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CONFORMATIONAL STUDIES BY DYNAMIC NMR—VI[1]

TORSIONAL BARRIERS IN 5-MEMBERED HETEROAROMATIC CARBAMIDES AND THIOCARBAMIDES

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Abstract—Thermodynamic parameters involved in the rotation of the partial C-N double bond in a series of 5-membered heteroaromatic *N,N*-dimethyl-carbamides and -thiocarbamides have been measured by total line shape (TLS) analysis of their NMR. Lanthanide induced shift (LIS) has been applied in two cases to determine the conformation of the CO moiety with respect to the heteroatom. The energy barriers of thiazolyl carbamides and thiocarbamides were found to be larger than those of furyl and thienyl analogues, and explained in terms of a perturbational molecular orbital analysis.

The possibility of measuring by means of NMR spectroscopy the torsional barrier of the C-N bond in carbamides, has been reported.[2,3] Improvements in experimental measurements and in theoretical methods led recently to more accurate measurements of the thermodynamic parameters involved in this dynamical motion.[4-7] It has been also recognized that the free activation energy depends upon the steric and electronic properties of the substituents.[8,9] On the other hand, the effect of solvents seems less important in modifying these torsional barriers, unless solvents with very different polarity (e.g. CCl_4 or iso-octane compared with water or formamide[10a]) are considered. Only few data concerning 5-membered aromatic carbamides are available,[11] none of them having been obtained by the total line shape (TLS) method.

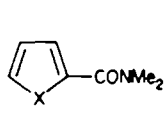
The aim of the present investigation is the determination of the free activation energies to rotation of the $CO-NMe_2$ moiety bonded to a variety of 5-membered heteroaromatics; these values can be used as a tool for assessing the conjugation capabilities of the various rings involved. A perturbational molecular orbital (PMO) approach will be finally employed to rationalize the observed values.

RESULTS

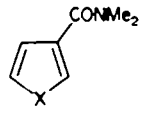
Rotation about the CO–NMe₂ bond

The molecules studied in the present work are listed below (**1–8**).

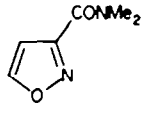
In four cases the corresponding thiocarbamides (**9–12**) have been also studied in order to check whether the conclusions regarding the properties of the 5-membered rings are affected by the type of the substituent.



1: X = O
2: X = S



3: X = O
4: X = S



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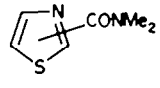
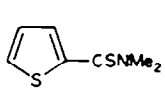


6: 2-(*N*, *N*-dimethylcarbamide)
7: 4-(*N*, *N*-dimethylcarbamide)
8: 5-(*N*, *N*-dimethylcarbamide)



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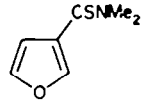

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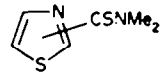
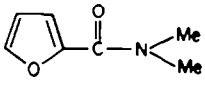
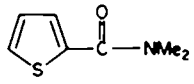
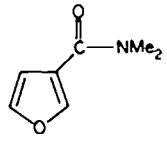
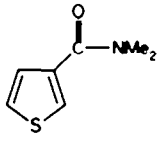
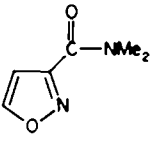
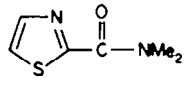
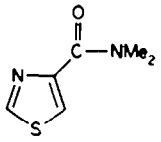
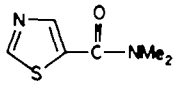


11: 4-(*N*, *N*-dimethylthiocarbamide)
12: 2-(*N*, *N*-dimethylthiocarbamide)

