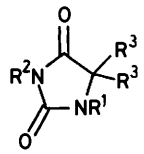
Ionization Constants of 5-Arylmethylenehydantoins in 80% (w/w) Dimethyl Sulphoxide–Water at 25 °C

Sau-Fun Tan, Kok-Peng Ang, Yoke-Fan Fong, and Harilakshmi Jayachandran
Department of Chemistry, National University of Singapore, Kent Ridge, Singapore 0511

The pK values of (*Z*)-5-arylmethylenehydrantoins, (*Z*)-5-arylmethylene-3-methylhydantoins, and (*Z*)- and (*E*)-5-arylmethylene-1-methylhydantoins with various *para*-substituents in the phenyl ring have been measured. The effects of structure and stereochemistry on acidity are discussed. For each series, a good linear correlation is obtained between the pK values and Hammett constants σ and σ^- in spite of the considerable distance of the site of deprotonation from the phenyl ring. The ρ values show that substituent effects are significantly greater on the acidity of N(1)–H than on that of N(3)–H, and are also greater for the *E*- than the *Z*-isomers of the 5-arylmethylene-1-methylhydantoins.

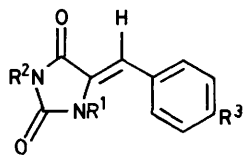
Hydantoin is a weak acid with pK 9.12 [1] in aqueous solution. Its 5,5-dimethyl and 5-benzyl derivatives have pK values comparable to that of the parent compound but the 5-benzyl-3-methyl derivative is too weakly acidic for its pK to be measurable in water. These observations show that deprotonation of hydantoin occurs at the N-3 rather than N-1 or C-5 positions. However, introduction of an unsaturated benzylidene side-chain at C-5 increases the acidity of the N-1 hydrogen, making the pK of 5-benzylidene-3-methylhydantoin measurable.[2]

Although the pK values of 5-benzylidenehydantoins with various substituents in the phenyl ring have been measured,[3,4] no study has been made of the substituent effects on the acidities of the corresponding 3- or 1-methyl-substituted compounds. It may reasonably be expected that such effects would be stronger on the ionization of the N-1 than that of the N-3 hydrogen which is more remote. Both the configurations of these compounds and the effect of stereochemistry on their acidities have not been investigated. Further, the pK values of some of them were previously obtained in several different solvents including water, aqueous ethanol, and aqueous dioxane. In view of these, we have extended the acidity study to three series of compounds: the (*Z*)-5-arylmethylene-3-methylhydantoins, and the (*Z*)- and the (*E*)-5-arylmethylene-1-methylhydantoins, each with a range of substituents in the phenyl ring. Owing to their low solubilities in water, pK determinations have been made in 80% (w/w) dimethyl sulphoxide–water. As this solvent differs from those previously used, we have, for better comparison, redetermined the pK values of hydantoin, its 5,5-dimethyl, 1-methyl, and 3-methyl derivatives as well as the series of *N*-unsubstituted 5-arylmethylenehydantoins in this same solvent.



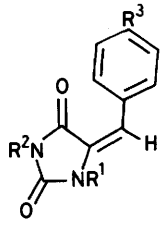
(1) - (4)

(1) $R^1 = R^2 = R^3 = H$
(2) $R^1 = R^2 = H$, $R^3 = Me$
(3) $R^1 = Me$, $R^2 = R^3 = H$
(4) $R^1 = R^3 = H$, $R^2 = Me$



(5)-*Z* - (21)-*Z*

(5)–*Z* $R^1 = R^2 = H$, $R^3 = OMe$
(6)–*Z* $R^1 = R^2 = H$, $R^3 = Me$
(7)–*Z* $R^1 = R^2 = R^3 = H$
(8)–*Z* $R^1 = R^2 = H$, $R^3 = Cl$
(9)–*Z* $R^1 = R^2 = H$, $R^3 = CN$
(10)–*Z* $R^1 = R^2 = H$, $R^3 = NO_2$
(11)–*Z* $R^1 = H$, $R^2 = Me$, $R^3 = OMe$
(12)–*Z* $R^1 = H$, $R^2 = R^3 = Me$
(13)–*Z* $R^1 = R^3 = H$, $R^2 = Me$
(14)–*Z* $R^1 = H$, $R^2 = Me$, $R^3 = Cl$
(15)–*Z* $R^1 = H$, $R^2 = Me$, $R^3 = CN$
(16)–*Z* $R^1 = H$, $R^2 = Me$, $R^3 = NO_2$
(17)–*Z* $R^1 = Me$, $R^2 = H$, $R^3 = OMe$
(18)–*E* $R^1 = R^3 = Me$, $R^2 = H$
(19)–*E* $R^1 = Me$, $R^2 = R^3 = H$
(20)–*Z* $R^1 = Me$, $R^2 = H$, $R^3 = Cl$
(21)–*Z* $R^1 = Me$, $R^2 = H$, $R^3 = CN$



