Conformational Effects in Sulfur-Containing Six-Membered Cycles and Macrocycles

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CONFORMATIONAL EFFECTS IN SULFUR-CONTAINING SIX-MEMBERED CYCLES AND MACROCYCLES

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Stereochemical studies of mono- and 2,3-disubstituted 1,4-dithianes and sulfur- and oxygen-containing macrocycles by means of NMR measurements, X-ray crystal structure analysis and molecular mechanics calculations revealed new conformational regularity and peculiarities.

KEY WORDS: crown thioethers, 1,4-dithianes, conformational analysis.

INTRODUCTION

Geometrical changes caused by sulfur atoms in cyclic molecules as compared to carbocyclic or oxygen-containing analogs often lead to unexpected conformational behaviour. It is well known that relatively long C-S bonds and sulfur atom's steric requirements as well as lone pair - lone pair interactions between sulfur atoms are important in determining conformational preferences and dynamics in thiacyclanes of various size (for some early reviews see [1-3]). However the conformational behaviour of sulfur-containing cyclic molecules remains so far less studied than that of analogous carbocycles or oxacyclanes. There are blind spots in fundamental conformational parameters even for such classical objects as six-membered cycles (*vide infra*). The conformational properties of much more flexible sulfur-containing macrocycles, especially in solution, still can be considered as *terra incognita* in spite of intensive and fruitful studies (for reviews see [4-6]). Taking into account a considerable interest in structure-dependent complexation of late transition metal ions with polythioethers [4-6] the additional efforts in this field are desirable.

CONFORMATIONS OF 1,4-DITHIANES

In contrast to a thoroughly performed conformational analysis of 1,3- and 1,4-dioxanes, -oxathianes and 1,3-dithianes (see [1-3,7-12] and Refs. therein) the data on conformational behaviour of 1,4-dithianes were rather limited [1-3,8]. The conformational peculiarity of 2-substituted 1,4-dithianes **1** (R = Hal, OR", SR") previously studied is the strong predominance of axial conformer **1A** due to the absence of an essential *syn*-1,3-diaxial repulsion and the stabilization by anomeric orbital interactions [2].

1A, 2A	R' = H (1); R = R' (2)	1E, 2E
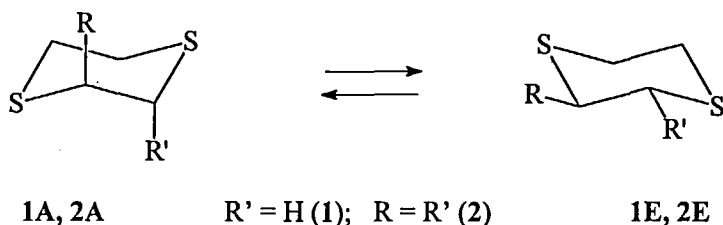
To the best of our knowledge, no examples of the opposite conformational properties of 1,4-dithiane derivatives were described earlier. In particular, the conformational behaviour of the methyl derivative or other alkyl derivatives was not studied. The same held true for 2,3-disubstituted 1,4-dithianes **2**.

To complete the conformational picture of this class of cyclohexane heteroanalogs we accomplished the conformational analysis of various 1,4-dithianes **1** and **2** with an alkyl or functionalized alkyl substituent(s) at C-2 or both C-2 and C-3 by ^{1}H and ^{13}C NMR, and molecular mechanics calculations (MMX; PCMODEL program) (Tables 1,2). [9,10] These compounds have been prepared by a very facile general method for 1,4-dithiane ring construction *via* the homolytic cycloaddition of 1,2-ethanedithiol to alkynes (*cis* : *trans* ratio was 2-10 : 1).
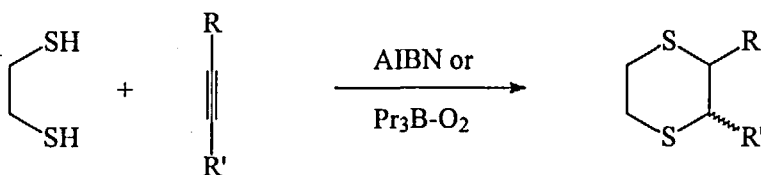
R' = H;   R = CMe$_2$OH (**3**), *n*-C$_6$H$_{13}$ (**4**), CH$_3$ (**5**), CH$_2$OH (**6**), CH$_2$OAc (**7**), CH$_2$Cl (**8**)

R = R' = CH$_3$ (**9**), *n*-C$_3$H$_7$ (**10**), CH$_2$OAc (**11**), CH$_2$Cl (**12**)

Full analysis of ^{1}H NMR spectra (300 and 400 MHz) using the PANIC program allowed us to estimate average vicinal spin-spin couplings and chemical shifts. [9,10] We calculated the conformer populations (n_A, n_E) using two *trans* coupling constants for the SCH_2CH_2S fragment according to the formula: $J_{obs} = J_A \cdot n_A + J_E \cdot n_E$ (Tables 1,2). The limiting parameters, J_A and J_E, were estimated from the spectra of compounds 3, 11-*t* and 12-*t*, which conformational equilibria were close to anancomeric. [9,10]

