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ROTATION ABOUT THE C–N BOND IN THIOAMIDES: INFLUENCE OF SUBSTITUENTS ON THE POTENTIAL FUNCTION

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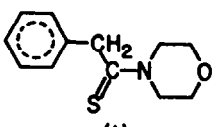
Abstract—Barriers to rotation about the C–N bond in several unusual thioamides have been studied with 100 MHz ^{1}H-NMR spectroscopy. This rotation is still frozen at 170°C in *p*-chlorophenylglyoxylthiomorpholide (**2**) in DMSO-d_6. NMR spectra and the IR carbonyl frequencies show that **2b** and **2c** are the most important resonance forms, the latter making a significant contribution to the bonding in the transition state. The high rotational barrier is related to preferential stabilization of the ground state by the opposed orientation of two parallel dipoles (**2b**). In the sterically crowded molecules 4-(2′-hydroxythiobenzoyl)morpholine (**3**) and 1-(2′-hydroxythiobenzoyl)piperidine (**4**) rapid ring inversion between two chair forms of slightly different energy superimposed on the much slower rotation about the C–N bond implies that only a mean value for the rotational barrier height can be obtained experimentally.

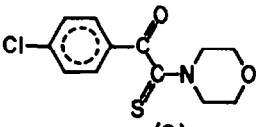
The high barrier to the rotation of the amino group in amides and thioamides is ascribed to conjugation between the N lone pair electrons and the CO (or CS) group, which stabilizes the ground state but is absent in the transition state for rotation.[1] Substituents with a double bond in conjugation with the CO (or CS) group lower the rotational barrier,[2] since such substituents interact more strongly with the CO (or CS) group in the transition state than in the ground state where a competing cross-conjugation with the amino group is operative.[3]

In this paper two experimental results are discussed which show that the influence of substituents on C–N rotation in thioamides can be more complex, and that sometimes only an average of two (or perhaps more) different torsional energy barriers can be determined experimentally. Both the electronegativity of the substituent with a double bond in conjugation with a CS group and the conformation of the substituent group can influence the potential function governing rotation about the C–N bond.

The introduction of a substituent with a double bond in conjugation with the CO group in a thioamide does not always lower the C–N rotational energy barrier, as has been considered to date,[1,3] but it can sometimes *raise* it as found in compound **2** relative to **1**.



(1)



(2)

The differences in the chemical shifts between the signals of the *cis* NCH_2 protons and those of the *trans* NCH_2 protons in $CDCl_3$ solution, at ambient temperature, when the rotation about the C–N bond is frozen on the 100 MHz NMR scale in both compounds, are nearly identical:

$$\tau_{trans} - \tau_{cis} = (6{\cdot}4 - 5{\cdot}7)\ \text{ppm} = 0{\cdot}7\ \text{ppm} \quad (1)$$

$$\tau_{trans} - \tau_{cis} \approx (6{\cdot}5 - 5{\cdot}8)\ \text{ppm} \approx 0{\cdot}7\ \text{ppm}.\ddagger \quad (2)$$

On the other hand, the coalescence temperature for **1** is $T_c \approx 120$°C but for **2** (where the CS group is conjugated with an adjacent CO group) the NCH_2 proton peaks are still sharp at 170°C in dimethylsulphoxide-d_6 solution (Fig. 1).§ Furthermore, the peaks of the OCH_2 protons in **2** are *not coalesced* but sharp at 170°C, when these peaks should coalesce first as the temperature is raised because of the smaller chemical shift difference (0·22 ppm). Space-filling molecular models show that in the ground state **2** is more sterically hindered than **1**, whereas in the transition state for C–N rotation both experience about the same steric hindrance. From the point of view of steric hindrance alone **1** should thus have the higher rotational barrier.

The resonance structures for the thioamide groups in **1** and **2** are shown in Fig. 2. Since **1** is white and **2** has a yellow colour, the resonance form **2c** must contribute extensively to the real molecular structure of **2**.

The CO stretching frequencies in some selected phenylglyoxylthiomorpholides are given in Table 1, in comparison with corresponding values in acetophenones having the same *p*-substituent. These figures show that:

(1) The CO group in the phenylglyoxylthiomorpholides is insensitive to the electronic effect of the substituent on the benzoyl ring, supporting the view that one of the resonance forms like **2c** must contribute extensively to the real molecular structure of **2**.[‖]

†Isaac Walton Killam Scholar; on leave of absence from the University of Bucharest.

