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Quantitative Estimation of the Electronic Effects of Substituents in Five-membered Nitrogen-containing Aromatic Heterocycles

V.A. Lopyrev, L.I. Larina, and T.I. Vakul'skaya

Data, characterising quantitatively the effect of substituents on the reactivity and physicochemical properties of five-membered nitrogen-containing heterocyclic compounds, which have accumulated in the literature during the last 15 years, are compiled in the review and discussed. The possibility of applying the Hammett and Jaffe equations in the determination of the direction of transmission of the electronic effects of substituents is analysed and the likely usefulness of this approach to the study of electronic influences by taking into account separately the inductive and resonance constants is demonstrated.
The bibliography includes 215 references.

CONTENTS

I.	Introduction	411
II.	Pyrroles, indoles, and carbazoles	411
III.	Pyrazoles and indazoles	413
IV.	Imidazoles	413
V.	Benzimidazoles	415
VI.	Azoles with two different heteroatoms	418
VII.	Azoles with three and more heteroatoms	420

I. INTRODUCTION

The current advances in theoretical organic chemistry are in many respects associated with the vigorous use of the principle of the linearity of free energies (LFE) in studies of a wide variety of reactions and physicochemical properties.

The Hammett equation makes it possible to obtain quantitative estimates of reaction rate and equilibrium constants and to predict many important physicochemical characteristics. It is used widely in the study of the relation between structure and biological activity. The greatest advances on these lines have been achieved in hydrocarbon systems.

During the last decade, the Hammett equation, which was initially proposed for simple aromatic systems, has undergone a series of modifications based on the separate allowance for the inductive and resonance effects of substituents and proved to be applicable to various heterocyclic compounds.[1-9] The application of correlation analysis to heterocycles is usually considered in terms of the following aspects:

(1) The heterocycle functions as a substituent and one estimates its influence on the reaction centre of the molecule.

(2) The heteroatom in heterocyclic compounds is regarded as a substituent introduced into the aromatic ring. Here one estimates its influence on the properties of the system.

(3) The heteroatom in the heterocyclic system behaves as the reaction centre.

(4) The heterocycle is regarded as a single system in which the substituent and the reaction centre interact.

Since the first three aspects have been dealt with in fair detail in other reviews,[5-7] we concentrated attention on the transmission properties of heterocyclic systems. Since the comprehensive review of Mamaev and Shkurko on the transmission of the effects of substituents in azines has been published recently,[9] we confined ourselves to the consideration of nitrogen-containing five-membered heterocycles and their condensed derivatives.

II. PYRROLES, INDOLES, AND CARBAZOLES

The pK_a for a large series of substituted pyrroles have been determined[10] by the method involving transmetallation in dimethyl sulphoxide and it was shown that the NH acidity of such derivatives is satisfactorily correlated with the inductive constants of the substituents:

$$pK_a = (23.4 \pm 0.1) - (17.4 \pm 0.5)\sum\sigma_I, \quad r = 0.994,\ S_0 = 0.37,\ n = 17. \qquad (1)$$

An equation was fitted in the same study to the available literature data for the acidity of the substituted pyrroles in water:

$$pK_a = (16.6 \pm 0.6) - (10.5 \pm 0.9)\sum\sigma_I, \quad r = 0.97,\ S_0 = 1.0,\ n = 11. \qquad (2)$$

The difference between the reaction constants in Eqns.(1) and (2) is due to the employment of different solvents in which the pK_a scales differ significantly. Furthermore, the formation of complexes between pyrroles and dimethylformamide (DMF) was investigated in the same study by IR spectroscopy. The $\Delta\nu$ in the infrared spectra of the complexes are proportional to the square of the energy of the N–H...O hydrogen bond and are therefore a measure of the relative acidities of these compounds. The relative acidities determined in this way are also satisfactorily correlated with σ_I. The data described enabled the authors[10] to conclude that the influence of substituents on the NH acidity of pyrrole is determined mainly by the inductive effect. The complex formation method for the estimation of the NH acidities of a series of pyrroles in which the substituent is separated from the ring by the methylene bridge has also been used by Janda et al.[11] A satisfactory linear relation between the relative acidities and the inductive constants of substituents was obtained for a series of 2(5)-substituted pyrroles. These results have been partly surveyed in a review.[12]

However, the vibration frequencies of the free NH groups in 2-ethoxycarbonylpyrroles vary linearly with the σ_p constants.[13] The study of the acidities of pyrrole-2-carboxylic and pyrrole-3-carboxylic acids[14,15] showed that the influence of the substituents is transmitted through the pyrrole ring via the same mechanism as for the phenylene fragment but with a somewhat higher intensity.

In a study of 2-phenylpyrroles containing different substituents in the *para*-position in the benzene ring[16] and of their *N*-vinyl derivatives,[17] it was observed that the $\delta(^{13}C)$

parameter for both the pyrrole ring and the β-atom of the vinyl group varies linearly with σ_p. It has been concluded[16] that the degree of conjugation of the phenylene fragment with the pyrrole ring is significantly greater than in the corresponding furan derivatives.

It has been shown that the ^1H and ^{13}C chemical shifts of the vinyl group in 2-alkyl- and 2,3-dialkyl-1-vinylpyrroles vary linearly with the steric constants of the subsituents.[18]

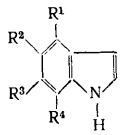
The ionisation energies, determined from the photoelectron spectra for two series of substituted pyrroles [5-R-3-ethoxycarbonyl-2,4-dimethylpyrroles (the α-series) and 4-R-2-ethoxycarbonyl-3,5-dimethylpyrroles (the β-series)][19] are linearly related to the σ_m, σ_p, and σ_p^+ constants ($r = 0.90$ to 0.97), the best correlation being obtained when σ_p constants are used. It is of interest that the ionisation potentials for the α- and β-series of substituted pyrroles[19] are satisfactorily correlated ($r = 0.97-0.99$) with the pK_a of 4-substituted[14,15] and 5-substituted[15] pyrrole -2-carboxylic acids.

A linear correlation between $E_{1/2}$ and the constant σ_p^+ has been noted in a study[20] of the electrochemical oxidation of 3,4,5-triphenyl-2-(4-R-phenyl)-, 3,4-diphenyl-2,5-di-(4-R-phenyl)-, 5-(4′-biphenylyl)-3,4-diphenyl-2-(4-R-phenyl)-, and 5-(2-naphthyl)-3,4-diphenyl-2-(4-R-phenyl)-pyrroles in DMF.

The theoretical reactivity indices have been calculated for a series of 2-monosubstituted pyrroles by the CNDO/2 method.[21] The correlations between the theoretical and experimental reactivity indices has led to the conclusion that the electronic effects of substituents are transmitted in different ways from the 2-position (correlation with σ_p^+ constants) and the 3-position (correlation with σ_m^+ constants) in the pyrrole ring.

There exist data showing that the rate constant for the decolorisation of benzene solutions of 2-aryl-3,4,5-tetraphenylpyrrolyl and 2-aryl-5-biphenylyl-3,4-diphenylpyrrolyl radicals are correlated with the overall σ constants.[22]

A quantitative estimation of the influence of the electronic effects of substituents on the acidity of indoles has been reported in only one communication:[23]



$$pK_a = 2.56 \sum\sigma - 2.55 \qquad r = 0.996,\ n = 9 \qquad (3)$$

The σ_m constants for the R^1 and R^4 substituents and the σ_p constants for the R^2 and R^3 substituents were used in the correlation in Eqn.(3).

The question of the electronic effects of the substituents in indole systems has been considered mainly from the standpoint of the determination of the path followed in the transition of these effects to the reaction centre. Jaffe[2] suggested that the equation

$$\lg K/K_0 = \rho_1\sigma_m + \rho_2\sigma_p \qquad (4)$$

be used to determine the direction of the transmission of the effects of substituents via carbon–carbon or nitrogen–carbon bonds. Having fitted this equation to the constants for the hydrolysis of indole-2-carboxylic acid esters and the ionisation constants of these acids, Jaffe failed to observe significant differences between ρ_1 and ρ_2. On this basis, he concluded that the transmission of the effects of substituents via the =CH– and –NH– groups is approximately the same.[2]

The study of the acidities of 5- and 6-substituted indole-3-carboxylic acids in aqueous ethanol showed[24] that the pK_a are satisfactorily correlated with the σ_m constants for the 5-substituted acids and the σ_p constants for the 6-substituted acids. Hence it was concluded that the electronic effects of the substituents are transmitted mainly via the hydrocarbon chain and not via the "pyrrole" nitrogen atom. However, the same data were treated in terms of Eqn.(25) and the results ($\rho_1 = 0.31$ and $\rho_2 = 0.42$) indicate the approximately equal contributions of the methylidyne groups and the "pyrrole" nitrogen atom to the transmission of the electronic effects. Eqn.(4) was also used to analyse the rate constants for the reactions of indole-2-carboxylic and indole-3-carboxylic acids with diphenyldiazomethane[25] and fairly high correlation coefficients were observed (0.980 and 0.997 respectively).

