

Conformational Studies by Dynamic NMR. 58.¹ Stereodynamics of C–C and C–N Rotation in Furan and Thiophene *o*-Amino Thioaldehydes and Aldehydes

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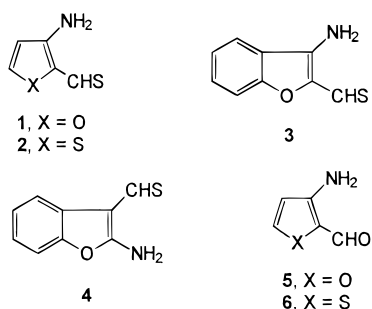
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Introduction

Thioaldehydes are, usually, unstable compounds that can, however, be stabilized either kinetically, *via* steric hindrance,^{3,4} or thermodynamically, *via* delocalization effects.^{5–7} As observed in the case of the corresponding radical anions,^{8,9} thioaldehydes can exhibit restricted rotation about the sp²–sp² carbon–carbon bond in compounds such as Ar–CH=S^{6,7} or R–CH=S, if R is an appropriate vinyl moiety.^{10,11} In particular, a number of five-membered heteroaromatic *o*-aminothioaldehydes derived from the furan, benzo[*b*]furan, thiophene, and benzo[*b*]thiophene rings have been recently found to be chemically stable, owing to stabilization of the thioformyl group brought about by the mesomeric effects of the amino-substituted heterocyclic rings (Scheme 1).¹²

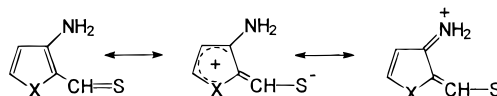
These compounds (e.g., **1–4**) seemed particularly well-suited for the investigation of the carbon–carbon rotational barrier about the Ar–CHS bond as well as the carbon–nitrogen rotational barrier about the adjacent Ar–NH₂ bond, which have not been reported as of yet. It was also of interest to compare the barriers determined for **1** and **2** with those of the corresponding aldehydes **5** and **6**, whose values, therefore, were also measured in the present study.



Results and Discussion

As a typical procedure, we describe in detail the results obtained for thioaldehyde **1**, whose ¹H NMR spectrum

Scheme 1



in DMSO displays, at room temperature, the signals corresponding to a pair of rotational conformers (rotamers) in an approximately 3.5:1 ratio. Difference NOE experiments, performed by saturating, alternatively, the NH₂ line of the major and the minor rotamer, are displayed in Figure 1. In the first case only a small enhancement (4.5%) is detected for the corresponding major HCS signal (10.12 ppm), whereas in the second case a very large enhancement (48%) is observed for the corresponding minor HCS signal (10.15 ppm). In both rotamers, as expected, saturation of the NH₂ line causes a significant enhancement of the corresponding H-4 signal. These results allow the unambiguous assignment of the S,NH₂-*anti* structure to the minor rotamer (**1-Z**) and the S,NH₂-*syn* structure to the major rotamer (**1-E**).



As expected, the ¹³C spectrum of **1** displays a pair of peaks for each carbon atom, with the same 3.5:1 ratio. In particular, the shift of the C=S carbon appears to be shielded (180.25 ppm) in the minor rotamer with respect to the corresponding signal (180.8 ppm) of the major rotamer. This is possibly a consequence of the steric hindrance occurring in the major rotamer **1-E** between the bulky sulfur atom and the adjacent NH₂ group, which would prevent coplanarity of the CHS substituent with the heteroaryl moiety, thereby causing less efficient delocalization of the positive charge on the C=S carbon over the ring. It is in fact well known¹³ that the ¹³C shifts of carbonyl (and thiocarbonyl) carbons are deshielded when this type of delocalization is somehow reduced. The reason why the more hindered rotamer **1-E** is, nonetheless, the more stable species is most likely ascribable to the occurrence of intramolecular hydrogen bonding between one amino hydrogen and the thiocarbonyl sulfur, an interpretation that is supported by experimental evidence (*vide infra*).

