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Z–E ISOMERISM OF 5-CYCLOHEXYLMETHYLENEHYDANTOINS

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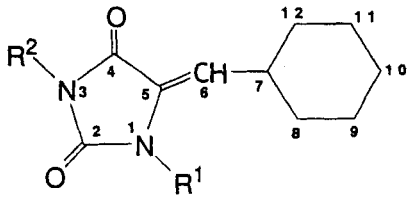
5-Cyclohexylmethylenehydantoin and its 1- and 3-methyl derivatives were studied as the aliphatic analogues of the 5-benzylidenehydantoins to examine the effects of replacing a benzene by a cyclohexane ring on *Z–E* isomerism. The relative stabilities of the *Z*- and *E*-isomers were compared by estimating the free energy differences from thermal equilibration experiments and the heats of formation by AM1 calculation. In the *Z*-isomers, the possible existence of weakly attractive interaction between the C(4) = O and C(6)—H groups, which form parts of a stereochemically favourable, conjugated α,β-unsaturated system, is suggested as a contributory factor to the observed configurational preference. Assignment of configurations was based mainly on NMR and is supported by IR and UV spectra. NMR spectra also revealed the conformation of the cyclohexane ring and the cyclohexyl proton signals were assigned by double resonance and by high-field NMR in two solvents where solubility allows.

INTRODUCTION

Previous studies of the *Z-E* isomerism of more than 40 compounds in four series of 5-(aryl/heteroaryl)-methylenehydantoins[1–3] have revealed consistent trends of configurational preferences. In the preparation of each of the *N*(1)-unsubstituted compounds by condensation of hydantoin or 3-methylhydantoin with an aromatic† aldehyde, only the *Z*-isomer is isolated. In contrast, a similar condensation of 1-methylhydantoin yields both *Z*- and *E*-isomers of the *N*(1)-methyl-substituted analogue, usually with the *E*-isomer as the major product. These trends parallel the relative stabilities of the geometric isometric pairs as shown by thermal equilibration experiments.[4] In addition to steric strain, other factors attributable to attractive or repulsive interactions of the aromatic ring with different parts of the hydantoin moiety have also been considered. Hence, it is pertinent to investigate how the *Z*/*E* preferences are affected by replacing the aryl with an alkyl group. We report here a study of 5-cyclohexylmethylenehydantoins as the aliphatic analogues of the 5-benzylidenehydantoins.

RESULTS AND DISCUSSION

5-Cyclohexylmethylenehydantoin (**1**) and its 3- and 1-methyl derivatives (**2** and **3** respectively) were synthesised by condensations of hydantoin, 3-methylhydantoin and 1-methylhydantoin, respectively, with cyclohexanecarboxaldehyde. Only one isomer of **1** or **2** but two isomers of **3** were isolated directly from the reaction mixtures (Table 1). The product **1** or **2** could be partially converted into its stereoisomer and the two stereoisomers of **3** could also be interconverted, either by thermal isomerism or photoisomerization, resulting in equilibrium mixtures.



Compd	R^1	R^2
1	H	H
2	H	Me
3	Me	H

^{1}H NMR spectra

Assignments of configurations

The ^{1}H NMR data of compounds 1–3 are summarized in Table 2. The relative chemical shifts of the vinyl

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† For the sake of brevity, the term aromatic is used to include heteroaromatic and aryl to include heteroaryl in the following discussion.