Thus the conclusions reached on the basis of the Jaffe equation are to a considerable degree contradictory and, as will be shown below, the application of Eqn.(4) and other multiparameter relations for the estimation of the paths followed in the transmission of the electronic effects of substituents in heterocyclic systems, inccluding condensed heterocycles, is unjustified without the analysis of the relation between the arguments.

Somewhat later the question of the transmission of the influences of substituents through the indole ring was examined by Bowden and Parkin.[26] The authors investigated the ionisation of indole-2-carboxylic acids containing substituents in various positions in the ring and concluded that, in contrast to benzene compounds, the pK_a for these acids cannot be expressed by any one correlation equation using different constants σ and the same value of ρ for all the positions in the indole ring. The correlation is satisfactory when the constants σ_D are calculated for each position of the substituent within the framework of Dewar's theory or ρ_1 and ρ_2 are fitted in the Jaffe equation (4). The authors therefore suggest that independent constants be fitted for each position of the substituent. However, this procedure cannot be regarded as promising.

The equilibrium constants for the formation of enzyme–indole complexes are correlated with the Hammett σ constants and, when the reaction centre in indoles is the nitrogen atom, the constants σ_p are used for 5-substituted derivatives and σ_m for the 4- and 6-substituted derivatives.[27]

The basicities of a series of carbazoles have been determined by the method of standard indicators in 20% ethanol[28] and it was shown that they are related to the σ constants by the expression

$$pK_{BH^+} = (-5.18 \pm 0.95) - (5.01 \pm 0.26)\sigma,\ r = 0.993,\ n = 6$$

The σ_m and σ_p constants were used respectively for the substituents in the 2- and 3-positions.

In a study of the mechanism of the acid hydrolysis of 3,6-disubstituted 9-(1-alkoxyethyl)carbazoles[29] and 9-alkenylcarbazoles,[30] it was observed that the reaction rate constants are correlated more effectively with the Hammett constants than with the Brown σ^+ constants, which indicates the absence of a direct polar conjugation of the substituents in the carbazole ring with the carbonium centre in the transition state. The amount of double bond character between the carbazole ring and the reaction centre in the transition state is then smaller in the hydrolysis of 9-vinylcarbazoles than in the hydrolysis of 9-(1-alkoxyethyl)carbazoles ($\rho = -2.24$ and -3.52 respectively).

The results of a study of the reactivities of 6-substituted 3-aminocarbazoles have been published.[31] The authors determined the basicity constants for the above compounds and the rate constants for their reactions with picryl chloride and *p*-nitrobenzenesulphonyl bromide. Correlations were noted between the experimental data and the σ^0 constants ($r = 0.962-0.999$). The reactivities of carbazoles have been compared with those of the analogous substituted diphenylamine derivatives and it was noted that the reactivities of carbazoles are somewhat higher, while their sensitivity

to the electronic influences of the substituents is lower than that of diphenylamines. In this approach no account is taken of the specific features of the carbazole ring as a single aromatic system, which undoubtedly reduces the value of the conclusions reached in the above study.

A thorough investigation of the transmision of the effects of substituents through the carbazole ring in 3-substituted 9-methylcarbazoles has been undertaken by ^{13}C NMR.[32] The authors of this study carried out one-parameter correlations between the chemical shift of the carbon atoms in the carbazole ring and the Brown σ_p and σ_p^+ constants as well as two-parameter correlations taking into account the σ_I and σ_R^0 constants. The results led to the conclusion that there is a direct polar conjugation within the limits of a single phenylene fragment. An attempt was also made to estimate the direction of the transmission of the effects of substituents on the basis of the satisfactory correlations $\Delta\delta[C(6)]-\sigma_p$ and $\Delta\delta[C(7)]-\sigma_m$ ($r = 0.964$ and 0.941 respectively). The "dominant" diphenylamine direction (i.e. via the nitrogen atom) proposed by the authors[32] apparently does not altogether correspond to reality, because, as will be shown below, it is not legitimate to employ one-parameter correlations for the determination of the paths followed in the transmission of the effects of substituents in heterocyclic systems.

III. PYRAZOLES AND INDAZOLES

A limited amount of data concerning the application of the LFE principle to pyrazoles and indazoles is available in the literature. The study of the basicities of 90 derivatives of pyrazole has shown[33] that the pK_{BH^+} are correlated with the Hammett σ_m constants. In a study of the electrochemical oxidation of pentacyanoferrate(II) complexes of pyrazole and indazole, an excellent correlation was observed ($r = 0.99$) between the oxidation potentials and the pK_{BH^+} for the ligand.[34] Although direct correlations with the parameters of the substituents are not quoted, presumably (bearing in mind the study of Elguero et al.[33]) the oxidation potentials of the pentacyanoferrate(II) complexes of pyrazole also depend linearly on the σ_m constants).

The equilibrium NH acidities of pyrazole derivatives (3,5-dimethylpyrazole, pyrazole, 4-chloro-3,5-dimethylpyrazole, and 4-bromopyrazole) are satisfactorily correlated with the sum of the σ_m constants of the substituents regardless of their positions in the heterocycle.[35] However, the authors themselves recognised that one cannot infer that the relations obtained are general on the basis of the four available points.

In the course of the study of the kinetics of the hydrolysis of *N*-acylazoles, it has been shown that the rate constants for the hydrolysis of 4-substituted *N*-acylpyrazoles are correlated with the σ_p parameters.[36] The reliability of this relation is difficult to assess, since the results of a statistical treatment are not quoted.

A study of the polarographic reduction of 3-aryl-1,2-dimethylpyrazolium perchlorates[37] has shown that the half-wave potentials for the two-electron transfer are satisfactorily correlated with the Hammett σ constants of the substituents in the 1-position. Unfortunately, correlation equations are not quoted in the above study and the relations are presented in the form of a graphical plot without a due statistical treatment.

The ^{13}C NMR spectra of 3-substituted indazoles have been investigated[39] but no correlation has been observed between the chemical shifts and the parameters σ_m, σ_p, σ_I, and σ_R. When the parameters of Swain and Lupton[40] ($\mathcal{F}$, $\mathcal{R}$) were used, a correlation was observed only for $\delta[C(5)]$,[39] but the large errors in the coefficients of the correlation equation and the unsuccessful selection of the points preclude the estimation of the influence of the electronic effects of the substituents.

IV. IMIDAZOLES

The influence of substituents on the acid–base properties of the imidazoles has been studied in fair detail.[41–52] The main contribution in this field is due to Charton,[7,41] who showed that the pK_{BH^+} of substituted imidazoles are better correlated with the σ_m or σ_I constants than with the σp constants. For certain series, the data have been treated in terms of a two-parameter correlation equation using the σ_I and σ_R constants.[43] These data led to the conclusion that the employment of two-parameter correlations does not improve the regression parameters.[41] However, this conclusion cannot be regarded as reliable because both the number and the selected sets of points in the series do not satisfy the recommended requirements for two-parameter correlations.[48,53]

The basicities of 2-phenyl-substituted 4,5-diphenylimidazoles in acetonitrile have been investigated[47] and it was found that the correlation between the basicity constants and the σ_p constants is excellent, while the correlation with the σ^+ constants is much worse. The same data have been treated in terms of a two-parameter equation using the σ_I and σ_R^+ constants and in terms of the Yukawa–Tsumo equation:[47]

$$pK_{BH^+} = 12.72 + 1.974(\sigma^0 + 0.269\Delta\sigma_R^+),\ R = 0.998\ n = 6\ .$$

A decrease of the basicity of the imidazole ring was noted after the introduction of aryl substituents in the 1-position.[49] When the substituents are in the aromatic ring, satisfactory correlations are obtained when σ constants are used ($r = 0.958$), electron-accepting substituents (NO_2 and $COCH_3$) deviating from the linear relation, which the authors explained by their polar conjugation with the reaction centre.

In a study of the basicity of nitroimidazoles, an attempt was made to introduce special σ constants for compounds of this class.[50] However, it is not possible to assess the reliability and the results of the above study because the correlation equations themselves are not quoted.

The acid properties of imidazoles have been investigated.[34, 43,51] The equilibrium NH acidities of imidazoles and their derivatives[35] are satisfactorily described, like the acidities of pyrazoles, by a linear relation between the pK_a and the sum of the σ_m constants of the substituents regardless of the positions which they occupy in the heterocycle:

$$pK_a = 18.9 - 9.5\sum\sigma_m,\ S = 0.25,\ r = 0.9991,\ n = 5\ .$$

The authors believe that, since there are no π-acceptor groups other than the phenyl group among the substituents investigated, it is diffiult to judge to what extent the relation found is general.