TABLE 1
Conformer populations and free energy differences for dithianes 1 (kJ/mol)

| Compound | R | ^{1}H NMR | | MMX | |
		n_A, %	ΔG_{E-A} (ΔG_R)	ΔE_{E-A}[a]	ΔG_{E-A}[b]
3	$C(OH)Me_2$	0	-	-11.5	-11.5
4	$n\text{-}C_6H_{13}$	12.0 ± 4.2	-5.0 ± 0.6	-3.3	-3.2
5	CH_3	12.0 ± 2.5	-5.0 ± 0.6	-4.2	-4.2
6	CH_2OH	33.8 ± 2.8	-1.7 ± 0.3	-4.0	-
7	CH_2OCOCH_3	54	0.4	-3.1	-4.1
8	CH_2Cl	58.9 ± 3.1	0.9 ± 0.3	-3.8	-4.1

[a] The energy difference between the most stable rotamers of group R in A- and E-positions.
[b] Calculated for 25°C using relative enthalpies of 3 possible rotamers in each (A or E) conformation.

The data in Table 1 reveal a prevalence of the equatorial conformers for the alkyl substituents; the A-value for methyl is about 5.0 kJ/mol, and this result seems to be quite reasonable. At the same time an increase of axial conformer population, n_A, is observed in the order $CH_3 < CH_2OH < CH_2OAc < CH_2Cl$. Moreover, the most bulky substituents of this series - CH_2OAc and CH_2Cl - prefer the axial position. This result is completely unexpected in the light of the properties of methyl and hexyl derivatives, and the MMX calculations (see Table 1). One can estimate the value of the effect as a difference between the ΔG_{E-A} values for R- and Me-substituted models. It is about 6 kJ/mol for 8.

The comparison of molecular mechanics calculations with experimental data (Table 1) shows that there is a moderate agreement for compounds 4-6. For 7 and 8 the calculations lead to the wrong prediction of almost the same relative stability of the equatorial conformer as for 2-methyl-1,4-dithiane 5. In our opinion, this discrepancy arises from a poor parametrization of Coulombic potentials in molecular mechanics.

Indeed, there is little doubt that this effect is a manifestation of the electrostatic attraction of the sulfur atom in the ring with positively charged carbon and hydrogen atoms in $R = CH_2X$ (scheme **13**; *cf.* **14** [11,12]).

13   **14**   **15**
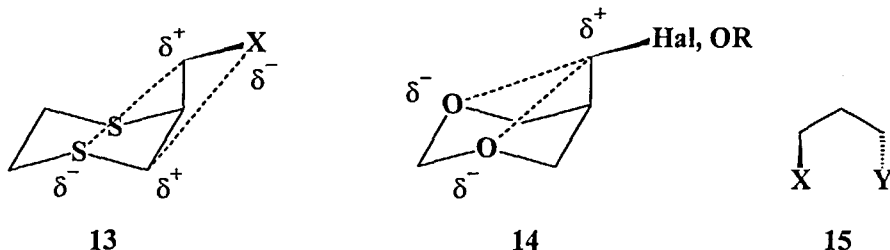
The interactions of this type are rather widespread, and they force the fragments XCCCY to adopt a *g,g*-conformation **15**, for example, in 1,3-dihalopropanes. [13]

In accordance with the properties of monosubstituted 1,4-dithianes **1**, the predominant conformers for *trans*-2,3-disubstituted 1,4-dithianes **2** are as follows: the diequatorial for *trans*-dimethyl derivative **9-t** and the diaxial for *trans*-$(XCH_2)_2$ derivatives **11-t** and **12-t** (Table 2).

TABLE 2

Conformer populations and free energy differences for dithianes 2 (kJ/mol)

| Compound	R	n_A, %	ΔG_{E-A}	ΔE_{E-A}[a]	$2\Delta G_R$[b]	$\Delta G_{R/R}$[c]
9-t	CH_3	12 ± 2	-5.0	-2.3	-10.0	5.0
10-t	$n-C_3H_7$	63 ± 2	1.7	2.5	-10.0	11.7
11-t	CH_2OCOCH_3	~100	> 10	-	0.8	> 9
12-t	CH_2Cl	~100	> 10	1.9	1.6	> 8

[a] The energy difference between the most stable rotamers of groups R in A- and E-positions (MMX);
[b] See Table 1; [c] $\Delta G_{R/R} = \Delta G_{E-A} - 2\Delta G_R$.