A brief description of the method employed can be introduced using **1**. Its 60 MHz spectrum at −45° in CS_2 displays two methyl lines separated by 19.2 Hz with a half height width ($\Delta\omega$) of 1.1 Hz. We checked that no "exchange broadening" is present at this temperature so that $\Delta\omega$ is essentially determined by unresolved methyl–methyl splittings and by the nuclear quadrupolar effects of nitrogen. The effect of the viscosity on the line width was also checked: it was found however that an increase or a decrease of the temperature by few degrees does not sharpen or broaden significantly the line width, as long as the not exchanging region is considered. In this particular case (i.e. derivative **1**) no temperature dependence of the shift difference between the methyls ($\Delta\nu$) was observed; in some other derivatives, however, $\Delta\nu$ slightly varied with temperature. In these cases the $\Delta\nu$'s were measured as function of the temperature in the region where either there was no exchange or the exchange was slow enough to not affect further the line position: the values were then extrapolated in the faster exchanging region. The spectra of **1** were simulated by a TLS procedure[12] at eight different temperatures in the interval −25°, +2° where the lifetime of topomers varies between 0.33 and 0.0218 seconds respectively. The Eyring and Arrhenius treatment of the first order rate constants gave the thermodynamic parameters of Table 1.

The $\Delta S^{\neq}$ value of **1** as well as those of the other carbamides and thiocarbamides investigated are negligible, in that are smaller or only slightly larger than the corresponding root mean square (RMS) deviations. Even in the latter event, however, it is well documented[12-14] that the real uncertainty on $\Delta S^{\neq}$ is far larger than the RMS deviation, since the latter does not include uncertainties on T_2 and on the temperature. $\Delta S^{\neq}$ being negligible, the

Table 1. Thermodynamic parameters, coalescence temperature (°C) and differences of chemical shifts of methyl signals ($\Delta\nu$) at 60 MHz for the torsional barrier of carbamides **1–8**

Product	Solvent	$\Delta G^{\neq}$*	$\Delta H^{\neq}$*	E_a*	$\Delta S^{\neq}$†	Coalescence temperature (°C)	$\Delta\nu$(Hz)
1 	CS_2*	13.89 ± 0.04	12.9 ± 0.5	13.46 ± 0.5	−3.77 ± 2.0	0	19.2
	($CDCl_3$)	14.66				+9.5	12.0)
2 	CS_2	12.83 ± 0.04	12.07 ± 0.9	12.6 ± 0.9	−3.06 ± 3.8	−23	16.4
	($CDCl_3$)	13.80				−9	9.4)
3 	CS_2*	14.22 ± 0.05	14.5 ± 0.9	15.0 ± 0.9	1.21 ± 3.58	−1	10.0
4 	CS_2	13.64 ± 0.02	12.7 ± 0.5	13.2 ± 0.5	−3.61 ± 1.9	−13	9.7
5 	C_2Cl_4	18.02 ± 0.05	16.2 ± 0.3	16.9 ± 0.34	−5.29 ± 1.0	+76	16.7
6 	C_2Cl_4	17.14 ± 0.02	16.9 ± 0.3	17.5 ± 0.3	−0.74 ± 0.9	+66.5	30.9
7 	CS_2	16.00 ± 0.02	15.6 ± 0.25	16.3 ± 0.25	−1.1 ± 0.8	+36.5	12.9
	(C_2Cl_4*)	16.05				+37	13.7)
8 	CS_2*	14.26 ± 0.03	13.4 ± 0.4	13.9 ± 0.45	−3.0 ± 1.7	+0.5	11.4

*A few percent of $CDCl_3$ was added to improve the solubility. †kcal mol^{-1}. ‡cal mol^{-1} degree^{-1}.

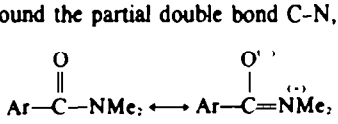
more accurately determinable $\Delta G^{\neq}$ values[14] were used as a measure of the torsional barrier. It can be also observed that the approximation[2,9] of measuring $\Delta G^{\neq}$ at the coalescence point seems justified for **1** as well as for all the other derivatives.