The acidity constants of 4(5)-substituted imidazoles are described by the equation[43]

$$pK_a = 13.90 - 6.72\sigma_I - 2.77\sigma_R,\quad R = 0.988,\ n = 5\ .$$

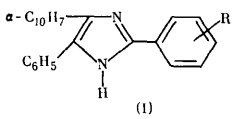
The limited set of substituents in this series (H, C_6H_5, CHO, $CONH_2$, NO_2) and the lack of electron-donating substituents lower the value of the above equation.

The acid dissociation constants of nitroimidazole have been determined recently[51] and it has been shown that the pK_a for 2-substituted 4(5)-nitroimidazoles vary linearly with the σ_m constants:

$$pK_a = 9.1625 - 8.8845\sigma_m.$$

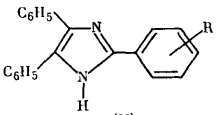
Similar relations have not been observed for 5(4)-substituted 4(5)-nitroimidazoles.[51]

The influence of the substituent in the arylene fragment on the acid properties in the series of imidazole derivatives (I)–(IV) has been investigated: [52]



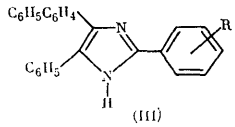
$\Delta\nu = 34\sigma + 221$, $r = 0.97$, $n = 7$;

(I)



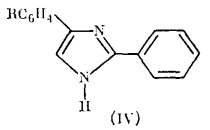
$\Delta\nu = 22\sigma + 215$, $r = 0.98$, $n = 10$;

(II)



$\Delta\nu = 15\sigma + 217$, $r = 0.96$, $n = 6$;

(III)



$\Delta\nu = 10\sigma + 210$, $n = 4$.

(IV)

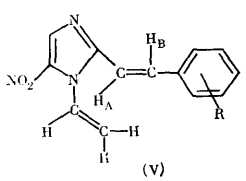
The authors explained the different sensitivities to electronic influences in the (I)–(IV) series by the effect of the direct polar conjugation between the substituents in the 2- and 4-positions in the imidazole ring. A deficiency of this treatment is that the differences between the steric effects of bulky subsituents in the 4- and 5-positions in the imidazole ring are excluded from consideration.

The heteroanalogues of triarylimidazoles have been investigated as inhibitors of the radical polymerisation of methyl methacrylate. [54] A linear relation has been observed between the logarithm of the inhibition factor and the Hammett σ^+ constants.

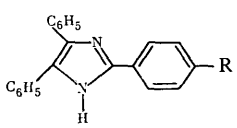
In a study of the photoelectron spectra of methylimidazole, it has been observed that the ionisation energies vary linearly with the basicity constants. [55] Since it is known that the latter are in their turn linearly related to the constants, [7,41] presumably their ionisation energies should also be correlated with these constants.

One-parameter correlations of the chemical shifts $\delta(^1H_A)$ with the σ_R^0 constants and two-parameter correlations of the chemical shifts with the σ_I and σ_R constants have been published for a series of substituted 5-nitro-2-styryl-1-vinylimidazoles (V). [56]

A correlation has been noted between the half-wave oxidation potentials of 2,4,5-triarylimidazoles (VI)–(VIII), [57,58] 2,4-diaryl-5-heterylimidazoles (IX), [59] and 4,5-diaryl-2-heterylimidazoles [59,50] and various constants. It is noteworthy that the potentials $E_{1/2}$ for the anions of the series (VI) depend on the σ_p constants. [57]

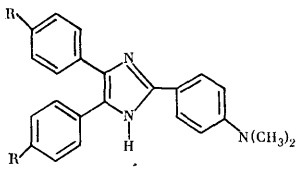


(V)



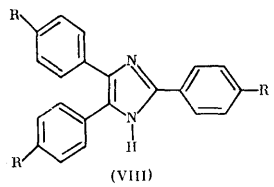
(VI)

R = $N(CH_3)_2$, OCH_3, CH_3, H, Cl, NO_2



(VII)

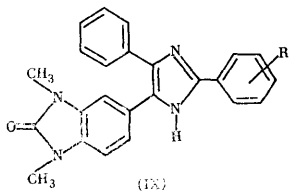
R = $N(CH_3)_2$, OCH_3, CH_3, H, Cl



(VIII)

R = $N(CH_3)_2$, OCH_3, C_6H_5, H, Cl

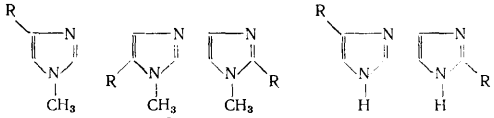
In the series (VI), 2-(*p*-nitrophenyl)-4,5-diphenylimidazole deviates from the correlation, which can be accounted for by the polar conjugation of the nitro-group with the reaction centre in the anion. The reaction constants for the series (VI) and (VII) are approximately equal ($\rho = 0.295$ and 0.284 respectively) and are smaller almost by a factor of 2 than for the series (VIII) ($\rho = 0.580$). [57] Unfortunately a statistical treatment of the correlations is not presented in the given communication. The σ^+ and σ constants were used by Shishkin et al. [58] and Blokhin et al., [59] on the one hand, and Rozin et al., [60] on the other, respectively in the statistical treatment of the results of the polarographic oxidation of the structurally similar compounds (IX):



(IX)

The relatively low reaction constants show, according to the authors, that the half-wave potential is determined mainly by the dimethylbenzimdazolone substituent. [59] However, this conclusion is inconsistent with other data. [57] Satisfactory correlations have been obtained ($r = 0.949$) between the rate constants for the quaternisation of 1-arylimidazoles and the Hammett σ constants of the substituents in the aryl fragment, although a low sensitivity of this reaction to electronic effects was noted. [49] A satisfactory correlation of the reaction rate constants for the azo-coupling of 2-substituted imidazoles and *p*-diazobenzenesulphonic acid with both σ_m and σ_p constants has been noted, [44] but, in view of the limited set of the substituents, the above relations cannot be treated as entirely reliable.

The influence of the electronic parameters of substituents on the solvolysis of *N*-acylimidazoles has been examined in several communications. [61–63] The rate constants for the acid [61] and base [62] hydrolysis of aroylimidazoles depend on the σ constants of the substituents in the aroyl fragment. The rate constants for the solvolysis of 1-(1-methyl-2-imidazolyl)-ethyl *p*-nitrobenzoates have been measured and it has been shown that they are linearly related to the σ_m^+ constants for the 4-substituted derivatives and to the σ_p^+ constants for the 5-substituted derivatives. [63] The base-catalysed isotope exchange involving the substituted imidazoles (X)–(XIV) has been investigated. [64]

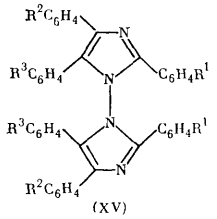


(X) (XI) (XII) (XIII) (XIV)

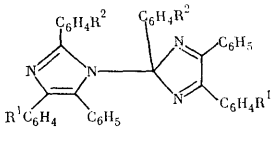
The set of substituents is the same in each case: NO_2, F, H, CH_3, and CF_3. The authors showed that the isotope exchange proceeds via two different mechanisms involving the intermediate formation of substrate anions or cations.

In the above study a significant difference between the transmission of the effects of substituents from the C(4) and C(5) positions to the C(2) position was noted for the first time and, what is particularly interesting, a difference was observed between the electronic conductivities on the pathway from the C(5) position to the C(2) position and in the opposite direction. Unfortunately, the correlation coefficients and other parameters of the statistical treatment are not quoted in this excellent investigation.

The influence of substituents on the thermal dissociation of the dimers (XV) and (XVI) has been studied in fair detail.[65–73]



(XV)



(XVI)

It has been reported that the constant for the equilibrium between compound (XV) and the corresponding free radical does not obey the Hammett equation,[65] but subsequently these results were disproved.[73] The activation energy for the dissociation of the majority of the dimers investigated is in the range 17–23 kcal mole^{-1}.[69] The rate constants for the dissociation of the dimers (XV) and (XVI) are well correlated with the σ constants.[66–73] The isokinetic temperature has been calculated on the basis of these correlations.[66] However, it cannot be regarded as reliable, because the measurements were performed over a narrow temperature range. It has also been shown that the nature of the solvent influences the reaction constants.[72,73]

V. BENZIMIDAZOLES

The question of the influence of the electronic effects of substituents in the 2-position on the basicities of benzimidazoles has been widely disucssed in the literature.[7,23,41,47,74–78] It has been suggested that this interaction has the character of direct polar conjugation.[74] However, more detailed investigations[7,23,41,75] have shown that better relations are obtained when the σ_m constants are used. It is noteworthy that, despite the large number of publications devoted to the study of the influence of substituents on acid–base properties, conclusions have been reached in many instances on the basis of clearly inadequate statistical data. The study of Rabiger and Joullii,[76] who investigated the basicities of two series of 5(6)- and 4(7)-halogenobenzimidazoles (four compounds in each series) is instructive in this respect. Both the character of the substituent and the number of compounds preclude any serious generalisations. Nevertheless, on the basis of correlations between the basicity indices of 4(7)-substituted benzimidazoles and the σ_m constants, the authors concluded that the tautomeric equilibrium has shifted, the 4-R-tautomer predominating. However, this conflicts with the available experimental data.[79] The basicity constants of 2-arylbenzimidazoles containing substituents in the aryl fragments are correlated more effectively with the Hammett σ constants than with the σ^+ constants.[47]