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Table 1. Melting points and analytical data

Compound	M.p. (°C)[a]	Found (%)			Calculated (%)		
		C	H	N	C	H	N
(*Z*)-**1**	262·5–264	61·6	7·3	14·5	61·8	7·3	14·4
(*Z*)-**2**	208·5–209	63·5	7·8	13·5	63·4	7·7	13·5
(*E*)-**3**	122–123	63·6	7·7	13·6	63·4	7·7	13·5
(*Z*)-**3**	140–141	63·0	7·5	13·3	63·4	7·7	13·5

[a] Melting points are uncorrected.

proton H(6) are most diagnostic of configuration since this proton is expected to be deshielded by the anisotropic C(4) carbonyl group in the *Z*-isomer but not in the *E*-isomer. Thus, the major product from the preparation of **3** is assigned the *E*- and the minor product the *Z*-configuration. Thermal isomerization of the only isolated isomer of **1** or **2** results in the emergence of a new H(6) signal at higher field, indicating that the product from direct synthesis is the *Z*-isomer. These H(6) signals appear as doublets, with $J = 10$–11 Hz, being coupled with H(7) of the cyclohexane ring. They occur at higher field than the corresponding signals for the 5-arylmethylenehydantoins, owing to the absence of the effects of an aromatic group.

Table 2. Chemical shifts (ppm from Me_4Si, *J* in Hz)

	^{1}H shifts									
Compound	N(1)H	N(3)H	H-6	*N*-CH_3	H(7)	H(8,12)e	H(9,10,11)e	H(9,11)a	H(10)a	H(8,12)a
(*Z*)-**1**[a]	10·12	10·91	5·36 (d, *J* 10·0)		2·36 (q, *J* 10·3)	1·67 (m)	1·62 (m)	1·25 (m)		1·13 (m)
(*Z*)-**1**[b]	10·12	10·91	5·36 (d, *J* 10·0)		2·36 (q, *J* 10·6, 3·6)	1·67 (d, *J* 12·8)	1·62 (d, *J* 12·9)	1·27 (q, *J* 12·2)	1·20 (q, *J* 11·9)	1·12 (q, *J* 12·1)
(*E*)-**1**[c]	9·86	10·45[e]	5·24 (d, *J* 10·1)							
(*Z*)-**2**[a]	10·37		5·48 (d, *J* 10·0)	2·88	2·40 (q, *J* 10·4, 3·2)	1·69 (m)	1·64 (m)	1·25 (m)		1·15 (m)
(*Z*)-**2**[d]	7·86		5·81 (d, *J* 9·8)	3·08	2·21 (q, *J* 10·1, 3·5)	1·74		1·33 (q, *J* 12·1, 2·7)	1·25 (m)	
(*E*)-**2**[c]	10·10		5·33 (d, *J* 10·1)	2·81						
(*Z*)-**3**[a]		11·17	5·42 (d, *J* 10·7)	3·19	2·69 (q, *J* 10·7)	1·66 (m)		1·31 (m)	1·17 (m)	
(*E*)-**3**[a]		11·12	5·32 (d, *J* 9·9)	2·91	3·30[f]	1·69 (m)	1·65 (m)	1·23 (m)	1·14 (m)	
(*E*)-**3**[d]		8·61	5·22 (d, *J* 10·1)	3·03	3·40 (q, *J* 10·9, 3·1)	1·72 (m)		1·39 (q, *J* 12·6)	1·19 (q, *J* 12·1)	1·12 (q, *J* 11·9)

	^{13}C shifts					
Compound	C(2)	C(4)	C(5)	C(6)	*N*-CH_3	C(7) – C(12)
(*Z*)-**1**	154·7	164·6	128·9	116·6	—	34·9, 31·6, 25·2, 24·9
(*Z*)-**2**	154·4	163·3	127·6	117·7	23·9	34·9, 31·6, 25·2, 24·9
(*E*)-**3**	153·2	163·5	129·0	122·1	25·1[g]	33·7, 32·7, 25·3, 25·2

[a] 300 MHz spectrum in $(CD_3)_2SO$.
[b] 500 MHz spectrum in $(CD_3)_2SO$.
[c] Deduced from 300 MHz spectrum of mixture obtained by thermal isomerization of the *Z*-isomer. The cyclohexyl proton signals of the two isomers are not distinguishable.
[d] 500 mHz in $CDCl_3$.
[e] Location uncertain owing to decomposition accompanying thermal isomerization.
[f] Splitting pattern partly obscured by the overlapping water signal.
[g] Assignment of the *N*-CH_3 signal is uncertain as it occurs within the range of the signals of cyclohexyl protons.

