An Electron Spin Resonance Reinvestigation of Dihydropyridyl Radicals

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An e.s.r. study of substituted dihydropyridyl radicals is reported. Some spectra previously described have been reinterpreted and the structures of the radicals reassigned. The factors influencing the persistence of dihydropyridyl radicals are discussed. In one case (4-aceteyl-1-methyldihydropyridyl) extraordinarily large variations of hyperfine splitting constants with solvent were observed; these were explained in terms of mesomerism. The large solvent-induced redistribution of spin density makes this radical a useful substrate for studying medium effects.

DIHYDROPYRIDYL radicals, because of their importance in organic[1] and biological[2] reactions, have been investigated extensively with regard to their reactivity,[1,3] their ability to associate intramolecularly to form paramagnetic dimers,[4] and the effect of ring substituents on their stability.[3,5-7]

Being interested in electron-transfer processes with nucleophilic species,[8] we wished to carry out a study of *N*-alkylated and *N*-protonated pyridines in view of their strongly electron-deficient character and because we thought that the dihydropyridyl radicals resulting from their electron-transfer reactions could be easily characterized on the basis of their e.s.r. spectra. However we found that the spectroscopic behaviour of these radicals, in spite of several papers on the subject, was not well understood, that often the e.s.r. spectra were not interpreted correctly, and that the structures of the radicals were assigned erroneously. We report here a reinvestigation of the e.s.r. spectra of dihydropyridyl radicals.

EXPERIMENTAL

The *N*-methylpyridinium [(1)—(3)] salts were prepared by reactions of the corresponding pyridines with methyl iodide.[9,10] The *N*-protonated analogue (4) was obtained by adding sulphuric acid to an ethereal solution of the organic base. The radicals were produced by a variety of methods as described in the following section. When ethers or mixtures containing ethers were used as solvents, the samples had to be carefully degassed and then sealed up under vacuum to obtain well resolved e.s.r. spectra. In other cases the exclusion of oxygen was found not to be necessary for the formation of the radical and for spectral resolution. The reaction of the *N*-protonated salt with zinc powder in methanol or ethanol was favoured by bubbling nitrogen through the mixture and by the presence of a small amount of trichloroacetic acid.

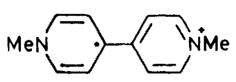
(1) R^1 = Me, R^2 = CN
(2) R^1 = Me, R^2 = COMe
(3) R^1 = Me, R^2 = Et
(4) R^1 = H, R^2 = CN

The e.s.r. spectra were recorded at room temperature with a V-4502 or E-4 Varian spectrometer, with 100 kHz field modulation.

RESULTS

The pyridinium salts show an exceptionally strong electron–acceptor character, being easily reduced to dihydropyridyl radicals by a large number of electron-donor agents.

4-*Cyano*-1-*methylpyridinium Iodide* (1).—This reacted with zinc powder or with a potassium mirror in tetrahydrofuran (THF) to give the corresponding dihydropyridyl radical, which was stable for several days. Treatment of the salt (1) with potassium t-butoxide in dimethyl sulphoxide (DMSO) also led to the dihydropyridyl, which changed during *ca.* 1 h into a second radical, the spectrum of which can be interpreted in terms of the following hyperfine splittings: a_H(4H) 1.29, a_H(4H) 1.60, a_H(6H) 4.02, a_H(2N) 4.15 G. The numbers of interacting nuclei and the magnitudes of the coupling constants suggest that this second species is the cation radical (5), even though the hyperfine splittings differ slightly from the values reported.[11] The cation radical (5) is also obtained by treating the salt (1) with zinc powder in acetonitrile or in ethanol. In the latter cases the measured splittings are coincident with those



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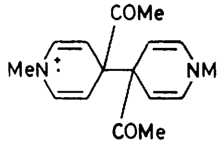

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[1] E. M. Kosower and E. J. Poziomek, *J. Amer. Chem. Soc.*, 1964, **86**, 5515; E. M. Kosower and J. L. Cotter, *ibid.*, p. 5524.

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[3] M. Frangopol, P. T. Frangopol, C. L. Trichilo, F. E. Geiger, and N. Filipescu, *J. Org. Chem.*, 1973, **38**, 2355.

[4] M. Itoh and E. M. Kosower, *J. Amer. Chem. Soc.*, 1967, **89**, 3655; 1968, **90**, 1843.

