Pergamon

Tetrahedron 56 (2000) 1739–1743

TETRAHEDRON

Hindered Inversion/Rotation in Diheteroaryl Alkyl Amines with a *N*-(1-Pyrazolyl) Group: Dynamic NMR and Molecular Modelling Studies

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Dedicated to Prof. José Elguero on the occasion of his 65th birthday

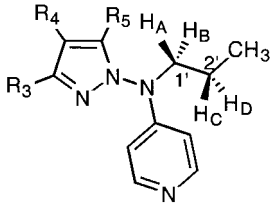
Received 25 October 1999; revised 24 November 1999; accepted 9 December 1999

Abstract—Hindered pyramidal inversion and restricted rotation in *N*-propyl-*N*-(4-pyridyl)-1-amino-1*H*-pyrazoles were studied by dynamic NMR spectroscopy and molecular modelling. From lineshape analyses of two sets of signals by ^{1}H NMR, thermodynamic parameters were obtained (ΔG, ΔH, and ΔS). The molecular modelling studies allowed us to assign the contribution of both nitrogen inversion (12.3 kcal mol^{-1}) and N–C rotation (2.7 kcal mol^{-1}) to the enthalpy of the energetic barrier.

Introduction

Since many pharmaceuticals have a tertiary amine in their structure, both the pyramidal inversion at nitrogen and rotation about the nitrogen–carbon bond are interesting processes in Medicinal Chemistry, in order to explain possible interactions with biological receptors. Although the stereodynamics of a wide range of trisubstituted amines have been studied over the last years,[1] to our knowledge, there is not any published work about tertiary amines with a *N*-(1-pyrazolyl) group.

In this paper we describe our findings about slow nitrogen inversion and restricted rotation in *N*-propyl-*N*-(4-pyridyl)-1-amino-1*H*-pyrazoles[2] with muscarinic and adrenergic properties. These compounds could be considered as sterically and electronically crowded amines, due to the presence of two aryl substituents and a N–N–N arrangement with associated lone pairs. The combination of the effects of steric volume, electronegativity, and lone pair–lone pair repulsions in the transition state[3] could lead to relatively high conformational barriers for these compounds.



1, $R_3 = R_5 = CH_3$, $R_4 = H$
2, $R_3 = R_5 = CO_2Et$, $R_4 = H$
3, $R_3—R_4 = (CH_2)_3$, $R_5 = CH_3$

Results and Discussion

Preliminary ^{1}H NMR spectra of compounds **1**–**3**, registered at room temperature, established the magnetic non-equivalence of the protons bound to carbons 1′ (H_A and H_B) and 2′ (H_C and H_D) of the *n*-propyl chain, in different deuterated solvents: chloroform, methanol, and dimethyl sulfoxide. These facts indicate the existence of a slow nitrogen inversion and/or a slow rotation on the NMR time-scale.[4]

Protons H_A and H_B showed two sets of a doublet–doublet–doublet system, due to a geminal constant (J_{AB}) and four vicinal constants (J_{AC}, J_{AD}, J_{BC}, and J_{BD}). Protons H_C and H_D appeared as two complex multiplets, that were fully resolved from the spectra irradiated at the chemical shifts of protons H_A and H_B. In this case, those coupling constants already known are eliminated and protons H_C and H_D became as two sets of a doublet–quartet system, due to the geminal (J_{CD}) and the vicinal coupling constant with the methyl group ($J_{2'3'}$), that appeared as a triplet in all compounds (Table 1). Addition of an excess of deuterated

Keywords: pyrazolic tertiary amines; nitrogen inversion; C–N rotation; dynamic NMR; molecular modelling.

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† This paper comprises a part of Isabel Dorronsoro's Ph.D. Thesis.