Before proceeding further in the discussion is worth comparing the results of **1** and **2** with those reported in Ref. 11, where the $\Delta G^{\neq}$'s were determined at the coalescence point by taking advantage of the lanthanide induced shift (LIS) effect. Since $CDCl_3$ was used,[11] our measurements were repeated in this solvent where values of 14.6 kcal mol^{-1} for **1** and 13.8 for **2** were obtained for $\Delta G^{\neq}$. Whereas the latter value is in reasonable agreement with that of Ref. 11 (14.1 kcal mol^{-1}) the former differs by more than 2 kcal mol^{-1} (16.8 in Ref. 11). A possible explanation of this discrepancy is the difficulty of measuring the real $\Delta\nu$ at the coalescence temperature when lanthanide complexes are involved: accordingly we feel that the value quoted in Ref. 11 does not represent the real rotational barrier for **1**.

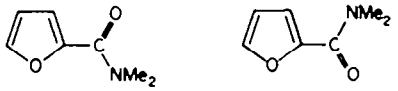
The free activation energies of **1** and **2** in $CDCl_3$ also indicate that solvents may affect the rotational barrier (e.g. the difference with respect to CS_2 is 0.9 kcal mol^{-1}). For technical reasons we had to use two solvents; one for the low temperature studies (CS_2) and one for those at high temperature (C_2Cl_4). Since, as opposite to $CDCl_3$, CS_2 and C_2Cl_4 are both non polar and aprotic, it is reasonable to expect that the activation energies in CS_2 (i.e. those of **1–4** and **7–9**) are comparable with those measured in C_2Cl_4 (i.e. those of **5**, **6**, **10**, **11**, **12**). In order to check this assumption, two compounds were selected (the carbamide **7** and the thiocarbamide **10**) whose dynamic exchange was detectable in a temperature range accessible to both CS_2 and C_2Cl_4. As shown in Tables 1 and 2 the $\Delta G^{\neq}$'s were found equal in both solvents. We may thus conclude that our data can be safely compared each other and also that solvents as $CDCl_3$ (i.e. protic and polar) may affect the determination of the torsional barriers in carbamides.

Rotation about the Ar–CO bond

In the molecules under investigation the motion detectable through the broadening of the line width is the rotation around the partial double bond C–N, i.e.



In principle, however, one could also detect another restricted rotation, that about the Ar–CO bond. In the case of **1**, for instance, this would generate the two rotamers *O,O*-cis and *O,O*-trans.



O, O – trans *O, O – cis*

Torsional isomers of this type have been detected in furan-2-carbaldehyde[15] and furan-2-acetyl,[16] whereas in thiophen-2-carbaldehyde[17] only one of the two possible rotamers has been actually found. Although some of the molecules of the present study were investigated at temperatures as low as −150°C (both at 60 and 100 MHz) no evidence was found of such rotational isomers.

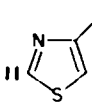
This can be due either to the existence of only one of the two possible rotamers, or to a free activation energy smaller than 5 ~ 6 kcal mol^{-1}; obviously both these situations can occur at the same time.

At least in the case of **1** and **2**, experiments with lanthanide shift reagents indicate that only the trans type conformer is present at the equilibrium.[11] In order to see whether the same conformational preferences also hold when the $CONMe_2$ group is in other ring positions or when more than one heteroatom is present in the 5-membered ring, studies with lanthanide complexes were repeated for derivatives **4** and **6**.

The method requires that the lanthanide induced shift (LIS) is determined as the slope of the straight line relating the shifts at various concentrations of the Ln complex vs the molar ratio of the latter with the molecule studied.[18] Assuming that the molecule of the Ln-complex is mainly attached to the carbonyl oxygen, the LIS values may be computed by fitting the relationship[18] (1):

$$\Delta\nu = K(3\cos^2\chi - 1)r^{-3}. \quad (1)$$

Table 2. Thermodynamic parameters, coalescence temperature (°C) and chemical shift differences ($\Delta\nu$) of methyl signals at 60 MHz for the torsional barrier of thiocarbamides **9–12**

