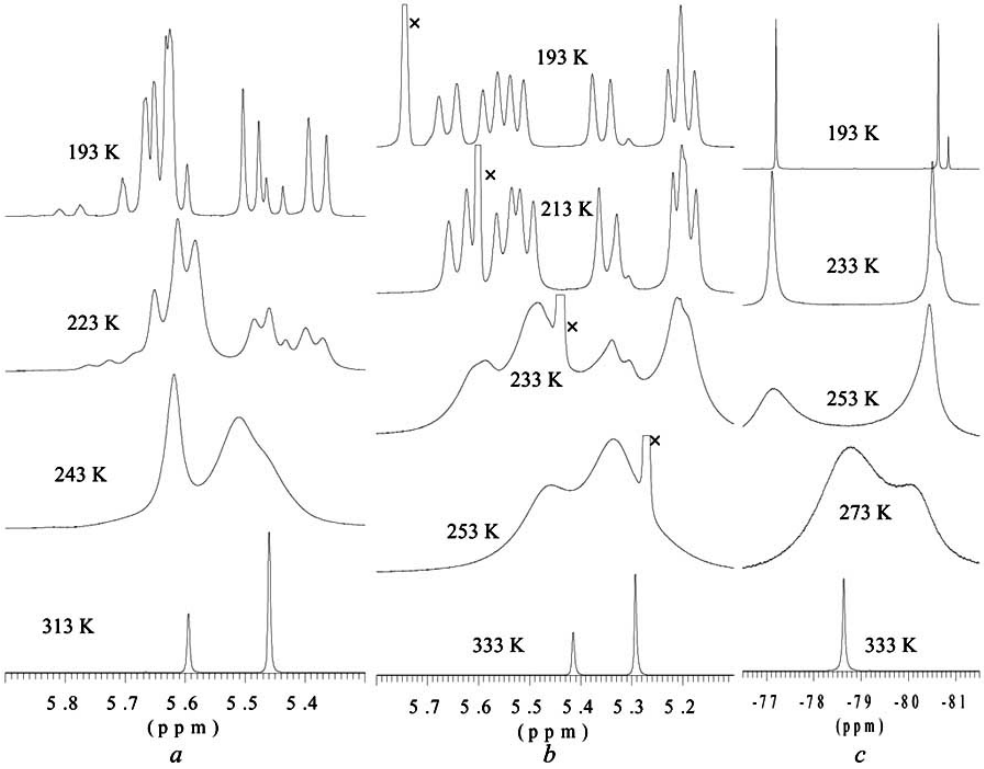

Fig. (6). *(a)* ^{1}H NMR spectra of **23** in acetone-d_6; (*b*) ^{1}H NMR spectra of **23** in methanol-d_4 (**×** denotes the residual OH signal); (*c*) ^{19}F NMR spectra of **23** in methanol-d_4.

increases $\Delta G^{\neq}$ for the ring inversion in **24** in spite of the presence of planar segments.

3,5-Bis(trifluoromethylsulfonyl)-1,3,5-oxadiazinane **23** displays dynamic NMR patterns similar to those of **24**. Two singlets at 5.45 and 5.60 ppm in the 2:1 ratio belonging to the NCH_2O and NCH_2N groups in acetone-d_6, decoalesce upon cooling (Fig. **6*a***). Note the appearance of small doublets at δ 5.75 and 5.41 ppm (Fig. **6*a***), which belong to the minor rotamer **23b** (Fig. **7**). The ratio of the two conformers, **23a:23b**, is about 7:1.

Compound **23** has only two bulky groups and, hence, more flexible ring than in **24** and a lower temperature of decoalescence (243 K and 263 K, respectively) [39, 40]. The ^{19}F NMR spectrum of **23** at 193^{o}K provides direct evidence for the presence and structure of rotamers **23a** and **23b**. The two signals of equal intensity belong to the inward and outward triflyl groups in **23a**, whereas the small upfield signal at δ_F –80.8 belongs to two equivalent triflyl groups in **23b** (Fig. **6*c***). The ratio **23a**:**23b** is 8.7:1, that corresponds to ΔE of 0.83 kcal/mol which excellently coincides with the calculated ΔE value of 0.81 kcal/mol.

