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$E \rightleftharpoons Z$ ROTATIONAL ISOMERIZATION IN THIOHYDROXAMIC AND HYDROXAMIC ACIDS. A ^1H NMR AND MNDO SCF-MO STUDY

The $E \rightleftharpoons Z$ isomerization of several hydroxamic and thiohydroxamic acids has been studied in CDCl_3 and in d_6 -DMSO by ^1H NMR spectroscopy. The differences observed in the rotational barriers obtained for some thiohydroxamic and hydroxamic acids are explained in terms of solvent, steric and electronic effects. Higher rotational barriers have been found for the thiocompounds. Theoretical calculations give support to the experimental results.

INTRODUCTION

Although the $E \rightleftharpoons Z$ isomerisation of amides [1] and thioamides [2] has been the subject of extensive investigation, little work has been done on the related hydroxamic and thiohydroxamic acids [3], which are compounds of biological and analytical importance [4]. Recently, results have been reported for the corresponding hydroxamate cations generated by protonation in strong media [5]. The aim of the present work is to extend the study of the $E \rightleftharpoons Z$ equilibrium to a set of N - and C -substituted hydroxamic and thiohydroxamic acids in solution, to enable a more complete understanding of the factors that govern the $C(X) - N$ ($X = O, S$) restricted rotation in these compounds.

The energy barriers to internal rotation measured using ^1H NMR spectroscopy are reported together with MNDO and *ab initio* SCF-MO calculations for the rotation around the $C - N$ bond in hydroxamic and thiohydroxamic acids.

EXPERIMENTAL

Details of the preparation of the substrates have been reported elsewhere [6].

^1H NMR spectra were recorded on a JEOL JNM-PS-100 (100 MHz) or a Bruker CXP 300 (300 MHz) spectrometer using *ca* 0.02M solutions, and tetramethylsilane as an internal reference.

Free energies of activation, ΔG^\ddagger , for the $E \rightleftharpoons Z$ interconversion were obtained by the well known approximate method [7] which involves the measurement of the coalescence temperature of the corresponding resonances in each pair of isomeric species E , Z . In cases of unequal populations the equations of Shanon-Atidi and Bar-Eli [8] were used.

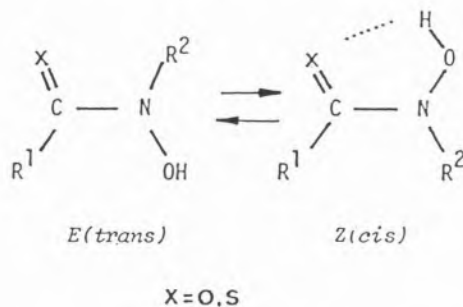
Rotational barriers around the $C - N$ bond were investigated using MNDO [9] and *ab initio* [10] SCF-MO methods on the model (thio) formohydroxamic acid. *Ab initio* calculations were carried out by using STO-3G

or 4-31G basis set on MNDO optimised geometries (the corresponding nomenclature is STO-3G/MNDO or 4-31G/MNDO). The E \rightleftharpoons Z isomerization reaction path calculations were carried out by varying the dihedral angle [ONCX], (X = O, S), with full geometry optimisation of the remaining variables for each increment.

RESULTS AND DISCUSSION

Spectral Analysis

The ^1H NMR results for thiohydroxamic and hydroxamic acids are summarised respectively in Tables 1 and 2. At room temperatures and in CDCl_3 solution almost all the compounds showed only one set of signals for the N-substituted proton groups, while in d_6 -DMSO solution two sets of signals were observed for the same groups. The occurrence of separate signals is attributed to the presence of the two isomers E and Z, characterized by a rotation around the C–N bond which is slow on the NMR time scale.



The differences between the chemical shifts of the two isomers E and Z must be mainly due to the magnetic anisotropy of the carbonyl or thiocarbonyl [11] for the C(X)-alkyl compounds, coupled with the anisotropy created by the benzene ring for the C(X)-aryl (X = O, S) derivatives.

