Conformational Studies by Dynamic Nuclear Magnetic Resonance. Part 30.[1] Exchange Kinetics between the Rotamers of 2-Acyl-furans and -thiophenes

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Low-temperature ^{13}C n.m.r. spectra allowed the observation of two different groups of signals, corresponding to the O,O-*anti*- and O,O-*syn*-rotamers, of a number of 2-acylfurans with the following alkyl groups bonded to carbonyl: Me, Et, $\mathrm{Pr^i}$, $\mathrm{Bu^t}$, pentan-3-yl. The ratios of these rotamers in dimethyl ether were thus obtained, and the barriers for the *syn–anti* interconversion were found to decrease with increasing bulkiness of the alkyl groups. Although separate ^{13}C signals could not be detected for the rotamers of the corresponding 2-acylthiophenes, line-broadening effects nonetheless allowed measurement of the interconversion barriers. Lanthanide-induced shift experiments carried out on the latter derivatives (at both ^{1}H and ^{13}C frequencies) showed that in all the 2-acylthiophenes investigated the S,O-*syn* rotamers are predominant.

A number of investigations have been carried out on the conformation of 2-acetylfuran by n.m.r. techniques.[2–6] Low-temperature experiments allowed the detection of separate n.m.r. spectra for the two rotamers as well as the determination of exchange kinetics, and hence the barrier for interconversion. Some of the analogous carbonyl halides were also investigated in this way.[7,8]

On the other hand 2-acylfurans, with the R groups of –COR larger than methyl, have not previously been investigated. Even less attention has been paid to the analogous carbonyl derivatives of thiophene: this stems from the fact that, in contrast to the furan analogues, thiophene derivatives of this type exist, at low temperature, mainly in a single conformation.[9–11] Only with the advent of superconducting spectrometers has it been possible to detect directly the presence (1.5% at – 100 °C in CD_2Cl_2) of the minor conformer (S,O-*anti*) in thiophene-2-carbaldehyde.[12]

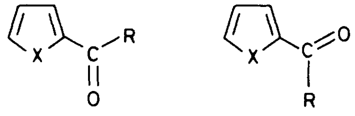
The presence of both conformers at equilibrium, even if the minor one is in such a small amount that its spectral lines are unobservable, is essential for measuring the barrier for interconversion. In such biased equilibria, the exchange process is nevertheless observable owing to the broadening of the lines of the major conformer: from this effect the rate of interconversion can be obtained.[12–17]

In the present work we have investigated the conformational preferences of derivatives having acyl groups (–COR) bonded to position 2 of both furan and thiophene and, by low-temperature ^{13}C n.m.r., have determined the interconversion barriers between the rotational conformers in solution. In the case of the thiophene derivatives we also made use of lanthanide-induced shift (LIS) experiments to ascertain the structure of the preferred rotational conformer.

Results and Discussion

Conclusive studies on furan- and thiophene-2-carbaldehyde (**1**) and (**7**) have been already reported;[4–6,12,18] the present investigation is therefore concerned mainly with the conformational behaviour of the ketones (**2**)—(**6**) and (**8**)—(**12**).

All the 2-acylfurans investigated in this study (**2**)—(**6**) show non-negligible amounts of both O,O-*syn* and O,O-*anti* rotational conformers: their ^{13}C n.m.r. spectra, taken at low temperature in dimethyl ether, all display pairs of signals for each carbon atom. On raising the temperature these signals broaden and eventually coalesce into single lines. A typical temperature-dependent ^{13}C spectrum is shown in Figure 1 for the derivative (**4**) (R = $\mathrm{Pr^i}$). Lines obtained by computer simulation, using the appropriate first-order rate constants for the *syn–anti* exchange, are also shown. From these rates the free energies for the interconversion were obtained and the $\Delta G^‡$ values are given in Table 1. In the case of the derivative (**4**) the values for $\Delta H°$ and $\Delta H^‡$ (0.44 ± 0.06 and 9.3 ± 0.3 kcal mol^{-1})† as well as for $\Delta S°$ and $\Delta S^‡$ (2.3 ± 0.3 and 1.6 ± 1.7 cal mol^{-1} K^{-1}) were also determined for the interconversion of the O,O-*syn* and O,O-*anti* rotamers. The activation entropy ($\Delta S^‡$) is, as expected,[2,18] negligible within experimental error; hence the values of $\Delta G^‡$ can be taken as reliable measures of the interconversion barriers.



