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GEMINAL PROTON NON-EQUIVALENCES AND INTERNAL ROTATION IN 2-AMINO-THIOPHEN DERIVATIVES.

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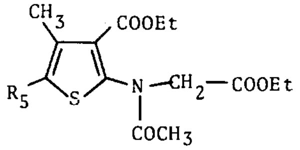
Astract—3-Substituted *N*-acetyl, *N*-ethoxycarbonylmethyl-2-aminothiophen derivatives are shown to exist in the *endo* (the amide carbonyl *cis* to the thiophen ring) and *exo* forms, the latter in predominant amount (92 to 98%). Proton nonequivalence reveals the absence of coplanarity between the thiophen and amide planes and the presence of two biphenyl-like enantiomers *d* and *l*. The barriers to rotation about the amide bond (R_X) and the aryl-to-nitrogen bond (R_N) have been measured in three solvents: $\Delta G^{\neq}(25°C) \sim 71$ and $54\,kJ.mole^{-1}$, respectively. Competitive delocalisation of the nitrogen doublet to the amide group or to the thiophen ring is shown to account for structural and solvent effects upon the *endo* to *exo* molar ratio, the degree of chemical shift nonequivalence and the kinetic parameters of processes R_X and R_N.

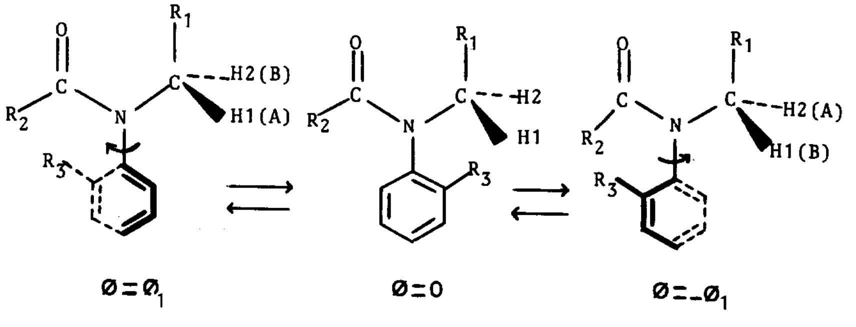
In the course of investigations of the structure of 2-aminothiophen derivatives, chemical shift non-equivalence of diastereotopic protons due to restricted rotation around aryl-to-nitrogen bonds was observed in certain N-acetyl, N-ethoxycarbonylmethyl-2-aminothiophen derivatives **1** and **2**



1 R_5 = $COCH_3$

2 R_5 = COOEt

This phenomenon is clearly related to the well-known restricted rotation about the benzene-to-nitrogen bond in *ortho*-substituted anilides.[1] In such compounds, two restricted rotations may be slow on the NMR time scale for appropriate R_1, R_2, R_3 substituents *either* (*i*) a rotation about the N-C(0) (amide) bond between *exo* and *endo* isomers (C = 0 *trans* or *cis* to the benzene ring, respectively), *or* (*ii*) a biphenyl-like rotation[2] about the N-C(aromatic) bond. Steric hindrance between the amide group and the bulky aromatic *ortho* substituent results into the plane of the benzene ring being twisted out of the average amide plane by a certain dihedral angle of tilt θ, as shown in the drawing below (for the *exo* isomer).

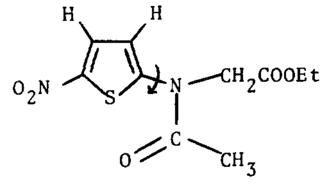


d-enantiomer planar transition state *l*-enantiomer

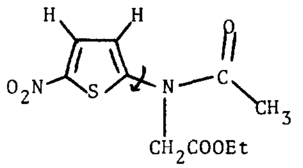
The process of torsion about the benzene-to-nitrogen bond may be visualised as one in which the molecule passes through two energy minima ($\phi = \pm\phi_1$)-corresponding to a pair of enantiomers (*d*, *l*)-and two energy maxima ($\phi = 0$ or 180°) which determine the planar transition state (e.g., $\phi = 0$ in the drawing). Each isomer (*endo* or *exo*) may thus give rise to a pair of biphenyl-like enantiomers. In many cases the *exo* isomer alone can be observed.[3] X-ray analysis has shown that, for *ortho* disubstituted anilides, the benzene ring occupies an average position perpendicular to the plane of the nitrogen atom and its substituents.[4,5] Similar tilt angles $\phi_1 = 90°$ have been generally assumed for singly *ortho* substituted anilides, although this is not a necessary condition.[6,7]

The object of the present investigations is to extend the above studies to molecules in which the benzene ring is replaced by a heteroaromatic pentagonal ring, such as thiophen.