The configurations of (*Z*)-**2** and (*E*)-**3** were confirmed by x-ray crystallographic studies.[5]

Although the *N*-methyl signals are found within a range similar to that for the methyl derivatives of the 5-arylmethylenehydantoins, one important difference is that the *N*(1)-methyl protons of (*Z*)-**3** are now observed at lower field than those of (*E*)-**3**. In (*Z*)-3, steric crowding by the cyclohexyl group probably causes distortion of the electron cloud around the *N*(1)-methyl protons, resulting in deshielding. This contrasts with the previously observed shielding of the corresponding protons in *Z*-isomers of 1-methyl-5-arylmethylenehydantoins by the aromatic ring current effect.

The NH protons give the most downfield signals at δ 10·12–11·91 in $(CD_3)_2SO$ or δ 7·86–8·61 in the less basic solvent $CDCl_3$, the N(3) proton being more deshielded than the N(1) proton. Following the trend shown by the *N*(1)-methyl protons, the proton at N(1) in the *Z*-isomer of compounds **1** or **2** resonates at lower field than that in the *E*-isomer but there is only small difference between the *N*(3)-H signals of the two isomers for each of compounds **1** and **3**.

Study of conformation

The proton signals of cyclohexane derivatives are often complex owing to coupling among the cyclohexyl protons themselves and possible conformational changes. Extensive studies by previous workers[6–10] have shown that equatorial protons generally resonate at lower field than axial protons and that geminal axial–equatorial and vicinal axial–axial couplings of a cyclohexane ring are much stronger than vicinal equatorial–equatorial and vicinal axial–equatorial couplings.

The study of the cyclohexyl protons of compounds **1–3** is simplified because these compounds are conformationally rigid as far as the cyclohexane ring itself is concerned. The bulky methylenehydantoin group, as an equatorial substituent, effectively prevents chair inversion so that the axial and equatorial protons are distinguishable at room temperature. However, rotation of the cyclohexane ring around the C(6) – C(7) single bond remains possible, with two limiting orientations with respect to the hydantoin ring. Conformations *Z*-A and *E*-A are probably preferred to *Z*-B and *E*-B, respectively, for steric reasons.

For each compound, the axial H(7) signal is well separated from the those of the remaining cyclohexyl protons, being most deshielded by proximity to the C(5)=C(6) double bond. In the *E*-isomers, H(7) is further deshielded relative to the corresponding proton in the *Z*-isomers, as shown by the strikingly large Δδ of 0·6 ppm for (*E*)-**3** and (*Z*)-**3** in $(CD_3)_2SO$. This is consistent with conformation *E*-A where H(7) approaches closely the anisotropic C(4) carbonyl group. Incidentally, this provides additional support for the configurational assignments deduced from consideration of the H(6) signal as discussed above.

The equatorial and the remaining axial protons form two groups of multiplets in the regions δ 1·55–1·75 and δ 1·05–1·35, respectively. More detailed analysis has been achieved by application of the spin-decoupling technique.

