The Barrier to Rotation around N−O Bonds in 4-Substituted *N*-Isopropoxythiazole-2(3*H*)-thiones and in *N*-Isopropoxy-2(1*H*)-pyridinethione[‡]

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Dedicated to Professor Dr.-Ing. Hartmut Fuess on the occasion of his 60th birthday

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Activation parameters [lg A, E_a, $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$] for the barriers to rotation around N–O bonds in *N*-Isopropoxy-2(1*H*)-pyridinethione (**1**) and two 4-substituted *N*-isopropoxythiazole-2(3*H*)-thiones **2** and **3** were determined by variable-temperature NMR spectroscopy [^{1}H (600 MHz) and ^{13}C (150 MHz)] in the temperature range 125–273 K. The measured $\Delta G^{\ddagger}_{200}$ values increase from 29 ± 2 kJ mol^{-1} (**1**) to 42 ± 7 kJ mol^{-1} (**2**) and 46 ± 1 kJ mol^{-1} (**3**). The ranking of observed rotational barriers in thiones **1**, **2**, and **3** is explained by differences in the steric congestion next to the *N*-alkoxy substituents.

Introduction

The dynamic behavior of N−O bonds has received considerable attention in the study of organic nitrogen compounds, since it generally originates from a superimposition of two fundamental motions: (i) an inversion of configuration at the nitrogen atom, and (ii) a rotation around the central nitrogen−oxygen bond.[1−3] Either phenomenon can be studied independently if the competitive process is inhibited by restraints. Therefore, N−O rotational barriers are experimentally accessible if the nitrogen atom is part of a rigid heterocyclic frame which inhibits the inversion motion.[4] If both heteroatoms are part of a small or medium sized cyclic compound, nitrogen inversion is the only feasible process.[5] A variety of $\Delta G^{\ddagger}$ values for N−O rotational barriers have been reported in the literature.[3−9] These values were calculated from coalescence temperatures in variable temperature NMR experiments and therefore, strictly speaking, refer only to a single temperature. Recent advances in NMR technology, especially in currently available devices for controlling temperature stability in variable temperature NMR experiments,[10] have encouraged us to readdress the problem of investigating rotational N−O barriers over a broader temperature range in order to derive more significant activation parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$) for this dynamic process. In view of the above mentioned issues we selected a small set of newly available heterocyclic *N*-alkoxides as probes [*N*-Isopropoxy-2(1*H*)-pyridinethione (**1**) and the 4-substituted thiazolethiones **2** and **3**, Figure 1][11−13] and investigated their hitherto unknown dynamic properties by variable-temperature NMR spectroscopy in the range 125−273 K.[7]

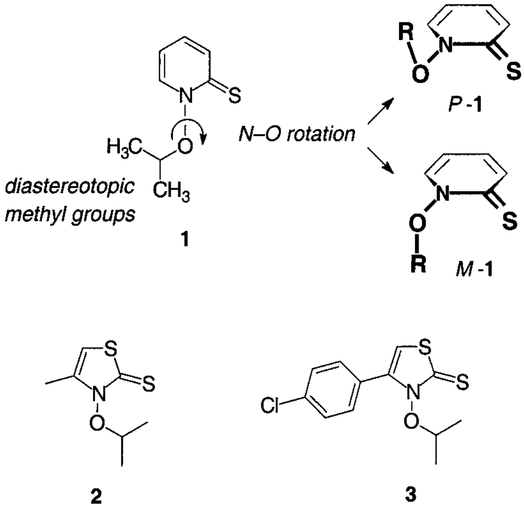
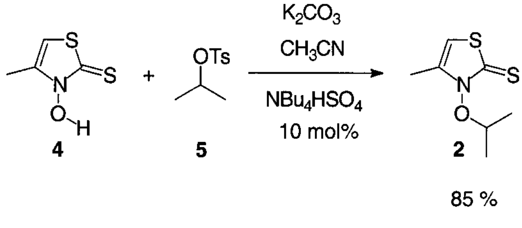


Figure 1. Topomerization of the CH_3 groups in *N*-isopropoxypyridinethione **1** by rotation around the stereogenic N−O bond [top, R = $CH(CH_3)_2$] and selected compounds **2**, **3** for DNMR experiments (bottom)

Results

N-Isopropoxy-2(1*H*)-pyridinethione (**1**)[12,13] and 4-(*p*-chlorophenyl)-*N*-isopropoxythiazole-2(3*H*)-thione (**3**)[14] were available from earlier studies. *N*-Isopropoxy-4-methyl-



Scheme 1. Preparation of *N*-isopropoxy-4-methylthiazole-2(3*H*)-thione (**2**)

[‡] Dynamic Behavior of Cyclic Thiohydroxamic Acid Derivatives, 1.

