

The Effect of Water on Proton Transfer in Pyrazole

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Azoles, Proton Transfer, Influence of Water

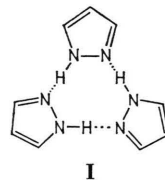
An NMR ^{13}C study has shown that proton rearrangement in pyrazole is decreased by adding small amounts of water to the sample. Single water molecules as coordination centres perturb the mechanism of cooperative proton transfer occurring in pyrazole selfassociates. The decrease of the rearrangement effect due to water is similar to the action of transition metal ions studied by the authors earlier.

Proton transfer does not occur in isolated azole molecules. To cause the prototropic rearrangement, an H-bond with the same or a different type of molecule is necessary. Proton transfer in azoles is usually an autoprotolysis, that is, proton migration occurs within the framework of $\text{N}-\text{H}\cdots\text{N}$ bonds which arrange the molecules to selfassociates. In biochemistry, however, *e. g.*, in protein-nucleic acid interactions, the effect of variable concentrations of water on proton transfer in nitrogen-containing bases in DNA-polymerase/DNA interaction is of interest. Pyrazole selfassociation is relatively small, therefore proton transfer in a pyrazole/aprotic solvent maybe expected to be very sensitive to water additives. The same maybe true with solutions of other nitrogen-containing bases. That is why we studied the effect of adding small amounts of water to a THF/ Et_2O solution of pyrazole. In this system, in principle, owing to selfassociation and hetero-association, several types of associates may exist: B_n , $\text{B}_n\text{H}_2\text{O}$, $\text{B}_n(\text{H}_2\text{O})_m$, $\text{B}(\text{H}_2\text{O})_m$, $(\text{H}_2\text{O})_m$. Suppose, by neglecting the dynamical role of the medium, that the proton transfer in the species B_n or $(\text{H}_2\text{O})_m$ is similar to that in the pure compounds, *i. e.*, in pyrazole/THF/ Et_2O our pure water. In the species $\text{B}_n\text{H}_2\text{O}$, $\text{B}_n(\text{H}_2\text{O})_m$, and $\text{B}(\text{H}_2\text{O})_m$, essentially non-equivalent $\text{N}-\text{H}\cdots\text{O}$ and $\text{O}\cdots\text{H}-\text{N}$ bonds will appear beside the of $\text{N}-\text{H}\cdots\text{N}$ and $\text{O}-\text{H}\cdots\text{O}$ bonds containing equivalent terminal atoms.

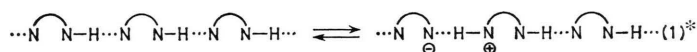
The elementary event proper inherent in proton transfer in water¹ or azoles^{2–4} is known to be a quantum process; the accompanying motion of the classical sub-system leads, however, to an activation-

nal kinetic of the whole process. On the other hand, proton transfer rates in aqueous imidazole were found⁵ to be controlled by diffusion and proton tunnelling in the system was verified by spectroscopy⁶. The authors⁶ worked with considerable water concentrations, so the solution studied may probably to contain $\text{B}_n(\text{H}_2\text{O})_m$ and $\text{B}(\text{H}_2\text{O})_m$ predominantly. Hence the question arises as to how proton transfer will occur in azoles containing very little water and, consequently, a great number of the $\text{B}_n\text{H}_2\text{O}$ species.

In its concentrated (above 0.1 M) solutions pyrazole occur mainly in the form of trimer self-associates⁷, with the hydrogen bridge structures being close to linear **I**.



The initial act of proton migration in the neutral hydrogen bridge generates the contact hydrogen-bonded ion pair.



From the point of view of thermodynamics this is an energetically unfavourable process and the concentration of such charged centres is low. Therefore reaction (1) must be considered as a fluctuating process, in which the dynamical role of the medium is of great importance. The fate of the created centre maybe double: a) a recombination

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* We consider the linear selfassociate here without losing generality.



