¹HNMR Utilization of Through-Space Effects

III[†]—Configuration of Oximes and Analogous Compounds

M. Rouillard,* Y. Girault, M. Decouzon and M. Azzaro

Laboratoire de Chimie Physique Organique, Institut Polytechnique Méditerranéen, Parc Valrose, 06034 Nice Cedex, France

The configurational assignment of Z and E nitrogen derivatives (>C=N-Y) of 3,5,5-trimethyl-2cyclohexen-1-one was made taking into consideration the through-space effects on oxime, O-methyloxime, dimethylhydrazone, *tert*-butylimine, N,N,N-trimethylhydrazonium iodide and oxime hydrochloride derivatives. The relationship between the magnitude of the chemical shifts of the α -protons and the dihedral angle formed by the α -C—H bond and the C=N—OH plane was interpreted in terms of the geometrical dependence of the electric field effect. For the different Y substituents, the change in chemical shift between the Z and the E configuration of the proton near the functional group was mainly dependent on the electric field effect.

The configurations of dienic nitriles have been previously assigned from through-space effects affecting proton chemical shifts¹. The application of cyclic compounds 1 and 2, obtained from isophorone (3,5,5)trimethyl-2-cyclohexen-1-one), has been demonstrated for this approach. The effect of the electric field is the determining factor in assigning configurational isomers, in both dienic nitriles and ketones.^{1,2} Our purpose is to extend this methodology to the evaluation of through-space effects on the two isomers of the nitrogen derivatives of ketones corresponding to the general formula $\geq C = N - Y$. The Z and E diastereoisomers in the following series of six isophorone derivatives were therefore synthesized and separated: oxime, O-methyloxime, dimethylhydrazone, tertbutylimine, N,N,N-trimethylhydrazonium iodide and oxime hydrochloride.



RESULTS AND DISCUSSION

Configurational assignment

The value of models 1 and 2 is due mainly to the simplicity of their ¹H NMR spectra. The assignment of the H-2, H-3 and H-5 proton signals is straightforward. Only H-4 exhibits a long-range coupling with the ethylenic proton, so that its signal is broader than that of H-6, as already demonstrated for dienic nitriles and ketones.¹ The NMR chemical shifts obtained for derivatives 1 and 2 are shown in Table 1. As observed

* Author to whom correspondence should be addressed.

† For Part II, see Ref. 2.

Table 1.	Proton	chemical	shifts	(ppm	from	TMS)	
Compound	Solvent	2	3	4	5	6	Y
1a	CCl₄	6.61	1.86	1.96	0.98	2.07	
	CDCl ₃	6.63	1.85	1.98	0.97	2.09	
2 a	CCl₄	5.90	1.82	1.92	0.99	2.34	_
	CDCl ₃	5.92	1.81	1.94	0.98	2.38	—
1b	CCl₄	6.44	1.82	1.92	0.97	2.00	3.73
	CDCl ₃	6.51	1.84	1.98	0.97	2.09	3.85
2b	CCl₄	5.80	1.81	1.91	0.97	2.21	3.76
	CDCl ₃	5.8 9	1.82	1.94	0.97	2.31	3.86
1c	CCl₄	6.52	1.83	1.95	0.95	2.05	2.35
	CDCl ₃	6.53	1.85	1.97	0.95	2.12	2.46
2c	CCl₄	5.88	1.81	1.94	0.98	2.29	2.38
	CDCl ₃	5.92	1.82	1.98	0.98	2.37	2.46
1d ^a	CCl₄	6.25	1.83	1.93	0.95	2.07	1.28
		6.29	1.84	1.95	0.95	2.13	1.33
2d ^a	CCl₄	5.84	1.78	1.93	0.99	2.20	1.28
	CDCI ₃	5.89	1.78	1.95	0.99	2.27	1.33
1e ^b	CDCl ₃	6.99	2.24	2.24	1.03	2.23	3.83
2e [⊳]	CDCI ₃	5.93	1.93	2.15	1.18	2.88	3.85
1f ^b	CDCI ₃	6.73	2.09	2.27	1.08	2.72	12.67
2f ^b	CDCI ₃	6.83	2.02	2.19	1.08	2.63	12.46
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^a Measured for the mixture **1d**+**2d**.