0040–4020/00/$ - see front matter
PII: S0040-4020(99)01086-8

Table 1. [1]H NMR parameters for the propyl chain of **1**–**3** at 293 K: chemical shifts (ppm) and coupling constants (Hz)

No.	Solvent	H_A	H_B	H_C	H_D	CH_3	J_{AB}	J_{AC}	J_{AD}	J_{BC}	J_{BD}	J_{CD}	$J_{2'3'}$
1	$CDCl_3$	3.76	3.60	1.64	1.60	0.97	−13.5	5.9	9.3	9.4	6.7	−13.5	7.4
1	$(CD_3)_2SO$	3.67	3.67	1.55	1.42	0.91	–	7.4	7.4	7.4	7.4	−13.4	7.4
2	$CDCl_3$	3.83	3.58	1.59	1.57	0.91	−14.2	6.0	8.9	9.0	6.5	−13.8	7.8
3	$CDCl_3$	3.76	3.60	1.69	1.61	0.97	−13.5	5.6	9.7	9.7	6.3	−13.5	7.4
3	CD_3OD[a]	3.99	3.91	1.90	1.80	1.20	−13.7	5.8	9.1	9.1	6.6	−14.4	7.4
3	$(CD_3)_2SO$[a]	3.72	3.64	1.59	1.48	0.91	−13.7	5.8	9.1	9.1	6.3	−14.5	7.4

[a] Addition of an excess of NaOD did not change the spectral appearance.

sodium hydroxide to samples in MeOD or $(CD_3)_2SO$ did not change the whole spectral appearance, pointing out that this fact was not due to the protonation of the tertiary amine, in contrast with a recent reported work about antidepressant drugs.[5]

It is worth mentioning that the spectrum of **1** in $(CD_3)_2SO$ showed a simple triplet for protons H_AH_B, that became isochronous by chance,[6] although they continued being diastereotopic. The H_CH_D resonance appeared as the complex multiplet already explained for the rest of the cases.