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thiazolethione (**2**) was obtained by selective *O*-alkylation of acid **4** with isopropyl tosylate **5** in the presence of potassium carbonate and catalytic amounts of NBu_4HSO_4 in acetonitrile in 85% yield (Scheme 1).

Solutions of heterocycles **1**, **2**, or **3** in $CHF_2Cl/(CD_3)_2O$ [approx. 3:1 (v/v)] were subjected to variable-temperature NMR studies. At room temperature the proton NMR spectra of thiones **1**, **2**, and **3** showed typical line patterns of unhindered rotating isopropyl groups. For example, a doublet at $\delta = 1.04$ (^{1}H NMR) and a singlet at $\delta = 19.0$ (^{13}C NMR) were recorded for both CH_3 groups in 4-(*p*-chlorophenyl)-*N*-isopropoxythiazole-2(3*H*)-thione (**3**).[14] These signals broadened on cooling. Coalescence was observed at 233 K and well-separated resonances of the individual rotamers were observed at 200 K [**3** (^{13}C NMR): $\delta = 19.4, 19.0$, Figure 2]. Coalescence for the diastereotopic methyl groups in pyridinethione **1** and 4-methylthiazolethione **2** was observed at 144 K (**1**) and at 213 K (**2**).

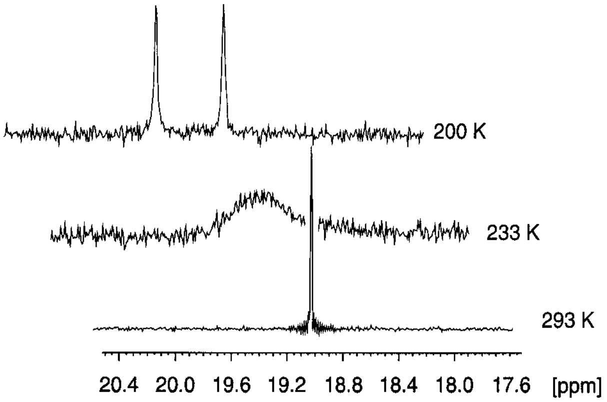

Figure 2. Stacking plot of carbon-13 NMR spectra of 4-(*p*-chlorophenyl)-*N*-isopropoxythiazole-2(3*H*)-thione (**3**) at different temperatures

Variable-temperature proton NMR spectroscopic data were analyzed by complete line-shape analysis in order to calculate the rate constants *k* for the exchange processes caused by the topomerizations in **1**−**3** (see Supporting Information). The rate constants from carbon-13 NMR spectra were accessible by analyzing the linewidths (*W*) and shift differences $\Delta\nu$ of exchange-related nuclei according to Equation (1) and (2) with $W_{ex(change)} = W_{obs(erved)} - W_{ref(erence)}$. The linewidths of C-5 were taken as the reference for pyridinethione **1**, and the thiazolethiones **2** and **3**.

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

$$k = \pi W_{ex} \tag{2}$$

Reliable temperatures (±1 K) were measured using a solution of a semibullvalene-derived high-precision carbon-13 shift thermometer in $CHF_2Cl/(CD_3)_2O$ [approx. 3:1 (v/v)].[15] These data were applied in order to calculate the activation parameters lg *A*, E_a, $\Delta H^\ddagger$, and $\Delta S^\ddagger$ for the topomerization process in pyridinethione **1** (125−185 K) and the thiazolethiones **2** and **3** [195−260 K, Figure 3, Equation (3), Table 1]. A full report on the experimental data (temperatures, linewidths, and rate constants) is provided in the Supporting Information.

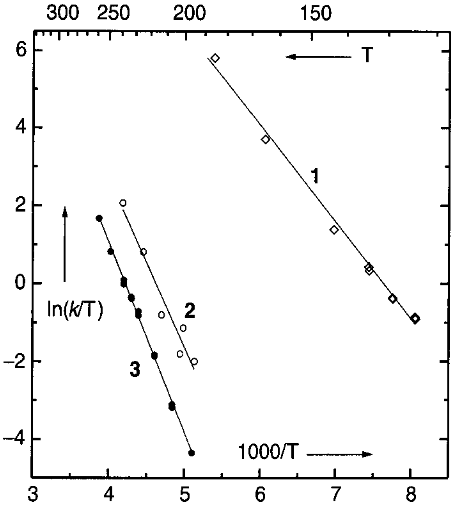

Figure 3. Eyring diagrams ln *k* values for N−O rotations in pyridinethione **1** (◇), methylthiazolethione **2** (○), and *p*-chlorophenylthiazolethione **3** (●)

