

NMR STUDY OF POLYCRYSTALLINE AZOLES

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Polycrystalline pyrazole, imidazole and benzotriazole were investigated by ^1H and ^2H NMR spectroscopy. In addition to the usual broad line of the ^1H NMR signal due to the dipole-dipole interaction, a significantly narrowed component ($\Delta\nu = 1-2$ kHz) of a complex triplet structure was detected in all three compounds. To interpret this observation, a mechanism with virtually complete averaging of the dipole-dipole interaction for a small part of the sample protons is suggested. The mechanism is based on proton interaction with the unpaired electron of a short-lived radical of the type Az^\cdot or $(\text{H}-\text{Az}^\cdot-\text{H})$.

INTRODUCTION

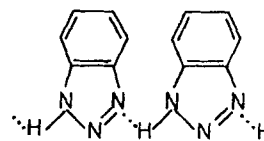
Five-membered polynitrogen heterocyclics (azoles) can form hydrogen-bonded associates¹ (solvates or self-associates) which serve as a structural basis for the occurrence of proton transfer and exchange processes. Thus, in certain diazoles, proton exchange reactions are known to proceed at a fairly high rate (10^6 s^{-1} and faster).² These high rates were shown to be caused by proton tunnelling in the elementary transfer event on the one hand and the cooperative nature of macroscopic proton transfer on the other. Such concerted processes are of great importance for the functioning of various biopolymers. In particular, hydrolases of the group of serine proteases contain so-called charge-transfer chains formed by hydrogen bonding and the enzymatic reaction event involves a concerted transfer of two or three protons along these chains. Cooperative transfer reactions probably play an important role in the conjugation of chromosomes. Realizing a cooperative process always requires structural ordering, perhaps even long-range ordering as, e.g., with DNA. A study of such processes in structures that are known to be regular and involve long-range ordering, such as crystalline solids, is therefore of obvious interest.

We chose polycrystalline azoles for investigation, as the dynamics of protons in these compounds is of particular interest. Earlier, crystalline azoles, in particular imidazole, were studied by NMR spectroscopy.³ Second moment measurements failed to detect cooperative proton-transfer processes.

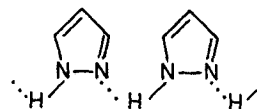
Owing to the development of pulsed Fourier transform NMR spectroscopy, which substantially increases the sensitivity of NMR measurements, the technique can now be applied to study the dynamics of protons in azoles more thoroughly.

EXPERIMENTAL AND RESULTS

Benzotriazole was obtained from *o*-phenylenediamine and sodium nitrate.⁴ Pyrazole was prepared from 1,1,3,3-tetraethoxypropane and hydrazine according to a published procedure.⁶ Commercial imidazole was also used. The purities and chemical compositions of all the compounds were monitored by precise chemical analysis and mass spectrometry; the results from both methods showed the absence of any liquid phase.

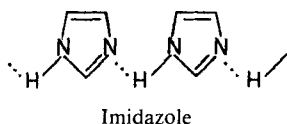


Benzotriazole



Pyrazole

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All operations involved in the preparation of samples for NMR measurements were carried out either in argon or under vacuum. Glass equipment was first annealed under vacuum and then filled with argon. Heterocyclic compounds and their derivatives were purified by distillation in an argon flow under reduced pressure, sublimed (also in argon) and then redistilled. Pure molten heterocyclics were collected in NMR tubes and sealed.

Powder x-ray analysis also showed the samples to be free from liquid components and to be typical polycrystalline substances containing a small (<5%) admixture of an amorphous phase. Probably the amorphous phase occurs between crystalline blocks.

The spectra of polycrystalline azoles were obtained on pulsed SXP-100/15" and CXP-200 NMR spectrometers (Bruker) with resonance proton frequencies of 90 and 200 MHz, respectively.

Figure 1 shows the absorption lines of the azoles studied: I = pyrazole (PzH); II = imidazole (ImH);

III = benzotriazole (BtH). In addition to the usual broad component ($\Delta\nu = 40\text{--}50\text{kHz}$) arising from the dipole-dipole interaction, all three spectra reveal a far narrower line ($\Delta\nu = 1\text{--}2\text{ kHz}$) indicative of the presence of a quasi-liquid 'phase' whose equilibrium concentration was about $10^{-2}\text{--}10^{-3}$ mole fractions. Additional purification of the samples (distillation, sublimation *in vacuo* under conditions excluding the presence of moisture and oxygen) did not result in the disappearance of the narrow component.