X,O-*syn* X,O-*anti*

X = O	R	X = S
(**1**)	H	(**7**)
(**2**)	Me	(**8**)
(**3**)	Et	(**9**)
(**4**)	$CHMe_2$	(**10**)
(**5**)	$CHEt_2$	(**11**)
(**6**)	CMe_3	(**12**)

Since it has been established[5,14,15,19] that the carbonyl moiety shifts upfield the ^{13}C signals of *ortho*-like carbon atoms (here C-3) when they are in a *syn*-relationship, the conformation assignment becomes straightforward (Table 2). Some doubt concerning the assignment might arise in the case of 2-pivaloylfuran (**6**) (R = $\mathrm{Bu^t}$) in that the difference between the shifts for the carbon atoms in position 3 in the *syn*- and *anti*-conformers is much smaller than in all the other acylfurans (Table 2). The possibility that a crossing of these shifts would lead to an opposite structural assignment cannot, in principle, be excluded. However in 2-formyl- and 2-acetyl-furan (**1**) and (**2**) the ^{13}C shifts of C-2 and CO in the *anti*-conformer are

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† 1 kcal = 4.184 kJ.

Table 1. Amounts of the O,O-*anti* conformer (column 3) in the 2-acylfurans (**1**)—(**6**) in dimethyl ether measured at the temperatures (column 2) where *syn–anti* exchange is slow on the n.m.r. time scale. The free energies of activation ($\Delta G^{\ddagger}$/kcal mol^{-1}) for the exchange are also given (columns 6 and 7), together with the temperatures (column 4) where they were measured. Also the amounts of the O,O-*anti* conformers used to calculate the $\Delta G^{\ddagger}$ values at the temperatures (column 5) where exchange occurs are reported. The data for furan-2-carbaldehyde (**1**) were taken from ref. 18 and corrected for the wrong assignment.[3] The errors in $\Delta G^{\ddagger}$ are estimated to be ± 0.15 kcal mol^{-1}

Compound	t/°C	% *anti*	t/°C	% *anti*	$\Delta G^{\ddagger}$ (*syn–anti*)	$\Delta G^{\ddagger}$ (*anti–syn*)
(**1**) (R = H)	−115	10	−57	21	10.9	10.3_5
(**2**) (R = Me)	−110	53	−71	42	9.4	9.3
(**3**) (R = Et)	−110	60	−86	55	9.1	9.1_5
(**4**) (R = Pr^i)	−110	44	−87	50	9.0	9.0
(**5**) (R = pentan-3-yl)	−110	23	−89	24	9.0	8.6
(**6**) (R = Bu^t)	−139	85	−120	85	7.0	7.5_5

