

The ^1H NMR spectrum of pyrazole in a nematic phase

Patricio Provasi,^a María Luisa Jimeno,^b Ibon Alkorta,^c Felipe Reviriego,^c José Elguero^c and Jukka Jokisaari^{d*}

ABSTRACT The experimental ^1H nuclear magnetic resonance (NMR) spectrum of 1*H*-pyrazole was recorded in thermotropic nematic liquid crystal N-(*p*-ethoxybenzylidene)-*p*-butylaniline (EBBA) within the temperature range of 299–308 K. Two of three observable dipolar D_{HH} -couplings appeared to be equal at each temperature because of fast prototropic tautomerism. Analysis of the Saupe orientational order parameters using fixed geometry determined by computations and experimental dipolar couplings results in a situation in which the molecular orientation relative to the magnetic field (and the liquid crystal director) can be described exceptionally by a single parameter. Copyright © 2016 John Wiley & Sons, Ltd.

Keywords: *D* couplings; 1*H*-pyrazole; DFT calculations; tautomerism; orientational order

Introduction

Nuclear magnetic resonance (NMR) spectroscopy of oriented molecules was first introduced by Saupe and Englert already over 50 years ago.^[1] In the course of time, it was further developed by many researchers.^[2–8] Important steps toward reliable and accurate molecular structure determination were taken when harmonic vibrational corrections as well as the so-called deformational corrections (due to interactions of molecular vibrational and reorientational motions) were introduced and implemented.^[9,10] The number of studied molecules is very large, although most of them share simplicity and symmetry. Concerning heterocycles, the only reported compounds are as follows: pyridine (**1**),^[11,12] pyrimidine (**2**),^[13–15] pyrazine (**3**),^[14,15] *s*-triazine (**4**),^[16] pyridine-3-carbaldehyde (**5**),^[17] methyl nicotinate (**6**),^[18] methyl isonicotinate (**7**),^[18] furan (**8**),^[19] thiophene (**9**),^[19,20] pyrrole (**10**),^[21–23] and 2,2-bithiophene (**11**) (Fig. 1).^[24] The results for pyrrole were obtained using the [$^{15}\text{N}_1$] derivative. Because no azole (imidazole, pyrazole, both triazoles, tetrazole, benzimidazole, indazole, benzotriazole) was ever studied in a nematic solvent, we decided to study 1*H*-pyrazole (**12**).

Experimental

Materials

Pyrazole (Sigma-Aldrich P56607) and N-(*p*-ethoxybenzylidene)-*p*-butylaniline (Sigma-Aldrich 269522) are commercially available and were used without further purification.

NMR experiments

A sample of 5.5 cm height was prepared in EBBA with 20 wt% of pyrazole. Before inserting the tube into the NMR spectrometer, it was heated and cooled several times and shaken vigorously to ensure optimum diffusion of solute throughout the solvent. The temperature was carefully controlled by means of a variable

temperature unit. A sealed capillary tube (1.4 mm OD, Symta) containing dimethyl sulfoxide (DMSO)- d_6 (50 mm height) was used as an external standard for experiments.

All NMR experiments were performed on a Varian INOVA-400 spectrometer equipped with a 5 mm inverse detection z-gradient probe head, operating at 399.90 MHz for ^1H . One-dimensional ^1H NMR spectra were measured with spectral width of 12 000 Hz, acquisition time 5 s, number of data points 48 k, and zero-filling to 128 k. The number of accumulated transients was 256, and the range of temperatures 299–308 K. Chemical shifts were referenced to residual DMSO peak at 2.50 ppm.

The experimental ^1H NMR spectrum was analyzed by using the program gNMR5.0.^[25] This program uses an iterative least-squares procedure that optimizes chemical shifts and coupling constants to produce an agreement between observed and calculated spectra.

