# 'H NMR Utilization of Through-space Effects in Configurational Assignments

I-Application to Nitriles; Determination of the Separate Effects of the Electric Field and Anisotropy of the CN Group

Michel Rouillard,\* Serge Geribaldi, Jean Khazarian and Marcel Azzaro

Laboratoire de Chimie Physique Organique, Institut Polytechnique Mediterranéen, Pare Valrose, 06034 Nice Cedex. France

The changes in chemical shift induced by isomerization for all the ring protons of the Z- and E-5,5-dimethyl-2-cyclohexenylidene acetonitriles depend only on the through-space effects of the cyano group. The configurational assignments were made taking into consideration the anisotropic and electric field effects, either separately or together. In the first case, the total effects are  $\Delta \chi_{CN}^{T} = -14.7 \times 10^{-6} \text{ cm}^3 \text{ mol}^{-1}$  and  $b\mu_{CN}^{T} = 14.7 \times 10^{-30} \text{ cm}^3$ , respectively. The second approach allows the estimation of the values  $\Delta \chi_{CN} = -4.9 \times 10^{-6} \text{ cm}^3 \text{ mol}^{-1}$  and  $b\mu_{CN} = 9.8 \times 10^{-3} \text{ cm}^3$ , reflecting the combined contributions of magnetic anisotropy and electric field to the total effect.

# **INTRODUCTION**

The structural problems posed by the identification of two configurations of a compound are often resolved using NMR. For proton NMR the geometrical dependence of vicinal or long-range couplings is the preferred method for such assignments, whereas chemical shifts are not so often used.<sup>1</sup> This situation is reversed for <sup>13</sup>C NMR, where the knowledge of the geometrical dependence of the chemical shift is well developed.<sup>2</sup>

The neglect of proton chemical shifts in the consideration of configurational problems is primarily due to a lack of appreciation of the effects of electric fields and of substituent anisotropy on the shifts. In this work we propose a method of precise configurational identification using through-space substituent effects. We have tested this approach by studying the Z-Eisomerization of the diene nitriles **1–9** in both the Z and E configuration, where IR and UV spectroscopies can only confirm the existence of the diene nitrile moeity.<sup>3</sup>



EXPERIMENTAL

The diene nitriles were synthesized using a modification of the Horner-Emmons method<sup>4</sup> applied to a series of 5,5-dimethylcyclohex-2-ene-1-ones with a variety of substituents in position  $3.5^{5}$  Each ketone

\* Author to whom correspondence should be addressed.

gave practically equimolar mixtures of the isomeric Zand E-nitriles.<sup>3</sup>

### General process for preparing the nitriles

Sodium hydride (4.8 g) (0.2 mole) as a 55-60% suspension in oil and anhydrous THF (100 ml) were placed in a 500 ml three necked flask equipped with a reflux condenser fitted with a calcium chloride trap, a nitrogen supply and a magnetic stirrer. To this was added dropwise a solution of diethyl cyanomethylphosphonate (0.2 mole) in 100 ml THF. Agitation was continued for 3 h at room temperature and under a nitrogen atmosphere after the completion of the addition. Cyclohexenone (0.1 mole) dissolved in THF was then added slowly and heated under reflux until the ketone peak was no longer detectable by GLC (10%) Carbowax 20 M, temperature 130-170 °C). The mixture was cooled and 150 ml water added. This was extracted with ether, neutralized and washed with saturated sodium chloride solution. The organic phase was dried over magnesium sulphate and the solvent evaporated at reduced pressure. The crude product was then either distilled or purified by liquid phase chromatography on silica gel (benzene solvent). The 'H NMR spectra were obtained on a Varian A60A in dilute carbon tetrachloride solution at 30 °C. TMS was used as internal standard.

The geometrical parameters needed for the calculation of field and anisotropy effects were obtained using Dreiding stereomodels.