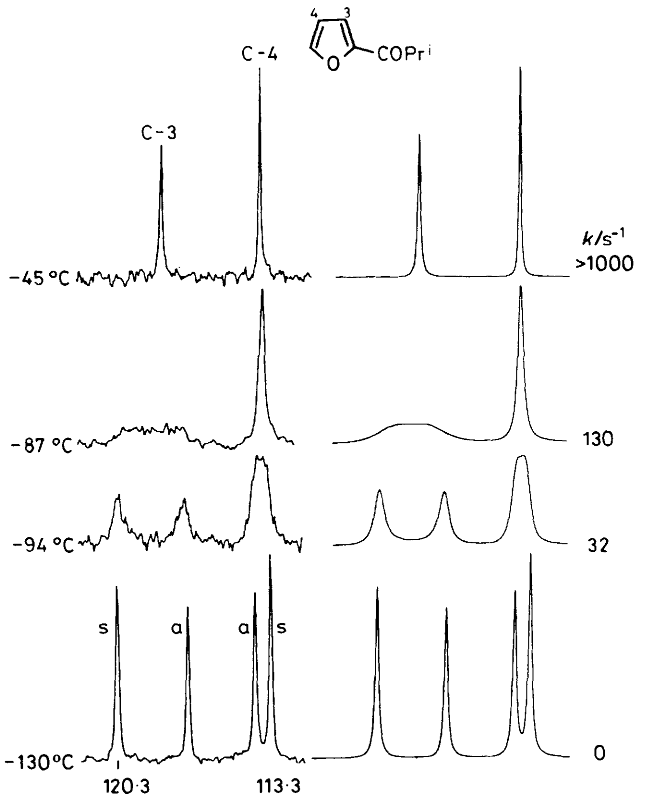

Figure 1. Experimental (left) and computer-simulated (right) ^{13}C signals (25.16 MHz) corresponding to C-3 and C-4 of derivative (**4**) (R = Pr^i) in dimethyl ether at selected temperatures. The first-order rate constants (in s^{-1}) obtained over the whole range where exchange significantly affects the spectral shape allowed us to obtain the activation enthalpy ($\Delta H^{\ddagger}$ = 9.3 ± 0.3 kcal mol^{-1}) and entropy $\Delta S^{\ddagger}$ = 1.6 ± 1.7 cal mol^{-1} K^{-1}) for the interconversion of O,O-*syn* and O,O-*anti* rotational conformers (see also Tables 1 and 2). The lines of the *anti* (a) and *syn* (s) conformer are identified in the spectrum at −130 °C

downfield[5] with respect to the *syn*: this is also so for the other acylfurans (**4**) and (**5**) reported in Table 2. It is thus reasonable to assign in (**6**) also the C-2 and CO signals at lower field (which turn out to belong to the more stable species) to the *anti*-rotamer, thus supporting the assignment based on the shift of C-3 (Table 1). A recent dipole-moment investigation[20] agrees with this conclusion: it indicates a preference for the O,O-*anti* conformer (67 ± 10% in CCl_4 at room temperature).

It is well known that in furan-2-carbaldehyde (**1**) the rotamer ratio is extremely dependent upon the polarity of the solvent.[6,21] Therefore it is not surprising that the corresponding ketones also change their conformational preference in different solvents. For instance we have verified that when R = Pr^i (**4**) the O,O-*anti* rotamer is about 44% of the mixture in Me_2O at −110 °C, whereas it becomes 10% at the same temperature in CCl_2F_2–$CHCl_2F$ (1:1). The value of $\Delta G^{\ddagger}$ for the *syn–anti* interconversion is also affected (9.45 ± 0.15 kcal mol^{-1}) by the change of the solvent. Acylfurans are in fact quite polar molecules, and the difference in the polarity between the two rotamers is quite large; as a consequence different solvents stabilize the two conformers to different extents. The introduction of substituents is also expected to modify the relative polarity of the conformers, and hence the *syn–anti* ratio; for instance, the introduction of even a methyl group in position 5 of furan-2-carbaldehyde is sufficient to affect dramatically the conformer ratio. We found that whereas in CS_2 the conformer ratio is about 1:1 for furan-2-carbaldehyde (**1**)[6] it becomes 3:1 for 5-methylfuran-2-carbaldehyde in the same solvent at the same temperature.[22] Such sensitivity to the effect of the substituent explains why there is not a regular trend (see Table 1) in conformer ratio with the increasing bulk of the alkyl group in COR, *i.e.* when R varies from hydrogen (**1**) to t-butyl (**6**). The modification of polarity due to different R groups seems to be more important than the steric requirements in determining the conformational behaviour.