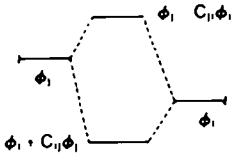
Product	Solvent	$\Delta G^{\neq}$[a]	$\Delta H^{\neq}$[a]	E_a[a]	$\Delta S^{\neq}$[b]	Coalescence temperature (°C)	$\Delta\nu$(Hz)
9 	CS_2[c]	14.14 ± 0.05	13.4 ± 0.5	13.98 ± 0.5	−2.6 ± 2.0	−2	10.0
10 	C_2Cl_4	15.20 ± 0.05	14.9 ± 0.5	15.53 ± 0.5	−1.07 ± 1.0	+14.5	6.5
	CS_2[c]	15.5				+22	9
11 	C_2Cl_4	18.00 ± 0.02	16.9 ± 0.3	17.5 ± 0.3	−3.3 ± 1.0	+71.5	11.0
12 	C_2Cl_4	18.18 ± 0.02	18.0 ± 0.2	18.7 ± 0.2	−0.4 ± 0.7	+71.5	10.9

[a] A few percent of C_6H_6 was added to increase the chemical shift difference. [b] kcal mol^{-1}. [c] cal mol^{-1} degree^{-1}.

This equation can be expressed in terms of parameters R, φ, ω as explained in Refs. 19 and 20: furthermore the value of R (the distance CO...Ln) is known to be about 3 Å.[19,20] Accordingly four unknowns have to be determined (the angles φ and ω, the constant K of equation 1 and, of course, the conformer ratio).

If at least four experimental LIS data are available, the problem is determined; this is actually the case of **4** and **6** at room temperature. As a result of these calculations we found that these molecules mainly exist in a single conformation (see Table 3). For the thiophen-3-dimethylcarbamide **4** is 73% in the *S,O*-cis, and thiazole-2-dimethylcarbamide is 100% in the *S,O*-trans conformation (see Table 3). Therefore, at the very low temperatures ($\simeq -150$°C) where direct evidence for these rotamers has to be searched, the most stable rotamer would become (according to the Boltzmann distribution, with ΔG° constant) 95–100%. This fact, obviously, would prevent the direct identification of the less stable rotamer, even if the rotation was slow on the NMR time scale.

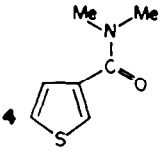
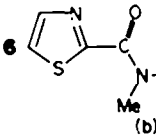
bonding and anti-bonding combination of the unperturbed orbitals) is produced:



Scheme 1.

When closed shell systems, like those under investigation, are studied, two important orbital interactions have to be taken into account: that between two filled orbitals and that between a filled and an unfilled orbital. Here we adopt a PMO approach with neglect of overlap and therefore we shall focus our attention just on the filled–unfilled two orbital two-electron interactions. It will be shown that even at this simple PMO level, it is possible

Table 3. Chemical shifts (ppm from TMS), experimental and computed lanthanide induced shifts (LIS) in ppm and structural data for thiophen-3- and thiazole-2-*N,N*-dimethylcarbamides. For the meaning of K, φ, ω see text and References 11

Product	Conformational preference		Shift from TMS	Experimental LIS	Calculated LIS	K	φ	ω
 **4**	= 73%	H2	7.51	5.75	5.72	741.5	35°	60°
		H4	7.20	5.66	5.64			
		H5	7.35	1.83	1.89			
		Me	3.06	5.66	5.69			
 **6**	= 100%	H4	7.77	2.52	2.50	1458	25°	70°
		H5	7.47	3.26	3.25			
		Me_a	2.98	8.45	8.43			
		Me_b	3.41	6.01	6.05			

DISCUSSION

The trend of $\Delta G^{\neq}$ values can be a valuable source of information for what concerns the properties of the heteroaromatic rings joined to the $CONMe_2$ (or $CSNMe_2$) group. Inspection of Tables 1 and 2 shows that the trend of $\Delta G^{\neq}$ is the same within the carbamide as well as within the thiocarbamide series.

Indeed, the ratio $\Delta G^{\neq}$ between a thiocarbamide and the corresponding carbamide is constant; the mean value of $\Delta G^{\neq}_{CS}/\Delta G^{\neq}_{CO}$, obtained dividing the free activation energies of **9**, **10**, **11**, **12** by those of **2**, **3**, **7**, **6** respectively, turns out to be 1.09 ± 0.03.

