

Pyramidal Nitrogen Inversion Hindered by a Strong Intramolecular Hydrogen Bond in 2-Diethylaminomethylphenols

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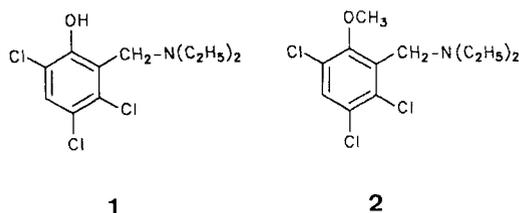
In the ^1H NMR spectra of 2-diethylaminomethyl-3,4,6-trichlorophenol (**1**) below 260 K, an additional splitting of the CH_2 signal was found, which can be ascribed to the hindered nitrogen inversion. In the molecule of the *O*-methylated derivative (**2**) this process is fast (on the NMR time-scale) down to 150 K. The frequencies and the activation parameters of the nitrogen inversion in (**1**) were measured by DNMR, which indicated that the inversion requires a preliminary stage of breaking an intramolecular hydrogen bond. The activation enthalpy, $\Delta H_{\text{inv}}^\ddagger$, of the inversion stage was evaluated as $28.5 \pm 6.7 \text{ kJ mol}^{-1}$.

KEY WORDS ^1H NMR Nitrogen inversion *ortho*-Mannich bases

INTRODUCTION

The potential barrier of the pyramidal nitrogen (sp^3) inversion process has been evaluated from IR spectra as a small value [$25\text{--}29 \text{ kJ mol}^{-1}$ for NH_3 , $29\text{--}34 \text{ kJ mol}^{-1}$ for $\text{N}(\text{CH}_3)_3$].¹ In light amine molecules this process proceeds mainly through tunnelling, causing very high inversion frequencies (e.g. 10^{11} s^{-1} at room temperature for NH_3). Heavier molecules such as substituted benzylamines should be characterized by inversion barriers of the same order of magnitude, but the lesser contribution of tunnelling makes the inversion frequencies low enough ($10^2\text{--}10^4 \text{ s}^{-1}$ in the temperature range 100–150 K) to be measured by means of NMR.^{2–6} For example, in the pyramidal RCH_2NXY molecules (where X and Y are different substituents), the slowing of the process is reflected in two diastereotopic CH_2 protons becoming anisochronous, which was used^{2,3} for evaluating the lifetimes of two equivalent isomers by various techniques of DNMR. The protonation of the nitrogen lone pair in amines eliminates the possibility of intramolecular inversion and thus results

in the CH_2 protons appearing at room temperature as an AB spin system in NMR spectra. When investigating 2-hydroxybenzylamines with a strong intramolecular hydrogen bond,^{7–9} we have been faced with a similar transformation of the spectra at temperatures as high as 240–260 K. In this paper, ^1H NMR spectra of 2-diethylaminomethyl-3,4,6-trichlorophenol (**1**) and of its methylated derivative **2** are discussed.



EXPERIMENTAL

2-Diethylaminomethyl-3,4,6-trichlorophenol (**1**) was obtained as described⁸ by the Mannich reaction and purified by repeated recrystallization from methanol. Methylation of **1** was carried out by heating with

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dimethyl sulphate in an aqueous solution (pH 10–11), followed by extraction with diethyl ether and recrystallization.

^1H NMR spectra (200 MHz) in CD_2Cl_2 and $\text{C}_2\text{D}_5\text{Cl}$ were obtained using a Bruker AC-200 instrument equipped with a BVT-1000 thermostabilizing system, calibrated by the OH signal of CH_3OH . The temperature was maintained and measured with an accuracy of ± 1 K. The frequencies of the process, averaging the CH_2 signals, were extracted from the spectra where the CH_3 protons were decoupled [see Fig. 2(d)] using a DNMR density matrix method.^{10,11} A simplified program¹² was applied. Two parameters, $\Delta\delta$ and τ^{-1} , were varied while the third, $J(\text{HH}) = 13.8$ Hz, was taken as independent of temperature. The line widths, not affected by the exchange, were obtained from the PhCH_2N singlet.

UV absorption spectra of **1** under the same conditions were recorded on a Shimadzu UV-3100 spectrophotometer with a JEOL optical cryostat.