Figure 1 illustrates the assignment, by spin decoupling, of the cyclohexyl protons of (*E*)-**3**. Because of solubility, spectra of all the compounds were obtained in $(CD_3)_2SO$. However, the significant downfield shift of the H-7 signal for (*E*)-**3** results in its merging with the water signal from this hydroscopic solvent. This problem is avoided by using $CDCl_3$ in which this compound is sufficiently soluble. Resolution is further enhanced in the spectrum obtained at 500 MHz. Not only is the H(7) signal now clearly seen as a quartet of triplets but also the axial-proton signal which appears as a complicated multiplet in $(CD_3)_2SO$ in the 300 MHz spectrum is separated into three quartets with finer splitting due to coupling with vicinal equatorial protons, representing two, one and two protons at δ 1·39, 1·19 and 1·12, respectively. Irradiation at H(6) reduces the H(7) signal to a triplet of triplets with $J = 11·3$ and 3·4 Hz from spin couplings with the adjacent axial and equatorial protons, respectively. Irradiation at H(7) changes not only the H(6) signal from a doublet to a singlet but also the axial quartet at δ 1·12 to a triplet with $J = 11·5$ Hz. This highest field signal is therefore assigned to H(8a) and H(12a), which experience additional anisotropic shielding by the C(6)—C(7) single bond. The appearance of the equatorial multiplet remains largely unaffected. On irradiation at the signal of equatorial protons, which resonate within a narrow range, H(7) becomes a well defined quartet with $J = 10·6$ Hz as the weaker vicinal axial–equatorial coupling is removed, leaving only the strong coupling with H(6), H(8a) and H(12a). The lowest field quartet of axial protons at δ 1·39 also changes to a triplet which is assigned to H(9a) and H(11a), leaving the signal at δ 1·19 to be assigned to the single proton H(10a). This conclusion is supported by the observed change of the latter signal, on irradiation at H(9a) and H(11a), to a broad doublet as H(10a) is now coupled strongly only to its geminal equatorial proton. Irradiation at H(8a) and H(12a) causes the H(7) quartet to collapse to a broad doublet. Applying similar technique to the spectra of other compounds, the spin–spin coupling of the cyclohexyl protons can be resolved and *J* values calculated to fall within the following ranges: *gem*-$J_{ae} = 10·6–11·8$ Hz, *vic*-$J_{ae} = 3·1–3·6$ Hz and *vic*-$J_{aa} = 11·9–12·8$ Hz.

^{13}C NMR spectra

The two lowest field signals are assigned to the carbonyl carbons C(2) and C(4) followed by the olefin carbons