^b Insoluble in CCl₄.

for the dienic nitriles and ketones, the greatest deviations between isomers are observed for H-2 and H-6. The Z/E configurational assignment to 1 to 2, for different Y substituents, is deduced from comparison with compounds having only one configuration owing to steric requirements. For this purpose were prepared piperitone derivatives 3, for which the through-space effects of the Y group should be identical with those observed for 1, and allow comparison of the effects on the ethylenic proton for these two frameworks. We also synthesized the camphor derivatives 4, having an α -methylene syn to the Y group, as in products 2.

The chemical shifts and $\Delta\delta$ increments, calculated relative to the parent ketone, are given in Table 2. The assignments of derivatives **1** (*Z* configuration) are supported by the very similar values of $\Delta\delta$ in this

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series (from the δ values of isophorone) and in series **3** (from the δ values of piperitone). For derivatives **2** (*E* configuration), $\Delta\delta_2$ values are not significant except in **2f**; this noticeable downfield shift for the α -proton on the opposite side to the OH group is in agreement with nitrogen as the site of oxime protonation.³ For the hydrochloride **1f** and **2f**, obtained from oximes **1a** and **2a**, respectively, the retention of configuration was obvious after subsequent regeneration of the oximes by treatment with base.

on the dihedral angle, θ , between the C_{α}-H and the C=N bonds. This dependence of the chemical shifts on geometry, and the general observations given above, induced us to connect the configurational effects with only the magnetic anisotropy and the electric field effect. To support this hypothesis we computed, as in previous work, the geometric parameters g and g' characteristic of anisotropic and field effects, respectively, for different θ values.^{1,2} In this approach we considered the anisotropic magnetic effect as resulting from an axially symmetric group, and the direction of the electric dipole affecting the configuration as being the N-O direction (or, more generally, the N-Y direction). The calculated values, g and g', and their differences between Z and Eisomers, Δg and $\Delta g'$, are given in Table 3. If configurational effects are considered as being essentially

Frame-		(8 ppm from TMS)									
work		3	3	1	2	4	4	4	4	1	2
Y	Solvent	δ2	$\Delta \delta_2^a$	$\Delta \delta_2^{b}$	$\Delta \delta_2^{b}$	δ _{3×}	δ _{3n}	$\Delta \delta_{3x}^{c}$	Δδ _{3n} c	Δδ ₆ ^b	$\Delta \delta_6^{b}$
a	CCI₄	6.54	0.85	0.84	0.13	2.49	2.04	0.27	0.27	-0.02	0.25
	CDCl ₃					2.54	2.09	0.22	0.22	-0.1	0.19
ь	CCI₄	6.46	0.69	0.67	0.03	2.37	1.9	0.15	0.13	-0.0 9	0.12
	CDCl ₃					2.42	1.98	0.10	0.11	-0.1	0.12
C	CCl4	6.45	0.76	0.75	0.11	2.41	1.93	0.19	0.16	-0.04	0.20
	CDCl ₃					2.47	1.97	0.15	0.10	-0.07	0.18
d	CCl₄	6.16	0.47	0.48	0.07	2.36	1.92	0.14	0.15	-0.02	0.11
	CDCl ₃					2.42	1.97	0.10	0.10	-0.06	0.08
е	CDCl ₂	6.83	0.98	1.11	0.05	3.17	2.87	0.85	1.00	0.04	0.69
f		6.62	0.77	0.85	0.95	2.93	2.50	0.61	0.63	0.53	0.44

^a Chemical shift difference compared with piperitone, $\delta_2 = 5.69$ (CCl_a), 5.85 (CDCl₃).

^b Chemical shift difference compared with isophorone, $\delta_2 = 5.77$ (CCl₄), 5.88 (CDCl₃); $\delta_6 = 2.09$ (CCl₄), 2.19 (CDCl₃).

^c Chemical shift difference compared with camphor, $\delta_{3x} = 2.22$ (CCl₄), 2.32 (CDCl₃); $\delta_{3n} = 1.77$ (CCl₄), 1.87 (CDCl₃).

Moreover, the configurations of **1** and **2** were also confirmed by comparison of $\Delta\delta_6$ (Table 2) with $\Delta\delta_{3x}$ and $\Delta\delta_{3n}$, the values related to the 3-methylene group in skeleton **4**. The parallel changes in $\Delta\delta_3$ and $\Delta\delta_6$ for framework **2** agrees with the *E* configuration.