The assignment to the two NMR signals, corresponding to the geometrical isomers, was based on the following:

- (1) Comparison of the spectra in CDCl_3 and in d_6 -DMSO. In CDCl_3 the Z isomer should be more stabilized by intramolecular hydrogen bonds, while in d_6 -DMSO the E isomer must be more stabilized by intermolecular bonds.
- (2) Comparison of the magnetic anisotropy created by the carbonyl and thiocarbonyl groups. It has been shown that the carbonyl group of amides and the thiocarbonyl group of thioamides have opposite effects [11] on the chemical shift of the N-substituents. Therefore, if the analogy holds for (thio)hydroxamic acids, the N-alkyl protons in the E-isomer of the C-alkyl hydroxamic acids should resonate at higher field, while the corresponding protons in the Z isomer of the analogous thiohydroxamic acids should appear at higher field.
- (3) Magnetic anisotropy created by the benzene ring. For $R^1 = o$ -substituted phenyl, the strong shielding effect of this ring on the R^2 substituent should be opposite to the anisotropic effect of the carbonyl group and cumulative to the anisotropic effect of the thiocarbonyl group.

E \rightleftharpoons Z Equilibrium and Rotational Barriers

A detailed analysis of Table 1 shows that, whereas in CDCl_3 all the thiohydroxamic acids present only one set of ^1H NMR signals, in d_6 -DMSO they present two sets of signals indicating the presence of two isomeric species in solution. This feature could be rationalised in terms of a greater stabilising effect in intramolecular hydrogen bonds over intermolecular hydrogen bonds in solvents of low polarity. Thus the lower polarity of CDCl_3 relative to d_6 -DMSO should favour the Z form, which is disrupted by the more polar d_6 -DMSO.

The hydroxamic acids show a similar behaviour (Table 2). However there are some exceptions, namely the C-nonsubstituted

Table 1

¹H NMR data for the C-N rotation in thiohydroxamic acids, R¹C(S)N(OH)R²

N.º	Compound R ¹ R ²	Solvent	δ_{NCH_3} (R ²) ^a		δ_{CH_3} (R ¹) ^a		E (%)	$\Delta\nu$ (Hz)	T (K)	ΔG_C^\ddagger		Coalescent group
			E	Z	E	Z				E	Z	
1	CH ₃ CH ₃	CDCl ₃ d ₆ -DMSO	3.61 (s) 3.68(s) 3.58(s)		2.57(s) 2.44(s) 2.49(s)		— 87	— 3	— 374	— 86.5 ^b		— N-CH ₃
2	CH ₃ CH ₂ Ph	CDCl ₃ d ₆ -DMSO	5.07(s) 5.39(s) 5.17(s)		2.61(s) 2.52(s) 2.60(s)		— 89	— 22.5 8.3	— 413 373	— 95.3 88.6 89.0 82.8		— N-CH ₂ C-CH ₃
3	CH ₃ Ph	CDCl ₃ d ₆ -DMSO	— —		2.49(s) 2.37(s) 2.66(s)		— 69	— 29	— 353	— 76.1 74.8		— C-CH ₃
4	Ph CH ₃	CDCl ₃ d ₆ -DMSO	3.54(s) 3.58(s) 3.45(s)		— —		— 60	— 33.2	— 363	— 77.0 75.7		— NCH ₃
5	Ph CH ₂ Ph	CDCl ₃ d ₆ -DMSO	5.04(s) 5.45(s) 4.97(s)		— —		— 67	— 48	— 353	— 81.1 79.0		— N-CH ₂
6	o-Br-Ph CH ₂ Ph	CDCl ₃ d ₆ -DMSO	4.85(s) 5.51(q) 4.77(s) (J=-14.7Hz)		— —		— 76	— 222.9	— 410	— >89.0 > 84.9		— N-CH ₂
7	m-MeO-Ph CH ₂ Ph	CDCl ₃ d ₆ -DMSO	5.00(s) 5.54(s) 4.95(s)		3.76(s) 3.76(s)		— 73	— 59	— 373	— 79.4 76.9		— N-CH ₂
8	o-MeO-Ph CH ₃	CDCl ₃ d ₆ -DMSO	3.42(s) 3.76(s) 3.31(s)		3.87(s) 3.73(s) 3.82(s)		— 45	— 9	— 407	— 90.7		— C-OCH ₃
9	o-MeO-Ph CH ₂ Ph	CDCl ₃ d ₆ -DMSO	4.81(s) 5.53(q) 4.79(s) (J=-15.7Hz)		3.73(s) 3.77(s)		— 63	— 74	— >405	— >84.9 > 83.2		— N-CH ₂
9	o-MeO-Ph Ph	CDCl ₃ d ₆ -DMSO	— —		3.46(s) 3.82(s) 3.47(s)		— 30	— 35.2	— 373	— 78.6		— C-OCH ₃