Broad component

Variations in the shape of the broad absorption signal component for the azoles studied (Figure 1) can be given a natural explanation by crystal structure variations and specific short-range interaction of spins according to a model suggested previously.^{7,8} The broad component in the pyrazole spectrum looks like a poorly resolved Pake doublet with a 27-kHz splitting. This is indicative of the presence of a sufficiently isolated pair of protons. The proton spacing corresponding to a 27-kHz Pake splitting was calculated to be 1.9 Å. This distance is obviously an intermolecular one.

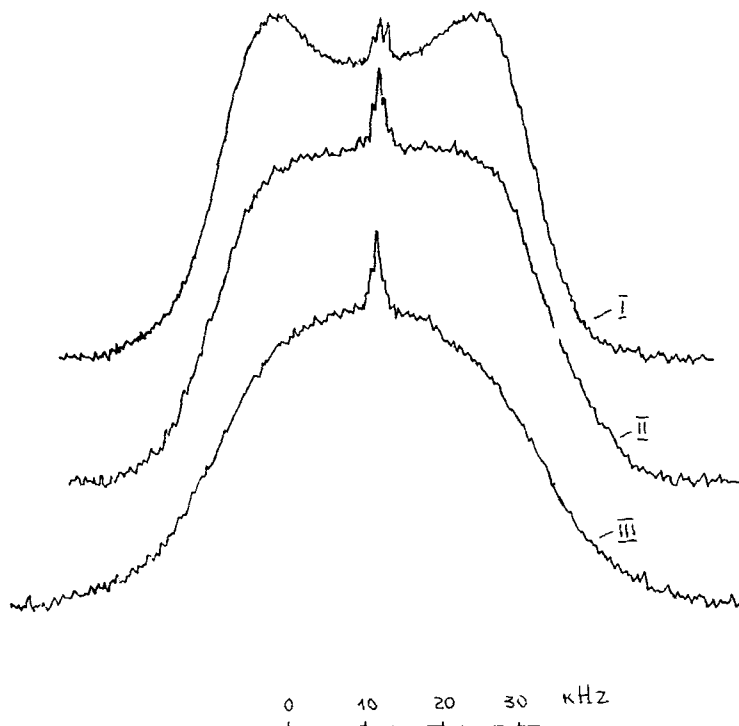


Figure 1. ^1H NMR spectra of polycrystalline azoles (room temperature). I = pyrazole (200 MHz); II = imidazole (90 MHz); III = benzotriazole (90 MHz)

The second moments (M_2) of the broad lines are fairly close together: $190 \pm 11 \text{ kHz}^2$ in imidazole, $220 \pm 14 \text{ kHz}^2$ in benzotriazole and $240 \pm 11 \text{ kHz}^2$ in pyrazole. It should be noted that an absolutely rigid structure would give second moment values not smaller than 450 kHz^2 , mainly as a result of intermolecular interactions. Thus in imidazole, the theoretical van Vleck second moment value for the rigid lattice, $M_{2\text{theor}}$, is about 635 kHz^2 . The experimental M_2 value for imidazole at 77 K was found to be $580 \pm 60 \text{ kHz}^2$ and agreed well with the calculated value.

Estimates show that $M_{2\text{theor}}$ can be decreased to the experimental value at room temperature by averaging M_2 over torsional vibrations in the chain imidazole molecules about the N—N axis by an angle of about 45° (the structural parameters for imidazole were taken from Ref. 9). The height of the energy barrier to these reorientations calculated using the approximation of atom—atom potentials¹⁰ is about 8 kcal mol^{-1} ($1 \text{ kcal} = 4.184 \text{ kJ}$). In this approximation, the interaction energy between the i th and k th non-bonded atoms is given by

$$\varphi_{ik} = -Ar_{ik}^{-6} + B \exp(-\alpha r_{ik})$$

where r_{ik} is the atomic spacing.

For the hydrogen—hydrogen interaction, the parameters are¹⁰ $A = 57 \text{ kcal mol}^{-1} \text{ \AA}^6$, $B = 4.2 \times 10^4 \text{ kcal mol}^{-1}$ and $\alpha = 4.86 \text{ \AA}^{-1}$. At 20°C , an 8 kcal mol^{-1} barrier height corresponds to the correlation time for the vibrational motions of $\tau_k \approx 10^{-6} \text{ s}$, which is one order of magnitude smaller than the reciprocal of the line width ($ca 10^{-5} \text{ s}$). It follows that this type of molecular reorientation is capable of decreasing the M_2 value to the observed value at room temperature.

