Bandshape Analysis with Internal Resolution Standard

Barriers to Internal Rotation in 3,5-Dimethyl-4-(N,N-dimethylthiocarbamoyl)pyrazoles

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The barriers to rotation of the dimethylamino group in a series of 4-N,N-dimethylthiocarbamoylpyrazoles have been determined by the ¹H n.m.r. technique. For one of the compounds the rate constants have been determined over a temperature interval of 113 degrees by monitoring the exchange rate in the fast and slow exchange regions by the intensity of the resonances of the exchanging protons relative to an internal reference signal, and in the intermediate region by the conventional complete bandshape technique. The entropy and enthalpy of activation have been calculated, and the values obtained by the intensity method are in reasonable agreement with those obtained by the complete bandshape analysis. For the other compounds the usual coalescence approximation has been used. The thiocarbamoylpyrazoles were prepared by reaction between N,N-dimethyl- α,α -diacetylthioacetamide and the appropriate hydrazines.

INTRODUCTION

Lozac'h et al.¹ have shown that rates of stereomutation in uncoupled, equally populated two-site exchange systems in the region of slow exchange can be conveniently monitored by the ratio of the intensity of one of the exchange-broadened signals to that of a suitable reference signal. Similarly, Dimitrov² has used the ratio of the intensity of the resonance at the centre of the exchange-broadened doublet to that of a reference signal to measure exchange rates from temperatures below the coalescence temperatures to the region of fast exchange. Though single operational parameter methods in general are inferior to the methods employing the total bandshape,³ the methods referred to above may be used with advantage near the fast and slow exchange limits. This is mainly because the bandshape in these regions is nearly Lorentzian and is a function of an 'effective T_2 ,' which is conveniently measured by the signal intensity, and which depends in a simple way on the rate constant for the exchange process.

A good molecule for study by these methods including a comparison with the complete bandshape method, should have a non-exchanging chemical shift between the exchanging sites that is not too small and not too temperature dependent, and the exchange process should occur in an easily accessible temperature region. Besides, the molecule should contain one or more groups which can give suitable reference signals, since it is likely that the relaxation of the exchanging nuclei and of the reference nuclei have similar temperature dependencies if they are in the same molecule. This is also a guarantee for a constant population ratio. We have found that 1-phenyl-3,5dimethyl - 4 - (N, N - dimethylthiocarbamoyl) - pyrazole (1c) fulfils these requirements. In order to study the effect of the 1-substituent on the barrier, the 1-methyl (1b) and 1-unsubstituted (1a) analogues have been investigated at the coalescence temperature only, since it can be assumed that the three compounds have very similar activation entropies.



These compounds are readily prepared by reaction between 3-(N,N-dimethylthiocarbamoyl)-2,4-pentanedione (2)⁴ and the appropriate hydrazines:



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EXPERIMENTAL

Preparative part

3,5 - Dimethyl - 4 - (*N*,*N* **- dimethylthiocarbamoyl)pyrazole (1a).** Equivalent quantities of hydrazine hydrate and **2** were refluxed in ethanol for $5\frac{1}{2}$ h, when TLC showed complete consumption of **2**. After evaporation and drying on a porous tile, the crystalline residue was repeatedly recrystallized from toluene to give a 55% yield of colourless prisms, m.p. 152-153.5 °C. Found: C 52.5; H 7.04; N 22.7; S 17.3. C₈H₁₃N₃S (mol. wt. 183.28) requires C 52.4; H 7.15; N 22.9; S 17.5%.

1,3,5 - Trimethyl - 4 - (N,N - dimethylthiocarbamoyl)pyrazole (1b) was prepared as 1a from 2 and methylhydrazine in 61% yield as colourless prisms, m.p. 68 -70 °C after recrystallization twice from light petroleum (b.p. 80–100 °C). Found: C 54.9; H 7.67; N 21.2; S 16.2. C₉H₁₅N₃S (mol. wt. 197.30) requires C 54.8; H 7.66; N 21.3; S 16.3%.

