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Hindered rotation in *N*-acyloxy-4-methylthiazole-2(3*H*)-thiones

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ABSTRACT

Experimentally determined barriers to *O*-acyl group topomerization in mixed anhydrides composed of β-disubstituted carboxylic acids and cyclic thiohydroxamic acid *N*-hydroxy-4-methylthiazole-2(3*H*)-thione were located in the range of $\Delta G^{\ddagger}_{320}=68\pm8$ kJ mol^{-1} (DNMR). According to modeling studies, the underlying exchange process is proposed to occur via rotation about the N,O bond for torsional movement of the *O*-acyl group past the heterocyclic 4-methyl substituent. The energetically lowest pathway for passing the *O*-acyl entity by the thione sulfur, is predicted to occur via sequential rocking about the C_{sp^2},O single bond in combination with an interlaced twist about the N,O axis.

1. Introduction

N-Acyloxy-4-methylthiazole-2(3*H*)-thiones[1] (e.g., **1a–d**) are chemical more robust derivatives of the *N*-acyloxypyridine-2(1*H*)-thiones, i.e., the prominent Barton-anhydrides.[2,3] Both sets of heterocycles share common chemical reactivity and therefore serve nowadays as standard reagents for carbon radical generation from carboxylic acids in solution.[4] Due to thermal and photochemical lability, the majority of *N*-acyloxypyridine-2(1*H*)-thione applications are, however, restricted to in situ transformations.[5] Data on structural properties and chemical behavior that would facilitate new reagent development for specialized purposes, therefore are surprisingly limited—even after a quarter of a century of their extensive use in radical chemistry.[6]

The key connectivity to be homolytically cleaved in *O*-acylthiohydroxamates for their use as radical source is the N,O bond. Notable differences in ground state stability in this product class therefore are expected to originate from variations that occur upon modifying electronic and in particular steric effects imposed by the thiohydroxamate entity onto the acyl unit by substituting, e.g., the 4-methyl-2-thiooxo-2,3-dihydrothiaz-3-yl group (in **1**) for 2-thiooxo-1,2-dihydropyrid-1-yl [in *O*-acylpyridine-2(1*H*)-thiones]. We therefore chose to explore substituent effects onto energetics and conformational behavior of the N,O bond in *N*-acyloxy-4-methylthiazole-2(3*H*)-thiones **1a–d**. The selected compounds were expected to show hindered rotation thus allowing to derive the requested information from variable temperature NMR studies.[7] In a static picture, an offset of a substituent at O from the thiazole-2(3*H*)-thione plane gives rise to *P* (clockwise helicity of substituents of highest CIP priority at either end of the N,O-axis, i.e., C=S at N and C=O at O) or *M* configuration along this connectivity (anticlockwise helicity), thus creating a diastereotopic environment for spectroscopically distinguishing otherwise prostereogenic subunits of the *O*-acyl group (Scheme 1).[7–9]

The most important findings from the present study showed that β-substituted *N*-acyloxythiazolethiones **1b–d** underwent surprisingly slow topomerization in solution at 25 °C. Barriers associated with the exchange processes were located in the range of $\Delta G^{\ddagger}_{320}=68\pm8$ kJ mol^{-1} (DNMR). Results from a supporting modeling study provided evidence that the underlying exchange process occurs via rotation about the N,O bond for torsional movement of the *O*-acyl group past the heterocyclic 4-methyl substituent. The energetically lowest pathway for passing the *O*-acyl entity by the thione sulfur, is predicted to occur via sequential rocking about

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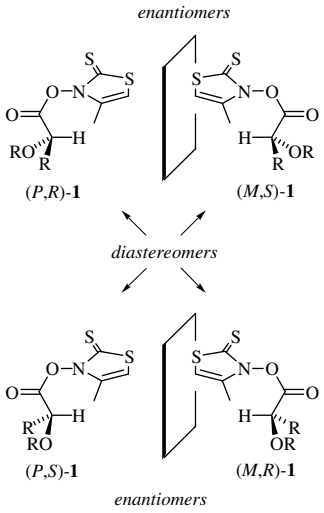


Scheme 1. Stereochemical relationship between axial chirality and centrochirality in *N*-acyloxy-4-methylthiazole-2(3*H*)-thiones, e.g., **1c**,**d** (see Table 1).

the C_{sp^2},O single bond in combination with an interlaced twist about the N,O axis. The barriers are proposed to have beneficial effects with respect to *O*-acyl thiohydroxamate ground state stability.

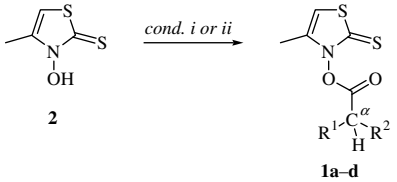
2. Results and interpretation

2.1. Preparation and properties of *N*-acyloxy-4-methylthiazole-2(3*H*)-thiones

The carboxylic acids that were selected for the pursuit of present study were adequate for comparing structural data from NMR, X-ray diffraction, and computational studies data in a straightforeward manner (**1a**), bore prostereogenic entities suitable for variable temperature NMR-spectroscopic analysis (**1b**), and showed a gradual increase in steric demand of substituents attached to an asymmetrically substituted C_α (**1c** and **1d**). Synthesis of target compounds **1a–d** was feasible by extending published procedures[10,11] starting from acyl chlorides in the presence of K_2CO_3 (Table 1, entry 1) or trispropanephosphonic acid anhydride-activated carboxylates (Table 1, entries 2–6) and thiohydroxamic acid **2**. The conversion of *N*-hydroxy compound **2** under such conditions was virtually quantitative, as judged on the basis of a spotting test on $FeCl_2$-coated TLC sheets. Due to limited stability toward SiO_2- or Al_2O_3-based stationary phases thiones **1a–d** were separated by crystallization and not by chromatography, which lowered the yields of analytically pure, tan crystalline thiones to 54–87%. Attempts to purify anhydride (*R*)-**1d** in a similar manner were for not successful since the oily product resisted crystallization. Final efforts to subject the material to chromatography using a short SiO_2-column resulted in complete decomposition of thione (*R*)-**1d**.