Through-space effects of oximes

We have verified that, for each configuration, the most definitive effect on chemical shifts is related to the proximity of the studied nucleus to the Y group. Through-space effects are notable for H-2 for configuration $\mathbf{1}(Z)$, but only on H-6 for configuration $\mathbf{2}(E)$. This differentiation between the two isomers is similar to the previous observations on dienic nitriles and ketones for an identical carbon frame. These chemical shift variations interpreted in terms of the magnetic anisotropic effect⁴ and electric field effect⁵ of the Y group determining the configuration.

Since through-space effects are appreciable only near the functional group, i.e. in an α -position to $>C=N \sim Y$, our quantitative approach was established from the experimental results of Durand *et al.*⁶ These workers showed that, for protons bound to the α -carbon of the oxime group, the difference between the chemical shifts of the Z and E forms is dependent dependent on through-space effects, the relationship $\Delta \delta_{exp} \approx K \Delta g + K' \Delta g'$, where K and K' are the two characteristic constants of the Y group accountable for through-space effects (for further details see Ref. 1), can be expected between the Z and E isomers. In Fig. 1, Δg and $\Delta g'$ are plotted as a function of θ , and the curve of Durand *et al.*⁶ is also reproduced, which gives $\Delta \delta$ variations in terms of θ .

While the Δg values alone could not describe the observed phenomenon, the $\Delta g'$ variation with θ follows a trend similar to that obtained with the experimental $\Delta \delta$ values. It is noticeable that only $\Delta g'$ undergoes a sign inversion, for a θ value of approximately 65°, which is also the case for the values observed by Durand *et al.* In the oximes the field effect therefore appears as the prevailing effect, the anisotropic magnetic effect being hardly significant. As for the nitrile and ketone groups the electric field effect plays the leading role in through-space effects on chemical shifts. In addition, the assignment given by Saika and Nukada⁷ for the Z/E isomers of isophorone oxime on the basis of only magnetic anisotropy was wrong. If only the electric field effect then

$$\Delta \delta_{\mathrm{exp}} \approx K' \Delta g'$$

Table 3. Geometric terms of McConnell and Buckingham's equation for the proton α to the not conjugated oxime group as a function of the angle θ

θ(°)		R(Å)	φ ₁ (°)	φ ₂ (°)	φ ₃ (°)	$g \times 10^3$ (Å ⁻³)	$\Delta g \times 10^3 (\text{\AA}^{-3})$	$g' \times 10^3$ (Å ⁻³)	$\Delta g' imes 10^3$ (Å ⁻³)
0	Sª Aª	2.00 3.60	106 10	94 67	156 58	96.51 -40.93	137.44	121.40 13.38	108.02
30	S A	2.15 3.60	103 12	92 63	149 61	85.35 -40.09	125.44	88.62 18.16	70.46
60	S A	2.45 3.65	94 20	72 60	125 66	67.01 33.91	100.92	34.61 20.61	14
90	S A	2.80 3.75	85 29	58 55	98 74	44.52 -24.55	69.07	12.65 23.31	-10.66
120	S A	3.15 3.85	77 35	38 51	81 78	27.14 17.75	44.89	12.01 23.46	-11.45
150	S A	3.30 3.90	73 38	20 48	68 80	20.69 	35.24	12.51 23.74	-11.23
180	S A	3.40 3.95	70 40	17 42	60 82	16.51 12.34	28.85	12.24 25.01	-12.77
^a S from H in syn position, A from H in anti position.									

where $K' = 8.3 \pm 1.6 \times 10^{-30}$ cm³. A correlation does, in fact, exist, as expected from the similarity of Durand's experimental curve and the relationship of $\Delta g'$ as a function of θ . This linear relationship is only of medium quality (r = 0.976). This could result, in part, from the $\Delta g'$ values obtained for the largest θ values, because for this calculation we used a molecular geometry where the C—C—H angle is 109°28' while, in Durand *et al.*'s study, the strain in the bicyclic structures would give relatively different geometries. Moreover, the choice of the dipole centre on oxygen is arbitrary, and a small variation could induce a change in $\Delta g'$. Nevertheless, it can be concluded that through-

space effects for oximes are essentially field effects, characterized by the constant K' given by

$$K' = b\mu \approx 8.3 \times 10^{-30} \,\mathrm{cm}^3$$

Generalization to analogues of oximes

The marked effects connecting configuration and chemical shifts are also observed for analogues of oximes. In Fig. 2 the $\Delta\delta_6$ values were plotted against $\Delta\delta_2$ for the different Y substituents, and for the dienic nitriles and ketones.



Figure 1. Differences between the chemical shifts of the α -protons, differences between the geometrical parameters of the anisotropic (Δg) and electric field ($\Delta g'$) effects v. the dihedral angle, θ .