### **RESULTS AND DISCUSSION**

#### General description of the method used in configurational identification

The nuclear screening constant for an atom in a nonisolated molecule can be described by the formula of

CC-0030-4921/80/0013-0323\$02.50

Saïka and Slichter<sup>6</sup>

$$\sigma = \sigma_d + \sigma_p + \sigma' \tag{1}$$

The diamagnetic contribution,  $\sigma_d$ , and the paramagnetic term,  $\sigma_p$ , can be defined to first order as being sensitive only to the magnetic and electronic effects arising in the immediate neighbourhood of the nucleus studied and transmitted through the bonding electrons. The term  $\sigma'$  describes all the diamagnetic and paramagnetic effects arising from the electronic circulation on the atoms near to the nucleus studied, i.e. from the magnetic anisotropy of these atoms, or groups of atoms, and from the effect of the electric field induced by the intramolecular dipole moments. These contributions to the screening are designated by  $\sigma_A$  and  $\sigma_E$ , respectively.

If Eqn (1) is applied to a given proton,  $H_i$ , in each configurational isomer then one obtains

isomer 1: 
$$\sigma_{i1} = \sigma_{p1} + \sigma_{d1} + \sigma_{A1} + \sigma_{E1}$$
 (2)

isomer 2: 
$$\sigma_{i2} = \sigma_{p2} + \sigma_{d2} + \sigma_{A2} + \sigma_{E2}$$
 (3)

If the group which determines the isomerism as Z or E is strongly anisotropic, the  $\sigma_{p1} - \sigma_{p2}$  and  $\sigma_{d1} - \sigma_{d2}$ changes are negligible relative to those terms which are a direct function of the position in space of this group, and the following equation can be written

$$\Delta \delta_i = \delta_{i1} - \delta_{i2} \simeq (\delta_{A1} - \delta_{A2}) + (\delta_{E1} - \delta_{E2}) \tag{4}$$

The terms  $\delta_{A1} \sim \delta_{A2}$  and  $\delta_{E1} - \delta_{E2}$  can be calculated using the simplified McConnell<sup>7</sup> and Buckingham<sup>8</sup> equations, respectively.

If the anisotropic moiety has axial symmetry (Fig. 1):

$$\sigma_{\rm A} = \frac{\Delta \chi}{3N_0} \left( \frac{1 - 3\cos^2 \theta_x}{R^3} \right) = \frac{\Delta \chi}{3N_0} g = Kg$$
(5)

and

$$\sigma_{\rm E} \simeq b\mu \frac{(3\cos\phi_1\cos\phi_2 - \cos\phi_3)}{R^3} = b\mu g' = K'g' \quad (6)$$

then

 $\Delta \delta_i = \frac{-\Delta \chi}{3N_0} \Delta g_i + b\mu \Delta g_i' \text{ and } K, K' \text{ are constants (7)}$ 

with

$$\Delta g_i = g_{i1} - g_{i2}$$
  $\Delta g_i' = g_{i1}' - g_{i2}'$ 

Knowledge of the terms  $\Delta \chi$ , b and  $\mu$  for the anisotropic group then allows the calculation of  $\Delta \delta_i$ . If the calculated and experimental values agree the initial



Figure 1. Geometric parameters.

assignment of the configurations is confirmed. Conversely, if the configurational assignment has already been made the value of  $\Delta \delta_i$  obtained for different protons,  $H_i$ , in the structure will allow  $\Delta \chi$ and  $b\mu$  to be calculated. In both cases, however, an initial assignment of the chemical shift of  $H_i$  in each isomer must be made. For this purpose it is sufficient to use a qualitative approach to the anisotropy and field effects, in which it is considered in general that the changes in chemical shift,  $\Delta \delta_i$ , are directly affected only by the anisotropy of the group causing the isomerization.