NMR spectra (^1H, ^{13}C) of mixed anhydrides **1b–d** showed twofold signal sets for parts of the acyl and the heterocyclic component (Table 2) in intensity ratios of 50:50 (for **1b** and **1c**) or 70:30 [(±)-**1d**, (***S***)-**1d**, (*R*)-**1d**, the latter not shown in Table 2]. The more intense signal set was invariant from absolute configuration of applied mandelic acid derivative [see Fig. 1 for (±)-**1d**]. The unit cell of (±)-**1d** (Z=4) comprised a racemate of (*M*,*R*)- and (*P*,*S*)-configured molecules (Fig. 3). Efforts to correlate this information with observed NMR data by dissolving crystals of (±)-**1d** at −78 °C in toluene-d_8 for recording a ^1H NMR spectrum at −70 °C, however, resulted in 70/30-mixture of diastereomeric thiones, presumably due to equilibration within the 2 min required to shim the spectrometer. If the well-known propensity of *O*-alkylthiohydroxamates to adopt lowest energy conformation in the solid state was taken as guideline for interpreting this observation, the major stereoisomer in solution would be expected to reflect combinations of axial-chirality and centrochirality equivalent to those found in the crystal structure of (±)-**1d**.

Table 1
Preparation of *N*-acyloxy-4-methylthiazole-2(3*H*)-thiones **1a–d**



Entry	1[a]	R^1	R^2	Conditions[b]	Yield/%	dr[c]
1	**1a**	H	H	*i*	74	—
2	**1b**	CH_3	CH_3	*ii*	87	50:50
3	(±)-**1c**	CH_3	OCH_3	*ii*	54	50:50
4	(*S*)-**1c**	CH_3	OCH_3	*ii*	55	50:50
5	(±)-**1d**	C_6H_5	OCH_3	*ii*	62	70:30
6	(*S*)-**1d**	C_6H_5	OCH_3	*ii*	65	70:30

[a] Stereodescriptor refers to configuration at C_α; (±) denotes racemic mixture.
[b] Conditions *i*: K_2CO_3, acetone, 25 °C, acyl chloride. Conditions *ii*: CH_2Cl_2, 1,4-diazabicyclo[2.2.2]octane (DABCO) or *N*-ethyl morpholine, carboxylic acid, trispropanephosphonic acid anhydride (T3P or PPAA), and 40 °C for **1b**, 20 °C for **1c–d**.
[c] Diastereomeric ratio (^1H NMR, toluene-d_8 or C_6D_6, 25 °C).

Table 2
Split signal sets in NMR spectra of *N*-acyloxythiazolethiones **1b–d** (25 °C)[a]

Signal	Measurement	1b[b]	(±)-1c	(±)-1d[c]
α-CH	δ ^1H	(2.51)	3.79/3.96[b]	4.82/5.04
	δ ^{13}C	(32.3)	75.2/75.4[c]	81.0/82.2
β-CH_3	δ ^1H	1.01/1.15	1.26/1.43[b]	—[d]
	δ ^{13}C	18.6/18.9	18.6/18.9[c]	—[d]
β-OCH_3	δ ^1H	—[d]	3.21/3.25[b]	3.35/3.50
	δ ^{13}C	—[d]	58.1/58.3[c]	58.2/58.9
4-CH_3	δ ^1H	(1.43)	(1.30)[b]	0.94/1.06
	δ ^{13}C	(12.5)	(12.5)[c]	12.0/12.2

[a] Figures in parentheses indicate unsplit signals.
[b] In toluene-d_8.
[c] In C_6D_6.
[d] Not available.

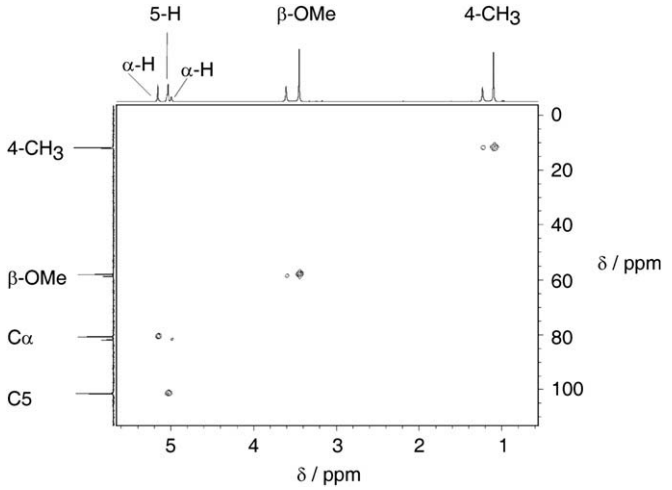


Figure 1. Selected part of the HMQC-spectrum of mandelic acid derivative (±)-**1d** (C_6D_6, 20 °C) showing correlation between split resonances of diastereotopic protons (top) and carbons (left).