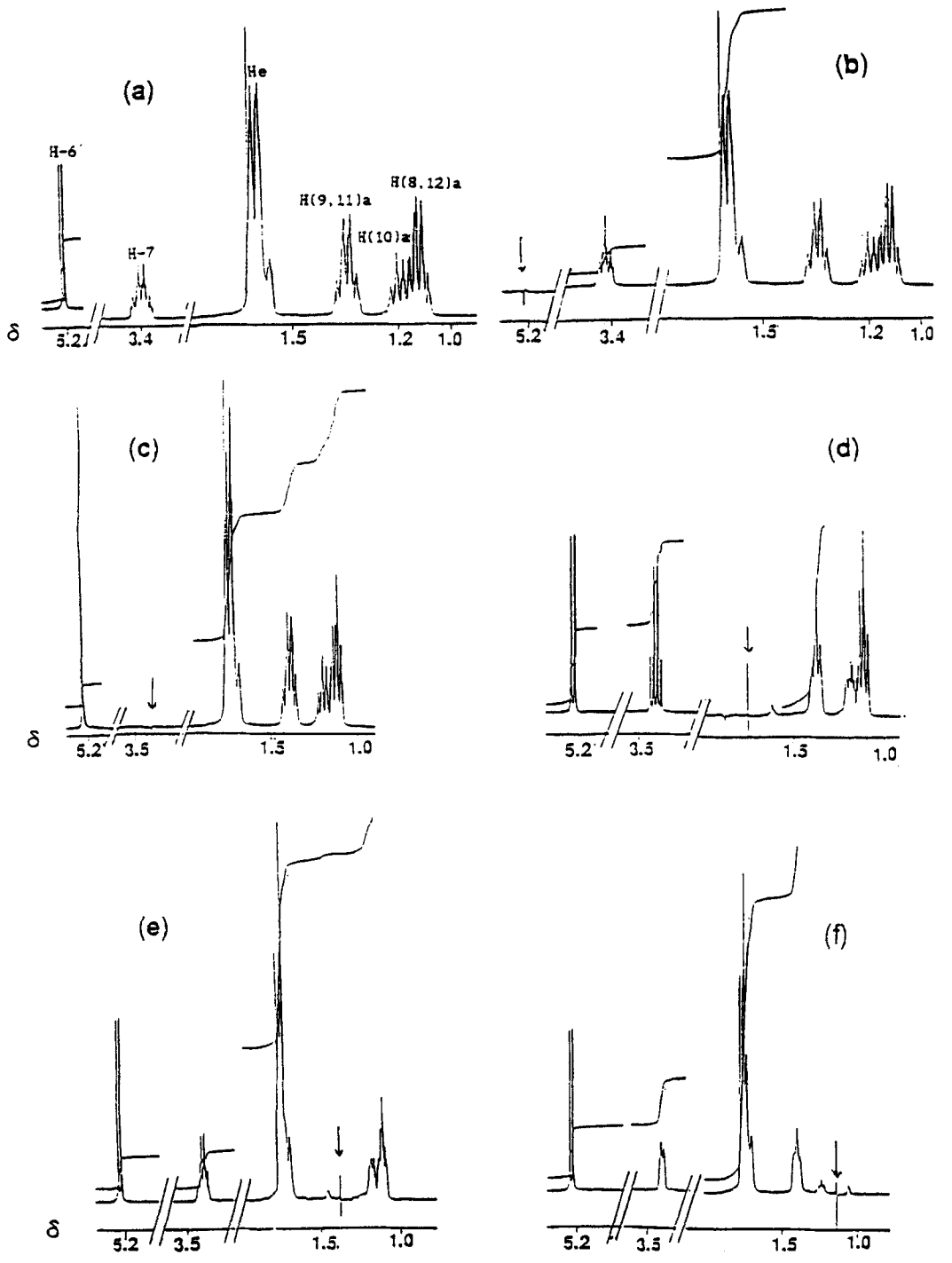


Figure 1. 500 MHz spectra of (*E*)-3 in $CDCl_3$, (a) before irradiation, and after irradiation (b) at H(6), (c) at H(7), (d) at He, (e) at H(9,10)a and (f) at H(8,12,10)a

C(5) and C(6). The presence of a methyl substituent at either N(1) or N(3) causes small additional shielding of the adjacent carbonyl carbons in **2** and **3** when compared with the *N*-unsubstituted compound **1**. The *Z*- and *E*-isomers are distinguishable by their C(6) signals, which occur at higher field in the *Z*- than in the *E*-isomer, similar to the trend observed in the ^{13}C spectra of the 5-arylmethylenehydantoins. The cyclohexyl carbons and the *N*-methyl carbon resonate within the range δ 23·9–34·9.

IR spectra

Among the many 5-arylmethylenehydantoins studied, it was observed that the C=C stretching frequency is a useful criterion of configurational discrimination. The lower stretching frequency of this bond has been attributed to more effective conjugation of this bond with the aromatic ring in the *E*-configuration.[1] Interestingly, this same trend is observed for the present 5-cyclohexylmethylenehydantoins although the aromatic ring is absent (Table 3). Therefore, the difference in C=C stretching frequencies shown by the two isomers are more likely to be the result of differences in spatial relationship between the C(5)=C(6) and C(4)=O bonds as the bond angles change with configuration. In the *E*-configuration, these move further apart owing to steric crowding of the aryl or alkyl group *cis* to the C(4)=O group than in the *Z*-configuration in which they are pushed closer together by the same aryl or alkyl group now *trans* to C(4)=O.

The C=O and N—H stretching bands occur at similar frequencies to those observed in the spectra of the 5-arylmethylenehydantoins. The expected C—H stretching and deformation vibrations are also observed.