[5] M. Itoh and S. Nagakura, *Bull. Chem. Soc. Japan*, 1966, **39**, 369.

[6] A. Katritzky and F. Soti, *J.C.S. Perkin I*, 1974, 1427.

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[9] E. M. Kosower, *J. Amer. Chem. Soc.*, 1958, **80**, 3253.

[10] A. Katritzky, *J. Chem. Soc.*, 1955, 2586.

[11] C. S. Johnson, jun., and H. S. Gutowsky, *J. Chem. Phys.*, 1963, **39**, 58.

reported.[11] The rate of formation of (5) from (1) increases along the series DMSO < MeCN < EtOH.

The splitting constants of 4-cyano-1-methyldihydropyridyl in THF and in DMSO are reported in Table 1.

4-*Acetyl*-1-*methylpyridinium Iodide* (2).—A solution of the salt (2) in THF gave the spectrum shown in Figure 1 when brought into contact with a mirror of sublimed potassium metal, or with zinc powder. This spectrum, which is better resolved than the one reported,[5] clearly shows that none of the ring protons are coupled to the same extent with the unpaired electron, *i.e.* no triplets are observed. This finding is not unexpected in view of the close similarity of the dihydropyridyl from (2) to the radical anions of aromatic aldehydes or acetyl derivatives in which rotation of the carbonyl group is always suppressed at room temperature, as revealed by the nonequivalence of the *ortho*- and *meta*-position.[12] Also in our case the presence of the 4-acetyl substituent makes the hyperfine splittings at the 2- and 3-protons different from those at the 6- and 5-protons, respectively. Attempts to produce exchange broadening by increasing the temperature to *ca.* 80 °C were unsuccessful. We may therefore estimate for the energy barrier to rotation of the acetyl group a lower limit of *ca.* 10—12 kcal mol^{-1}.

TABLE 1

Hyperfine splitting constants (G) of the dihydropyridyl radicals from the 4-cyano-1-methylpyridinium (1) and 4-cyanopyridinium (4) salts

Compound	Solvent	a_N	a_R^{NR}	$a_{2,6}$	$a_{3,5}$	a_N^{CN}
(1)	THF	6.40	5.47	4.01	0.25	1.95
	DMSO	6.48	5.75	3.48	0.54	2.01
(4)	MeOH	5.38	5.22	3.88	0.58	2.16

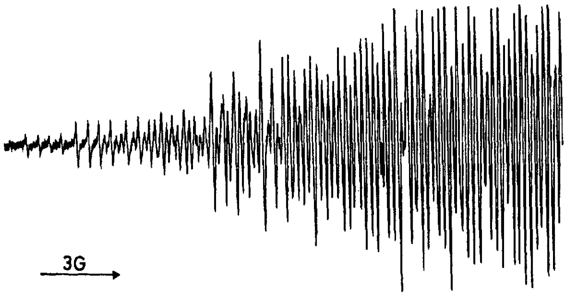

FIGURE 1 E.s.r. spectrum of 4-acetyl-1-methyldihydropyridyl in THF

The hyperfine splittings measured in THF are reported in Table 2.

Figure 2 shows the e.s.r. spectrum obtained by dissolving the salt (2) in aqueous N-sodium hydroxide. Since the pattern is completely different from that of the spectrum recorded in THF (Figure 1), it could be inferred that, as with the 4-cyano-derivative (1), 4-acetyl-1-methyldihydropyridyl is unstable in polar solvents and gives other radicals. In fact the same spectrum has been reported by others,[3] and was interpreted in terms of the following coupling constants: a_H(4H) 1.54, a_H(4H) 1.80, a_{CH_3}(2CH$_3$) 5.10, a_N(2N) 5.39 G. On this basis these authors claimed that the species observed in sodium hydroxide solution was the radical dimer (6). This assignment seems dubious, since the interaction of the free electron with both halves of the dimer molecule implies through-space conjugation, which is unlikely given the distance between and the symmetry of the two π-systems. In fact close inspection of the experimental and computer-simulated spectra [3] shows that the agreement between them is not so good as would be desirable. We therefore tried to reinterpret this spectrum, and found that it could be perfectly reproduced, as shown in Figure 2(b), only by assuming that the unpaired electron is in the same environment as for 4-acetyl-1-methyldihydropyridyl. We must therefore conclude that no decomposition occurs in solvents of high polarity, even though the values of the hyperfine splittings are extraordinarily different from those measured in apolar solvents, as reported in Table 2. The assignment of these splittings is discussed in the following section.