a) s = singlet, q = quartet; b) reference 3

Table 2

¹H NMR data for the C-N rotation in hydroxamic acids, R¹C(O)N(OH)R²

N.º	Compound R ¹ R ²	Solvent	δ_{NCH_3} (R ²) ^a		E (%)	$\Delta\nu$ (Hz)	T (K)	ΔG_C^\ddagger		Coalescent group
			E	Z				E	Z	
11	o-MeO-Ph CH ₃	CDCl ₃ d ₆ -DMSO	3.23(s) 3.22(s) 2.99 (s)		— 62	— 69	— 321	— 66.8	— 65.6	— N-CH ₃
12	o-MeO-Ph CH ₂ Ph	CDCl ₃ d ₆ -DMSO	4.67(s) 4.87(s) 4.47(s)		— 56	— 123	— 328	— 66.0	— 65.5	— N-CH ₂
13	o-Br-Ph CH ₂ Ph	CDCl ₃ d ₆ -DMSO	4.99(s) 4.64(s) 4.88(s) 4.46(s)		13 69	140 29	335 335	66.4 71.7 71.8 66.8		N-CH ₂ C-CH ₃
14	o-Br-Ph CH ₃	CDCl ₃ d ₆ -DMSO	3.22(s) 3.27(s) 3.02(s)		— 75	— 25	— 318	— 70.3	— 67.4	— N-CH ₃
15 ^b)	H CH ₃	CDCl ₃ d ₆ -DMSO	3.35(d) 3.34 (s) (J=0.4Hz)		32	5.5	306	68.8 ^b)		N-CH ₃
16 ^b)	H CH ₂ Ph	CDCl ₃	4.66(s) 4.50 (s)		34	9.5	309	67.7 ^b)		N-CH ₂

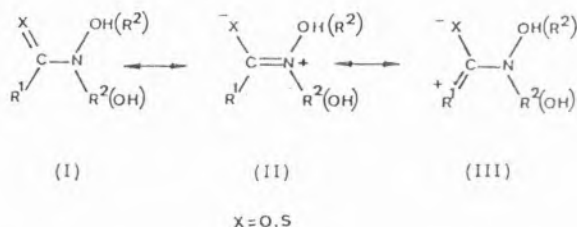
a) s = singlet, d=duplet; b) reference 3

hydroxamic acids (compounds 15 and 16), and the *N*-benzyl-*o*-bromo-benzohydroxamic acid, 13, that present two sets of signals in $CDCl_3$. We also found hydroxamic acids that present only one set of signals in both solvents (cf. 17 to 23)



R^1	R^2
17 CH_3	$CH(CH_3)_2$
18 $C(CH_3)_3$	CH_3
19 $CH(CH_2)_5$	CH_3
20 CH_3	CH_3
21 Ph	CH_2Ph
22 <i>o,m</i> - Me, Me - Ph	CH_3
23 <i>o</i> - MeO Ph	Ph

The rotational barriers calculated for the thiohydroxamic acids ($\Delta G^\ddagger = 75\text{--}95 \text{ kJmol}^{-1}$) and hydroxamic acids ($\Delta G^\ddagger = 66\text{--}72 \text{ kJmol}^{-1}$) are attributed to the partial double bond character of the C - N bond that is conferred by electronic donation of the nitrogen lone pair to the electrophilic carbon of the (thio)carbonyl group (structure II).



The difference between the rotational barriers in the oxo- and the sulfur-compounds is consistent with the previous results obtained for amides and thioamides [12] and it has been attributed to the higher double bond character of the C - N bond in thiohydroxamic acids relative to the corresponding hydroxamic acids.