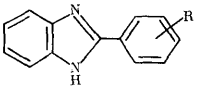
It is of interest that the more pronounced are the electron-accepting properties of the substituent in the 2-position in the benzimidazole ring, the more sensitive is the given series to the electronic effects of the substituents in the phenylene fragment of the molecule.[23] Data based on the two-parameter correlations of the basicity indices and the electronic parameters of the substituents have been published.[42,77,78] The satisfactory (r = 0.993–0.999) correlations between the pK_{BH^+} for the 5(6)-substituted benzimidazole in both one-parameter (σ_m, $\Sigma\sigma$) and two-parameter ($\sigma_I\sigma_R$, $\sigma_I\sigma_R^0$, $\mathscr{F}\mathscr{R}$) equations[23,77,78] are striking. This is evidence that the thermodynamic stabilities of the 5- and 6-tautomers are similar.

The percentage contribution of the resonance component to the overall transmission of electron effects from the 5(6)-position to the "pyridine" nitrogen atom has been calculated.[78] Regardless of the set of parameters employed ($\sigma_I\sigma_R^0$ or $\mathscr{F}\mathscr{R}$), the percentage of the resonance component is almost the same (37 ± 2% in the former case and 33 ± 2% in the latter). One should therefore consider the numerous instances of the satisfactory correlations between the acid–base properties of the same compounds and σ_m constants.[23,41,75]

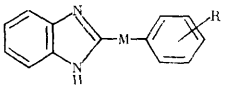
The σ_m constant, the nature of which is complex, takes into account the inductive and resonance effects of the substituents with rigorously defined contributions by each. For example, according to Swain and Lupton,[40] the contribution of $\mathscr{R}$ to σ_m is 22%. From the foregoing follows the important conclusion that, despite the satisfactory one-parameter correlations with σ_m constants,[23,41,75] in the transmission of the effects of substituents in benzimidazoles from the 5(6)-position to the nitrogen atoms in the 1- and 3-positions, the contribution of the resonance component is different from that for the benzene series.[78] Admittedly, the set of substituents employed[38] does not meet the requirements of the "minimum set"[48,53] necessary for a sufficiently reliable separation of the effect into the inductive and resonance components and the above conclusions therefore require further tests on a larger series of compounds.

The acidities of benzimidazole derivative have been investigated.[78,80–87] Data have been published on the acidities of a series of 5(6)-substituted 2-phenyl- and 2-pyridyl-benzimidazoles together with the results of their correlation with the σ_p constants.[80–82] The acidities of 4(7)-substituted 2-pyridylbenzimidazoles are correlated with the Taft σ^* constants.[82]

The conductivities of certain bridging groups in benzimidazole systems have been studied.[83,84] 2-Arylbenzimidazoles (XVII), whose acidities have been measured potentiometrically, have been used as the standard series. The introduction of the –CH=CH– (XVIII), –S– (XIX), or –CH_2– (XX) bridge between the arylene and benzimidazole fragment weakens the electronic influence of the substituent approximately by a factor of two:



(XVII), ρ_{st} = 1.25

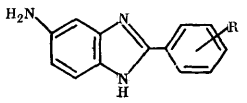


(XVII), ρ/ρ_{st} = 0.60
(XIX), ρ/ρ_{st} = 0.46
(XX), ρ/ρ_{st} = 0.46

The virtually identical conductivities of bridging groups of such different nature are surprising. Compounds of the (XVII)–(XX) series exhibit a spasmolytic activity and for this reason the electronic structures and the hydrophobic properties have been analysed within the framework of the partition coefficient model[88] in order to derive structure–activity relations.[85] It was found that the spasmolytic activity of these compounds is determined predominantly by their hydrophobic properties and is described by a parabolic relation with the hydrophobic constant taken from Leo et al.[88]

1-Methyl-5-R-benzimidazole-2-aldoximes exhibit acidity owing to the presence of the oxime group and their pK_a depend linearly on σ_m [86] The results of two-parameter correlations of the ΔpK_a for the 5-substituted benzimidazoles with the $\sigma_I\sigma_R^0$ constants ($r = 0.989$) and the Swain and Lupton parameters $\mathcal{FR}$ ($r = 0.992$) have shown, as for the correlation of the pK_{BH^+}, that the percentage contribution of the resonance component is virtually identical regardless of the parameters selected.[78] On this basis, one may conclude that the substituent in the 5(6)-position influences both the acid and basic properties via a special mechanism, which differs from that characteristic of the benzene series. Naturally this conclusion requires additional tests on a wider series of compound.

The transmission factor γ has been calculated for the series of 2-aryl-substituted 5(6)-aminobenzimidazoles (XXI) from the ionisation constants of the ammonium groups (the reaction state), from the stretching vibration frequencies ν of the amino-group (the ground state), and from the wavenumbers in the electronic absorption spectra (the excited state).[89]



(XXI)

Analysis of the correlation of the above physicochemical quantities with the Hammett σ constants led to the conclusion that the conductivity of the system (XXI) and the excited state is higher than that in the reaction of static states. However, this conclusion is doubtful, since quantities measured in terms of different scales were used in comparing the conductivites. It is noteworthy that, in order to explain the differences between the conductivities of the system (XXI) and the structurally analogous 5(6)-amino-2-(X-phenyl)-benzotriazoles,[89] the authors also used erroneous ideas, assuming that the electronic influences of the substituents in benzimidazoles are transmitted preferentially via the "imine" nitrogen atom.

It has been shown[90] for 2-substituted benzimidazoles that the intramolecular interaction between the substituent and the acidity centre is described quantitatively by the function $pK_a = f(\sigma_m)$ with a correlation coefficient of 0.998.

The differences between the conductivities with respect to the electronic effects of the substituents in the benzene and benzimidazole series were mentioned as early as 1966 in a study,[87] where a correlation was observed between the pK_a for the 5- and 6-substituted benzimidazole and the "mixed" constants $\sigma = \frac{1}{2}(\sigma_m + \sigma_p)$ and $\sigma = \frac{1}{2}(\sigma_m + \sigma_o)$ for the 4- and 7-substituted derivatives.

The electronic influence of substituents and the chemical shifts of the protons of the *N*-methyl group in the ^1H NMR spectra of 5-substituted 2-chloro-1-methylbenzimidazoles have been studied.[91] The ^1H chemical shifts vary linearly with σ_p; in the case of solutions in deuteriochloroform the correlations are significantly between when the σ_p^- constant is used for the NO_2 group, while for solutions in trifluoroacetic acid it is better to employ σ_p. This difference can be accounted for by the direct polar conjugation of the nitro-group with the indicator centre, while in trifluoroacetic acid the "pyridine" nitrogen atom is protonated.[91] It is of interest that a linear relation between $\delta[^1H(CH_3)]$ and σ_m has not been observed for 6-substituted 2-chloro-1-methylbenzimidazoles.[91]

Two-parameter Jaffe and Dewar–Grisdale correlations have led to the hypothesis that the substituents in the 5-position in 1,3-dimethyl-2-benzimidazolones influence the vibration frequency of the carbonyl group and the chemical shifts of the protons in the methyl group mainly via the field effect.[92,93]

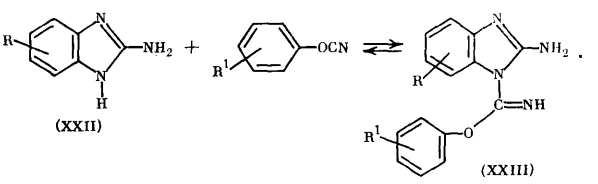
The kinetics of nucleophilic substitution in 2-chlorobenzimidazoles and their salts have been studied.[94–97] 5(6)-Substituted 2-chlorobenzimidazoles react with piperidine, the rate constants for this reaction depending linearly on the "mixed" $\sigma = \frac{1}{2}(\sigma_m + \sigma_p)$ constant.[94] The rate constants for the same reactions of 4(7)-derivatives of 2-chlorobenzimidazoles are correlated with $\frac{1}{2}(\sigma_m + \sigma_o)$.

The study of the kinetics of the substitution of chlorine by piperidine and the methoxide anion in 5- and 6-derivatives of 2-chloro-1-methylbenzimidazole,[95] where the Jaffe equation [Eqn.(4)] was fitted to the reaction rate constants, led the authors to the conclusion that the electronic spectra of the substituents are transmitted from the benzene ring to C(2) position mainly via the "pyridine" nitrogen atom, but the contribution of the "pyrrole" nitrogen atom to the transmission of the electronic influences is also considerable. As will be shown below, the authors lack adequate grounds for this conclusion.