(17) - *E* - (22) - *E*

(17)–*E* $R^1 = Me$, $R^2 = H$, $R^3 = OMe$
(18)–*E* $R^1 = R^3 = Me$, $R^2 = H$
(19)–*E* $R^1 = Me$, $R^2 = R^3 = H$
(20)–*E* $R^1 = Me$, $R^2 = H$, $R^3 = Cl$
(21)–*E* $R^1 = Me$, $R^2 = H$, $R^3 = CN$
(22)–*E* $R^1 = Me$, $R^2 = H$, $R^3 = NO_2$

Results and Discussion

The ionization constants of compounds (**1**)—(**22**), determined by spectrophotometric methods in 80% (w/w) dimethyl sulphoxide–water solvent at 25 °C, are reported in Table 1.

The very close pK values of hydantoin and its 5,5-dimethyl (**2**) and 1-methyl (**3**) derivatives confirm that deprotonation of all three compounds occurs at the common N-3 position. The N-3 anion from each of compounds (**1**)—(**3**) is resonance-stabilized with the negative charge delocalized into two adjacent carbonyl groups. Absence of the N-3 proton makes 3-methylhydantoin (**4**) much more weakly acidic since the anion, which could theoretically be formed by abstraction of the N-1 proton, cannot be stablized to the same extent by only one adjacent carbonyl group. Instead, the added base probably reacts at the 4-carbonyl causing hydrolytic ring opening [5,6] as suggested by changes with time in the u.v. spectrum of compound (**4**) in alkaline solution which does not revert to its neutral–acidic spectrum on acidification. Therefore, an approximate value for its pK can only be estimated by extrapolation.

All the compounds in the series of *N*-unsubstituted 5-arylmethylenehydantoins (**5**)—(**10**) and the series of 5-arylmethylene-3-methylhydrantoins (**11**)—(**16**) have been shown to have the *Z*-configuration but compounds in the series of 5-arylmethylene-1-methylhydantoins (**17**)—(**21**) have been obtained in both *Z*- and *E*-forms.[7] Only the *E*-form of compound (**22**) has been isolated. These are all stronger acids than hydantoin, undoubtedly due to the additional stabilization of their anions by the unsaturated arylmethylene side-chain.

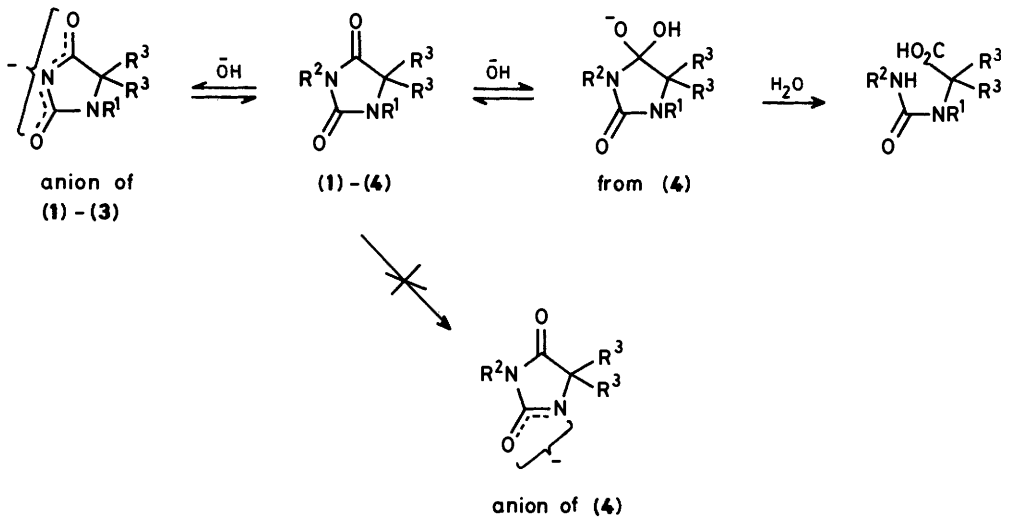


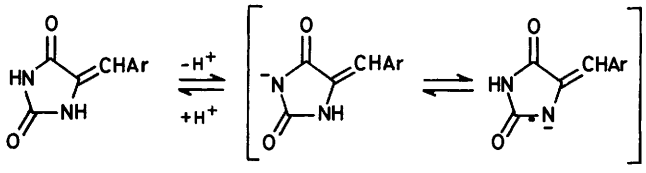
Table 1. pK in 80% (w/w) dimethyl sulphoxide–water solvent at 25 °C