Treatment of the salt (2) with potassium t-butoxide or with 1-methylpiperidine in DMSO or in hexamethylphosphoramide (HMPA), or dissolution in methanol containing sodium methoxide or zinc powder, gives the corresponding dihydropyridyl radical. The hyperfine splittings measured in these solvents are intermediate between those determined in THF and in H$_2$O.

TABLE 2

Hyperfine splitting constants (G) of the 4-acetyl-1-methyldihydropyridyl radical produced from the salt (2)

Solvent	a_2	a_3	a_5	a_6	a_{Me}^{Ac}	a_N	a_{Me}^{NMe}
THF	2.94	0.48	0.88	3.58	1.95	5.76	5.13
HMPA *	2.70	0.73	1.14	3.45	2.31	5.72	5.31
DMSO	2.52	0.86	1.27	3.20	2.61	5.70	5.24
MeOH	2.10	1.38	1.76	2.75	4.10	5.61	5.34
H$_2$O	1.64	1.85	2.20	2.20	5.41	5.70	5.41

* Not anhydrous.

Further, the spectra of the salt (2) in sodium ethoxide–ethanol and in pyrrolidine–dimethoxyethylene attributed [3] to unknown radicals are almost certainly due to 4-acetyl-1-methyldihydropyridyl.

4-*Ethyl*-1-*methylpyridinium Iodide* (3).—The reaction of the salt (3) with potassium t-butoxide or with 1-methylpiperidine in DMSO or HMPA leads to the 4-acetyl-1-methyldihydropyridyl radical. Oxidation of the ethyl group also occurs when the salt (3) is dissolved in alkaline alcoholic solution or brought into contact with a potassium mirror in THF. No e.s.r. signals were observed on treating the salt (3) with aqueous sodium hydroxide or with zinc powder in THF. In no case was 4-ethyl-1-methyldihydropyridyl obtained.

The behaviour of the salt (3) is similar to that shown by the radical anions of *para*-ethyl- and -methylnitrobenzene and of 5-ethyl- and 5-methyl-2-nitrothiophens:[13] in both cases the ethyl group is oxidized

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[12] N. Steinberger and G. K. Fraenkel, *J. Chem. Phys.*, 1964, **40**, 723.

[13] W. Kaminski and K. Mobius, *J. Magnetic Resonance*, 1971, **5**, 182.

[13] C. M. Camaggi, R. Leardini, and G. Placucci, *J.C.S. Perkin II*, 1974, 1195; A. Alberti and G. F. Pedulli, unpublished results.

to acetyl, and the methyl derivatives give first aldehydes and then carboxylic acids.

4-Cyanopyridinium Sulphate (4).—The *N*-protonated 4-cyanodihydropyridyl develops after a few hours when the salt (4) is brought into contact with zinc powder in methanol deoxygenated by bubbling nitrogen. If a small amount of trichloroacetic acid is added to the solution the radical is observed immediately. The e.s.r. spectrum is shown in Figure 3. In contrast to its *N*-methylated homologue, this radical shows no tendency to give a cation radical even in pure ethanol.