An analogous study has been made for 4- and 7-derivatives of 2-chloro-1-methylbenzimidazole[96] and it was established that, together with the electronic factors, the reaction rate constants are influenced also by the steric effects of the substituents.

The rate constants for the nucleophilic substitution of chlorine in the perchlorates of 5-substituted 2-chloro-1,3-dimethylbenzimidazolium derivatives by thiophenol are correlated with the "mixed" $\sigma = \frac{1}{2}(\sigma_m + \sigma_p)$ constants.[97] The substitution of the chlorine atom in an acid medium in the perchlorates of 5- and 6-derivatives of 2-chloro-1-methylbenzimidazolium derivatives was investigated in the same study in their reactions with thiophenol. Statistical treatment of the results in terms of the Jaffe equation (4) led the authors to the conclusion that the effects of the substituents are transmitted from the benzene ring via the "pyrrole" nitrogen atom to the extent of 39.3%.[97] This conclusion cannot be regarded as sufficiently well-founded (see below). It is of interest to note that the σ_p^- constant is used in these correlations for the NO_2 group in the 2-chloro-1-methyl-5-nitrobenzimidazolium cation, while in the correlations of the chemical shifts of the protons in the $N-CH_3$ group the σ_p constants are employed[91] (see above). The kinetic measurements were performed in aqueous methanol and the ^1H NMR spectra were recorded in trifluoroacetic acid and the differences between the solvating capacities of these solvents in relation to the $-\overset{+}{N}H=$ group was in fact the reasons for the necessity to employ different σ constants.

In the study of the kinetics of the addition of substituted 2-aminobenzimidazoles (XXII) to aryl isocyanates, it was observed that the rate constants for the consumption of compound (XXII) (k_2^V) and the formation of compound (XXIII) (k_2^E) vary linearly with the σ constants of the substituents R [98] and that the best correlations are obtained when the σ_p constants are used for electron-donating substituents and σ_m constants for electron-accepting substituents.



(XXII) (XXIII)

The reaction mechanism proposed by the authors, which involves the formation of a six-membered transition state, is confirmed by the negative values of ρ in the regression equations, indicating the acceleration of the reaction by electron-donating substituents:

$$\lg k_2^V = -1.66\sigma + 2.07 \quad (r = 0.995),$$
$$\lg k_2^E = -1.22\sigma + 2.04 \quad (r = 0.999).$$

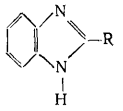
The ^{13}C NMR spectra of 5(6)-substituted benzimidazoles have been studied comparatively recently,[99] and it has been shown that the δ[C(2)] are very satisfactorily correlated both with the σ_p constants and the "naphthalene" constants σ_6. In the same study it was noted that the δ[C(8)] vary linearly with the constants σ_p and σ_p^+.

In order to infer the character of the transmission of the electronic influence of substituents in the opposite directions in benzimidazole derivatives, the correlation of the C[5(6)] chemical shifts in 2-substituted benzimidazoles and the C(2) shifts in their 5(6)-isomers was traced:[100–102]

$$\delta[C(5(6))] = (0.80 \pm 0.06)\delta[C(2)] + 8.19,$$
$$r = 0.981,\ S = 0.37,\ n = 7.$$

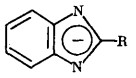
The high correlation coefficient in this equation indicates that the electronic effects of substituents in benzimidazole systems are transmitted in opposite directions via the same mechanism. However, the value of ρ shows that the intensity of the transmission of the effects of substituents from the 2-position to the 5(6)-position is weaker by approximately 20% than in the opposite direction. This non-equivalence is apparently caused by the different environments of the C(2) and C[5(6)] atoms.

The transmission of the electronic influences of substituents in 2-substituted benzimidazoles (XXIV), their anions (XXV),[100,103] 2-substituted 1,3-dimethylbenzimidazolium perchlorates (XXVI),[104] 2-substituted 1-methylbenzimidazoles (XXVII),[105] and 2-substituted 5(6)-nitrogenzimidazoles (XXVIII)[101] has been investigated by ^1H and ^{13}C NMR:



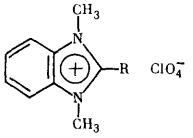
(XXIV)

R = $N(CH_3)_2$, NH_2, OCH_3, CH_3, C_2H_5, SCH_3, C_6H_5, H, Cl, $COOCH_3$, $COCH_3$, CF_3, NO_2



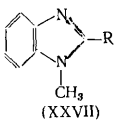
(XXV)

R = H, CH_2OH, Cl, $COOCH_3$, $COCH_3$, C_3F_7, CF_3, NO_2



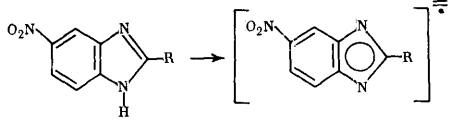
(XXVI)

R = $N(CH_3)_2$, NH_2, CH_3, C_2H_5, SCH_3, C_6H_5, H, Cl, $COCH_3$, CF_3



(XXVII)

R = NH_2, OC_2H_5, OCH_3, CH_3, C_2H_5, H, Cl, CF_3, $COOCH_3$, $COCH_3$, CN, SO_2CH_3, NO_2



(XXVIII) (XXIX)

R = $N(CH_3)_2$, NH_2, OCH_3, OC_2H_5, CH_3, C_2H_5, H, Cl, $COCH_3$, CF_3, CN

In the above studies the chemical shifts of the protons and ^{13}C carbon nuclei of the benzimidazole ring were subjected to a regression analysis using two-parameter correlation equations and various sets of substituent constants ($\sigma_I\sigma_R$, $\sigma_I\sigma_R^0$, $\mathcal{FR}$, etc.) and it has been shown that the electronic influences of substituents are transmitted via the benzimidazole ring of the neutral molecule[100,101,105] and the cation[104] in accordance with the same mechanism. Under these conditions, the resonance mechanism plays a more important role in the transmission of the effects of substituents in the 4- and 7-positions in the benzimidazole ring in all the series investigated than in the 5- and 6-positions. The introduction into the correlation equation of a third semiempirical parameter Q, which takes into account magnetic shielding together with the electronic factors,[106] appreciably improves the correlation coefficients. Nevertheless, it is difficult to infer the contributions of a particular effect owing to the linear relation ($r > 0.9$) between the resonance and Q constants.[100,105] The attempts to replace σ_I in correlation equations by the constant ι [107,108] resulted in the impairment of the correlation coefficients.[100,105]

It is of interest that, in contrast to the neutral molecules (XXIV), in the benzimidazole anions (XXV) the electronic effects of substituents are transmitted exclusively via the resonance mechanism.[100] It may be that this effect is associated with the presence of a delocalised negative charge on the molecule, which can increase the polarisability as a whole.

Attempts have been made with the aid of Eqn.(4) to establish the direction of the transmission of the electronic effects of substituents in certain condensed heterocyclic systems.[24,95–97,109,110] Formal analysis of the results of the two-parameter correlation of the ^{13}C NMR shifts of 2-substituted 1-methylbenzimidazoles (XXVII) in terms of Eqn.(4) led to the unexpected conclusion that the electronic effects of the substituents are transmitted from the 2-position to the 5-position mainly via the "pyrrole" nitrogen atom, while the transmission to the 6-position is via the "pyridine" nitrogen atom.[105] However, this conclusion is not reliable, because a linear relation between the parameters σ_m and σ_p is observed for the series of compounds investigated (with a partial correlation coefficient $r_{12} = 0.959$). According to Jaffe, $r_{12} < 0.9$ serves as a criterion of the applicability of Eqn.(4).[2] By varying the set of points, it is possible to reduce r_{12} only to 0.896,[104] but this leads to a series of substituents which do not satisfy the "minimum set" requirements.[48,53] Thus, it is not possible to reach correct conclusions in terms of Eqn.(4) about the involvement of the "pyridine" and "pyrrole" nitrogen atoms in the transmission of the effects of substituents.

Unfortunately the partial correlation coefficients have not been analysed in the above investigations,[95–97,109] etc., where it was concluded on the basis of Eqn.(4) that the effects of substituents are predominantly transmitted via the "pyridine" nitrogen atom in benzazoles, although such partial coefficients are greater than 0.9, which throws doubt on the validity of the conclusions reached. However, these erroneous ideas have found their way into certain reviews[3] and monographs.[1] Thus the question of the role of a particular heteroatom in the transmission of the electronic influences of substituents remains open.

