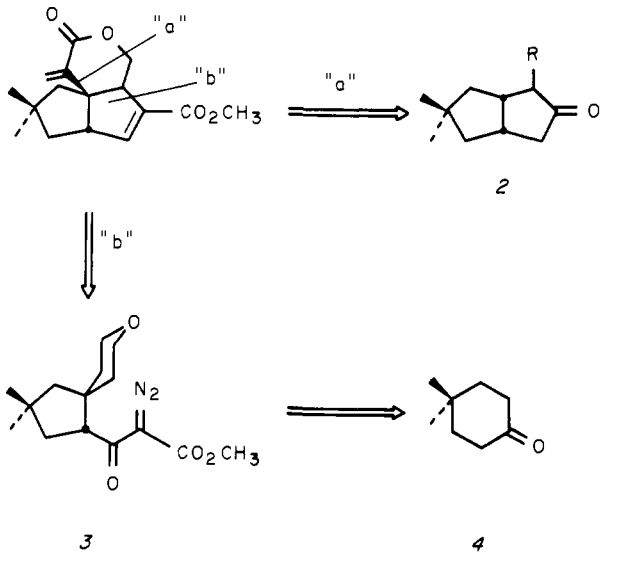
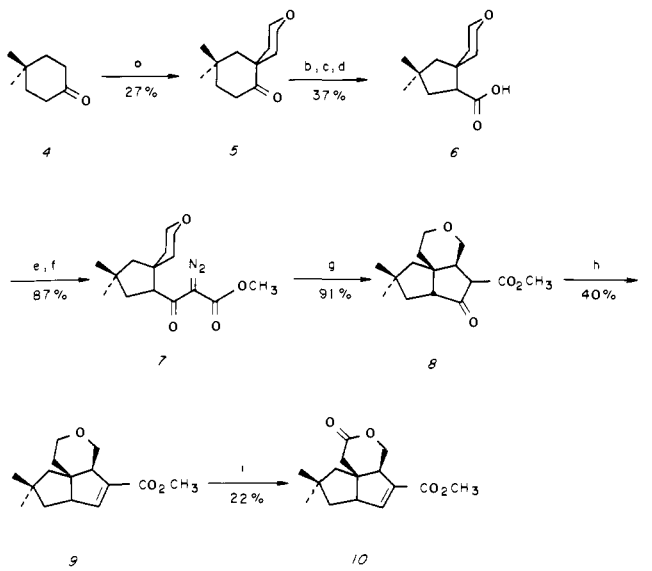
Scheme I



Scheme II[a]



[a] (a) $(ICH_2CH_2)_2O$, NaH, THF, Δ; (b) trisyl azide, KOH, $PhCH_3$, PTC; (c) MeOH, $h\nu$; (d) LiOH, DME, Δ; (e) oxalyl chloride, $LiCH_2COOMe$; (f) TsN_3, Et_3N; (g) $Rh_2(OAc)_4$, CH_2Cl_2, room temperature; (h) $NaBH_4$, MeOH, 0 °C, dicyclohexylcarbodiimide, Cu_2Cl_2, THF, Δ; (i) CrO_3, HOAc, CH_2Cl_2, room temperature.

molecular complexity of **1** is assembled by *forming* the carbon-carbon bond at "b". We have found that rhodium-mediated intramolecular C-H insertion is particularly effective in this application.

The starting point for the synthesis (Scheme II) is the readily available[6] 4,4-dimethylcyclohexanone (**4**). Spiroannulation with bis(2-iodoethyl) ether[7] proceeded smoothly to give **5**. Diazo transfer by the method of Mander[8] followed by photolysis in methanol and saponification then gave the crystalline acid **6**, which was homologated to **7** by the method of Rathke.[9] This set the stage for the anticipated C-H insertion.