In a previous publication,[8] we described the NMR properties of N-acetyl, N-ethoxycarbonylmethyl-2-amino-5-nitrothiophen **3**. In sharp contrast with compounds **1** or **2** no magnetic non-equivalence of the N-methylenic protons was observed due to the absence of a substituent in position 3 (*ortho* like) of the thiophen ring. It was therefore assumed that the aromatic ring and the amide group are nearly coplanar. Two groups of lines are observed in the ^{1}H NMR spectrum which were assigned to the two *endo* isomers α and β.



3α



3β

In compounds **1** and **2**, two isomers can be observed at -60°: a major isomer x in which the N-methylene protons H_A, H_B are non-equivalent, a minor isomer y (2–8%) which is detected by the presence of two N-acetyl methyl lines (It is impossible, because of its low ratio, to assess whether non-equivalence is also existing in isomer y). Two NMR site exchanges are shown to occur on raising the temperature (*i*) an identity exchange of protons H_A and H_B in isomer x between −60° and −20°, (*ii*) an exchange between the N-acetyl methyl lines of isomers x and y in the temperature range 40° to 120°. The object of this paper is to report on these observations more fully.

EXPERIMENTAL

Materials and solutions. Deuterated solvents ($CDCl_3$, CD_3COCD_3, $(CD_3)_2NCDO$), were obtained from the Commissariat á l'Energie Atomique (CEA) and were checked for purity before use. Compounds **1** and **2** were synthesized according to a procedure described in a previous publication.[9] The colourless solids (F = 90° and 98°, respectively) were purified by recrystallisation from EtOH. They were dissolved at concentrations sufficiently high to have a good sensitivity in the NMR spectra, and however as low as possible both to avoid the precipitation of the solid at low temperatures (up to −60°) and to prevent any intermolecular amide-amide associations.[10] An optimum concentration of 0.2 mol.dm^{-3} was found which satisfied approximately all these requirements. The solvents were chosen so as to obtain good solubilities of **1** and **2**, to remain in the liquid state over a large interval of temperature (from −60° up to 50–110°), and to cover a wide range of polarities.

NMR spectroscopy. Spectra without any line-broadening due to exchange phenomena were obtained at −60° and 250 MHz. High frequencies were necessary to disentangle methylenic lines between 3.5 and 5 ppm which are overlapping at 60 MHz. The use of Fourier Transformation was necessary to detect the weak N-acetyl methyl line of isomer y (1000 scans of 8 K points over a frequency range of 2 kHz using the deuterium signal of the solvent as an internal lock). Chemical shifts were found to be independent from temperature within experimental error (± 0.1 to ± 0.5 Hz) except for the high-field doublet A of the AB type spectrum of protons H1, H2. The corresponding resonance frequency ν_A is decreasing by 0.1 Hz per degree in chloroform and by 0.6 Hz per degree in DMF and acetone. Chemical shifts were found concentration independent (0.1–0.4 mol.dm^{-3}) and strongly dependent on the solvent (Table 1). Intensity measurements of the methyl lines allow one to compute the molar fractions p_x, p_y of the two isomers x and y, the equilibrium constant $K = p_y/p_x$ and the related thermodynamic function $\Delta G_R = -RT \log K$ (Table 2). The temperature coefficient of K is very close to unity, and the corresponding equilibrium enthalpy ΔH_R close to zero within large experimental errors. The value of K is strongly dependent on the solvent (Table 2). DNMR spectra were recorded from −60° to 110° either on a Jeol C60-HL spectrometer operating at 60 MHz or on a Cameca superconducting spectrometer at 250 MHz. Operations at 60 MHz were necessary to bring the exchange to the NMR timescale at a temperature below the boiling point of the solvent. The temperature was periodically checked with a calibrated thermometer immersed in the sample tube and was found constant within ± 0.5°.

