

A Spectrophotometric Study of the Tautomeric Monoanions of (Z)-5-Arylmethylenehydantoins

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First ionization of (Z)-5-arylmethylenehydantoins in aqueous dimethyl sulphoxide yields a tautomeric mixture of monoanions by deprotonation at N-1 or N-3. By using appropriate 3-methyl and 1-methyl derivatives as models, the equilibrium proportions of the monoanions of the *N*-unsubstituted compounds have been estimated from the electronic spectra. The percentage of the N-1 anion increases with electron-withdrawing substituents in the benzene ring and with increasing concentration of dimethyl sulphoxide in the solvent mixture.

Early studies have shown that deprotonation of hydantoin and its 5-alkyl derivatives occurred first at N-3¹ but the acidity of 1-H could be increased by introduction of an unsaturated side chain at C-5.² Recently, we have measured the p*K* values in 80% (w/w) dimethyl sulphoxide-water of three series of 5-arylmethylenehydantoins: the *N*-unsubstituted, the 3-methyl-substituted, and the 1-methyl-substituted compounds, each series with a range of *para*-substituents in the benzene ring.³ The p*K* values of the latter two series provide estimations of the relative acidities of the protons at the two nitrogen atoms. The results show that, in spite of the acidifying effect of the benzyldene side chain, 1-H in these compounds remains less acidic than 3-H in this solvent system. However, the aryl substituent understandably exerts greater influence at N-1, through direct conjugation, than at N-3 so that, with increasingly strong electron-withdrawing *para*-substituents, the acidities of the two ionizable protons become closer together. Under such circumstances, the first ionization of an *N*-unsubstituted 5-arylmethylenehydantoin is likely to yield, not just one anionic species, but a mixture of tautomeric monoanions. This situation is similar, to some extent, to that of the uracils the deprotonation of which to a tautomeric mixture of monoanions has been extensively investigated.⁴⁻¹⁰ This paper reports a spectrophotometric study of the tautomeric equilibria of the monoanions of 5-arylmethylenehydantoins in aqueous dimethyl sulphoxide and their dependence on substituent and solvent effects. All the compounds studied have the *Z*-configuration.

Results and Discussion

In the study of prototropic tautomerism, appropriate methyl derivatives are commonly used as models for the individual tautomers. First deprotonation of the (Z)-5-arylmethylenehydantoins (1)–(5) of structure A could theoretically give two possible monoanions A¹ and A³ (the superscripts denote the sites of ionization), which are not experimentally separable. However, the 3-methyl-substituted compounds (6)–(10), of structure B, and the 1-methyl-substituted compounds (11)–(15), of structure C, each with only one dissociable proton, should furnish anions B¹ and C³, by deprotonation at N-1 and N-3, as suitable models for A¹ and A³, respectively.

U.v-visible spectroscopy is applied as the two types of anions can be readily distinguished from the spectra taken in alkaline solutions. It is observed that, on ionization, the spectra of compounds (6)–(10) show large red shifts while those of compounds (11)–(15) show relatively smaller red shifts (Table 1). This indicates that the negative charge of anion B¹ is

much more extensively delocalized than that of anion C³. That ionization of each of compounds (1)–(5) gives a mixture of monoanions A¹ and A³ is suggested by the shape of the alkaline spectra which appear to be composite of those of B¹ and C³, with the band at longer wavelength corresponding to A¹ and that at shorter wavelength to A³.

The spectra of compounds (1)–(5) are recorded in aqueous dimethyl sulphoxide of various compositions, in neutral and in alkaline solutions with different concentrations of sodium hydroxide. The pH values of the solutions are monitored although the exact values cannot be accurately determined because of the slow response of the electrode in the basic regions particularly in solutions with high percentages of the organic solvent. For the *N*-methylated compounds (6)–(15), each with only one dissociable proton, addition of sodium hydroxide results in changes of spectra with distinct isosbestic points until ionization is complete, when further increase in sodium hydroxide concentration does not produce further spectral change. On the other hand, for each of the *N*-unsubstituted compounds (1)–(5), two stages of ionization are possible. Formation of the monoanion is first indicated by changes in the spectra with increasing pH with distinct isosbestic points similar to those observed for compounds (6)–(15) until pH *ca.* 12. Further additions of the base cause further shifts in the spectra which no longer pass through the same isosbestic points while the appearance of another isosbestic point suggests the beginning of the second stage of ionization.

