Carbon-13 Magnetic Resonance Study of Solvent Stabilized Tautomerism in Pyrazoles

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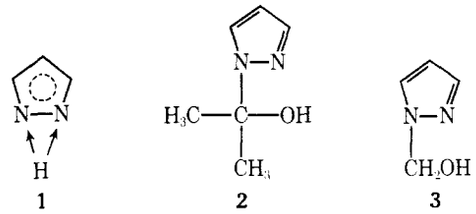
Using ^{13}C NMR methods, the interactions of pyrazole with an appropriate solvent (HMPT) allow the rate of tautomeric exchange to be reduced, and thereby the coalescence of the tautomeric lines appears at room or higher temperatures. Unlike acetone solutions no addition product was observed in the HMPT solutions. Instead, solvent stabilized tautomeric structures account for the increased activation energies between the alternative forms.

Tautomerism in pyrazoles has been studied by many techniques,[1] with special attention given to the problem with NMR.[2] These NMR experiments at ambient temperature failed to detect the two tautomers N(1)H and N(2)H since the processes were in the fast exchange limit on the NMR time scale for the solvents selected. Two studies[3,4] at lower temperatures have identified tautomeric forms of pyrazole, but in these instances the temperature had to be reduced below −100 °C. We wish to report that it is possible to reduce significantly the rate of tautomeric exchange in pyrazoles with an appropriate solvent and thereby preventing coalescence of the tautomeric lines at room temperature or even higher.

Three polar aprotic solvents with increasing basicity[5] (acetone, Me_2SO, and HMPT; $[(CH_3)_2N]_3PO$) were selected for the study. As reported earlier[3] extra lines were observed in acetone solution for the addition compound (**2**) of acetone with pyrazole (**1**). Furthermore, these lines do not exhibit the



1 **2** **3**

proper temperature dependence expected for rapidly interconverting tautomers. The presence of an additional compound was confirmed as the intensities of these lines depend on the amount of acetone in the mixtures. The structure proposed for **2** has also been corroborated by ^{13}C NMR data obtained for **3** (see Table I).

The solvation effect on the tautomeric exchange rate is demonstrated graphically in Figure 1. For pyrazole dissolved in HMPT the exchange rate is sufficiently slow at ambient temperature that separate signals are found for C-3,5. At their coalescence temperature (47 °C in a 1 M solution) a $\Delta G^{\ddagger}$ value of 15 kcal/mol can be evaluated from the corresponding exchange rate. At low temperature, the acetone/HMPT solution exhibits additional broadening while an intermediate exchange rate with a very broad line is found for the acetone/Me_2SO mixture. Such a broad line is also observed for a Me_2SO solution (1 M) at 6 °C, the temperature that may be reached before freezing the sample; at ambient temperature the NH exchange rate is in the fast exchange limit, as it was already observed by ^{14}N NMR.[6] Only the fast exchange limit is found for acetone solutions at corresponding temperatures. These results reflect the respective basicities of the solvents.

The data obtained for 3-methylpyrazole (**4**) exhibit the same characteristics as those of pyrazole (**1**). An addition complex is observed only when the solutions contain some acetone, and the exchange rate is reduced with increasing solvent basicity. For a 1 M solution in HMPT the signals of C-3, C-5, and CH_3 relative to the two tautomeric forms are well separated at −17 °C (see Figure 2). Both the C-3 and C-5 pairs of signals coalesce at approximately 30 °C and the CH_3 lines at 13 °C. Corresponding $\Delta G^{\ddagger}$ values of 14 kcal/mol are similar to those observed for pyrazole. Integration of the two CH_3 lines obtained without NOE effect by a gated decoupling experiment indicates essentially equal populations for the N(2)H form (about 54%) and the N(1)H form (about 46%). This result is at variance with LCAO–MO calculations,[7] which suggest the predominance of the N(2)H tautomer. It may be that the HMPT solvent interaction is invalidating the previous findings. No quantitative conclusions had been drawn from previous extensive NMR studies[2] of tautomerism in 3-methylpyrazole.

