NOE Difference Spectroscopy of some 5-Substituted and 5,5-Disubstituted Hydantoins

Michael De Rosa* [1] and Alan J. Freyer [2]

[1] Department of Chemistry, The Pennsylvania State University, Delaware County Campus, 25 Yearsley Mill Road, Media, PA 19063

[2] Department of Chemistry, The Pennsylvania State University, University Park, PA 16802

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The nOe difference (NOED) spectra of twelve 5-substituted- and 5,5-disubstituted hydantoins were recorded in deuteriochloroform. The nOe's observed from the interaction of substituents on C-5 with the proton on N-1 are more reliable than the chemical shift of the N-1 proton for structure determination.

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Introduction.

It was recently observed by one of us that, in the reaction of 1,3-dichloro-5,5-disubstituted hydantoins with 1-methylpyrrole, a pyrrole moiety became attached to one of the nitrogens of the hydantoin ring [3]. It was not possible to determine, by chemical shift data, on which nitrogen of the hydantoin ring the pyrrole group was found. The nOe difference spectroscopy was successfully used to determine the position of substitution [4].

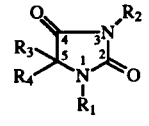
A search of the literature for other applications of nOe-based techniques to hydantoins indicated that nOe, NOED and NOESY spectra have been used to study conformation in solution [5], to study rotamers [6] and to establish relative configuration [7] respectively but did not appear to have previously been used to determine the nitrogen substitution pattern in hydantoins. In this work we present the nOe difference data for twelve hydantoin derivatives and examine the interaction of substituents on C-5 with the proton on N-1. The results of this study will show that the nOe observed from the interaction of substituents on C-5 and N-1 can be used to determine whether N-1 is substituted in hydantoins much more reliably than chemical shifts. This interaction can also be used to study restricted rotation in hydantoin derivatives [5,8].

Results and Discussion.

^{1}H NMR Signals.

The ^{1}H chemical shifts and multiplicities for hydantoins **1-11** are summarized in Table 1. Hydantoin was insoluble in deuteriochloroform and its chemical shifts have not been included. The assignments for the proton spectra were based on chemical shift and nOe data. Compounds **1-7** give relatively simple, first order spectra. The methylene protons in the ethyl group for **8** and **9** are nonequivalent, as are the isopropyl methyl groups for **10** and **11**. Chemical shifts for hydantoin **12** are illustrated in the following figure. The H-6 equatorial proton at δ 2.85 shares a 16.5 Hz geminal coupling with H-6_{ax} δ 3.39 and a small 2.2 Hz W coupling with H-10_{eq} δ 2.02.

It has generally been observed that the proton on N-3 appears at lower field compared to the proton on N-1 [9,10]. The data in Table 1 shows the same trend for most of the hydantoins studied and the proton attached to N-1 resonates at δ 5.94-5.30 compared to the proton attached to N-3 which resonates at δ 8.64-7.55. However in the case of hydantoins **7** and **9** the NH-1 resonance is found considerably further downfield than normal at δ 7.05 and δ 7.96 respectively. If one were to assign these protons based on the general chemical shift trend, these hydrogens would erroneously be thought to be attached at N-3 with the other substituent attached to N-1. Nuclear Overhauser effects between NH-1 and the C-5 substituents clearly establish that the proton is indeed located on N-1 and the methyl group at N-3.



1-11

	R_1	R_2	R_3	R_4
1	CH_3	H	H	H
2	H	H	CH_3	H
3	H	H	CH_3	CH_3
4	H	Ph	H	CH_3
5	H	H	Ph	Ph
6	H	H	CH_3	Ph
7	H	CH_3	CH_3	Ph
8	H	H	CH_3	Et
9	H	CH_3	Ph	Et
10	H	H	H	*i*-Pr
11	H	H	CH_3	*i*-Pr

A search was made for other examples of anomalous chemical shifts for the proton on N-1. The N-1 and N-3