The spin—lattice relaxation times for the protons responsible for the broad lines are very long, being of the order of 10^3 s ($ca 1000 \text{ s}$ in imidazole and $ca 650 \text{ s}$ in benzotriazole).

Narrow component

Protons of the quasi-liquid phase (the narrow line in the spectra) have a longitudinal relaxation time, T_{1N} , that is substantially (several orders of magnitude) shorter than that of the bulk of ordinary protons, $T_{1N} \approx 10^{-2} - 10^{-1} \text{ s}$. This circumstance enabled the narrow component to be isolated and analysed in detail. In the accumulation of the free induction decay by the sequence of coherent 90°_x pulses $90^\circ_x - \tau - 90^\circ_x - \tau \dots$ with a dwell time $t_d = 10 - 25 \mu\text{s}$. τ is under condition $T_{1W} \gg \tau \gg T_{1N}$ (where T_{1W} is the ordinary spin—lattice relaxation time). The signal of ordinary protons was then virtually absent, whereas the narrow component was well resolved. Figure 2 shows the spectra obtained as indicated above at two values of the constant external magnetic field, $H_0 = 2.114$ and 4.697 T (the

corresponding proton resonance frequencies are 90 and 200 MHz, respectively).

In all three compounds the narrow lines are incompletely resolved triplets with components differing in intensity. Pyrazole and imidazole have similar spectra, whereas the spectrum of benzotriazole differs significantly. The dependence of both the triplet splittings and the widths of their components on the external magnetic field H_0 is of interest.

The narrow signal is seen up to a temperature of at least 225 K (Figure 3).

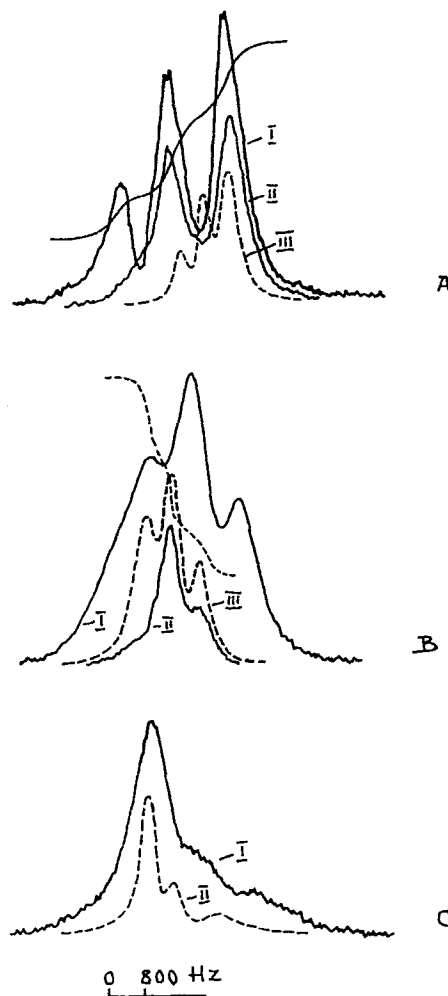


Figure 2. Narrow components in ^1H NMR spectra of azoles (room temperature). (A) Pyrazole: I = PzH (200 MHz); II = 3-D-PzH (200 MHz); III = PzH (90 MHz). (B) Imidazole: I = ImH (200 MHz); II = 2-D-ImH (90 MHz); III = ImH (90 MHz). (C) Benzotriazole: I = BtH (200 MHz); II = BtH (90 MHz)

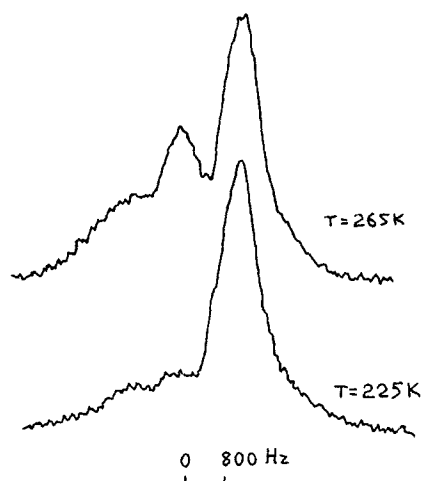


Figure 3. Narrow component of pyrazole spectrum at low temperature (200 MHz)

DISCUSSION

Of the observations mentioned above, the presence of narrow (for crystalline solids) lines having a complex triplet structure in all the spectra is in our view the most interesting one. The splitting (of about 6.2 ppm) and their dependence on the external magnetic field suggest that a small fraction of sample protons are under conditions such that their direct dipole-dipole interactions are averaged almost to zero. The absorption line width, which in solids is mainly determined by the dipole-dipole interactions, then narrows sharply, and chemical and/or coordination differences between the heterocycle protons become manifest.

