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Multinuclear NMR Structural Study on Some Hydrazones of O,O-Dialkyl 1-Oxoalkanephosphonates

by
Ryszard B. NAZARSKI(*), Dorota K. GRALAK and Zbigniew H. KUDZIN

Presented by H. RATAJCZAK on October 15, 1999

Summary. An unambiguous method for determination of the configuration of any single O,O-dialkyl 1-oxoalkanephosphonate hydrazones based on $^1$H, $^{13}$C, $^{31}$P NMR data has been elaborated; the use of $^1J_{CP}$ (P–C=–N) couplings is the most fruitful. The $^{12}$C/$^{13}$C isotope effects on the $^{31}$P chemical shifts of selected compounds have been measured. For primary hydrazones the E/Z isomerisation with stabilisation of their Z forms through an intramolecular H-bonding has been proven. In addition, for the latter stereoisomers small scalar couplings between H-bonded groups N–H...O–P have been found, $J_{HP}$ 2.4–3.4 Hz. The possibility of the across H-bridge transfer of spin-spin interactions in these forms is also discussed.

The configuration determination of the C=–N double bond in hydrazones of keto compounds is routinely accomplished using various experimental techniques, especially spectroscopic ones. The majority of these molecular systems are known to exist in the solution as single E and Z forms (or their E/Z mixtures), while for the others, not numerous, only average values of their individual NMR observables were determined, most likely due to a rapid interconversion $E \rightleftharpoons Z$ [2]. Such derivatives of ketones bearing in an α position the atom doubly-bound to the oxygen, e.g. α-oxo esters and structurally related α-oxo phosphonates (1-oxoalkanephosphonates), belong to the first class of the above systems. The stereochemical behaviour of hydrazones of the former difunctional objects is established sufficiently well

Key words: NMR, $J_{HP}$ and $J_{CP}$, $^{12}$C satellite spectra, $^{12}$C/$^{13}$C isotope effects, stereochemistry, hydrazones, 1-oxoalkanephosphonates, E/Z isomerisations, intramolecular H-bonding, scalar couplings across H-bond.

(*) To whom the correspondence should be addressed.
[3–5], whereas there is relatively little information concerning the latter ones [6–11]. Moreover, such scarce structural data obtained in infrared (IR) and $^1$H NMR studies, are not completely consistent.

The aim of this work was to elaborate a rapid and unequivocal method for investigating the stereochemistry of isomeric $O, O$-dialkyl 1-oxoalkanephosphonate hydrazones (1) by means of the NMR spectroscopy [12]. Such a method can provide more information on some side-reactions occurring during the preparation of hydrazones 1 [9, 10, 13, 14] as well as on equilibria existing between their $E$ and $Z$ isomers [7–10, 13, 14]. Hydrazones 1 ($R = i$-Pr) were selected for this research, as model compounds. The study is in progress and its final results will be published elsewhere.

\[
\begin{align*}
\text{(E)-1} & \quad \xrightleftharpoons{R^1 = H} \quad \text{(Z)-1} \\
R^1 & = H, \, \text{Me or Ph}, \, R^2 = \text{Me, Ph, }, R^3 = \text{Me, CH}_2\text{Ph, } t\text{-Bu or Ph} \\
\end{align*}
\]

Experimental

Materials. All studied hydrazones 1 ($R = i$-Pr, $R^1 = H, \text{Me or Ph}, R^2 = \text{Me, Ph, } R^3 = \text{Me, CH}_2\text{Ph, } t\text{-Bu or Ph}$) were synthesised recently [13, 15] from adequate $1$-oxoalkanephosphonates following the reported method [9]. Details of used procedure, the separation of products (column chromatography on silica gel) and full characterisation of such obtained single substances, will be published in future. Some representative, difference NMR data concerning selected $E/Z$ isomeric pairs of compounds 1, are given in Table 1.

NMR spectroscopy. $^1$H, $^{13}$C and $^{31}$P NMR spectra were recorded in a 5 mm diameter tubes on a Varian Gemini-200 BB spectrometer operating at frequencies 199.98, 50.29 and 80.95 MHz for $^1$H, $^{13}$C and $^{31}$P nuclei, respectively, with magnetic field $B_0$ of 4.7 T.

