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Conformational Analysis of 2,3-Disubstituted 1,4-Dithianes by NMR Spectroscopy and MMX Calculations

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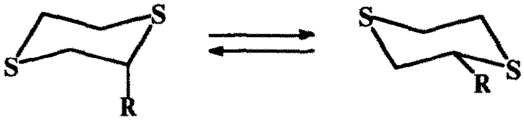
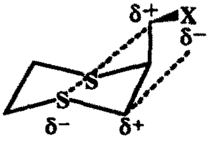
Abstract: *The conformer populations for trans- and cis-2,3-disubstituted 1,4-dithianes have been determined by ^1H and ^{13}C NMR spectroscopy and calculated by molecular mechanics (MMX). The CH_2X-substituents demonstrate the strong preference for axial position. The remarkable difference originating from intramolecular steric interactions has been observed between two trans-dialkyl derivatives: the trans-2,3-dimethyl-1,4-dithiane is predominantly equatorial whereas trans-2,3-dipropyl-1,4-dithiane prefers diaxial conformation. The properties of cis-2,3-dipropyl-1,4-dithiane are also unusual: its ring interconversion is unexpectedly slow ($\Delta G^{\neq} = 11.2$ kcal mol^{-1} at 260K).*

In our previous work on the conformational properties of 2-substituted 1,4-dithianes **1** we have shown[1] that the compounds **1** with R = Alk exist preferentially in the equatorial conformation **1*e***.



1*a* **1*e***

The A-value for methyl was estimated to be 1.2 kcal/mol, and an increase of axial conformer population, n_a, was observed in the order $CH_3 = n\text{-}C_6H_{13} < CH_2OH < CH_2OAc < CH_2Cl$. The last two substituents preferred the axial position in contrast with properties of alkyl groups and results of MMX calculations. This effect was rationalized in terms of intramolecular electrostatic attraction of type **2**.



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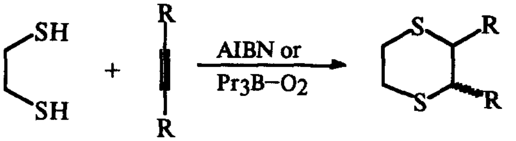
In this paper we report the results of conformational study of related *trans*- and *cis*- 2,3-disubstituted 1,4-dithianes **3** with R = Alk, CH_2X and Ph. These compounds have been prepared by a very facile general method for 1,4-dithiane ring construction via the homolytic cycloaddition of 1,2-ethanedithiol to alkynes. [2]



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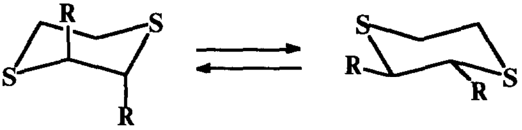
R= CH_3 (**4**), *n*-C_3H_7 (**5**), CH_2OAc (**6**), CH_2Cl (**7**), Ph (**8**)

Mixtures of isomers with *cis* one strongly dominating (*cis:trans* ratio was 2-10 : 1) have been investigated without isolation of individual stereoisomers. Assignment of the signals to each stereoisomer was accomplished on the basis of the ^1H NMR data (Table 1). In chair-like conformers of unsubstituted 1,4-dithiane vicinal spin-spin coupling constants are 11.5 ($^3J_{aa}$), 4.6 ($^3J_{ee}$), and 4.2 ($^3J_{ae}$) Hz. [3] In *cis*-isomers **4-*c*** - **8-*c*** due to energetical degeneracy and, therefore, equal population of conformers average couplings $^3J_{BB'}$ and $^3J_{CC'}$ are equal and close to the mean value of $^3J_{aa}$ and $^3J_{ee}$ [1/2 (11.5 + 4.6) $\simeq$ 8 Hz]. In *trans*-isomers **4-*t*** - **7-*t*** the same average couplings generally differ one from another because of different conformer population (see also $^3J_{AA'}$). For both isomers the couplings $^3J_{BC'}$ and $^3J_{B'C}$ practically do not alter on conformational transition ($^3J_{ae} \rightleftharpoons {}^3J_{ea}$) and equal ~ 2.5 Hz.