We were gratified to observe that exposure of α-diazo-β-keto ester **7** to catalytic $Rh_2(OAc)_4$ in CH_2Cl_2 at room temperature led to smooth conversion to a single substance, shown by subsequent transformation to be the desired tricyclic ether **8**. Reduction and dehydration[10] of **8** gave **9**, which was regioselectively oxidized[11] to the previously prepared[5] lactone **10**. The alternative lactone, from oxidation of the more hindered methylene, was observed as a minor product from the oxidation. Methylenation of **10** to give pentalenolactone E methyl ester (**1**) has been demonstrated by previous investigators.[5]

The synthetic utility of intramolecular C-H insertion is apparent. Unlike most methods for ring construction, in which two functionalized carbon atoms are joined, intramolecular C-H insertion allows bond formation to an unfunctionalized carbon atom, generating a striking increase in molecular complexity[12] in a single step. Further investigations of the scope and limitations of this reaction are under way.[13]

Acknowledgment. We thank the National Science Foundation (CHE 8306692) for support of this work. We also thank Professor David Cane for sharing his results with us prior to publication. D.F.T. acknowledges an unrestricted research grant from ICI Americas.

Supplementary Material Available: Full experimental details for the preparation of **1-10** (10 pages). Ordering information is given on any current masthead page.

(6) (a) Flaugh, M. E.; Crowell, T. A.; Farlow, D. S. *J. Org. Chem.* **1980**, *45*, 5399. (b) Bordwell, F. G.; Wellman, K. M. *J. Org. Chem.* **1963**, *28*, 1350.
(7) Gibson, C. S.; Johnson, J. D. A. *J. Chem. Soc.* **1930**, 2525.
(8) Mander, L. N.; Lombardo, L. *Synthesis* **1980**, 368.
(9) Rathke, M. W.; Deitch, J. *Tetrahedron Lett.* **1971**, 2953.
(10) Knochel, P.; Seebach, D. *Synthesis* **1982**, 1017.
(11) Harrison, I. T.; Harrison, S. *J. Chem. Soc., Chem. Commun.* **1966**, 752.
(12) Bertz, S. H. *J. Am. Chem. Soc.* **1981**, *103*, 3599.
(13) It should be noted that the studies of Rh-mediated intramolecular C-H insertion described here and in our previous work are directly pertinent to the stoichiometric studies being carried out in other laboratories. For leading references, see: (a) Periana, R. A.; Bergman, R. F. *Organometallics* **1983**, *3*, 508. (b) Jones, W. D.; Feher, F. J. *J. Am. Chem. Soc.* **1984**, *106*, 1650.

Dynamic Intermolecular Tautomerism of 3,5-Dimethylpyrazole in the Solid State by ^{13}C CP/MAS NMR Spectroscopy and X-ray Crystallography

Andrē Baldy,[†] Josē Elguero,*[‡] Robert Faure,[§] Marcel Pierrot,[†] and Emile-Jean Vincent[§]

Service de Cristallochimie, Facultē des Sciences et Techniques, 13397 Marseille, France
Instituto de Quimica Mēdica, CSIC Juan de la Cierva 3, 28006 Madrid, Spain
Laboratoire de Chimie Organique Physique Universitē d'Aix-Marseille III 13397 Marseille, France

Received March 11, 1985

The combined use of CP/MAS carbon-13 NMR spectroscopy and X-ray crystallography is giving new insights on the dynamic phenomena in the solid state. Among the dynamic phenomena that have interested the chemist, prototropic tautomerism is one of the most elusive, due to the sensitivity of the activation energy to environmental effects (concentration, nature of the solvent, water traces, etc.). Heterocyclic prototropic tautomerism[1] in the solid state concerns almost exclusively static studies, i.e., the structure of the most abundant tautomer.[1a] Up to now the only dynamic study of heterocyclic tautomerism in a crystal concerns

[†] Facultē des Sciences et Techniques.
[‡] Instituto de Quimica Mēdica.
[§] Universitē d'Aix-Marseille III.
(1) Elguero, J.; Marzin, C.; Katritzky, A. R.; Linda, P. "The Tautomerism of Heterocycles"; Academic Press: New York, 1976. (a) p 325; (b) p 266; (c) p 268; (d) p 285; (e) p 291; (f) p 295.