In contrast to the 2-acylfurans, the 2-acylthiophenes (**8**)—(**12**) never show, in the low-temperature ^{13}C spectra, pairs of signals corresponding to S,O-*syn* and S,O-*anti* rotamers. However, some of the ^{13}C lines of (**8**) and (**11**) broaden between −90 and −100 °C and sharpen again on further cooling (below −120 °C). This broadening is so small as to be barely detectable at 25.16 MHz, in contrast to the case of thiophene-2-carbaldehyde (**7**) where it is quite large.[4,12] As already mentioned, this effect is indicative of an exchange between two species one of which is present in such a small amount as to escape detection. According to the theory[13,17] the maximum observed linewidth ($\Delta\omega$/Hz) is equal to $p\Delta\nu$, where p represents the percentage of the minor conformer (not visible) and $\Delta\nu$ the chemical-shift difference (in Hz) between the two exchanging lines (the visible and the invisible one). It can be predicted accordingly that in spectrometers with higher magnetic fields the increase in the shift differences will also increase the line broadening.

Indeed spectra taken in a superconductive spectrometer (75.47 MHz) not only increased the line broadenings of (**8**) and (**11**) but showed that the same effect is present in (**9**) and (**10**) as well. In the case of (**12**) the effect was never observed. Attempts to detect the signals of the minor conformers of (**8**)—(**11**) failed: this means that at the low temperatures required to 'freeze' the exchange process (below −120 °C) the less stable rotamers are

Table 2. ^{13}C Shifts (in p.p.m. from Me_4Si) measured in dimethyl ether at temperatures where the *syn–anti* exchange is still fast and at temperatures where different signals for the O,O-*anti* and O,O-*syn* conformers are observable. The ^{13}C spectrum of furan-2-carbaldehyde (**1**) at low temperature in Me_2O has already been published, in ref. 5.

R		t/°C		C-2	C-3	C-4	C-5	CO	CH_3	Others
Me	(**2**)	−58		154.3	117.9	113.3	147.9	186.5	26.1	
		−110	*syn*		120.5	113.1	148.5		25.8	
			anti		115.7	113.8	147.3		26.4	
Et	(**3**)	−70			116.7	113.1	147.3		7.8	31.9
		−110	*syn*		119.2	112.8	148.2		7.9	31.3
			anti		115.3	113.5	147.1		7.3	32.0
Pr^i	(**4**)	−30			117.5	113.1	147.5	192.8	19.1	36.8
		−130	*syn*	152.1	120.3	113.3	149.2	192.6	19.8	36.5
			anti	153.8	117.0	113.9	147.5	193.8	18.6	36.8
pentan-3-yl	(**5**)	−73		155.1	119.4	113.7	148.8	193.3	12.6	50.7; 26.4
		−110	*syn*	154.6	121.2	113.3	149.5	192.9	12.8	50.6; 27.4
			anti	155.0	116.8	114.1	147.8	193.8	12.5	50.0; 25.7
Bu^t	(**6**)	−80		154.1	119.4	113.3	147.3	194.2	26.7	43.8
		−110	*syn*	150.5	120.7	113.9	148.1	194.2	28.1	44.1
			anti	154.5	120.0	113.9	147.6	194.7	26.5	44.1