2.2. Variable temperature NMR

Variable temperature NMR spectra were recorded from solutions of thiones **1b**, (±)-**1c**, and (±)-**1d** in toluene-d_8 in the temperature range between 298 K to ~365 K. Temperatures were in all instances calibrated with the methanol thermometer.[12,13] Signal coalescence was observed at 320 K (**1c**), 323 K (**1d**) and 330 K (**1b**). Above 340 K, all spectra showed averaged data sets thus pointing to fast exchange. For reasons of more pronounced ^{1}H NMR signal separation, we restricted ourselves to analysis of variable temperature ^{1}H NMR spectra. Rate constants of topomerization were determined via line shape analysis (Experimental and Supplementary data). Eyring-analysis[14] of the data provided linear correlations for thiazolethiones **1b** and (±)-**1c** (Fig. 2). Free energies were calculated from the Gibbs–Helmholtz relationship using activation enthalpies and entropies that were taken from slope and intercept of Eyring-plots (Table 3).

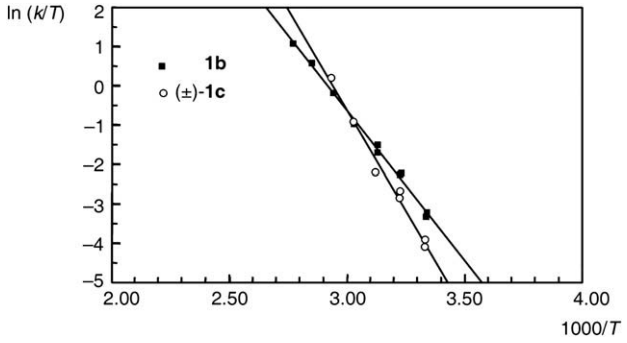


Figure 2. Correlation of ln(k/T) and reciprocal temperatures for *N*-acyloxythiazolethione topomerization (see also Supplementary data and Table 3).

Table 3
Activation parameters (Eyring analysis) for topomerization (variable temperature NMR) of *N*-acyloxythiazolethiones **1b–c**

Entry	Compound	$\Delta G^{\ddagger}_{320}$[a]/kJ mol^{-1}	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
1	**1b**	67±2	63±1	−12±4
2	(±)-**1c**	68±8	85±4	52±14

[a] experimental errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ refer to standard deviation; experimental errors in $\Delta G^{\ddagger}_{320}$ were calculated on the basis of errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

Kinetic data determined for topomerization of mandelic acid derivative (±)-**1d** in the temperature range between 300 and 367 K provided a scatter in the Eyring-diagram (not shown). This observation was correlated with the propensity of thione (±)-**1d** to decompose upon elevating the temperature above ~320 K. Since the observed 70/30-population (ΔG_{300} ~ 2.1 kJ mol^{-1}) was fairly close to an equipartition, the free activation energy for topomerization of (±)-**1d** was approximated on the basis of $\Delta\nu_i$ values and the coalescence temperature leading an estimated barrier of $\Delta G^{\ddagger}_{323}$ ~ 65 kJ mol^{-1} (Supplementary data).

The barriers to topomerization of thiones **1b–d** ($\Delta G^{\ddagger}_{320}$=68±8 kJ mol^{-1}) rank among the highest determined so far for substituted hydroxylamines.[7,9,15–18] Significantly lower barriers (~30 kJ mol^{-1}) were found for hydroxylamine itself and *N*-isopropoxypyridine-2(1*H*)-thione.[7,15] The magnitude of the latter values was related to a lack in significant steric encroachment at the N,O bond in H_2NOH and lone pair delocalization from N to C=S and thus lowering of lone pair repulsion between N and O in *N*-isopropoxypyridine-2(1*H*)-thione. An increase in steric demand of substituents attached at N and/or O in all investigated instances was paralleled by a rise in barriers to N,O rotation from $\Delta G^{\ddagger}$ ~ 40 kJ mol^{-1} (cyclic *O*-alkyl thiohydroxamates, *N*-aryloxysuccinimides, *N*-acyloxyhydroxylamides)[9,16] to $\Delta G^{\ddagger}$ ~ 50–60 kJ mol^{-1} (sterically demanding trisubstituted hydroxylamides).[17,18]

In view of a rather low barrier to N,O rotation in *N*-isopropoxy-4-methylthiazole-2(3*H*)-thione ($\Delta G^{\ddagger}_{200}$=42±7 kJ mol^{-1}) a more detailed description on the origin of the notable barrier in *O*-acyl analogue **1c** was considered in part to originate from repulsion between carbonyl and thiocarbonyl group. For further disussing this aspect, a model for describing conformational characteristics of the exchange process was devised (Section 2.3).

