N.m.r. Spectra and Stereoisomerism in Pyrazolines

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Cis-trans isomerism in pyrazolines and the application of n.m.r. spectroscopy in differentiating between such isomers is discussed. Theoretical calculations of chemical shifts for some *cis*- and *trans*-4,5-disubstituted 2-pyrazolines are in agreement with assignments based on chemical considerations.

Cis-trans isomerism in pyrazolines is limited to 4,5-disubstituted 2-pyrazolines because of the well known lack of preferred stereochemistry of substituents on tertiary nitrogen. Additional stereoisomerism becomes possible in 1-pyrazolines, but these generally isomerize to the more stable 2-pyrazolines.[2] Although the latter represent a well known and easily accessible class of organic compounds, *cis-trans* isomerism in these systems has apparently been observed only in two cases.[2–4] Since ultraviolet and infrared spectra do not serve to distinguish between such geometrical isomers, we have turned to n.m.r. to provide additional support for structure assignments based on chemical evidence.[3] Chemical shift and proton coupling constant differences have been observed for *cis-trans* isomer pairs in olefins and cyclic compounds and have been used in structure assignments.[5] For the 4,5-*trans*- and 4,5-*cis*-1,5-diphenyl-3,4-tetramethylene-2-pyrazolines, III and IIIa,[3] we found the spin coupling constant of the C-5 hydrogen with the C-4 hydrogen (J) to be 9 and 12 c.p.s., respectively. These values agree well with the J values (8 and 12 c.p.s.) in 1,3,5-triphenyl-2-pyrazoline (I). They do not fit the Karplus curve (plotting of J *vs.* angle between protons) established for simpler compounds,[6] but the relative position of this curve is known to vary with structural features of the molecule.[7] There first appeared to be a lack of simple relationship between the J values (9 and 12 c.p.s.) for our pyrazolines III and IIIa and those observed (*ca.* 4 c.p.s.)[8] for some 4,5-*trans* disubstituted pyrazolines. Only after we had studied a few more examples of this series did it become clear (see Table I) that *cis* pyrazolines exhibit higher coupling constants than the corresponding *trans* isomers with the J values for a few *cis* isomers in the range of 10–14 c.p.s., and for many more *trans* isomers in the range of 3–10 c.p.s. This trend ($J_{cis} > J_{trans}$) is opposite to the trend in *cis-trans* olefins and differs from earlier observations reported[9] for cyclopropanes; it is, however, in agreement with a similar trend established for *cis* and *trans* ethylene oxides,[7a] and for five-membered ring compounds.[9b,10] The angle between *cis* or *trans* hydrogens in the pyrazolines studied (see Table I) is not expected to vary greatly and it appears that the large observable differences in coupling constants are best attributed to electronic environment effects. There is some indication that J_{trans} decreases with increasing polarity[11] of substituents of C_4—compare J for I, VII, and VI—but a generalization is still premature. Since substituents on N have a marked effect on the J value, comparison of coupling constants of pyrazoline with more than one variable substituent is not recommended.

We then turned our attention in these pyrazolines to chemical shift values, the interpretation of which lends itself better to verification by theoretical calculations than do coupling constant data. The difference in chemical shifts between pyrazolines III and IIIa had previously been explained[3] by a difference in shielding due to the influence of the magnetic anisotropy of the phenyl group at C-5. Thus a C-4 substituent *cis* to the phenyl group, as in IIIa, would be expected to interfere with the free rotation of that group, causing a deshielding of the C-5 proton in *cis* pyrazoline IIIa as compared to the same proton in the *trans* isomer III. It appears reasonable to assume and it is borne out by examination of models that introduction of a *trans* substituent (alkyl) at C-4 will have little or no influence on the free rotation of phenyl at C-5. Therefore, the chemical shift for the C-5 proton is expected to be nearly the same in pyrazolines II and III but greatly different in II and IIIa. The large chemical shift difference (0.5 p.p.m.) between pyrazolines II and III as compared to the difference (0.21 p.p.m.) between II and *cis*

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[1] Du Pont Teaching Fellow, 1960–1961. Presented in part before the Organic Division of the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962.