The relative population of the tautomeric anions A¹ and A³ of each *N*-unsubstituted compound can be estimated from the absorbances at the appropriate bands which correspond closely to the absorption maxima of the model anions B¹ and C³ of the respective methylated compounds as shown in Table 1. Since the extinction coefficients of A¹ and A³ are not accessible experimentally, they have to be estimated by some method of approximation. One approach uses the relationships (1) and (2)⁴ where the ϵ values are taken at the respective λ_{\max} . This

$$\frac{\epsilon(A^1)}{\epsilon(A)} = \frac{\epsilon(B^1)}{\epsilon(B)} \quad (1)$$

$$\frac{\epsilon(A^3)}{\epsilon(A)} = \frac{\epsilon(C^3)}{\epsilon(C)} \quad (2)$$

method, which assumes that *N*-methylation has similar effects on the extinction coefficients of the neutral and anion species, is adopted in the present calculations.

The relative concentrations of A¹ and A³ may be calculated in

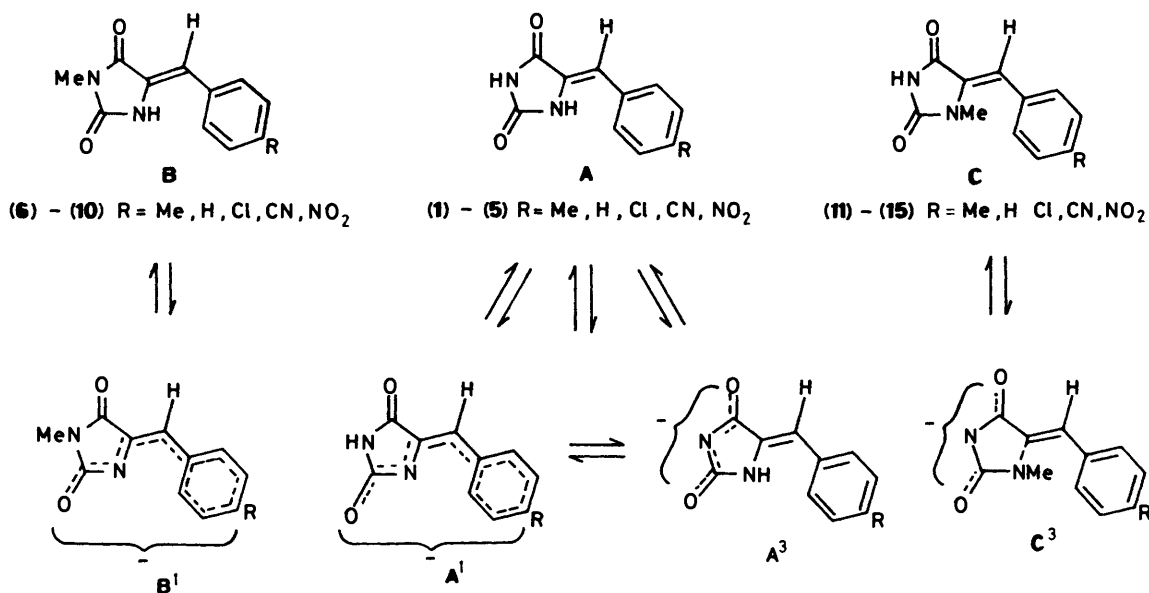


Table 1. U.v. absorptions of compounds (1)–(15) and their anions in Me₂SO–H₂O.

