

Retention Indices and Basicity of N^1N^1 -Dimethyl- N^2 -phenylformamidines. *ortho*-Substituent Effect

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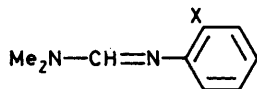
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A series of *ortho*-substituted N^1N^1 -dimethyl- N^2 -phenylformamidines (*o*-FDMP) have been synthesized and their structure determined by i.r. and ^1H n.m.r. methods. All, except the hydroxy derivative, have the same structure (*E*). In the case of the hydroxy derivative an intramolecular hydrogen bond appears, and thus two structures *Z* (20%) and *E* (80%) are observed in the ^1H n.m.r. spectrum in CDCl_3 . The influence of the *ortho*-substituent on the retention indices, determined on a non-polar column, and on the $\text{p}K_a$ values, measured in 95.6% ethanol (azeotrope) and in water is discussed, and compared with those observed for *meta*- and *para*-derivatives. The retention indices of the *ortho*-derivatives, except the hydroxy derivative, obey the same linear correlation as *meta*-, *para*-, and other alkyl and aralkyl derivatives. A deviation of the $\text{p}K_a$ values of the *ortho*-derivatives from the linear correlations found for the *meta*- and *para*-derivatives are explained by steric effects of the substituent and medium effects.

This paper reports the influence of *ortho*-substituents on the physicochemical properties of N^1N^1 -dimethyl- N^2 -phenylformamidines (*o*-FDMP). Investigations were carried out for compounds (1)–(6). Their retention indices on a non-polar column have been determined and their $\text{p}K_a$ values in 95.6% ethanol and in water measured. The data have been compared with those observed for *meta*- and *para*-derivatives.



- | | | |
|-------------------------|------------|-------------|
| (1) X = NO ₂ | (3) X = Cl | (5) X = OMe |
| (2) X = Br | (4) X = Me | (6) X = OH |

Experimental

Materials.—The *ortho*-substituted N^1N^1 -dimethyl- N^2 -phenylformamidines (1)–(6) were synthesized according to the procedure described in ref. 1 from dimethylformamide dimethyl acetal and the corresponding primary amines. The amidines, except the hydroxy derivative, which was recrystallized from CCl_4 , were distilled under reduced pressure. Yields were over 90%. Physical constants were consistent with those reported in the literature. Purity (>99%) was checked by g.l.c. Structures were confirmed by i.r. spectra (Specord) recorded for CCl_4 solutions at room temperature and ^1H n.m.r. spectra (JEOL) recorded at 100 MHz for CDCl_3 solutions at room temperature.

Gas Chromatography.—The g.l.c. measurements were performed on a Czech Chromatograph Chrom 5 equipped with a stainless steel column (2 × 3 mm i.d.), and a flame ionization detector. Analyses were made at 240 °C for formamidines and at 180 °C for the corresponding primary amines. The carrier gas was helium at a flow rate of 20 ml min⁻¹. A column of GE SE-30 silicone gum rubber on Chromosorb W AW (60–80 mesh) was used. The real coverage of the support of 13% was checked using a 1090 B Thermal Analyser equipped with a 951 Thermogravimetric Module (DuPont). Thermogravimetric analysis was carried out at 200–800 °C with a heating rate of 10 °C min⁻¹. For calculations the 'TGA analysis V2.0' program was used.

$\text{p}K_a$ Measurements.—The $\text{p}K_a$ values of *o*-FDMP were determined by a potentiometric method in 95.6% ethanol (azeotrope) and in water at 25 °C using an apparatus and method similar to that described. The $\text{p}K_a$ values of N^1N^1 -dimethyl- N^2 -phenylformamide measured in ethanol¹ and in water² were taken as standards.

Results and Discussion

Structure of Formamidines.—The physicochemical properties of amidines depend on their structure and configuration. Therefore the determination of their constitution and stereochemistry is important. For solving structural problems for *ortho*-substituted N^1N^1 -dimethyl- N^2 -phenylformamidines ^1H n.m.r. and i.r. methods have been used.

It is well known that in the case of amidines, rotation around the C–N single bond is hindered by conjugation between the C=N double bond and the lone electron pair on the amino nitrogen. Two conformations are thus possible, one with an antiperiplanar and the other with a synperiplanar substituent to the imino nitrogen atom. Moreover, because of the C=N double bond, amidines can exist in the *E* or *Z* configuration.

For *o*-FDMP restricted rotation around the C–N single bond is not observed at room temperature in CDCl_3 as solvent, and the NMe_2 group gives one signal as observed for *meta*- and *para*-derivatives.^{1,3,4} The identical, except for the *o*-hydroxy derivative (6), chemical shifts of protons in the NMe_2 group [$\delta(\text{NMe}_2)$ 3.0 ± 0.1 for *ortho*-, *meta*-, and *para*-derivatives] indicates that the configuration at the C=N double bond of all the amidines studied is the same. Comparison of the n.m.r. data obtained here with those in the literature⁵ indicates that formamidines studied exist in the *E* form in CDCl_3 at room temperature.