Line-shape measurements. Two types of exchange are examined in this paper: the exchange (I) of the methylic protons of the amide group between two inequal singlets; the identity interchange (II) $AB \rightleftarrows BA$ of the AB type quartet of the N-methylene non-equivalent protons H1, H2 in isomer x. Theoretical line-shapes are computed using a matrix formulation due to Anderson *et al.*[11] and the program ECHGN[12] for exchange (I), and the density matrix formalism[13] in the second case (program EXCH 14[14]). These computations required introducing the following parameters: (*i*) for exchange (I), the equilibrium constant K (see above) and the unknown rate constant k_x (or $k_y = k_x/K$) for the forward (or reverse) process $x \rightarrow y$, assuming constant chemical shift separation between exchanging lines (*ii*) for exchange (II), the chemical shift separation $\nu_A - \nu_B$ (depending on the temperature, see above) and the unknown rate constant k_N for the AB interchange process. These parameters were adjusted by trial and error so as to obtain the best fit between experi-

Table 1. ^1H Chemical shifts (in ppm from TMS) of 0.2 molar solutions of compounds **1** and **2** (1st and 2nd lines, respectively) in three solvents at −60°

		$CDCl_3$	Acetone-d_6	DMF-d_7
$N\text{-}C\underline{H}_2COOCH_2CH_3$	δ_A	3.87 3.83	4.11 4.07	4.34 4.34
	δ_B	4.94 4.95	4.76 4.78	4.72 4.75
$N\text{-}CH_2COOC\underline{H}_2CH_3$	δ_C	4.22 4.21	4.18 4.18	4.19 4.21
	δ_D	4.28 4.27	4.18 4.18	4.19 4.21
$N\text{-}CH_2COOCH_2C\underline{H}_3$		1.32 1.28	1.24 1.24	1.25 1.23
$N\text{-}CO\text{-}C\underline{H}_3$	x	2.07 2.03	1.95 1.94	2.00 2.00
	y	2.26 2.21	2.19 2.18	2.26 2.25
$3\text{-}COOCH_2C\underline{H}_3$		1.36 1.33	1.29 1.29	1.29 1.28
$3\text{-}COOC\underline{H}_2CH_3$		4.35 4.33	4.31 4.31	4.32 4.32
$4\text{-}C\underline{H}_3$		2.70 2.70	2.64 2.66	2.68 2.71
$5\text{-}COC\underline{H}_3$ or		2.60 -	2.37 -	2.64 -
$5\text{-}COOCH_2C\underline{H}_3$		- 1.36	- 1.34	- 1.34
$5\text{-}COOC\underline{H}_2CH_3$		- 4.38	- 4.34	- 4.37

Table 2. The equilibrium constant $K = p_y/p_x$ at various temperatures T and the equilibrium free energy ΔG_R at 55°

Compound	Solvent	K(T°C)	ΔG_R ($kJ.mol^{-1}$)
1	$CDCl_3$ CD_3COCD_3 DMF-d_7	0.02(−30°); 0.03(+55°) 0.025(−30°); 0.04(+55°) 0.045(−45°);0.055(−10°);0.080(+55°)	9.55 8.77 6.88
2	$CDCl_3$ CD_3COCD_3 DMF-d_7	0.02(−30°); 0.025(+55°) 0.02(−30°);0.03(+55°) 0.04(−30°);0.05(+10°);0.06(+55°)	10.05 9.55 7.66

mental and theoretical curves (Table 3). Satisfactory Arrhenius plots are obtained for rate constants k_x and k_N, from which a least squares analysis yields the activation parameters $\Delta H_X^\ddagger$, $\Delta S_X^\ddagger$ and $\Delta H_N^\ddagger$, $\Delta S_N^\ddagger$, respectively, and, in turn, the smoothed values of k_x and k_N at 25° (and the corresponding free energies $\Delta G_X^\ddagger$ and $\Delta G_N^\ddagger$, using Eyring's equations) (Table 4). Because of the poor accuracy over K, uncertainties may be as large as 8 to 13 $kJ.mol^{-1}$ over $\Delta H_X^\ddagger$, and 25 to 38 $J.mol^{-1}K^{-1}$ over $\Delta S_X^\ddagger$ (at least for the solvent with the largest K values, i.e. DMF). Uncertainties over k_N, $\Delta H_N^\ddagger$ and $\Delta S_N^\ddagger$ should not be larger than ±5%, 2.0 to 4.0 $kJ.mol^{-1}$, and 6.3 to 12.5 $J.mol^{-1}K^{-1}$, respectively.