Quantum chemical calculations verified two transition states for interconversion of rotamers **23a** and **23b**. The lower transition state gives the energy barrier of 11.7 kcal/mol, that is in excellent agreement with the experimental value of 11.5 kcal/mol.

A remarkable result was obtained from X-ray study (Fig. **8**). While in solution the major rotamer of **23** has two different trifyl groups, in the crystal the less stable rotamer **23b** is frozen, apparently, due to its higher symmetry leading to more dense packing in the crystal [40].

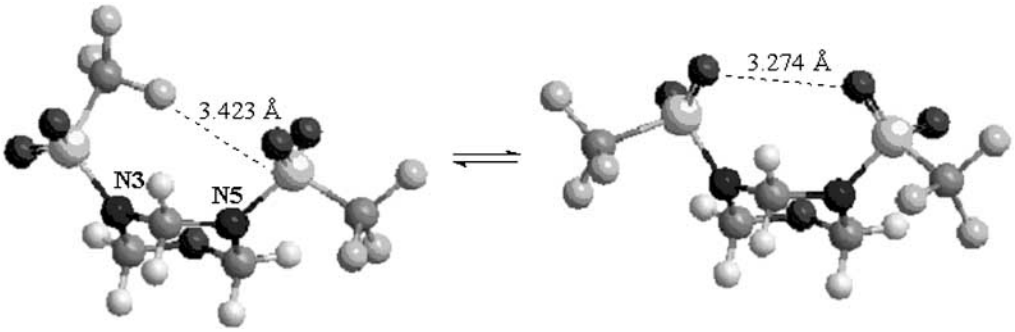

Fig. (7). Equilibrium between the inward **23a** and outward **23b** rotamers of 3,5-bis(trifluoromethylsulfonyl)-1,3,5-oxadiazinane **23**.

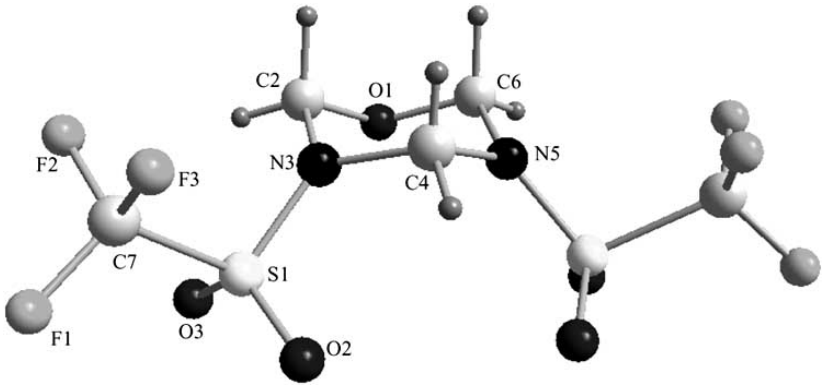

Fig. (8). Single crystal X-ray structure of 3,5-bis(trifluoromethylsulfonyl)-1,3,5-oxadiazinane **23**.

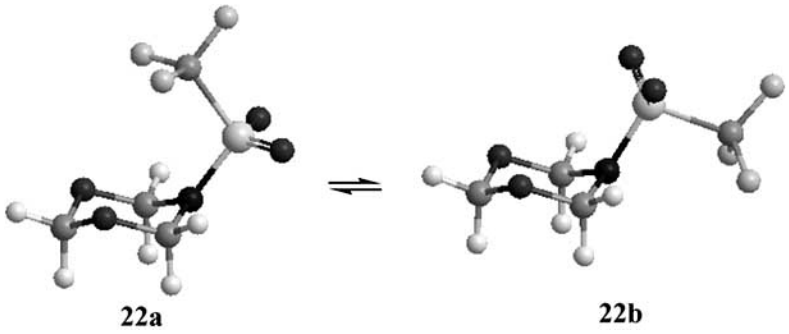

Fig. (9). The inward **22a** and outward **22b** conformers of 5-(trifluoromethylsulfonyl)-1,3,5-dioxaazinane **22**.

For compound **22** containing only one trifyl group the B3LYP/6-311+G(d,p) calculations also revealed two conformational minima. The more stable rotamer **22a** has the triflyl group directed inward with respect to the ring, and rotamer **22b** (both of C_S symmetry) is 0.46 kcal/mol higher in energy and has the triflyl group directed outward from the ring (Fig. **9**).