1 - Phenyl - 3,5 - dimethyl - 4 - (*N*, *N* - dimethylthiocarbamoyl)-pyrazole (1c) was prepared as before from **2** and phenylhydrazine in refluxing glacial acetic acid. Complete reaction required $11\frac{1}{2}$ h, and the product was purified by column chromatography on silica. A 2:1 (v/v) mixture of chloroform and 2-butanone eluted the desired product, and after recrystallization twice from light petroleum (b.p. 80–100 °C), colourless prisms were obtained in 67% yield, m.p. 79–82 °C. Found: C 64.8; H 6.55; N 16.3; S 12.6. C₁₄H₁₇N₃S (mol. wt. 259.38) requires C 64.8; H 6.61; N 16.2; S 12.4.

N.m.r. spectra and evaluation of rate constants

The spectra were recorded on a JEOL MH-100 spectrometer equipped with a standard variable temperature probe and temperature controller. The spectra were recorded on 0.5 M solutions in *o*-dichlorobenzene (ODC) with the radiofrequency field well below the saturation level. Hexamethyldisiloxane ($\delta = 0.055$) was added with the solvent to provide the internal lock signal. The temperatures were measured as described in Ref. 5.

The rate constants (k) were evaluated by three different methods (a-c).

(a) Near the slow exchange limit. In this region the broadening is independent of the non-exchanging chemical shift, $\Delta \nu_0$, if the signals are sufficiently well separated for the overlap to be negligible. The signals are Lorentzian with a width, w, given by Eqn (1), where $T_{2\text{eff}}$ is

$$w = \frac{1}{\pi T_{2\text{eff}}} = \frac{1}{\pi} \left(\frac{1}{T_2} + k \right)$$
 (1)

the apparent transverse relaxation time including exchange and T_2 is the same parameter with the effects of exchange excluded. Resolution of k gives Eqn (2), and since T_2 and $T_{2\text{eff}}$ are proportional to the amplitudes of the signals,⁶ this expression can be transformed into Eqn (3).

$$k = \left(\frac{T_2}{T_{\text{2eff}}} - 1\right) \frac{1}{T_2} \tag{2}$$

$$k = \left(K\frac{I_{\text{ref}}}{I} - 1\right)\frac{1}{T_2} \tag{3}$$

I and I_{ref} are the intensities of the exchanging and reference signals respectively, and K is the ratio of the intensity of the reference signal to that of the exchange ing signal in the temperature region where exchange effects are negligible. Since we have two reference signals and two exchange-broadened signals, we have used their mean values in the evaluation of K (K = 1.02).

In Ref. 1 the rate constants were calculated with the T_2 value from one selected temperature (T_0) , using the ratio of the reference signal intensity at this temperature and at the actual temperature (T_i) and taking the effect of the temperature on the population of the nuclear spin levels into account [Eqn (4)].

$$k = \left(K\left(\frac{I_{\text{ref}}}{I}\right)_{i} - 1\right) \left[\frac{(I_{\text{ref}})_{0}}{(I_{\text{ref}})_{i}}\right] \left(\frac{T_{0}}{T_{i}}\right) \left(\frac{1}{T_{2}}\right)_{0}$$
(4)

The advantage with this method is that the calculation of a whole series of rate constants can be based on the measurement of only one line-width, for $(T_2)_0$, a measurement that is generally less precise than that of an intensity, and furthermore, an error in this parameter affects only ΔS^{\dagger} and not ΔH^{\dagger} [Eqn (6)]. This technique, however, requires that all spectra are recorded with constant radiofrequency field and constant gain, and since we have had difficulties in fulfilling these conditions, we have preferred to use Eqn (3) and to determine T_2 at each individual temperature. This determination was performed as described previously.⁷ The rate constants determined by method (a) are found in Table 1.

 Table 1. Data obtained by method (a) in the region of slow exchange

т(К) 303.6	Δνο(Hz) 41.4	τ ₂ (s) 0.258	/ _{ref} // 1.33	k (s ⁻¹) 1.36	∆G*(kJ mol ⁻¹) 73.57
309.6	41.5	0.261	1.62	2.50	73.51
312.9	41.6	0.279	1.92	3.42	73.51
317.4	41.7	0.286	2.38	5.00	73.61
321.4	41.6	0.252	2.97	8.03	73.29
325.4	41.6	0.275	3.78	10.4	73.55
327.3	41.7	0.290	4.22	11.4	73.44
331.6	41.6	0.302	5.36	14.6	74.06

(b) In the region of intermediate exchange rates the conventional complete bandshape method was employed. T_2 was determined as in (a), and $\Delta \nu_0$ was determined by bandfitting from the low temperature side until about 5 °C below the coalescence temperature. A plot of $\Delta \nu_0$ against temperature was quite linear, and $\Delta \nu_0$ values at and above the coalescence temperature were obtained by extrapolation of this plot. The bandfitting was performed by visual comparison. The results are found in Table 2.