RESULTS AND DISCUSSION

A. *General spectroscopic features*

The NMR spectrum of compound **1** is included in Figure 1. The N-acetyl methyl protons appear as two lines (Fig. 1c) between 2.0 and 2.3 ppm: an intense line X accompanied by a very weak line Y at lower field, thus revealing the presence of two stereoisimers x and y (major and minor isomers, respectively). These two lines coalesce into a singlet on raising the temperature above 40°. This can be accounted for by the existence of *endo* and *exo* forms, mutually exchanging at higher tem-

Table 3. Rate constants for internal rotations about the C(O)-N(amide) bond (k_x) and the aryl-to-nitrogen bond k_N (1st and 2nd lines, respectively) at various temperatures.

Compound	Solvent	Rate constants (s^{-1})
1	$CDCl_3$	0.90(30°); 1.8(40°); 4.5(50°); 8.0(58°) 3.5(-55°); 9.0(-45°); 30(-30°); 55(-20°); 120(-10°)
	CD_3COCD_3	1.75(35°); 2.5(40°); 4.0(45°); 7.0(50°); 11(55°) 7.0(-60°); 15(-50°); 35(-40°); 80(-30°); 150(-20°)
	DMF-d_7	4.5(40°);11(55°);27(70°);55(85°);100(100°);180(115°) 7.0(-55°);11(-50°C);30(-40°);70(-30°);160(-20°)
2	$CDCl_3$	0.75(35°); 2.5(45°); 7.0(55°) 6.0(-30°); 16(-20°); 40(-10°); 100(0°)
	CD_3COCD_3	2.2(40°); 4.0(45°); 9.0(52°) 2.0(-60°); 6.0(-50°);17(-40°);45(-30°);90(-20°)
	DMF-d_7	3.5(40°); 12(55°); 30(70°); 90(85°); 190(100°) 7.0(-40°); 20(-30°); 40(-25°); 60(-20°)

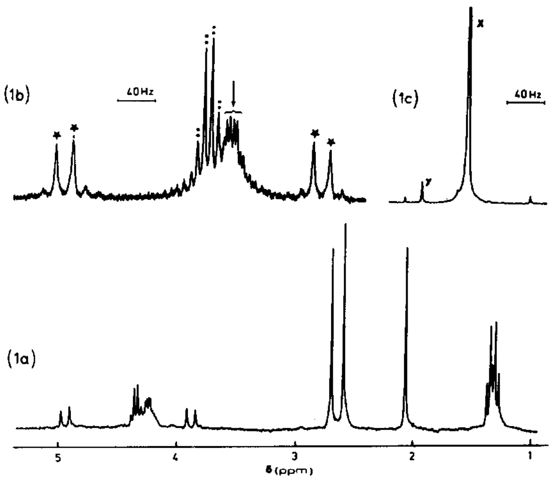


Fig. 1. (a) The ^1H NMR spectrum of *N*-acetyl, *N*-ethoxycarbonylmethyl, 2-amino, 3-ethoxycarbonyl, 4-methyl, 5-acetyl thiophen (0.2 molar solution in $CDCl_3$ at −55° and 250 MHz) (b) Enlarged spectrum of the *N*-methylene protons showing the nonequivalence of protons H_A, H_B (starred lines, see the text) and H_C, H_D (lines shown by an arrow) (c) Enlarged spectrum of the *N*-acetyl methyl protons showing the lines X and Y of the *exo* and *endo* isomers.

perature, as the result of a restricted rotation about the amide bond. The decomposition of the NMR spectrum into two subspectra is however limited to the N-acetyl methyl lines, presumably because of smaller chemical shift differences for the other substituents and of the complexity of the N-methylene protons spectrum.