#### Application to the diene nitriles

Qualitative approach. Almost all the NMR signals of the different protons of **1–9** show variations in  $\Delta \delta_i$ , which can reach 0.5 ppm between the Z- and E- isomers. If it is considered that these variations are related only to the magnetic anisotropy of the cyano group they can be qualitatively estimated and we conclude that, first, there will be screening of protons 5 and 6 and descreening of protons 2 (and 3 for 1 and 2) in form Z, and the inverse effect for form E. These differences should be more obvious for protons 2 and 6 than for protons 3 and 5. Second, there will only be a small effect at position 4, which changes very little relative to the nitrile group from one isomer to the other. This qualitative reasoning applies to all the derivatives and is confirmed by the chemical shifts of the different protons for each type of substitution (Table 1).

If no account is taken of the ethoxyl and benzyl substituents, which possess their own very marked effects because of the existence of preferred rotamers,<sup>9</sup> it appears that the variation in  $\Delta \delta_2$  is practically independent of the nature of substituent X and is a function only of the position of the cyano group. This, in the first analysis, confirms our working hypothesis and is further demonstrated by the existence of a relationship between the chemical shifts of protons 2 for the Z-and E-isomers.

$$(\delta_2^{x})_z - 6.000 = (1.011 \pm 0.027)[(\delta_2^{x})_E - 6.000] + 0.454 \text{ ppm}$$

Correlation coefficient equals 0.9982 for 7 points with standard deviation of 0.02 ppm.

Since the slope is almost unity then the value of the intercept at the origin (0.454 ppm) represents solely the through-space effects of the cyano group, as is also found for proton 6

$$(\delta_6^{X})_Z - 2.200 = (1.033 \pm 0.055)[(\delta_6^{X})_E - 2.200] - 0.228 \text{ ppm}$$

Correlation coefficient equals 0.9902 for 9 points with standard deviation of 0.01 ppm.

These results then allow a more quantitative approach to be made to the through-space effects of the cyano group according to the manner in which they are interpreted: (a) uniquely in terms of the magnetic anisotropy, (b) uniquely in terms of an electric field effect or (c) in terms of electric field and anisotropy effects acting together.

Nitriles	x	lsomer	۱′	2		3	4	5	6
1	н	Ζ	4.93	6.65		6.20	2.08	0.96	2.19
		Ε	5.07	6.18		6.12	2.09	1.00	2.41
		$\Delta \delta_i$		0.47		0.08	-0.01	-0.04	-0.22
2	CH3	z	4.80	6.43		1.90	1.98	0.94	2.12
	-	E	4.92	5.96		1.83	1.97	0.99	2.33
		Δδί		0.47		0.07	+0.01	-0.05	-0.21
3	C <sub>6</sub> H₅	Z	4.97	7.03	between	7.20 and 7.55	2.44	1.03	2.23
		Ε	5.13	6.56			2.44	1.08	2.44
		$\Delta \delta_i$		0.47			0	-0.05	-0.21
4	CI	Z	4.98	6.83			2.38	1.04	2.19
		Ε	5.11	6.37			2.38	1.08	2.41
		$\Delta \delta_i$		0.46			0	-0.04	-0.22
5	Br	Ζ	4.93	6.98			2.50	1.03	2.18
		E	5.07	6.55			2.50	1.08	2.41
		$\Delta \delta_i$		0.43			0	-0.05	-0.23
6	OC₂H₅	Ζ	4.63	5.77	1.37	3.98	2.11	0.99	2.13
		E	4.80	5.36	1.33	3.85	2.08	1.04	2.35
		$\Delta \delta_i$		0.41			0.03	-0.05	~0.22
7	SC₂H₅	Ζ	4.73	6.35	1.39	2.93	2.13	0.98	2.18
		E	4.90	5.92	1.33	2.82	2.13	1.03	2.40
		$\Delta \delta_i$		0.43			0	-0.05	-0.22
8	CH₂C <sub>6</sub> H₅	Ζ	4.85	6.57	3.43		1.88	1.01	2.09
		E	4.93	5.98	3.36		1.88	1.07	2.33
		$\Delta \delta_i$		0.59			0	-0.06	-0.24
9	p-NO₂C <sub>6</sub> H	₄ Ζ	5.15	7.16	7.67	8.08	2.50	1.08	2.31
		Ε	5.29	6.69	7.58	8.07	2.50	1.13	2.53
		$\Delta \delta_i$		0.47			0	-0.05	-0.22