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

Eyring plots for *p*-chlorophenylthiazolethione **3** from ^{1}H (600.13 MHz) *and* from ^{13}C NMR (150.90 MHz) experiments were in excellent agreement (Figure 3). A numerical analysis of the pre-exponential factor afforded lg $A = 11.6 \pm 0.2$. Similar lg *A* values were calculated for pyridinethione **1** (lg $A = 10.9 \pm 0.2$, ^{13}C NMR) and thiazolethione **2** (lg $A = 11 \pm 1$, ^{1}H NMR, Table 1). Since no baseline separation of the diastereotopic CH_3 signals was observed in the proton NMR spectra of pyridinethione **1** (600.13 MHz), only the ^{13}C NMR spectroscopic data (150.90 MHz) are reported in Table 1. Furthermore, the results from variable-temperature ^{13}C NMR experiments (150.90 MHz) with 4-methylthiazolethione **2** have been omitted from Table 1 because the observed shift differences $\Delta\nu$ were too small for a precise analysis of linewidths. In order to allow a direct comparison of the obtained experimental data, $\Delta G^{\ddagger}_{200}$ values were calculated which refer to a temperature that is very close to the experimental data of all compounds in this study: 29 ± 2 kJ mol^{-1} (pyridinethione **1**), 42 ± 7 kJ mol^{-1} (4-methylthiazolethione **2**), and 46 ± 1 kJ mol^{-1} for 4-(*p*-chlorophenyl)thiazolethione **3**.

Discussion

The phenomenon of slowed rotation of molecular entities around heteroatom−heteroatom bonds is well documented in the literature.[3,5,16] Thus, barriers to rotation around N−O bonds originate from the electronic (repulsion of lone pairs)[17] and steric effects of substituents at nitrogen and at

Table 1. Activation parameters for N−O rotations in pyridinethione **1**, and thiazolethiones **2** and **3**

Entry	Compound	NMR method	$\Delta G^{\ddagger}_{200}$ [a] [kJ mol^{-1}]	$\Delta H^{\ddagger}$ [kJ mol^{-1}]	$\Delta S^{\ddagger}$ [J K^{-1}mol^{-1}]	lg A	E_a [kJ mol^{-1}]
1	**1**	^{13}C	29 ± 2	20.6 ± 0.6	−40 ± 4	10.9 ± 0.2	22.1 ± 0.6
2	**2**	^{1}H	42 ± 7	36 ± 4	−32 ± 15	11 ± 1	38 ± 3
3	**3**	^{1}H and ^{13}C	46 ± 1	40.6 ± 0.7	−28 ± 3	11.6 ± 0.2	42.1 ± 0.7

[a] The reported uncertainties in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ refer to standard deviations while the error $\Delta G^{\ddagger}{}_{200}$ was calculated from the individual uncertainties in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$.