MM calculations¹⁴ predict that rotamer **1-E** should have a dipole moment (0.85 D) much lower than that of

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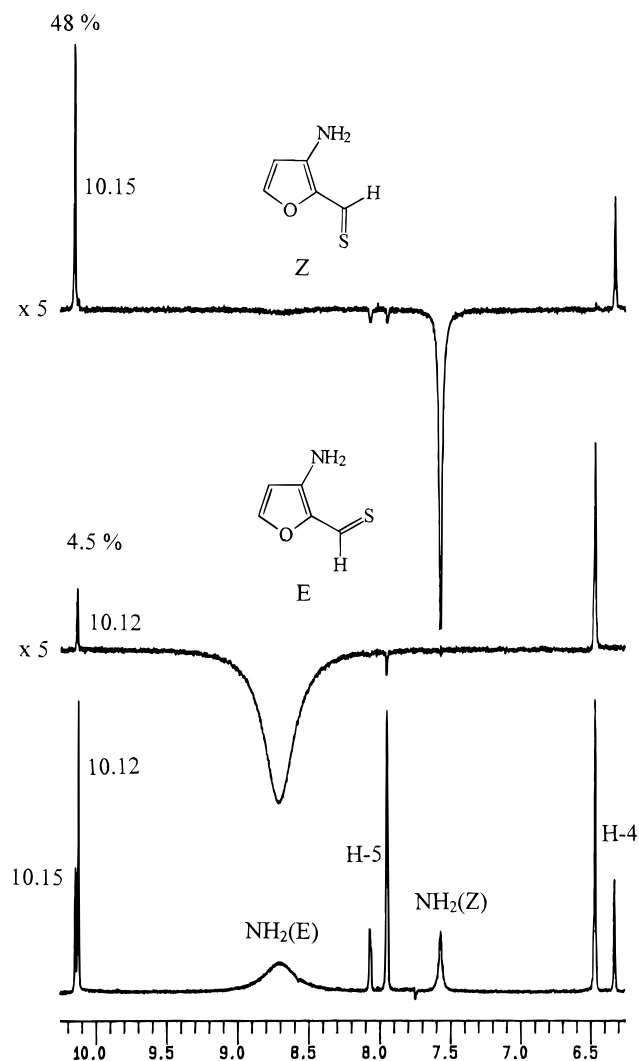


Figure 1. NOE difference spectra (300 MHz in DMSO at room temperature) of **1** obtained by saturating the NH₂ signal (middle trace) of the major rotamer (population = 78%) and the NH₂ signal (top trace) of the minor rotamer (population = 22%). The NOE spectra are vertically amplified by a factor of 5 with respect to the control spectrum (bottom trace). The enhancements observed for the major (4.5%) and for the minor (48%) HCS signals (at 10.12 and 10.15 ppm, respectively) are also indicated.

1-Z (2.4 D). As a consequence, the population of the latter rotamer is expected to decrease significantly in favor of the former one in apolar solvents. Indeed, in both CDCl₃ and CD₂Cl₂ solvents the spectrum of a unique rotamer was observed, which was identified as **1-E** (100% population) on the basis of the values of the appropriate H,H coupling constants across five bonds (⁵*J*). By analogy with the corresponding aldehydes,¹⁵ the ⁵*J* coupling constants between H-4, HCS and H-5, HCS in five-membered rings are stereospecific, having finite value only when the so-called zig-zag patterns are available to the appropriate bonds. Thus, in DMSO the major rotamer **1-E** exhibits a H-4, HCS coupling constant value of 0.75 Hz, whereas that between H-5, HCS is 0 Hz. The opposite occurs in **1-Z** where the corresponding values