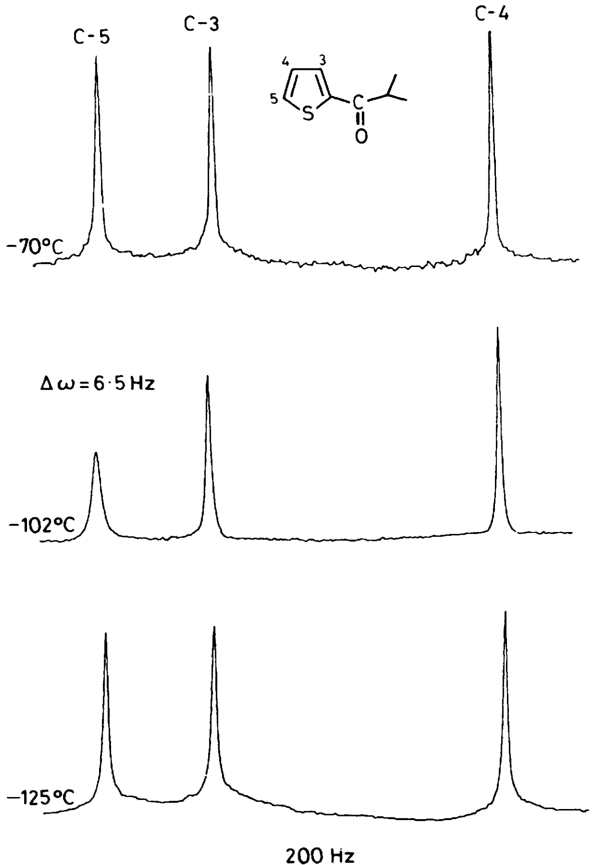

Figure 2. Part of the aromatic region of the ^{13}C spectrum (75.47 MHz) of (**10**) (R = Pr^i) in CHF_2Cl as a function of temperature. At −102 °C the line broadening of C-5 is evident ($\Delta\omega = \omega_{max.} - \omega_0 = 6.5$ Hz) whereas that of C-4 is nil. At the same temperature the line broadening of C-3 is barely visible: it can be detected only because its height is reduced with respect to the height of C-4

Table 3. Free energies of activation ($\Delta G^{\ddagger}$/kcal mol^{-1}) relative to the S,O-*syn*/S,O-*anti* interconversion for 2-acylthiophenes (**8**)—(**11**) as measured by ^{13}C n.m.r. (75.47 MHz) in CHF_2Cl. The value for thiophene-2-carbaldehyde (**7**) is for a solution in CD_2Cl_2 (ref. 12)

Compound	$\Delta G^{\ddagger}$	t/°C
(**7**) (R = H)	10.15 ± 0.15	−75
(**8**) (R = Me)	8.8 ± 0.2	−95
(**9**) (R = Et)	8.6 ± 0.2	−101
(**10**) (R = Pr^i)	8.5 ± 0.2	−102.5
(**11**) (R = pentan-3-yl)	8.8 ± 0.2	−92

present in amounts lower than 5%, in the solvent employed (CHF_2Cl).

The impossibility of detecting these signals did not prevent the determination of the free energy of activation for the *syn–anti* interconversion, with the exception of (**12**) where line broadening was not detected. At the temperature where maximum broadening occurs for a given line, the rate constant k can be obtained from the equation: $k = 2\pi p\Delta\nu$ with $p\Delta\nu = \Delta\omega$ [p and $\Delta\nu$ have the meanings previously indicated; $\Delta\omega = \omega_{max.} - \omega_0$, where $\omega_{max.}$ is the maximum observed line width (in Hz), and ω_0 is the linewidth in the absence of exchange].

An example of such temperature dependence observed at 75.47 MHz is shown in Figure 2 for the aromatic CH lines of the derivative (**10**) (R = Pr^i). The $\Delta G^{\ddagger}$ values obtained in this way are listed in Table 3. Although reliable $\Delta G^{\ddagger}$ values could be obtained in this way, we could not assign the structure of the preferred rotamers on the basis of the ^{13}C chemical shifts, as was possible in the case of the corresponding acylfurans.

The simplest member of the series of 2-acylthiophenes [thiophene-2-carbaldehyde (**7**)] is known to adopt essentially the S,O-*syn* conformation,[9–11,23–25] the amount of S,O-*anti* conformer being only a few percent.[12] Dipole moment[20,24,25] and n.m.r. investigations (lanthanide-induced shift[23] and nuclear Overhauser enhancements[26]) favour the S,O-*syn* structure also for 2-acetyl- (**8**)[20,23,25] and 2-pivaloyl-thiophene (**12**).[26] In order to assess by a uniform and reliable method the conformational preferences of all the 2-acylthiophenes (**7**)—(**12**), accurate lanthanide-induced shift (LIS) experiments were carried out for the whole series in $CDCl_3$. These shifts (ΔM) were measured at both ^1H and ^{13}C frequencies, using $Yb(fod)_3$ (known to minimize the contact contribution to the induced shift,[11,27] ΔM). The ΔM values were corrected, in the case of ^{13}C, for the contribution of the diamagnetic complexation shift (ΔD) using $La(fod)_3$.[11,27,28]