2.3. Modeling *N*-acyloxy group topomerization

The *O*-acyl substituent resides in crystal structures of anhydrides **1a** and (±)-**1d** approximately at the vertical that divides the 4-methylthiazole-2(3*H*)-thione nucleus into structurally different hemispheres (Fig. 3). The carbonyl oxygen in both structures is oriented toward the heterocycle thus directing the alkyl entity into opposite direction. This arrangement was observed previously for other derivatives of this product class in the solid state[11,19] and in solution.[6]

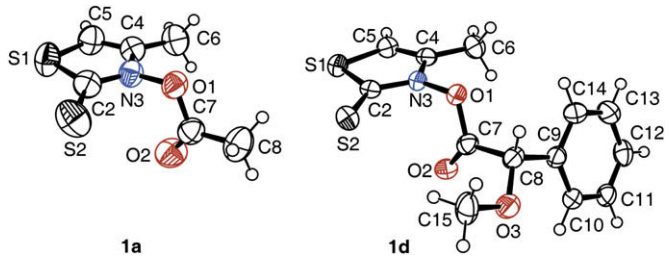


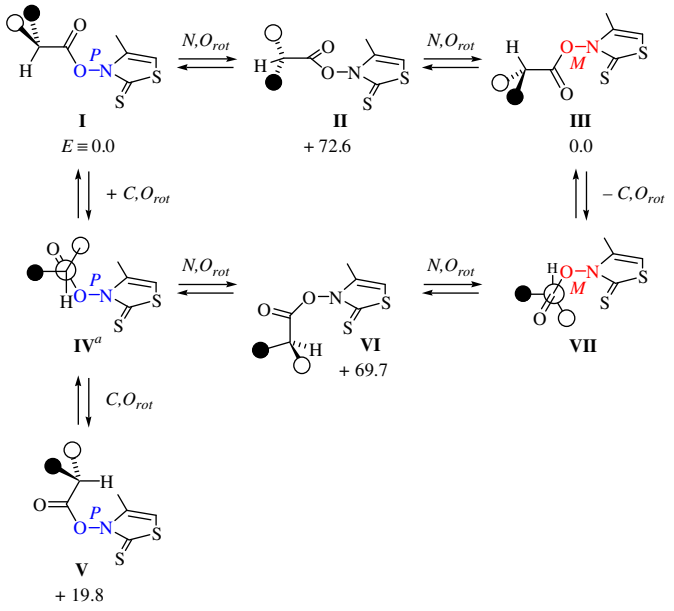
Figure 3. Geometry of *N*-acetyloxythiazolethione **1a** (left, 299 K) and (*P*,*S*)-**1d** (right, 153 K) in the solid state (ellipsoids are drawn at the 50% probability level; the *P*-enantiomer was in both instances selected arbitrarily for presentation purposes from the racemate; H-atoms were drawn as circles of an arbitrary radius).

Translation of structural information into a model that takes free energy changes that occur upon conformational changes associated with topomerization into account is feasible on the basis of an appropriate electronic structure method. According to a more detailed assessment of methods suitable for *O*-alkylthiazole-2(3*H*)-thiones conformational analysis,[20] and the fact that major solid state structural parameters of *N*-acetyloxythiazole-2(3*H*)-thione **1a** were adequately reproduced by Becke's 3 parameter hybrid functional[21,22] in combination with the 6-31+G** basis set,[23–25] we selected the density functional theory method for modeling *O*-acyl topomerization (Table 4).

Table 4
Experimental (X-ray crystallography) and computed[26] (equilibrium structure) geometrical parameters of selected *N*-acyloxythiazolethiones

Entry	Parameter/Å or °	**1a**/299 K X-ray cryst.	(±)-**1d**/153 K X-ray cryst.	**1a**/0K B3LYP/6-31+G**
1	S1–C2	1.719(3)	1.732(3)	1.769
2	C2–N3	1.339(3)	1.358(4)	1.374
3	N3–C4	1.392(3)	1.394(4)	1.398
4	C4–C5	1.332(4)	1.323(4)	1.351
5	C5–S1	1.717(3)	1.739(3)	1.756
6	S1–C2–N3	106.3(2)	105.7(2)	105.5
7	C2–N3–C4	119.5(2)	119.5(2)	119.7
8	N3–C4–C5	109.0(3)	109.7(3)	110.3
9	C4–C5–S1	112.5(2)	112.4(3)	112.0
10	C5–S1–C2	92.6(2)	92.7(2)	92.6
11	C2–S2	1.654(3)	1.656(3)	1.656
12	N3–O1	1.387(3)	1.402(3)	1.381
13	N3–O1–R	113.1(2)	112.5(2)	113.5
14	C4–N3–O1	120.1(3)	120.3(2)	120.7
15	C2–N3–O1	120.3(3)	120.0(2)	119.3
16	S2–C2–N3	127.0(2)	127.6(2)	127.4
17	S1–C2–S2	126.8(2)	126.7(2)	127.1
18	N3–C4–C6	120.1(3)	119.7(3)	120.3
19	C2–N3–O1–R	−95.8(3)	−80.5(3)	87.6

Topomerization **I**→**III** in *N*-acyloxythiazolethiones was expected to occur either via N,O-rotation or a combination of C,O- and N,O-rotation (Scheme 2). Contributions from nitrogen inversion were considered not to interfere for its embedding into a rigid planar frame.[7,9] Conformation **I** poses the global and C,O-rotamer **V** a local minimum (B3LYP/6-31+G**, Table 5, entries 1 and 4). The sum of bond angles pointed to planar arrangement at N3. Negligible pyramidalization was only found for the high energy conformer **V-1a** (Table 4, entry 4). Population of the latter conformer in solution was expected to be insignificant on the basis of its relative free energy. From an experimental point of view, no evidence for close proximity between methyl groups from the heterocycle and the acetyl substituent were evident from the NOESY spectrum of **1a** ($CDCl_3$, 25 °C).