[2] W. M. Jones, *J. Am. Chem. Soc.*, **81**, 5153 (1959).

[3] A. Hassner and M. J. Michelson, *J. Org. Chem.*, **27**, 298 (1962).

[4] E. E. Baroni, K. A. Kovyrzina, and E. A. Andreeshchev, *Zhur. Obshchei. Khim.*, **30**, 2002 (1960), have reported *cis-trans* isomers of 2-pyrazolines which we have shown to be *trans*-pyrazolines and pyrazoles (A. Hassner and M. J. Michelson, unpublished results).

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[6] M. Karplus, *J. Chem. Phys.*, **30**, 11 (1959); F. A. L. Anet, *Can. J. Chem.*, **39**, 789 (1961).

[7] (a) C. A. Reilly and J. D. Swalen, *J. Chem. Phys.*, **32**, 1378 (1960). (b) C. N. Banwell and N. Sheppard, *Mol. Phys.*, **3**, 351 (1960).

[8] Private communication from Dr. W. Brey, University of Florida, Gainesville, Fla.

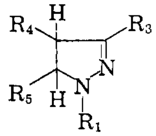
[9] (a) G. L. Closs and L. E. Closs, *J. Am. Chem. Soc.*, **82**, 5723 (1960); (b) H. Conroy quoted in ref. 9a.

[10] J. B. Hyne, *J. Am. Chem. Soc.*, **81**, 6058 (1959).

[11] Similar effects of decreasing J values with increasing electronegativity of substituents on olefins have been observed by J. S. Waugh and S. Castellano, *J. Chem. Phys.*, **35**, 1900 (1961); see also ref. 7b.

TABLE I

N.M.R. SPECTRA OF PYRAZOLINES



Cpd.	R_1	R_3	R_4	R_5	$H_4 - H_5$	J (c.p.s.)[a]	τ (p.p.m.)[a]
I	C_6H_5	C_6H_5	H	C_6H_5	*trans, cis*	8, 12	4.88
II	C_6H_5	CH_3	H	C_6H_5	*trans, cis*	8, 12	5.15
III	C_6H_5	$CH_2CH_2CH_2CH_2$		C_6H_5	*trans*	9	5.65
IIIa	C_6H_5	$CH_2CH_2CH_2CH_2$		C_6H_5	*cis*	12	4.94
IV	C_6H_5	$CH_2—CH_2—CH_2$		C_6H_5	*trans*	10	5.53
IVa	C_6H_5	$CH_2—CH_2—CH_2$		C_6H_5	*cis*	12	5.00
V	H	CO_2CH_3	CO_2CH_3	C_6H_5	*trans*	10	4.87
Va	H	CO_2CH_3	CO_2CH_3	C_6H_5	*cis*	13	4.62
VI	C_6H_5	C_6H_5	$C_6H_{11}NH$	C_6H_5	*trans*	3	5.02
VII	C_6H_5	C_6H_5	C_6H_5	C_6H_5	*trans*	5.5	5.02
VIIa	C_6H_5	C_6H_5	C_6H_5	C_6H_5	*cis*	10.4	4.51
VIII	*p*-BrC_6H_4	C_6H_5	C_6H_5	C_6H_5	*trans*	5	5.03
IX	2,4-$Br_2C_6H_3$	C_6H_5	C_6H_5	C_6H_5	*trans*	4	4.30
X	2,5-$Cl_2C_6H_3$	C_6H_5	H	C_6H_5	*trans, cis*	5, 10	4.20
XI	2,5-$Cl_2C_6H_3$	C_6H_5	C_6H_5	C_6H_5	*trans*	3.1	4.28
XII	2,4,6-$Cl_3C_6H_3$	C_6H_5	C_6H_5	C_6H_5	*trans*	7.7	4.60
XIII	CH_3	C_6H_5	H	C_6H_5	*trans, cis*	9.5, 14	6.05

[a] J = spin-spin splitting of H at C-5 by H at C-4; τ = chemical shift of H at C-5.

pyrazoline IIIa suggests that long range shielding effects of substituents on C-4 are at least as important as shielding effects due to preferential orientation of the phenyl group.