DFT calculations

Geometries of the structures were fully optimized with the internal 6-311++G(2d,2p) basis set^[26] at the B3LYP^[27–29] theoretical level using procedures implemented in the Gaussian 09 programs.^[30] We report in Fig. 2 the main geometrical parameters of the optimized geometry (remember that 1*H*-pyrazole is planar).

* Correspondence to: Jukka Jokisaari, NMR Research Group, University of Oulu, 90014 Oulu, Finland. E-mail: Jukka.Jokisaari@oulu.fi

a Physics Department, University of Northeast, Av. Libertad 5500, W 3404 AAS, Corrientes, Argentina

b CENQUIOR (CSIC), Juan de la Cierva, 3, E-28006, Madrid, Spain

c Instituto de Química Médica (CSIC), Juan de la Cierva, 3, E-28006, Madrid, Spain

d NMR Research Group, University of Oulu, 90014, Oulu, Finland

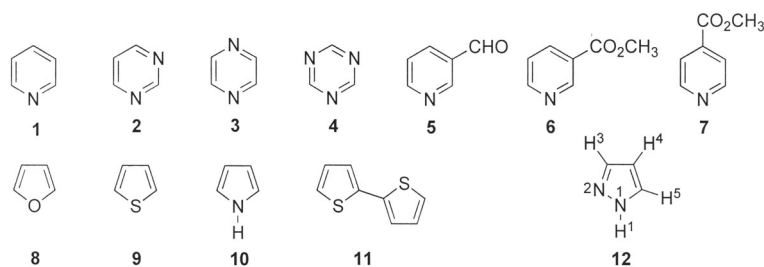


Figure 1. Aromatic heterocycles studied by nuclear magnetic resonance in nematic solvents.

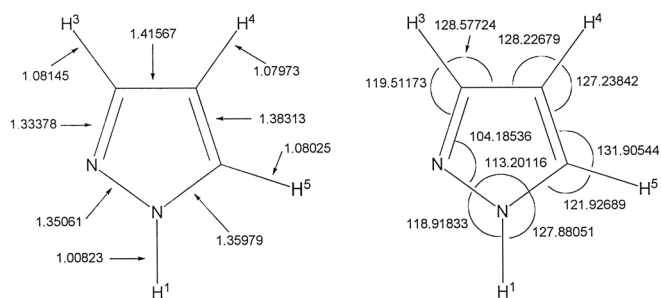


Figure 2. Bond lengths and angles for 1H-pyrazole.

Results and discussion

1H-Pyrazole (**12**) exists in solution as a mixture of two identical tautomers (degenerate tautomerism) in rapid to medium prototropic rates in NMR time scale (Fig. 3).^[31] It is slow in dipolar aprotic solvents (DMSO-*d*₆, HMPA-*d*₁₈) and in THF-*d*₈ at low temperature.^[31]

In the present study, we recorded the ¹H NMR spectrum of 1H-pyrazole in EBBA at five temperatures within the range of 299–308 K. The anisotropy of the diamagnetic susceptibility tensor of EBBA is positive, which means that its director orients along the external magnetic field in the magnet of an NMR spectrometer. All spectra were similar as shown in Fig. 4.

Dipolar coupling between nuclei N and M in a molecule partially oriented in a liquid-crystalline solution can be written in the general form of (in Hz)

$$D_{NM} = -\frac{\mu_0 \gamma_N \gamma_M \hbar}{8\pi^2} \left\langle \frac{S_{NM}}{r_{NM}^3} \right\rangle \quad (1)$$

where μ_0 is the permeability in vacuum, γ 's are gyromagnetic ratios, and \hbar is the Planck constant divided by 2π . The $\langle \rangle$ brackets indicate the ensemble average of the ratio of the momentary orientational order parameter, $S_{NM} = \frac{1}{2} (3\cos^2\theta_{NM,Z} - 1)$, where $\theta_{NM,Z}$ is the angle between the r_{NM} vector and external magnetic field, and the inverse cube of the distance r_{NM} between the nuclei N and M. Averaging is made over the vibrational motions and the