In this case the MMX data reproduce the real tendency - relative stability of diaxial XCH_2 groups. Unexpectedly the predominance of diaxial form for *trans*-2,3-dipropyl-1,4-dithiane **10-t** was calculated and the experimental measurements confirmed this prediction. The difference in ΔG_{E-A} values between di(*n*-alkyl) derivatives **9-t** and **10-t** is 6.7 kJ/mol in spite of equal ΔG_R values for the substituents (Table 1). To the best of our knowledge this is the first observation of 'switch-on' of the conformational preference due to relatively small change in effective steric volume of alkyl substituents.

The data obtained demonstrate the great deviation of ΔG_{E-A} values from the sum of substituents conformational energies. Such non-additivity, $\Delta G_{R/R} = \Delta G_{E-A} - 2\,\Delta G_R$, in *trans*-1,2-disubstituted cyclohexanes is commonly attributed to a *gauche* R···R interaction. The Me···Me *gauche* repulsion in **9-*t*** thus estimated is 5 kJ/mol, whereas the *n*-Pr···*n*-Pr repulsion in **10-*t*** is more than twice stronger (11.7 kJ/mol) (Table 2). The CH_2X···CH_2X repulsions are not less than 8 kJ/mol. All these values exceed substantially the corresponding parameters for cyclohexane series (3.1 kJ/mol [14] for Me···Me *gauche* repulsion) indicating a more pronounced steric proximity of diequatorial substituents in 1,4-dithianes **2**. Indeed, MMX calculated RC-CR dihedral angle comprises 52° for E-**9-*t*** and 59° for *trans*-1,2-dimethylcyclohexane.

The dipropyl derivative **10-*t*** much more suffers from *gauche* R...R repulsion in diequatorial conformation than the dimethyl one, **9-*t***. This effect also involves steric hindrance from sulfur atoms and geminal H atoms, *i.e.* it depends on the structure of the cycle as a whole. The MMX energies of various diequatorial forms relative to the most stable diaxial one presented below (in kJ/mol) demonstrate that there are no rotamers of *n*-Pr (or CH_2X) groups in equatorial positions free of rather intensive steric strain.


3.0   9.3   2.5

13.4   3.8   18.7
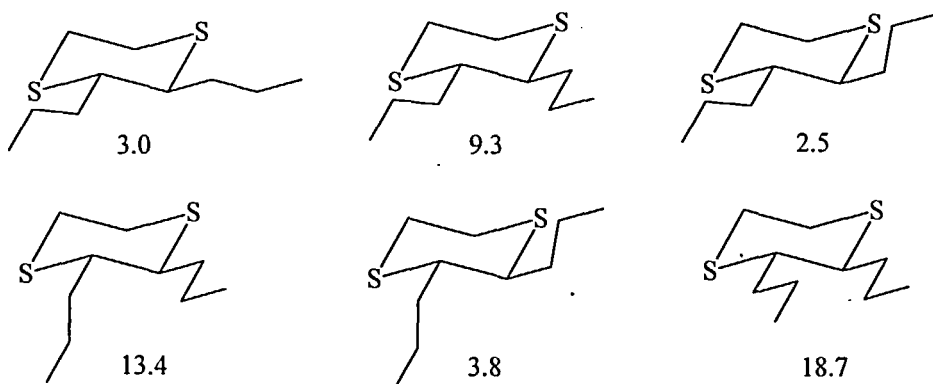
Considering the data of our work[9,10] and literature data (*e.g.* [2]) we can conclude that the most typical conformational behaviour for substituted 1,4-dithianes, contrary to cyclohexane series, is the predominance of the axial conformer owing to intramolecular dipolar and steric interactions. The 2,3-dialkyl-1,4-dithianes appeared to be the unique 6-membered cyclic molecules able to 'switch-on' the sign of their conformational preference due to small change in steric volume of alkyl substituents.

TRANS-CYCLOHEXANOCROWN THIOETHERS

Conformational properties of crown thioethers are essentially different from those of oxygen analogs. Structural data on a variety of thiacrowns revealed a tendency for the CS-CC units to prefer *gauche* conformation and for the SC-CS and SC-CC units to adopt *anti* conformation, whereas in oxacrowns, by contrast, the analogous fragments CO-CC and OC-CO have a strong preference for *anti* and *gauche* conformation respectively. [4-6] Almost all these data were obtained by X-ray crystal structure analysis, and little is known about the conformational changes of thiamacrocycles in solution. [4-6,15]