The ^{1}H NMR spectrum of **22** in acetone-d_6 at 298 K or at higher temperatures shows two narrow singlets at δ 5.24 and 5.36 in the 1:2 ratio belonging to the OCH_2O and NCH_2O groups, respectively. Below 233K the signals decoalesce (Fig. **10**, *a*); note the appearance of a small doublet at δ 5.4 ppm (Fig. **10**, *a*), which belongs to the NCH_2O group in the minor rotamer **22b**. The most direct indication of the existence an equilibrium between two rotamers is the splitting of one singlet signal in the ^{19}F NMR spectrum of **22** into two singlets upon cooling. The ratio of the signals is 84:16 and corresponds to a free energy difference of 0.64 kcal/mol, which nicely correlates with the calculated value of 0.46 kcal/mol.

The presence of only one bulky group in molecule **22** makes it conformationally more flexible and further lowers the temperature of decoalescence to 238 K from 263 K for compounds **24** (three RSO_2 groups) [39] or 243 K for compound **23** (two CF_3SO_2 groups) [40].

For compounds **23** and **24** containing two or three trifyl groups, the ring inversion proved to be not the only dynamic process determining their stereodynamics since it led to conformers with two or even three trifyl groups directed inward that is sterically impossible. Therefore, the ring inversion and internal N–S rotation in those systems are interwined and one cannot occur without the other. As distinct from that, compound **22** has only one trifyl group and, hence, the question arises as to how the interconversion between **22a** and **22b**, depicted in Fig. (**9**), occurs?

The B3LYP/6-311+G(d,p) analysis revealed the existence of a high-lying transition state [**TS-1**]‡ for the internal rotation about the N–S bond, and two transition states, [**TS-2**]‡ and [**TS-3**]‡, and one local minimum corresponding to the intermediate *twist* conformer **15c** for the ring inversion (Fig. **11**). The energy diagram in Fig. (**11**) via the transition states [**TS-2**]‡ and [**TS-3**]‡ is very similar to that of silacyclohexane [42].

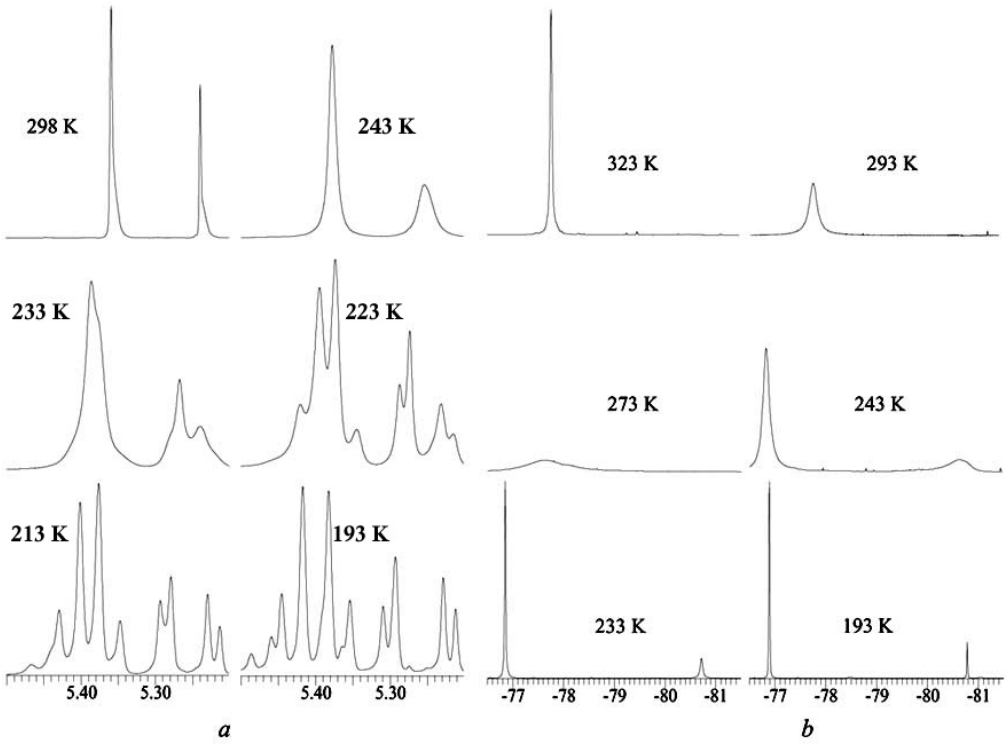

Fig. (10). (*a*) ^{1}H NMR spectra of **22** in acetone-d_6; (*b*) ^{19}F NMR spectra of **22** in acetone-d_6.