Table 4 gives the parameters obtained with the LIRAS computer program:[28] the values for thiophene-2-carbaldehyde (**7**) were recalculated[29] using the experimental shift of ref. 11 but

Table 4. Results of the analysis of LIS data for 2-acylthiophenes (**8**)—(**12**). The values for thiophene-2-carbaldehyde have been recalculated[29] using the data of ref. 11 (see text). For the meaning of the symbols used see the Experimental section and references 11, 28, and 30

Compound	S,O-*anti* (%)	Agreement factor	R.m.s. deviation (p.p.m.)	r/Å	φ/°	ψ/°	f	*endo* population (%)
(**7**) (R = H)	7	0.014	0.8	2.60	65	140	3 460	0
(**8**) (R = Me)	15	0.014	0.65	3.0	50	155	3 618	10
(**9**) (R = Et)	16	0.013	0.60	3.2	40	170	4 135	40
(**10**) (R = Pr^i)	25	0.014	0.50	3.4	30	170	3 310	60
(**11**) (R = pentan-3-yl)	10	0.010	0.43	3.6	20	170	4 373	50
(**12**) (R = Bu^t)	20	0.014	0.68	3.5	30	170	4 685	90—100

Table 5. Chemical shifts (^{13}C) of derivatives (**8**)—(**12**) in $CDCl_3$ (p.p.m. from Me_4Si)

	C-2	C-3	C-4	C-5	C–(CO)	CO	CH_3	
(**8**) (R = Me)	144.6	132.5	128.1	133.8	26.9	190.7	26.9	
(**9**) (R = Et)	144.2	131.6	128.0	133.2	32.6	193.8	8.5	
(**10**) (R = Pr^i)	143.7	131.6	128.1	133.4	37.2	195.4	19.4	
(**11**) (R = pentan-3-yl)	145.7	131.5	128.1	133.6	51.6	197.3	12.6	(CH_2 25.5)
(**12**) (R = Bu^t)	142.5	131.8	127.6	132.2	43.8	198.8	28.2	

allowing for the existence of the S,O-*anti* conformation, which had been recently detected[12] at low temperature. The small deviations observed indicate that, at least in $CDCl_3$, all the acylthiophenes exist as pairs of conformers, with S,O-*syn* predominant, a conclusion that agrees with those of previous investigations with different techniques.[20,24–26]

The LIS parameters of Table 4 are internally consistent; thus additional confidence can be given to the conformational assignment. In particular the distance (r/Å) between CO and Yb increases regularly from 2.6 Å when R = H (**7**) to 3.6—3.5 Å when R = pentan-3-yl or Bu^t [(**11**) and (**12**)]. This agrees with expectation since the bulkier the substituent the larger will be the distance of the lanthanide from the binding site of the molecule. The bulk is also expected to affect, in a two-site model, the population of the lanthanide in the positions *exo* and *endo* to the thiophene ring. Indeed when R = H (**7**) the Yb atom is found to stay on the side of the hydrogen atom (*endo* population with respect to thiophene, 0%) whereas when R = Bu^t (**12**), the opposite situation applies (*endo* population 100%): increasing *endo*/*exo* ratios are observed for R of intermediate dimensions. As observed in another case,[30] the conformational conclusions (and also the variation of the CO–Ln distance) are essentially the same when a one-site model (*e.g.* that employed in the MOLA program[24,31]) is used to analyse these results. This means that the conclusions concerning the conformational analysis are not reversed by a different treatment of the data.

Finally the trend of the measured $\Delta G^\ddagger$ values for the rotational process deserves some comment. Both in the furan derivatives (**1**)—(**6**) and in the thiophene derivatives (**7**)—(**11**) the $\Delta G^\ddagger$ values decrease with increasing bulk of the alkyl moiety, a feature often observed in homogeneous series of molecules having a planar rotational ground state.[32] In these conformational arrangements the bulky substituents reduce the efficiency of the conjugation, and hence destabilize the planar ground state. On the other hand in the excited (perpendicular) rotational state the steric effect of the bulky substituents is much lower, since there is little or no conjugation and, in addition, through-space interactions are lower. As a consequence the difference in energy between the excited and the ground rotational state (*i.e.* the rotational barrier) decreases when the bulk of the substituent increases.