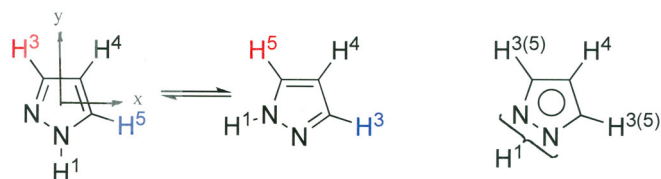


Figure 3. 1H-Pyrazole and its tautomerism. Numbering of pyrazoles always starts from the N-H group. Therefore, prototropy exchanges H³ and H⁵. The molecule is in the *xy* plane of the Cartesian coordinate frame.

deformational effects, as mentioned previously. In the present case, we neglect these effects as they are small for the H-H couplings in general, and then Eqn (1) transforms to

$$D_{NM} = -\frac{\mu_0 \gamma_N \gamma_M \hbar}{8\pi^2} \frac{S_{NM}}{r_{NM}^3} \quad (2)$$

where $S_{NM} = \langle \frac{1}{2} (3\cos^2\theta_{NM,Z} - 1) \rangle$ is the orientational order parameter of the r_{NM} vector with respect to the external magnetic field. For a molecule without symmetry in the *xy* plane of the Cartesian frame, S_{NM} can be written as

$$S_{NM} = S_{xx}\cos^2\theta_{NM,x} + S_{yy}\cos^2\theta_{NM,y} + 2S_{xy}\cos\theta_{NM,x}\cos\theta_{NM,y} \quad (3)$$

In Eqn (3), $S_{\alpha\beta} = \langle \frac{1}{2} (3\cos\theta_{NM,\alpha}\cos\theta_{NM,\beta} - \delta_{\alpha\beta}) \rangle$ ($\alpha, \beta = x, y, z$) are the elements of the Saupe orientational order tensor, $\theta_{NM,\alpha}$ are angles between the NM direction and the coordinate axes, and $\delta_{\alpha\beta}$ is the Kronecker delta.

Consequently, the H-H couplings for the two tautomers can be written in the form

$$D_{NM} = -\frac{\mu_0 \gamma_N \gamma_M \hbar}{8\pi^2} \frac{1}{r_{NM}^3} (S_{xx}\cos^2\theta_{NM,x} + S_{yy}\cos^2\theta_{NM,y} + 2S_{xy}\cos\theta_{NM,x}\cos\theta_{NM,y}) \quad (4)$$

or equivalently

$$D_{NM} = -\frac{\mu_0 \gamma_N \gamma_M \hbar}{8\pi^2} \frac{1}{r_{NM}^3} \left[\frac{1}{2} (S_{xx} - S_{yy}) (\cos^2\theta_{NM,x} - \cos^2\theta_{NM,y}) + \frac{1}{2} S_{zz} (3\cos^2\theta_{NM,z} - 1) + 2S_{xy}\cos\theta_{NM,x}\cos\theta_{NM,y} \right]. \quad (5)$$

The application of Eqn (4) for the calculation of the averages (assuming fast exchange) of the D_{34} , D_{35} , and D_{45} in the two tautomers (Fig. 3) indicates that $D_{34} = D_{45}$. (One should note that D_{35} is the same for the two tautomers.) This result was utilized in the analyses of the experimental spectra. The indirect couplings (J couplings) were taken from the literature, and they were kept constant during the iteration process: $J_{34} = J_{45} = 1.9$ Hz and $J_{35} = 0$ Hz.^[32] The fast prototropic exchange suppresses the scalar coupling constants between H¹ and the other protons.^[33] The H-H dipole-dipole couplings at different temperatures are shown in Table 1.

Table 1 shows that the ratio of the experimental H-H dipolar couplings is practically independent of temperature. Both couplings behave linearly as a function of temperature within the given (narrow) range, as shown in Fig. 5.