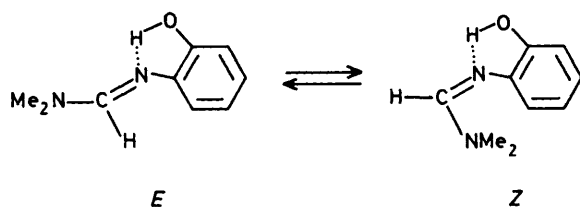
I.r. and ^1H n.m.r. studies suggest that in the case of the *o*-hydroxy compound (6) the hydrogen atom of the hydroxy group is completely associated with the imino nitrogen atom, and the *E*–*Z* isomerization appears at room temperature. For the hydroxy group in i.r. spectra only one, associated $\nu(\text{OH})$ band (3425 cm⁻¹ in CCl_4 as solvent) has been observed. Moreover association does not shift the $\nu(\text{C}=\text{N})$ band (1640 ± 1 cm⁻¹ for *ortho*-, *meta*-, and *para*-derivatives). The ^1H n.m.r. spectra in CDCl_3 show two different signals for the protons at the functional carbon atom [$\delta(\text{CH})$ 7.71 for *E*, and

Table 1. Retention indices on a GE SE-30 column for *ortho*-substituted N^1N^1 -dimethyl- N^2 -phenylformamidines (*o*-FDMP) and corresponding anilines (PA)

X	<i>o</i> -FDMP	PA
NO ₂	1 784 ± 6	1 402 ± 10
Br	1 657 ± 4	1 229 ± 2
Cl	1 574 ± 9	1 144 ± 2
Me	1 470 ± 4	1 083 ± 1
OMe	1 557 ± 3	1 181 ± 1
OH	1 078 ± 8	1 251 ± 2
H	1 402 ± 5 ^a	983 ± 3 ^b

^a Ref. 10 gives 1 585 ± 7. ^b Ref. 10 gives 995 ± 0.

8.24 for *Z* form], and for the NMe₂ group [$\delta(\text{NMe}_2)$ 3.02 for *E*, and 2.48 for *Z* form]. The effect of the aryl group at the imino nitrogen atom on $\delta(\text{CH})$ in the *E* configuration, and $\delta(\text{NMe}_2)$ in the *Z* configuration, is the same. In both cases the aryl group causes an upfield shift of the corresponding signal (0.5 p.p.m.).



It seems possible that the intramolecular hydrogen-bond formation observed for the *o*-hydroxy derivative (6) lowers the barrier for rotation around the C=N bond, and thus the equilibrium between the *E* and *Z* isomers can be observed. From the n.m.r. spectra it was found that the *E* isomer predominates (80%). Experimental evidence for the existence of the *Z* form of amidines has been found in only a few cases;⁵⁻⁷ the *Z*-isomers, which are thermodynamically unstable, completely isomerized to *E* isomers above room temperature, or in the presence of acid. The *o*-hydroxyformamidinium (6) is the first amidine found to exist in both *E* and *Z* forms at room temperature.

Retention Indices of Formamidines.—Of the many possible retention parameters used in g.l.c. Kováts indices^{8,9} are the most suitable for investigation of structure-retention relations. The retention indices calculated for *o*-FDMP and the corresponding anilines are given in Table 1. Their values have been compared with those obtained for *meta* and *para* derivatives.¹⁰ The comparison indicates that the retention indices depend to a considerable degree on the position of the substituent in the phenyl ring. Moreover the retention index of the *o*-hydroxy derivative (6) is considerably lowered by intermolecular hydrogen-bond formation.

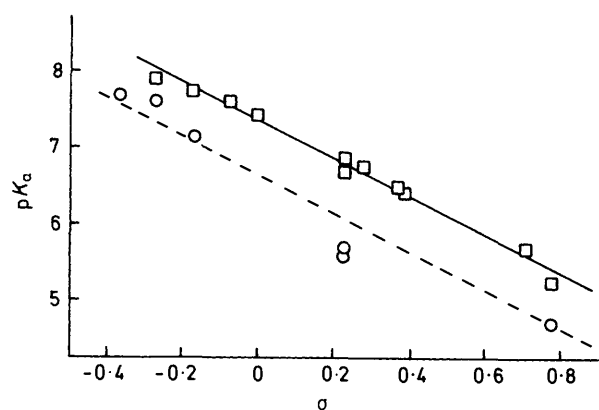
For studies of structure-retention relationships the methods of correlation analysis can be applied. Our results show that the retention indices of all N^1N^1 -dimethylformamidines (FDM) containing an *ortho*-, *meta*-, and *para*-substituted phenyl ring, as well as alkyl and aralkyl groups, can be correlated with those of the corresponding primary amines (PA) according to equation (1). For calculation of the parameters of equation (1) the data

$$I(\text{FDM}) = 283 + (1.10 \pm 0.03) I(\text{PA}) \quad (r \ 0.998, n \ 31) \quad (1)$$

obtained here, except for the *o*-hydroxy-derivative (6) (Table 1), and given in ref. 10 have been taken into account. The correlation found is of very good quality, and of good predictive