Therefore, within each class of compounds (either carbamides or thiocarbamides), the trend of $\Delta G^{\neq}$ is determined by the nature of the 5-membered ring.

In order to rationalize the observed variation of rotational barriers it is convenient to investigate the factors that control the rotational barriers in these systems. Since the rotational barrier can be taken as a measure of the energy difference between the ground and transition state of the torsional process, we shall investigate the key orbital interactions operating in both such states.

Perturbation theory[22] provides the framework for discussing these interactions. It is well known that, when two orbitals ϕ_i and ϕ_j, interact, a new pair of orbitals (the

to provide a rationalization of various observed trends. A two orbital two electron interaction of the type under investigation generates a net energy stabilisation (SE) as well as a net charge transfer (q) between the interacting orbitals, given by the following equations:

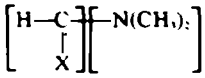
$$SE = 2\frac{H_{ij}^2}{\Delta E_{ij}} \simeq \frac{\sum 2C_{ri}^2 C_{sj}^2 (H_{ij}^{rs})^2}{\Delta E_{ij}} \simeq \frac{\sum 2K^2 C_{ri}^2 C_{sj}^2 (S_{ij}^{rs})^2}{\Delta E_{ij}} \qquad (2)$$

$$q = 2\frac{H_{ij}^2}{\Delta E_{ij}^2} \simeq \frac{\sum 2K^2 C_{ri}^2 C_{sj}^2 (S_{ij}^{rs})^2}{\Delta E_{ij}^2} \qquad (3)$$

where ΔE_{ij} (the energy factor) is the energy difference between the two interacting MO's, H_{ij} is their interaction matrix element, C_{ri} and C_{sj} are the coefficients of the rth and sth atomic orbitals belonging to the MO's ϕ_i and ϕ_j respectively, and H_{ij}^{rs} is the resonance integral between the two interacting atomic orbitals. Finally the usual approximation $H_{ij} = KS_{ij}$ has been used.

It seems convenient to discuss first the appropriate interactions in the simplest dimethylcarbamide (X = O), or thiocarbamide (X = S), i.e. $HC(X)\cdot NMe_2$. To this purpose we consider the molecule to be divided into two fragments A and B and then discuss the key orbital

interactions occurring in the course of the union of the two fragments.



A B

The orbitals of fragment A and B involved in the key interactions are those of π symmetry: they are shown in the figure (the relative energies are in agreement with SCF MO ab-initio computations). In the ground state, there is just one MO of fragment B (which is mainly a nitrogen lone pair) that can interact with the π system of the adjacent A fragment, while in the transition state the π orbitals of fragment A can interact with an empty and a doubly occupied MO of the fragment B.

In the ground state the energy stabilization arising from the two-orbital two electron interaction should be quite large both with X = O and S since in both cases the LUMO's of the A fragment are located at low energy. Correspondingly we can expect a significant charge transfer from B to A, a lengthening of the C–X bond and a significant double bond character in the C–N bond. Because of the large energy difference between the interacting orbitals in the transition state, the corresponding energy stabilization and related effects, in particular the double bond character in the C–N bond, should be much smaller.

Therefore, in such species, where the interactions in the ground state are largely dominant, the trend of the rotational barriers should follow the trend of the stabilization energy in the ground state. On this basis we can compare carbamide versus thiocarbamide. In the latter species, the LUMO is located at lower energy so that the corresponding ΔE_{II} term is significantly smaller than in carbamides. Therefore, since the H_{II} terms should not differ significantly in the two cases, the ground state stabilization energy, and therefore the rotational barrier should be larger in thiocarbamides, in agreement with experimental evidence.