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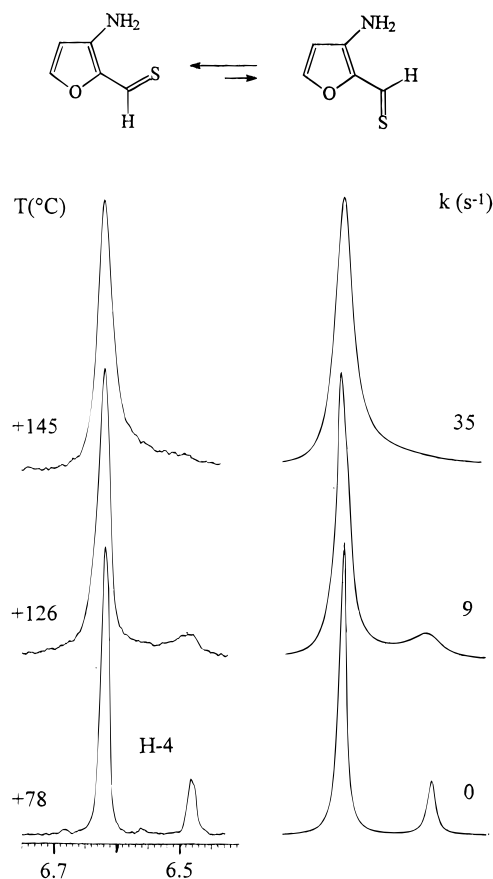


Figure 2. Left: temperature dependence of the experimental NMR signals (300 MHz in DMSO) of H-4 in the *E* (78%) and *Z* (22%) rotamers of **1**. Right: line-shape computer simulation obtained using the rate constants (*k* in s⁻¹) indicated.

are, respectively, 0 and 0.95 Hz. In the single rotamer detected in CD₂Cl₂ or CDCl₃ the HCS signal appears to be coupled solely with H-4 (⁵*J* = 0.8 Hz), thus establishing that its structure is **1-E**. Incidentally, this feature lends further support to the structural assignments achieved by NOE experiments and ¹³C shifts of the thioaldehyde carbons.

On raising the temperature of a DMSO solution of **1** the signals of the **1-E** and **1-Z** rotamers broaden, eventually yielding an averaged spectrum above 145 °C. Line-shape simulations of the ¹H signals of H-4 (Figure 2) provide the rate constants for the exchange of the more into the less stable rotamer at various temperatures. Since the corresponding free energies of activation (ΔG^\ddagger) were found to be independent of temperature within the errors (± 0.2 kcal mol⁻¹), the averaged value (22.2 kcal mol⁻¹) was taken as a reliable measure of the interconversion barrier (Table 1). Such a relatively large value suggests a substantial double-bond character of the Ar–CHS bond due to mesomeric conjugation.

Restricted rotation about the Ar–NH₂ bond was also detected by NMR spectroscopy. Indeed, in CD₂Cl₂ the NH₂ signal of rotamer **1-E** is split, below –20 °C, into a pair of widely separated lines (9.0 and 5.6 ppm) with a relative 1:1 intensity.

Line-shape simulation afforded a ΔG^\ddagger value of 11.4 kcal mol⁻¹ for the C–N rotation in **1-E** (Table 1). Since, as mentioned above, only the **1-E** rotamer is populated in the apolar CD₂Cl₂ solvent, which allows sufficiently low temperatures for observing the C–N rotational process, the corresponding C–N rotational barrier of rotamer **1-Z**

Table 1. *E,Z* Rotamer Ratio (at Room Temperature) and Free Energies of Activation (ΔG^\ddagger) for C–C and C–N Rotation of **1**, **2**, **5**, and **6**

compd	<i>E/Z</i> ratio ^a	ΔG^\ddagger (C–C) ^a (kcal mol ⁻¹)	ΔG^\ddagger (C–N) ^c (kcal mol ⁻¹)
1	78:22	22.2	11.4, ^d 11.9 ^d 9.0 ^e
2	72:28	17.9	11.2
5	57:43	16.2	8.4
6	85:15 ^b	13.7 ^f	9.7

^a In DMSO. ^b In CD₃CN, at –20 °C. ^c Barrier referred to the *E*-rotamers in CD₂Cl₂. ^d See text for the two different conditions. ^e Barrier for the 1-*Z* rotamer (see text). ^f In CD₆CN.

could not be measured under these circumstances. To overcome this difficulty we performed the following alternative experiment.