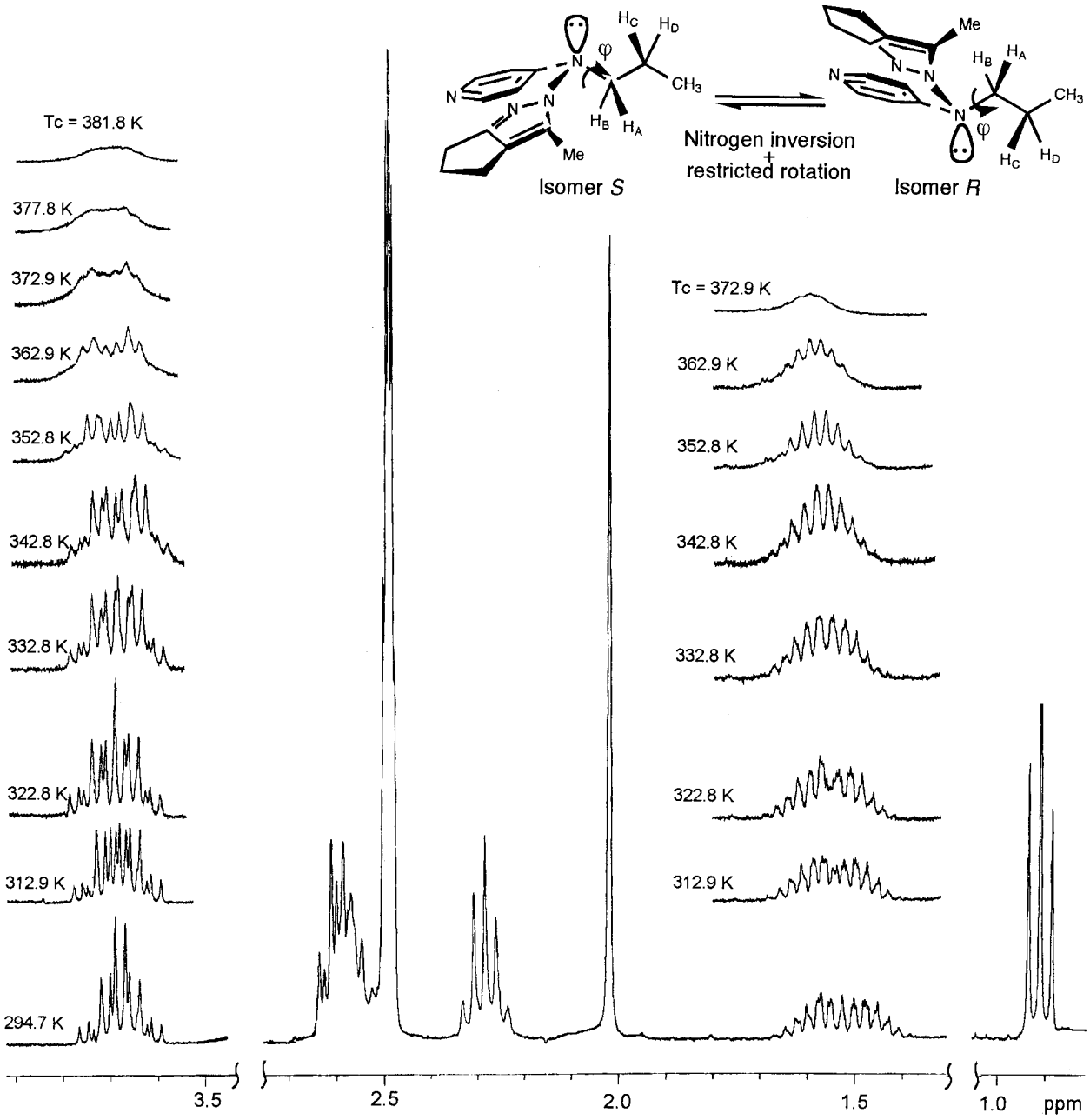

Figure 1. [1]H NMR spectra of **3** at several temperatures in the range 294–383 K.

Table 2. Chemical shifts (ppm) of protons H_A–H_D at the studied temperatures

T (K)	H_A	H_B	H_C	H_D
294.7	3.717	3.641	1.587	1.473
303.0	3.721	3.640	1.594	1.484
312.9	3.723	3.634	1.598	1.492
322.8	3.728	3.632	1.604	1.500
332.8	3.732	3.630	1.610	1.508
342.8	3.737	3.628	1.617	1.516
352.8	3.740	3.625	1.621	1.525
362.9	3.744	3.622	1.628[a]	1.533[a]
372.9	3.747	3.619	1.633[a]	1.542[a]
377.8	3.749[a]	3.617[a]		
381.8	3.751[a]	3.616[a]		

[a] Estimated values.

Table 3. Experimental line width ($\Delta\nu$, Hz) and calculated rate constants (k, s^{-1})

T (K)	$\Delta\nu_{AB}$[a]	k_{AB}	$\Delta\nu_{CD}$[a]	k_{CD}
332.8	2.8	6.2	2.4	7.0
342.8	3.8	10.0	4.7	12.1
352.8	5.1	18.1	8.7	24.7
362.9	9.3	41.5	15.7	44.2
372.9	24.0	75.3	45.8	80.2
377.8	28.8	95.0		
381.8	67.5	127.2		

[a] $\Delta\nu$ is the difference between line width of each methylene and the line width of the central signal of DMSO-d_6 used as reference.

The above findings prompted us to carry out a dynamic-NMR study, increasing the temperature. As the simplest compound, **1** was not suitable for this study due to the isochrony of its protons H_AH_B in deuterated dimethyl sulfoxide, we chose compound **3** as model. ^{1}H NMR spectra of **3** in deuterated dimethyl sulfoxide (0.023 M) at temperatures ranging from 294 to 383 K were measured, including spectra with the H_AH_B resonances decoupled. As the temperature was increased, both systems H_AH_B and H_CH_D broadened significantly, and their coalescences could be observed at 381.8 and 372.9 K, respectively (Fig. 1).[7] Cooling the sample to room temperature produced a spectrum identical to the original, confirming the existence of a dynamic and reversible process.

Resolutions of the spin systems at each temperature were first carried out manually, and then were refined by the use of the gNMR program[8] until each theoretical spectrum fit with the experimental one with an error of ± 0.001 ppm (± 0.3 Hz). Chemical shifts of implicated protons at several temperatures are gathered in Table 2. In temperatures near to coalescences, it was difficult to measure chemical shifts, but they were estimated from the linear drifts observed for all protons at lower temperatures. It is interesting to note that as the temperature increases the frequency difference between H_A and H_B increases, whereas in the couple H_C, H_D this difference decreases (Fig. 2).

In order to obtain thermodynamic parameters, lineshape analyses for both couples H_AH_B and H_CH_D, were carried out using the gNMR program. Calculations were made considering that the processes are degenerative, since in both methylenes H_AH_B and H_CH_D, protons interconverted ($H_A \leftrightarrow H_B$ and $H_C \leftrightarrow H_D$). As the multiplets were symmetrical over the whole temperature range, we assumed that populations were the same in the two sites. For each temperature, the rate constants (k) were obtained by trying several values until the theoretical spectrum fit with the corresponding observed one (Table 3). An example of a calculated and the corresponding experimental spectrum is shown in Fig. 3.