The average value of the D_{34}/D_{35} ratio, 3.87, appears to be equal, within error limits, to the third power of the inverse distance ratio: $(r_{35}/r_{34})^3 = 3.86$. This means that the average orientational order

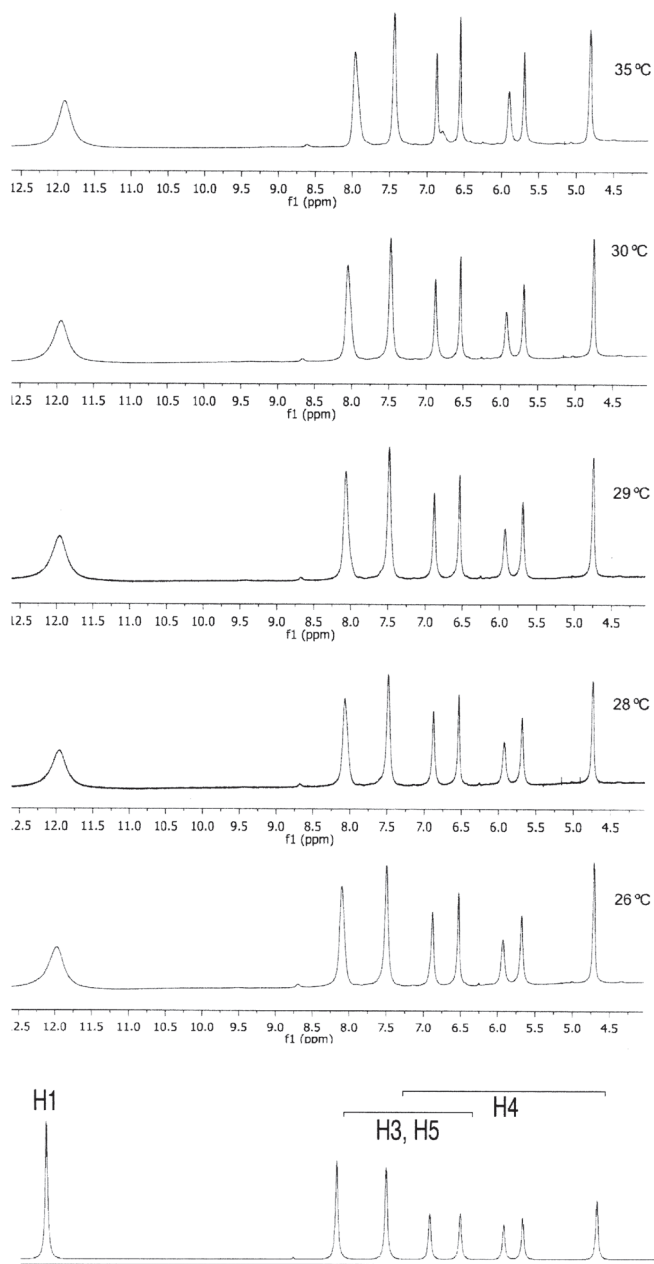


Figure 4. Experimental ^1H NMR spectrum of $1H$ -pyrazole in EBBA at variable temperatures. As an example, the bottom spectrum shows the simulated spectrum at 26°C .

Table 1. Experimental H-H dipole-dipole couplings and their ratio in $1H$ -pyrazole dissolved in liquid crystal EBBA at different temperatures			
T (K)	$D_{34} = D_{45}$ (Hz) ^a	D_{35} (Hz) ^a	Ratio ^b
308	195.0	50.0	3.90
303	213.3	55.1	3.86
302	216.0	56.0	3.86
301	221.0	57.0	3.88
299	227.7	59.0	3.86

^aEstimated error is ± 0.2 Hz for the dipolar couplings.
^b D_{34}/D_{35} .