Measurements were run at a probe temperature in diluted solutions. In the case of $^1$H and $^{13}$C spectra CDCl$_3$ solutions containing TMS as an internal reference standard were used. For $^{31}$P NMR spectra the CH$_3$COOH-toluene (1:1, by volume) solvent system was used in addition; small amounts of C$_6$D$_6$ (0.05 cm$^3$) were added into the NMR tube, only for locking. Positive shifts are downfield from external 85% H$_3$PO$_4$; no magnetic susceptibility correction.

Results and Discussion

The performed configurational study revealed that, in isotropic solutions, for the NMR differentiation of $E$ and $Z$ isomers of hydrazones 1 ($R = i$-Pr) values $^1J_{CP}$ (P—C=N), $\delta_H$ (N—H) and, in some cases, $\delta_P$ are of diagnostic importance. Corresponding parameters can be derived directly from $^{13}$C$^1$H (usually using APT sequence and/or from $^{13}$C satellites in
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\( ^{31}P \{^{1}H \} \) spectra), \(^{1}H \), and \( ^{31}P \{^{1}H \} \) NMR spectra, respectively. To our best knowledge this is the first instance of determination of such spectral parameters, except \( \delta_H \) (N—H) data, for \( Z \) forms of objects under investigation (see below). Thus both stereoisomers of primary hydrazones 1 (\( R^1 = H \)) may be readily distinguished from each other on the basis of the following experimental findings concerning their \( Z \) forms; entries (a)—(f). All results, determined for single isomers of 1 in CDCl\(_3\) solutions (except entry (b)), are briefly summarised in Table 1.

**Table 1**

NMR data (CDCl\(_3\)) for the \( E/Z \) isomeric pairs of primary hydrazones 1 (\( R = i\text{-}Pr, R^1 = H \); \( \delta_Z - \delta_E \) [ppm] or \( J_Z - J_E \) [Hz])\(^{(a)}\)

<table>
<thead>
<tr>
<th>Entry (see text)</th>
<th>a</th>
<th>b</th>
<th>c</th>
<th>d</th>
<th>e</th>
<th>f</th>
</tr>
</thead>
<tbody>
<tr>
<td>( R^2 )</td>
<td>( R^3 )</td>
<td>( \Delta \delta_H ) (NH)</td>
<td>( \Delta \delta_P )</td>
<td>( \Delta \delta_C ) (P(_C))</td>
<td>( \Delta \delta_C ) (P(_C))</td>
<td>( \Delta J_{CP} )</td>
</tr>
<tr>
<td>Me Ph</td>
<td>4.1</td>
<td>-1.8</td>
<td>-10.61</td>
<td>6.60</td>
<td>-88.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Ph Me</td>
<td>(c)</td>
<td>-5.0</td>
<td>-7.31</td>
<td>8.32</td>
<td>-88.8</td>
<td>2.8</td>
</tr>
<tr>
<td>Ph CH(_2)Ph</td>
<td>2.9</td>
<td>-4.7</td>
<td>-6.40</td>
<td>7.02</td>
<td>-86.8</td>
<td>2.2</td>
</tr>
<tr>
<td>Ph Ph</td>
<td>4.1</td>
<td>-1.0</td>
<td>-9.89</td>
<td>6.62</td>
<td>-89.5</td>
<td>3.6</td>
</tr>
</tbody>
</table>

\( (a) \) All results determined for single stereoisomers.
\( (b) \) In AcOH-toluene (1:1 v/v) solution.
\( (c) \) The NH resonance signal not observed for the \( Z \) form.

(a) Protons of the NH fragments were found to absorb at a slightly lower magnetic field, \( \delta_Z - \delta_E = 3.5 \) (±0.6), and their resonances usually exhibit an adequate multiplet structure; Fig. 1. In spite of the strong influence of the substituent \( R^3 \) character on individual chemical shifts, two distinct ranges of \( \delta_H \) values were found, namely 5.7–8.5 (on dilution, a diamagnetic shift \( \Delta \delta_H \) of 0.1–0.6 ppm was observed) and 9.9–12.2 ppm for \( E \) and \( Z \) forms, respectively. Similar data were reported for \( \alpha \)-oxo-ester hydrazones, \( \delta_Z - \delta_E = 2.4 \) (±0.2) \(^{(3, 5)}\) as well as for \( \alpha \)-oxo-phosphonate tosylhydrazones, \( \delta_Z - \delta_E = 3.6 \) (±0.3) and \( \Delta \delta_H \) of 0.1–0.8 ppm \(^{(6–8)}\), respectively.