Figure 2. Relationship between the chemical shift of ethylenic and methylenic protons in α -position and the configuration. (**g** and **h** are the homologous dienic nitrile and ketone, respectively.)

If hydrazonium salts **e** and, to a certain extent, hydrochlorides **f**, are not taken into account we obtain an excellent correlation with a slope of -2.33. This slope is equal to the $\Delta g'_2/\Delta g'_6$ ratio, $\Delta g'_2$ and $\Delta g'_6$ being the geometric parameters of the field effect calculated for positions 2 and 6 in dienic nitriles.¹ This correlation agrees with the predominance of the field effect for the different Y substituents. The non-alignment of iodides **e** and hydrochlorides **f** results from the nonapplication of Buckingham's equation to an entirely ionic system.

It is likely that the graph given by Durand *et al.* for oximes can be extended to any Y group by a relationship between the direction parallel to the $\Delta\delta$ axis and of the K ratio, K being equal to $\Delta\delta_2$ for the considered substituent Y versus $\Delta\delta_2$ for the oximes.

This hypothesis has been verified by Durand⁸ for Y groups other than those studied in this work. It seems that for all Y groups agreeing with correlation shown in Fig. 2 the most marked effect on chemical shift is caused by the electric field effect.

EXPERIMENTAL

The oximes 1a, 2a and 3a were prepared using hydroxylamine hydrochloride and hydrogen chloride under acidic conditions, while 4a was prepared with sodium hydrogen carbonate to neutralize the excess acid.⁹ The oximes were purified or separated by recrystallization from methanol-water (2a, 4a) or from hexane (1a, 3a). The O-methyloximes of type b were obtained using methoxylammonium chloride.¹⁰ The N,N-dimethylhydrazones of type **c** were prepared from the ketones and N,N-dimethylhydrazine using acetic acid as catalyst,¹¹ while a mixture of isomers 1c/2c (E enriched) was obtained from isophorone in basic medium.¹² Quaternization of compounds \mathbf{c} with methyl iodide in ethanol gives the N,N,N-trimethylhydrazonium iodides e. The Z and E isomers (1e, 2e)were separated by recrystallization from ethanol. The ketimines **d** were obtained by the TiCl₄-mediated condensation of ketones and tert-butylamine.¹³ The oxime hydrochlorides **f** were prepared by adding a dry ethereal solution of HCl to pure oxime \mathbf{a} . The Z and E derivatives (1 and 2) from **b** and **c** were cleanly separated by GLC using a 2 m column of Carbowax 20M, 10% on 80-100 mesh Chromosorb P with 1% KOH

¹H NMR spectra were recorded on a Varian A-60A (60 MHz) spectrometer in CCl₄ and CDCl₃ solutions, with internal TMS as a standard. Line positions are reported in ppm from the reference. The isophorone derivatives **1** and **2** were recorded separately, while most previous spectra were performed on the Z+E mixture.

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

REFERENCES

- 1. M. Rouillard, S. Geribaldi, J. Khazarian and M. Azzaro, Org. Magn. Reson. 13, 323 (1980).
- M. Rouillard, S. Geribaldi and M. Azzaro, Org. Magn. Reson. 16, 94 (1981).
- H. Saitô, I. Terasawa, M. Ohno and K. Okada, J. Am. Chem. Soc. 91, 6696 (1969).
- 4. H. M. McConnell, J. Chem. Phys. 27, 226 (1957).
- 5. A. D. Buckingham, Can. J. Chem. 38, 300 (1960).
- 6. R. Durand, P. Geneste, C. Moreau and A. Pavia, *Org. Magn. Reson.* 6, 73 (1974).
- 7. H. Saika and K. Nukada, J. Mol. Spectrosc. 18, 1 (1965).
- 8. R. Durand, personal communication.

- 9. T. Sato, H. Wakatsuka and K. Amano, *Tetrahedron* 27, 5381 (1971).
- C. W. Shoppee, G. Kruger and R. N. Mirrington, J. Chem. Soc. 1050 (1962).
- G. R. Newkome and D. L. Fishel, J. Org. Chem. 31, 677 (1966); S. Sato, Bull. Soc. Chem. Jpn. 41, 1440 (1968).
- 12. R. Chaabouni and A. Laurent, Synthesis 464 (1975).
- H. Weingarten, J. P. Chupp and W. A. White, J. Org. Chem. 32, 3246 (1967).

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