‡Because of the complicated signal patterns, $\Delta\tau$ for **2** was not determined precisely.

§The same results are obtained for the parent molecule (unsubstituted aromatic ring) and the *p*-Me derivative. The *p*-chloro compound is used in this discussion since the inductive effect of that substituent is expected to lower the coefficient of resonance form **2b** in the wave function of **2**, as described by valence bond theory.

‖Resonance form **2e** cannot make a significant contribution to the real molecular structure of **2** because of the higher electronegativity of oxygen relative to sulfur. One of the referees has pointed out that the frequency differences in Table 1 could arise from the inductive effect of the aromatic ring substituent, but for the three substituents considered the overall change in $\nu_{C=O}$ is 9 cm^{-1} for the acetophenones (combined inductive and resonance effect, *cf* P. J. Krueger and H. W. Thompson, *Proc. Roy. Soc.* **A**, **250**, 22 (1959) but only 3 cm^{-1} (i.e. constant) for the phenylglyoxylthiomorpholides.

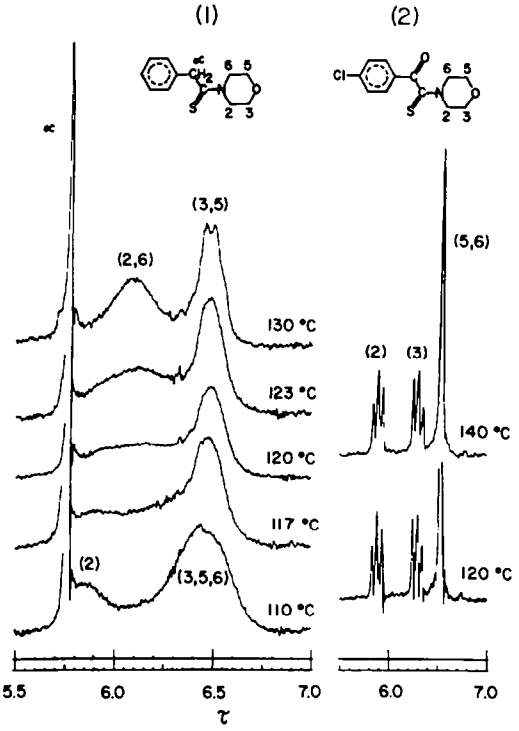
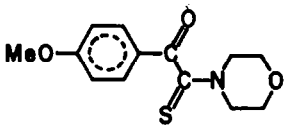
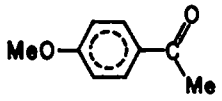
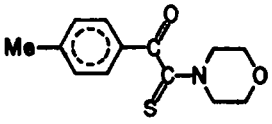
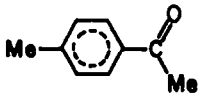
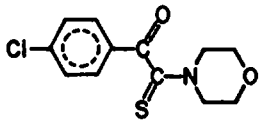
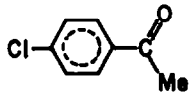


Fig. 1. ^{1}H-NMR spectra (100 MHz) of **1** and **2** in DMSO-d_6. Internal TMS reference. Peak assignments given.

(2) $\nu_{C=O}$ in the phenylgloxylthiomorpholides are 30–40 cm^{-1} lower than in the corresponding acetophenones, indicating a reduced double bond order and suggesting a larger contribution from resonance forms **2b** and **2c**.[1] The opposed orientation of dipoles in **2b** should stabilize that electronic arrangement.

Table 1. Carbonyl stretching frequencies in some selected phenylglyoxylthiomorpholides and related acetophenones (in cm^{-1})

Compound	Infrared (KBr pellet)	Raman (solid)
	1652	1652
	1683[s],[d]	
	1653	1654
	1687[s],[d]	
	1655	1660
	1692[s],[d]	

[d] In dilute CCl_4 solution.