Full analysis of ^1H NMR spectra (300 and 400 MHz) using the PANIC program allowed us to estimate average vicinal spin-spin couplings and chemical shifts (Table 1, 2). The spectra have been treated as a superposition of two weakly connected spin systems AA' and BB'CC', because the long-range couplings through sulfur atoms are quite small. We calculated the conformer populations (n_i) for compounds **4** and **5** using two *trans* coupling constants for the SCH_2CH_2S fragment ($J_{BB'}$ and $J_{CC'}$) according to the formula $J_{obs} = J_{aa} \cdot n_{aa} + J_{ee} \cdot n_{ee}$ (Table 1, 3). The limiting parameters, J_{aa} and J_{ee}, were estimated from the spectra of compounds **1** (R=CMe_2OH)[1], **6-*t*** and **7-*t***, which conformational equilibria were close to anancomeric.

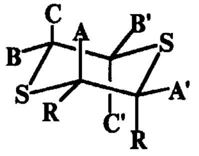


3aa ***3ee***

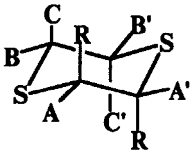
We also have carried out the temperature variable ^{13}C NMR measurements (Fig. 1, 2; Table 4), which allowed us to estimate the barriers of chair-chair ring interconversion for *cis* isomers of **4** and **5** (Table 5). Conformational determinations by low-temperature ^{13}C NMR for *trans* isomers, except **5-*t***, were impossible because of their low concentration in the mixture of isomers.

All the data obtained confirm the existence of two rapidly interconverting conformers for all compounds investigated. They are identical for *cis* isomers and differ in form and energy for *trans* ones (Table 3). In accordance with previously reported[1] properties of monosubstituted 1,4-dithianes **1**, the predominant conformers are as follows: the diequatorial for *trans*-dimethyl derivative **4-*t*** and the diaxial for *trans*-$(XCH_2)_2$ derivatives **6-*t*** and **7-*t*** (Table 3).

Table 1. ^1H-^1H Spin-spin Coupling Constants (Hz)[a] in 1,4-Dithianes **4-8**



cis



trans

Compound	R	Solvent	T, K	$J_{AA'}$	$J_{BC,B'C'}$	$J_{BB'}$	$J_{BC',B'C}$	$J_{CC'}$
4-*cis*	CH_3	$CDCl_3$	300	2.65	-13.87	8.14	2.50	8.14
4-*trans*				8.97	-13.72	11.24	2.41	5.08
5-*cis*	*n*-C_3H_7	DMSO-d_6	363	2.58	-13.72	8.14	2.47	8.14
5-*trans*				~6	-13.85	7.13	2.46	9.18
6-*cis*	CH_2OAc	$(CD_3)_2CO$	300	2.27	-14.01	8.13	2.36	8.13
6-*trans*				2.82	-14.23	4.39	2.76	12.06
7-*cis*	CH_2Cl	$(CD_3)_2CO$	300	2.0±0.2	-14.08	8.06	2.46	8.06
7-*trans*				2.40	-14.19	3.57	2.78	12.15
8-*cis*[b]	Ph	$CDCl_3$	300	3.53[c]	-13.95	8.28	2.66	8.28

[a] The average accuracy of J_{HH} measurement is 0.1 Hz
[b] The *trans*-isomer signals are not detectable
[c] Measured from ^{13}C satellites.