No addition complex was observed for 3,5-dimethylpyrazole (**5**) in acetone. This is consistent with earlier ^{1}H NMR data[3] and is probably due to steric interference. For a 1 M solution of **5** in HMPT, the methyl signals coalesce at 35 °C ($\Delta G^{\ddagger} \sim$ 15 kcal/mol) and the C-3,5 resonances have line widths of about 40 Hz. However, upon further reduction in temperature to −10 °C these signals narrow to 9 Hz.

The chemical shifts of the N(1)H and N(2)H tautomers of the several compounds are summarized in Table I. It is interesting to note that the difference of the chemical shifts of a carbon adjacent to a nitrogen in the two tautomers [$\delta_{N(1)H} - \delta_{N(2)H}$] decreases from 10.5 to 8.5 ppm when this carbon is substituted by a methyl group. In pyrazole and 3,5-dimethylpyrazole C-4 is not affected by the tautomeric process as might be expected from the identical structural relationship of C-4 and the labile proton in both the N(1)H and N(2)H structures. In the 3-methylpyrazole C-4 also exhibits a single line for both tautomeric structures. Again similarity of structural relationships could account for the single line, but the possibility of the tautomeric exchange not being slow enough even at low temperatures to reveal two very closely positioned lines cannot be ruled out.

It was not possible to observe separate tautomeric lines in the ^{1}H NMR spectra of pyrazole in HMPT even at −17 °C, the lowest temperature which could be reached without freezing the solution. This is in contrast with the data on 1,2,4-triazole in HMPT.[8] The absence of ^{1}H NMR lines due to addition products, however, confirms our conclusion that only tautomeric forms need to be considered for pyrazole in HMPT.

In concentrated solutions of pyrazole in an inert solvent, the solute mainly consists of hydrogen bonded pyrazole polymers.[4] Thus, the formation of hydrogen bond complexes between pyrazole and a basic solvent is competitive with this self-association process. The more basic the solvent is, the more the relative amount of complexes increases at the expense of polymerization as shown by IR data[9] and the ^{1}H NMR data in Table II. The downfield shift of the NH line

Table I. ^{13}C NMR Chemical Shifts[a] of Certain Pyrazoles

Compd	Concn, M	Temp, °C	Tautomeric form	C-3	C-4	C-5	3-CH_3	5-CH_3
1	2	−17	N(1)H	138.1_2	103.9_0	127.6_0		
			N(2)H	127.6_0	103.9_0	138.1_2		
2[b]	0.2	−17		139.2_2	(105.4)	126.5_5		
3[c]	1	35		139.9_3	106.3_6	129.7_5		
4	1	−17	N(1)H	146.0_5	103.1_7	128.3_4	13.6_8	
			N(2)M	137.1_8	103.1_7	138.5_9	10.5_5	
5	1	−10	N(1)H	146.5_3	102.6_7	138.0_3	13.8_4[d]	10.6_1[d]
			N(2)H	138.03	102.6_7	146.5_3	10.6_1[d]	13.8_4[d]

[a] Chemical shifts are in parts per million with respect to Me_4Si. Solvent is HMPT for **1**, **4**, and **5** and acetone for **2** and **3**. [b] $\delta_{C(CH_3)_2}$ 87.0_7 ppm. [c] δ_{CH_2} 74.7_1 ppm. [d] At −10 °C, these signals are not totally separated.

Table II. ^1H NMR Chemical Shifts[a] of Pyrazole in Some Polar Aprotic Basic Solvents

Solvent	H-4	H-3, H-5	NH
Acetone	6.27	7.61	12.26
Me_2SO	6.26	7.61	12.82
HMPT	6.16	7.48	13.74

[a] The chemical shifts are in parts per million with respect to Me_4Si. Pyrazole concentration 1 M. T = 27 °C.