A drop of an almost saturated solution of **1** in DMSO, where both rotamers are present, was introduced into an NMR tube containing CD₂Cl₂, cooled at –80 °C, and then the sample was quickly transferred into the spectrometer probe kept at –90 °C. This procedure prevented the equilibration of the two rotamers, as they have half-lives of many centuries at such a low temperature. Under these conditions, we were thus able to observe a pair of equally intense NH₂ lines for both the 1-*Z* and 1-*E* rotamers. These lines broadened (Figure 3) and coalesced at about –72 °C and about –5 °C, respectively, so that line-shape simulations allowed the ΔG^\ddagger values for both C–N rotations to be determined. The value for 1-*E* (11.9 kcal mol⁻¹) was very close, as conceivable, to that previously determined in CD₂Cl₂ alone, whereas that for 1-*Z* (9.0 kcal mol⁻¹) turned out to be significantly lower (Table 1).

This experiment also provided evidence of an intramolecular hydrogen bonding in rotamer 1-*E*. The presence of even a minute amount of DMSO in the CD₂Cl₂ solution greatly reduces the separation of the two NH peaks of 1-*E*. This is because one of two such peaks has been remarkably deshielded (from 5.6 to 8.45 ppm at –93 °C), whereas the other NH peak (9.0 ppm) remains virtually unaffected. The latter peak corresponds to one of the two NH₂ hydrogens that is involved in the intramolecular hydrogen bond with the thiocarbonyl sulfur. Addition of DMSO evidently fails to break such a relatively strong interaction, so that the corresponding NH shift remains unchanged. On the other hand, the chemical shift of the second NH hydrogen, which is available for an *intermolecular* hydrogen bond with DMSO, is strongly deshielded, eventually reaching a value similar to that of the intramolecularly bonded NH hydrogen.

Similar investigations were carried out for thioaldehyde **2** and for aldehydes **5** and **6**, although in these cases the C–N rotational barriers were only determined for the major rotamers *E*. Ratios of the *E*, *Z* rotamers (whose structures were assigned on the basis of NOE experiments, ¹³C chemical shifts, and ⁵J values, as previously discussed) as well as C–C and C–N rotational barriers for compounds **2**, **5**, **6** are collected in Table 1.

The ΔG^\ddagger values measured for the C–C rotation in the furan derivatives **1** and **5** are significantly greater than those of the corresponding thiophene derivatives **2** and **6**. This reflects a greater ability of the furan than the thiophene moiety to release electron density to the thioformyl or formyl substituent. An analogous trend had been observed for the unsubstituted 2-furyl and 2-thienyl carbaldehydes, although in these cases the