This also helps to explain why, in contrast to the other acylthiophenes, line-broadening effects were not observed with the hindered 2-pivaloylthiophene (**12**). The rotational barrier when R = Bu^t is expected to be at least 1.5—2 kcal mol^{-1} lower than for the other ketones in the same series [see in Table 1 the barrier of (**6**) with respect to (**2**)—(**5**) in the furan derivatives]. As a consequence *syn–anti* exchange would be detectable in (**12**) at temperatures much lower (at least by 30 °C) than for the less hindered ketones. However, on lowering the temperature the amount of the minor conformer decreases, thus making the line-broadening effect [already quite small in (**8**)—(**11**)] even less remarkable. Moreover the possibility of a smaller chemical-shift difference between the two conformers of (**12**) should not be neglected: this would further reduce the broadening of the lines, making the effect undetectable even at the high field employed.

Experimental

Compounds.—The acetyl derivatives (**2**) and (**8**) were commercially available and were distilled before use. The other derivatives were prepared by acylation of furan and thiophene with the appropriate anhydrides according to the general method of ref. 33. The boiling points of (**3**) (63 °C at 6 mmHg), (**4**) (65 °C at 5 mmHg), (**6**) (60 °C at 5 mmHg), (**9**) (78 °C at 3 mmHg), (**10**) (114 °C at 20 mmHg), and (**12**) (75 °C at 2 mmHg) agree with those reported.[34]

The two ketones having R = $CHEt_2$ [(**5**) and (**11**)] are not reported in the literature. Their b.p.s were 97 °C at 22 mmHg (**5**) and 105 °C at 5 mmHg (**11**). As an example the synthesis of (**11**) is given here. In a 250 ml flask, thiophene (16 g, 0.2 mol) and 2-ethylbutanoic anhydride (51 g, 0.24 mol) were kept at 115 °C for 3.5 h in the presence of boron trifluoride–diethyl ether (2.8 g, 0.02 mol). The system was then cooled and 30% sodium hydroxide (30 ml; 0.3 mol) solution was added dropwise with stirring, with the temperature lower than 40 °C. After 2 h the mixture was diluted with water and extracted with CH_2Cl_2. The organic layer was washed to neutrality, dried, and evaporated under vacuum. The residue was distilled at 5 mmHg to give the ketone (**11**). All the compounds mentioned gave the expected ^{1}H and ^{13}C n.m.r. spectra. The ^{13}C shifts are collected in Table 2 for the furan derivatives (**2**)—(**6**) and in Table 5 for the thiophene derivatives (**8**)—(**12**).

Spectral Measurements.—The samples for the low-temperature studies were prepared by condensing (with liquid nitrogen) the gaseous solvents into n.m.r. tubes connected to a vacuum line. The tubes were then sealed and allowed to reach room temperature before being introduced into the precooled probes of the spectrometers. The 25.16 MHz ^{13}C spectra were recorded with a Varian XL-100 instrument: the temperatures were monitored by inserting a thermocouple into the probe before or after each measurement. The 75.47 MHz ^{13}C spectra were obtained with a Bruker CXP-300 instrument (high-field n.m.r. service, CNR, Italy) equipped with a special probe for reaching very low temperatures: the latter were measured by means of a calibrating sample introduced into the probe after each determination. This sample is made from [$^2H_6$]acetone (1 ml at 0 °C) and CHF_2Cl (3 ml at -80 °C). The difference between the shifts of CO and CH had been previously measured at 25.16 MHz at various temperatures (23 values in the range -26 to -159 °C) using thermocouples and thermistors. A linear relationship (correlation coefficient 0.998) between the temperature t (in °C) and the shift difference ($\Delta\nu$ in Hz at 25.16 MHz) was obtained: $t = 3\,286—1.440\ \Delta\nu$. This equation reproduces the measured temperatures with r.m.s. deviation 1.7 °C. By dividing the $\Delta\nu$ values observed at 75.47 MHz by three, this equation allowed measurement of the temperature inside the probe of the superconducting spectrometer.