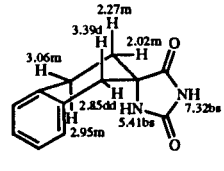


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Table 1

^{1}H NMR Assignments of 5-Substituted- and 5,5-Disubstituted Hydantoins

No.	R_1	R_2	R_3	R_4	J (Hz)
1	2.97 (CH_3)	8.64 (NH,bs)	3.92 (H)	3.92 (H)	
2	5.47 (NH, bs)	7.61 (NH, bs)	1.49 (CH_3, d)	4.18 (H, q)	7.0
3	5.81 (NH, bs)	8.15 (NH, bs)	1.48 (CH_3)	1.48 (CH_3)	
4	5.30 (NH, bs)	7.54-7.31 (Ph, m)	1.60 (H)	7.54-7.31 (Ph, m)	
5	5.92 (NH, bs)	7.55 (NH, bs)	7.39 (Ph, m)	7.39 (Ph, m)	
6	5.92 (NH, bs)	7.72 (NH, bs)	1.88 (CH_3)	7.53-7.38 (Ph, m)	
7	7.05 (NH, bs)	3.02 (CH_3)	1.87 (CH_3)	7.55-7.51 (Ph, m)	
8	5.94 (NH, bs)	NH [a]	1.45 (CH_3)	1.87 (CH_A, m), 1.69 (CH_B, m), 0.94 (CH_3, dd)	7.4
9	7.96 (NH, bs)	3.00 (CH_3)	7.61-7.32 (Ph)	2.19 (CH_2, m), 0.91 (CH_3, t)	
10	5.93 (NH, bs)	8.14 (NH, bs)	4.01 (H, d)	2.24 (CH, m), 1.07 (CH_3, d), 0.98 (CH_3, d)	3.9, 7.0
11	5.70 (NH, bs)	7.89 (NH, bs)	1.44 (CH_3)	2.04 (CH, m), 1.00 (CH_3, d), 0.95 (CH_3, d)	6.8

[a] Signal for this proton was not observed.

protons of 5-benzalhydantoin are indistinguishable [9]. This has been attributed to the unusual acidity of the N-1 proton. In a study by Trigo and coworkers [11], of five *N*-alkylgranatine-3-spiro-5'-hydantoins, it was found that all the compounds studied adopted the chair conformation in dimethyl sulfoxide. Their ^{1}H nmr data indicated that in two of these compounds the N-1 protons (δ 7.78) appear at lower field compared to the N-3 protons (δ 3.5-4.0). All the compounds have the same dihedral angles and the variable substituent is distant from the N-1 proton.

Table 2

NOED of 5-Substituted- and 5,5-Disubstituted Hydantoins

No.	irrad. reson.	NOED (%)
1	R_1	$R_3 = R_4$ (7.6)
	$R_3 = R_4$	R_1 (7.4)
2	R_1	R_4 (6.9)
	R_3	R_4 (7.5)
	R_4	R_3 (4.2)
3	R_1	$R_3 = R_4$ (4.6)
	$R_3 = R_4$	R_1 (9.0)
4	R_1	R_4 (17.4)
	R_3	R_1 (2.4)
	R_4	R_1 (18.8)
5	R_1	$R_3 = R_4$ (10.2)
	$R_3 = R_4$	R_1 (14.5)
6	R_1	R_3 (2.1), R_4 (9.9)
	R_3	R_1 (9.9), R_4 (15.2)
	R_4	R_1 (7.9), R_3 (3.4)
7	R_1	R_3 (4.8), R_4 (14.8)
	R_3	R_1 (7.9), R_4 (23.2)
8	CH_A	CH_B (4.9), CH_3 (2.9)
	CH_B	CH_A (7.3), CH_3 (2.5)
	CH_3	CH_A (9.7), CH_B (8.4)
9	R_1	R_4 (10.7, *o*-H; -2.0, *m*-H),
	R_3	CH_3 (2.4), CH_2 (4.6)
	CH_2	R_4 (5.7), CH_3 (16.4)
	CH_3	R_4 (1.97), CH_2 (24.6)
10	R_1	R_3 (8.3), CH_3 (3.1), CH_3 (2.4)
	R_3	R_1 (4.8), CH (6.5), CH_3 (2.6), CH_3 (1.2)
	CH	R_3 (8.1), CH_3 (5.6), CH_3 (5.3)
	CH_3	R_1 (6.5), R_3 (9.4), CH (19.4)
	CH_3	R_1 (4.1), R_3 (5.1), CH (22.9)
11	CH	CH_3 (4.9)
	R_3	R_1 (1.2), CH (2.9)
	CH_3	R_1 (1.5), CH (5.3)
	CH_3	CH (6.5)
	CH_3	CH (6.5)

Hydantoins **5**, **7** and **12** were modeled using MM2 (Chem 3-D Plus from Cambridge Scientific) and in all cases the hydantoin ring is planar. Puckering of the hydantoin ring might help explain the NH-1 shifts. There appear to be no obvious stereo or electronic factors to explain the anomalous NH-1 shifts observed in this study and by Trigo [11]. Therefore caution should be used when proposing hydantoin structures solely on the basis of the relative chemical shift of the NH protons on the hydantoin ring.