Table 2. Chemical Shifts (δ, ppm) in ^1H NMR Spectra of 1,4-Dithianes **4-8**

Compound	R	Solvent	T, K	$\delta_{A(A')}$	$\delta_{B(B')}$	$\delta_{C(C')}$
4-*cis*	CH_3	$CDCl_3$	300	2.74	2.87	3.06
4-*trans*				2.72	2.71	2.90
5-*cis*	*n*-C_3H_7	DMSO-d_6	363	3.00	2.74	2.85
5-*trans*				2.65	2.61	2.92
6-*cis*	CH_2Cl	$(CD_3)_2CO$	300	3.48	2.84	3.03
6-*trans*				3.00	2.52	3.14
7-*cis*	CH_2Cl	$(CD_3)_2CO$	300	3.56	2.91	3.04
7-*trans*				3.22	2.54	2.96
8-*cis*	Ph	$CDCl_3$	300	4.53	3.11	3.36
8-*trans* a)				4.48		

a) Only single line of AA' protons was observed for **8-*trans*** in the mixture of isomers of **8**.

Table 3. Conformer Populations and Free Energy Differences (kcal mol^{-1})

Compound	R	n_{aa}, % a)	$\Delta G_{ee\text{-}aa}$ a)	$\Delta E_{ee\text{-}aa}$ b)	$2\Delta G_R$ c)	$\Delta G_{R/R}$ d)
4-*trans*	CH_3	12	-1.2	-0.55	-2.4	1.2
5-*trans*	*n*-C_3H_7	63	0.4	0.60	-2.4	2.8
6-*trans*	CH_2OAc	~ 100	>2.5	-	0.2	>2
7-*trans*	CH_2Cl	~ 100	>2.5	0.45	0.4	>2

a) The average accuracy of conformer population determination ~ 2% was estimated from the accuracy of coupling constant J_{HH} measurements (0.1 Hz). Estimated $\Delta G_{ee\text{-}aa}$ accuracy was 0.1 kcal mol^{-1}.

b) The energy difference between the most stable rotamers of groups R in *ee*- and *aa*-positions (MMX).

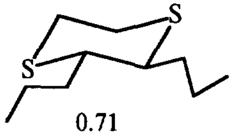
c) See ref. 1.

d) $\Delta G_{R/R} = \Delta G - 2\Delta G_R$

The molecular mechanics calculations (MMX, PCMODEL program) demonstrate a moderate agreement with experimental data (Table 3). In contrast to previous investigation of mono-substituted models[1] the MMX data reproduce the real tendency - relative stability of diaxial position of XCH_2 groups.[4] Unexpectedly the predominance of diaxial form for *trans*-2,3-dipropyl-1,4-dithiane **5-*t*** was calculated and the experimental measurements confirmed this prediction. The difference in $\Delta G_{ee\text{-}aa}$ values between di(*n*-alkyl) derivatives **4-*t*** and **5-*t*** is 1.6 kcal mol^{-1} in spite of equal A values for the substituents (ΔG_R was determined to be -1.2 kcal mol^{-1} both for R = CH_3 and *n*-C_6H_{13} [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 free energy of conformational equilibria, $\Delta G_{ee\text{-}aa}$, from the sum of substituent conformational energies. This non-additivity, $\Delta G_{R/R}=\Delta G_{ee\text{-}aa} - 2\,\Delta G_R = \Delta G_{ee\text{-}aa} + 2A$, in *trans*- disubstituted cyclohexanes and related six-membered cyclic systems are commonly attributed to a *gauche* R...R interaction.[5-8] The Me...Me *gauche* repulsion in **4-*t*** thus estimated is 1.2 kcal mol^{-1}, whereas the *n*-Pr...*n*-Pr repulsion in **5-*t*** is more than twice stronger (2.8 kcal mol^{-1}) (Table 3). CH_2X...CH_2X repulsions are not less than 2 kcal mol^{-1}.[4] All these values exceed substantially the corresponding parameters for cyclohexane series (0.74 [6] or 0.92 kcal mol^{-1} [7] for Me...Me *gauche* repulsion) indicating a more pronounced steric proximity of substituents in diequatorial positions of 1,4-dithianes **3**. Indeed, MMX calculated R-C-C-R dihedral angle comprises 52° for *ee*-**4-*t*** and 59° for *ee-trans*-1,2-dimethylcyclohexane.