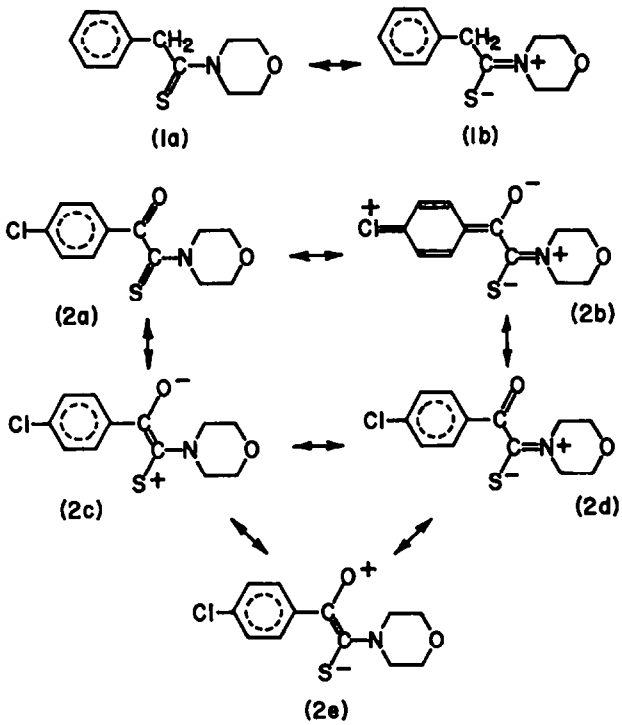
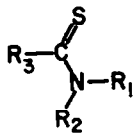


Fig. 2. Thioamide group resonance structures for **1** and **2**, with the latter in an *s-trans* conformation, as suggested by space-filling models.

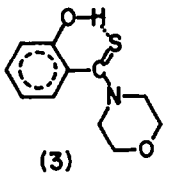
While **2b** and **2d** would both contribute to the observed high rotational barrier, the latter is not consistent with the lower $\nu_{C=O}$ value in **2**. Therefore **2b** and **2c** are the most significant resonance forms for **2**; as **2c** must be very important in the transition state for rotation about the C–N bond, the ground state is discussed further in terms of structure **2b**.

It is known that the rotational barrier height for thioamides can be lowered by preferential stabilization of the transition state[1]; here we present an example of a case (**2**) where the rotational barrier height is raised relative to that in **1** because of preferential stabilization of the ground state. The lone pair electrons on N in the morpholine ring in **2** thus are more sensitive to the electron-withdrawing effect of substituents on the thioamide group than are the π-electrons of the C=S bond, which is surprising in view of the known high polarizability of the S atom.

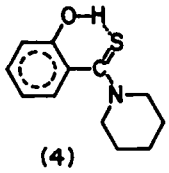
The influence of substituent groups (R_1, R_2) with conjugated double bonds on the C–N torsional barrier in compounds like



has already been studied.[1] We explore here further the situation where the N atom is in a 6-membered heterocyclic ring and the rapidly interconverting chair conformations have different energies due to different interactions with R_3. In compounds **3** and **4** we have found that the morpholine and piperidine rings, respectively, exist in two rapidly interchanging chair conformations, both with very strong intramolecular OH···S hydrogen



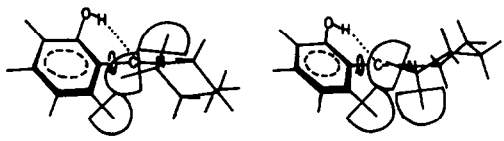
(3)



(4)

bonds, and with the bulky N-thiobenzoyl group (with an effectively planar N atom) remaining in an orientation in which it nearly eclipses the equatorial H atoms of the methylene groups adjacent to N in the piperidine ring,[6] as shown in Fig. 3 for **4**. For **3** the conformational free energy difference is $\Delta G^\circ \approx 200$ cals/mole,[6] while for **4** it is only 70 cals/mole,[6] both obtained from NMR data in $CDCl_3$ at −30°C. The principal difference in the two chair

Hydrogen bond to thiocarbonyl S atom which is located directly behind thioamide C atom



	(4a)	(4b)
Twist angle*	~60°	~50°
$d_{OH\cdots S}$	3.05 Å	3.00 Å
$\angle OH\cdots S$	~147°	~147°

Fig. 3. The two energetically different conformations of **4** (related by piperidine ring inversion) based on a photograph of Dreiding models. The view is in the plane of the thioamide group with the thiocarbonyl S atom (not shown) directed away from the observer. The van der Waals radii of the critical protons are shown.