oxygen.[3] The ground state geometry of *N*-isopropoxy-4-(*p*-chlorophenyl)thiazole-2(3*H*)-thione (**3**) in the solid state shows an almost orthogonal transposition of the *N*-alkoxy substituent with respect to the thiazolethione plane.[14] According to NOE experiments[12] and to theoretical investigations,[18] this geometry should also represent the most significantly populated conformer of *N*-alkoxypyridinethiones, for instance **1**, and presumably of thiones **2** and **3**, in solution. Thus, the change in position of the isopropoxy substituent caused by an N−O rotation through the heterocyclic plane leads to higher energy conformers. The activation energy E_a for this dynamic process increases in the series of studied compounds from pyridinethione **1** (22.1 ± 0.6 kJ mol^{-1}) to 4-methylthiazolethione **2** (38 ± 3 kJ mol^{-1}) to 4-(*p*-chlorophenyl)thiazolethione **3** (42.1 ± 0.7 kJ mol^{-1}). Since all calculated lg A values in this study are identical within the experimental error, the mechanism of the individual topomerization processes is assumed to be similar. For further analysis, $\Delta G^{\ddagger}_{200}$ values of the N−O rotation for thiones **1**−**3** were calculated (Table 1). The existing body of $\Delta G^{\ddagger}$ data for N−O rotational barriers in the literature for comparison with $\Delta G^{\ddagger}_{200}$ values from the present study is relatively small.[3−9] Organization of the available material leads to three major groups of compounds. First, the parent compound $H_2N{-}OH$ itself. In view of the issues mentioned above, the energetics of N−O rotation in hydroxylamine have until today only been accessible using ab initio molecular orbital calculations. The most recent computational data by Chung-Phillips and Jebber indicate that the difference in heats of formation between the gauche conformer (global minimum, staggered lone pairs at nitrogen and at oxygen) and the highest energy conformer (with eclipsing orbitals) is 30 kJ mol^{-1} at 0 K at an MP2/6-311+G** level of theory.[19] The second category of compounds contains *N*-acceptor substituted *O*-alkyl hydroxylamines. $\Delta G^{\ddagger}$ values between 36−42 kJ mol^{-1} have been reported for these molecules ($\Delta G^{\ddagger}$ then refers to temperatures between 300−187 K).[6,7] The third class of hydroxylamine derivatives are trisubstituted hydroxylamines with a large alkyl group attached to oxygen. The barriers to N−O rotation in these compounds range between 50 and 63 kJ mol^{-1} ($\Delta G^{\ddagger}_{273}$).[8,9] A comparison of these data with $\Delta G^{\ddagger}$ values from the present work indicates that the barrier to rotation in pyridinethione **1** ($\Delta G^{\ddagger}_{200}$ 29 ± 2 kJ mol^{-1}) is the lowest to be experimentally determined so far for this class of compounds. Compared to the calculations by Chung-Phillips and Jebber, $\Delta H^{\ddagger}$ for N−O rotation in **1** (valid for the experimentally observed temperature range) is even lower than the calculated value for hydroxylamine at 0 K. This observation is likely to reflect a depletion in the electron density at nitrogen in pyridinethione **1**, presumably caused by interactions with both vicinal C=S and C=C π-systems. Raban and Kost investigated the oxo derivative of **1**, i.e. *N*-isopropoxy-2(1*H*)-pyridone, by low temperature NMR spectroscopy. The authors estimated a $\Delta G^{\ddagger}_{180}$ value of 36−39 kJ mol^{-1} for N−O rotation from line broadening, although for experimental reasons they could not reach the coalescence temperature.[4] However, they determined the rotational barrier in 6-chloro-*N*-isopropoxy-2(1*H*)-pyridone ($\Delta G^{\ddagger}_{200}$ = 42 kJ mol^{-1}). This energy value is, presumably for steric reasons, substantially larger than the more precisely measured barrier in pyridinethione **1**. However, this value comes close to the corresponding data for 4-methylthiazolthione **2** ($\Delta G^{\ddagger}_{200}$ = 42 ± 7 kJ mol^{-1}) but it is slightly smaller than the figure obtained for the *p*-chlorophenyl derivative **3** ($\Delta G^{\ddagger}_{200}$ = 46 ± 1 kJ mol^{-1}). These findings clearly point to the significance of steric contributions to the barriers of N−O rotation, since thiones **1**−**3** only differ in their heterocyclic substructures while the alkoxy substituents are structurally identical.

Finally, the experimental error that has been calculated for $\Delta G^{\ddagger}_{200}$ of 4-methylthiazolethione **2** deserves a comment. The diagram in Figure 3 shows a slight scatter of data of ln (k/T) values for temperatures between 195−202 K. The observed temperature-dependent changes in the lineshape of thione **2** are relatively small below 202 K. Therefore, the corresponding rate constants are possibly afflicted with a higher experimental error than the estimated ±5% which finally adds up to the calculated experimental uncertainties in activation parameters for 4-methylthiazolethione **2**.

Conclusion

The activation parameters ($\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$) for rotation around the N−O single bonds in cyclic thiohydroxamic acid *O*-esters have been measured in the temperature range 125−273 K by variable-temperature NMR experiments. The calculated $\Delta G^{\ddagger}_{200}$ values for *N*-Isopropoxy-2(1*H*)-pyridinethione (**1**) and two 4-substituted *N*-isopropoxythiazole-2(3*H*)-thiones **2** and **3** indicate that steric encroachment in the vicinity of the N−O bond decelerates the underlying rotation process thus leading to higher barriers of activation. The presented new data on activation parameters of *N*-alkoxy-substituted heterocycles form a profound basis for further detailed investigations of these and related classes of compounds by high-level ab initio molecular orbital calculations.

Experimental Section

General Remarks: IR spectra were measured in CCl_4 in NaCl cuvettes (0.5 mm). C,H,N,S analysis was carried out in the Mikroanalytisches Labor in the department of Anorganische Chemie at the Universität Würzburg. All solvents were distilled prior to use and purified according to standard procedures.[20] *N*-Isopropoxy-2(1*H*)-pyridinethione (**1**)[12,13] and 4-(*p*-chlorophenyl)-*N*-isopropoxythiazole-2(3*H*)-thione (**3**)[14] were prepared as reported previously.