Table 2. Data obtained by complete bandshape analysis

т(к) 336.5	Δν₀(Hz) ^ª 41.7	<i>T₂(s)</i> 0.307	k(s ⁻¹) 25.6	ΔG^{+} (kJ mol ⁻¹) 73.63
339.0	41.9	0.316	29.9	73.76
340.4	41.9	0.321	35.7	73.57
342.0	42.0	0.326	37.0	73.83
345.0	41.7	0.326	46.5	73.85
350.8	41.9	0.331	71.4	73.89
355.4	41.9	0.326	102	73.84
360.0	42.0	0.321	137	73.95
365.2	42.0	0.302	185	74.15
369.9	42.1	0.321	250	74.22
374.1	42.1	0.302	270	74.86
377.6	42.1	0.284	357	74.72
382.3	42.2	0.294	476	74.77
387.2	42.2	0.290	667	74.68

^a Obtained by band-fitting below 360.0 K, extrapolated from this temperature and upward.

(c) In the region near the fast exchange limit the expression derived by $Dimitrov^2$ [Eqn (5)] has been used, though without assuming

$$k = \frac{\frac{I}{KI_{\text{ref}}} (1 + \pi^2 \Delta \nu_0^2 T_2^2) - 2}{2T_2 \left(2 - \frac{I}{KI_{\text{ref}}}\right)}$$
(5)

that T_2 is equal for the exchanging system and the reference signal. This expression is not an approximation, and it is valid throughout the whole exchange region, but we have only used it in the range of I/I_{ref} from 0.4 to 1.1, corresponding to a temperature range of 25 °C. At lower intensity ratios the accuracy becomes questionable, and the normal total bandshape technique is to be preferred. The results obtained by method (c) are found in Table 3.

 Table 3. Data obtained by method (c) in the region of fast exchange

				_	
т(к) 392.0	∆ _{ν₀} (Hz) [*] 42.3	^{7₂(s)} 0.423	^{//I} ref 0.390	^{k(s⁻¹)} 930	∆G [‡] (kJ mol ⁻¹) 74.57
396.9	42.3	0.282	0.635	1190	74.72
401.9	42.3	0.290	0.770	1660	74.61
406.5	42.4	0.385	0.740	2060	74.76
411.9	42.4	0.371	0.910	2840	74.70
416.7	42.5	0.336	1.09	3750	74.65

* Extrapolated values.

In this temperature region the reference signals showed some overlap, and the correct intensity values were found by simulating the experimental signals by two overlapping Lorentzians.

The fast exchange limit cannot be reached for 1c, and the correction constant K [Eqns (3) and (5)] can therefore not be measured for the upper temperature region. It is assumed to have the same value over the entire range of temperatures. This assumption is also implicit in the method used to evaluate T_2 .⁷

The activation enthalpies and entropies derived by

these three methods and by their combinations are collected in Table 4. The data are obtained by a linear regression analysis of $\ln (k/T)$ versus (1/T) according to the Eyring equation⁸ in the form of Eqn (6). The plot for the combination of all three methods is shown in Fig. 1.

$$\ln\frac{k}{T} = -\frac{\Delta H^{\dagger}}{RT} + \frac{\Delta S^{\dagger}}{R} + \ln\frac{k_B}{h}$$
(6)

The free energy barriers for **1a**, **1b** and **1c** at the coalescence temperature, calculated by the simple expression $(7)^9$ are found in Table 5.

$$\Delta G_{T_c}^{\dagger} = 0.01913 T_c (9.972 + \log T_c - \log \Delta \nu_0) \quad (7)$$