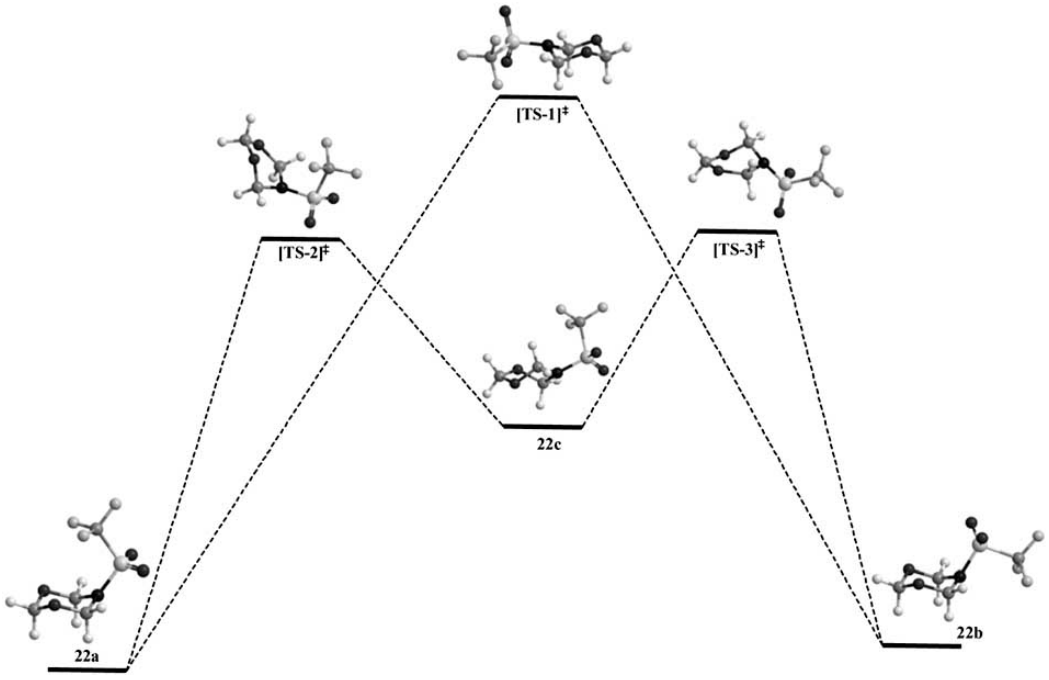

Fig. (11). Interconversion of conformers **22a** and **22b** via internal rotation (route **22a** ⇆ **[TS-1]**‡ ⇆ **22b**) and ring inversion (route **22a** ⇆ **[TS-2]**‡ ⇆ **22c** ⇆ **[TS-3]**‡ ⇆ **22b**).

The calculated barrier via the transition states [**TS-2**]‡ and [**TS-3**]‡ of 11.2 kcal/mol is in excellent agreement with the experimental value of 11.7 kcal/mol found for compound **22** [41].

Finally, let us consider the dynamic behavior of the product of cross condensation **25** [43]. As compared to its symmetrically substituted analog **24**, compound **25** has a $MeSO_2$ group that might serve as a convenient NMR indicator in both ^{1}H and ^{13}C spectra for monitoring the conformational behavior. Besides, due to lower symmetry of molecule **25** as compared to **24**, the former has three conformational minima, namely, **25a** with the $MeSO_2$ group directed inward the ring (C_S symmetry), **25b** with the CF_3SO_2 group inward (C_1 symmetry), and **25c** with all three substituents directed outward from the ring (C_1 symmetry) (Fig. **12**).