Now, if we replace the hydrogen atom in the fragment A with substituents that can act as donors, i.e. substituents containing a highly lying HOMO, we must take into account additional HOMO–LUMO interactions. As a result the energy of the LUMO of fragment A (Ar–C(=X)) should increase and the subsequent interaction of this LUMO with the nitrogen lone pair (fragement B) should decrease. As a whole the rotational barrier is expected to be smaller than in the simpler unsubstituted Me_2NCOH, as it has been actually observed (compare the $\Delta G^{\ddagger}$ = 21.8 kcal mol^{-1} for Me_2NCHO in reference 10*b* with the data of Table 1). From the first ionisation potential of the various ring substituents we can locate their HOMO's and therefore estimate the trend of energy increase of the LUMO of fragment A. The first ionisation potentials for furan, thiophen, thiazole and isooxazole are, respectively 8.90,[21a] 8.90,[21b] 9.50[21c] and 10.15 eV.[21d]

It readily follows that, when the substituents are thienyl and furyl the rotational barriers about the C–N bond should be smaller with respect to those for thiazolyl and isooxazolyl derivatives. Also, the $\Delta G^{\ddagger}$ of isooxazolyl carbamides is predicted to be larger than for thiazolyl since the ionisation potential of isooxazole is the largest (10.15 eV).

On the other hand, when we compare the two substituents thiophene and furan, the denominator of eqns (2) and (3) is no longer the cause of the observed differences in $\Delta G^{\ddagger}$, since the first ionization potentials are the same in both cases. Furthermore the trends of the

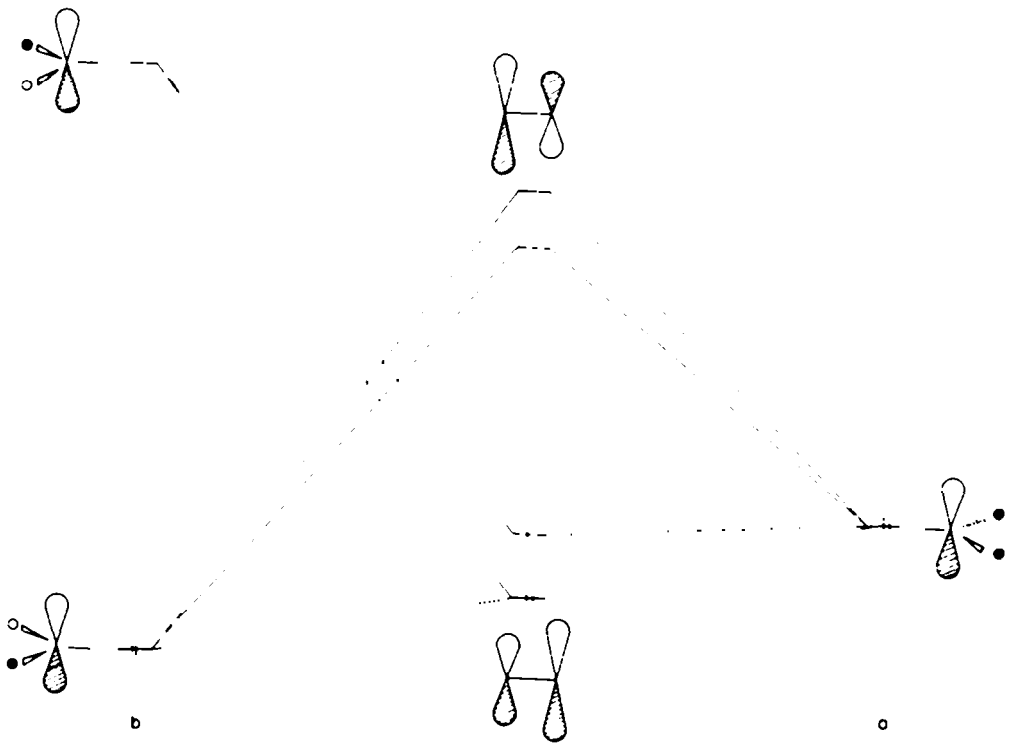
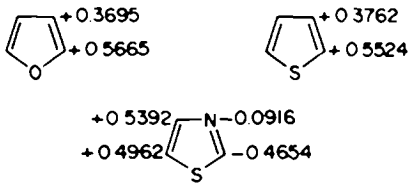


Fig. 1. Orbital interaction diagram between the πMO's of fragment A and those of fragment B in the ground (a) and transition (b) states of the torsional process.

matrix elements are not easily assessed in qualitative terms (see the close agreement of the coefficients below), and therefore the qualitative PMO approach adopted here seems insufficient to provide a rationalization of the observed trends and a more quantitative approach should be used.

