A NATURAL ABUNDANCE ^{17}O NMR INVESTIGATION OF SUBSTITUTED 1-METHYL AND 1-PHENYL-2-THIOHYDANTOINS

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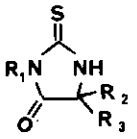
Abstract - Natural abundance ^{17}O nmr spectroscopic data for seventeen 1-methyl- and 1-phenyl-2-thiohydantoins obtained in acetonitrile are reported: the relationship of ^{17}O chemical shift to structure is discussed.

The chemistry of thiohydantoins constitutes an important area of heterocyclic chemistry.[1,2] The Edmans approach, a useful method for identification of N-terminal amino acids in peptides and proteins, involves characterization of 1-methyl and 1-phenyl-2-thiohydantoins.[3,4] A number of spectroscopic studies on thiohydantoins have been reported;[2,5,6] however, no study of the ^{17}O nmr spectroscopic properties of these compounds has appeared. The rapidly expanding field of ^{17}O nmr spectroscopy of organic systems is an increasingly important method for addressing a wide variety of structural questions.[7] ^{17}O nmr spectroscopy has been successfully used to estimate electronic characteristics of a number of functional groups and changes in the environment near oxygen-containing functional groups resulting from both electronic[8] and steric factors.[9] Recent reports have shown that ^{17}O chemical shifts correlate well with torsion angles for a wide range of functional groups attached to aromatic rings.[10,11,12] In rigid systems in which conformational flexibility is restricted, it has been demonstrated that the large t-butyl group causes in-plane distortions of molecular structure.[13] The influence of structure variation on the ^{17}O nmr chemical shifts of thiohydantoins is of interest not only because of their importance in the protein field but also because they provide a framework to systematically assess the influence of structure variation on cyclic amide chemical shifts. This report describes the ^{17}O chemical shifts and their relationship to structure for twelve 1-methyl and five 1-phenyl thiohydantoins.

The ^{17}O nmr data for the thiohydantoins (**1-17**), determined from 0.5 M solutions at natural abundance in dry acetonitrile at 75°C, are listed in Table 1. The ^{17}O chemical shifts of the thiohydantoins appear in the range of 340 to 360 ppm which is consistent with values reported for simple N,N-dialkylamides[14] and cyclic dipeptides.[15] Comparison of the two parent molecules 1-methyl (**1**) and 1-phenyl thiohydantoin (**13**) shows a chemical shift difference of 4 ppm, the shift

of **1** being downfied of **13**. This result is consistent with the electronic properties of the two groups assuming that for **13** the phenyl group is not coplanar with the thiohydantoin ring. This

Table 1. ^{17}O nmr Chemical Shift Data for 1-Methyl and 1-Phenyl-2-Thiohydantoins in CH_3CN at 75°C.[a]



Comp. No.	R_1	R_2	R_3	δ(ppm)
1	CH_3	H	H	348.0
2	CH_3	CH_3	H	343.0
3	CH_3	CH_3	CH_3	341.0
4	CH_3	C_2H_5	H	346.5
5	CH_3	$CH(CH_3)_2$	H	352.0
6	CH_3	$-CH_2CH(CH_3)_2$	H	346.5
7	CH_3	$-C(CH_3)C_2H_5$	H	351.0
8	CH_3	$-CH_2CH_2CH_2CH_3$	H	346.0
9	CH_3	$-CH_2PH$	H	347.7
10	CH_3	b	H	349.2
11	CH_3	c	H	349.8
12	CH_3	CH_2SCH_3	H	346.4
13	Ph	H	H	352
14	Ph	CH_3	H	349.4
15	Ph	C_2H_5	H	351.7
16	Ph	$CH_2CH_2CH_2CH_3$	H	350.7
17	Ph	$CH(CH_3)_2$	H	356

a) Reported in ppm; taken at 75°C as 0.5 M solutions in dry acetonitrile, with 2-butanone as an internal control. b) The thiohydantoin resulting from CH_3NCS and proline. c) The thiohydantoin resulting from CH_3NCS and hydroxyproline; the OH signal appears at 27.7 ppm.

difference of approximately 4 ppm is consistent throughout the comparable 1-methyl and 1-phenyl thiohydantoins (**1**, **2**, **4**, **5**, **8** and **13-17**). These results suggest very similar solution phase geometry for the thiohydantoins.

In the series of 4-alkyl-substituted 1-methylthiohydantoins **2-8** the ^{17}O chemical shifts are affected by the various alkyl groups in a fashion analogous to the influence of alkyl groups on ^{17}O chemical shifts reported for simple aliphatic aldehydes and ketones;[16] γ substituents cause shielding and δ substituents cause deshielding. The chemical shift of the 4-methyl compound **2** is upfield (343 ppm) of the parent **1** (348 ppm); introduction of a second methyl group at position-4, **3**, produces a further upfield shift (341 ppm). These upfield shifts are consistent with the γ shielding effect described for aldehydes and ketones.[16] Introduction of substituents in the δ position as in **4**, **6** and **8** results in deshielding (346 ppm) which was expected based upon the earlier carbonyl results.[16]. As anticipated, introduction of a second δ substituent as in **5** and **7** results in greater downfield shifts (352 and 351 ppm). The signal for benzyl derivative **9**, for which there is not a published precedent in the aldehyde-ketone work, is only slightly deshielded as a consequence of the "branched" δ effect of the phenyl group. Introduction of a fused ring derived from proline (**10**) and hydroxyproline (**11**) causes a slight increase in deshielding (3 ppm) over that noted from a single δ substituent (compare to **4** and **8**). This result may reflect a modest change in the thiohydantoin ring conformation.

In the more limited series of 1-phenylthiohydantoins (**13-17**) similar, though less pronounced, trends are noted for γ and δ substituents. In the cyclic amides (thiohydantoins) studied here, it is apparent that the ^{17}O chemical shift of the amide carbonyl is affected by alkyl substituents in a manner analogous to that reported earlier for acyclic aliphatic aldehydes and ketones.[16]

EXPERIMENTAL

The ^{17}O spectra were recorded on a Varian VXR-400 spectrometer equipped with a 10 mm broad-band probe operated at 54.22 MHz. All spectra were acquired at natural abundance at 75°C in dry acetonitrile (Aldrich) containing 1% of 2-butanone. The concentration of the thiohydantoins (Sigma) employed in these experiments was 0.5 M. The signals were referenced to external deionized water at 75°C. The 2-butanone resonance (558±1 ppm) was used as an internal check on the chemical shift measurements for these compounds. The instrumental settings were: spectral width 35 kHz, 2 K data points, 90° pulse angle (40 μs pulse width), 300 μs acquisition delay, 29 ms acquisition time and ca. 30,000 scans. The spectra were recorded with sample spinning and without lock. The signal-to-noise ratio was improved by applying a 25 Hz exponential broadening factor to the FID prior to Fourier transformation. The data point resolution was improved to ±0.1 ppm by zero filling to 8 K data points. The reproducibility of the chemical shift data is estimated to be ±1.0.

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