Substituent Effects in Heterocyclic Systems

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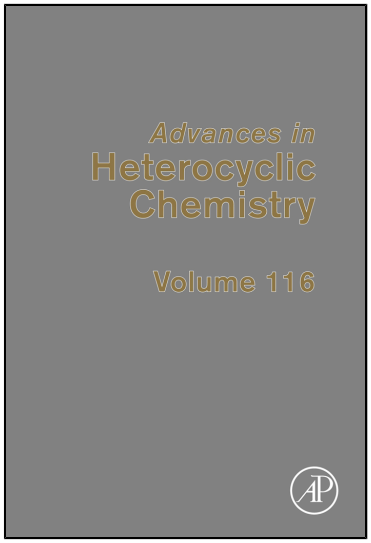

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CHAPTER FOUR

Substituent Effects in Heterocyclic Systems

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Contents

Abstract

The substituent effect is one of the most important concepts in chemistry, biochemistry, and related fields. In this chapter, we collected the works devoted to this issue in relation to heterocyclic compounds and published mainly after 2000. Due to the wide range of properties, heterocycles find their applications in medical, pharmaceutical, and other fields of chemistry. Importantly, substituents incorporated in the different positions of molecules may serve as effective tool for modification of various characteristics and physicochemical properties of the heterocycles. Effects of substituents in the heterocycles containing one heteroatom: nitrogen, oxygen, sulfur, and some other ones, are reviewed in order of increasing ring size and the number of rings, followed by compounds with two or more various heteroatoms. Due to their great importance, nucleic acid bases and their analogs are presented in a separate section.

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The substituent effect is demonstrated by classical approaches and some modern ones. Where possible, the comparison with carbocyclic compounds is presented.

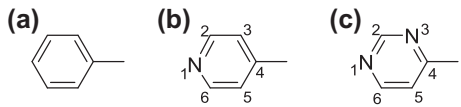
Keywords: Aromaticity; Azole; Indole; Nucleobases; Pyridine; Pyrrole; Quinolone; Substituent effect; Tautomers; Thiophene

1. INTRODUCTION

The chemistry of heterocyclic compounds is a part of organic chemistry comprising cyclic molecules in which one or more carbon atoms belonging to the cycle is replaced by one or more atoms of other chemical elements, the so-called heteroatoms. Most often nitrogen, oxygen, or sulfur atoms serve as heteroatoms while phosphorus, silicon, selenium, boron, arsenic, tellurium, or other atoms are less frequently found. Generally, the heterocyclic compounds may be divided into three main groups: (1) fully saturated systems, (2) systems with π-electron fragments in the cycle, and finally (3) π-electron systems in which all atoms forming the cycle are in the sp^2 hybridization state.

The main distinction between cyclic hydrocarbons and their heterocyclic analogs relies on differences in valence and electronegativity of heteroatoms in comparison with the carbon atom. This is possibly less important in the case of saturated systems, since the effect of electronegativity operates over a short-distance (2004JPCA(108)4940), but in the case of π-electron systems it may be of a great importance. Undoubtedly, depending on electron-donating or electron-accepting properties of a heteroatom, replacement of a carbon atom in the cyclic system may have substantial consequences. A good example is a comparison of the Hammett substituent constants σ_m and σ_p estimated for phenyl and its monoaza- and diaza-analogs (Scheme 1; Table 1; 1991CR(91)165).

Apparently, phenyl as a substituent is a very weakly interacting partner, whereas its aza-analogs are moderate electron-accepting systems. Increasing the number of nitrogen atoms leads to a greater electron-accepting ability of the π-electron system. Interestingly, the inductive substituent constant σ_I of



Scheme 1 Phenyl (a), 4-pyridyl (b), and 4-pyrimidyl (c) substituents.

Table 1 Values of σ_m and σ_p for phenyl, pyridyl, and pyrimidyl substituents*

Substituent	σ_m	σ_p
Phenyl	0.06	−0.01
2-Pyridyl	0.33	0.17
3-Pyridyl	0.23	0.25
4-Pyridyl	0.27	0.44
2-Pyrimidyl	0.23	0.53
4-Pyrimidyl	0.30	0.63
5-Pyrimidyl	0.28	0.39

*Data taken from Ref. (1991CR(91)165).