It is extremely difficult to perform the complete conformational analysis for (thia)crown compounds due to enormous number of possible conformers. Some additional devices are necessary to limit this variety and thus to simplify the analysis. An introduction of *trans*-fused cyclohexane moiety restricts a movement of one X-C-C-Y fragment to only two possible conformations - *gauche* and *anti* - thus restraining a flexibility of the macrocycle as a whole. [16-24] Moreover, the six-membered cycle in these molecules provides a 'probe' for the study of conformational preference: the well developed methods of conformational measurements for cyclohexane derivatives can be used for determination of free energy difference between A conformer ('stretched', 'oval' form of crown cycle) and B conformer (ring-shaped macrocycle is possible).
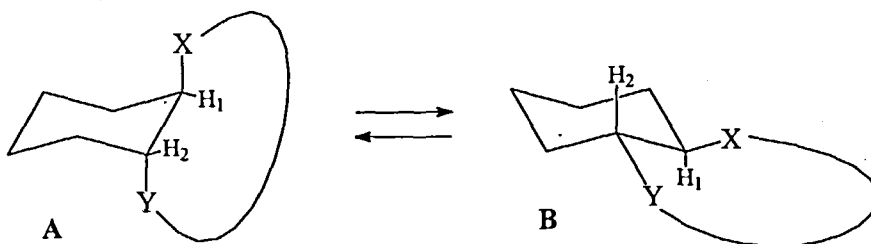

Although the main part of macrocycle beyond the bridge fragment XCCY is not described by the parameters of cyclohexane moiety, this approach permits to receive useful information. [16-24]

The free energy difference between A and B conformers (ΔG_{B-A}) for a series of *trans*-cyclohexanocrown thioethers was estimated by ^{1}H NMR measurements. [21,23,24]

The conformer populations (n_A, n_B) were determined using the averaging formula for H_1 and/or H_2 signal widths ($W = \Sigma J_{HH}$) measured as a distance between terminal peaks of well resolved multiplet: $W_{obs} = W_A \cdot n_A + W_B \cdot n_B$; $\Delta G_{B-A} = -RT \cdot \ln(n_B/n_A)$. The $W_A \cdot$and W_B parameters for individual conformers were estimated from measurements for closely relative cyclohexane derivatives with completely biased conformational equilibrium.

The **B** conformer with diequatorial orientation of C-S and C-O bonds was found to be predominant for monothiacrown ethers **16** and **17**.[21] The predominance increases in polar solvent.
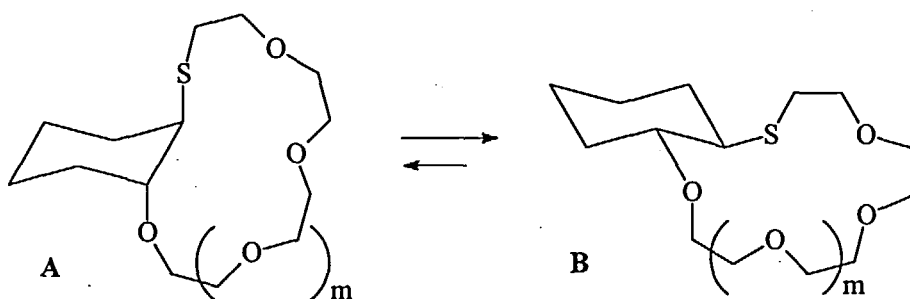
Crown	Solvent	n_A, %	ΔG_{B-A}, kJ/mol
16 (m=1)	C_6D_{12}	40	-1.0
	$(CD_3)_2CO$	32	-1.9
17 (m=2)	C_6D_{12}	31	-2.0
	$(CD_3)_2CO$	20	-3.4

The ratio of conformers for **17** is practically the same as for *trans*-1-methylthio-2-methoxy-cyclohexane (**18**) (n_A = 33%, ΔG_{B-A} = -1.8 kJ/mol·in CCl$_4$ [25]). For **16** the diaxial form **A** is even more populated. Thus, the thiamacrocycle seems not to have a 'contraction effect' on the C-O and C-S bonds at cyclohexane fragment in contrast to analogous all-oxacrowns.[16-20,22] The comparison of conformers' relative stability for thiacrowns **16** and **17** with that one for model compound **18** allows us to estimate the energy difference between 'stretched' and 'ring-shaped' conformers of macrocycle: it comprises about 0.8 kJ/mol in favor of 'stretched' one in the case of **16** in nonpolar solvent. It is interesting that the 15-membered cycle can be stretched more easily than the 18-membered one. The same was observed for all-oxa analogs.[16,20]