It is therefore useful to consider a study[111] in which data obtained by studying the transmission pathways of the electronic effects in benzothiazoles with the aid of Eqn.(4) have been analysed. It was shown that the use of this equation can lead to mutually exclusive results: ranging from the insulating influence of the sulphur atom in the transmission of electronic effects to its greater activity compared with the nitrogen atom. However, the relation between the arguments in Eqn.(4) is not analysed in the above study either and yet such analysis would throw light on the causes of the above contradiction. It is noteworthy

that the partial correlation coefficients for all the set of substituents employed by the authors of the communcations quoted by Attanasi et al.[111] are high and likewise preclude a reliable conclusion about the involvement of nitrogen or sulphur atoms in the transmission of the electronic effects of substituents.

In 2-substituted 1-methylbenzimidazoles (XXVII) the substituent is in the *ortho*-position relative to the N–CH_3 group. The simple Hammett equation is not applicable to the *ortho*-derivatives,[112] but Charton has shown that two-parameter correlation equations with the constants σ_I and σ_R in general describe satisfactorily the electronic effects of substituents for *ortho*-derivatives and an additional parameter taking into account the size of the substituent is necessary only in a few instances.[113] The results of the two-parameter correlation of the $\delta(NCH_3)$ in the series (XXVII) with different sets of substituent constants ($\sigma_I\sigma_R$, $\sigma_I\overset{0}{\sigma}_R$, $\iota\sigma_R$, $\mathcal{FR}$) show that the electronic influences of substituens are transmitted to the methyl group via the "pyrrole" nitrogen atom with approximately equal contributions by the inductive and resonance components.[105]

The electronic effects of substituents in the neutral molecules of 2-substituted 5(6)-nitrobenzimidazoles (XXVIII) and in their radical-dianions (XXIX), generated electrochemically, are transmitted to the nitrogen atoms of the nitro-group by the same mechanism according to ^{15}N NMR and EPR data with approximately equal contributions by the inductive and resonance components.[101]

In connection with the above data, it is of interest to compare the conductivities of the benzimidazole ring in 5(6)-nitrobenzimidazoles with the conductivities of the benzene ring in *para*- and *meta*-substituted nitrobenzenes. For this purpose, the results of the regression analysis of the ^{15}N chemical shifts of the nitro-group in the above compounds were compared.[101,114] Since Craik et al.[114] do not quote the contributions of the inductive and resonance components, an additional statistical treatment of the $\delta(^{15}N)$ for *para*- and *meta*-nitrobenzenes was carried out in terms of the two-parameter equation using the $\sigma_I\sigma_R$ and $\sigma_I\overset{0}{\sigma}_R$ constants. The results proved to be extremely unexpected. Regardless of the set of the inductive and resonance constants the electronic influences of the substituents in both the *para*- and *meta*-positions are transmitted to the nitrogen atom of the nitro-group with approximately the same contribution of the resonance component (approximately 20%). Thus the nitro-group is apparently more strongly conjugated with the benzimidazole fragment in compound (XXVIII) than with the benzene ring in the *para*- and *meta*-derivatives of nitrobenzene.

The electronic influence of substituents on the HFS constants of the protons in the 4-, 6-, and 7-positions in the radical-dianions (XXIX) is not exerted in the same way, their effects on the H(4) and H(7) HFS constants being exerted to a greater extent via the resonance mechanism regardless of the sets of the inductive and resonance parameters of the substituents employed.[101] It has been shown that allowance for the radical-stabilising factor $\sigma^{\cdot}$ [115] improves the correlation coefficients, while the contribution of $\sigma^{\cdot}$ to the transmission of the effects of substituents for H(6) and heterocyclic nitrogen atoms is ~30%.[101]

The pK_a for the 2-substituted 5(6) nitrobenzimidazoles (XXVIII), determined by potentiometric titration, depend mainly on the inductive effects of the substituents.[116] The correlation analysis of the polarographic data for these compounds has shown that the influence of substituents on the $E'_{1/2}$ is exerted via both the inductive and resonance mechanisms with approximately equal contributions by each, while the effect on $E''_{1/2}$ is mainly via the resonance mechanism (85 ± 5%) regardless of the set of parameters of the substituents ($\sigma_I\sigma_R$, $\sigma_I\overset{0}{\sigma}_R$, $\sigma_I\overset{+}{\sigma}_R$, $\mathcal{FR}$). The quantities $E_{1/2}$ are in their turn satisfactorily correlated ($r = 0.987$) with the energies of the LUMO calculated theoretically.[116]

The results of two-parameter correlations of the dipole moments of 2-substitued 5(6)-nitrobenzimidazoles, calculated by the MINDO/3 method using various sets of parameters of the substituents, have shown that the inductive and resonance effects make approximately equal contributions to the overall influence of the substituent.[117,118]

VI. AZOLES WITH TWO DIFFERENT HETEROATOMS

The acid ionisation of 2-substituted thiazole-4- and thiazole-5-carboxylic acids and the alkaline hydrolysis of their esters have been studied[119] and it has been noted that the pK_a and the rate constants for the hydrolysis of 2-substituted thiazole-4-carboxylic acids are correlated with the σ_m constants, while in the case of the 2-substituted thiazole-5-carboxylic acids the correlation is with the σ_p constants. The acidities of 2-arylthioazole-4-carboxylic acids in aqueous ethanol solution with different alcohol contents were investigated later.[120] With increase of the content of ethanol in the system, the reaction constant increases somewhat, which can be accounted for by the increased planarity of the arylene and thiazole rings.

It has been noted that the enthalpy of ionisation of alkylthioazoles varies linearly with the constant σ^*.[121]

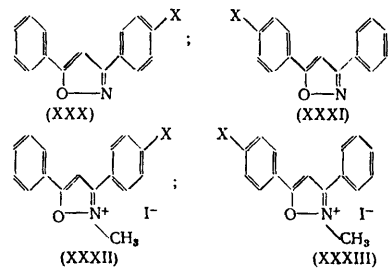
The basicities of 2- and 5-substituted thiazoles have been studied in greater detail by Forlani et al.[122] The authors used the σ_m constants for the correlation and concluded that the substituent in the 2-position interacts with the nitrogen atom via the resonance and inductive mechanisms, with the latter predominating. The reaction constants for 2- and 5-substituted thiazoles ($\rho = -9.9$ and -6.0 respectively) are comparable to those for other nitrogen-containing heteroarylenes. It is of interest that 2-amino- and 2-dimethylaminothiazoles deviate from the overall correlation, which may be due to the fact that their protonation involves the endocyclic nitrogen atom. The influence of substituents on the acid–base properties of 2-aminothiazoles has also been studied in other investigations.[123,124] Since the reaction constants for two different series—5-substituted 2-amino and 2-dimethylamino-thiazoles—are similar, the authors concluded that the amine–imine tautomerism does not occur in 2-aminothiazoles.[124] The legitimacy of the use of the σ_m constants in these series has been confirmed by the results of two-parameter correlations ($\rho_I/\rho_R \cong 0.5$), the endocyclic nitrogen atom proving to be the protonation centre.

The basicity constants of isoxazoles are also correlated with the σ_m constants.[125] The dipole moments of 4-substituted 3,5-dimethylidoxazoles are also satisfactorily correlated with the σ_m constants.[126]

The influence of substituents on the ^1H, ^{13}C, and ^{14}N chemical shifts for the substituted oxazoles has been studied[127] and linear relations have been observed between the corresponding $\delta(^{13}C)$ for 4,5-disubstituted oxazoles and the *ortho*-disubstituted benzenes. The possibility of calculating $\delta(^{13}C)$ from the three parameters $\Delta[C(2)]$, $\Delta[C(4)]$, and $\Delta[C(5)]$ characterising the contributions of substituents to the shielding of the C(2), C(4), and C(5) carbon atoms has been demonstrated.