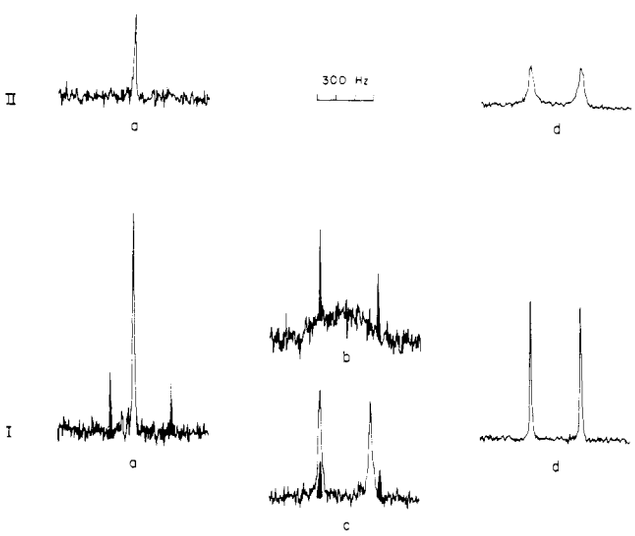


Figure 1. The ^{13}C NMR signals of carbons 3 and 5 of pyrazole in various solvents: Ia, IIa, 1 M in acetone; Ib, 1 M in 1/1 acetone/Me_2SO; Ic, 1 M in 1/1 acetone/HMPT; and Id, IID, 2 M in HMPT. The temperature was 29 °C for IIa and 33 °C for IId; all I spectra were recorded at −17 °C. Addition products with acetone indicated by darkened peaks.

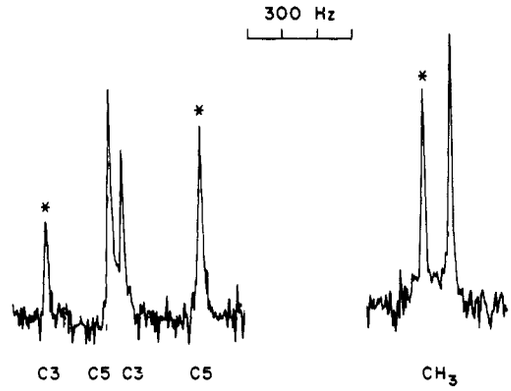


Figure 2. The ^{13}C NMR signals of carbons 3, 5, and methyl group of 3-methylpyrazole, 1 M in HMPT, at −17 °C. Lines from the N(1)H tautomer are indicated with an asterisk.

increases with the basicity of the solvent. In light of these data it is also interesting to compare the $\Delta G^{\ddagger}$ values obtained at 47 °C for pyrazole in HMPT solution (~15 kcal/mol) and in ether/tetrahydrofuran mixture (~11 kcal/mol, evaluated from data in ref 4). As competing solvation processes can be expected to lower the average energy of the solvated pyrazoles in more basic solvent, the increase in $\Delta G^{\ddagger}$ in HMPT is compatible with both the IR and ^1H NMR studies. The solvation process will also change the averaged energy of the activated complex. Unfortunately, little is known about such effects and therefore the above interpretation of the significant effect of solvent upon $\Delta G^{\ddagger}$ must be considered to be tentative. The common practice[10] in ^1H NMR to use Me_2SO to slow down exchange of –OH protons in alcohols and thus observe coupling to adjacent protons is based on this same solvation process: bonding of a labile hydrogen to a polar aprotic basic solvent.

It has been shown that hexamethylphosphoric triamide (HMPT) is a very effective solvent for studying tautomerism by ^{13}C NMR spectroscopy in a more convenient and accessible range of temperatures. However, according to a recent report,[11] HMPT appears to be toxic and must be handled with appropriate precaution. This ability to determine the chemical shifts of the different tautomeric forms allows avoidance of the cumbersome and indirect method of using model compounds to estimate chemical shifts from which tautomeric populations can be calculated,[12] and tautomeric equilibrium constants determined.

Experimental Section

Compounds were obtained from commercial sources except for 1-hydroxymethylpyrazole (**3**), which was synthesized according to published procedure.[13] The samples were dissolved in dry spectroquality solvents. The ^1H NMR spectra were recorded on a Varian HA-100 spectrometer and the ^{13}C spectra on a Varian XL-100-15-FT except for data on **3**, which were obtained on a Varian CFT-20.

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Registry No.—**1**, 288-13-1; **2**, 60803-64-7; **3**, 1120-82-7; **4**, 1453-58-3; **5**, 67-51-6.