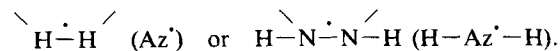
The evaluation of the integral intensities of the triplet components in pyrazole and imidazole gave a peak ratio fairly close to 1:2:2. The triplet components in PzH and ImH can therefore be assigned to three chemically non-equivalent types of protons in the heterocycles. With BtH the situation is far more complex, and it will be considered in detail below.

In order to verify the chemical origin of the splitting of the narrow line, ^1H NMR spectra of 2-D-ImH and 3-D-PzH were measured and are presented in Figure 2 (the deuterated azoles were obtained by a known method¹¹). One can see that in both spectra one of the triplet components disappears.

It should be noted that a ^2H NMR spectrum (resonance frequency 30.7 MHz) was obtained for 3-D-PzH. The spectrum is singlet, ca 240 Hz wide. The absence of quadrupole broadening is indicative of almost complete averaging of the electric field gradient on the ^2H centre. The signal width is mainly determined by the H-D dipole-dipole interaction. Calculations show that the root-mean-square signal width

determined by intramolecular H-D interactions, $(\Delta\nu_D^2)_{\text{HD}}^{1/2} \approx 153$ Hz, has the same order of magnitude as the experimental line width. The latter is larger probably because of an intermolecular contribution.

A model described previously¹² was applied to explain the almost complete averaging of the dipole-dipole interaction. We suggest that the substances studied contain a low stationary concentration of short-lived radicals of the type



The radical lifetime, t , is much shorter than the characteristic NMR experiment time T_2 : $t \ll T_2 \approx 10^{-5}$ s. Since the radical concentration was very low, the correlation time for the unpaired electron, τ_e , was determined mainly by the electron spin-lattice interaction and was in the range $10^{-8} > \tau_e > 10^{-12}$ s. Such a small τ_e value leads to an averaging by the flip-flop of the static electron spin field almost to zero and the narrow-line isotropic paramagnetic shift is absent in the present case.

Nuclear spins at a distance r from the unpaired electron interact with its spin and therefore undergo random reorientations at a frequency $\omega_n = C/r^6$,¹³ where

$$C = 2/5 [\gamma_{\text{H}} g \beta^2 S(S+1) \tau_e] / [1 + \omega_{\text{H}} \tau_e]^2$$

ω_n is resonance proton frequency, γ_{H} is the nuclear gyromagnetic ratio, β is Bohr's magneton, g is the electron g -factor and S is its spin. If $\omega_n \gg 1/T_2$ ($[T_2 = 1/(\pi \Delta\nu)]$ is the proton spin-spin relaxation time $\Delta\nu$ is the line width), these random reorientations will result in averaging of nuclear local magnetic fields¹⁴ and in the almost complete disappearance of the dipole-dipole interaction for these nuclear spins, whose temperature then becomes equal to the lattice temperature. The effective radius of the region containing such 'cold' (i.e. having the lattice temperature) spins is: $R = 0.68(C/D)^{1/4}$,¹³ where $D \approx 10^{-12} \text{ cm}^2 \text{ s}$ is the spin diffusion coefficient. The 'cold' spins cannot exchange the spin polarization with the ordinary spins because the spin polarization diffuses a distance $d = \sqrt{DT_2}$ ¹³ $\approx 3 \times 10^{-9} \text{ cm}$ during the experimental time, i.e. in the situation under review quasi-liquid protons form the isolated spin subsystem and T is different in the 'cold' and ordinary spin systems.