Table 2. pK_a Values of *ortho*-substituted N^1N^1 -dimethyl- N^2 -phenylformamidines (*o*-FDMP) in 95.6% ethanol (azeotrope) and in water at 25 °C

Compound	pK_a	
	Ethanol	Water
(1)	4.67 ± 0.09	5.65 ± 0.08
(2)	5.58 ± 0.07	6.71 ± 0.06
(3)	5.66 ± 0.08	6.85 ± 0.04
(4)	7.17 ± 0.04	8.27 ± 0.08
(5)	7.64 ± 0.05	8.12 ± 0.04
(6)	7.69 ± 0.06	7.41 ± 0.05

**Figure 1.** pK_a Values in ethanol of *ortho*- (○), and *meta*-, *para*- (□) substituted formamidines versus σ constants

value. It can be applied for predicting the retention index of any N^1N^1 -dimethylformamidinium, as the retention indices of primary amines can be easily determined. Moreover the choice of the primary amines as the standard in equation (1) has the additional advantage that they are easily available and amidines are usually synthesized from them.

Basicity of Formamidines.—Comparison of the pK_a values obtained for *ortho*-substituted N^1N^1 -dimethyl- N^2 -phenylformamidines (Table 2) with those for *meta*- and *para*-derivatives in 95.6% ethanol¹ and in water² indicate that a substituent in the *ortho*-position considerably decreases the pK_a values of amidines as observed for primary anilines. However, the interaction of substituents in the *ortho*- or *para*-position with the reaction centre (the imino nitrogen atom) seems to be the same.

The proper choice of substituent constants for investigation of the correlation of reaction series of *ortho*-substituted benzene derivatives is very difficult.¹¹ In 1969 Charton¹² assembled 32 sets of *ortho*-substituent constants (σ_o). The difficulties of determining satisfactory σ_o values are caused by interactions with the solvent as well as that lack of a satisfactory standard scale for σ_o values.

According to the theory¹¹ that *para*-substituent constants (σ_p) can be approximated to Taft σ_o values for several substituents, σ_p constants have been used in the present study.

The pK_a values obtained for *ortho*-derivatives in 95.6% ethanol as well as in water have been plotted against σ_p constants.¹³ The pK_a values *meta*- and *para*-derivatives in ethanol¹ (Figure 1) and in water² (Figure 2) are also plotted. In Figure 2, for comparison, the pK_a values of *ortho*-, *meta*-, and *para*-anilines taken from literature¹⁴⁻¹⁶ have been also plotted against the σ^- constants.¹⁷

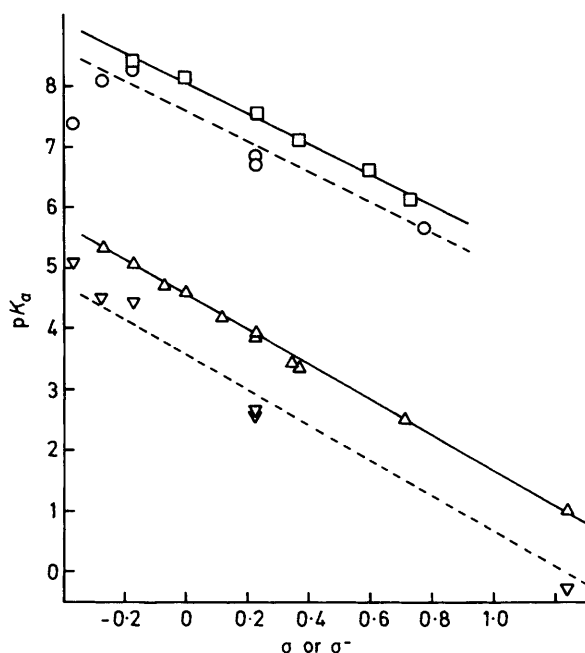


Figure 2. pK_a Values in water of *ortho*- (○), and *meta*-, *para*- (□) substituted formamidines versus σ constants. Comparison with pK_a values in water of *ortho*- (▽), and *meta*-, *para*- (△) substituted anilines versus σ^- constants