NOE Difference Data.

The nOe difference (NOED) data are reported as a percent of the maximum possible nOe and are summarized in Table 2. Of particular interest is the interaction between substituents on C-5 (R_3 and R_4) with those on N-1(R_1). In the series of hydantoins **1-11** it is possible to study the interaction of the proton on N-1 with the hydrogen, methyl, ethyl, isopropyl and phenyl group on C-5. These interactions were compared within the 5-methylhydantoin series consisting of **2**, **3**, **6**, **8** and **11**. The relative order of the nOe's was phenyl>methyl>hydrogen. When the second substituent on C-5 has two or more carbons, interactions can occur between the proton on N-1 and the various protons of the group (Table 2) at C-5. It was therefore not possible to obtain an enhancement factor for the ethyl or isopropyl group as a whole. But it can be seen that an enhancement exists whenever the group on C-5 is larger than a proton and no interaction was noted between the group(s) on C-5 and the proton/substituent on N-3. For compounds with groups larger than hydrogen on N-1 analogous results would be obtained [4].

Similar NOEDs were observed with the other hydantoins studied. In the case of the spirohydantoin **12** the only

NOEDs observed, involving the NH, were as follows:

$$N\text{–}H \underset{4.7\%}{\overset{8.6\%}{\rightleftharpoons}} H_{\delta\ 2.85}$$

This implies that the proton at δ 2.85 is close to the proton on N-1 (about 3.0 Å). Modeling indicates that the ring is not a chair but is puckered or a flattened chair. In the case of 5-ethyl-3-methyl-5-phenylhydantoin (**9**) there is an NOED observed between the proton on N-1 and an *ortho* hydrogen on the ring, and the *meta* proton experiences a negative NOED (-2.0%).

The NOED values obtained from different portions of a group interacting with the proton on N-1 can be used to obtain a more complete view of conformer populations in a hydantoin derivative. This can be seen in comparing the NOEDs obtained from 5-isopropylhydantoin (**10**) and 5-isopropyl-5-methylhydantoin (**11**). In hydantoin **10** both methyl groups of the isopropyl group interact with the proton on N-1 and nOe's are observed for both methyls. In contrast only one of the methyls in the isopropyl group of 5-isopropyl-5-methylhydantoin (**11**) interacts with the proton on N-1. This would seem to indicate that in **11** the barrier to rotation is sufficiently large that only one of methyls of the isopropyl groups is near the proton on N-1.

Conclusions.

The nOe's observed from the interaction of substituents on C-5 with the proton/substituent on N-1 are more reliable than the chemical shift of the N-1 proton for structure determination. In 5,5-disubstituted hydantoins with one or more nonplanar substituents NOE difference spectroscopy can be used to help determine the principal conformer present.

EXPERIMENTAL

The hydantoins used were all commercially available (Aldrich and Alfred Bader) and used without further purification.

NMR.

All of the ^1H nmr spectra were collected on a Bruker AMX 400 MHz spectrometer at 25°. Approximately 10 mg of each sample were dissolved in 0.8 ml of deuteriochloroform (MSD, 99.96 atom % D), and these samples were then degassed by freeze-thaw cycling. The chemical shifts were referenced to tetramethylsilane. Nuclear Overhauser effect (nOe) experiments were measured on the same samples. A series of proton spectra were collected for all of the samples in which each individual proton signal and one off-resonance frequency were selectivity saturated with low RF power for 10 seconds prior to acquisition. The signal was averaged for 16 scans per irradiation in this fashion. The process was repeated several times to improve the signal/noise ratio. After data collection the off-resonance fid was subtracted from the appropriate on-resonance fid to create a series of difference fids which were then transformed and integrated. The nOe results are presented as the percentage of the maximum possible enhancement (i.e. 0-100% of the maximum possible 0.5 enhancement).

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[1] Delaware County Campus.

[2] University Park Campus. Present address: SmithKline Beecham Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, USA.

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