Electronic spectra

5-Cyclohexylmethylenehydantoins differ from their aryl analogues significantly in the electronic spectra. Although introduction of the unsaturated side-chain at C(5) of the hydantoin ring gives rise to additional intense absorption band in all cases, this band is observed at shorter wavelength (272–284 nm) for the cyclohexyl compounds (Table 3) than the corresponding band for the aryl compounds, which is red shifted to above 300 nm owing to extended conjugation with the aromatic ring.

It is also noted that the difference in the absorption maxima of the *Z*- and *E*-isomers in a cyclohexyl compound is small compared with the large difference of 25–30 nm observed between the geometric isometric pair of an aryl compound. A consequence of this is that photoisomerization becomes a less practical means of obtaining the minor isomer unless highly selective filters are available for irradiation at narrow wavelength ranges.

Mass spectra

The mass spectra of **1**–**3** are similar. The major fragmentation pathway involves breaking the C(6)—C(7) bond, giving rise, in each case, to a base peak corresponding to the loss of C_6H_9 radical from the molecular ion. The C_6H_{10} radical ion is also found in all the spectra (Table 3).

Unlike the other spectroscopic methods discussed above, mass spectrometry does not provide useful criteria for configuration assignment.

Relative stabilities of *Z*- and *E*-isomers

The relative stabilities of each isometric pair of **1**–**3** were estimated by thermal equilibration. Experiments were conducted in $(CD_3)_2SO$ at 160 °C. Starting with either isomer, changes were monitored by ^1H NMR until thermal equilibrium was reached. The ratio of isomers present at different time intervals was deduced from the relative intensities of the readily identifiable H(6) signals and, for the methyl-substituted compounds **2** and **3**, also of the *N*-CH_3 signals of the two isomers.

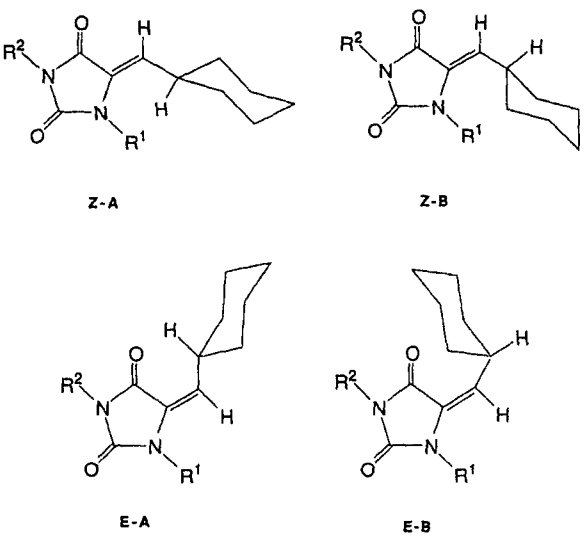
Table 3. IR[a], UV[b] and mass spectrometric data

Compound	ν (cm^{-1}) C=O	ν (cm^{-1}) C=C	λ_{max} (nm) (log ε)	*m/z* (M^+ significant ions)			
(*Z*)-**1**	1763 1725	1677	220 (3·90) 270 (4·12)	194	113[c]	82	67
(*Z*)-**2**	1784 1715	1673	230 (4·00) 274 (4·08)	208	127[c]	82	67
(*E*)-**3**	1756 1716	1644	222 (3·78) 284 (3·89)	208	127[c]	82	67

[a] KBr discs.
[b] In methanol.
[c] Most abundant.

For **1** or **2**, the *Z*-isomer was found to be more stable than the *E*-isomer but the reverse was observed for **3**. However, the standard free energy differences calculated for these 5-cyclohexylmethylenehydantoins (Table 4) are smaller than the corresponding values previously obtained for the 5-benzylidenehydantoins.[4]