The methylene protons appear in the spectrum as three groups of lines:

(*i*) An AB type quartet (Fig. 1b, starred lines), enclosing

(*ii*) A sharp quadruplet (doubly starred lines), typical of the methylene protons in an ethyl group, overlapping with

(*iii*) A broad multiplet (shown by an arrow).

The AB type quartet reveals the existence of two geminal nonequivalent protons, with a large chemical shift difference $\delta_A - \delta_B = 1.07$ ppm in $CDCl_3$ at −60° and a coupling constant of 17.5 Hz. These lines coalesce into a singlet (Fig. 2) on raising the temperature from −60° to +50°. These results clearly demonstrate a biphenyl-like restricted rotation about the aryl-to-nitrogen bond and the presence of two enantiomers *d* and *l*. As in substituted anilides, the aromatic ring is twisted out of the amide plane by a dihedral angle $\pm \phi_1$. In contrast with the planar compound **3** previously described,[8] the N-acetyl

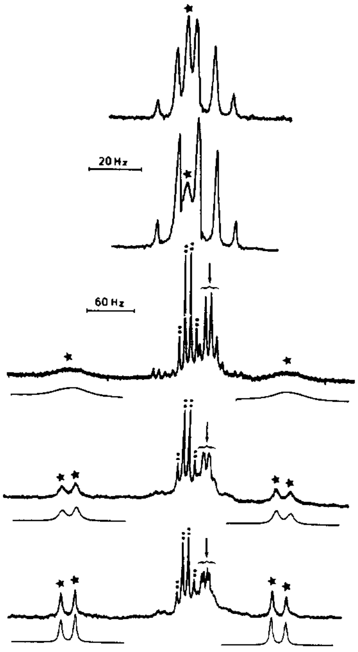


Fig. 2. Experimental and theoretical curves (above and below, respectively) for the AB⇄BA identity exchange of the N-methylene protons (starred lines) of compound **1** (0.2 molar solution in $CDCl_3$) at −45°, −30°, −10° (250 MHz spectra); 25° and 50° (60 MHz spectra) from the bottom to the top, respectively.

substituents *cis* isomer *exo* to the thiophen ring are lying nearly perpendicular to the thiophen plane and are therefore shielded by the magnetic field arising from the thiophen ring. We are thus led to assign lines X and Y to the *exo* (x) and *endo* (y) forms, respectively. The enantiomers *d* and *l* thus refer to the major *exo* form of compound **1** (or **2** as well). Rotation of protons H_A, H_B about the alkyl-to-nitrogen bond, as shown by the dashed arrows in Fig. 3, is however possible to a certain extent. Several rotamers are therefore possible, depending on steric constraints, so that chemical shift nonequivalence presumably results from weighted means over these rotamers. Apparent changes in rotamer populations are taking place in these conformationally mobile systems and result into a steady increase of $(\delta_A - \delta_B)$ as the temperature is varied, by *ca*, 0.6 Hz/degree at 250 MHz (The literature seems to report irregular decreases of $\delta_A - \delta_B$ with the temperature for the analogous substituted anilides[7]). Magnetic nonequivalence is still possible for the geminal methylene protons H_C, H_D four bonds further in the N-ethoxycarbonylmethyl substituent $N{-}C(H_AH_B){-}COO{-}C(H_CH_D){-}CH_3$. This is shown by the presence of a complicated multiplet (see above), the CD part of a CDX_3 (or ABX_3) type spectrum (δ_C, δ_D, δ_X = 4.22, 4.28 and 1.32 ppm in $CDCl_3$), which can be reduced to a methylene quadruplet (C_2X_3 type spectrum) on raising the temperature or to a broad AB (or CD) type quartet by decoupling the methyl protons X. This allows us to make the distinction between the ethyl groups in the above N-ethoxycarbonylmethyl and 3-ethoxycarbonyl substituents (Table 1).