Compound	pK	Compound	pK
(1)	11.25	(15)-*Z*	9.28
(2)	11.10	(16)-*Z*	9.15
(3)	11.20	(17)-*Z*	9.75
(4)	> 13.5*	(18)-*Z*	9.72
(5)-*Z*	10.22	(19)-*Z*	9.62
(6)-*Z*	10.13	(20)-*Z*	9.53
(7)-*Z*	9.97	(21)-*Z*	9.17
(8)-*Z*	9.76	(17)-*E*	10.40
(9)-*Z*	9.22	(18)-*E*	10.30
(10)-*Z*	9.01	(19)-*E*	10.15
(11)-*Z*	10.78	(20)-*E*	9.96
(12)-*Z*	10.70	(21)-*E*	9.49
(13)-*Z*	10.49	(22)-*E*	9.44
(14)-*Z*	10.08		

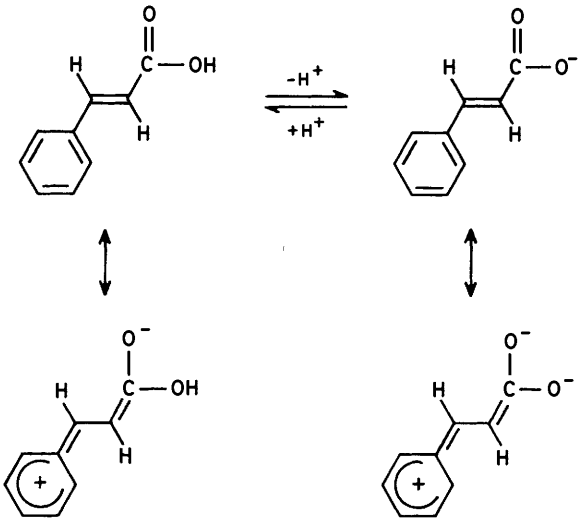
* Approximate.

A few interesting observations may be made from these results. First, the 1-methyl-substituted compounds are more acidic than the 3-methyl-substituted analogues. This shows that, in spite of the greater acidifying influence of the unsaturated side-chain on the N-1 proton, its tendency to ionize remains lower than that of the N-3 proton.

Secondly, the *N*-unsubstituted compounds have pK values intermediate between but not average of those of the corresponding 1- and 3-methyl derivatives. This suggests the possibility that when both N-1 and N-3 hydrogens are present, first deprotonation could, at least theoretically, occur from either site. When the difference between the acidities of the two protons is not too great, the first deprotonation may produce a pair of tautomeric monoanions.



Thirdly, the effects of configuration on acidity is revealed by comparison of the pK values of the *Z*- and *E*-isomers of the 5-arylmethylene-1-methylhydantoins. Of each pair, the *Z*-isomer is more acidic than the *E*-isomer. Similar differences in acidity between geometrically isomeric acids have been observed. For instance, *trans*-cinnamic acid is weaker than its *cis*-isomer [8] because for the *trans*-acid, resonance stabilization of the undissociated molecule is more important than of its anion where two negative charges accumulate in close proximity resulting in some acid-weakening effect.



For the *cis*-acid, steric crowding between the phenyl and carboxy group inhibits resonance, hence lessening this effect. A rather similar situation exists with the 5-arylmethylene-1-methylhydantoins. It has been demonstrated that there is effectively more extended conjugation in the *E*-isomers where the aryl and hydantoin rings are nearly coplanar while steric crowding between the aryl and the 1-methyl groups in the *Z*-isomers favours a twisted conformation.[7] Therefore, similar resonance effects may have stabilized the neutral molecule with respect to the anion, thus leading to the lower acidity of the *E*-isomers. In addition, it should be noted that, while the anionic group and the benzene ring are '*trans*' to each other in the anion of the *Z*-isomer, they are '*cis*' in the anion of the *E*-isomer. The proximity of these two groups of high electron-density possibly destabilizes the anion and lowers the acidity of the *E*-isomer.