For comparison, the heats of formation of **1–3** were calculated using the AM1 method.[11] Calculations carried out separately for the different conformations A and B clearly show that *Z*-A and *E*-A conformations are consistently more stable than *Z*-B and *E*-B, supporting the conformational preferences deduced from simple examination of molecular models and from study of ^{1}H NMR data. In addition to steric factors, interactions of the aromatic ring with either the N(1)—H/Me or C(4)=O group of the hydantoin ring have been considered to rationalize the observed differences in stabilities of the *Z*- and *E*-isomers of various 5-arylmethylenehydantoins. These latter effects obviously do not apply in the case of the 5-cyclohexylmethylenehydantoins studied here. However it is found that the *Z*-configuration is still overwhelmingly preferred in the synthesis of the *N*(1)-unsubstituted compounds **1** and **2**. Molecular models show little or no steric congestion in the conformation *Z*-A and that the small steric strain caused by close approach of H(7) to C(4)=O in the conformation *E*-A can be alleviated by slight rotation around the C(6)—C(7) bond. This leads us to query what this common factor among all these *N*(1)-unsubstituted aryl and cyclohexyl compounds is that contributes to the consistently superior stability of the *Z*-configuration. Could there be some intramolecular attraction between C(4)=O and H(6)? This was not considered previously because the CH group is a poor hydrogen-bond donor. However, the possible existence of C—H···X hydrogen bonds, where X is an acceptor atom O, N, Cl or S, in many systems has been extensively discussed and reviewed.[12–15] Evidence for both inter- and intramolecular C-H···O hydrogen bonds has been provided by spectroscopic studies and accurate x-ray and neutron



diffraction analyses.[16–20] Although these are only weak interactions of electrostatic nature, they may become important in favourable structural and stereochemical situations. Such a situation may exist in the *Z*-configuration of the 5-methylenehydantoins, whether aryl or cyclohexyl substituted. Here, the C(6)—H and C(4)=O groups not only enjoy a suitable stereochemical relationship but also form parts of a conjugated α,β-unsaturated carbonyl system, where polarisation enhances simultaneously their proton-donor and -acceptor capabilities. The electron density around O(4) is further enriched as C(4)=O is also conjugated with the electron-releasing *N*(3)-R group. The C(5)—C(6) bond, being part of the hydantoin, is not free to rotate and resonance ensures coplanarity of the system which brings H(6) close to O(4). X-ray diffraction studies[5,21–23] of the *Z*-isomers of some of the 5-arylmethylenehydantoins and of compound **2**, which form sufficiently good single crystals, give the H(6)—O(4) distance in the range 2·54–2·67 Å, which is

Table 4. Thermal equilibration in $(CD_3)_2SO$ at 433 K and AM1-calculated heats of formation

						ΔH° (kJ mol^{-1})	
Compound	*Z* (%)	*E* (%)	*K*[a]	ΔG° (kJ mol^{-1})[b]	Compound	Conformation A	Conformation B
1	89	11	8.1	−7·5	(*Z*)-**1**	−285·0	−277·8
					(*E*)-**1**	−281·2	−277·8
2	91	9	10.1	−8·3	(*Z*)-**2**	−264·3	−257·5
					(*E*)-**2**	−260·3	−248·0
3	23	77	0.3	+4·3	(*Z*)-**3**	−260·6	−240·1
					(*E*)-**3**	−261·5	−248·0

[a] $K = [Z]/[E]$ at equilibrium.
[b] Standard free energy difference $\Delta G^\circ = -RT \ln K$.

less than the sum of van der Waals radii of H and O,[24,25] although the use of this sum of van der Waals radii of the hydrogen and acceptor atoms as a criterion for the presence of a hydrogen bond remains controversial and the values of the van der Waals radii are often ill-defined.

The relationship between C(6)—H and C(4)=O, which is the only common structural feature among the *Z*-isomers of all the 5-arylmethylenehydantoins and 5-cyclohexylmethylenehydantoins, suggests that an attractive C(6)—H···O=C(4) interaction could possibly make a significant contribution to their stability.