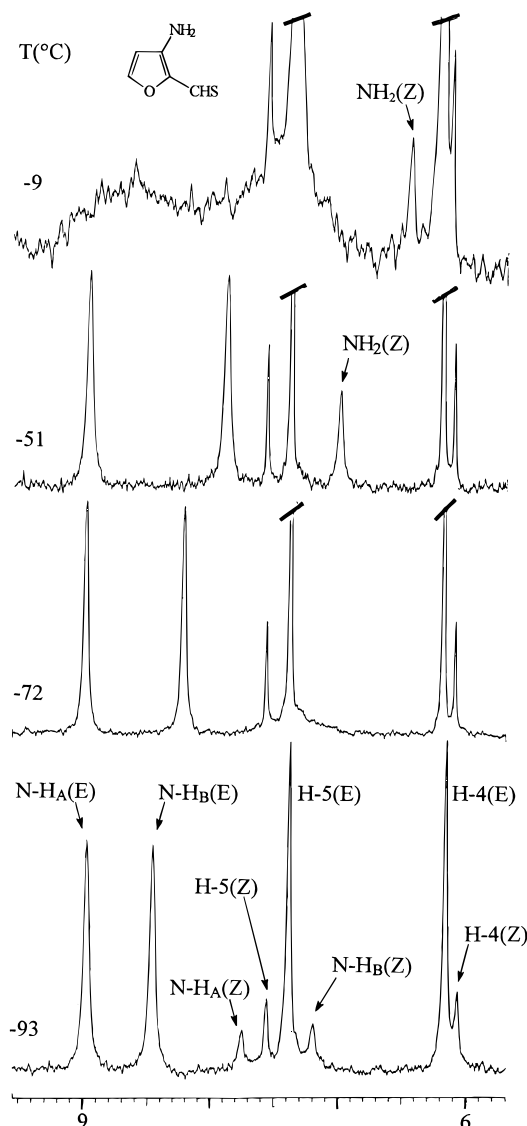


Figure 3. Temperature dependence of the 6–9 ppm region (the HCS signals are not reported) of the proton spectrum (300 MHz) of **1** obtained under conditions of nonequilibrium, as described in the text. The two NH₂ lines (at –93 °C) of the minor (1-*Z*) rotamer coalesce at about –72 °C, yielding a single sharp line at about –50 °C. On the contrary, the two NH₂ lines of the major (1-*E*) rotamer only begin to broaden above this temperature (see, for instance, the spectrum at –9 °C), indicating different barriers for the ArNH₂ rotation in the two rotamers (see text).

corresponding ΔG^\ddagger values are much more similar, being 10.9 and 10.15 kcal mol⁻¹, respectively.¹⁶ Furthermore, the ΔG^\ddagger (C–C) values are larger for thioaldehydes **1** and **2** than for the aldehyde analogs **5** and **6**. This suggests greater electron donation by the heteroaryl ring to the thioformyl than to the formyl function. This trend parallels that observed for thioamides with respect to amides,^{17a} which has been recently explained on the basis of *ab initio* MO calculations.^{17b} Contrary to the ΔG^\ddagger (C–C) values, the corresponding ΔG^\ddagger (C–N) values were

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Table 2. Percentage of the *E*, *Z* Rotamers (at Room Temperature) and Free Energies of Activation (ΔG^\ddagger) for C–C and C–N Rotation of **3 and **4****

compd	<i>E</i> (%)	<i>Z</i> (%)	ΔG^\ddagger (C–C) (kcal mol ⁻¹)	ΔG^\ddagger (C–N) (kcal mol ⁻¹)
3	72 (S,NH ₂ -syn) ^a	28 (S,NH ₂ -anti) ^a	20.7 ^a	11.4 ^c
4	55 (S,NH ₂ -anti) ^a	45 (S,NH ₂ -syn) ^a	18.1 ^a	13.0 ^d
4	17 (S,NH ₂ -anti) ^b	83 (S,NH ₂ -syn) ^b		14.2 ^e 11.1 ^f

^a In DMSO. ^b In CD₃CN/DMSO (10:1, v:v). ^c Barrier referred to the **3**-*E* rotamer in CD₂Cl₂. ^d Barrier referred to the **4**-*Z* rotamer in CD₂Cl₂. ^e Barrier referred to the **4**-*Z* rotamer in CD₃CN/DMSO (10:1, v:v). ^f Barrier referred to the **4**-*E* rotamer in CD₃CN/DMSO (10:1, v:v).

found to remain virtually constant, or even increase, on going from **1**-*E* to **2**-*E* and **5**-*E* to **6**-*E*. This trend suggests that delocalisation of the amino nitrogen lone pair occurs to a comparatively larger extent with thiophene than with furan derivatives as a result of the competing delocalisation of the adjacent C=S or C=O group with the same heteroaromatic rings.