0002-7863/85/1507-5290$01.50/0

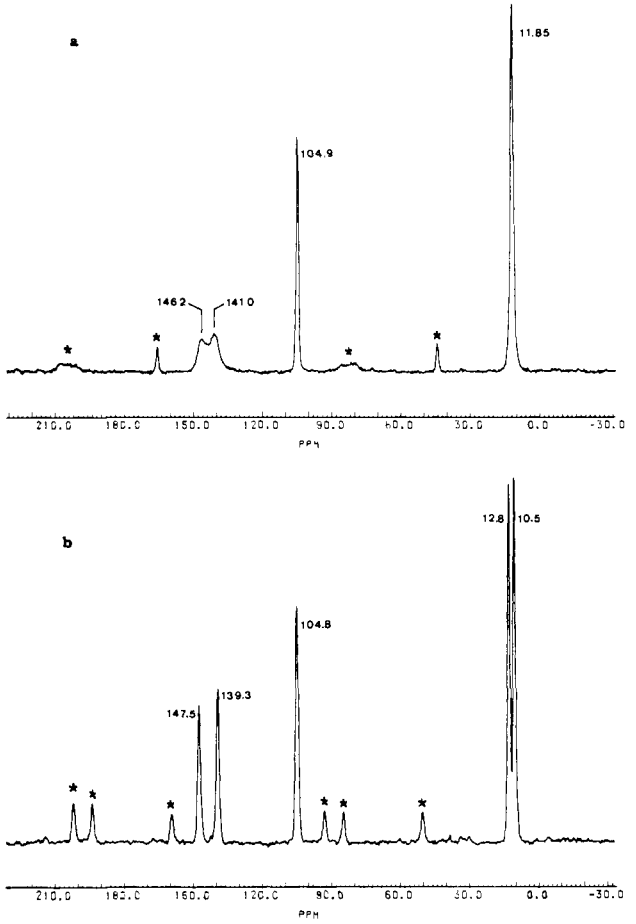


Figure 1. ^{13}C CP/MAS spectra of 3,5-dimethylpyrazole at 75.5 MHz: (a) at 303 K; (b) at 233 K. Asterisks denote spinning sidebands.

porphines as determined via ^{15}N CP/MAS NMR.[2]

Annular tautomerism is defined[1b] as the prototropy involving exclusively ring nitrogens and is common to all N-unsubstituted azoles.[3] Preliminary studies[4,5] on azoles in the solid state by ^{13}C CP/MAS NMR show two important features: (i) "Narrow" singlets corresponding to a unique tautomer are always observed. (ii) The structure of the tautomer present in the crystal always agrees with the previous X-ray results. Well-resolved spectra were obtained for autotropic[1d] systems like pyrazole,[4] imidazole,[4] and benzimidazole;[5] moreover, the tautomeric structures of 1,2,4-triazole,[5] indazole,[5] and benzotriazole[5] [all N(H)1 tautomers] correspond to those found by crystallography.[1d-1f]

In the course of a systematic study of pyrazoles by ^{13}C CP/MAS NMR[6] it was found that 3,5-dimethylpyrazole (**1**) showed broad bands for carbon atoms C_3 and C_5 at 50 MHz. The spectrum recorded at 75.5 MHz at room temperature (303 K) with a Bruker CXP 300[7] is shown in Figure 1a. Only one peak for the methyl substituents and two broad singlets at 146.2 and 141.0 ppm for carbons C_3 and C_5 are observed. The apparent splitting (5.2 ppm) is reduced from the low-temperature limiting value. For comparison, the chemical shifts of **1** in Me_2SO solution

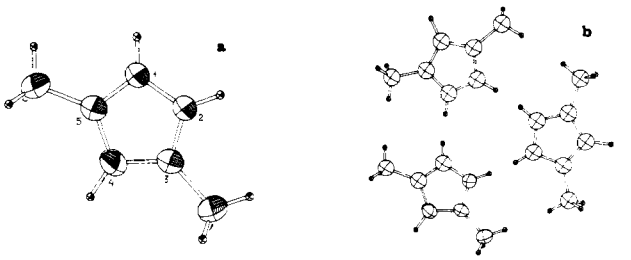
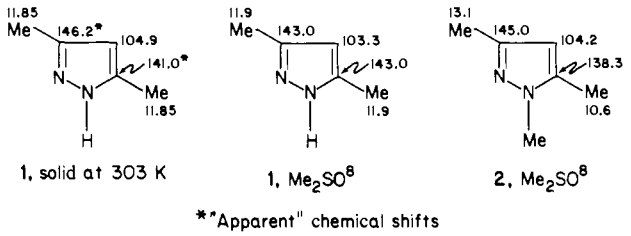


Figure 2. X-Ray structure of 3,5-dimethylpyrazole: (a) isolated molecule; (b) cyclic trimer.