Scheme 2. Proposed pathway for topomerization of substituents in *N*-acyloxy-4-methylthiazole-2(3*H*)-thiones **1a–d** [symbols ○ and ● refer to CH_3, C_6H_5, or OCH_3 substituents; numbers refer to B3LYP/6-31+G**-calculated ΔG_{298} values of computed structures for acetyl derivative **1a** (see Table 5)].

Starting from equilibrium structure **I-1a**, virtually every conformational change is associated with an approach of substituents and thus with an increase in free energy of the system. Conformations with maximum energy pose transition structures, which may be localized and verified using adequate numerical procedures and computer programs.[26,27] The transition structure determined for torsional movement of the acetyl group past the 4-methyl substituent showed coplanar arrangement between heterocyclic core and the substituent at O (**II-1a**, Table 5, entry 2). This arrangement was associated with a stretch of the N3,O1 bond to 1.404 Å (**II-1a**). Its computed Gibbs energy ΔG_{298}=72.6 kJ mol^{-1} (**II-1a**) was surprisingly close to experimentally determined barriers to topomerization of thiones **1b–d**.

The transition structure **VI-1a** for passing the acetyl group by the thione sulfur shows puckered arrangement originating from ~90° rotations about adjascent C,O and the N,O bonds (Table 5, entry 3). This arrangement was 69.7 kJ mol^{-1} higher in free energy than the global minimum and thus in the same order of magnitude as the barrier to acetyl group topomerization into the opposite direction, i.e., past 4-CH_3.

If computed data for *N*-acetylthiazolethione **1a** served as guideline for interpreting the mode of topomerization in *O*-acyl derivatives of *N*-hydroxythiazole-2(3*H*)-thiones in general, the following picture would result. The torsional movement of the acyl component toward the thione sulfur occurred via a puckered energetic maximum, and that toward the heterocyclic methyl substituent via a coplanar transition state. Both processes are predicted to occur with similar activation energy. These findings would imply that an increase in steric demand of substituents attached to C4 (e.g., R′ in Fig. 4) would not neccessarily lead to a higher experimental barrier since the system could topomerize by transposing the substituent past the thione sulfur via an intermediate similar to computed structure **VI-1a**. The barrier, however, is expected to rise

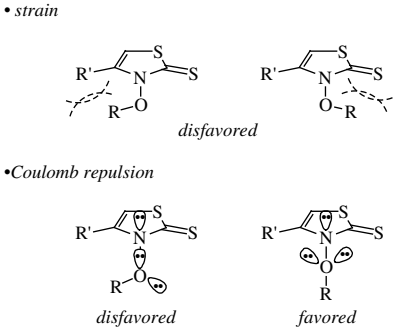
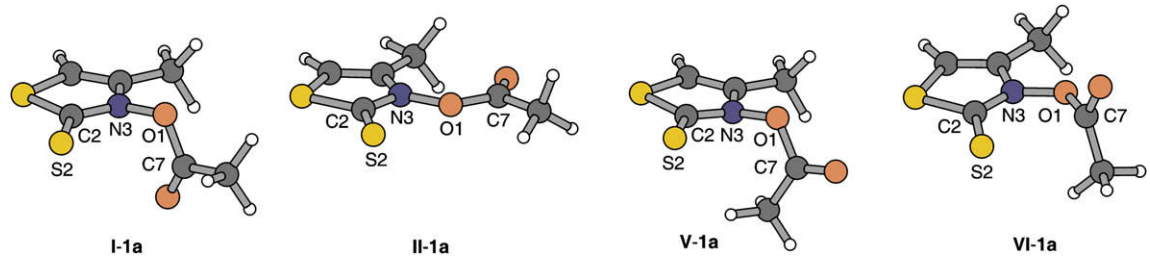


Figure 4. Proposed effects for explaining the origin of barriers to N,O-rotation in *N*-acyloxythiazole-2(3*H*)-thiones, e.g., **1a–d**.

Table 5
Computed[a,26] energies and parameters of distinguished *N*-acetyloxy-4-methylthiazole-2(3*H*)-thione conformers



Entry	Compound	*E*/Hartree[b]	ZPVE/Hartree	G_{298}/Hartree	ΔG_{298}/kJ mol^{-1}	N3–O1/Å	C2–S2/Å	$\Sigma\alpha_i$(N3)[c]/°	C2–N3–O1–C7/°
1	**I-1a**	−1234.411684	0.126094	−1234.324388	≡0.0	1.381	1.656	359.7	87.6
2	**II-1a**[d]	−1234.384544	0.125689	−1234.296724	+72.6	1.404	1.656	360.0	179.3
3	**VI-1a**	−1234.385965	0.124999	−1234.297824	+69.7	1.387	1.667	359.9	1.7
4	**V-1a**[e]	−1234.404883	0.126108	−1234.316843	+19.8	1.387	1.654	357.8	89.3

[a] B3LYP/6-31+G**//B3LYP/6-31+G**.
[b] 1 Hartree=2625.5 kJ mol^{-1}.
[c] sum of bond angles at N3.
[d] NIMAG=−133 cm^{-1}.
[e] NIMAG=−157 cm^{-1}.

according to this picture, if tertiary acyl groups were substituted for acetyl or secondary derivatives.