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^1H and ^{13}C Nuclear Magnetic Resonance Spectroscopic Study of 6,6-Disubstituted Fulvenium Ions[1]

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A series of 6,6-disubstituted fulvenes including 6-cyclopropyl-6-methylfulvene (**5**), 6-cyclopropyl-6-phenylfulvene (**6**), 6,6-(2-norbornylidene)fulvene (**7**), and 6,6-admantylidenefulvene (**8**) were prepared by the condensation of cyclopentadiene with the corresponding ketones. Precursor fulvenes were protonated to give the corresponding fulvenium ions under superacidic conditions at low temperatures. Protonation takes place exclusively at the C_2 position of the fulvene ring in accord with the calculated electron density distributions. The effects of substituent at C_6 on charge distributions in the studied fulvenium ions are discussed with regard to their respective ^1H and ^{13}C NMR data.

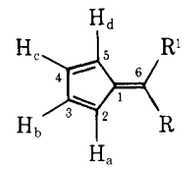
Fulvenes are highly colored compounds with considerable chemical reactivity, isomeric with benzenes, but with properties intermediate between those of aromatic and olefinic systems. Synthesis and properties of fulvenes have been reviewed.[2] For theoretical studies, fulvenes have been of great interest because they represent relatively simple nonalternate hydrocarbons which are readily adaptable to quantum mechanical treatment by either simple valence bond or molecular orbital methods. Thus, for example, the rather large dipole moments found for many 6,6-disubstituted fulvenes have been accounted for by several refinements of HMO type calculations of the parent fulvene.[3-5] Recently more sophisticated calculations were reported on fulvalene ions.[6] These calculations agree on the point that the dipole moment of the fulvenes is a direct consequence of their electronic structure and the moment is directed with its negative pole toward the ring.

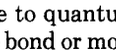
Fulvenes undergo a variety of reactions,[2d] but relatively little is known about their electrophilic reactions.[2c] Such reactions, however, are reported on heptafulvenes.[7] In continuation of our studies on the carbocationic intermediates of electrophilic reactions and particularly on the nature of substituent effects adjacent to carbocationic centers, we wish to report the study, based on ^1H and ^{13}C NMR spectroscopic data, of the carbocations obtained upon protonation of 6,6-disubstituted fulvenes in superacidic media.

Results

6,6-Dicyclopropylfulvene (**1**), 6,6-dimethylfulvene (**2**), 6,6-diphenylfulvene (**3**), and 6-methyl-6-phenylfulvene (**4**) were prepared by reported methods.[8] 6-Cyclopropyl-6-methylfulvene (**5**), 6-cyclopropyl-6-phenylfulvene (**6**), 6,6-(2-norbornylidene)fulvene (**7**), and 6,6-adamantylidenefulvene (**8**) were prepared by the condensation of cyclopentadiene with the corresponding ketones in the presence of sodium ethoxide in ethanol.

Protonation of studied fulvenes was carried out in FSO_3H/SO_2ClF or SO_2F_2 at −78 or −120 °C (using an ethanol/liquid nitrogen bath), respectively. Precursors **2**, **5**, and



1, R = R′ = 
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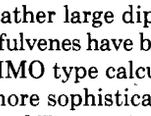
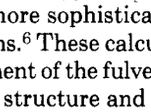
3, R = R′ = 
4, R =  R′ = CH_3
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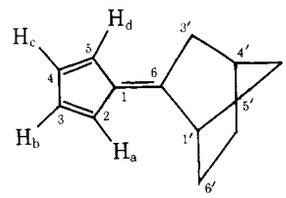

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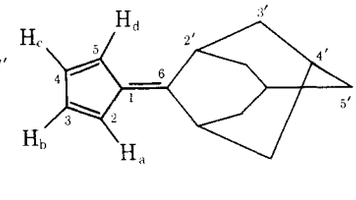

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7 gave only polymeric materials with all-acid systems such as HF/SbF_5, FSO_3H/SbF_5, and HF/BF_3. Precursors **1**, **3**, **4**, **6**, and **8** gave clean solutions of the resulting ions and the ^1H NMR spectrum of the ion obtained from **1** is shown in Figure 1 together with the ^{13}C NMR spectrum of the precursor **7**. The ^1H and ^{13}C NMR spectra of the ion generated from precursor **8** as representative are shown in Figure 2. The ^1H NMR shifts of the ions obtained are tabulated in Table I. The ^{13}C NMR data of the ions as well as their precursors along with the assignments are listed in Tables II and III, respectively.

Discussion

The bonding nature of fulvenes can be qualitatively described in terms of the mesomeric covalent structure **9** and the