Compound	λ_{\max} nm								
	50% Me ₂ SO–H ₂ O			80% Me ₂ SO–H ₂ O			95% Me ₂ SO–H ₂ O		
	neutral	N-3 anion	N-1 anion	neutral	N-3 anion	N-1 anion	neutral	N-3 anion	N-1 anion
(1)	327	330	364	326	330	370	326	330	380
(6)	326		364	325		370	325		380
(11)	320	326		315	326		318	328	
(2)	321	326	363	321	327	374	321	329	382
(7)	322		363	321		374	321		382
(12)	315	326		314	326		314	329	
(3)	326	331	368	325	332	378	325	335	388
(8)	325		368	325		378	325		388
(13)	318	328		314	330		315	330	
(4)	331	343	391	333	353	408	333	368	418
(9)	331		391	332		408	333		418
(14)	326	345		326	355		330	358	
(5)	355	378	433	364	401	465	365	409	492
(10)	353		433	364		465	363		490
(15)	345	375		358	395		356	409	

Table 2. Equilibrium percentages of N-1 anions A¹ and equilibrium ratios $K_T = \%A^1/(100 - \%A^1)$ in various Me₂SO–H₂O mixtures.

Compound	50% Me ₂ SO		80% Me ₂ SO		95% Me ₂ SO	
	%A ¹	K_T	%A ¹	K_T	%A ¹	K_T
(1)	5	0.05	7	0.08	21	0.27
(2)	5	0.05	9	0.10	24	0.32
(3)	8	0.09	17	0.20	34	0.54
(4)	14	0.16	29	0.41	46	0.72
(5)	22	0.28	40	0.67	70	2.45

two ways. The percentage of A¹ may be obtained from the measured absorbance of the band at the longer wavelength in the alkaline spectrum of each N-unsubstituted compound and the corresponding estimated $\epsilon(A^1)$. Then $\%A^3 = 100 - \%A^1$. Alternatively, the percentage of A³ can be calculated from the measured absorbance of the band at the shorter wavelength in the same spectrum and the estimated $\epsilon(A^3)$ and this leads to A¹. Examination of the spectrum reveals that the maximum of the

A³ absorption band overlaps the tail-end of the absorption band of A¹ and therefore appropriate wing correction is required to deduce more accurately the absorbance due to A³. On the other hand, the maximum of the A¹ band either does not overlap or overlaps only to a negligible extent the tail-end of the A³ band so that no wing correction is necessary in this case. As wing correction is possibly an additional source of error,⁴ the values calculated from absorbances of the A¹ anions are preferred (Table 2).

Substituent Effects.—The pK values of compounds (1)–(14) were previously measured in 80%(w/w) dimethyl sulphoxide–water.³ The pK of the remaining compound (15) has now been similarly determined and found to be 9.13. In this solvent mixture, the 1-methyl-substituted compounds (11)–(15) are more acidic than the corresponding 3-methyl-substituted compounds (6)–(10) but the difference ΔpK between each pair of compounds, with the same *para* substituent R in the benzene ring, decreases from 0.98 for R = CH₃ to 0.02 for R = NO₂ (Table 3). From this observation, one may anticipate that, in the

Table 3. Effect of substituent R on the difference in pK between the 3-methyl- and the corresponding 1-methyl-5-arylmethylenehydantoin measured in 80%(w/w) dimethyl-sulphoxide-water.

R	ΔpK^a
CH ₃	0.98
H	0.87
Cl	0.55
CN	0.11
NO ₂	0.02

^a pK Values of compounds (6)–(14) in 80% dimethyl sulphoxide-water are taken from ref. 3.

Table 4. Correlation between percentage of N-1 anions of compounds (1)–(5) formed in Me₂SO–H₂O with Hammett constants σ^- .