The fact that Coulomb-repulsion between lone pairs at heteroatoms[15] have been entirely omitted from the discussion deserves a final comment. In order estimate energetic contributions from proposed repulsive orbital interactions (Fig. 4) on a more scientific basis, experimental electron density studies are required. Since this information was not available by the time the study was performed, lone pair repulsion should be kept in mind as additional energetic contribution when interpreting the phenomenon of hintered rotation about N,O bonds in *O*-acyl thiohydroxamates.

3. Concluding remarks

The present investigation stresses the significance of steric effects for describing barriers to topomerization in mixed anhydrides composed of carboxylic and thiohydroxamic acids. Although experimental data for topomerization of the more prominent *N*-acylpyridine-2(1*H*)-thiones were not available from the literature, it is expected that such barriers are notably smaller due to the lack of steric repulsion from the CH_3 substituent next to the thiohydroxamate group. A lower barrier, in turn, correlates with higher frequency for the incidence of coplanar acyloxy and thiohydroxamate arrangement. Even in the simplest orbital picture, this arrangement implies repulsive and therefore destabilizing interactions between heteroatoms that are connected by a comparatively weak bond (Fig. 4). Steric repulsion between the 4-CH_3 and the *N*-acyloxy entity in this interpretation is expected to increase population of less reactive conformations having the acyl group oriented in orthogonal position with respect to the heterocyclic core (Fig. 3), which in turn contributes to *N*-acyloxythiazole-2(3*H*)-thione stabilization. Whether a methyl group attached to the thiazole-2(3*H*)-thione nucleus constitutes the most suitable combination for this purpose remains to be uncovered in future studies.

4. Experimental

4.1. General

For general laboratory practice and instrumentation see Ref. 28 and Supplementary data. DTA is short for differential thermal analysis, whereby endothermic signals refer to melting, and exothermic signals to decomposition of **1**.

4.2. Variable temperature NMR

Bruker DMX 600 operating at 600.13 MHz equipped with a temperature control assembly B-VT-2000, display and control unit BTO-2000-E and probe head heater BMT 05.

4.2.1. Sample preparations

Solutions of thiones **1b–d** (40 mg) in toluene-d_8 were injected in high precision 5 mm tubes (Varian 507 PP) and frozen to 77 K. The samples were sealed with a torch and *very slowly* allowed to warm to room temperature. Rapid warming may result in hazardous NMR tube breakage.

4.2.2. NMR experiments

Samples were thermally equilibrated for 15 min. Temperatures inside the spectrometer cavity were measured with the aid of the MeOH thermometer. Receiver circuit impedance was compensated. NMR spectra were recorded with the spinning velocity set to zero. Zero filling to four times the number of measured data points was performed. Particular attention was paid to appropriate phase and the baseline corrections.

4.2.3. Determination of Eyring parameters

Rate constants were calculated from line widths $W_{ex(change)}=W_{obs(served)}-W_{ref(erence)}$ on the basis of Eqs. 1 and 2. Rate constants were deduced from iterative line shape analysis using the Bruker program WINDYNA. Fits were continually repeated until calculated and experimental spectra matched. The error in k originating from errors in line width W_{ex} and shift differences $\Delta\nu_i$ was estimated to be 5%. Temperatures were kept constant with a precision of ±1 K. Eyring parameters were deduced on the basis of linear correlations of $\ln(k/T)$ versus $1/T$ according to in Eq. 3 (Table 3, Fig. 2).

$$k = \frac{\pi(\Delta\nu)}{2W_{ex}} \quad (1)$$

$$k = \pi W_{ex} \quad (2)$$

$$\ln(k/T) = \ln\frac{k_b}{h} - \frac{\Delta H^{\ddagger}}{RT} + \frac{\Delta S^{\ddagger}}{R} \quad (3)$$

4.3. *N*-acyloxythiazole-2(3*H*)-thiones 1a–d

4.3.1. From acyl chlorides

In a typical run, K_2CO_3 (0.41 g, 3.00 mmol) was added to a solution of thiohydroxamic acid **2** (147 mg, 1.00 mmol) in acetone (9 mL). The slurry was stirred for 10 min at 20 °C and treated hereafter with neat acid chloride (1.10 mmol). Stirring was continued at 20 °C (30–90 min). Consumption of acid **2** was evident from the absence of a green color upon spotting a drop of the reaction mixture onto $FeCl_2$-coated TLC sheets. Solids were removed by filtration. The filtrate was evaporated to dryness to leave a residue that was purified by (re)crystallization.

*4.3.1.1. N-Acetyloxy-4-methylthiazole-2(3H)-thione (**1a**).* Yield: 280 mg (74%); tan solid from Et_2O/petroleum ether; mp 94–96 °C (dec). ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.17 (s, 3H, 4-CH_3), 2.44 (s, 3H, α-CH_3), 6.23 (s, 1H, 5-H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 13.3 (4-CH_3), 18.8 (α-CH_3), 102.4 (C5), 136.8 (C4), 165.9 (C=O), 180.8 (C=S). Anal. Calcd for $C_6H_7NO_2S_2$: C, 38.08; H, 3.73; N, 7.40. Found: C, 37.95; H, 3.67; N, 7.35. Crystals suitable for X-ray diffraction were grown from a saturated solution in CH_2Cl_2. X-ray crystallography: T=293(2) K, λ=0.71073 Å, monoclinic, $P2_1/n$, a=7.410(2) Å, b=13.452(3) Å, c=8.910(2) Å, β=96.50(3)°, Z=2, μ=0.554 mm^{-1}, completeness to 2θ=95.5%, goodness-of-fit on F^2=0.774, final R indices [$I>2\sigma(I)$]: $R1$=0.0322, $wR2$=0.0630.