Plotting $\ln(k/T)$ vs. $1/T$ gave straight lines, that were subject to least-squares linear regression analyses (Fig. 4), rendering enthalpy $\Delta H^{\neq}$, entropy $\Delta S^{\neq}$, and free energy of activation $\Delta G^{\neq}$ (Table 4) by means of the Eyring equation.[9] These experimentally obtained values are equivalent within

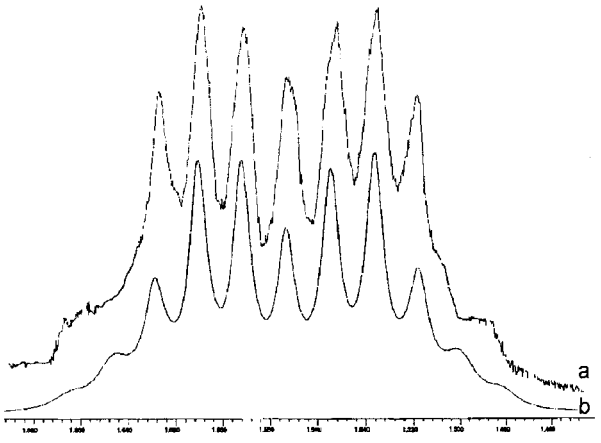

Figure 3. Experimental (a) and calculated (b) spectra of H_CH_D at 352.8 K (with H_AH_B resonances decoupled).

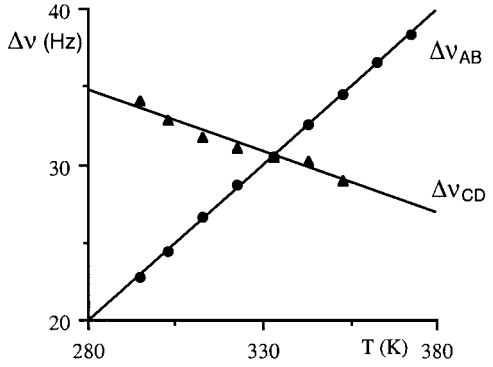

Figure 2. Frequency differences (Hz) in each couple H_AH_B and H_CH_D.

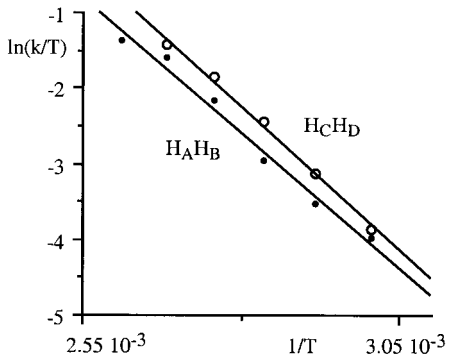

Figure 4. Plots of $\ln(k/T)$ vs. $1/T$.

Table 4. Calculated activation parameters using the Eyring equation

	T_c (K)	$\Delta G^{\neq a}$	$\Delta H^{\neq a}$	$\Delta S^{\neq b}$
H_AH_B	381.8	19.0±0.5	14.2±0.3	−12.6±0.7
H_CH_D	372.9	18.8±0.5	14.5±0.3	−11.5±0.7

[a] In kcal mol^{-1} (1 cal=4.184 J).
[b] In e.u. (cal mol^{-1} K^{-1}).

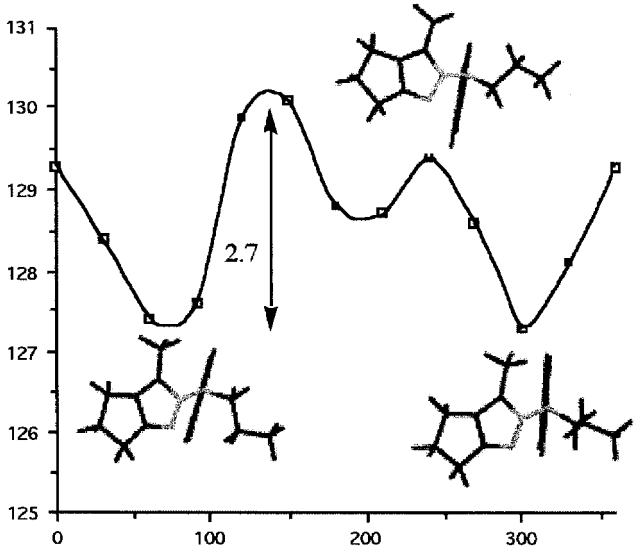

Figure 5. Conformational analysis of enantiomer *S*.[11]

the experimental error and are attributable to the sum of the nitrogen inversion and the restricted rotation of the alkyl chain around this nitrogen.