The lowest energy minimum corresponds to rotamer **25a**, rotamer **25b** is 4.42 kcal/mol higher in energy, and rotamer **25c** is 5.57 kcal/mol higher than **25a**. The energy difference between **25b** and

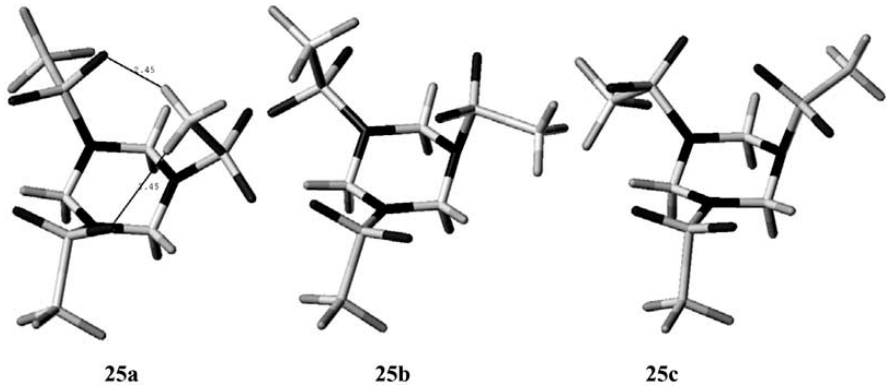

Fig. (12). The $MeSO_2$-inward **25a**, CF_3SO_2-inward **25b**, and all-outward **25c**, rotamers of 1-methylsulfonyl-3,5-bis(trifluoromethylsulfonyl)-1,3,5-triazinane **25**.

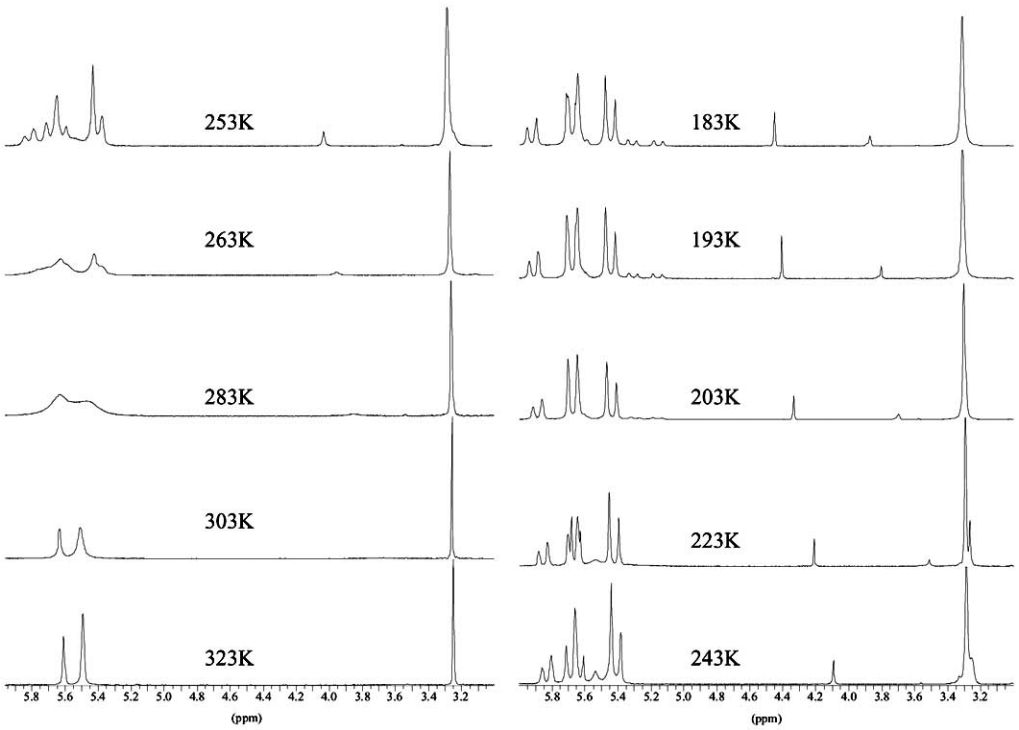

Fig. (13). Temperature dependence of the ^1H NMR spectra of 1-methylsulfonyl-3,5-bis(trifluoromethylsulfonyl)-1,3,5-triazinane **25** in acetone-d_6.