(b) \( ^{31}P \) nuclei absorb (in AcOH-toluene, \( \approx 1:1 \) v/v) at a slightly higher field, \( \delta_Z - \delta_E = -3.3 \) (±2.3). Unfortunately, \( \Delta \delta_P \) values are strongly dependent on the nature of the substituent \( R^3 \).

(c) \(^{13}C \) nuclei in the \( \alpha \) position of the carbon chain (P—C\(_\alpha\)), analogically to the case of oximes (or their methyl ethers) \(^{(2)}\), absorb at a higher magnetic field, \( \delta_Z - \delta_E = -8.5 \) (±2.1).

(d) \(^{13}C \) nuclei in the \( \beta \) position (P—C—C\(_\beta\)) similarly to hydrazones of close structurally related 2-oxopropanoates \(^{(4)}\), resonate at a lower magnetic field, \( \delta_Z - \delta_E = 7.5 \) (±0.9).

(e) \( 1J_{CP} \) couplings give two quite distinct clusters, i.e. 238–243.5 Hz for \( E \) forms and 140–155 Hz [or 151–155 Hz, excluding object 1 (\( R^1 = H \),
Fig. 1. Slightly resolution-enhanced, see ref. [1]. $^1$H NMR spectrum (in CDCl$_3$) of an equilibrated $E/Z$ isomeric mixture (53 % $Z$) of hydrazone 1 (R = $i$-Pr, R$^1$ = H, R$^2$ = Ph, R$^3$ = CH$_2$Ph) with coupling $J_{HH}$ $\approx$ 2.6 Hz observed for its $Z$ form. Two small signals of impurities, the high-field one most likely of silicone grease [23], are asterisked. Expanded regions of resonances of two NH and two Me groups, are shown additionally; vertically plotted values in Hz

R$^2$ = Ph, R$^3$ = $t$-Bu)] for Z forms, respectively. High consistency of such substantial $\Delta J$ values, 88.0 (±1.5) Hz, determined for E/Z isomeric pairs of the studied compounds, is remarkable.

(f) The ranges of $^2J_{CCP}$ couplings are very similar, i.e. 22–23.5 and 24.5–27 Hz, respectively for E and Z forms. Therefore, the diagnostic value have only the corresponding $\Delta J$ values, 2.9 (±0.7) Hz, found for isomeric pairs.

Thus when only one of two E/Z stereoisomers of compound 1 is available for spectral examination, an unambiguous deduction of its configuration may be made exclusively on the basis of $\delta_{HH}$ (NH) and/or $^1J_{CP}$ findings described above, entries (a) and (e), respectively. However, the former guideline is slightly less reliable and can be applied only to objects 1 (R$^1$ = H).

Moreover, it was found that the studied primary hydrazones 1 (R = $i$-Pr, R$^1$ = H) undergo the E/Z isomerisation, i.e. (i) in AcOH-toluene ($\approx$ 1 : 1 v/v) solution E isomers are the predominating forms in due time, whereas (ii) in chloroform solution their Z counterparts gradually dominate. The above observations can be interpreted as caused by (i) the existence, in a relatively polar medium, of strong intermolecular hydrogen bonding
involving amine protons, probably initially mediated by acetic acid [10], and
(ii) by the formation of relatively weak, intramolecular H-bonds of the
type N—H...O=P stabilising more hindered Z forms (in less polar solvent
like CDCl₃), respectively.