52 various heterocyclic systems (saturated and aromatic) with N, O, S heteroatoms is always positive (see Table VII in (1991CR(91)165)). Another interesting fact is that the saturated substituent cyclohexyl with $\sigma_m = -0.05$ and $\sigma_p = -0.15$ is similar to the adamantyl substituent with the sigma values −0.12 and −0.13, respectively (data taken from Ref. (1991CR(91)165)). Unfortunately, there is a lack of the appropriate data for saturated aza-derivatives of cyclohexane. Nevertheless, the available data suggest a different behavior of heterocyclic systems when they are considered as transmitting moieties for the substituent effect.

Substituent effects are classically considered for X−R−Y systems, where Y is the so-called reaction site or more generally a fixed functional group in a reaction series, X is a varying substituent, and R denotes the transmitting moiety (1940MI1, 1953CR(53)191, 1972MI(1), 1973MI1). However, the results of the influence of X on a moiety R, without a particular reaction/process site, have been also reported. There are two ways of describing the substituent effects. The classical way uses Hammett-like approaches (1940MI1, 1953CR(53)191, 1972MI(1), 1973MI1, 1991MI(2)), where the electron-withdrawing or electron-donating power of a substituent X is characterized by substituent constants (1991CR(91)165, 2005CR(105)3482, 2006COC(10)763). In principle, this kind of substituent effect description is based on the Hammett equation (1) or its modifications:

$$\lg k_{p,m} = \lg k_0 + \rho \cdot \sigma_{p,m} \quad (1)$$

where $\sigma_{p,m}$ denotes substituent constants for the para- and meta-positions, $k_{p,m}$ and k_0 are the rate constants for substituted and unsubstituted systems, respectively, whereas ρ is the reaction constant (so-called slope) describing the sensitivity of the reaction/process to the substituent effect. In the Hammett-like equations, lg k has been replaced by P(X)—representing

various quantitative characteristics of chemical or physicochemical properties. Depending on the nature of the reaction/process site the appropriate substituent constants should be used (1991CR(91)165).

Another way of describing the substituent effect involves quantum-chemical modeling of various physical or physicochemical properties, such as electrostatic potentials at ring carbon atoms or at atoms of reaction centers (2007JPCA(111)11134, 2008JPCA(112)6700), ionization potentials (2000JOC(65)2195), the energy of decomposition analysis (2001JCC(22)931), the charge of a substituent active region (cSAR) (2007PJC(81)1123, 2007CPL(447)192), the energetic characteristics of the substituent effect based on the isodesmic reactions approach (1970JACS(92)4796, 1976JCS(P2)1222, 1980JOC(45)818, 1986MI1), and many others. These approaches, named as a modern way of substituent effect description, have also been applied to heterocyclic systems. It is important to note that these characteristics are almost always confronted with the classical Hammett-like descriptors.

In this chapter, both ways of substituent effects description will be considered for monocyclic and polycyclic compounds with one or more heteroatoms.

2. NITROGEN-CONTAINING HETEROCYCLIC SYSTEMS

The substituent effects in nitrogen-containing systems can be discussed in three ways. First, this class of compounds often undergoes tautomerization that may be dependent on the substituent effect. An excellent review on tautomeric equilibria in relation to π-electron delocalization, published in 2005 by Raczynska et al. (2005CR(105)3561), describes tautomerism in various substituted aromatic nitrogen heterocycles. Second, there are investigations of the influence of a substituent X on some properties of heterocyclic systems. And finally, there are considerations of interactions in X—R—Y systems, where changes in properties of the fixed group Y (reaction site) are a function of varying substituents X.

Due to the exceptional importance of the basic components of DNA and RNA, the substituent effects in these systems will be discussed in a separate section addressed only to these problems.