For the more complicated trithiacrown compounds **19** and **20** the position of conformational equilibrium A $\rightleftarrows$ B depends both on the macrocycle and the nature of R substituents. [23] The ΔG_{B-A} value for compound **19** is only by 0.5 kJ/mol lower than for its open chain precursor. This parameter is also close to the conformational free energy for *trans*-1-methylthio-2-acetoxy-cyclohexane (ΔG_{B-A} = -2.8 kJ/mol in CCl_4 [25]). So, the 'contraction effect' of macrocycle [16-20,22] is very weak in this case as well.
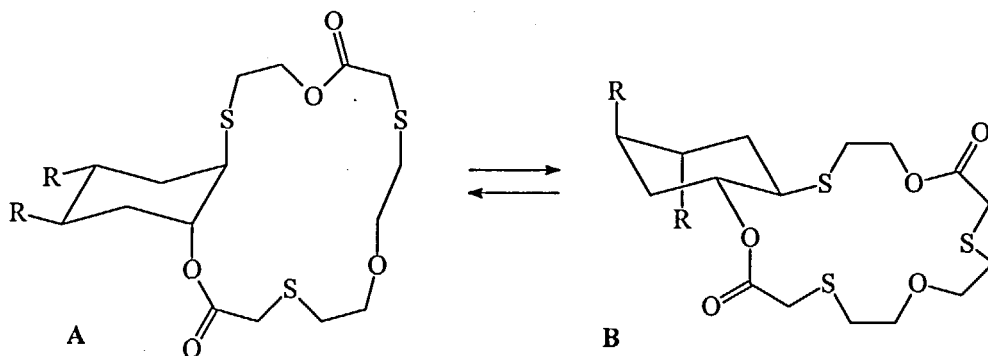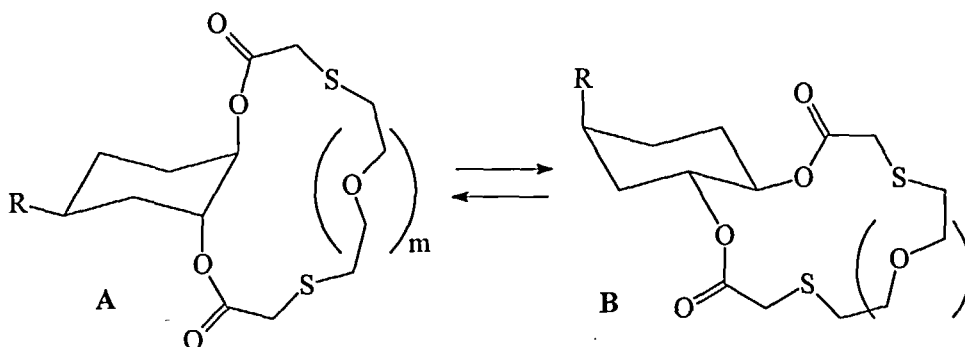

Crown	Solvent	n_A, %	ΔG_{B-A}, kJ/mol
19 (R=H)	C_6D_{12}	26	-2.6
	$(CD_3)_2CO$	12	-4.9
20 (R=CO_2Et)	C_6D_{12}	87	4.8
	$(CD_3)_2CO$	89	5.2

The **B** conformer dominates when R = H, and the **A** conformer is preferred when R = COOEt. Thus, in these structures the substituents R play a role of a *'conformational lever'* and the cyclohexane moiety works as a *mechanical transmitter*. These equilibria exemplify a new principle for modification of crown ethers' complexing ability - the **conformational control** *via* introduction of various substituents into *trans*-fused six-membered cycle. [17-19,22-24] *trans*-Diaxial orientation of the bridge fragment O-C-C-S makes impossible for A conformer the complex formation with metal ions. Conversely, the *gauche* form of this fragment in B conformer corresponds to an *endo*-dentate orientation of heteroatoms which is necessary for metal ion complexation. [4-6] Indeed, the cyclohexanocrown ethers in complexes have to adopt the conformation B (the cyclohexanotetrathio-14-crown-4 as well [26]) with substituent(s) R in unfavourable axial position. [17-19] The axial R destabilizes these complexes in accordance with its

conformational energy. For example, the destabilization of **B** form of **20** by two axial COOEt groups amounts to 7-8 kJ/mol in C_6D_{12} (*vide supra*).

Moreover, two carboxylic groups (R = COOH) at cyclohexane moiety can operate as a pH-sensitive conformational trigger capable to change the preferred conformation of complexing agents (*e.g.* of the type **20**) therefore modifying their complexing ability. [27] This study is currently in progress in our laboratory.

The conformational properties of cyclohexanomacrocycles (**21-23**) [24] differ essentially from those described above. Firstly, the measurements demonstrate the strong 'contraction effect' of macrocycle. While the conformational preference for intermediate compounds - *trans*-1,2-bis(chloroacetoxy)cyclohexanes - depend almost completely on the steric volume of R substituent (n_A = ~100, 19 and ~0% in C_6D_{12} for R = H, Me and t-Bu, respectively), the predominant conformer for corresponding crown compounds **21-23** is determined mainly by the macrocycle:


Crown	Solvent	n_A, %	ΔG_{B-A}, kJ/mol
21 (R= *t*-Bu)	C_6D_{12}	16	-4.2
	CD_3CN	14	-4.6
22 (R= CH$_3$)	C_6D_{12}	12	-5.0
	CD_3CN	4	-7.9
23 (R= *t*-Bu)	C_6D_{12}	89	5.2
	CD_3CN	74	2.6

Even such conformational anchor as *tert*-butyl group is unable to destabilize essentially the **B** conformer in **21**. The **A** conformer with the stretched macrocycle becomes predominant due to *tert*-Bu counterbalance only for 18-membered thiacrown **23**.

