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Dynamic Behaviour of Cyclic Thiohydroxamic Acid Derivatives – Barrier to Rotation about N–O bonds in 4-substituted *N*-Isopropoxythiazole-2(3*H*)-thiones and *N*-Isopropoxy-pyridine-2(1*H*)-thione

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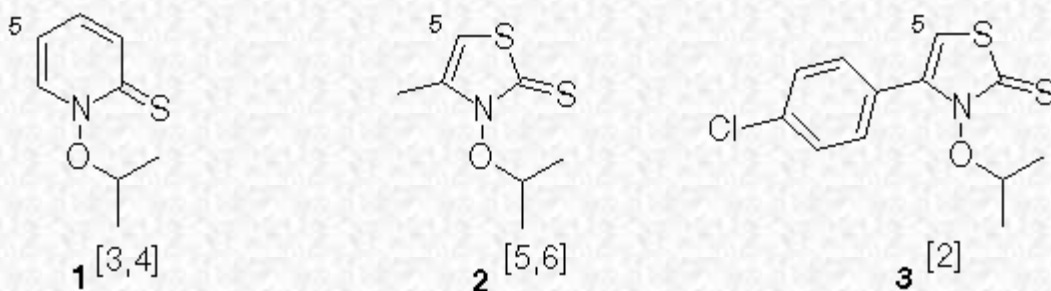
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Abstract: Activation parameters [DG^\ddagger_{200} , DH^\ddagger , DS^\ddagger] for barriers to rotation about N–O bonds in *N*-isopropoxy-pyridine-2(1*H*)-thione (**1**) and two 4-substituted *N*-isopropoxythiazole-2(3*H*)-thiones **2** and **3** were determined by variable-temperature ¹H (600 MHz) and ¹³C (150 MHz) NMR spectroscopy in the temperature range of $T = 135$ – 250 K. The barriers to rotation about N–O bonds in cyclic thiohydroxamic acid *O*-esters **1**, **2**, and **3** are explained by a superposition of steric and electronic effects.

Keywords: Barrier to rotation, Dynamic NMR, Pyridinethione, Thiazolethione, Nitrogen-Oxygen bond

Introduction

Recent advances in low temperature NMR studies[1] and the synthetic access to new mechanistic probes[2] have encouraged us to determine hitherto unknown barriers to rotation about N–O bonds in cyclic thiohydroxamic acid *O*-esters, e.g. *N*-isopropoxy-pyridine-2(1*H*)-thione (**1**) and the 4-substituted thiazolethiones **2** and **3** (Figure 1) .



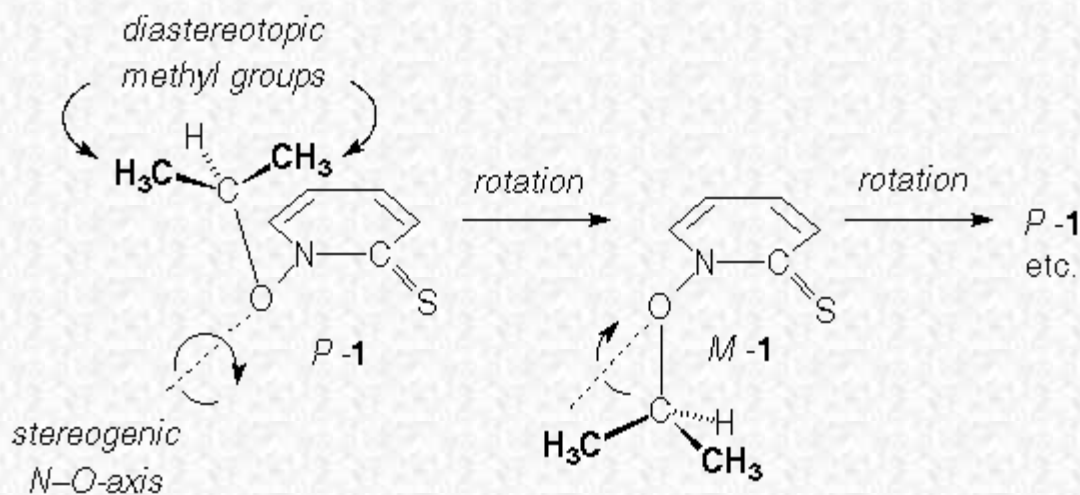


Figure 1. Pyridinethione and thiazolethione-derived cyclic thiohydroxamic acid *O*-esters **1–3** (top) and topomerization of CH₃ groups in *N*-isopropoxy-pyridinethione **1** via rotation about the stereogenic N–O bond (bottom).