However the present PMO approach seems able again to rationalize the variations of the rotational barriers in species with the same substituent, but with union of the $CONMe_2$ group at different positions of the ring. Since in such cases the energy factor will be the same, it is the matrix element that controls the trend of the rotational barrier. The dominant term here should be that referring to the union site. The values of the coefficients of the HOMO's of furan, thiophen and thiazole as obtained from SCF-MO ab-initio computations at the STO-3G level are reported below.



It follows that in the furan containing species the $\Delta G^{\neq}$ value of **1** (where $CONMe_2$ is in position 2) is expected to be smaller than that of **3** (where $CONMe_2$ is in position 3) and similarly in the thiophen-containing species the $\Delta G^{\neq}$ of **2**, is expected to be smaller than that in **4**, since in both furan and thiophen the HOMO's coefficients in position 2 are larger than in position 3. Accordingly the rotational barriers in **1** and **2** have been found to be smaller than those in **3** and **4**.

In the thiazole series, again to the smallest coefficient (that in position 2) it corresponds the largest rotational barrier (that of **6** with respect to **7** and **8**).

EXPERIMENTAL

Materials

The *N,N*-dimethylcarbamides **1–8** were prepared from the corresponding acylchlorides by reaction with dimethylamine according to the following general scheme. To solutions of 0.03 mol dimethylamine in 300 ml ether cooled by means of a dry ice/acetone bath, an ethereal solution (50 ml) of 0.01 mol acylchloride was added dropwise under vigorous stirring. When the addition was complete, the mixture was left overnight at room temperature, poured on water, extracted with ether, and dried over Na_2SO_4. The product obtained on evaporation was purified by chromatography on SiO_2 (n-penthane:ether 80/20) and by distillation. All the products gave the expected molecular weights (mass spectrometry), consistent NMR spectra and correct elemental analysis (yields 70–85%). The melting (boiling) points were: (1) 44–45°C; (2) 45–46°C (142°C/15 mm); (3) 70–71°C; (4) 44–45°C; (5) (85°C/1 mm); (6) 36–37°C; (7) 76–78°C; (8) 37–38°C.

The acylchlorides used for the syntheses were all obtained from the corresponding carboxylic acids by reaction with an excess of $SOCl_2$ in benzene. After vacuum elimination of the solvent and of the residual $SOCl_2$, the product is used without further purification. The 2-thienyl and 3-furyl carboxylic acids were commercial products (Schuchardt and Fluka respectively). The 2-furyl,[24] 3-isooxazolyl[25] and 4-thiazolyl[26] carboxylic acids were prepared according to the literature. The 3-thienyl,[27] 2-thiazolyl[28] and 5-thiazolyl carboxylic[28] acids were prepared from the corresponding bromo derivatives by reaction with butyl-lithium followed by reaction of solid CO_2 in ethereal solution.[27,28]

The *N,N*-dimethylthiocarbamides **9–12** were obtained from the corresponding amides by reaction with P_2S_5 in benzene, according to the following method. A mixture of amide (1 equiv) and 0.1 equiv P_4S_{10} was refluxed in benzene for 1 h. The solution was filtered and evaporated under vacuum. The residual thiocarbamide was purified by chromatography on a SiO_2 column using *n*-pentane/ether (80:20) as eluent and finally distilled. The yields were 75–85%. The following b.ps at 1 mm were observed: (9) 138°C; (10) 119°C; (11) 140°C; (12) 130°C.

In all four cases the elemental analysis (C, H, N, S) as well as the molecular weight (mass spectrometry) was in agreement with the expected structures.

Spectral measurements

NMR spectra were obtained on a JEOL 60 MHz instrument equipped with standard low temperature apparatus. The temperature was measured before and after each spectral record by inserting a thermocouple in a dummy tube. The spectral simulation were obtained by the using the DNMR program[12] obtained through the QCPE: the CDC 6600 computer of the University of Bologna was employed.

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