RESULTS AND DISCUSSION

Figure 1 shows the ^1H NMR spectrum of **1** at room temperature. The signal of the $\text{OH}\cdots\text{N}$ bridge proton is localized at a very high value of the chemical shift (13.52 ppm), which indicates the existence of a strong hydrogen bond. This type of hydrogen bond is characteristic of systems where the proton is markedly shifted towards the centre of the bridge, but no proton transfer from the OH group to the nitrogen atom takes place. In fact, our studies of UV spectra over a broad temperature range did not reveal the presence of a $^1\text{L}_b$ absorption band at about 310–350 nm characteristic of phenolate anions.¹³ Figure 2 shows the evolution of the ^1H NMR CH_2 signal of ethyl groups with decrease in temperature.

Transformation of the CH_3CH_2 spin system A_2X_3 to ABX_3 is observed, corresponding to slowing down an averaging process, involving nitrogen inversion.

In the spectra of the methylated phenol **2**, no signs of a similar transformation were observed down to temperatures as low as 150 K (the thermostabilizing system

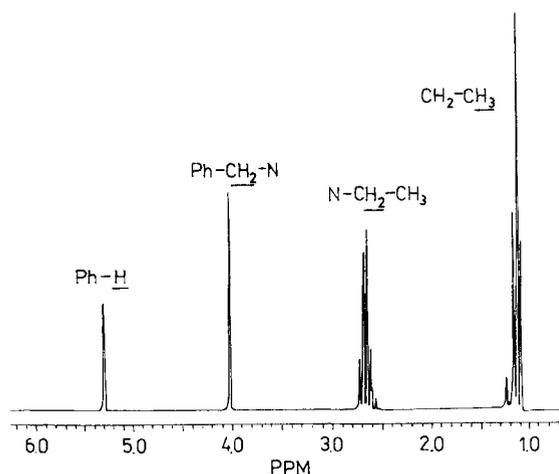


Figure 1. ^1H NMR spectrum of **1** at room temperature in CD_2Cl_2 .

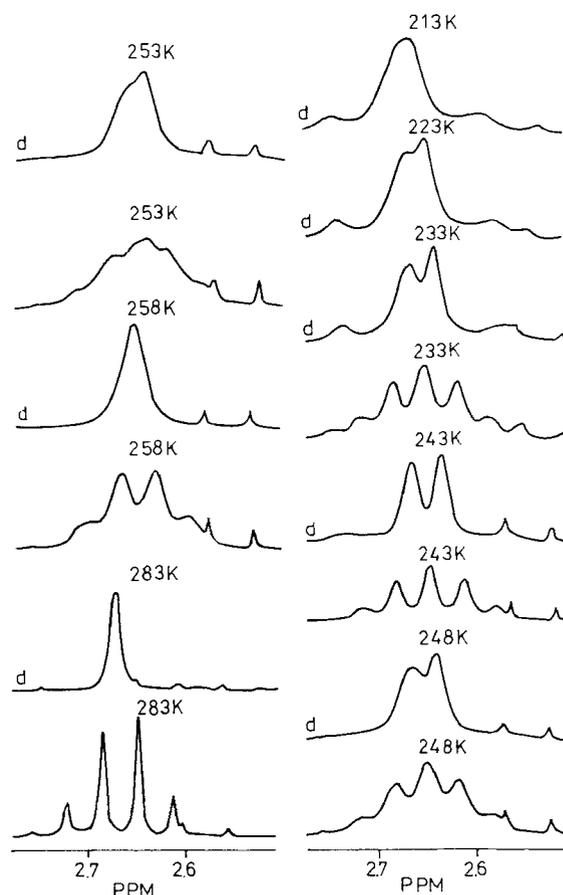


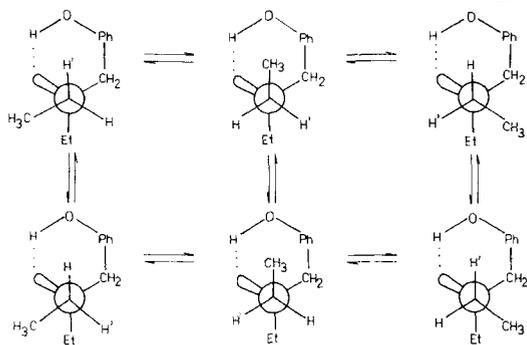
Figure 2. Evolution of the ^1H NMR CH_2 signal of the CH_3CH_2 groups in **1**; d = with CH_3 resonances decoupled.

did not allow us to reach even lower temperatures as used elsewhere.^{2–6}) Most likely, slowing the inversion in **2** would occur in the range 110–130 K, as in other amines with bulky substituents.²

The spectra presented in Figs 1 and 2 do not depend on concentration in the range 10^{-4} – 10^{-2} M, which indicates the intramolecular character of the averaging process.