Table 1. Chemical shift in ppm of the protons of the nitriles 1-9

Quantitative approach using the magnetic anisotropy of the cyano group. The through-space effects of the cyano group are often considered to result only from its magnetic anisotropy.<sup>10</sup> In fact, we can conclude that the variation of shift,  $\Delta \delta_i$ , of any ring proton,  $H_i$ , is uniquely dependent on the anisotropy if a linear relationship exists between the various  $\Delta \delta_i$  values and the changes in the geometric terms  $\Delta g_i$  (Table 2). This is in effect observed.

 $\Delta \delta_i = (8.11 \pm 0.17) \Delta g_i + 0.01 \text{ ppm}.$ 

Correlation coefficient equals 0.9991 for 6 points with standard deviation of 0.01 ppm.

If this value of the slope is substituted into Eqn (7) and the term  $b\mu\Delta g_i'$  is assumed to be zero the overall magnetic anisotropy is obtained  $\Delta\chi_{CN}^{T} =$  $(-14.7 \pm 0.3) \times 10^{-6}$  cm<sup>3</sup> mol<sup>-1</sup>. This value is comparable with those already proposed<sup>11</sup> (between  $-10 \times$  $10^{-6}$  and  $-20 \times 10^{-6}$ ).

Quantitative approach using the intramolecular electric field of the cyano group. Despite the excellent results obtained by treating  $\Delta \delta_i$  as arising only from the anisotropy, as above, it must be tested whether the intramolecular field effect can be used to interpret the  $\Delta \delta_i'$  values.

The electric field effect can also be used to describe the long-range effects if a linear relationship exists between the various  $\Delta \delta_i$  and  $\Delta g'$  values (Table 2). The following equation was obtained.

$$\Delta \delta_i = (14.7 \pm 0.9) \Delta g_i' + 0.008 \text{ ppm}.$$

Correlation coefficient equals 0.9917 for 6 points with standard deviation 0.032 ppm.

The existence of this correlation shows that in the case of these diene nitriles  $\Delta \delta_i$  may equally well be treated as arising from only the electric field. If this slope is substituted into Eqn (7) with the first term taken as zero an overall value is obtained of  $(b\mu)^{T} = (14.7 \pm 0.9) \times 10^{-30}$  cm<sup>3</sup>. If the value of 3.6 debyes is taken for the dipole moment of a C = N bond, attached to an  $sp^2$  carbon,<sup>13</sup> then  $b = 4.09 \times 10^{-12}$  esu is obtained. This value is higher than that proposed by Buckingham  $(2 \times 10^{-12})$ ,<sup>8</sup> which indicates that the electric field effect cannot be the only through-space effect.

Quantitative approach using electric field and anisotropy effects of the cyano group together. For the structures studied it appears that the through-space effects may be equally described as being related solely either to the magnetic anisotropy or to the electric field effects. This is only possible because a fortuitous proportionality exists between the g and g' terms. For a structure in which the geometric terms g and g' have opposite signs the direction of the through-space effects will depend on the model chosen. It is then necessary to consider  $\Delta \delta_i$  simultaneously as a function of the electric field and anisotropy of the cyano group.

An estimation of the relative contribution of each effect requires the use of a known value of one of the two parameters  $\Delta \chi$  or  $b\mu$ , determined by a method for which one of the effects is inoperative. Thus, Flygare *et al.*<sup>14</sup> have determined, for the cyano group, the values  $\chi_{\parallel} = -16.5$  and  $\chi_{\perp} = -11.6 \times 10^{-6}$ , i.e.  $\Delta \chi = -4.9 \times 10^{-6}$  cm<sup>3</sup> mol<sup>-1</sup>, by using a method which allows the evaluation of the separate magnetic components of the magnetic susceptibility localized on the