Lastly, the pK values of all four series of compounds show excellent linear correlations with Hammett's substituent constants σ or σ^- (Table 2).[9] That such good correlations are observable at reaction sites so far from the substituent is significant. While conjugation of N-1 with the benzylidene side-

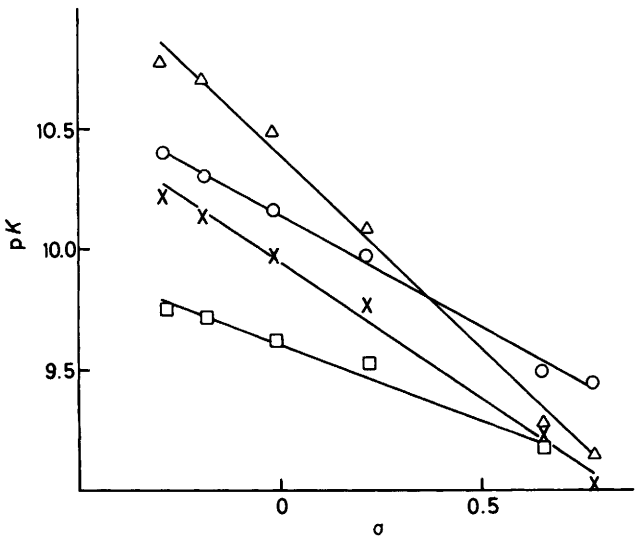


Figure 1. Plot of pK values against σ values: ×, (**5**)-*Z*—(**10**)-*Z*; △, (**11**)-*Z*—(**16**)-*Z*; □, (**17**)-*Z*—(**21**)-*Z*; ○, (**17**)-*E*—(**21**)-*E*

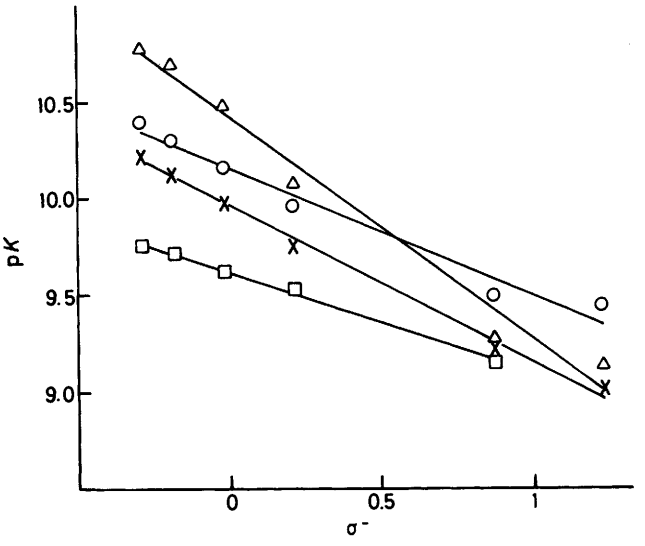
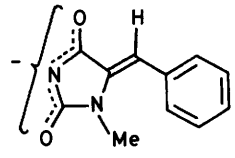


Figure 2. Plot of pK values against σ$^-$ values: ×, (**5**)-*Z*—(**10**)-*Z*; △, (**11**)-*Z*—(**16**)-*Z*; □, (**17**)-*Z*—(**21**)-*Z*; ○, (**17**)-*E*—(**22**)-*E*

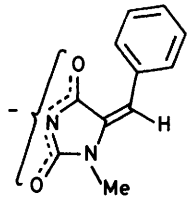
Table 2. Correlations between pK values with Hammett substitution constants

	σ			σ$^-$		
Compounds	γ	ρ	S.d.	γ	ρ	S.d.
(**5**)-*Z*—(**10**)-*Z*	0.996	−1.143	0.0491	0.998	−0.817	0.0381
(**11**)-*Z*—(**16**)-*Z*	0.996	−1.636	0.0630	0.989	−1.159	0.1160
(**17**)-*Z*—(**21**)-*Z*	0.989	−0.620	0.0406	0.999	−0.507	0.0131
(**17**)-*E*—(**22**)-*E*	0.998	−0.935	0.0274	0.986	−0.659	0.0774

γ = Correlation coefficient; ρ = slope; S.d. = standard deviation.

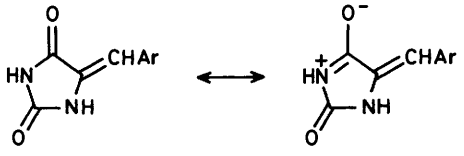


Z - isomer
'*trans*' anionic and phenyl groups



E - isomer
"*cis*' anionic and phenyl groups

chain is obvious, that of N-3 is less evident and the observed correlation suggests contribution from some dipolar structures in which N-3 is conjugated with the benzylidene side-chain.