2.1 Five-Membered Rings

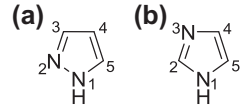
In this group, compounds very frequently studied are azole systems, which may contain several nitrogen atoms. On one of them an acidic proton is

located, hence this particular nitrogen atom possesses a lone pair orbital perpendicular to the molecule's plane. All other nitrogen atoms, if present in the system, possess a lone electron pair orbital in the plane of the molecule. Scheme 2 shows the two types of nitrogen atom in diazoles. Since different nitrogen atoms can be protonated, several tautomeric forms are possible depending on the position of the proton. Such prototropy is usually accompanied by a low energy barrier, which is obviously dependent on the substituent effects.

2.1.1 Pyrrole, Diazoles, and Triazoles

Pyrrole has only one nitrogen atom in the cycle. The effect of substitution at the nitrogen atom on the aromaticity and comparison with the appropriate data for benzene have been reported for N-pyrrole derivatives with substituents of the second and the third row of the periodic table (2007SC(18)797). A significant difference between data for benzene and pyrrole rings was found. The ranges of aromaticity indices for the most aromatic and the least aromatic molecules (bold numbers in Table 2) are dramatically greater for pyrrole derivatives than for benzene ones. In the former case, values of the ranges of aromaticity indices are 3.6 times greater than for benzene for both harmonic oscillator model of aromaticity (HOMA) (1972TL3839) and (1993JCICS(33)70) (for review see (2014CR(114)6383)) and aromatic stabilization energy (ASE) (2005CR(105)3773) parameters. This means that the less aromatic pyrrole ring is much more sensitive to a substituent effect than the more aromatic benzene ring, which is in agreement with previous reports indicating that systems with $4n + 2$ π-electrons are not able to change their π-electron structure (2004JOC(69)6634), (2014CR(114)6383). An additional factor, which may explain these relations, is the change of the energy of the nitrogen lone pair orbital, and as a consequence its occupation, due to the electron-withdrawing/electron-donating power of the N-substituent in the pyrrole ring.

According to Scheme 2, diazoles are represented by two isomers—pyrazole (1,2-diazole) and imidazole (1,3-diazole). Investigation of the tautomerism in C5-substituted imidazole (2001JMS(565–566)107) and



Scheme 2 Two types of nitrogen atom in 1,2- (a) and 1,3-diazoles (b), pyrazole and imidazole, respectively.

Table 2 The lowest (l/a) and the highest (h/a) aromaticity indices (substituents are in parentheses) for monosubstituted benzenes and pyrroles*

	HOMA	NICS(0)	NICS(1)	NICS(1)zz	ASE
Ph-X (l/a)	0.90 (Li)	−6.72 (Li)	−8.92 (NH_2)	−24.4 (NH_2)	126.24 (BH_2)
Ph-X (h/a)	0.98 (F)	−9.99 (F)	−10.37 (Li)	−28.83 (H)	139.31 (BH_2)
Δ§ (Ph-X)	**0.08**	**−3.27**	**−1.45**	**−4.43**	**13.07**
Pyr-X (l/a)	0.61 (BH_2)	−9.22 (BH_2)	−8.21 (BH_2)	−24.0 (BH_2)	35.32 (F)
Pyr-X (h/a)	0.90 (F)	−16.53 (F)	−10.41 (Li)	−32.86 (Li)	82.58 (Li)
Δ§ (Pyr-X)	**0.29**	**−7.31**	**−2.20**	**−8.86**	**47.25**

HOMA, harmonic oscillator model of aromaticity; NICS, nucleus independent chemical shift; ASE, aromatic stabilization energy.
* Data taken from (2007SC(18)797).
§Ranges of aromaticity indices values between the most and the least aromatic molecules.

pyrazole (2004JMST(673)17) derivatives revealed that in both cases the 1*H*-tautomer with electron-withdrawing BH_2, CFO, COOH, and CHO groups is the most stable one whereas the other tautomers (2*H*- for pyrazole and 3*H*- for imidazole) are strongly stabilized by OH, F, NH_2, Cl, $CONH_2$, CN, NO_2, and CH_3 groups. Interestingly, two substituents with totally opposite electronic properties, NO_2 and NH_2, stabilize the same type of tautomers of pyrazole and imidazole. Therefore, the electronic nature of the substituent cannot be considered as the only decisive factor for the tautomeric preference.