Protons studied and isomers		R (Å) <sup>a</sup>	$\theta_x = \phi_1^{0a}$	¢2 <sup>0</sup>	φ3 <sup>0</sup>	g × 10 <sup>3</sup> (Å <sup>3</sup> )	g (average) × 10 <sup>3</sup> (Å <sup>-3</sup> )	$\Delta g \times 10^3$ (Å <sup>-3</sup> )	g′ × 10 <sup>3</sup> (Å <sup>-3</sup> ) <sup>b</sup>	g′(average) × 10 <sup>3</sup> (Å <sup>-3</sup> )	Δg′×10 <sup>3</sup> (Å <sup>-3</sup> )
H-2	Ζ	2.6	69	111	180	+35.0		+54.2	+35.0		+31.8
	Ε	4.7	2	60	58	-19.2			+4.2		
H-3	Ζ	5.1	63	57	120	+2.88		+9.18	+9.4		+2.9
	Ε	6.4	20	17	3	-6.3			+6.5		
3-CH₃°	Ζ	5.6	72	48	120	+4.06		+8.38	+6.4		110
	Ε	7.3	18	16	2	-4.32			+4.5		+1.9
H-4 <sup>d</sup>	Za	6.0	42	80	80	~3.28	-2.42		+1.0	<b>⊤</b> 30	
	Ze	6.6	46	24	62	- 1.56			+5.0	+3.0	
						e	e	-0.28	e	e	-0.6
	Ea	5.9	46	81	95	-2.1	-2.14		+2.0	+3.6	
	Ee	6.6	43	25	60	-2.17			+5.2		
5-CH <sub>3</sub> c,d	Za	5.4	39	82	100	-5.15	-4.64		+3.2	+ 3.75	
	Ze	7.2	22	21	2	-4.13			+4.3		
						e	e	5.78	е	e	-2.1
	Ea	5.2	51	66	75	-1.34	+1.14		+3.6		
	Ee	5.75	71	50	120	+3.61			+8.1	+ 5.85	
H-6 <sup>d</sup>	Za	4.9	18	70	70	-14.50	-16.50		+5.4	+4.9	
	Ze	4.7	9	75	72	-18.50			+4.4		
						e	e	-29.93	е	е	-13.55
	Ea	3.5	60	78	100	+5.84	+13.43		+11.3	10 /F	
	Ee	2.7	66	105	145	+21.03			+25.6	+ 18.45	

Table 2. Geometric terms for the equations of McConnell and Buckingham for each isomer

<sup>a</sup> Evaluated relative to the centre of anisotropy of the C≡N bond, which was taken as being 0.6 Å from the sp carbon.

<sup>b</sup> Calculated assuming that the centre of the C=N dipole,  $\mu$ , and the centre of anisotropy, A, are situated at the same point on the bond.

<sup>c</sup> The three hydrogen atoms of the methyl group are differently situated relative to the C=N bond; according to the classical method only a single value of the R and  $\theta_x$  parameters is measured at a point where the C--CH<sub>3</sub> bond and the plane defined by the three hydrogen atoms intersect.

<sup>d</sup> a = axial; e = equatorial.

<sup>e</sup> The cyclic structure undergoes interconversion and there is only one NMR signal corresponding to two different protons (or two different methyl groups) in the molecular models. For sites 4, 5, and 6 the geometric terms were calculated for each of the pseudo-axial and pseudo-equatorial positions and an average value taken.

different atoms of an anisotropic moiety. In the present case, it is then possible to estimate the effective contribution of the magnetic anisotropy upon  $\Delta \delta_i$ : -4.9/-14.7 = 0.33. We can, by difference, obtain the field effect of the cyano group, which contributes effectively 0.67 of the overall effect, or:  $b\mu =$  $14.7 \times 0.67 = 9.8 \times 10^{-30}$  cm<sup>3</sup>. If  $\mu = 3.6$  debyes, b is then equal to  $2.7 \times 10^{-12}$ , close to the theoretical value proposed by Musher<sup>15</sup> ( $2.9 \times 10^{-12}$ ).