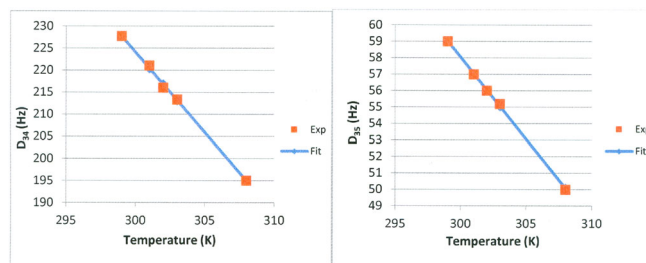


Figure 5. Temperature dependence of the dipolar H-H couplings in $1H$ -pyrazole dissolved in EBBA liquid crystal. Straight lines indicate linear fits to the experimental values.

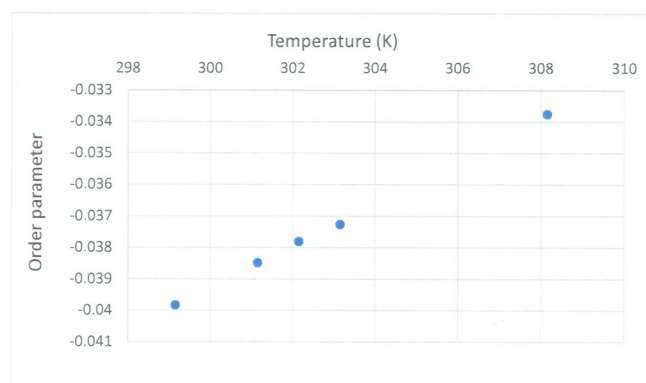


Figure 6. Temperature dependence of the average orientational order parameter in the plane of $1H$ -pyrazole.

parameters S_{34} and S_{35} [Eqn (3)] are equal. This should be valid for all dipolar couplings in $1H$ -pyrazole. The temperature dependence of this single orientational order parameter appears to be linear, as indicated in Fig. 6.

Conclusion

We have illustrated in this example the interest to use NMR spectroscopy in nematic solvents for studying problems of tautomerism. Further studies of heterocycles will need ^{15}N -labeled samples to obtain supplementary information. In the case of $1H$ -pyrazole, the application of the experimental H-H dipolar couplings results in a situation where the molecular orientational order can be described by a single parameter instead of three parameters that are needed in cases of similar heterocycles.

Acknowledgements

This work was supported by the Spanish Ministry of Economy and Competitiveness (grant CTQ2012-13129-C02-02) and the Comunidad Autónoma de Madrid (Project Fotocarbon, ref. S2013/MIT-2841). F. R. acknowledges a CSIC JAE-Doc contract cofunded by EU (ESF, European Social Fund).

References

- [1] A. Saupe, G. Englert. *Phys. Rev. Lett.* **1963**, *11*, 462–464.
- [2] P. Diehl, C. L. Khetrpal, NMR studies of molecules oriented in the nematic phase of liquid crystals, in *NMR Basic Principles and Progress*, vol. 1 (Eds: P. Diehl, E. Fluck, R. Kosfeld), Springer, Berlin, **1969**, pp. 1–95.