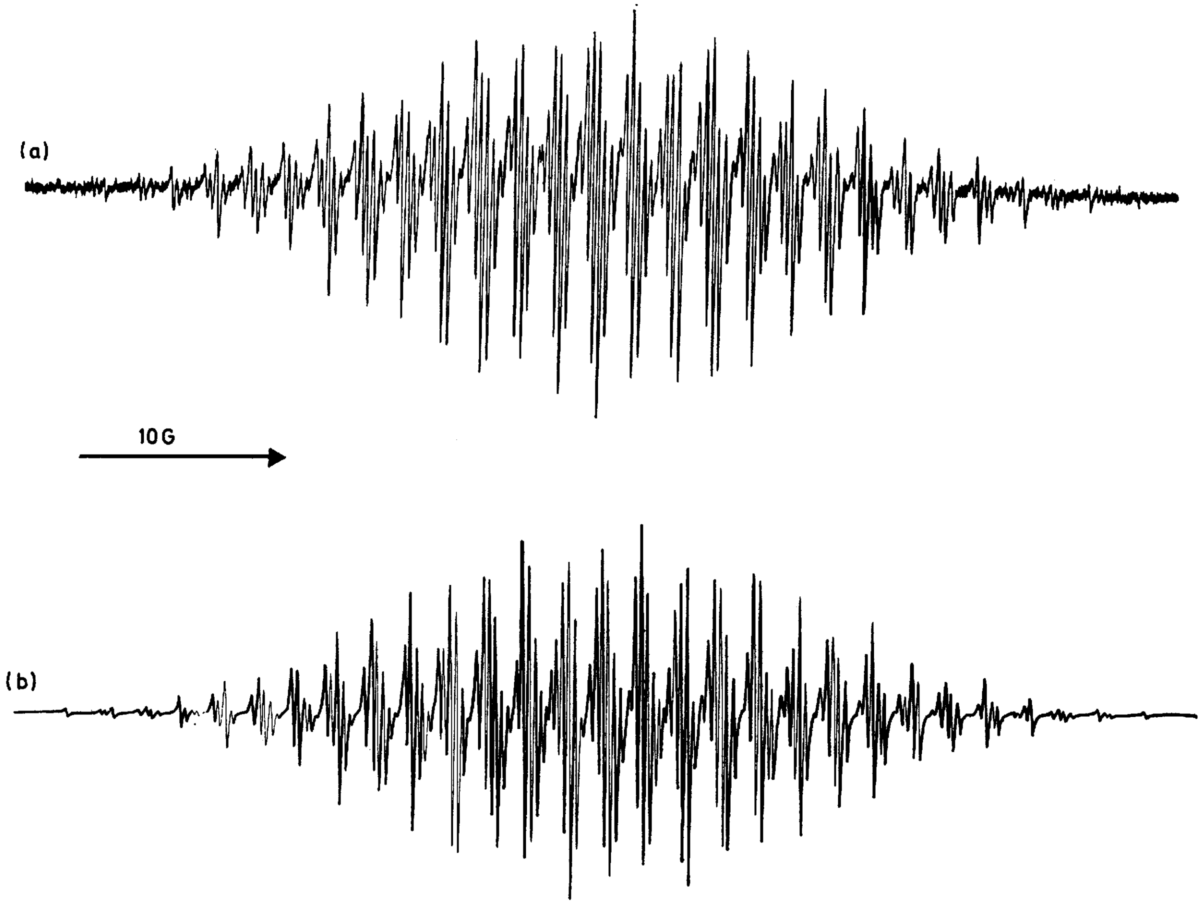


FIGURE 2 Experimental (a) and computer-simulated (b) e.s.r. spectra of the radical produced by dissolving the salt (2) in aqueous sodium hydroxide

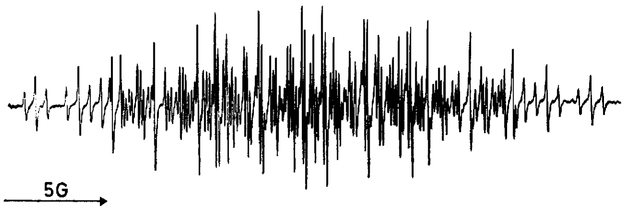
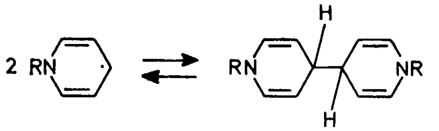


FIGURE 3 E.s.r. spectrum of 4-cyanodihydropyridyl from the salt (4) in methanol

DISCUSSION

Dihydropyridyl radicals show in solution a strong tendency to undergo dimerization according to equation (i). In 1-alkyldihydropyridyls the equilibrium is shifted to the right and no e.s.r. spectra have been detected; only when R is a trimethylsilyl group has it been possible to obtain a sufficient concentration of monomer (at 110 °C in decalin).[7] The *N*-protonated dihydropyridyl (R = H) has been observed in the reaction of photolytically generated 1-hydroxy-1-methylethyl radicals with pyridine.[14]

Dihydropyridyls can however be stabilized by electron-withdrawing 4-substituents such as CN, COMe, and $CONH_2$.[5] Recently Katritzky and Soti have shown that these substituents have a similar stabilizing effect when introduced at the 2- and 6-positions, particularly if the 4-position is blocked by an alkyl group.[6] This effect is due to reduction of unpaired electron density at C-4, which makes dimerization more difficult. The resonance stabilization exerted by the above substituents can be completely overwhelmed when they are prevented