This is the second distinction of this series: the 18-membered macrocycle is more flexible than 15-membered one. The conformational peculiarities of cyclohexanocrown thioethers **21-23** most probably originate from conformational rigidity of the ester fragments incorporated into macrocycle.

An interesting example of conformational rigidity was observed for two diastereomers of dicyclohexano trithia-12-crown-4 (**24**), obtained by treatment of [2 + 1]-adducts of cyclohexene and SCl_2 by corresponding dithiol. [28] The vicinal spin-spin

24
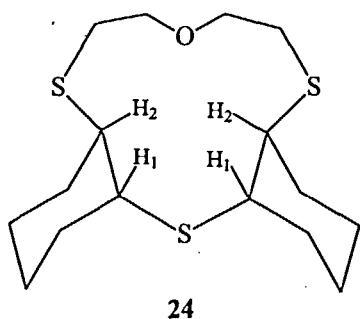
couplings of H^1 and H^2 in both diastereomers (solution in $CDCl_3$) equal to approximately 4 Hz and 3 Hz, pointing at practically complete predominance of the diaxial conformation for cyclohexane fragments. As far as we know, the incorporation of two successive *trans*-S-C-C-S fragments ('bracket unit') in the relatively small 12-membered cycle was described earlier only for 12-tetrathiacrown-4 in solid state. [29]

CONFORMATIONS OF MACROCYCLE

We have developed recently a new general approach to the various crown thioethers based on one-step homolytic cycloaddition of α,ω-dithiols to alkynes (see [30] and Refs. therein):
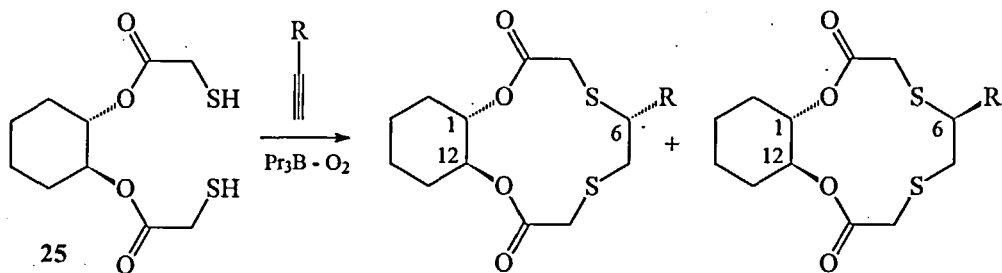
26   (1S*, 6R*, 12S*)   **27**   (1S*, 6S*, 12S*)

R	Ratio 26 : 27	Overall yield of 26 + 27
Me (a)	2.1 : 1	30 %
Bu (b)	2.4 : 1	23 %
CH₂OMe (c)	3.1 : 1	28 %

It was found that for *trans*-dithiol **25** cycloaddition proceeded with unexpectedly high diastereoselectivity to afford the mixtures of stereoisomeric *trans*-cyclohexane-fused 12-membered crown thialactones **26a-c**, **27a-c** with significant predominance of **26**.[30] In contrast to reactions of *trans*-**25** no remarkable stereoselectivity has been observed in cycloaddition of analogous *cis*-dithiols to alkynes.

The major stereoisomers **26a-c** crystallized spontaneously from their mixtures with **27a-c** on keeping. (1*S**, 6*R**, 12*S**)-configuration of **26c** was established from X-ray crystallographic data (Figure 1). Due to close similarity of ^{1}H and ^{13}C NMR spectra the same configuration was assigned to the major stereoisomers **26a** and **26b**.[30]
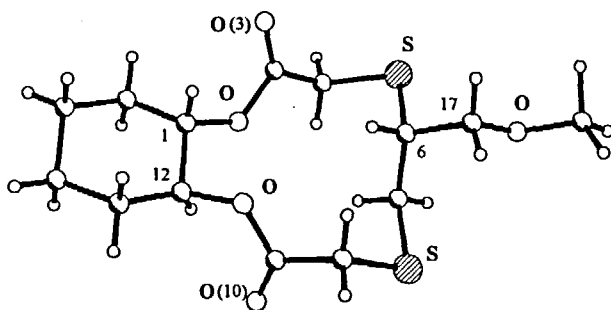

FIGURE 1   Molecular structure of (1*S**, 6*R**, 12*S**)-**26c**.