The occurrence of the above-mentioned chelation with a strongly basic
oxygen of phosphoryl (P=O) group in the Z isomers of hydrazones 1 (R =
i-Pr, R¹ = H) was additionally supported for object (Z)-1 (R² = Me,
R³ = Ph) by detection of a coupling between the NH and Me protons
through three bonds, ³J₇HNC₇ = 3.7 Hz. Usually there are no such spin-
spin interactions (e.g. in the object (E)-1, R² = Me, R³ = Ph), unless
an intramolecular H-bridge fixes an exchangeable proton in the molecule.
Therefore, the formation of intramolecular H-bonds in hydrazones (Z)-1,
which up to now was suggested only from IR and ¹H NMR data [6–8, 10, 11],
was proven definitively by this multinuclear NMR study. Simultaneously, in
most cases of these stereoisomers, the coupling constants ¹H₉P = 2.4–3.4 Hz
were measured for the first time. Such scalar ¹H, ³¹P couplings involving the
nuclei of NH and P=O fragments of compounds 1, were found in both the
¹H and ³¹P proton-coupled NMR spectra; Figs. 1 and 2.

Fig. 2. Representative ³¹P proton-coupled NMR spectrum (in CDCl₃) of an equilibrated
E/Z isomeric mixture (53 % Z) of hydrazone 1 (R = i-Pr, R¹ = H, R² = Ph, R³ =
CH₂Ph); the E form (δ₉ = 10.14, ³J₇HCC₇ = 11.6 and ³J₇HOCP = 7.5 Hz) and the Z form
(δ₉ = 7.00, ³J₇HCC₇ = 10.0, ³J₇HOCP = 7.45 and ¹H₉P = 2.8 Hz). Only two expanded
spectral regions are presented; vertically plotted values in Hz

In contrast, no similar couplings were found for E isomers of primary
hydrazones 1. It was expected that the transoid-type orientation around the
N=C double bond in such stereoisomers should be privileged for the exis-
tence of interactions in question. In fact only small couplings, \( ^4J_{PCNNC} = 0.9 \) (± 0.1) Hz, were detected for objects \((E)-1\), where \( R^1 = H, R^2 = Me, R^3 = Me, CH_2Ph \) or Ph. All above experimental findings allow one to consider a very interesting possibility, namely whether the couplings \( J_{HP} \) measured for objects \((Z)-1\) are real spin-spin interactions operating across the acceptor oxygen of the H-bridge instead of conventional long-range ones. It would be the first example of such a transfer of spin-spin interactions observed on a heavy atom exteriorly of the H-bridge, i.e. on phosphorus. Undoubtedly, this problem demands further investigations. Scalar couplings via H-bridges have recently been discovered in various intermolecularly H-bonded systems (including biopolymers) carrying A—H...B bridges, where A, B = F or N [16–20], and they were rationalised by assuming a covalent, three-centre nature of the H-bond [17]. Support for this position is provided by the last X-ray Compton-scattering experiment concerning ordinary ice Ih [21, 22].

The results reported here allow one to perform a more detailed discussion on the stereochemical behaviour of other hydrazones 1, where \( R = Me \) or Et [6–11]. For instance, the literature values of \( ^1J_{CP} = 230.1 \) Hz [11], which were found for three different species 1 (\( R = Et, R^1 = H \)), are in sharp contrast to those of this work (see entry (e)) and strongly suggest that the \( Z \) configuration assigned to these compounds is not correct. In addition, the reported \( \delta_H \) (NH) data [5.8–8.6 ppm (in CDCl3)], confirm this opinion as well (entry (a)).

Finally, the \( ^{12}C/^{13}C \) isotope effects on the \( ^{31}P \) chemical shifts of selected hydrazones 1 (\( R = i-Pr \)) were determined originally. The examination of acquired \( ^{13}C \) satellite \( ^{31}P\{^1H\} \) spectra with easily observed \( ^1J_{GCP} \) and \( ^2J_{BCCP} \) couplings (ten and five analysed entries, respectively) reveals the existence of only minimal isotope effects, \( \Delta\delta^{iso} \), measured as \(-0.010 \) (± 0.002) ppm (upfield shift) and \( \cong 0.0 \) ppm, for \( \alpha \) and \( \beta \) \( ^{13}C \) nuclei, respectively.

DEPARTMENT OF ORGANIC CHEMISTRY, UNIVERSITY OF ŁODŹ, NARutowicza 68, 90-136 ŁODŹ 1, P.O. BOX 376, POLAND
(KATEDRA CHEMII ORGANICZNEJ, UNIVERSYTET ŁODZKI)
E-mail: ryanaz@chemul.uni.lodz.pl

REFERENCES