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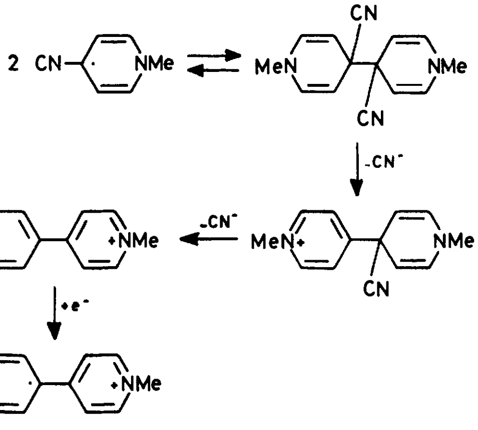
[14] H. Zeldes and R. Livingston, *J. Phys. Chem.*, 1973, **76**, 3348.

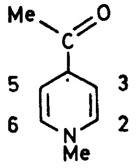
from being coplanar with the aromatic ring by alkyl groups at the adjacent ring positions.[5]

The nature of the solvent can also be important in determining the stability of dihydropyridyls. This is particularly evident in the case of the 4-cyano-1-methyl derivative, which is stable for several days in apolar solvents such as ethers, whereas it decays rapidly in polar solvents such as MeCN, DMSO, or EtOH, to give the cation radical (5). A plausible mechanism as proposed by Kosower and Cotter,[1] is shown in Scheme 1. This mechanism perfectly accounts for the high sensitivity of the reaction to solvent polarity.



SCHEME 1

With regard to the 4-acetyl-1-methyldihydropyridyl we will first discuss the assignment of the hyperfine splitting constants. In THF solution there is no doubt that the two smaller ring proton splittings come from H-3 and -5, and the two larger ones are due to H-2 and -6. The only problem concerns the attribution within each of these pairs. It seems reasonable to assume that, as in aromatic ketyls the primary cause of differences in splitting constants is the strong electrostatic interaction between the electronegative oxygen and the adjacent ring atoms. This interaction induces larger spin densities on carbon atoms of the aromatic ring which are *trans* to the carbonyl oxygen,[12] and therefore the 0.88 and 3.58 G splittings should be assigned to H-5 and -6 and the 0.44 and 2.94 G splittings to the H-3 and -2, respectively.



In HMPA, DMSO, and MeOH the coupling constants, although different from those measured in THF, still show the same trend and therefore can be assigned in parallel. However, the situation is different in water: the four ring proton splittings are similar in magnitude and their assignment is not so straightforward. In this connection it is important that on going from THF to MeOH, through HMPA and DMSO, the H-3 and -5 splittings increase markedly, but their difference remains almost constant at *ca.* 0.4 G. The same is true for H-2 and -6, the values for which in spite of their considerable decrease, continue to differ by *ca.* 0.65 G. Since it seems reasonable that in water also the differences between the above splittings should remain unchanged, the 1.85 and 1.64 g couplings may be assigned to H-3 and -2, respectively; the other two ring splittings are equal (2.20 G). Support to this assignment is given by a plot of coupling constants as a function of a solvent polarity parameter, such as the Kosower Z value.[15] This plot (Figure 4) shows a good straight line for all the four couplings; any other assignment would give some discontinuity corresponding to the values measured in water solution.

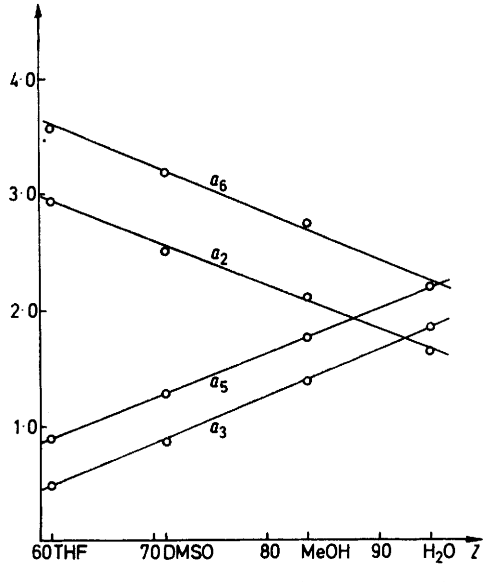


FIGURE 4 Correlation between the ring proton splittings of 4-acetyl-1-methyldihydropyridyl measured in several solvents and the corresponding Kosower Z values

Further we emphasize that the 4-acetyl-1-methyldihydropyridyl radical shows an extraordinarily large variation of the splittings at the protons of both the aromatic ring and the acetyl group. These variations (*ca.* 300—400%) are most unusual when one recalls that known radicals showing the greatest changes of the hyperfine splitting with solvent are some nitroxides [16] and some nitroaromatic anions,[17] and even these changes are at most *ca.* 50%. We also note the reversal in the relative magnitudes of the H-2 and -3 couplings on going from THF to water.