As can be seen in Fig. 2, the CH_2 signal of CH_3CH_2 group in **1** on r.f. saturation of the CH_3 groups below 250 K is a slightly asymmetric AB quartet. The additional broadening of the downfield part of the quartet probably originates from unresolved long-range spin-spin coupling with the OH bridge proton and the PhCH_2N group, characteristic of one of the two diastereotopic CH_2 protons. When comparing the experimental spectra with the simulated spectra for elucidating the frequencies of the averaging process, we used the upfield part of the AB system only.

The splitting of the CH_2 signal is manifested most sharply at 245 K; further lowering the temperature to 200 K results in a decrease in the splitting value, $\Delta\delta_{\text{HH}}$, and, therefore, in the reverse 'coalescence' of the signals. This can be accounted for by shifting the equilibrium between three non-equivalent pairs of rotamers (Scheme 1). The internal rotation around the $\text{CH}_3\text{CH}_2\text{—N}$ single bond must be immeasurably fast down to at least 150 K. Hence the signals observed are averaged by this process. As the splitting values, $\Delta\delta_{\text{HH}}$, in these three

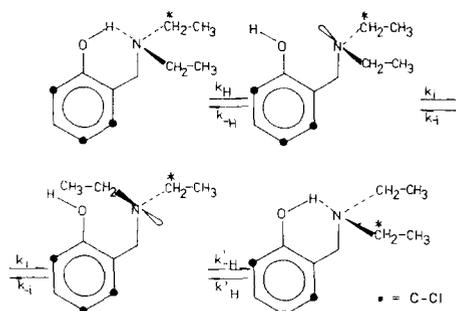


Scheme 1

pairs are different, the effective value is markedly dependent on temperature. The question of the influence of the fast internal rotation on the NMR spectra of diastereotopic nuclei was considered in detail by Raban.¹⁴

The values related to the frequencies of the CH₂ signals, obtained by using the DNMR computing program, are as follows: $\Delta\delta_{\text{HH}} = 0.031 \pm 0.002$ ppm (in the region 230–260 K); $J(\text{HH}) = 13.8$ Hz; $\tau^{-1} = 14.2$ (248 K), 25.0 (253 K), 43.7 (258 K), 73.5 (263 K), 125 (268 K), 198 (273 K) and 330 s⁻¹ (278 K). These frequencies, plotted (as $\ln \tau$) against T^{-1} , show a linear dependence, which allowed us to evaluate the Arrhenius activation parameters: $E_a = 63.4 \pm 3.5$ kJ mol⁻¹, $A = 5.6 \times 10^{13}$ s⁻¹. By assuming the transmission factor κ to be 1, one obtains the Eyring parameters¹⁵ $\Delta G^\ddagger = 54.7 \pm 3.5$ kJ mol⁻¹, $\Delta H^\ddagger = 61.2 \pm 3.5$ kJ mol⁻¹, $\Delta S^\ddagger = 11.0 \pm 0.4$ J mol⁻¹ K⁻¹.

The fact that the additional splitting of CH₂ signals for **1** occurs in a temperature range at least 100 K higher than for its methylated derivative **2** shows that intramolecular hydrogen bonding plays an important role in hindering the process. It seems possible that the inversion is able to proceed only in a state with completely broken hydrogen bond. (Similarly, the racemization of the R₁R₂R₃NH⁺ cations requires the stage of deprotonation.²) One can imagine the mechanism shown in Scheme 2 for the degenerated averaging process in 2-hydroxybenzyl-diethylamines (in this scheme the exchange of the position of two homotopic ethyl groups is shown, but one can see that the process involves also the exchange of each of two pairs of the diastereotopic CH₂ protons). The conformations of the intermediates are represented arbitrarily, since on breaking the hydrogen bond a free rotation around all the single C—C and C—N bond takes place.



Scheme 2

On deriving kinetic equations and equalizing all the derivatives to zero, for the frequency τ^{-1} we obtain

$$\tau^{-1} = k_{\text{H}} k_i (k_i + k_{-\text{H}})^{-1} k'_{-\text{H}} (k'_{-\text{H}} + k_i)^{-1}$$

Since $k_{-\text{H}}, k'_{-\text{H}} \gg k_i, k_{-i}$,

$$\tau^{-1} = k_i k_{\text{H}} k_{-\text{H}}^{-1} = k_i K_{\text{H}}$$

where K_{H} is the equilibrium constant for the first stage (i.e. for the hydrogen bond breaking). For the observed activation enthalpy we have, after differentiating, $\Delta H^\ddagger = \Delta H_{\text{inv}}^\ddagger + \Delta H_{\text{H}}$, where $\Delta H_{\text{inv}}^\ddagger$ is the inversion barrier and ΔH_{H} is the intramolecular hydrogen bond energy.

