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ANNULAR TAUTOMERISM OF BENZIMIDAZOLES : EFFECT OF A HYDROGEN BOND ON THE PROTOTROPIC RATE

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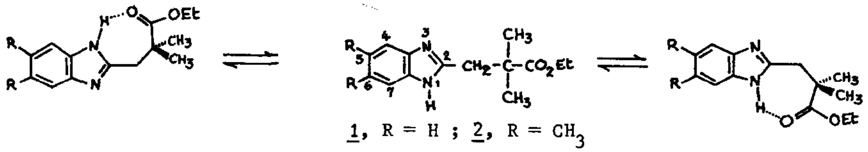
The prototropic equilibrium between two tautomers has both a thermodynamic and kinetic aspect. If the influence of an intramolecular hydrogen bond on the equilibrium constant is a well-known fact [see ref.(1) for examples in the heterocyclic series], on the contrary there is no example of a change in the energy of activation $\Delta G^{\ddagger}$. The annular tautomerism of azoles is such a fast process that in NMR (^{1}H, ^{14}N, ^{13}C) only averaged signals are observed <u>at room temperature</u> (1) and very seldom separated signals at low temperature (1,2,3). From a study of compounds <u>1</u> (F = 163°C) and <u>2</u> (F = 136°C), it has been possible to demonstrate the slowing of the proton exchange between atoms N-1 and N-3 due to the occurence of an intramolecular hydrogen bond.



<u>1</u>, R = H ; <u>2</u>, R = CH_3

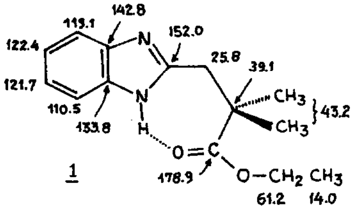
<u>^{1}H NMR Spectroscopy</u>.

In $CDCl_3$ at 60 MHz the two aromatic protons in positions 4 and 7 of compound <u>2</u> appear as a singlet at 7.30 ppm <u>at room temperature</u>; at 198 K the spectrum of these protons shows two peaks separated by 18.5 Hz. The free energy of activation can be calculated at the coalescence temperature using the Eyring equation: $\Delta G^{\ddagger}_{208\ K} = 44$ kJ/mole. This value is close to that found for the 2-chloro-5-methoxybenzimidazole in THF: $\Delta G^{\ddagger} = 45.6$ kJ/mole (2).

In the case of compound <u>1</u> at 100 MHz in $CDCl_3$ the spectrum, in the aromatic region, shows a multiplet for protons H-5, H-6 (7.14-7.24 ppm) and two broad resonances for protons H-4, H-7 (7.45 and 7.70 ppm); if a trace of acid is added, the aromatic protons appear as an AA'BB' system, the high frequency part of which being situated in the middle of the two broad peaks; this same phenomenon occurs on the spectrum of compound <u>2</u> if the temperature is increased in pyridine-d_5 (T ~ 383 K).

<u>^{13}C NMR Spectroscopy</u>.

The value of the ^{13}C chemical shifts, in ppm from TMS, measured <u>at room temperature</u> on the spectrum of <u>1</u> taken at 25.03 MHz in $CDCl_3$ are shown on the following figure. The signals have been assigned by off-decoupling experiments, comparison with data from the literature or with other compounds in the same series (4).



1

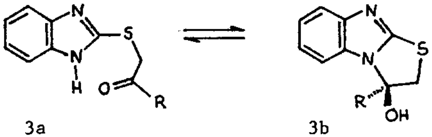
It can be seen that the aromatic part is unsymetrical. If a trace of acid is added carbons 3a and 7a coalesce as do carbons 5 and 6, carbons 4 and 7 are greatly broadened.

IR Spectroscopy.

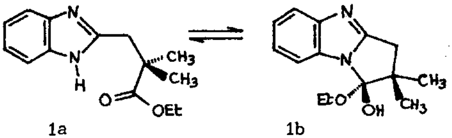
The IR spectrum of 1 with or without acid traces exhibits a $\nu_{C=O}$ absorption at 1710cm^{-1}; this value is low compared to the $\nu_{C=O}$ band of the ethylpivalate [1721 cm^{-1} (5)]. In the ν_{NH} region appears a sharp band at 3410 cm^{-1}($CHCl_3$), corresponding to an intramolecularly bonded NH stretching absorption.

Discussion.

From all these data one could have thought that a ring-chain tautomerism was occuring as is the case for compound 3 (6).



3a 3b



1a 1b

But this possibility can be ruled out for two reasons:

- The measured barrier (44 kJ/mole) is much smaller than that existing between the cyclic and chain isomers: in NMR signals corresponding to forms a and b are observed, even if acid traces are present ($\Delta G^{\neq} \geqslant 100$ kJ/mole).(7).
- The cyclic form 1b could explain the asymetry of the aromatic part of the NMR spectrum (^1H and ^{13}C) but neither the presence of a strong $\nu_{C=O}$ band in IR nor the isochrony of the methyl and methylene groups (at low temperature these last signals are broadened because of a slowing of the chain conformational motions).

Thus the presence of the hydrogen bond explains better the slowing of the exchange rate of the proton between the two nitrogen atoms, the bonding being favoured by the gem-dimethyl group. The frequency of the phenomenon under study is such that its observation depends on the spectroscopic method used: in IR spectroscopy it is always observed whereas in NMR it depends on the experimental conditions.

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