- [3] J. W. Emsley, J. C. Lindon, *NMR Spectroscopy Using Liquid Crystal Solvents*, Pergamon Press, Oxford, **1975**.
- [4] E. E. Burnell, C. A. de Lange (Eds), *NMR of Ordered Liquids*, Kluwer Academic Publishers, Dordrecht, **2003**.
- [5] R. K. Harris, R. E. Wasylshen (Eds), *Encyclopedia of NMR, 10 Volume Set*, Wiley, Chichester, **2012**.
- [6] J. Vaara, J. Jokisaari, R. E. Wasylshen, D. L. Bryce. *Prog. Nucl. Magn. Reson. Spectrosc.* **2002**, *41*, 233–304.
- [7] J. Jokisaari, J. Autschbach. *Phys. Chem. Chem. Phys.* **2003**, *5*, 4551–4555.
- [8] J. Jokisaari, J. Zhu. *Magn. Reson. Chem.* **2014**, *52*, 556–559.
- [9] S. Sýkora, J. Vogt, J. Bösigler, P. Diehl. *J. Magn. Reson.* **1979**, *33*, 113.
- [10] a J. Lounila, P. Diehl. *J. Magn. Reson.* **1984**, *56*, 254; b J. Lounila, P. Diehl. *Mol. Phys.* **1984**, *52*, 827; c J. Lounila. *Mol. Phys.* **1986**, *58*, 897.
- [11] P. Diehl, C. L. Khetrapal, H. P. Kellerhals. *Mol. Phys.* **1968**, *15*, 333–337.
- [12] D. Catalano, C. A. Veracini, P. L. Barili, M. Longeri. *J. Chem. Soc., Perkin Trans. 2* **1983**, 171–174.
- [13] C. L. Khetrapal, A. V. Patankar, P. Diehl. *Org. Magn. Reson.* **1970**, *2*, 405–407.
- [14] P. Diehl, T. Bjorholm, H. Bösigler. *J. Magn. Reson.* **1981**, *412*, 390–395.
- [15] S. Craddock, P. B. Liescheski, D. W. H. Rankin, H. E. Robertson. *J. Am. Chem. Soc.* **1988**, *110*, 2758–2763.
- [16] J. P. Marchal, D. Canet. *J. Chem. Phys.* **1977**, *66*, 2566–2568.
- [17] L. Lunazzi, C. Zannoni, C. A. Veracini, A. Zandanel. *Mol. Phys.* **1977**, *34*, 223–230.
- [18] M. Kon, H. Kurokawa, H. Takeuchi, S. Konaka. *J. Mol. Struct.* **1992**, *268*, 155–167.
- [19] P. Diehl, C. L. Khetrapal, H. P. Kellerhals, U. Lienhard, W. Niederberger. *J. Magn. Reson.* **1969**, *1*, 527–533.
- [20] J. Jokisaari, Y. Hiltunen, T. Väänänen. *Mol. Phys.* **1984**, *51*, 779.
- [21] J. M. Briggs, E. J. Rahkamaa. *J. Magn. Reson.* **1975**, *17*, 55–65.
- [22] J. W. Emsley, E. W. Randall. *J. Magn. Reson.* **1976**, *22*, 481–483.
- [23] T. Väänänen, J. Jokisaari, A. Kääräinen, J. Lounila. *J. Mol. Struct.* **1983**, *102*, 175–182.
- [24] P. Bucci, M. Longeri, C. A. Veracini, L. Lunazzi. *J. Am. Chem. Soc.* **1974**, *96*, 1305–1309.
- [25] gNMR 5.0, IvorySoft, AmorWay, Letchworth, Herts. SG61ZA, United Kingdom, **2004**.
- [26] R. Krishnan, J. S. Binkley, R. Seeger, J. A. Pople. *J. Chem. Phys.* **1980**, *72*, 650–654.
- [27] A. D. Becke. *Phys. Rev. A* **1988**, *38*, 3098–3100.
- [28] A. D. Becke. *J. Chem. Phys.* **1993**, *98*, 5648–5652.
- [29] C. Lee, W. Yang, R. G. Parr. *Phys. Rev. B* **1988**, *37*, 785–789.
- [30] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G. A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H. P. Hratchian, A. F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S. S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L. Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, Ö. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, D. J. Fox, *Gaussian 09, Revision A.1*, Gaussian, Inc., Wallingford CT, **2009**.
- [31] V. I. Minkin, A. D. Garnowski, J. Elguero, A. R. Katritzky, O. V. Denisko. *Adv. Heterocycl. Chem.* **2000**, *76*, 157–323.
- [32] R. M. Claramunt, D. Sanz, I. Alkorta, J. Elguero. *Magn. Reson. Chem.* **2005**, *43*, 985–991.
- [33] J. Elguero, R. Jacquier. *J. Chim. Phys.* **1966**, *63*, 1242–1246.