For the 1-methyl-substituted compounds (**17**)—(**21**), this conjugation effect at N-3 is more important in the *E*-isomers where the benzene and hydantoin rings can be coplanar than in the *Z*-isomers where coplanarity is not achievable due to steric interference by the 1-methyl group. This is reflected in the slightly greater ρ value for the *E*- than the *Z*-correlation line. In the *Z*-isomers of the 3-methyl-substituted compounds (**11**)—(**16**), the absence of similar steric effect permits molecular planarity and therefore stronger resonance interactions. This together with the expected larger substituent effects on the acidity of N(1)–H than that of N(3)–H accounts for the significantly larger ρ value for the correlation line of these compounds. The correlation line for the *Z*-isomers of the *N*-unsubstituted compounds (**5**)—(**10**) has intermediate ρ values as substituent effects at N-1 and N-3 positions are involved. It is interesting to observe that the lines representing the three series of *Z*-isomers appear to converge, suggesting that, with strongly electron-withdrawing substituents present, the acidities of N(1)–H and N(3)–H approach each other.

Experimental

Materials.—Hydantoin and its 5,5-dimethyl and 1-methyl derivatives were obtained commercially. The 3-methyl derivative was prepared by methylation of hydantoin with dimethyl sulphate.[10,11] The preparations of 5-arylmethylenehydantoins (**5**)—(**14**) and (**17**)—(**20**) were previously reported.[7] Compounds (**15**), (**16**), and (**21**) have been prepared by similar methods. Preparation of compound (**22**) yielded the *E*-isomer in low yield and the *Z*-isomer was not isolated. The purity of all compounds used for pK measurement was checked by n.m.r. spectra, h.p.l.c., and microanalysis.

Spectrophotometric grade dimethyl sulphoxide and triply distilled water were used for preparing the solvent mixture, and carbonate-free sodium hydroxide solution for the buffer solutions. Indicators with suitable known ionization constants in 80% (w/w) dimethyl sulphoxide–water solvent[12,13] were used: Bromothymol Blue, Cresol Red, and 2,4-dinitrodiphenylamine. These were purified according to conventional methods.

Measurements.—Ionization constants were determined spectrophotometrically, using either the buffer method or indicator method.[14] Measurements were made in triplicate with a Shimadzu uv-260 u.v.–visible recording spectrophotometer

with cell compartment thermostatted at 25 ± 0.2 °C. The stability of each compound was checked by recording its u.v. spectra at regular intervals over a period of time as required for measurements. For compound (**4**) which was unstable in alkaline solution, the absorbance at a fixed wavelength at the time of mixing the solutions was found by extrapolation. Its estimated p*K* value was included for the purpose of comparison.

Acknowledgements

The awards of a research grant to K. P. A. and S. F. T. and a research scholarship to Y. F. F. by the National University of Singapore are gratefully acknowledged.

References

1 M. Zief and J. T. Edsall, *J. Am. Chem. Soc.*, 1937, **59**, 2245.
2 L. W. Pickett and M. McLean, *J. Am. Chem. Soc.*, 1939, **61**, 423.
3 B. A. Ivin, G. V. Rutkovskii, V. A. Kirillova, and E. G. Sochilin, *Reackts. Sposobnost. Org. Soedin.*, 1969, **6**, 1055 (*Chem. Abstr.*, 1970, **73**, 13,947w).
4 G. V. Rutkovskii, B. A. Ivin, V. A. Kirillova, N. A. Smorygo, and E. G. Sochilin, *Zh. Obshch. Khim.*, 1970, **40**, 1583 (*Chem. Abstr.*, 1971, **74**, 69,783c).
5 G. Billek, *Monatsh. Chem.*, 1961, **92**, 343.
6 I. B. Blagoeva, I. G. Pojarlieff, and V. S. Dimitrov, *J. Chem. Soc., Perkin Trans. 2*, 1978, 887.
7 S. F. Tan, K. P. Ang, and Y. F. Fong, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1941.
8 E. L. Eliel, 'Stereochemistry of Carbon Compounds,' McGraw-Hill, New York, 1962, pp. 328—329.
9 J. Shorter, 'Correlation Analysis in Organic Chemistry: an Introduction to Linear Free-energy Relationships,' Oxford University Press, London, 1973.
10 R. E. Stuckey, *J. Chem. Soc.*, 1947, 331.
11 H. Blitz and K. Slotta, *J. Prakt. Chem.*, 1926, **113**, 240.
12 E. H. Baughman and M. M. Kreevoy, *J. Phys. Chem.*, 1974, **78**, 421.
13 M. Georgieva, P. Zikolov, and O. Budevsky, *Anal. Chim. Acta*, 1977, **90**, 83; 1978, **101**, 139; 1980, **115**, 411.
14 S. F. Tan, K. P. Ang, and H. Jayachandran, *J. Chem. Soc., Perkin Trans. 2*, 1983, 1011.

Received 26*th February* 1987; *Paper* 7/364