The dipropyl derivative **5-*t*** much more suffers from '*gauche* R...R repulsion in diequatorial conformation than the dimethyl one, **4-*t***. This effect, along with the direct R...R interactions, also involves steric hindrance from sulfur atoms and geminal H atoms, *i.e.* it depends on the structure of the cycle as a whole. MMX energies of various diequatorial conformers relative to the most stable diaxial one (in kcal mol^{-1}) are presented below (*n*-Pr groups are treated as planar zigzags).



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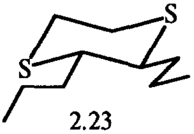

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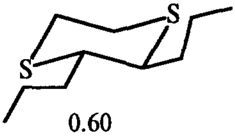

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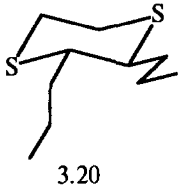

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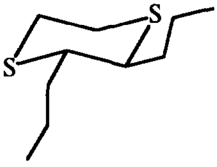

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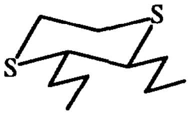


4.47

These data demonstrate that there are no rotamers of *n*-Pr groups in equatorial positions which are free of intensive steric repulsion. Considering this result one can suppose that complete predominance of axial conformer for **6-*t*** and **7-*t*** is not only based on the electrostatic interactions of type **2** [1] (*vide supra*) but also has sterical origin. Analogous effect was observed for *trans*-2,3-bis(RS)-1,4-dioxanes where an increasing bulk of R group (from Me to *tert*-Bu and Ar) leads to additional destabilization of diequatorial conformer

Table 4. Chemical Shifts (δ, ppm) in ^{13}C NMR Spectra of 1,4-Dithianes **4-8** at 300 K in acetone-d_6.

Compound	S-CH_2	S-CH	R
4-*c*	26.77	39.78	CH_3: 16.98
4-*t*	30.51	42.79	CH_3: 19.11
5-*c*	27.98	45.75	*n*-Pr: 32.99, 20.66, 14.36
5-*t*	27.04	44.92	*n*-Pr: 36.13, 21.08, 14.36
6-*c*	28.15	41.92	CH_2OAc: 20.68 (CH_3), 63.95 (OCH_2), 170.66 (C=O)
6-*t*	24.15	36.83	CH_2OAc: 20.66 (CH_3), 64.61 (OCH_2), 170.46 (C=O)
7-*c* a)	28.37	46.15	CH_2Cl: 44.80
7-*t* a)	23.68	38.85	CH_2Cl: 46.83
8-*c*	28.53	48.91	Ph: 140.2 (*ipso*), 128.6 (*ortho*), 127.7 (*meta*), 127.1 (*para*)
8-*t*	32.51	52.26	Ph: 139.5 (*ipso*)

a) Solution in $CDCl_3$.

Table 5. Activation Parameters of Cycle Inversion Calculated from Line Shape Analysis of Low-temperature ^{13}C NMR Spectra.

Compound	R	T, K	$\Delta H^{\neq}$, kcal mol^{-1}	$\Delta S^{\neq}$, cal mol^{-1} K^{-1}	$\Delta G^{\neq}$, kcal mol^{-1}
4-*cis*	CH_3	213	8.77 ± 0.02	-3.01 ± 0.8	9.41 ± 0.18
		300			9.68 ± 0.24
5-*cis*	*n*-Pr	260	10.21 ± 0.07	-3.87 ± 0.4	11.21 ± 0.17
		300			11.37 ± 0.18
5-*trans* a)	*n*-Pr	200	9.0	-3.3	9.3

a) Estimated from two points.