It is possible to rationalize the observed stereoselectivity in terms of the kinetic control of the reaction. To estimate the relative energy of intermediates leading to products 26 and 27 we have calculated the energies of nearest molecular forms, including thiacrowns 26 and 27, by the molecular mechanics (MMX, PCMODEL program).[30]

To achieve the complete screening of all possible conformers of 26 and 27 we started calculations from the known conformers of cyclododecane [31] and placed sulfur and oxygen atoms, carbonyl group and cyclohexane fragment in all of the 12 possible positions within the cycle and then minimized the energy of molecule. Alternative route was also used when the macrocycle geometry was optimized separately, then cyclohexane moiety was added with subsequent full optimization of geometry (only in a very few cases these two approaches led to different results). The first 20 most stable conformers of cyclododecane [31] within 23 kJ/mol from the global energy minimum were used as starting points. Thus the number of calculated conformers of

unsubstituted *trans*-cyclohexane-fused 12-membered crown thialactones exceeded 240, while many of them were equivalent. The most stable forms were generated several times starting from various cyclododecane conformations. The structures **26a** and **27a** were obtained by adjustment of methyl group to appropriate position of S-C-C-S fragment and subsequent optimization of molecular geometry.

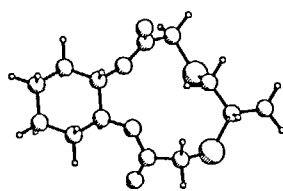26a (1S*,6R*,12S*)   27a (1S*,6S*,12S*)
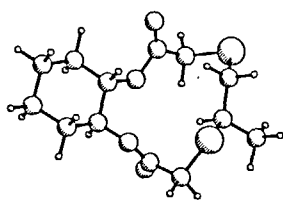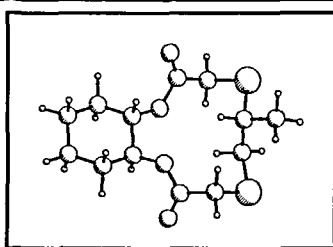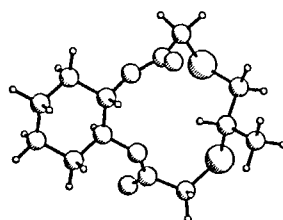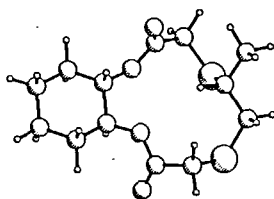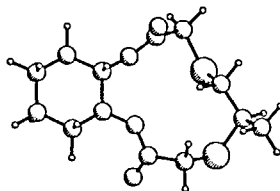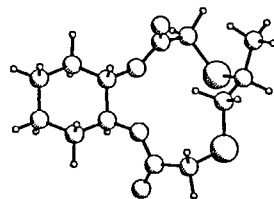

1.7   3.3   0.0
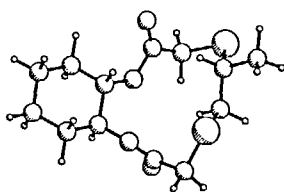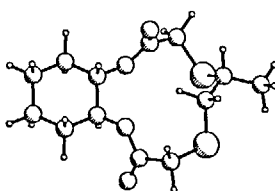
3.7   4.0   5.5
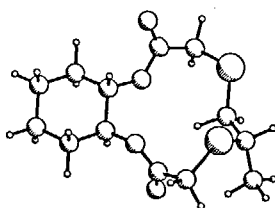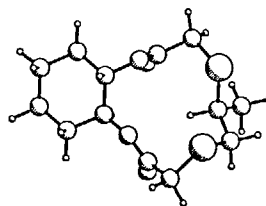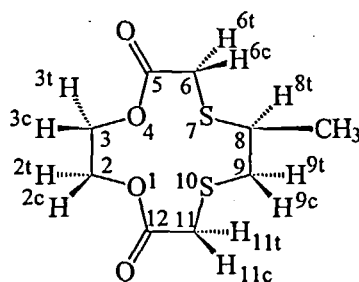
4.3   5.2   5.9

5.9   7.1

SCHEME 1

Eleven most stable conformers for both **26a** and **27a** are depicted in Scheme 1 with corresponding energy values in kJ/mol relative to global energy-minimum (within 10 kJ/mol from the last one). All other conformers could be neglected because of their high steric energy. The conformer related to X-ray determined structure of **25c** is placed in a box. It is important to note that this form is not the most stable one as it could be expected. Probably it is preferred in the crystal due to higher level of macrocycle's symmetry. The ^{1}H NMR spectra for **26a-c** exhibit rather large value of spin-spin coupling between two vicinal hydrogens in $SCHRCH_2S$ fragment [$^3J_{HH}$ = 10.3 (**26a**), 8.0 (**26b**), 9.4 Hz (**26c**)] indicating their predominantly *antiperiplanar* conformation (cf. [9,10]). According to Scheme 1 the most part of stable conformers possesses this internal arrangement, and therefore it is not easy to determine the preferred conformer in solution basing on the NMR data (*vide infra*).