%Me ₂ SO	Correlation coefficient (γ)	Slope (ρ)	Intercept (γ)	Standard deviation
50	0.977	11.81	5.65	1.78
80	0.995	23.12	10.32	1.65
95	0.973	32.22	24.95	5.33

<i>para</i> -substituent	Me	Cl	CN	NO ₂
σ^-	-0.17	0.23	0.88	1.24

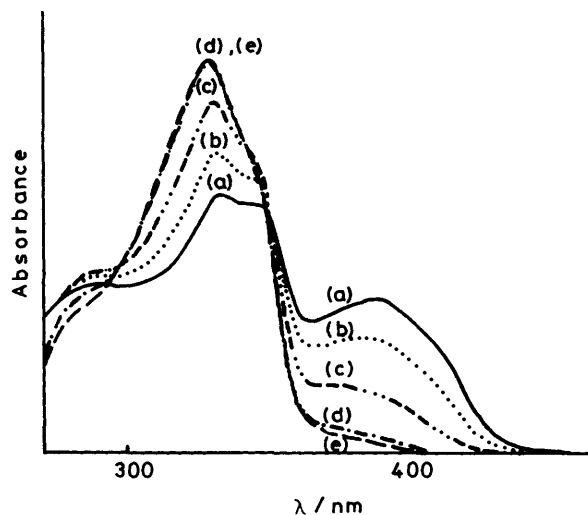


Figure. Electronic spectra of compound (3) 3.8×10^{-3} mol dm⁻³ in 3×10^{-4} mol dm⁻³ NaOH in various Me₂SO–H₂O solvents: (a) 95% DMSO, (b) 90% DMSO, (c) 80% DMSO, (d) 50% DMSO, (e) 35% DMSO.

case of the *N*-unsubstituted compounds (1)–(5), the equilibrium populations of A³ would be higher than A¹ but the differences between them should decrease as the substituent R becomes more strongly electron withdrawing. This expectation is borne out by the experimentally found percentages in this solvent mixture. As N-1 is directly conjugated with the *para* substituent via the benzylidene group, the percentage population of A¹ anion shows good linear correlation with the Hammett σ^- constants.⁵ Similar correlations are found for data obtained in 50% and 95% dimethyl sulphoxide-water (Table 4). The ρ value is higher for the line derived from measurements in the solvent richer in dimethyl sulphoxide, which has larger effect on N-1 than on N-3 anions as explained below.

Solvent Effects.—The tautomeric equilibria between the monoanions of uracils have previously been studied in water,

aqueous dioxane, and dimethyl sulphoxide and changes in the equilibrium ratio of these monoanions have been attributed to differences in the dielectric constants of these solvents.^{6–11} However, this ratio has also been reported to be influenced by the nature and concentration of the buffer used to attain the alkaline pH.

In the present investigation of the tautomeric monoanions of the 5-arylmethylenehydantoin (1)–(5), dimethyl sulphoxide-water mixtures of various compositions have been used as solvent. Because of the low solubilities of these compounds, water alone is not used. Solvent composition is found to have a very marked influence on the equilibrium populations of the tautomeric monoanions in each case. The Figure illustrates this clearly for compound (3). The relative intensities of the two absorption bands in the alkaline spectra ascribable to anions A¹ and A³ change dramatically as the proportion of dimethyl sulphoxide varies from 35 to 95%. These spectra pass through isosbestic points, consistent with shifts in the equilibrium between the two anionic species. Increase in the proportion of dimethyl sulphoxide is accompanied by sharply increased concentration of A¹ (Table 2) at the expense of that of A³.