The 3,5-diarylisoxazoles (XXX) and (XXXI) and their quaternary salts (XXXII) and (XXXIII) have been studied by ^1H [128–131] and ^{13}C [132,133] NMR. Both the one-parameter correlations of $\delta[H(4)]$, $\delta[C(4)]$, and $\delta[C(5)]$ with the σ^+ constants and the two-parameter correlations using $\sigma_I\sigma_R$ for neutral molecules[132] and $\sigma_I\sigma^*_R$ for quaternary salts[133]

proved to be excellent. It was shown that the sensitivity to the influence of substituents is smaller by a factor of three in the series (XXXIII) than in the series (XXXII) for both δ[H(4)] and δ[C(4)] [128,133] and that the mechanisms of the transmission of the electronic effects in these series is apparently unaltered. However, compared with the neutral molecules of compounds (XXX) and (XXXI), an increased sensitivity of δ[C(4)] to the electronic influence of the substituent has been observed only in the series (XXXII).[133]



In a series of investigations Noyce and co-workers[134–136] studied the solvolysis of ring-substituted 1-thiazolylethyl chlorides.[134–136] The solvolysis rate constants for the substituted 1-(5-thiazolyl)ethyl chlorides are extremely satisfactorily correlated with the σ_p^+ constants.[134,135] On the basis of two-parameter correlations between the solvolysis rate constants and $\sigma_I\sigma_R$ or , the authors concluded that the resonance effects predominate over the inductive effects in the above reaction of substituted 1-(4-thiazolyl)-ethyl chlorides.[136]

Nucleophilic substitution in 2-chlorothiazoles has been studied.[137–139] The rate constants for the substitution of chlorine in 4- and 5-substituted 2-chlorothiazoles on treatment with thiophenol in acid and alkaline media are correlated with the Hammett σ constants,[137,138] the σ_m and σ_p constants corresponding to the substituent in the 4- and 5-positions respectively. In an acid medium, the rate-determining stage of the reaction is protonation of the thiazole ring.[138] Somewhat later the interaction of 4-substituted 2-chlorothiazoles with the methoxide and thiophenoxide anions was investigated, using σ constants, as in previous studies.[139]

The polarographic reduction of 2-amino-4-aryl-5-phenylisothiazoles has been investigated.[140] The substitutents in the phenylene fragment influence the polarographically active azo-group via the thiazole ring, although the absolute value of the reaction constant is low (0.12). In the polarographic reduction of 4-arylisoxazoles, the half-wave potentials are correlated with the σ constants of the substituents in the aryl fragment.[141,142]

The study of the influence of substituents on the reaction constants and the physicochemical characteristic of condensed azoles with two different heteroatoms has involved mainly benzothiazole and benzoxazole derivatives. The ionisation constants of 5- and 6-substituted benzothiazolecarboxylic acids[143] and benzoisoxazole-3-carboxylic acid[144] are correlated with the Hammett σ constants. The σ_m and σ_p constants correspond respectively to the substituents in the 5- and 6-positions.[143,144] From this, the authors[143] concluded that the sulphur atom has an insulating effect; the electronic influences of the substituents are transmitted from the benzene ring to the 2-position mainly via the nitrogen atom.

The dissociation constants of 2-benzoxazolines in 2-benzoxazolinethiones have been measured in solution in aqueous acetone.[145] The correlation of the pK_a based on the Hammett and Jaffe equations led to the conclusions that the the compounds exist in the benzoxazoline and the benzoxazolinethione forms and not in the lactim and thiolactim forms respectively.

The basicities of 2-aryl-substituted benzoxazoles and benzothiazoles have been measured in acetonitrile[147] and it has been shown that the basicity constants of the above compounds are correlated best with the σ^+ constants, while for the corresponding imidazoles and benzimidazoles the best correlation is observed with the σ constants.[47] The conductivities with respect to the electronic effects in 2-arylbenzoxazoles and 2-arylbenzothiazoles have been compared with those in 2-arylimidazoles and 2-arylbenzimidazoles on the basis of two-parameter correlation equations. The transmission of the resonance effects of substituents in the aryl fragment to the imidazole and benzimidazole rings is more intense than the transmission of the influences to the oxazole and thiazole rings, which can be accounted for, according to the authors, by the smaller involvement of the oxygen and sulphur atoms in the conduction of the effects of substituents.[47]

The basicities of a series of carbocyanine dyes based on benzothiazoles have been measured and a satisfactory correlation between the basicity constants and the σ_p constants has been demonstrated.[146,147] The influence of substituents in the polymethine chain on the absorption spectra of such dyes has been studied with the aid of two-parameter correlations, which led to the observation that the effects of substituents are transmitted mainly via a resonance mechanism.[148,149]

The relation between the ^1H or ^{13}C chemical shifts and the electronic effects of substituents in various benzoazoles has been studied in a number of investigations.[150–154] The relation between $\delta[^1H(2)]$ and the effects of substituents in benzothiazoles in positions ranging from 4 to 7 was first reported by Taddei et al.[150] Later a linear relation was observed between the chemical shifts of the protons in the methyl group in the 5- and 6-positions in 2-methylbenzothiazoles, 2-methylbenzoxazoles, and 2-methylbenzoselenazoles and the σ constants.[151,152] The influence of substituents in benzothiazoles was studied in greater details in two investigations.[153,154] It was shown that the C(4) and C(5) chemical shifts in 2-substituted benzothiazoles are linearly related to the σ_p constants (r = 0.9945 and 0.9862 respectively).[153] Three-parameter correlation equations relating $\delta(^{13}C)$ and the parameters $\mathcal{F}$, $\mathcal{R}$, and $\mathcal{Q}$ are quoted in the same communication. Unfortunately these results do not allow the separate estimation of the influences of the inductive and resonance components on the chemical shifts, since $\mathcal{R}$ and $\mathcal{Q}$ are linearly related and the results of two-parameter correlations are not presented. It has been established with the aid of the Jaffe equation (4) [154] that the electronic effects of substituents are transmitted to the benzene and thiazole ring mainly via the nitrogen atom. Shegal et al.[154] arrived at an analogous conclusion. Since the partial correlation coefficients between the arguments are not quoted in the above studies, this conclusion requires additional confirmation. It has also been observed[154] that the intensity of the transmission of the electronic effects of substituents from the 2-position to the 6-position in the benzothiazole ring is weaker by 1/3 than in the opposite direction.

The frequencies of the symmetrical and antisymmetrical stretching vibrations of the amino-group have been measured for twelve 6-substituted 2-aminobenzothiazoles.[156] Having interpreted the results in terms of Eqn.(4) the authors also concluded that the electronic effects of substituents are transmitted to the amino-group preferentially via the nitrogen atom. The transmission factor for benzothiazole, which

is in the range 0.33–0.37, indicating a weaker transmission of the effects of substituents by the benzothiazole ring compared than by the phenylene ring, was determined in the same study.

The investigation of the IR spectra of 2-subsituted benzothiazoles showed that the intensity of the C=N stretching vibrations is linearly related to $(\sigma_R^0)^2$.[157]

A linear relation has been observed between the two-electron reduction potentials of 2-aminobenzothiazoles in the presence of various metal ions and the sum of the Hammett constants.[158] The positive value of ρ indicates a nucleophilic mechanism of the electrochemical reaction. The authors believe that the $\diagdown\!\!\diagup$C=NH double bond of the imino-tautomer is reduced, although it is known that 2-aminobenzothiazoles exist in the amino-form.[159,160]

Nucleophilic substitution in 4–7-substituted 2-halogenobenzothiazoles has been studied.[109,161–165] The rate constants for the nucleophilic substitution of the halogen by sodium methoxide or piperidine in 5- and 6-substituted 2-halogenobenzothiazoles are correlated with the usual Hammett σ constants.[109,161] On the other hand, special σ_4 constants were introduced for 4-substituted 2-halogenobenzothiazoles and were subsequently employed for the correlation of the rate constants for the oxidation of 4-substituted 2-mercaptomethylbenzothiazoles.[162] The rate constants for the hydrolysis of 2-aryl-6-isothiocyanatobenzothiazoles are linearly related to the σ constants of the substituents.[166] The reaction constant for this series (ρ = 0.50) is virtually identical with the reaction constant (ρ = 1.51) determined for the addition of glycine to 2-aryl-6-isothiocyanatobenzothiazoles.[166] The half-wave potentials for the reduction of these compounds also depend on the σ constants.[167]

The base-catalysed hydrogen exchange in the 2-position in benzazoles has been studied in a series of investigations.[111,168,169] The rate constants for the proton exchange are satisfactorily correlated with Hammett σ constants,[168] while in the case of 6-substituted derivatives it is necessary to employ two-parameter correlations based on the Jaffe equation.[111] The earlier studies,[109,165] in which it was claimed that the electronic effects of substituents in benzothiazoles are transmitted from the phenylene ring to the 2-position exclusively via the "aza" group were examined critically in two investigations.[111,169] Attanasi et al.[111] acknowledged the appreciable role of the sulphur atom in the transmission of the electronic effects of substituents, but their conclusions are based on the results involving the use of the two-parameter Jaffe equation (4) without the analysis of the correlations between the arguments (see above).

VII. AZOLES WITH THREE AND MORE HETEROATOMS

A detailed analysis of the transmission of the influences of substituents in the series of 1,2,4-triazoles has been carried out in a study[170] where the concept of the limited applicability of one-parameter correlation equations to heterocyclic compounds was developed. Data published previously[171,172] on the quantitative allowance for the influence of substituents in the triazole ring on the physicochemical properties and reaction rates were treated in terms of the two-parameters equation using the σ_I and σ_R constants. The results show that the inductive effects predominate over the resonance effects.[170] However, it is extremely difficult to make correct estimates owing to the lack of knowledge about the absolute errors in the coefficients of the arguments.