## CONCLUSION

Two configurations can be successfully identified if the variation in chemical shift of any proton in the structure is considered to be due only to through-space effects of the group causing the isomerization. These effects can be given an overall interpretation either in terms of anisotropy or in terms of the field effect of the group. The application of this approach to a series of diene nitriles leads to the overall values of  $\Delta \chi_{\rm CN}^{\rm T}$  and  $b\mu_{\rm CN}^{\rm T}$  of  $(-14.7\pm0.3)10^{-6}$  cm<sup>3</sup> mol<sup>-1</sup> and  $(14.7\pm0.9)10^{-30}$  cm<sup>3</sup>, respectively.

However, if for the series of isomers studied no proportionality exists between the geometric parameters g and g', relating to the anisotropy and field effect, respectively, an estimate should be made of the simultaneous contribution of the two effects:  $\Delta \chi_{\rm CN} = -4.9 \times 10^{-6} \, {\rm cm}^3 \, {\rm mol}^{-1}$  and  $b \mu_{\rm CN} = 9.8 \times 10^{-30}$ cm<sup>3</sup>. It then appears that, contrary to suggestions in the literature, the contribution of anisotropy if often overestimated and that the intramolecular electric field effect of the substituent may become the more important. These different approaches to the configurational problem which we have tested on the Z/E isomerization of a series of diene nitriles, can be applied to other types of configurational isomerization (Z-E, endo-exo, syn-anti) and even to problems of confor-mational isomerism s-cis-s-trans.<sup>16</sup> Such applications will be the subject of a further paper.

## REFERENCES

- (a) M. Karplus, J. Chem. Phys. **30**, 11 (1959); (b) M. Barfield, J. Chem. Phys. **41**, 3825 (1964); (c) M. Barfield and B. Chakrabarti, Chem. Rev. **69**, 757 (1969).
- (a) D. K. Dalling and D. M. Grant, J. Am. Chem. Soc. 89, 6612 (1967); (b) A. S. Perlin, B. Casu and H. J. Koch, Can. J. Chem. 48, 2599 (1970).

- 3. J. Khazarian, Thesis, University of Nice, (1977).
- W. S. Wadsworth and W. D. Emmons, J. Am. Chem. Soc. 83, 1733, (1961).
- 83, 1733, (1961).
  5. M. Azzaro, J. F. Gal, S. Geribaldi and N. Novo-Kremer, Spectrochim. Acta Part A, 34, 157 (1978).
  6. A. Saïka and C. P. Slichter, J. Chem. Phys. 22, 26 (1954).
- 7. H. M. McConnell, J. Chem. Phys. 27, 226 (1957).
- 8. A. D. Buckingham, Can. J. Chem. 38, 300 (1960).
- 9. A. C. Rojas and J. K. Crandall, J. Org. Chem. 40, 2225 (1975).
- 10. E. Giralt, F. Lopez and M. Alvarez, Org. Magn. Reson. 7, 585 (1975).
- 11. (a) J. A. Pople, J. Chem. Phys. 37, 53 (1962); (b) G. S. Reddy and J. H. Goldstein, J. Chem. Phys. 39, 3509 (1963); (c) N. Zeil and H. Buchert, Z. Phys. Chem. 38, 47 (1963).

- 12. A. D. Cross and I. T. Harrison, J. Am. Chem. Soc. 85, 3223 (1963).
- 13. O. Exner, Dipole Moments in Organic Chemistry, p. 48 Georg Thieme Verlag, Stuttgart (1975). 14. T. G. Schmalz, C. I. Norris and W. H. Flygare, J. Am. Chem.
- Soc. 95, 7961 (1973).
- 15. J. I. Musher, J. Chem. Phys. 37, 34 (1962).
- 16. M. Rouillard, Thesis, University of Nice (1978).

Received 15 December 1978; accepted in the UK in French (revised) 18 June 1979; accepted in the UK (translated) 29 November 1979

© Heyden & Son Ltd, 1980