The $Yb(fod)_3$ for the LIS measurements was sublimed *in vacuo* immediately before use. Increasing amounts were added to $CDCl_3$ solutions (*ca.* 0.5M) of ketones (**8**)—(**12**): the maximum molar ratio (ρ) between $Yb(fod)_3$ and the substrate was about 0.17. Usually four additions were made and each solution was divided in two parts to be studied at ^1H (300 MHz, Bruker CXP 300) and ^{13}C (Varian XL-100) frequencies: the measurements were completed the same day to avoid deterioration of the complex. The linear relationships ($\Delta\delta = a + b\rho$) between the shift differences ($\Delta\delta$ in p.p.m.) and the molar ratios (ρ) for the five points (initial solution plus four additions) had correlation coefficients equal to or better than 0.999, with intercepts (a) lower than 0.1 p.p.m. In the first-order 300 MHz proton spectra of (**8**)—(**11**) the assignment of the shifts to positions 3, 4, and 5 is straightforward (derived from knowledge of J_{HH} of thiophene). The assignment of the ^{13}C signals for 2-acetylthiophene (**8**) was made[35] by Huckerby, who demonstrated that the shifts of C-3 and C-5 are reversed with respect to the case of the corresponding aldehyde (**7**). In the acyl derivatives (**9**)—(**11**) these shifts are close to those of (**8**), and their separations (the $\Delta\delta$ values are in the range 1.3—2.1 p.p.m.) are rather similar (Table 5); as a consequence the same assignment was maintained. On the other hand in the case of the t-butyl derivative (**12**) (Table 5) the separation of the C-3 and C-5 shifts is greatly reduced ($\Delta\delta$ = 0.4 p.p.m.): a crossover of the signals cannot therefore be excluded, leading to an assignment opposite to that of (**8**)—(**11**). To remove this ambiguity the fully coupled spectrum of (**12**) was recorded: comparison of the carbon–hydrogen splittings between one ($^1J_{Cn,H}$ = 168.3, 169.5, and 184.9 Hz for n = 3, 4, 5, respectively), two ($^2J_{Cn,H}$ = 5.7, 4.3, and 6.9 Hz for n = 3, 4, and 5, respectively) and three bonds ($^3J_{Cn}$, H = 9.1 and 10.7 Hz for n = 3 and 5, respectively) with the corresponding values of the unsubstituted thiophene[35] allowed unambiguous assignment of the shifts of C-3 and C-5 (Table 5) in the case of (**12**) also.

The experimental LIS values were fitted according to the McConnel–Robertson equation assuming a 1:1 molar lanthanide–substrate complex. The 'two-sites' model described in ref. 27 (LIRAS computer program) was employed. In this model the lanthanide bonded to the oxygen of carbonyl can be either '*endo*' or '*exo*' with respect to the thiophene ring, and its position is described[27] by three co-ordinates (r, φ, and ψ). In addition to these four unknowns the normalizing factor (f) and the proportions of the S,O-*syn* and S,O-*anti* conformers have also to be determined. If the basic geometry of the molecule (bond angles and bond distances) is assumed, a total of six unknowns has to be determined. The same geometry of ref. 11 was maintained for the thiophene ring: a CO–R distance of 1.5 Å and an Ar–C(O)–R angle of 119° were employed. Since nine experimental shifts (three for ^1H and six for ^{13}C) are available, the system is sufficiently overdetermined to give reliable results.

In the case of the hindered 2-pivaloylthiophene (**12**) attempts were also made to fit the experimental LIS values assuming the existence of a single conformer having a nonplanar structure (*i.e.* a torsion angle different from zero between the plane containing the CO group and that of the ring). The agreement factor with experiment turned out to be unacceptable (more than twice that of Table 4), whichever value of the twist angle was employed.

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