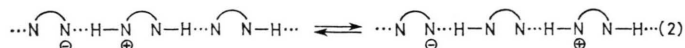
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to the initial uncharged structures is possible, b) under the favourable configuration of the classical subsystem, *e.g.* shortening the H-bond due to the translational displacement of the molecule proton in the adjacent bridge starts moving, etc.



Therefore, in this reaction the real proton transfer occurs within the network of the charged bridge $(\text{N}-\text{H}\cdots\text{N})^+$ or $(\text{N}-\text{H}\cdots\text{N})^-$. In a solution with an excess or a deficit of protons the propagation reaction is going in this way, except that in these cases the concentration of the centres $(\text{N}-\text{H}\cdots\text{N})^+$ or $(\text{N}-\text{H}\cdots\text{N})^-$ is greater. If proton motions are correlated in the adjacent hydrogen bridges or in all the bridges of the self-associate, then this will be a cooperative or, in other words, a concerted proton transfer^{3,8}. Since the concentration of charged centres in the neutral azole solution apparently is low it is clear that to provide the effective symmetry of the azole molecules in NMR experiments, reaction (2) must be fast enough and embrace the whole associate. Especially, in cyclic pyrazole trimers the cooperative proton transfer occurs as proton ring current. Just the fact that the reaction (2) includes the whole selfassociate rather than a single bridge, *i.e.* has a cooperative nature, explains dramatic effect of small transition metal complex additives on proton transfer in pyrazole⁹.

This may be explained by assuming that H-bonds in the associates are broken by complex formation. Ligand exchange in the first and second coordination spheres (the second sphere is formed by pyrazole molecules linked by hydrogen bonding with a ligand of the first sphere) generates species of various degree of association in the solution. Then, to come to the "usual" proton transfer characteristics, a relaxation to the usual trimer selfassociates is necessary. It requires that species of different degree of association exchange their molecules, that associates undergo ring closure, etc. Ligand exchange in the second coordination sphere is fast enough at low temperatures (below -60°C). Characteristic times of these reactions are lower than the lifetime of any limiting tautomeric state. Therefore, tunnelling is unobservable and the proton transfer rate is lower than it is in the free pyrazole⁹. In other words, even below -60°C the rate of second sphere exchange is fast enough to

ruin the classical subsystem, configuration, which is favourable for cooperative proton transfer.

The discussion above shows that the indirect effect of small metal additives on proton transfer is governed by the exchange of hydrogen-bonded ligands of the second coordination sphere. A water molecule, which forms hydrogen bonds, may play the part of a coordination centre with respect to a pyrazole associate, therefore small water amounts added to pyrazole in an "inert" solvent maybe expected to cause a similar effect. An increase in the water concentration in pyrazole may create, on the whole, rather peculiar kinetical effect. Insofar as the water concentration is sufficiently low for single water molecules to work as the coordination centres, the proton transfer rates will go down for the reasons exposed above. After the water concentration has risen so as to allow water molecules to form self-associates there will rise the role of proton transfer in the species $\text{B}_n(\text{H}_2\text{O})_m$. This will gradually accelerate the proton transfer. Just this is the mechanism of tautomeric rearrangement and proton transfer from cations to neutral molecules in aqueous imidazole¹⁰.

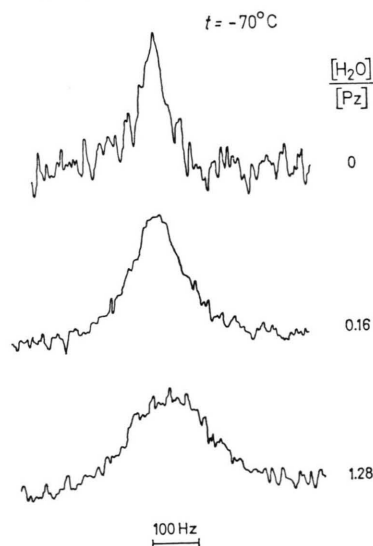
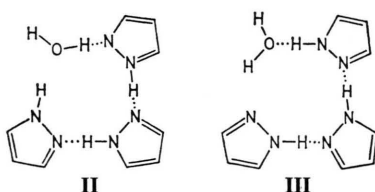


Fig. 1. NMR ^{13}C spectra of the pyrazole ring C^3 and C^5 carbons *vs* water content in the samples.