The effect of the solvents on the rotational barrier (higher values were found with d_6 -DMSO than with $CDCl_3$) could equally

be rationalized in terms of the higher polarity of d_6 -DMSO relative to $CDCl_3$ and consequently greater stabilization of the more polar resonance structure (II).

The general decrease in the rotational barriers with the bulk of the C-substituents (cf. compounds 2 and 7-Table 1; compounds 11 and 15-Table 2) could be explained by unstabilization of the expected nearly planar ground state. The bulk of the N-substituents must have similar effect on the rotational barriers. However we were not able to confirm this from our results, because both the N-substituents that have been used (methyl and benzyl) have similar bulky effects. The existence of a lower rotational barrier for the C-phenyl compounds than for the corresponding C-alkyl compounds (compounds 1 and 4) and for the N-phenyl relative to the corresponding N-alkyl (compounds 1 and 3) should be attributed respectively to the conjugation between the phenyl and the C = X group (major contribution of the resonance structure III) and between the N-phenyl and the C = N group (resonance structure II). However an opposite effect was observed in *ortho*-substituted benzo(thio)hydroxamic acids (compounds: 4 and 8; 5 and 9), where the inhibition of this conjugation is certainly due to the orthogonality of the aryl and the (thio)carbonyl groups as a consequence of steric interactions [13]. This effect was proved to increase with the bulk of the *ortho*-substituents (compounds: 5 and 6; 12 and 13). The *m*-MeO- substituent does not seem to affect the conjugation between the phenyl and the C = X group [13], and so an effect of increasing of the bulk of the C-substituents is observed (cf. compounds 5 and 7).

Theoretical Calculations

Analysis of MNDO and STO-3G//MNDO potential energy curves, describing the internal rotation around the C - N bond in the models formohydroxamic and formothiohydroxamic acids, correctly predicts the

existence of two energy minima (see Fig. 1a and Fig. 1b), corresponding to configurations where the nitrogen lone pair is approximately orthogonal to the mean plane of the (thio)amide group [XCN]. For these configurations there should be an increase on the efficiency of the stabilizing interaction between the nitrogen lone pair orbital and the empty anti-bonding orbital (π^*) of the (thio)carbonyl group.

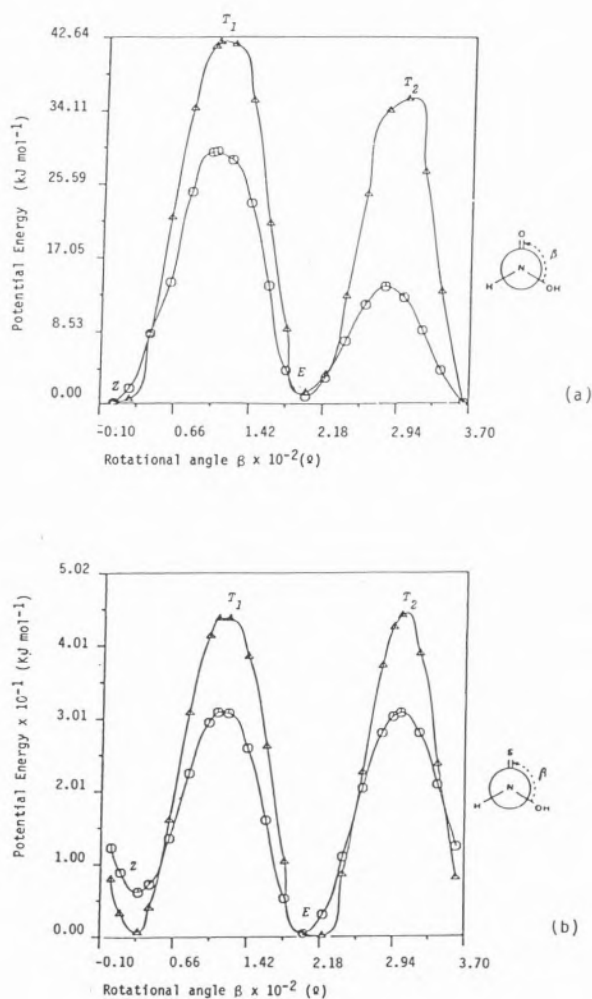


Figure 1

Potential energy curves for the C — N rotation in: a) formohydroxamic acid; b) formothiohydroxamic acid