The last value cannot be measured independently because the equilibrium is almost completely shifted to the hydrogen-bonded state (in fact, no band which may be attributed to the 'free' OH bond stretching vibration is observed up to $T = 350$ K in IR spectra). In order to estimate the ΔH_{H} value the calculations of the energy (after the structure optimization) with the MNDO-PM3¹⁶ and AM1¹⁷ techniques by means of the MOPAC.5 program¹⁸ were performed. The differences in calculated heat of formation (ΔH_f°) for conformation with the intramolecular OH...N hydrogen bond and the 'open' conformation with opposite OH group orientation are 12.6 and 6.7 kJ mol⁻¹, respectively, for the PM3 and AM1 methods. The PM3 calculations seem to be more reliable because they reproduce better the dipole moment: $\mu_{\text{calc.}} = 3.43$ D, $\mu_{\text{exp.}} = 3.96$ D (in benzene¹⁹) than AM1 calculations, which give 2.60 D. The calculated dipole moments for 'open' structures are 0.91 and 1.56 D with the PM3 and AM1 method, respectively. This is consistent with the fact that in solution there exists only the OH...N hydrogen bonded form. The dihedral C-1—C-2—C-3—N angle is equal to 33.9° and 69.5° with the PM3 and AM1 procedures, respectively, while the experimental value (from X-ray diffraction) is 30°. ²⁰ The calculated PM3 structure is shown in Fig. 3.

The energy of breaking of the intramolecular hydrogen bond should be higher than that obtained in the above calculations. The 'open' state is also stabilized by the intramolecular hydrogen bond of the OH...Cl

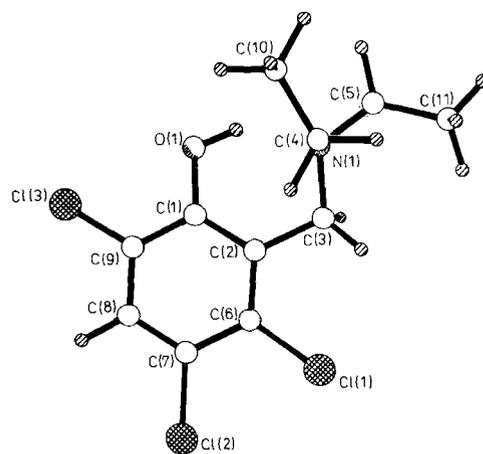


Figure 3. The most stable conformation of **1** with intramolecular OH...N hydrogen bond calculated by PM3 method.

type. For this reason the calculations with perpendicular orientation of the OH group with respect to the phenyl plane were repeated. The differences in $\Delta H_{\text{I}}^{\circ}$ of these structures and OH...N hydrogen bonded ones give $\Delta H_{\text{H}} = 25.3$ and 13.5 kJ mol^{-1} with the PM3 and AM1 procedures, respectively.

The ΔH_{H} value in solution should be larger than that obtained from calculations in the gas phase; for instance the $\nu_{\text{s}}(\text{OH})$ frequency of **1** in CH_2Cl_2 solution is lower by about 360 cm^{-1} than that in the gas phase.²¹ The order of magnitude of ΔH_{H} may also be evaluated from the linear correlation $\Delta H_{\text{H}} = 1.1 \Delta\delta_{\text{OH}}$.²² Taking

the chemical shift of pentachlorophenol in 0.001 M solution in CD_2Cl_2 at 230 K (8.7 ppm) as δ_{OH}^0 , and the value 15.8 ppm measured under the same conditions for **1** as δ_{OH} , we would obtain $\Delta H_{\text{H}} \approx 32.7 \text{ kJ mol}^{-1}$. This gives the value $\Delta H_{\text{inv}}^{\ddagger} = 28.5 \pm 6.7 \text{ kJ mol}^{-1}$ for the activation enthalpy of the inversion stage.

The proposed mechanism is consistent with the results of the OH internal rotation study in 2,6-bis(dimethylaminomethyl)phenols.²³ The effect of the increase in the rotation barrier by the hydrogen bond was estimated in that case to be 17–29 kJ mol^{-1} .

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