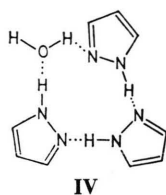
Fig. 1 shows a concentration dependence of an NMR ^{13}C spectrum recorded for the C^3 and C^5 carbons of the pyrazole ring. The $\text{C}^{3,5}$ line broadening as a function of water concentration (the C^4 signal width is invariable) demonstrates that the tautomeric state lifetime increases, in other words,

the tautomeric rearrangement making the C³ and C⁵ positions isochronous slows down. The deceleration is, however, markedly less pronounced than it is in the case of the Ni(acac)₂ additive⁹. This may be attributed to two factors. Firstly, water molecules from clusters even at low concentrations, which makes less numerous the coordination centres perturbing the pyrazole selfassociation equilibrium. Secondly, water is bifunctional in Bronsted terms, so it can add pyrazole to form not only the open species of the types **II** and **III**

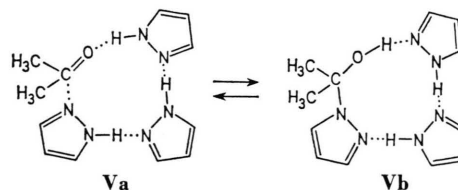
In associates of the type **IV** ligand exchange processes are, naturally, hindered. Indeed, we



but also the closed ones



showed¹¹ earlier that interaction of pyrazole with a ketone solvent, acetone, does not affect the proton transfer rate in pyrazole clusters since the **Va** and **Vb** lifetimes are high.



However, the **IV** lifetime is lower and therefore we are still able to observe the decrease of the proton transfer process.

The effects observed maybe expected to be quite wide-spread among various bi- or poly-functional nitrogen-containing bases.

It should be also expected, however, that the effect of ligand exchange in the second coordination sphere may differ depending on selfassociation, thermodynamical characteristics of molecules as coordination centres, and of nitrogen-containing bases.

The preparation of the samples were described previously. Pyrazole was purified by chromatography through alumina before distillation.

¹ M. Eigen and L. De Mayer, *Proc. Roy. Soc. A* **247**, 505 [1958].

² G. Zundel, *Hydratation and Intermolecular Interaction*, Academic Press, New York and London 1969.

³ G. Zundel, *The Hydrogen Bond* (P. Shuster, G. Zundel, and C. Sandirfy, eds.), **vol. II**, pp. 683–766, Amsterdam 1976.

⁴ A. N. Nesmeyanov, V. N. Babin, E. B. Zavelovich, and N. S. Kochetkova, *Chem. Phys. Lett.* **37**, 184 [1976].

⁵ M. Eigen, G. G. Hammes, and K. Hustin, *J. Amer. Chem. Soc.* **82**, 3482 [1960].

⁶ G. Zundel and J. Muelinghaus, *Z. Naturforsch.* **26b**, 546 [1971].

⁷ D. M. M. Anderson, J. L. Duncan, and F. J. Rosotti, *J. Chem. Soc.* **1961**, 4201.

⁸ R. R. Dogonadze, Y. I. Kharkats, and J. Ulstrup, *J. Chem. Soc. Faraday II* **70**, 64 [1974].

⁹ V. N. Babin, E. B. Zavelovich, and E. I. Fedin, *Z. Naturforsch.* **31c**, 353 [1976].

¹⁰ E. Grunwald and E. K. Ralph, *J. Amer. Chem. Soc.* **91**, 2422 [1969].

¹¹ A. N. Nesmeyanov, E. B. Zavelovich, V. N. Babin, N. S. Kochetkova, and E. I. Fedin, *Tetrahedron* **31**, 1463 [1975].