It should be pointed out that in the *E*-isomers of compounds **1–3**, H(7) probably approaches O(4) even more closely. However, interaction between these two atoms is not likely to be attractive because C(7) is sp^3 hybridized, unlike C(6), which is sp^2 hybridized. Moreover, C(7)—H is not conjugated to C(4)=O so that the type of polarization enhancement discussed above for the C(6)—H···O=C(4) attraction does not apply. Instead, the interaction between H(7) and O(4) may even be repulsive. X-ray crystallographic examination of (*E*)-**3** reveals that the cyclohexane ring is unsymmetrically disposed with respect to the plane of the hydantoin ring, as a result of rotation about the C(6)—C(7) bond to alleviate the steric crowding between H(7) and O(4).

The reversal of configurational preference for the *N*(1)-methyl substituted compound **3** can be viewed as the result of relative destabilization of the *Z*-isomer due to steric congestion between the 1-methyl and the cyclohexyl groups, which now offsets the stabilization by the attractive interaction between C(6)—H and C(4)=O, rather than increased stabilization of the *E*-isomer. There is probably little difference in stability among the *E*-isomers of **1–3** as far as the interaction between C(4)=O and the cyclohexane ring is concerned.

EXPERIMENTAL

Cyclohexylmethylenehydantoins **1–3** were prepared by condensation of hydantoin, 3-methylhydantoin or 1-methylhydantoin (10 mmol) with cyclohexanecarboxaldehyde (10 mmol) in an aqueous solution (10 ml) of glycine (10 mmol) and sodium carbonate (5 mmol).[26,27] The mixture was refluxed for 4–5 h. Crude products were formed on cooling and a further amount on acidification. HPLC examination revealed that the crude products of **3** obtained before and after acidification consisted mainly of the *E*- and *Z*-isomers, respectively. All compounds were recrystallized from methanol, except the more soluble (*Z*)-**3**, which was obtained only with addition of a small amount of cyclohexane.

Thermal equilibration was carried out in a WTC Binder F115 oven at 160 °C. The solution of a pure isomer in $(CD_3)_2SO$ in a 5 mm NMR tube was heated in the oven. At appropriate time intervals, it was removed, cooled quickly to room temperature and its ^1H NMR spectrum was determined. Integration of the signals of the vinyl protons and/or the *N*(1)-methyl protons of the two isomers provided a measure of their relative concentrations.

Photoisomerization was carried out using a Hanovia 200 W high-pressure lamp (Model 654–0360) placed in a quartz tube which, in turn, was housed in a brass tube with a window. The lamp was cooled continuously with a stream of chilled nitrogen during operation. Approximately 5×10^{-3} M solutions of the compounds in methanol were irradiated and the changes were monitored by HPLC analysis of samples at various time intervals. Isomerization was found to be accompanied by decomposition. The low percentage of isomerization observed before extensive decomposition set in rendered separation impractical. Instead, the mixture obtained after 10–20 min of irradiation was used for ^1H NMR determination to characterize the minor isomer, complementing the results from thermal isomerization.

The heats of formation of the *Z*- and *E*-isomers of **1–3** were calculated by the AM1 method. Data obtained from X-ray studies of (*Z*)-**2**, (*E*)-**3**, some 5-arylmethylenehydantoins[5,21–23] and related compounds[28] were used as input and the optimized geometries were then used in the calculations.

^1H and ^{13}C NMR spectra were recorded in $(CD_3)_2SO$ and, where solubility allowed, also in $CDCl_3$ solution with tetramethylsilane as internal reference using a Brucker ACF 300 MHz or Brucker AMX 500 MHz spectrometer.

Infrared spectra of all compounds in KBr discs were recorded on a Shimadzu IR-170 infrared spectrophotometer.

UV spectra were obtained in methanol solutions with a Hewlett-Packard 8452A diode-array spectrophotometer.

Mass spectra were obtained with a VG Micromass 7035E spectrometer.

HPLC was performed using a Shimadzu SPD-6AV instrument with a UV detector and a Whatman Partisphere C_{18} column with methanol– water(55 : 45) as the solvent system.

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