B. *Equilibrium constants*

The equilibrium constants $K = p_y/p_x$ are fairly insensitive to the temperature (Table 2), i.e. the equilibrium enthalpies ΔH_R are very close to zero: $\Delta H_R = 3.6$ and $3.1 \pm 2\,kJ.mol^{-1}$ for compounds **1** and **2** respectively (in DMF-d_7). This is in line with the results obtained for the analogous *ortho* substituted N-alkylated anilides where slightly positive or negative enthalpies have been reported in the literature.[1,15–16]

There is a slight decrease of K, i.e. of the *endo* to *exo* molar ratio, from compound **1** to compound **2**, e.g. K(55°, in DMF-d_7) = 0.08 and 0.06, respectively. The two substituents ($R_5 = COCH_3$ and COOEt) are endowed with Hammett σ (para) constants of 0.50 and 0.45,[17] respectively, which reflect a slight difference in their electron-withdrawing power. We note a parallel increase of the degree of nonequivalence between the N-methylene protons of the *exo* isomer, $\delta_A - \delta_B = 1.07$ and 1.12 ppm (in $CDCl_3$ at −60°). Increasing the polarity of the solvent in the sequence $CDCl_3 < CD_3COCD_3 <$ DMF-d_7 (electric dipole moment $\mu = 1.63$, 2.49 and 3.82 Debye, respectively) is accompanied both by a net increase of the equilibrium constant (K(55°) = 0.03, 0.04 and 0.08, respectively, for compound **1** and 0.025, 0.03 and 0.06 for compound **2**) and a large decrease of nonequivalence ($\delta_A - \delta_B = 1.07$, 0.65 and 0.38 ppm respectively, for compound **1** at −60°, and 1.12, 0.71 and 0.41 ppm for compound **2**; $\delta_C - \delta_D = 0.06$, 0.00 and 0.00 ppm for both compounds **1** and **2**).

All these observations may be rationalised if we admit the reasonable assumptions below:

(*i*) A reinforced delocalisation of the nitrogen free electron pair onto the nitrogen-to-aryl bond (either by electron-withdrawing substituents in the thiophen ring or through an increased polarity of the solvent) results into a smaller tilt angle ϕ_1.

(*ii*) Decreasing the twist angle ϕ_1 results in turn into a diminished degree of nonequivalence, as shown by the limiting case $\phi_1 \rightarrow 0$, where $\delta_A - \delta_B = 0$.

(*iii*) A smaller twist angle ϕ_1 results into an increase of the *endo* to *exo* molar ratio (i.e. of K), as shown by the limiting case $\phi_1 = 0$, where we have shown, on the example of compound **3**, the existence of the *endo* isomer alone[8] (see above).

C. *Barriers to rotations R_N and R_X about the N-C(aromatic) and the amide bonds.*

The rate constants for internal rotations R_N and R_X are derived from the study of the two NMR site exchanges, AB⇄BA and X⇄Y, respectively. The kinetic data reported in Tables 3 and 4 offer some interesting features.

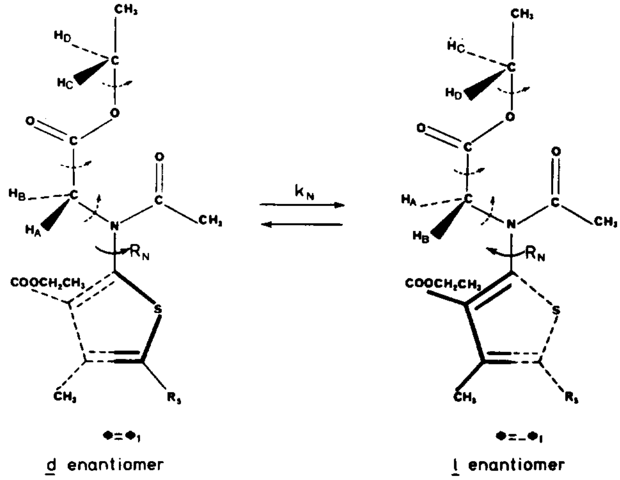


Fig. 3. The two biphenyl-like enantiomers *d* and *l* of compounds **1** and **2**. Various rotamers are still possible through internal rotations about single bonds as shown by the dashed arrows.];