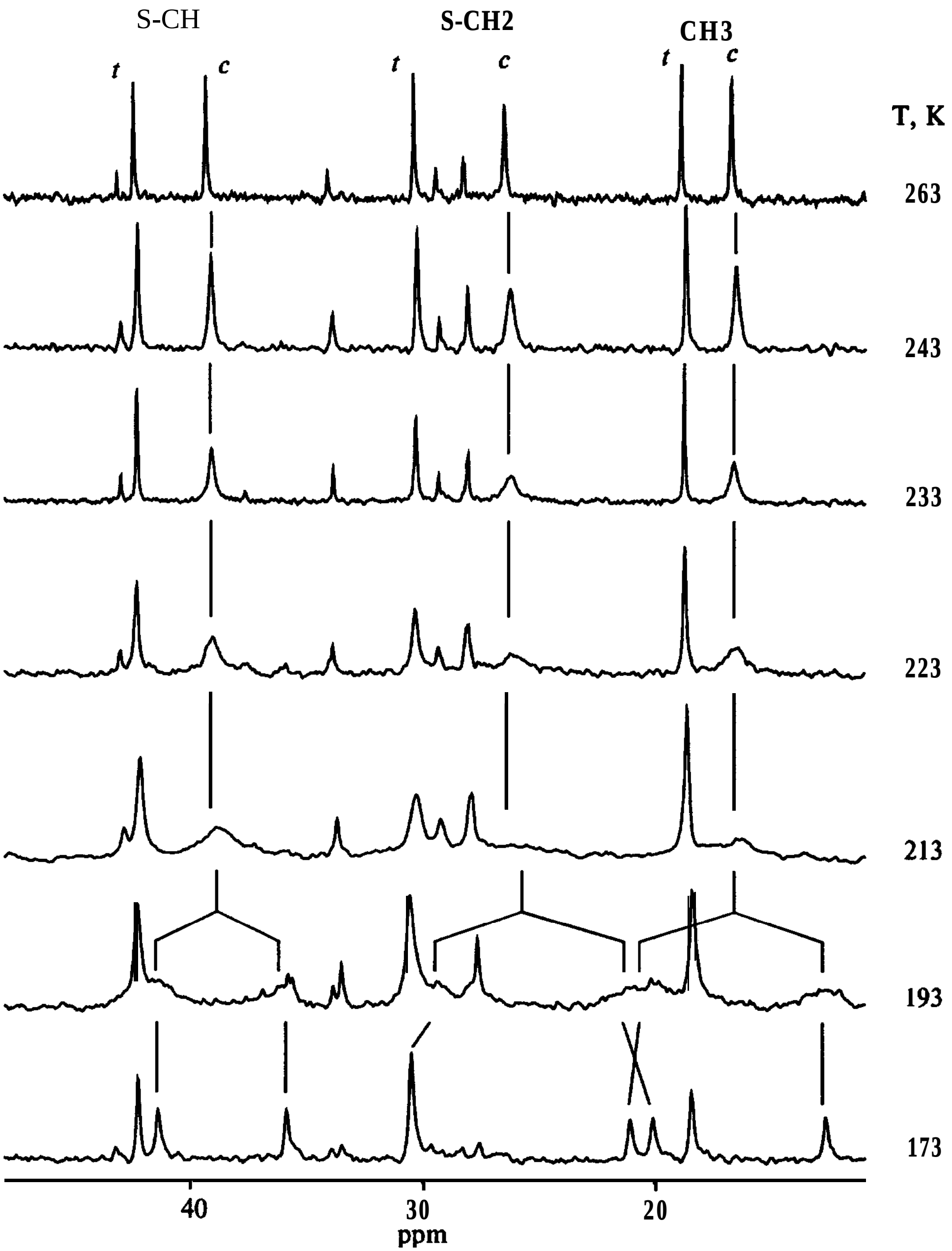


Figure 1. **Variable** temperature spectra of **2,3-dimethyl-1,4-dithianes 4c** + **4t**.