More detailed study of macrocycles' conformations we undertook [32] for 8-methyl-5,12-dioxo-1,4-dioxa-7,10-dithiacyclododecane (**28**), prepared by the same method [33].
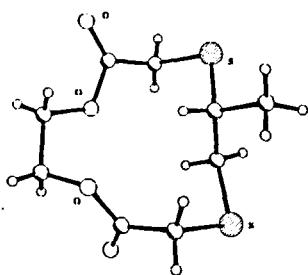
FIGURE 2 Molecular structure of **28**.   SCHEME 2

The molecular structure of **28**, established from X-ray crystallographic data (Figure 2), although a little less symmetrical, closely resembles the structure of macrocycle in the cyclohexano-derivative **26** (Figure 1).

The molecular mechanics calculations carried out in the manner described above furnished a great number of possible conformers for **28**. In contrast to **25** their energies present a continuous sequence without pronounced interruptions. Again the crystal structure's image was not the most stable conformer, exceeding the global energy minimum by 5.4 kJ/mol (the 8th place in succession). The relative energies of the first

60 conformers within 17 kJ/mol from the global minimum allowed us to calculate their population using a Boltzmann distribution: the most stable conformer occupied 22.6%, the first 28 conformers covered 95% of the total.

The spin-spin coupling constants measured in the ^{1}H NMR spectra (400 MHz, C_6D_{12} solution) for vicinal hydrogens in SCHMeCH$_2$S fragment are 4.78 Hz (H^{8t}-H^{9t}) and 10.02 Hz (H^{8t}-H^{9c}; Scheme 2) pointing at a preference for the *anti* conformation of S-C-C-S fragment in solution. However, the other rotamers also participate in the equilibrium enhancing their role with the increase of solvent polarity: $^3J_{HH}$ = 4.84 Hz and 10.17 Hz in C_6D_6, 4.94 Hz and 9.63 Hz in CDCl$_3$, 5.09 Hz and 9.23 Hz in CD$_3$OD. The corresponding individual $^3J_{HH}$ values for all conformers were calculated by PCMODEL program and then weighted in a Boltzmann proportion resulting in 5.92 Hz and 7.82 Hz. These values are in a rough agreement with the experimental ones.

The S-C-C(Me)-S torsion angle is the main structural characteristic of the macrocycle **28**. According to the MMX data all conformers of **28** can be divided into three large groups - **A**, **B** and **C** - with different conformations of this fragment. Their population is 55%, 36% and 9% respectively. Each group of conformers can roughly be considered as a single conformer, because its members possess rather close structures which differ mainly in the terminal torsion angles of ester moieties. The internal CC(O)-OC bond of ester fragments appeared to be fixed in the *anti* conformation. In all the calculated structures the O-C-C-O fragment was strictly *gauche*. So, both O-C-C-O and ester fragments rigidify the structure thus facilitating the conformational study.
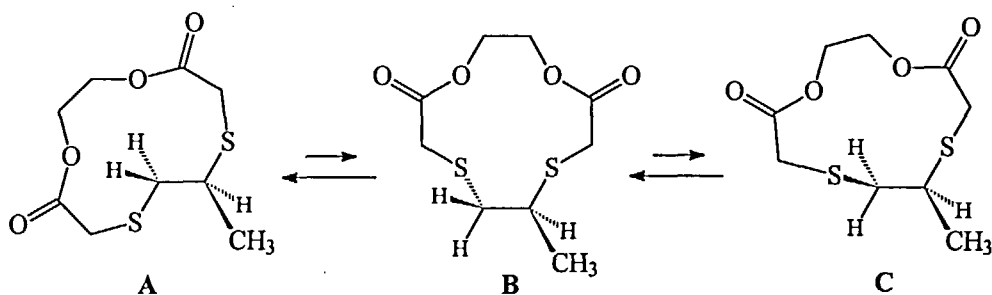
We estimated the $^3J_{HH}$ parameters for **A**, **B** and **C** conformers by averaging of individual parameters for calculated conformers within each group. The analysis of

^{13}C NMR spectra provided us with the experimental values of vicinal $(H_3)C-H^{9c}$ and $(H_3)C-H^{9t}$ spin-spin coupling (in C_6D_6). We calculated these parameters for individual conformers using the Karplus formula [34,35], and estimated C-H coupling for **A**, **B** and **C** by averaging. Then four equations using $^3J_{HH}$ and $^3J_{CH}$ could be composed of the type: $J_{obs.} = n_A \cdot J_A + n_B \cdot J_B + n_C \cdot J_C$. A statistical treatment of this system - multiple regression with unexpectedly high $R = 0.9987$ - gave the following participation of conformers for **28** in C_6D_6 solution: 75% **A**, 23% **B** and 2% **C**.

Thus, in particular cases the combination of X-ray crystal structure analysis, NMR spectroscopy and computational methods yet allows to perform rather complete analysis of conformational structure and distribution for such difficult objects as macroheterocycles. Further improvement of experimental conformational determinations can be achieved by consecutive subdivision of conformers' groups and use of more spectral parameters along with improvement of the methods for calculations.

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