Results

Thiones **1–3** were prepared according to standard procedures and were fully characterized.[2–6] Proton NMR spectra of thiones **1**, **2**, and **3** in either deuteriochloroform or a mixture of chlorodifluoromethane and perdeuterodimethyl ether showed typical line patterns of unhindered rotating isopropyl groups at $T = 293$ K. Thus, topomerization of CH₃ groups is fast with respect to the NMR time scale at that temperature. For example, a doublet at 1.04 ppm (¹H NMR) and a singlet at 19.0 ppm (¹³C NMR) was recorded for both CH₃ groups in *N*-isopropoxy-4-*p*-chlorophenylthiazole-2(3*H*)-thione (**3**). On cooling these signals broadened. Coalescence was observed at $T = 235$ K (¹³C NMR, Figure 2). If temperatures were further lowered, the topomerization (exchange) became slow with respect to the NMR time scale. At $T = 200$ K, well separated signals were recorded for both diastereotopic methyl groups at 19.4 ppm and 19.0 ppm in the ¹³C NMR spectrum of **3**. The respective ¹H resonance lines were observed at 0.69 ppm and at 1.23 ppm (both d, $J = 4.5$ Hz). Coalescence of signals and their separation into individual sets of resonances on further cooling were also observed for diastereotopic methyl groups in pyridinethione **1** ($T_{\text{coal}} \sim 145$ K) and 4-methylthiazolethione **2** ($T_{\text{coal}} \sim 200$ K).

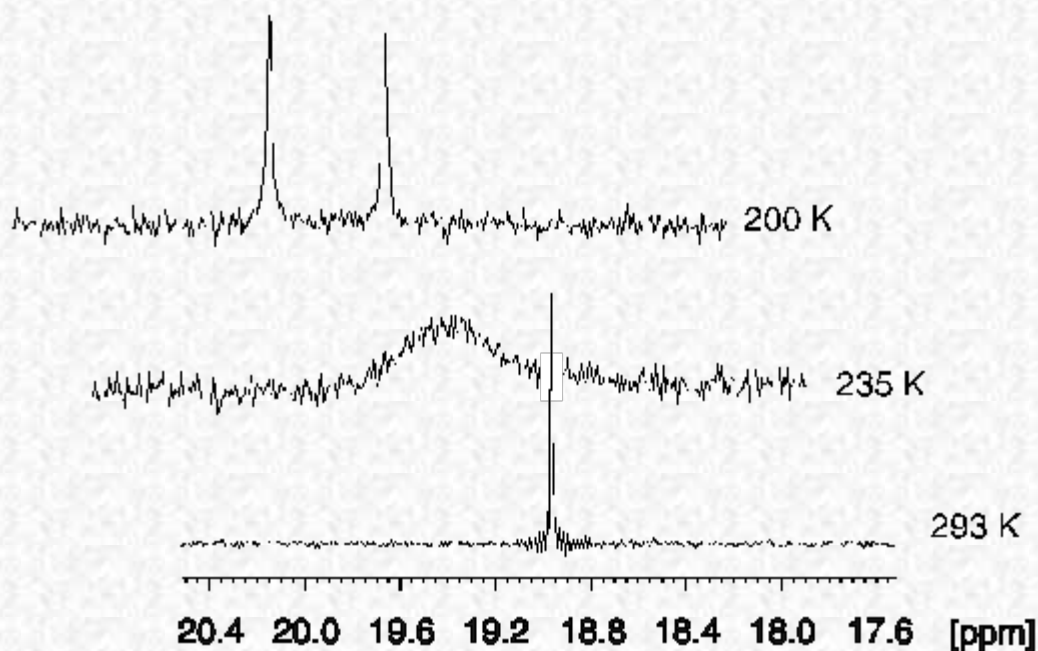


Figure 2. Stacking plot of carbon-13 NMR spectra of *N*-isopropoxy-*p*-chlorophenylthiazolethione **3** at different temperatures.