The acidities of C-substituted 1,2,4-triazoles have been studied in relation to five different series[170,172–174] in which the influence of substituents on the acidity constants was taken into account mainly in terms of the inductive mechanism. However, the resonance influence of the substituent cannot be neglected either except in those cases where the system ceases to be aromatic.[170,174]

The data on the correlations of the acid–base properties of substituted tetrazoles and the electronic parameters of the the substituents published after 1978 have been described in a series of studies[43,175–183] and have been surveyed in a review.[184] On the basis of the effective correlations of the pK_a for several series of 5-substituted tetrazoles and various σ constants, the authors[177,178] concluded that the compounds indicated exist in a single tautomeric form (1-H). The correlations of the pK_{BH^+} and the σ constants for a different series of tetrazole derivatives, taking into account the correlation of the charge density on the nitrogen atoms and the σ_p constants,[180] established that the tetrazole ring is protonated at the nitrogen atom in the 4-position.[176,181–183] These investigations were continuned in subsequent years in relation to aryltetrazoles and tetrazolylacetic acid.[185–187] Excellent correlations have been found between their ΔpK_a and the Swain and Lupton parameters for both *meta*- and *para*-derivatives.[185] The pK_{BH^+}–σ correlations observed[186] confirmed the earlier hypothesis concerning the protonation centre of the tetrazole ring.

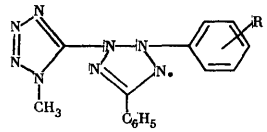
It has been shown for 5-R-tetrazoles that the influence of substituents on the acidity and basicity of these compounds is manifested in the same way; a satisfactory linear relation has been observed between their pK_a and pK_{BH^+},[188] which permits a quantitative estimation of the acid–base properties of 5-substituted tetrazoles.

The influence of substituents on the position of the long-wavelength maximum in the electronic spectra of 1-methyl-3-nitro- and 1-methyl-5-nitro-1,2,4-triazoles.[170,189] The electronic and infrared spectra of 5-aryltetrazoles have been investigated by a group of Polish workers,[190,191] who correlated different frequencies in the spectra of these compounds with the σ constants, but the correlation coefficients obtained are as a rule low.

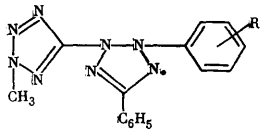
The chemical shifts of the protons in the ^1H NMR spectra of 3(5)-substituted 1,2,4-triazoles are linearly related to the σ_p constants.[192] It was demonstrated later that the correlations of the inductive and resonance components to the overall transmission of the effects of substituents are approximately the same.[170] Attempts have been made to estimate the influence of substituents on the chemical shifts of the protons in the methyl group in 3-substituted 1-methyl-5-nitrotriazoles,[173,193] but the correct analysis of these relations was complicated by the powerful shielding effects. The influence of substituents in the benzene ring on the H(5) chemical shifts in 4(5)-aryl-1,2,3-triazoles and 1-amino-4-aryl-1,2,3-triazoles has been studied.[194] It is noteworthy that the reaction constants for the above series of compounds are virtually identical (0.35 and 0.36 respectively). What is in essence the converse problem has been solved in a study[195] where the influence of the tetrazolyl group on the chemical shifts of the protons in the phenylene ring was investigated and the Swain and Lupton constants were calculated for the 5-tetrazolyl fragment.

A linear dependence of the spin–spin coupling constants j'[C(5)H] and the δ[C(5)] chemical shift for the 1-substituted tetrazoles on the σ_I constants has been observed by ^1H and ^{13}C NMR.[196]

The satisfactory correlations between the nitrogen HFS constants in the EPR spectra of the radicals (XXXIV) and (XXXV) indicate that the variation of the parameters of the isotropic HFS by the N(3) atom is determined by the electronic influence of the substituents, while the geometry of the radicals does not change significantly.[197]



(XXXIV)



(XXXV)

The influence of the solvent on the transmission of the electronic effects of substituents in *para*-substituted 4-aryl-1,2,4-selenodiazoles has been investigated with the aid of the Swain and Lupton parameters.[198] It was then shown by ^{1}H NMR that the nature of the solvent does not have a significant influence on the ratio of the contributions of the inductive and resonance components in the overall transmission of the substituent effects.

The ionisation potentials of 3,5-diphenyl-1,2,4-oxadiazoles substituted in the 3- or 5-phenyl rings are linearly related to the σ^+ constants.[199] In later studies, the authors showed that only the intensity of the peaks due to the aroyl ions in the mass spectra of 5-amino-3-aroyl-1,2,4-oxadiazoles is correlated with the σ^+ constants albeit with a low correlation coefficients.[200]

In relation to the nucleophilic substitution of the nitro-group in 3-substituted 1-methyl-5-nitro-1,2,4-oxadiazoles 5-substituted 1-methyl-3-nitro-1,2-triazoles, it has been observed that the intensity of the transmission of conjugation effects from the 5- to the 3-position is approximately three times greater than in the opposite direction, while the inductive influence of substituents is transmitted to virtually identical extents in both directions.[170,201]

Alkylation of substituted 5-aryltetrazoles and their potassium salts by dimethyl sulphate[202,203] or ethyl bromoacetate[204] showed that the ratio of the 1- and 2-isomers in the reaction product is correlated with the σ constants of the substituents in the benzene ring. Electron-accepting substituents inhibit the reaction and increase the fraction of the 2-isomer. An analogous behaviour has been observed in the alkylation of 5-aryltetrazoles by methyl iodide under the conditions of phase-transfer catalysis.[205] However, similar correlations have not been observed in the alkylation by dimethyl sulphate in a two-phase system. These data led to the conclusion that the alkylation of tetrazoles by methyl iodide takes place in the organic phase, while the alkylation by dimethyl sulphate takes place in both the organic and aqueous phases.

The rate constants for the substitution of the hydrogen in the methyl group by deuterium in 5-methyl-1-(R-phenol)-tetrazoles are correlated with the substituent constants σ^0 ($\rho = 3.0$).[206,207]

The half-wave potentials for the reduction of 1-amino-4-(X-aryl)-1,2,3-triazoles, 1-H-4-(X-aryl)-1,2,3-triazoles,[208] and 1-(X-aryl)-5-mercaptotetrazoles[209] are correlated with the σ constants.

Much less information is available about the transmision of the effects of substituents in condensed azoles with three heteroatoms. It has been shown that the pK_a for benzotriazoles are correlated with the Hammett σ constants.[23] The half-wave potentials for the reduction of 1-aryl-2-aryl-5-isothiocyanatobenzotriazoles are also linearly related to the σ constants, the 2-substituted isomers being reduced more readily and their reaction constants being lower.[167]

Benzothio- and benzoseleno-diazoles have been investigated thoroughly.[210] An approximate correlation has been obtained for these compounds between the positions of the maxima in the electronic absorption spectra and the σ constants. Their electrochemical reduction potentials are also correlated with these constants. The replacement of selenium by sulphur increases somewhat the influence of the substituent and the authors believe that the inductive effect plays a decisive role. The intensity of the influence of the substituent is almost independent of its position in the molecule.[210]

The rate constants for the thermal decomposition of benzo-1,2,3-thiadiazole-1,1-diozide, containing substituents in the aromatic ring, are linearly related to the σ constants.[211] The attempt by the above authors to estimate the direction of transmission of the effects of substituents with the aid of the Jaffe equation cannot be regarded as successful, in our view, because the relation between the arguments was not analysed.

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The studies quoted in this review are not equivalent as regards their importance. Some of them have been carried out for a series of compounds with a limited set of substituents which we believe reduces the reliability of the results and sometimes leads to clearly erroneous conclusions, as happened, for example, in the study of Rabiger and Joullie.[76] On the other hand, an inadequate statistical treatment can also result in unjustified conclusions.[95,97,111,157,165,212]

In many cases it has been possible to apply the Hammett equation in its original form to various heterocycles. However, arbitrarily selected constants (σ_m, σ_p, σ^0, σ^+, σ^-, etc.) were then used without any justification. In other investigations, several different types of constants were compared and the authors inferred their applicability to a specific type of heterocycles on the basis of the correlation coefficient. However, in all cases it is implied that the relative contributions of the inductive and resonance mechanisms to the overall effect of the substituent on the reaction or indicator centre is the same as in benzene derivatives. Where it was not possible to select the type of constants for the benzene series for a quantitative description of the process, special sets of σ constants characteristic of the given type of heterocycles only were introduced.[50,162,213] This procedure, involving the specification of a new set of σ parameters for each type of heterocycle and for each relative disposition of the substituents and the reaction centre, rules out the possibility of comparing the reactivies of different classes of compounds, is extremely laborious, and vitiates the practical significance of such correlations.

The approach which takes into account separately the influence of the inductive and resonance effects of substituents on the reaction centre with the aid of many-parameter equations is more promising. It has made it possible to discover the specific features of the transmission of the electronic influences of substituents via the benzothiazole,[154] 1,2,4-triazole,[170] and benzimidazole [100-104,214,215] rings.

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Irkutsk Institute of Organic Chemistry,
Siberian Division of the USSR
Academy of Sciences