The unusual solvent dependence of the hyperfine splitting constants may be explained in terms of the

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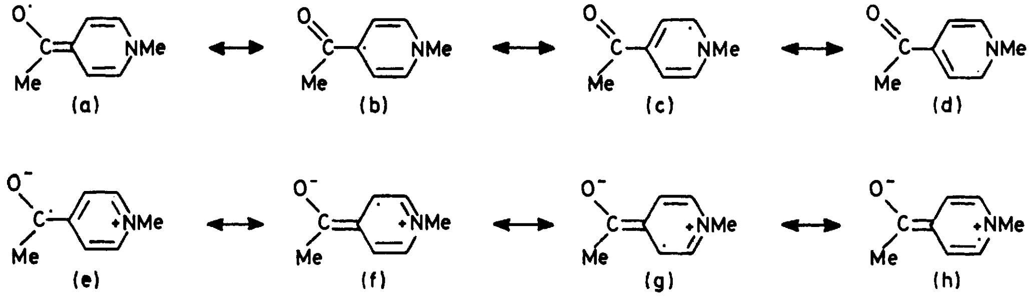
[15] E. M. Kosower, 'An Introduction to Physical Organic Chemistry,' Wiley, New York, 1968.

[16] R. Brieve, H. Lemaire, and A. Rassat, *Tetrahedron Letters*, 1964, 1775.

[17] J. Howard Sharp and M. C. R. Symons, ' Ions and Ion Pairs in Organic Reactions,' ed. M. Szwarc, Wiley–Interscience, New York, 1972, vol. 1.

resonance structures (a)—(h) which may be written for the 4-acetyl-1-methyl dihydropyridyl radical. Besides the apolar structures (a)—(d), the zwitterionic forms (e)—(h) should also have considerable importance. When low polarity solvents are employed, large spin densities are observed at the 2- and 6-positions, whereas the methyl of the acetyl group and the 3- and 5-protons show relatively small splitting constants; this means that the major contribution to the mesomeric system comes from the apolar structures (a)—(d) as expected. On the other hand, the increase of the methyl and H-3 and -5 splittings and the parallel decrease of the H-2 and -6 coupling observed in solvents of higher polarity indicates that these solvents strongly favour the zwitterionic forms (e)—(h). In protic solvents such as water or methanol, additional stabilization of the polar structures may come from hydrogen bonding to the negative carbonyl oxygen.



Scheme 2

Apparently inconsistent with the above interpretation is the behaviour of the splittings at the nitrogen atom and at the attached methyl group, which are almost independent of solvent, whereas they should be greater in water than in THF on the basis of structure (h). As a possible explanation we tentatively suggest that this invariance is connected with the fact that the energy gap between planar and pyramidal configurations at the nitrogen atom is relatively small. Consequently solvent variation could induce not only a drastic redistribution of spin density, but also a change of configuration at nitrogen. Therefore if we admit that with decreasing solvent polarity the configuration changes from planar to slightly pyramidal, the decrease of spin density at the nitrogen atom itself could be counterbalanced by delocalization of the unpaired electron into an orbital having a greater *s* character. We are at present carrying out MO calculations which seem to support this interpretation.

Also the greater stability in polar solvents of the 4-acetyl-1-methyldihydropyridyl than of the corresponding 4-cyano-derivative may arise from the greater importance of the zwitterionic structures in the case of the former radical; the resulting reduction of unpaired electron density at the 4-position would prevent dimerization.

Finally we note that the 4-acetyl-1-methyldihydropyridyl radical, because of the extreme sensitivity of its hyperfine splitting constants to solvent polarity and because of its stability in a great variety of solvents, may be conveniently employed as substrate for investigating medium effects. Figure 4 in fact shows the good correlation between the ring proton splittings of the 4-acetyl-1-methyldihydropyridyl radical in several solvents with the corresponding Kosower *Z* values.

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