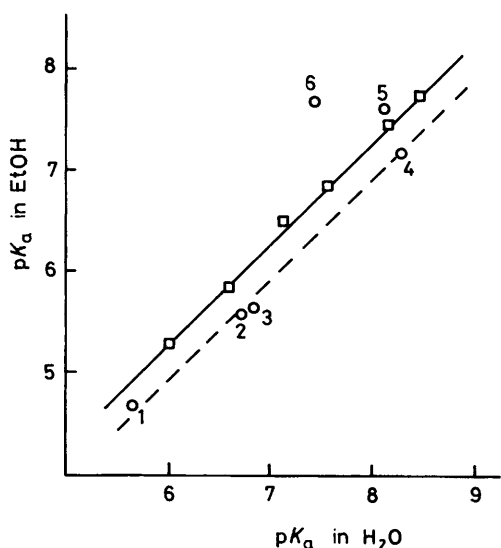


Figure 3. pK_a Values in ethanol versus pK_a values in water for *ortho*- (○), and *meta*-, *para*- (□) substituted formamidines

Figures 1 and 2 show that the *ortho*-substituted formamidines and anilines give a correlation line below that obtained for *meta*- and *para*-derivatives. Moreover the parent system ($X = H$) deviates from the correlation for the *ortho*-derivatives. This suggests a difference in steric, field, and/or solvent effects between the parent, *meta*-, and *para*-substituted systems and the *ortho*-substituted system.

The pK_a values of *o*-FDMP measured in two different solvents (water and ethanol), and compared with those for *meta*- and *para*-derivatives,^{1,2} indicate differences in the influence of solvent on the basicity of *ortho*-, *meta*-, and *para*-systems. The results show differences in medium effects not only between the *ortho* and the other systems, but also between differently substituted *ortho*-derivatives.

In Figure 3 the pK_a values obtained in ethanol for *ortho*-, *meta*-, and *para*-substituted formamidines FDMP are plotted against the pK_a values in water. The points for the *ortho*-substituted compounds (1)–(6) do not obey the same correlation line for the *meta*- and *para*-derivatives. The points for (1)–(4) give an additional correlation line (slope 0.95) situated below that for the *meta*- and *para*-systems (slope 0.99), but compounds (5) and (6) deviate from the correlation. It seems possible that compounds (5) and (6), with OMe and OH groups, produce additional specific interactions with ethanol or water, e.g. hydrogen bonding, which destroy the linear relationship. However the correlation line obtained from compounds (1)–(4), parallel to that for the *meta*- and *para*-substituted compounds, suggests that generally the solvent effects for the *ortho*-derivatives are more or less the same. On this basis the parameters of the Hammett equation $\Delta pK_a = -\rho\sigma$ have been calculated for the data obtained in ethanol and in water (Figures 1 and 2).

In the case of the *ortho*-substituted formamidines the following slopes of the correlation lines, based on the Hammett equation, have been found [only compounds (1)–(4) have been taken into account]:

	ρ (<i>ortho</i>)	ρ (<i>meta</i> , <i>para</i>)
EtOH	2.55 (r 0.961)	2.52 (r 0.973)
H ₂ O	2.69 (r 0.977)	2.55 (r 0.998)

For comparison, the ρ values obtained for *meta*- and *para*-substituted formamidines are given.¹⁸ In both cases (ethanol and water) the ρ (*ortho*) values are not different from ρ (*meta*, *para*) values. This means that the transmission of polar substituent effects to the reaction centre of protonation (the imine nitrogen atom) for *ortho*-substituted formamidines (except those which deviate from linear relationships) is the same as for the other derivatives. Moreover it can be assumed that the steric effects are constant as in the case of the protonation (deprotonation) of the other organic basic (acidic) *ortho*-systems.^{19–21}

To summarize, the changes in the pK_a values due to variation of the substituents in the *ortho*-position in *N*¹*N*¹-dimethyl-*N*²-phenylformamidines depend mainly on the polar effects of the substituent. Thus other *ortho* effects, e.g. steric and/or medium effects, can be neglected, except for some cases where specific interactions with solvent or reaction centre take place.

In the search for a general relation enabling prediction of the pK_a of any substituted formamide (FDMP), the pK_a values of *ortho*-, *meta*-, and *para*-derivatives have been correlated with the pK_a values of the corresponding anilines (PA) also measured in water.^{14–16} Neglecting points which deviated from the correlation [compounds (5) and (6)] equation (2) has been

$$pK_a(\text{FDMP}) = 5.34 + (0.59 \pm 0.05)pK_a(\text{PA}) \quad (r \text{ } 0.973, n \text{ } 17) \quad (2)$$

found. The correlation obtained, in spite of some inaccuracies caused by differences in interactions between substituent and reaction site in formamidines and anilines (e.g. for NO₂ and CN in the *ortho*- or *para*-position), is still of good quality, and can be applied with satisfactory accuracy (error < 0.5 pK_a units) for predicting pK_a values of any formamide in water.

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