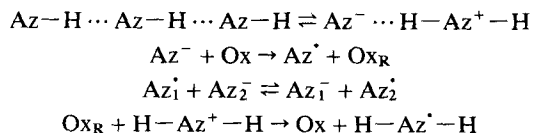
Locating the unpaired electron at the heterocycle centre and taking its correlation time to be 10^{-9} s yields: $R \approx 5 \text{ \AA}$. Not all the protons within this 'cold' region undergo reorientations at frequencies meeting the condition $\omega_n \gg 1/T_2$, however. Thus, for spins of neighbouring heterocycles which are at a distance $r \approx 4.5 \text{ \AA}$ from the unpaired electron, $\omega_n \approx 3 \times 10^3 \text{ s}^{-1}$, which is 2.5 orders of magnitude below $1/T_2 \approx 10^5 \text{ s}^{-1}$. These protons do not contribute to the narrow component. It follows that the protons of the heterocycle bearing the

unpaired electron are only responsible for the narrow line. For these protons, $r \approx 2.24 \text{ \AA}$ and $\omega_n \approx 2 \times 10^5 \text{ s}^{-1}$. With benzotriazole the situation is probably different, and the paramagnetic centre acts not only on the five-membered ring protons, but also on those on the benzo group.

The narrow signal splitting value (*ca* 6 ppm) agrees well with the aromatic protons chemical shift tensor anisotropy parameter, $\Delta\sigma \approx 6.5 \text{ ppm}$.¹⁵ For the hydrogen-bonded protons $\Delta\sigma$ can reach 30 ppm.¹⁵

A noticeable asymmetry of the triplet components, especially strong in the PzH spectrum [see Figure 2(A)], and the dependence of the component widths on the external magnetic field suggest that the width and the shape of the triplet components were determined mainly by the chemical shift anisotropy.

It should be stressed that the questions of whether paramagnetic free-radical centres can occur in diamagnetic polycrystalline azoles and what the mechanism of their formation is are complex and will be considered in future publications. The presence of hydrogen bonds in the structure under investigation and the ability of the hydrogen-bond proton to oscillate rapidly between the equilibrium positions of the two-well hydrogen-bond potential suggests that proton-electron transfer and exchange reactions are responsible for the formation of the free azole radicals:



Generally these reactions can be at admixture centres (Ox) and dislocations as a source of paramagnetism which act as one-electron oxidants.

It is probable that the $\text{H-Az}^\cdot - \text{H}$ radicals are the longest lived and hence they have the highest stationary concentration of all the possible radical species. Hence just these species form the narrow line in the first place and therefore the integral ratio is 1:2:2.

It should be noted that for solutions, the possibility of the existence of azolyl radicals has already been demonstrated. They were generated in the one-electron oxidation of deprotonated azoles and detected by ESR spectroscopy using spin traps.^{16,17} It should also be noted that simultaneously the possibility of electron exchange reactions between azole anions and the corresponding free radicals was demonstrated.¹⁸ Hence all the elementary events that can result in the formation and migration of free radical centres are well known.

Certainly we do not consider our hypothesis to be the only possible one. It is probable that other interpretations of the observed phenomena could be suggested; in particular, the presence of a quasi-liquid phase on crystalline grain surfaces in polycrystalline samples cannot be ruled out. It is important, however, that the

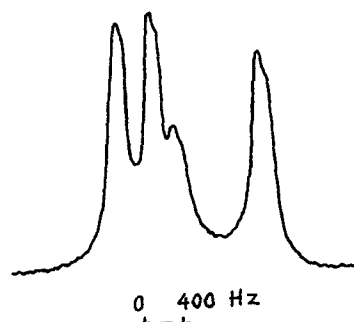


Figure 4. Narrow component of room-temperature single-crystal pyrazole spectrum. Random orientation (200 MHz)

narrow line typical of polycrystals (see Figure 2) and determined by the anisotropy of the chemical shift tensor indicates that most protons giving a narrow signal occur within the crystalline phase. We also obtained the spectra of a pyrazole single crystal. It should be noted that with the same coefficient of filling the detector, the signal-to-noise ratio in the narrow line of a single crystal was about four times larger than that of polycrystalline samples. This is further evidence that the phase in question is quasi-liquid only in the 'spin sense' and not crystallographically. The narrow component of the single-crystal spectrum also has a complex shape (see Figure 4) and exhibits a distinct orientation dependence.

The increase in the narrow line intensity in a monocrystal in comparison with a polycrystal is accounted for mainly by more long chains of hydrogen-bonded molecules in a perfect structure. It can be assumed that this leads to a greater probability of proton transfer as the initial step and therefore to a greater concentration of free radical intermediates.

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