4.3.2. From carboxylic acids

In a typical run, trispropanephosphonic acid anhydride (PPAA) [955 mg, 3.00 mmol, 1.91 g, 50% in DMF (w/w)] was added at 0 °C to a solution of thiohydroxamic acid **2** (294 mg, 2.00 mmol), DABCO (674 mg, 3.00 mmol) or *N*-ethyl morpholine (0.6 ml, 4.70 mmol) and a carboxylic acid (2.00 mmol) in dry CH_2Cl_2 (16 mL). The reaction mixture was refluxed (for **1b**) or stirred at 20 °C (for **1c** and **1d**) for 16 h. The solvent was removed under reduced pressure (10 mbar, 20 °C) to furnish a residue that was taken up in H_2O (5 mL) and Et_2O (10 mL). The organic phase was separated, washed successively with aq $NaHCO_3$ [5 mL, 50% (w/w)] and H_2O (5 mL), and dried ($MgSO_4$). The solvent was removed under reduced pressure to leave a residue that was (re)crystallized from Et_2O/petroleum ether [1:1 (v/v)], to afford compounds **1b–d** as tan solids.

*4.3.2.1. N-(2-Methylpropionyloxy)-4-methylthiazole-2(3H)-thione (**1b**).* Yield: 377 mg (87%); R_f=0.30 [SiO_2, Et_2O/petroleum ether=1:1 (v/v)]; tan solid from Et_2O/petroleum ether; DTA 51 °C (endotherm.), 82 °C (exotherm.). ^{1}H NMR (600 MHz, toluene-d_8) δ 1.01 (d, J=6.9 Hz, 3H, β-CH_3), 1.15 (d, J=6.9 Hz, 3H, β-CH_3), 1.43 (d, J=1.2 Hz, 3H, 4-CH_3), 2.51 (sept, J=6.9 Hz, 1H, α-H,), 5.09 (q, J=1.2 Hz, 1H, 5-H); ^{13}C NMR

(100 MHz, toluene-d_8) δ 12.5 (4-CH_3), 18.6 (β-CH_3), 18.9 (β-CH_3), 32.3 (C_α), 101.3 (C5), 136.4 (C4), 172.2 (C=O), 181.0 (C=S). *m*/*z* (EI) 217 (M^+, 55%), 147 (88), 71 (30), 43 (100). Anal. Calcd for $C_8H_{11}NO_2S_2$: C, 44.21; H, 5.10; N, 6.45. Found: C, 44.06; H, 4.96; N, 6.33.

*4.3.2.2. (±)-N-(2-Methoxypropionyloxy)-4-methylthiazole-2(3H)-thione (±)-(**1c**).* Yield: 250 mg (54%); R_f=0.20 [SiO_2, Et_2O/petroleum ether=1:1 (v/v)]; tan solid from Et_2O/petroleum ether; DTA 51 °C (endotherm.); 62 °C (exotherm.). ^{1}H NMR (600 MHz, toluene-d_8) δ 1.26 (d, *J*=7.3 Hz, 1.5H, β-CH_3), 1.30 (s, 3H, 4-CH_3), 1.43 (d, *J*=6.5 Hz, 1.5H, β-CH_3), 3.21 (s, 1.5H, β-OCH_3), 3.25 (s, 1.5H, β-OCH_3), 3.79 (q, *J*=7.3 Hz, 0.5H, α-H), 3.96 (q, *J*=6.5 Hz, 0.5H, α-H), 4.90 (s, 1H, 5-H). ^{13}C NMR (63 MHz, C_6D_6) δ 12.5 (4-CH_3), 18.6 (C_β), 18.9 (C_β), 58.1 (β-OCH_3), 58.3 (β-OCH_3), 75.2 (C_α), 75.4 (C_α), 101.6 (C5), 101.7 (C5), 136.2 (C4), 165.6 (C=O), 181.0 (C=S). *m*/*z* (EI) 233 (M^+, 15%), 147 (41), 71 (11), 59 (100). Anal. Calcd for $C_8H_{11}NO_3S_2$: C, 41.18; H, 4.75; N, 6.00. Found: C, 41.39; H, 4.59; N, 5.89.

*4.3.2.3. (2S)-N-(2-Methoxypropionyloxy)-4-methylthiazole-2(3H)-thione (S)-(**1c**).* Yield: 254 mg (55%) as tan solid from Et_2O/petroleum ether; R_f=0.20 [SiO_2, Et_2O/petroleum ether=1:1 (v/v)]. $[\alpha]_D^{25}$ 6.7 (*c* 0.1, EtOH). ^{1}H NMR (250 MHz, C_6D_6) δ 1.27 (d, *J*=6.8 Hz, 1.5H, β-CH_3), 1.31 (s, 3H, 4-CH_3), 1.44 (d, *J*=7.0 Hz, 1.5H, β-CH_3), 3.21 (s, 1.5H, β-OCH_3), 3.25 (s, 1.5H, β-OCH_3), 3.81 (q, *J*=6.8 Hz, 0.5H, α-H), 3.97 (q, *J*=7.0 Hz, 0.5H, α-H), 4.91 (s, 1H, 5-H). ^{13}C NMR (63 MHz, C_6D_6) δ 12.5 (4-CH_3), 18.7 (C_β), 18.9 (C_β), 58.2 (β-OCH_3), 58.3 (β-OCH_3), 75.2 (C_α), 75.5 (C_α), 101.6 (C5), 101.7 (C5), 136.2 (C4), 165.4 (C=O), 181.1 (C=S).