25c (1.15 kcal/mol) is close to that calculated for the inward and all-outward conformers of **24** at the same level of theory [1.44 kcal/mol, B3LYP/6-311+G(d,p)] and, therefore, can be considered as reflecting the energy difference between the inward and outward orientation of the trifyl group.

Estimation of the energy of activation at the coalescence temperatures for the two dynamic processes, that is, for the ring inversion and rotation about the N–S bonds in **25**, gives for both processes $\Delta G^{\neq}$ = 13.5 kcal/mol. This value coincides with the values obtained in [39] for its symmetric analog **24**.

The low-temperature NMR dynamic pattern for **25** is very similar to that for **24** (Fig. **13**). Detailed ^1H, ^{13}C and ^{19}F NMR analysis is given in [43]. At 243 K, a small singlet appears upfield to the main $MeSO_2$ signal suggesting the appearance of the second conformer of **25**, and below 203 K the corresponding ring protons of this conformer emerge (Fig. **13**). The approximate relative intensities of the not fully resolved $MeSO_2$ signals are ~1:6. The ^{13}C NMR spectrum in acetone-d_6 at 183K shows two sets of the signals of all carbons belonging to two rotamers.

3.2. Stereoelectronic Effects and the Perlin Effect in N-trifyl Substituted Azinanes

One of the most remarkable results obtained by detailed NMR structural analysis of the six-membered heterocyclic products of condensation of triflamide with formaldehyde **22–25** was the observation that coupling constants $^1J_{CH}$ with axial protons in CH_2 groups adjacent to such strong acceptor as the CF_3SO_2N group may be larger than the corresponding $^1J_{CH}$ with equatorial protons, in other words, may show the reverse Perlin effect [40, 41, 43]. The Perlin effect, that is, the difference $\Delta J = {}^1J_{CHeq} - {}^1J_{CHax}$, is a powerful tool for analyzing

Table 1. Calculated [GIAO/B3LYP/6-311+G(d,p)//B3LYP/6-311+G(d,p)] and Experimental (in acetone-d_6) Perlin Effect ($\Delta J = J_{CHeq} - J_{CHax}$) in Molecules 22–25

Molecule	Rotamer	Position	ΔJ_{clcd}, Hz	ΔJ_{expl}, Hz
22	**22a**	2-CH_2	17.8	13.2
		3(5)-CH_2	9.1	2.4
	22b	2-CH_2	18.5	7.1
		3(5)-CH_2	10.2	4.3
23 [a]	**23a**	2-CH_2	9.0	2.3 (3.0)
		4-CH_2	-4.4	-9.8 (-9.0)
		6-CH_2	7.5	2.2 (2.5)
	23b	2(6)-CH_2	9.0	3.4
		4-CH_2	-5.5	-10.3
24	**24a**	2(6)-CH_2	-2.3	-9.4
		4-CH_2	-2.9	-9.8
	24b	all CH_2	-4.5	-9.3
25 [b]	**25a**	2-CH_2	-4.4	-10.6 (-8.6)
		4-CH_2	-5.3	-9.6 (-8.7)
		6-CH_2	-4.4	-10.6 (-8.6)
	25b	2-CH_2	-5.7	
		4-CH_2	-3.0	
		6-CH_2	4.7	
	25c	2-CH_2	2.6	
		4-CH_2	-3.1	
		6-CH_2	-4.8	

Notes. [a] Values in parentheses are for solutions in CD_3OD. [b] Values in parentheses are for solutions in CD_3CN.

orbital interactions and stereoelectronic effects in heterocycles (e.g., anomeric effect). Detailed analysis of the normal and the reverse Perlin effects was given in the literature [40, 44], therefore, here we only briefly outline the main points.

Since 1969, when Perlin and Casu first demonstrated that $^1J_{CH}$ in β-D-glucose is 9 Hz smaller than in α-D-glucose [45], a number of works appeared concerning the relationship between J_{CHax} and J_{CHeq} in the anomeric position of the N-, O-, and S-containing six-membered heterocycles (see [46] for the references available to that time). The stereoelectronic effect upon $^1J_{CH}$ has been called the Perlin effect and was originally interpreted in terms of hyperconjugation $n_X \rightarrow \sigma*(C–Hax)$. The normal Perlin effect ($J_{CHax} < J_{CHeq}$) was considered as the above effect of the lone pair of a heteroatom. The involvement of the lone pair was proved experimentally [47] though in the same work the reverse Perlin effect ($J_{CHax} > J_{CHeq}$) was also found. This phenomenon was analyzed experimentally and theoretically in a number of works [32c, 48-51].