Table 4. Rate constants k_x and $k_N(s^{-1})$ at 25, and the related thermodynamic functions $\Delta G_X^\ddagger$, $\Delta G_N^\ddagger$; $\Delta H_X^\ddagger$, $\Delta H_N^\ddagger$ (kJ.mol^{-1}), $\Delta S_X^\ddagger$, $\Delta S_N^\ddagger$ (J.mol^{-1}.K^{-1}) for compounds **1** and **2** (1st and 2nd lines respectively) and three solvents

Solvent	$CDCl_3$	CD_3COCD_3	DMF-d_7
k_X	0.55 0.22	0.58 0.32	1.80 1.03
$\Delta G_X^\ddagger$	74.2 76.5	74.3 75.8	71.4 72.8
$\Delta H_X^\ddagger$	63.5 91.2	76.5 97.0	47.2 62.3
$\Delta S_X^\ddagger$	-35.9 49.3	7.4 71.1	-81.1 -35.2
k_N	839 657	1853 2158	3059 2898
$\Delta G_N^\ddagger$	56.1 56.6	54.0 53.6	52.2 53.0
$\Delta H_N^\ddagger$	34.3 48.9	32.2 40.5	38.5 51.0
$\Delta S_N^\ddagger$	-73.2 -25.9	-73.2 -43.9	-46.0 -6.7

(*i*) Rate constants k_N for R_N processes are higher than those for R_X processes by *ca.* three orders of magnitude, reflecting the large differences between the corresponding temperatures of coalescence. The barrier to rotation about the amide bond has an expected order of magnitude ($\Delta G_X^\ddagger \sim 71$ kJ.mol^{-1} at 25°) as compared to the values reported for N,N'-dimethylacetamides, for acetanilides or N-substituted anilides.[1] The barriers to rotation about the aryl-to-nitrogen bond are surprisingly low ($\Delta G_N^\ddagger \sim 54$ kJ.mol^{-1} at 25°) as compared to the values reported for N-substituted anilides.[1] They are in fact closely similar to those obtained for formanilides.[15] The lowering of the barrier height may be attribued to a release of steric hindrance in the pentagonal thiophen ring as compared to the hexagonal benzene ring.

(*ii*) Rate constants for processes R_X and R_N both decrease from compound **1** to compound **2** and both increase with the polarity of the solvent. These observations can be rationalised again using the concept of a variable delocalisation of the nitrogen doublet onto the thiophen ring. If we examine first the case of the rotation about the aryl-to-nitrogen bond, the unfavourable stabilisation of the non-planar ground state as a result of an increased electronic delocalisation (with a diminished twist angle $\emptyset_1$, as stated above) is more than counterbalanced by a larger stabilisation of the transition state in which the thiophen ring is presumably approximately coplanar with the amide group. Rotation R_N is therefore expected to be easier for an increased partial double bond character of the C–N(aromatic) bond, thus accounting for the above mentioned structural and solvent effects upon k_N values. The nitrogen doublet may be in fact delocalised in either of two ways, either to the amide group or to the thiophen ring. An increase of the partial double bond character of the N–C(aromatic) bond is therefore accompanied by a decrease of that of the amide bond, thus lowering the barrier to rotation R_X and increasing the rate constant values k_x.

(*iii*) Finally, these considerations are also reflected in the activation enthalpies $\Delta H_X^\ddagger$ and $\Delta H_N^\ddagger$, which are higher for compound **2** than for compound **1**.

The activation entropies, which are determined with a large degree of uncertainty, are however significantly negative for the rotation about the aryl-to-nitrogen bond. This point has already been mentioned for hindered rotation in *o*-toluidine derivatives.[18] A nearly coplanar arrangement of the 3-substituted thiophen ring with the bulky amide group in the transition state should effectively result in large restraints of some internal motions and therefore in negative $\Delta S_N^\ddagger$ values.

CONCLUSION

The whole set of data reported in Tables 1–4 is clearly consistent with the existence of a major *exo* form for compounds **1** and **2**, itself consisting of two conformationally mobile enantiomers *d* and *l*. Competitive delocalisation of the nitrogen doublet to the amide group and to the thiophen ring may account for structural and solvent effects upon the degree of chemical shift nonequivalence in the *exo* isomer, the *endo* to *exo* molar ratio, and the kinetic parameters for the two dynamic processes exchanging the *exo* and *endo* forms on the one hand, the *d* and *l* conformers on the other hand.

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