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

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

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

Variable-temperature proton-NMR data were subjected to complete line-shape-analysis in order to derive rate constants k for the exchange process caused by the rotation about the N–O bond. Rate constants from carbon-13 NMR spectra were accessible by analyzing line widths of half height and shift differences $\Delta\nu$ of exchange-related nuclei according to eq. 1 and eq. 2 with $W_{\text{ex}}(\text{change}) = W_{\text{obs}}(\text{erved}) - W_{\text{ref}}(\text{erence})$. [1] Line widths of C-5 (Figure 1) were taken as reference for pyridinethione **1**, thiazolethiones **2**, and **3**. Experimental errors in k were estimated to be $\pm 5\%$. Temperatures were measured using a solution of a barbaralane-derived high-precision carbon-13 shift thermometer in chorodifluoromethane/perdeuterodimethyl ether [$\sim 3/1$ (v/v)] which is suitable for a temperature range of $T = 100\text{--}300$ K. [7] Activation parameters ΔH^{\ddagger} , ΔS^{\ddagger} (Table 1) were calculated from eq. 3.

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

compound	NMR method	$\Delta G^{\ddagger}_{200}$ [a]	ΔH^{\ddagger}	ΔS^{\ddagger}	lgA	Ea
		[kJ mol ⁻¹]	[kJ mol ⁻¹]	[J K ⁻¹ mol ⁻¹]		[kJ mol ⁻¹]
1	13C	29 \pm 2	20.6 \pm 0.6	-40 \pm 4	10.8 \pm 0.2	21.9 \pm 0.6
2	1H	42 \pm 7	34 \pm 4	-40 \pm 19	11 \pm 1	36 \pm 3
3	1H and 13C	46 \pm 1	11.7 \pm 0.7	-40.6 \pm 0.7	11.7 \pm 0.2	42.4 \pm 0.7

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

Discussion

The phenomenon of slowed rotation of substituents which are covalently bound via heteroatom-heteroatom single bonds is well documented. [8–10] Two factors contribute to barriers of N–O rotation: (i) electronic (repulsion of lone pairs) and (ii) steric effects at nitrogen and oxygen. Cyclic thiohydroxamic acid *O*-esters adopt an almost orthogonal transposition of substituents at nitrogen and at oxygen in the solid state. [2,3] This arrangement would have been predicted by the VSEPR principle [11] alone if steric interactions were neglected. However, proton NMR spectra of *N*-isopropoxy substituted heterocycles **1**, **2** and **3** in CDCl₃ solution at room temperature indicate that topomerization of the methyl groups is fast with respect to the NMR time scale, since signals of both diastereotopic methyl groups are not split into separate sets of lines (Figures 1 and 2). [2–4] On cooling, topomerization of CH₃ groups becomes slow and coalescence is observed. On further lowering of the temperature, exchange becomes slow with respect to the NMR time scale. Line-shape analyses and examination of widths of half height of exchange-related nuclei affords barriers to rotation about N–O bonds in thiones **1**, **2** and **3** (Table 1). The lowest barrier was observed for pyridinethione **1** ($\Delta G^{\ddagger}_{200}$ 29 \pm 2 kJ mol⁻¹). 4-Substituted thiazolethiones **2** ($\Delta G^{\ddagger}_{200}$ 42 \pm 7 kJ mol⁻¹) and **3** ($\Delta G^{\ddagger}_{200}$ 46 \pm 1 kJ mol⁻¹) showed substantially higher barriers. Since the alkoxy moiety is identical in all compounds, the ranking of calculated $\Delta G^{\ddagger}_{200}$ values should majorly reflect steric contributions from heterocyclic part of the structures.

Conclusions

Activation parameters (DH^\ddagger , DS^\ddagger) for rotations about N–O single bonds in cyclic thiohydroxamic acid *O*-esters have been measured in the temperature range of 130–273 K by variable-temperature NMR experiments for the first time. Calculated DG^\ddagger_{200} values for *N*-isopropoxy-pyridine-2(1*H*)-thione (**1**) and two 4-substituted *N*-isopropoxythiazole-2(3*H*)-thiones **2** and **3** indicate that steric encroachment in vicinity of the N–O bond decelerates the underlying rotation process thus leading to higher barriers of activation.

Acknowledgement

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