DISCUSSION

The method. It follows from the data in Table 4 that the three methods give reasonably similar results, even if the spread in ΔH^{\ddagger} and ΔS^{\ddagger} is greater than the standard deviation. The separate results from methods (a) and (c), however, being obtained over rather limited temperature regions, must be viewed with some caution. However, assuming a maximal error of 10% in the rate constants (mainly originating in uncertainty in T_2), and of 1.0 K in the temperatures, maximal errors of ± 0.53 kJ mol⁻¹ and 0.50 kJ mol⁻¹ at the high and low temperature extremes are obtained from Eqn (8). Making the

$$\frac{\mathrm{d}\Delta G^{\dagger}}{\Delta G^{\dagger}} = \frac{R}{\Delta G^{\dagger}} \left| \mathrm{d}T \right| + \frac{RT}{\Delta G^{\dagger}} \left| \frac{\mathrm{d}k}{k} \right| + \left| \frac{\mathrm{d}T}{T} \right| \tag{8}$$

probably grossly exaggerated assumption that the errors in all points are equal to the maximum error (σ_{max}) , we can calculate the maximal errors in ΔS^{\dagger} and ΔH^{\dagger} , using Eqns (9).

δ

$$\Delta G^{\dagger} = \Delta H^{\dagger} - T \Delta S^{\dagger} \tag{9a}$$

$$\Delta S_{\max}^{+} = \frac{\sigma_{\max}}{T_{\max} - T_{\min}} \tag{9b}$$

$$\delta \Delta H_{\rm max}^{\dagger} = \frac{T_{\rm max} \sigma_{\rm max}}{T_{\rm max} - T_{\rm min}} \tag{9c}$$

These errors are probably more realistic than those obtained from the standard deviations. It is also obvious that the rate constants calculated by Eqns (3) and (5) are increasingly unreliable as (I_{ref}/I) approaches 1 and 0.5, respectively.

To sum up the results, the points in favour of methods (a) and (c) are the following:

1. Used together, they give a larger temperature interval than the complete bandshape method, and this decreases the errors in ΔH^{+} and ΔS^{+} (Table 4).

2. Changes in intensity ratio that result from changes in rate of exchange are more readily observed and are measured with greater precision than changes in band-width. The calculation of rate constants by Eqns (3) and (5) involves only one band-width measurement, whereas the conventional expressions used near the fast and slow exchange limits require two

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Method(s) a	∆ <i>н</i> ** 70.2	δ∆H ^{+b} ±2.5	δ∆ <i>H</i> ^{+°} ±5.9	∆ <i>S</i> ^{+d} −11	δΔS ^{+b} ±8	δΔS ⁺ ° ±17.9	$\Delta G_{298,2}^{+2}$ 73.5
u	(16.8)	(±0.6)	(±1.4)	(-2.6)	(±1.9)	(±4.3)	(17.56)
b	65.5	±1.0	±3.9	-24.2	±2.7	±10.2	72.7
	(15.7)	(±0.2)	(±0.9)	(-5.8)	(±0.6)	(±2.4)	(17.38)
c	73.5	±1.6	±8.9	-3.0	±3.9	±21.5	74.4
	(17.6)	(±0.4)	(±2.1)	(→0.7)	(±0.9)	(±5.1)	(17.78)
a+c	69.7	±0.4	±2.0	-12.3	±1.1	±4.7	73.37
	(16.7)	(±0.1)	(±0.5)	(-2.9)	(±0.3)	(±1.1)	(17.54)
a+b+c	69.2	±0.4	±2.0	-13.9	±1.2	±4.7	73.34
	(16.5)	(±0.1)	(±0.5)	(-3.3)	(±0.3)	(±1.1)	(17.53)

Table 4. Activation parameters for 1c

^a ln kJ mol⁻¹ (in parentheses kcal mol⁻¹).





Figure 1. Eyring plot of data from method a (\bigcirc), b (+), and c (\square).

Table 5. Free energy barriers at the coalescence temperature (solvent ODC, 60 MHz)

Compound 1a	Δν ₀ (Hz) 28.8	т _с (К) 339.8	∆G [†] (kJ mol ^{−1ª}) 71.8 (17.2)
1b	29.8	341.2	72.0 (17.2)
1c	25.0	350.2	74.5 (17.8)

^a In kcal mol⁻¹ in parentheses.

line-width measurements with a concomitant larger uncertainty.

3. The combined use of methods (a) and (c) allows reliable values for ΔH^{\dagger} and ΔS^{\dagger} for an exchange process to be obtained with much less labour than using the complete bandshape method.