The *E*, *Z* assignment for the two rotamers of **3** and **4** in DMSO was attributed (Table 2) on the basis of the ¹³C shifts of their thiocarbonyl carbons. In the case of **4** this was further supported by the large NOE effect (25%) experienced by the HCS signal of the minor (population = 45%) rotamer upon irradiation of the corresponding minor H-5 signal (thus, S,NH₂-syn, hence, **4**-*Z*) as well as by the large NOE effect (35%) experienced by the HCS line of the major (population = 55%) rotamer upon irradiation of the corresponding major NH₂ signal (thus, S,NH₂-anti, hence, **4**-*E*).

The *E*,*Z* rotamer ratios and Ar–CHS rotational barriers, ΔG^\ddagger (C–C), for aminothioaldehydes **3** and **4** as well as the Ar–NH₂ rotational barriers, ΔG^\ddagger (C–N), are collected in Table 2. Only in the case of **4** it was possible to measure the ΔG^\ddagger (C–N) value for both *E* and *Z* rotamers, by making use of a 10:1 CD₃CN:DMSO mixture, in which appreciable populations of both species were observed at sufficiently low temperature (–40 °C).¹⁸ As additionally shown in Table 2, a substantial increase in the proportion of **4**-*Z* at the expense of **4**-*E* was encountered on passing from DMSO to CD₃CN:DMSO. Evidently, acetonitrile, similar to dichloromethane, favors, with respect to DMSO, that species that has the lower dipole moment. Actually, **4**-*Z* is predicted to have a dipole moment lower than **4**-*E* by molecular mechanics calculations,¹⁴ the respective values being 1.0 and 1.3 D.

Comparison of the ΔG^\ddagger (C–C) and ΔG^\ddagger (C–N) values of the amino thioaldehyde **3** with those of its positional

isomer **4** suggests that, with respect to 3-thioformyl, the 2-thioformyl moiety can be mesomerically stabilized by the benzo[*b*]furan ring to a greater extent and, instead, to a lesser extent by the adjacent amino function. This finding reflects the known preference of benzo[*b*]furan to donate electron density to the 2- over the 3- position.¹⁹ Moreover, the ΔG^\ddagger (C–C) data for the above compounds **3** and **4**, as compared with those of the furan analog **1**, clearly indicate a more efficient stabilization of thioformyl by furan relative to benzo[*b*]furan.¹⁹ This observation is consistent with the known fact that benzo[*b*]furan lowers the electron-releasing power of the furan ring.

In the case of the aminothioaldehyde **4**, the S,NH₂-syn rotamer **4**-*Z* was found to exhibit a C–N rotational barrier significantly higher than that of the *anti* analog **4**-*E* (Table 2). Similar evidence was also encountered with the two rotamers of the amino thioaldehyde **1** (*vide supra*). It is conceivable that the *syn* rotamer can display a higher energy rotation about the C–N bond as a result of the feasible intramolecular C=S⋯HN bonding. The *quasi* planar C–N rotational ground state can therefore be stabilized, whereas the perpendicular rotational transition state remains unaffected. Consequently, the *syn* rotamers exhibit an energy difference between the two states larger than the *anti* rotamers.

Experimental Section

Thioaldehydes **1–4** have been prepared according to the literature.¹² Aldehydes **5** and **6**, as well as the azido intermediates for **1–4**, were obtained as previously described.²⁰ The variable-temperature NMR spectra were recorded at 300 MHz (¹H) and 75.5 MHz (¹³C). The simulation of the line shape was performed by a computer program based on the Bloch equations, and the best fit was visually judged by superimposing the plotted and experimental traces. The difference NOE measurements were carried out in solutions, purged of dissolved oxygen using a nitrogen stream, by presaturating the signal for about 10 s and acquiring the spectrum with the decoupler turned off. The various lines of the multiplets were saturated by cycling the irradiation frequencies about 40 times. A program that accumulates the difference between the two FID's (that being irradiated and that acquired with the irradiation frequency kept away from any signal) was employed. The control spectrum was subsequently acquired with half the number of scans.

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(18) At the same temperature in neat CD₃CN only the **4**-*Z* rotamer is populated.