The normal Perlin effect is associated with elongation and weakening of the C–Hax bond due to hyperconjugation $n_X \rightarrow \sigma*(C–Hax)$. However, the rule [46a] that *the shorter bond is characterized by the larger* $^1J_{CH}$ may not be fulfilled and it was even declared that there is *no correlation between* $^1J_{CH}$ *constants and the C–H bond distances* [44a]. Moreover, the very concept of the $n_O \rightarrow \sigma*(C–Hax)$ delocalization was recently questioned as primarily responsible for $^1J_{CH}$ [44e]. Hyperconjugation effects on $^1J_{CH}$ were studied experimentally and theoretically and the conclusion has been made that they are often intertwined with electrostatic effects in such a way that the two effects can either enhance or weaken each other [52].

More entangled is the situation with the reverse Perlin effect found in a number of heterocyclohexanes [48d, 49a-d]. Comprehensive theoretical analysis [44a-d] showed that the values of $^1J_{CH}$ in heterocyclohexanes with heteroatom(s) X are governed by $n_X \rightarrow \sigma*(C–Hax)$ and $\sigma(C–X) \rightarrow \sigma*(C–Heq)$ interactions for the α-C–H bonds, and by the homoanomeric Plough effect $(n_X)_{ax} \rightarrow \sigma*(C–Heq)$, W-effect $(n_X)_{eq} \rightarrow \sigma*(C–Heq)$ and $\sigma(C–Heq) \rightarrow \sigma*(C–X)$ for the β-C–H bonds, as well as the $\sigma(C–Hax) \rightarrow \sigma*(C–Hax)$ interaction between the vicinal C–Hax bonds. The relative contribution of these effects is strongly dependent on the nature of X.

The results of our studies [40, 41, 43] of the Perlin effect in compounds **22–25** are summarized in Table **1**. First, as follows from these data, the sign of the experimental values of the Perlin effect for all compounds is correctly reproduced by calculations. Second, all CH_2 groups in molecule **22** show the normal Perlin effect though its value for the NCH_2O groups is much lower than for the OCH_2O group. Third, following this trend, compound **23** shows normal Perlin effect for the NCH_2O groups whereas the reverse Perlin effect is observed for the NCH_2N group. Forth, all CH_2 groups in compounds **24** and **25** (as well as the NCH_2N group in compound **23**) demonstrate unprecedented large reverse Perlin effect ($J_{CHax} > J_{CHeq}$). Finally, *larger* values of J_{CH} in compounds **23–25** are observed for *longer* C–Hax bonds since the C–Hax bonds in molecules **22–25** are by ~0.01 Å longer than the corresponding C–Heq bonds. Several conclusions can therefore be drawn. (i) The presence of oxygen in the α-position to a CH_2 group decreases J_{CHax} with respect to J_{CHeq}, whereas the NSO_2CF_3 group has the opposite effect. This either gives the reverse Perlin effect (for NCH_2N group in compounds **23–25**) or attenuates the normal Perlin effect of the NCH_2O group with respect to the OCH_2O group. (ii) The observed reverse Perlin effect should be considered as a *genuine* reverse Perlin effect (according to [44c]) as distinct from the reverse Perlin effect recently found by us in some 4-silathiane S-oxides [44f], where the *larger* J_{CH} values were observed for *shorter* C–Hax bonds due to the buttressing effect of the S=O group in these heterocycles. (iii) One of possible reasons for such a large reverse Perlin effect in the studied compounds may be the presence of a strong electronwithdrawing trifyl group that makes the nitrogen atom planar and sharply decreases the electron density on it, as was proved by calculation of model compounds with the nitrogen atom either bearing a strong acceptor or formally positive [43]. (iv) Solvent effect

may reach 2 Hz and, therefore, should be taken into account when considering small differences of J_{CH} values.

ACKNOWLEDGEMENTS

This work was supported by Russian Foundation for Basic Research (Grant 07-03-00425).

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Received: February 13, 2008 **Revised: May 28, 2008** **Accepted: May 29, 2008**