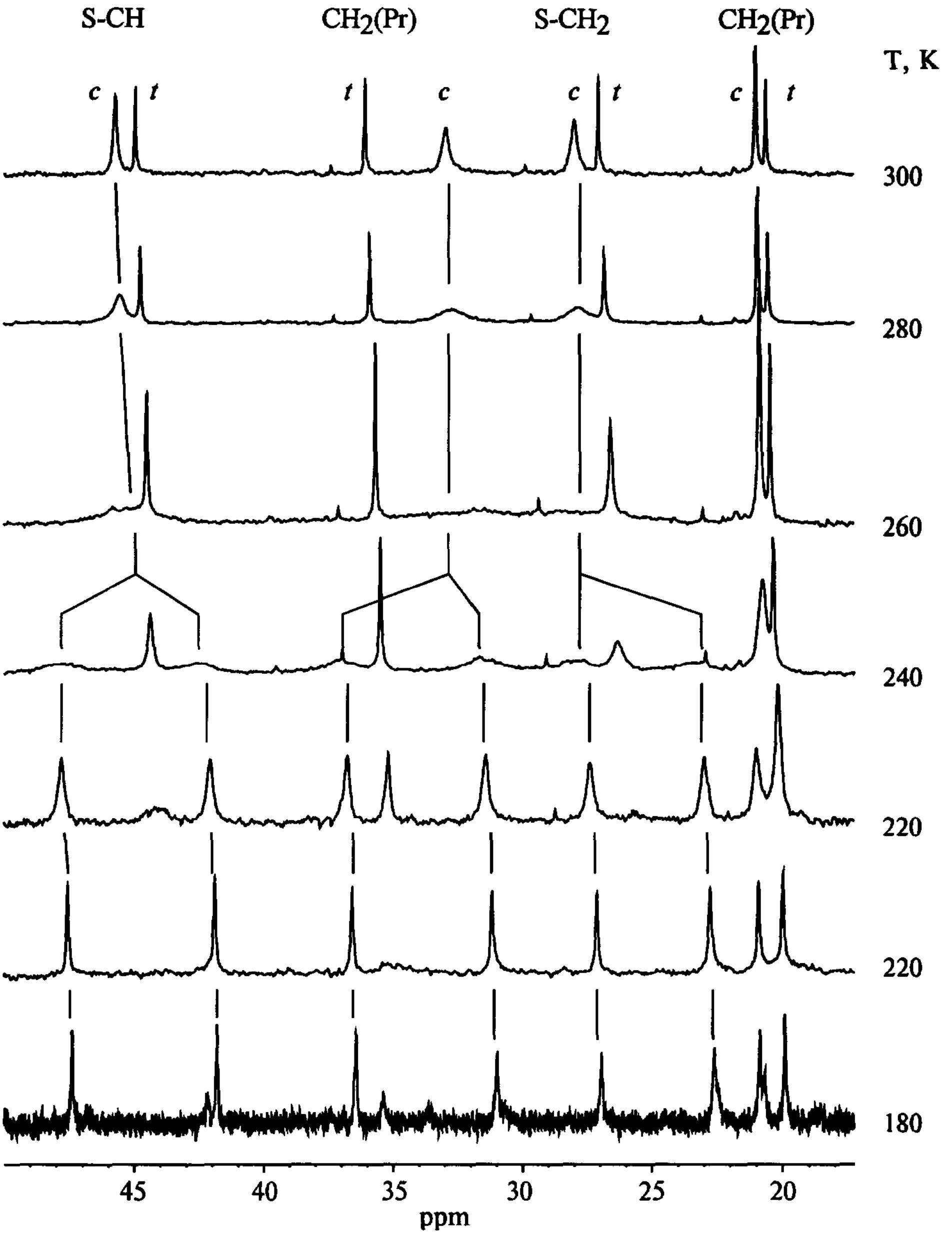
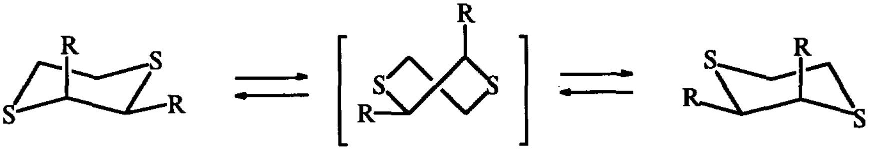


Figure 2. Variable temperature spectra of 2,3-dipropyl-1,4-dithianes **5c** + **5t**.

relative to diaxial one [8] (population of diaxial form increases from 71 to 85 and 91%, respectively). Obviously, this effect is rather weak as compared with the one described above.