It is known that long range shielding effects associated with the diamagnetic anisotropy of C—C bonds influence the magnitude of the chemical shift of closely located hydrogens.[5] According to McConnell's equation 1 the contribution to the shielding of a proton ($\Delta\sigma$) due to neighboring C—C bonds can be calculated from the distance (r) of the proton from the mid-point of the C—C bond dipole, the acute angle (θ) that the vector of r makes with the symmetry axis of the group of electrons in the C—C bond, and the difference in longitudinal and transverse magnetic susceptibilities of the electrons of the C—C bond ($\Delta X = X_L - X_T$).[12]

$$\Delta\sigma = \frac{(1-3\cos^2\theta)\Delta X}{3\,r^3} \tag{1}$$

The following approximations are inherent in the use of this equation: The major long range shielding contribution by C—C bonds is assumed to come from the $\beta - \gamma$ bond but it is possible to take into account contributions from bonds farther removed by summating the terms of equation 1.[12] The C—C bond is considered axially symmetric and the geometric center of this bond is assumed to be the same as the electrical center of gravity of the C—C bond dipole. The magnetic anisotropy ΔX is an experimentally determined number based itself on approximations. The shielding effects of C—H bonds are considered negligible. In our calculations we have assumed standard bond lengths and tetrahedral bond angles. Nevertheless, equation 1 should be useful at least in predicting, relative to a compound chosen as a standard, the direction of chemical shifts due to the anisotropy of a $\beta - \gamma$ C—C bond.* In our system we chose 1,5-diphenyl-3-methyl-2-pyrazoline (II) as a standard compound in order to minimize the large shielding effects by unsaturated linkages in the molecule. The *cis-trans* pairs IIIa–III and IVa–IV differ from II solely by an alkyl chain at C-4 which is either *cis* (in III) or *trans* (in IIIa) to the C-5 proton. The long range shielding contribution of the C-4 alkyl bond in III and IIIa to the total shielding of the H at C-5 can then be calculated from equation 1. Musher's recent value[13] of 8.3 × 10^{-30} cm.^{3}/molecule was used for the magnetic anisotropy of the C—C single bond, ΔX. The values of θ and r were calculated from the trigonometric relationships (2) and (3) given by Bothner-By and Naar-Colin[14] where b is the C—H bond length, c the C—C bond length, φ the dihedral angle formed by the planes containing H_5—C_5—C_4 and C_5—C_4-alkyl, r the radius vector, and θ the vector angle as in equation 1. The dihedral angle φ, obtained from Dreiding models by projection of the C_5—H and C-4 alkyl bonds on a plane perpendicular to the C_4—C_5 axis is approximately 10° for the *trans* isomer III and hence 130° for the *cis* isomer IIIa.

$$r = \left[\frac{19}{12}c^2 + b^2 + \frac{bc}{9}(7-8\cos\varphi)\right]^{1/2} \tag{2}$$

$$\cos\theta = \frac{15c + (2-16\cos\varphi)b}{18r} \tag{3}$$

The calculated and observed contributions ($\Delta\sigma$)

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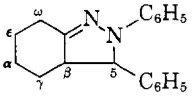
[12] H. M. McConnell, **27**, *J. Chem. Phys.* 226 (1957).

[13] J. Musher, *ibid.*, **35**, 1159 (1961).

[14] A. A. Bothner-By and C. Naar-Colin, *Ann. N. Y. Acad. Sci.*, **70**, 833 (1958).