*4.3.2.4. (±)-N-(2-Methoxy-2-phenylacetyloxy)-4-methylthiazole-2(3H)-thione (±)-(**1d**).* Yield: 364 mg (62%), R_f=0.20 [SiO_2, Et_2O/petroleum ether=1:1 (v/v)]. ^{1}H NMR (250 MHz, C_6D_6) δ 0.94 (s, 2.1H, 4-CH_3), 1.06 (s, 0.9H, 4-CH_3), 3.35 (s, 2.1H, β-OCH_3), 3.50 (s, 0.9H, β-OCH_3), 4.82 (s, 0.3H, α-H), 4.86 (s, 1H, 5-H), 5.04 (s, 0.7H, α-H), 6.97–7.14 (m, 5H, Ph–H). ^{13}C NMR (63 MHz, C_6D_6) δ 12.0 (4-CH_3), 12.2 (4-CH_3), 58.2 (β-OCH_3), 58.9 (β-OCH_3), 81.0 (C_α), 82.2 (C_α), 101.5 (C5), 101.6 (C5), 125.7, 126.7, 127.3, 127.5, 128.9, 129.6 (Ph–C), 135.8 (C4), 136.3 (C4), 167.0 (C=O), 181.2 (C=S). Anal. Calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.74. Found: C, 52.62; H, 4.32; N, 4.67. Crystals suitable for X-ray diffraction were grown from a saturated solution in $CHCl_3$/pentane. X-ray crystallography: *T*=153(2) K, λ=1.54184 Å, monoclinic, $P2_1/c$, *a*=8.2215(3) Å, *b*=17.0689(7) Å, *c*=9.8572(5) Å, β=98.039(4)°, *Z*=4, μ=3.564 mm^{-1}, completeness to 2θ=97.2%, goodness-of-fit on F^2=0.974, final *R* indices [$I>2\sigma(I)$]: *R*1=0.0433, *wR*2=0.1163.

*4.3.2.5. (2S)-N-(2-Methoxy-2-phenylacetyloxy)-4-methylthiazole-2(3H)-thione (S)-(**1d**).* Yield: 384 mg (65%); R_f=0.20 [SiO_2, Et_2O/petroleum ether=1:1 (v/v)]; tan solid from Et_2O/petroleum ether; DTA 89 °C (exotherm.). $[\alpha]_D^{25}$ 176.0 (*c* 0.1, EtOH). ^{1}H NMR (250 MHz, C_6D_6) δ 0.95 (s, 2H, 4-CH_3), 1.06 (s, 1H, 4-CH_3), 3.34 (s, 2H, β-OCH_3), 3.50 (s,1H, β-OCH_3), 4.81 (s, 0.3H, α-H), 4.85 (s, 1H, 5-H), 5.03 (s, 0.7H, α-H), 7.00–7.12 (m, 5H, Ph–H). ^{13}C NMR (100 MHz, toluene-d_8) δ 12.0 (4-CH_3), 12.1 (4-CH_3), 58.2 (β-OCH_3), 58.9 (β-OCH_3), 80.9 (C_α), 82.2 (C_α), 101.3 (C5), 101.4 (C5), 125.7, 127.2, 127.7, 128.6 (Ph–C), 135.9 (C4), 136.2 (C4), 137.3 (Ph–C), 166.9 (C=O), 181.2 (C=S). Anal. Calcd for $C_{13}H_{13}NO_3S_2$: C, 52.86; H, 4.44; N, 4.74. Found: C, 52.78; H, 4.22; N, 4.66.

*4.3.2.6. (2R)-N-(2-Methoxy-2-phenylacetyloxy)-4-methylthiazole-2(3H)-thione (R)-(**1d**).* ^{1}H NMR (600 MHz, C_6D_6) δ 0.98 (s, 2H, 4-CH_3), 1.11 (s, 1H, 4-CH_3), 3.33 (s, 2H, β-OCH_3), 3.49 (s, 1H, β-OCH_3), 4.88 (s, 0.3H, α-H), 4.92 (s, 1H, 5-H), 5.04 (s, 0.7H, α-H), 7.03–7.09 (m, 3H, Ph–H), 7.38 (d, *J*=6.9 Hz, 1.3H, Ph–H), 7.49 (d, *J*=6.4 Hz, 0.6H, Ph–H). ^{13}C NMR (150 MHz, C_6D_6) δ 12.0 (4-CH_3), 12.2 (4-CH_3), 58.2 (β-OCH_3), 58.7 (β-OCH_3), 80.9 (C_α), 82.2 (C_α), 101.7 (C5), 101.8 (C5), 127.3, 127.7, 128.0, 128.4, 128.5, 129.0, 129.3, 129.4 (Ph–H), 135.7 (C4), 135.8 (C4), 136.3 (Ph–C), 167.1 (C=O), 167.5 (C=O), 181.2 (C=S).

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication [CCDC 733594 (**1a**), CCDC 733595 (**1d**)]. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 (0)1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Instrumentation, kinetic data for topomerization of **1b–c**, atomic coordinates and energies of computed structures **I-1a**, **II-1a**, **V-1a**, **VI-1a** (B3LYP), HMQC for (±)-**1d** (10 pages). Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2009.06.124.

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