Difference in the interactions of the two monoanions with the different components of the mixed solvent probably plays an important role in determining the equilibrium position. It is well known that water solvates both cations and anions mainly by electrostatic interactions. It strongly solvates anions, particularly those with concentrated charges at electronegative atoms, through hydrogen bonds. By contrast, aprotic dimethyl sulphoxide cannot form hydrogen bonds with anions. It generally solvates cations better than anions, with the exception that, being a larger and more polarizable molecule than water, it can interact more favourably with delocalized anions through dispersion effects.^{12,13}

This type of dispersion interaction has been shown to be specially important between delocalized hydrocarbon anions and polar aprotic solvents, notably dimethyl sulphoxide.^{14,15} For acid dissociation in dimethyl sulphoxide-water, dispersion effects of the organic solvent molecules may conceivably oppose the preferential solvation by electrostatic and/or hydrogen-bond effects of the water molecules, depending on the charge character of the anion formed. The situation of the singly deprotonated 5-arylmethylenehydantoin (1)–(5) provides an interesting example of the interplay of these factors. The tautomeric monoanions A¹ and A³ differ to some extent in their charge characters. In A³, the negative charge resides mainly at the 3-nitrogen and the two adjacent carbonyl oxygen atoms. These electronegative atoms are particularly prone to form hydrogen-bonds with water molecules but would have little interaction with the dimethyl sulphoxide molecules. On the other hand, the negative charge in A¹ is more dispersed. There is only one adjacent carbonyl oxygen, so that the extent of hydrogen bonding these N-1 anions have with water is less than that possible for the N-3 anions. Moreover, the charge density in A¹ is also reduced because of extensive delocalisation into the benzylidene group, which does not hydrogen-bond with water. Hence, these highly delocalized A¹ anions should interact more favourably with the polarizable dimethyl sulphoxide molecules whereas the A³ anions are preferably stabilized by water molecules. Although solvation of either anion cannot be exclusively by one component only of a solvent mixture, it is possible that the dominant solvent interaction is different for the two monoanions. Hence, it is not surprising that the tautomeric equilibrium between A¹ and A³ should shift as the composition of these solvent mixtures changes.

It is further noted that (Table 1) the absorption maxima of all the N-1-anions, A¹ of compounds (1)–(5) and B¹ of compounds (6)–(10) show significant red shifts as the percentage of dimethyl sulphoxide increases. The extent of this

red shift is more pronounced when the aryl substituent is more electron withdrawing. Both observations reflect the enhanced stabilization of these extensively delocalized anions by the aprotic polar solvent molecules. The absorption maxima of the N³-anions, A³ of compounds (1)–(5) and C³ of compounds (11)–(15), show smaller red shifts with these variations of solvent compositions.

Experimental

Compounds (1)–(14) were prepared according to literature methods.¹⁶

Preparation of (Z)-1-Methyl-5-(4-nitrophenyl)methylenehydantoin (15).—1-Methylhydantoin (2.5 g) and *p*-nitrobenzaldehyde (3.7 g) were mixed with fused sodium acetate (3.7 g) and glacial acetic acid (2.5 cm³) and the mixture was refluxed for 90 min at 135–140 °C on an oil-bath. Ice-water was added with stirring to the cooled mixture and the orange solid formed was collected. This crude mixture of *E*- and *Z*-isomers were separated by repeated recrystallisation from ethanol, the major *E*-isomer being less soluble. The purity of the samples was checked by elemental analysis and by h.p.l.c., m.p. 226 °C (Found: C, 53.4; H, 3.7; N, 17.0, Calc. for C₁₁H₉N₃O₄: C, 53.4; H, 3.6; N, 17.0%).

Spectrophotometric Measurements.—Electronic spectra were recorded with a Shimadzu spectrometer model UV-260 using matched 1.0 cm silica cells. Solutions of compounds (1)–(15) of concentrations ranging from 3 × 10⁻⁵ to 6 × 10⁻⁵ mol dm⁻³ were prepared by dissolving weighed samples of each compound in spectroscopic grade dimethyl sulphoxide and adding distilled water or standardized aqueous NaOH until the mixture had the required dimethyl sulphoxide and water percentages by weight. The weights of the dissolved compounds were neglected in the

calculation of the solvent composition. The pH of the solutions were monitored using Chemtrix 40E pH meter.

The p*K* of the new compound (15) was determined in 80%(w/w) dimethyl sulphoxide-water using *p*-cyanophenol buffers by the spectrophotometric method.¹⁷

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