Another interesting effect is observed for *cis*-2,3-dipropyl-1,4-dithiane **5-*c***. The ring interconversion for this molecule is so slow that the corresponding signals in ^{13}C NMR spectrum are strongly broadened even at room temperature (Fig. 2). The temperature variable measurements give an interconversion barrier $\Delta G^{\neq}$ as much as 11.2 kcal mol^{-1} (at 260 K) as compared with 9.4 kcal mol^{-1} for **4-*c*** at (213 K) (Table 5). A possible explanation of this effect involves an increase in steric energy of transition state due to bulky *n*-Pr groups. We attempted to check up this assumption by MMX calculation using twist-conformations as models for intermediates of interconversion but failed to reproduce the observed difference in barriers: $\Delta\Delta H^{\neq} = 10.2 - 8.8 = 1.4$ kcal mol^{-1} (Table 5). The twist conformation pictured on the scheme is the lowest in energy from a variety of possible twist-forms.



$\Delta E_{\text{twist-chair}} = 3.22$ kcal mol^{-1} ($R=CH_3$), 3.27 kcal mol^{-1} ($R=n\text{-}C_3H_7$).

This disagreement probably reflects rather serious structural difference between the twist-form (intermediate) and the transition state.

SUMMARY

The data of this article provide additional arguments in support of our previous statement[1] that the most typical conformational behaviour for substituted 1,4-dithianes, including a significant part of alkyl derivatives, 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.

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EXPERIMENTAL SECTION

Synthesis of substrates **4** - **8** was described earlier.[2] NMR spectra of all compounds studied (except **4*c*** and **5*c***) were recorded on AM 300 and AMX 400 Bruker instruments. The chemical shifts are presented in δ scale relative to TMS. The assignments of ^{13}C signals were performed using two-dimensional ^{13}C - ^{1}H correlation spectra. The iterative programs PANIC (Bruker) and CALM (Resonance Co., Moscow) were used for analysis of high resolution ^{1}H NMR spectra.

Temperature dependence of ^{13}C NMR spectra of compounds **4*c*** and **5*c*** was studied on JEOL-FX90Q instrument (frequency 22.55 MHz for ^{13}C). There were performed 6 measurements for **4*c*** in the temperature interval 173-263 K and 9 measurements for **5*c*** in the interval 190-300 K. The error in temperature placing did not exceed 1 K.

Exchange rate constants were determined separately for each pair of exchanging positions via analysis of temperature dependence of full line shape.[9] For better coincidence of calculated and experimental spectral data the iterative DYNNMR program was developed. Thermodynamic characteristics of the transition state were determined from the temperature dependence of exchange rate constants using Arrehnius equation, while correlation coefficient was found to be 0.9992 and 0.9952 for **4c** and **5c**, respectively.

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4. Our consideration neglects the solvent dependence of conformational equilibria. It is quite reasonable for dialkyl derivatives **4** and **5**, because both diequatorial and diaxial conformers of these molecules possess very small dipole moments (MMX calculations). For compounds **6** and **7** such simplification seems to be less reliable. For example, the calculated dipole moments for the most polar rotamers of diequatorial and diaxial forms of 7 are 3.19 D and 3.34 D, respectively. Therefore, some additional stabilization of diaxial form by polar solvent (d_6-acetone) can affect the conformational equilibrium and the correct evaluation of intramolecular interactions needs thorough investigation of this factor.
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