4. In exchange systems where the coalescence temperature cannot be reached or where the coalescence is unobservable due to overlap with other signals, but where one signal of the exchange doublet can be observed at slow exchange together with a suitable reference, method (a) can be used instead of Eqn (7) to obtain reasonably reliable rate constants and free energies of activation in the accessible temperature region.

On the negative side, the following factors should be mentioned:

1. The need for a reference signal, which should be a singlet with an intensity similar to that of the ex-

 $^{\rm c}$ Maximal deviation according to Eqn. 9. $^{\rm d}$ In J mol $^{-1}$ K $^{-1}$ (in parentheses cal mol $^{-1}$ K $^{-1}$).

changing signals. As mentioned above, the reference nuclei should preferably be attached to the same molecule as the exchanging nuclei, since then the correlation times for molecular motion will be the same, and the temperature dependencies of T_2 in the absence of exchange will be similar. At ambient and higher temperature in low-viscosity solvents, however, the effective T_2 is probably mainly determined by homogeneity factors, and in this region it is probably acceptable to add a suitable reference substance with low volatility.

2. Method (c) is very sensitive to the value of $\Delta \nu_0$, and if this cannot be extrapolated with certainty from low temperatures, this method is likely to produce large systematic errors. The case of 1c is especially favourable with a very slight temperature dependence of Δv_0 , but one generally finds very moderate and linear changes of Δv_0 with temperature. However, cases with non-linear behaviour are known from molecules involved in strong association^{10,11} or other temperature dependent equilibria,¹² and these are not amenable to the use of method (c).

The method with an internal resolution standard in the version presented here can in principle also be used for other exchange systems. In coupled systems, however, the same effect is often obtained within the exchange system, since different signals are very differently affected by the exchange.¹³ In uncoupled unpopulated two-site systems, equally however, method (a) can be used directly, each signal giving the rate constant for escape from that site. Near the fast exchange limit, however, no simple expression like Eqn (5) can be obtained for the rate constants as functions of the intensity of the single line, and it is advisable to use the complete bandshape method.

The barriers. The barriers to rotation of the dimethylamino group in ortho-substituted (hetero)aromatic N,N-dimethylthioamides are modified by the following effects, the barrier in N,N-dimethylthioformamide $(\Delta G_{443}^{+} = 101.2 - 102.9 \text{ kJ mol}^{-1} \text{ in } meta$ dichlorobenzene¹⁴) being taken as a reference.

1. A conjugation effect of the aromatic or heteroaromatic ring, which lowers the barrier.

2. A steric effect of the ortho substituent(s) may turn the thioamide group out of the ring plane and diminish the first effect, thus raising the barrier. A considerable deviation from the planar state $(c. 40^{\circ})$ already exists in N,N-dimethylthiobenzamides without ortho substituents.15

3. A strong steric effect of the *ortho* substituents may even hinder the rotation of the dimethylamino group in the twisted thioamide and cause a further increase of the barrier. Such effects have been observed by Mannschreck¹⁶ and by Staab and Lauer.¹⁷

The first effect is generally observed in aromatic amides¹⁸ and thioamides,¹⁹ and aromatic groups with π -donor character are more barrier-lowering than those with π -acceptor character. This is readily rationalized by a consideration of the interactions in the ground state and in the transition state. The thiocarbonyl group is an electron sink, which is cross-conjugated with the aromatic ring and the dimethylamino group in the ground state, but conjugated only with the aromatic ring in the transition state, which leads to a relatively stronger interaction with the aromatic ring is π -excessive, and the 4-position is the centre of electrophilic reactivity.²⁰ Therefore the π -donor character of the pyrazole ring is probably responsible

for the lowering of the thioamide barrier by c. 25 kJ mol^{-1} . It is possible that the 3- and 5-methyl groups contribute to a steric effect of type 2 above, but this will be smaller than in an *ortho-ortho*-disubstituted 6-membered ring.

Slightly lower free energy barriers are found for **1a** and **1b** than for **1c** (Table 5), and this is probably because the 1-phenyl ring diminishes the electron density in the pyrazole ring and notably in the 4-position, since the 1-nitrogen atom is the source of the excess of π -electrons in the ring. A similar coupling between the 1- and 4-positions was observed in a study of 1-N,N-dimethylthiocarbamoylpyrazoles with donor and acceptor substituents in position 4.²¹

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