○ — MNDO Calculations
△ — STO - 3G / MNDO Calculations

The energy barriers to internal rotation through the different transition states are collected on Tables 3 and 4. As was shown in preliminary studies undertaken by us on (thio)formamide [14], the mixed method 4-31G//MNDO predicted rotational barriers (formohydroxamic acid $\Delta H_Z^\ddagger = 56.6 \text{ kJmol}^{-1}$ and $\Delta H_E^\ddagger = 62.1 \text{ kJmol}^{-1}$; formothiohydroxamic acid $\Delta H_Z^\ddagger = 73.7 \text{ kJmol}^{-1}$ and $\Delta H_E^\ddagger = 79.9 \text{ kJmol}^{-1}$) which are reasonably close to the ^1H NMR experimental values obtained by us (conf. Tables 1 and 2).

Table 3

Calculated barriers to internal C — N rotation in formohydroxamic acid (kJmol^{-1})

Method	Via ^a			
	ZT ₁	ZT ₂	ET ₁	ET ₂
MNDO	28.76	13.25	27.96	12.46
STO-3G//MNDO	41.38	33.52	40.34	32.48
4-31G//MNDO	87.03	56.60	92.55	62.11

^a — For instance, via ZT₁ means rotation from the ground state Z through the transition state T₁

Table 4

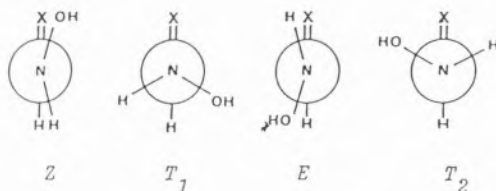
Calculated barriers to internal C — N rotation in formothiohydroxamic acid (kJmol^{-1})

Method	Via ^a			
	ZT ₁	ZT ₂	ET ₁	ET ₂
MNDO	24.87	24.70	30.64	30.47
STO-3G//MNDO	43.26	43.51	43.51	43.81
4-31G//MNDO	75.99	73.65	82.26	79.92

^a — For instance, via ZT₁ means rotation from the ground state Z through the transition state T₁

The higher rotational barriers that have been calculated for the thiohydroxamic acid, relative to the corresponding oxo-compound ($\Delta\Delta H_Z = 17.1 \text{ kJmol}^{-1}$ and $\Delta\Delta H_E = 17.8 \text{ kJmol}^{-1}$) are in accordance with the experimental results. This is due to the greater preference for resonance form II, in which the C = S double bond character is greatly reduced.

Particularly noteworthy is the calculated lengthening of the C - N bond ($\sim 0.04 - 0.05\text{\AA}$) in the theoretical models with rotation from the ground state (*E* or *Z*) to the transition state (T_1 or T_2). This feature is in accordance with the expected lack of delocalization of the nitrogen lone pair in the C = Z system in both orthogonal conformers (T_1 and T_2).



CONCLUSIONS

The results presented here show that the energy barriers to rotation about the C - N bond are higher in thiohydroxamic acids than in the corresponding hydroxamic acids, being strongly dependent on both the electronic and the steric characteristics of the substituent present.

The observed differences of the rotational barriers on the solvent used probably reflect the different degrees of stabilization of the ground and/or the excited state, with the consequent competition between the intramolecular and intermolecular hydrogen bond.

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SUMÁRIO

Isomerização Rotacional E \rightleftharpoons Z em Ácidos Hidroxâmicos e Tio-hidroxâmicos. Um estudo de ^1H RMN e de SCF-MO

A isomerização E \rightleftharpoons Z de vários hidroxâmicos e tiohidroxâmicos foi estudada por espectroscopia de RMN protônica. As barreiras rotacionais que foram obtidas para vários ácidos tiohidroxâmicos e hidroxâmicos são explicadas em termos de efeitos de solvente, efeitos esterequímicos e eletrônicos. As barreiras encontradas para os tiocompostos foram mais elevadas do que as dos correspondentes oxo-compostos. Os cálculos teóricos efectuados dão suporte a alguns resultados experimentais.