(rapid tautomerism) and of 1,3,5-trimethylpyrazole (**2**) in the same solvent[8] are given below:



*"Apparent" chemical shifts

At this point, the X-ray structure of **1** was determined on a CAD4 Enraf Nonius diffractometer and refined until a final $R = 0.79$. The ORTEP projections of a single molecule and of the unit cell, a trimer, are represented in Figure 2a,b.

The most remarkable facts about the structure are (i) a C_{2v} structure of the monomer,[9] (ii) a trifold symmetry of the cyclic trimer, and (iii) a half-proton intensity spot for the tautomeric proton.

Simultaneously, a ^{13}C CP/MAS NMR spectrum at 233 K was determined (Figure 1b). At this temperature, the annular tautomerism is frozen and the spectra ressembles that of **2**: C_3, 147.5; C_4, 104.8; C_5, 139.3; Me_3, 12.8; Me_5, 10.5 ppm.

In conclusion, at room temperature, a trimer $\rightleftharpoons$ trimer intermolecular tautomerism is taking place in 3,5-dimethylpyrazole (**1**) with a $\Delta G^{\ddagger} \geq 57$ kJ mol^{-1}. In solution, using HMPT as solvent,[10] the activation energy for the isomerization of **1** is 63 kJ mol^{-1}. Thus, the results described here provide a proof of how easy intermolecular proton migration can be (tunnel effects must be considered).[11] In solution these intermolecular mechanisms do not necessarily involve cyclic trimers or linear polymers but more probably solvent molecules (water for instance).[12]

The crystal structure can account for the absence of a similar intermolecular process in pyrazole itself:[13] the distorted tetrameric geometry is less favorable to the concerted proton migration. In X-ray or neutron diffraction structure[13] the NH proton is well located and in the ^{13}C CP/MAS NMR spectrum[4] there is no appreciable broadening of the signals belonging to carbons C_3 and C_5 compared with that of carbon C_4.

It seems likely that, depending on the C substituents, other pyrazoles and, more generally, other azoles crystallize in such structures that dynamic annular prototropic tautomerism will be observed in the solid state.

(2) Limbach, H. H.; Hennig, J.; Kendrik, R.; Yannoni, C. S. *J. Am. Chem. Soc.* **1984**, *106*, 4059.

(3) Katritzky, A. R.; Lagowski, J. M. "Comprehensive Heterocyclic Chemistry"; Katritzky, A. R., Rees, C. W., Eds.: Pergamon Press: Oxford, 1984; Vol. 5, p 35.

(4) Elguero, J.; Fruchier, A.; Pellegrin, V. *J. Chem. Soc., Chem. Commun.* **1981**, 1207.

(5) Faure, R.; Vincent, E. J.; Elguero, J. *Heterocycles* **1983**, *20*, 1713.

(6) Faure, R.; Rousseau, A.; Claramunt, R. M.; Elguero, J., unpublished results.

(7) We acknowledge Dr. G. Hermann (Bruker GmbH, Karlsruhe, Germany) for recording the spectra of **1** at 75.5 MHz.

(8) Cabildo, P.; Claramunt, R. M.; Elguero, J. *Org. Magn. Reson.* **1984**, *22*, 603.

(9) Bonds: N_1–N_2 1.334, N_2–C_3 1.311, C_3–C_4 1.368, C_3–Me 1.491 Å, Angles: N_1–N_2–C_3 109.0°, N_2–C_3–C_4 106.2°, N_2–C_3–Me 123.1°. Intermolecular distances: N_1–N_1' 2.98 Å. Angle of the trimer central hexagon: N_2–N_1–N_2, 124.9°.

(10) Chenon, M. T.; Coupry, C.; Grant, D. M.; Pugmire, R. J. *J. Org. Chem.* **1977**, *42*, 659.

(11) Gerritzen, D.; Limbach, H. H. *J. Am. Chem. Soc.* **1984**, *106*, 869 and references therein.

(12) Bernaude, O.; Chevrier, M.; Dubois, J. E. *Tetrahedron* **1978**, *34*, 2259. Catalān, J.; de Paz, J. L. G.; Sānchez-Cabezudo, M.; Elguero, J. *Bull. Soc. Chim. Fr.*, submitted for publication.

(13) Elguero, J. "Comprehensive Heterocyclic Chemistry"; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: Oxford, 1984; Vol. 5, p 179 and references therein.