conformations, as seen in Fig. 3, is that the twist angle of the phenyl ring with respect to the thioamide plane is different, and that the *trans* NCH_2 protons in the piperidine ring interact in a different way with the 6′ proton of the phenyl ring.[6] Steric interference between the phenolic O and thiocarbonyl S atoms also forces the phenyl ring out of planarity, the measured O···S distances on Dreiding models which form the basis for Fig. 3 being 3·00–3·05 Å in the two conformers,* in good agreement with the sum of the van der Waals radii ($r_O + r_S$ = 1·40 + 1·85 = 3·25 Å).[8] Shrinkage on hydrogen bond formation is well known.[8]

NMR spectra show that rotation about the C–N bond is slow below −20°C for both **3** and **4** on the 220 MHz scale. The chemical shift difference between axial and equatorial *cis* NCH_2 protons is 2·49 ppm in N-thiobenzoylpiperidine,[9] and a similar value in the morpholine analog is likely, while the difference between the average *cis* and *trans* NCH_2 chemical shifts is less than 1 ppm in both **3** and **4**. Thus many ring inversions will take place in these compounds during the time necessary for rotation about the C–N bond from one rotational energy minimum to the next. The barrier to rotation about the C–N bond in **3** and **4** is likely to be of the order of 15 kcal/mole,[10] while the barrier to ring inversion should be less than 11 kcal/mole.[11] In the ground state the energy difference between **4a** and **4b** and the corresponding morpholine analogs is due mainly to the difference in the van der Waals interactions emphasized in Fig. 3, to the difference in conjugation between the phenyl ring and the thioamide group as the twist angle changes, and perhaps to slight differences in OH···S hydrogen bond strength.[6] Molecular models show that in the transition state all three factors would be the same for both conformers. These concepts are shown schematically in Fig. 4.† For an assemblage of a large number of molecules, unequal populations are ascribed to the two interconverting chair conformations at all rotational angles about the C–N bond (θ) other than $\theta = 90°$, the transition state for conversion of one form into the other by rotation about the C–N bond. The difference in population of the two conformers remains a function of θ.

In the case of compounds like **3** and **4** only a mean $\overline{\Delta G^\ddagger}$ can be obtained experimentally, i.e. $\overline{\Delta G^\ddagger} = p\Delta G_1^\ddagger + (1-p)\Delta G_2^\ddagger$ where p is the fractional population of the less stable ground state conformation, $K = p/(1-p)$, and $\Delta G_0 = -RT(\ln K)$. Therefore $\Delta G^\ddagger_{exp't} = \overline{\Delta G^\ddagger} = f(\Delta G_0)$ where ΔG_0 is the energy difference between the two conformers in the ground state.

*While **4a** and **4b** appear to differ only in non-bonded interactions, in order to accommodate these the twist angle between the phenyl ring and the thioamide group is different, implying a difference in conjugation in the two conformers. Heterocyclic ring distortions and intramolecular OH···S bond energies are also likely to differ in **4a** and **4b**, so that the sum of non-bonded interactions, conjugation energy, intramolecular OH···S bond energy and ring strain for each conformer determines ΔG_0 between them. Similar arguments hold for **3a** and **3b**.

†Ideally a potential energy surface should be envisaged, with the inversion co-ordinate perpendicular to the plane of Fig. 4, the inversion barriers then being displayed in cross-sections parallel to the inversion co-ordinate and the energy axis. Rapid chair–chair inversion and slow rotation about the C–N bond would then correspond to appropriate movement on this surface.

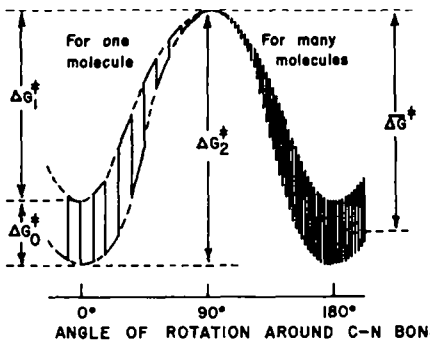


Fig. 4. Schematic view of potential energy profile for rotation about the C–N bond in **3** and **4**, with more rapid ring interconversion between two chair conformations of unequal energy in the ground state but equal energy in the transition state. For clarity ΔG_o is grossly exaggerated relative to $\Delta G_2^{\ddagger}$.

It remains to be seen how this type of potential energy function affects the torsional vibration about the C–N bond in the far infrared region.

EXPERIMENTAL

100 MHz ^{1}H-NMR spectra were obtained with a Varian HA-100 spectrometer equipped with a variable temp probe.

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