***N*-Isopropoxy-4-methylthiazole-2(3*H*)-thione (2):** *N*-Hydroxy-4-methylthiazole-2(3*H*)-thione (**4**) (120 mg, 0.815 mmol) was dissolved in anhydrous CH_3CN (1.6 mL). K_2CO_3 (338 mg, 2.45 mmol) and NBu_4HSO_4 (27.7 mg 0.082 mmol) were added at 20 °C and the slurry was stirred for 15 min. Neat isopropyl tosylate **5** (157 mg, 0.734 mmol) was added and the reaction mixture, which remained a thick slurry, was stirred for 24 h at 20 °C in the dark. The brown reaction mixture was then diluted with water (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic phases were washed with a 2 N aqueous NaOH solution, dried ($MgSO_4$) and concentrated in vacuo. The residue was purified by column chromatography [SiO_2, petroleum ether/diethyl ether, 1:1 (v/v), $R_f = 0.35$] to afford isopropoxythiazolethione **2** as a tan oil (118 mg, 85%). ^1H NMR (250 MHz, $CDCl_3$): $\delta = 1.31$ (d, $J = 6.4$ Hz, 6 H, CH_3), 2.22 (d, $J = 1.2$ Hz, 3 H, CH_3), 5.48 (sept, $J = 6.4$ Hz, CH), 6.17 (q, $J = 1.2$ Hz, 1 H, CH). ^{13}C NMR (63 MHz, $CDCl_3$) $\delta = 14.0$, 20.3, 78.3, 102.8, 138.9, 180.7. MS (70 eV, EI): m/z (%) = 189 (43) [$M^{\cdot+}$], 147 (54) [$C_4H_5NOS_2^+$], 130 (100) [$C_4H_4NS_2^+$]. IR: $\tilde{\nu} = 3095$ cm^{-1}, 2980, 1465, 1380, 1310, 1175, 1140. $C_7H_{11}NOS_2$ (189.3): calcd. C 44.41, H 5.86, N 7.40, S 33.88; found C 44.66, H 5.93, N 7.27, S 33.76.

DNMR Experiments: Bruker DMX 600 operating at 600.13 MHz for proton and 150.90 MHz for carbon-13, equipped with a temperature control assembly B-VT-2000, display and control unit BTO-2000-E and a probe head heater BMT 05.
Sample preparations: Samples of **1**, **2**, and **3** (40 mg each) in a solution of $CHClF_2$ and [D$_6$]dimethyl ether [3:1 (v/v)][15] were prepared in high precision 5 mm tubes (Varian 507 PP) which were attached to a vacuum line (10^{-2} Torr) connected to the sources of $CHClF_2$ and [D$_6$]dimethyl ether. The tubes were evacuated at 77 K/10^{-2} Torr and the solvents were added carefully at this temperature in a ratio of 3:1. Eventually, the tubes were sealed with a torch and allowed to thaw *very slowly* to prevent breakage due to rapid expansion.
NMR experiments and determination of the Eyring parameters: The sample tubes were allowed to equilibrate thermally for 15 min at each temperature before any changes of the frequencies of proton and carbon-13 channels and the impedance of the receiver circuit were carefully compensated for; NMR spectra were recorded without spinning. Each temperature was calibrated with the help of an NMR shift thermometer. Carbon-13 spectra were recorded with WALTZ-16 decoupling.[15] Zero filling to four times the number of measured data points was performed. Particular attention was paid to the phase and the baseline corrections. Carbon-13 linewidths were determined with the Lorentzian lineshape least-squares fitting routine, which is part of the Bruker software package. Rate constants were calculated from linewidths from Equation (1) and (2) as appropriate with $W_{ex} = W_{obs} - W_{ref}$. Proton spectra were iterated to determine the rate constants from a complete lineshape analysis with the Bruker program WINDYNA. Each fit was repeated until the agreement between the calculated and experimental spectra optically matched completely. The error in k was carefully estimated to 5% owing to the error in linewidth W_{exp} and shift difference $\Delta\nu$. The error in temperature was estimated to ± 1 K. The Eyring parameters were calculated from rate constants and temperatures (Figure 3) with Equation (3), which results from the Eyring and the Gibbs−Helmholtz equations. The values are calculated with the least-squares method and results are displayed in Table 1.

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