Both the coalescence temperatures and the free energies of activation $\Delta G^{\neq}$ found in this work are higher than those reported for open-chain amines containing heteroatoms, suggesting that the steric effects of the pyridine and the pyrazole nucleus have an important contribution to the energetic barrier. Moreover, the negative activation entropy found experimentally supports this idea, since slight negative activation entropies are often found in dynamic-NMR studies of intramolecular processes with a crowded transition state.[10]

With the aim of understanding the contribution of the nitrogen inversion and the alkyl rotation in the above energetic barrier of compound **3**, some molecular modelling studies were carried out.

Firstly, in order to evaluate the rotational barrier, a conformational analysis of both enantiomers *R* and *S* was achieved. Compound **3** was built with Spartan software and conformational search was performed using rotation in 30° increments for torsion angle φ (see Fig. 1) followed by geometric optimisation using semiempirical method AM1. As a result, the enthalpy vs. torsion angle plot was obtained (Fig. 5), showing a barrier rotation of 2.7 kcal mol^{-1}. On the other hand, the nitrogen inversion was evaluated simulating the transition state from the lowest minima found for *R* enantiomer to the lowest minima found for the *S* one, finding an inversion barrier of 12.3 kcal mol^{-1} (Fig. 6). The sum of the two processes yields a value of $\Delta H_f°$=15 kcal mol^{-1} which is in agreement with the experimental determination described above.

Experimental

Compounds **1**–**3** were previously prepared by our group.[2] The ^{1}H NMR spectra were recorded in a Varian VXR 300 spectrometer. Chemical shifts (ppm) were referenced to the solvent peaks at 7.24 ($CDCl_3$), 2.49 [$(CD_3)_2SO$] and 3.50 (CD_3OD). Calculations for complete lineshape analyses were carried out using the gNMR program.[8] Theoretical spectra were calculated to obtain the best fit with the observed spectra by varying the rate constants for each temperature. The activation parameters were obtained from the Eyring equation, plotting $\ln(k/T)$ as a function of $1/T$ and performing regression analyses of these data.

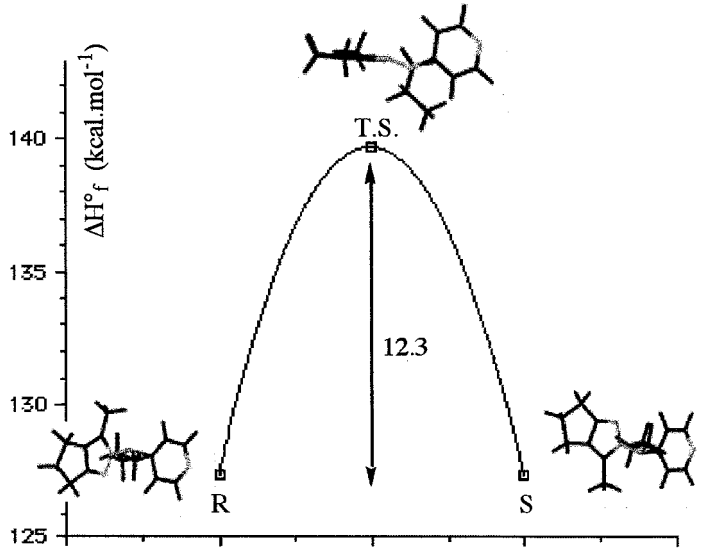

Figure 6. Simulated nitrogen inversion.

Spartan software[12] implemented on a Silicon Graphics working station was used in the molecular modelling studies. Input geometries were taken from the standard ones within Spartan program. Semiempirical calculations were performed using the AM1 method.[13] In all cases, full geometry optimisations with Fletcher–Power algorithm were carried out.

Acknowledgements

The authors gratefully acknowledge the fellowship to one of us (I.D.) from the Fundación Ramón Areces and the financial support of C.I.C.Y.T. (Projects no. SAF 99-0098 and SAF 99-0063). The Sociedad Española de Química Terapéutrica awarded the 'Laboratorios Faes Prize for Young Researchers—1999' to a part of this work.

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