TABLE II

LONG RANGE SHIELDING OF THE C-5 PROTON IN PYRAZOLINES



Pyrazoline	Method[a]	φ (°)	$r \times 10^8$ (cm.)	θ (°)	Calcd.,[b] Δσ (p.p.m.)	Obsd.,[b] Δσ (p.p.m.)
III (*trans*)	A	0–15	2.19	78.7–78.4	+0.23	+0.50
	B		2.19	76	+0.22	
	C				+0.13	
IV (*trans*)	A	0–15	2.19	78.7–78.4	+0.23	+0.38
	B		2.28	73	+0.17	
	C				+0.11	
IIIa (*cis*)	A	120–135	2.66–2.72	44.1–39.1	−0.09 to −0.11	−0.21
	B		2.61	40	−0.11	
	C				−0.13	
IVa (*cis*)	A	120–135	2.66–2.72	44.1–39.1	−0.09 to −0.11	−0.15
	B		2.58	41	−0.11	
	C				−0.18	

[a] Method A: use of equations 2 and 3; Method B: measurement of r and θ from Dreiding models; in Method A and B we considered only the shielding effect of the β—γ C—C bond; Method C = Method B, but the shielding effects of the γ—δ, δ—ϵ, and ϵ—ω bonds were added. [b] $+\Delta\sigma$ means shift to higher magnetic field with respect to model compound II which absorbs at τ 5.15 p.p.m.

to shielding of the C-5 proton by the C-4 alkyl bond in III and IIIa relative to II are shown in Table II. Variation of the dihedral angle φ between 0 and 15° for III and analogously between 120 and 135° in IIIa causes virtually no change in the calculated values of $\Delta\sigma$. Similarly, no significant variation in $\Delta\sigma$ is observed if θ and r, instead of being calculated from equations 2 and 3, are measured as best possible from Dreiding models. The results of the calculations—namely, an upfield shift for the *trans* isomer and a shift downfield for the *cis* isomer—are in agreement with assignments based on chemical evidence.[3] Qualitatively the results remain unchanged if long range shielding effects of γ—δ, δ—ϵ, and ϵ—ω bonds in III and IIIa are taken into account by summation of equation 1—see Table II, method C. The resonance of the proton at C-4 likewise occurs at higher field in the *trans* pyrazolines—(*i.e.*, VII)—than in the *cis* pyrazolines—*i.e.* VIIa. The same directional trend—*trans* isomer absorbing at higher field—was observed for *cis-trans* 1,2-diphenylcyclopentanes and 1,2-diphenylcyclopropanes, but an opposite trend applies to *cis-trans* stilbenes.[15] It may be noticed that the chemical shift differences between *trans* and *cis* pyrazolines in this study range from +0.25 to +0.71 p.p.m. which agrees in order of magnitude with differences observed (+0.40 and +0.32 p.p.m.) between *trans* and *cis* 1,2-didiphenylcyclopentanes and cyclopropanes.[15] Better agreement between the calculated and the observed shift is found in trimethylenepyrazolines IV than in the tetramethylenepyrazolines III.

Experimental

The n.m.r. spectra of all pyrazolines were determined at 60 Mc. in deuterochloroform or in carbon tetrachloride at a concentration of *ca.* 50 mg. per ml. on a Varian A-60 high resolution n.m.r. spectrometer. Tetramethylsilane was used as an internal standard and the chemical shifts in Table I are reported on the τ scale.[16] Pyrazolines I, II, III, IIIa, V, and VII, synthesized according to reported procedures, had the following properties (literature melting points in parenthesis): I, m.p. 136–137° (136–137°)[3]; II, m.p. 115–115.5° (115°)[3]; III, m.p. 139–140° (138–140°)[3]; IIIa, m.p. 137–138° (137–139°)[3]; V, oil (oil)[2]; VII, m.p. 164° (164°)[4]; Va, m.p. 132–134° (130–132°)[2]; VI, m.p. 147° (143–145°).[17] The syntheses and properties of pyrazolines IV, IVa, VIIIa, and VIII–XIII are reported in a forthcoming paper. Assignments of stereochemical configurations (*cis* or *trans*) for all compounds used are based on chemical evidence and are found consistent with n.m.r. interpretations.

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