Substituent effects on geometric and electronic properties of N-substituted diazoles have been analyzed for a wide range of N-pyrazole and N-imidazole derivatives (2007SC(18)965, 2011JPCA(115)8571). These series have also been compared with corresponding derivatives of pyrrole and benzene. It was found that observed trends in properties of diazoles correlate very well with the results for analogous N-pyrroles. An application of differently defined aromaticity indices: HOMA, nucleus independent chemical shift (NICS) (1996JACS(118)6317) (for review see (2005CR(105)3842)), multicenter bond index (2005JPOC(18)706), and aromatic fluctuation index (FLU) (2005JCP(122)014109) showed that for a series of monosubstituted benzene molecules the change of the substituent has a minor effect on the π-electron delocalization of the ring (2004JOC(69)6634, 2004PJC(68)2213), whereas N-substitution of imidazole and pyrazole dramatically influences the aromaticity of both rings. The different resistance of the π-electron system in the above-mentioned molecules is nicely illustrated in Figure 1. It should be noted that the aromaticity of diazoles is lower than that of benzene because of a smaller contribution of the 2p lone pair of the nitrogen atom to

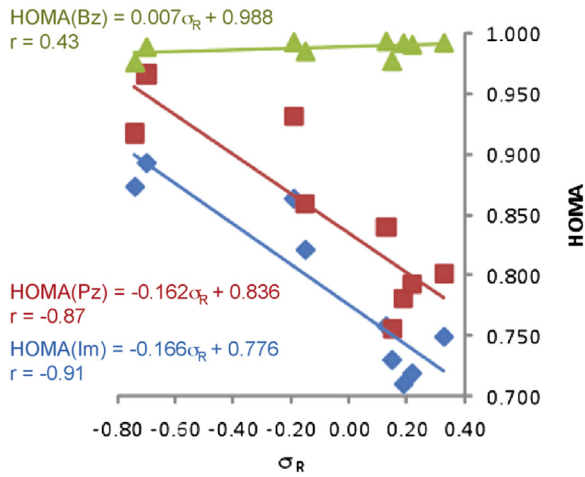
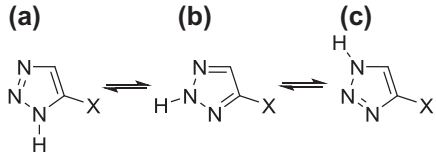


Figure 1 Correlations between HOMA aromaticity index and resonance substituent constant (σ_R) for substituted benzene (Bz), pyrazole (Pz), and imidazole (Im) derivatives. HOMA, harmonic oscillator model of aromaticity. *Reprinted with permission from (2011JPCA(115)8571). Copyright 2011 American Chemical Society.*

the aromatic ring, caused by its greater electronegativity. The large decrease of the aromaticity is particularly observed in the case of substituents with electron-withdrawing properties. The effect of π-donor substituents is less pronounced and can probably be explained by the blocking of the π-donation from N-substituents to the ring of diazoles.

The results of the substituent effect on the electronic structure of C-substituted imidazoles have also been reported (2012CTC(994)97). As in the previous case, based on several aromaticity scales, it was concluded that the aromaticity changes caused by substituents of a different nature in imidazole derivatives are much greater than those observed for monosubstituted benzene (2004JOC(69)6634, 2004PJC(68)2213). This is in line with N-substituted imidazoles, the aromaticity of the investigated species decreases with the increase of the electron-donor character of substituents attached to the imidazole ring. It was also found that protonated species are less aromatic than the neutral ones. Moreover, a lack of correlation between various aromaticity indices was shown, which is in agreement with earlier observations (2002JOC(67)1333).

In the case of triazoles there are two isomers differing by the location of nitrogen atoms—1,2,3- and 1,2,4-triazoles. For unsubstituted isomers, two positions of the pyrrole-type N atom are possible in each species: 1*H*- or 2*H*- in the former case and 1*H*- or 4*H*- in the latter one. However, if

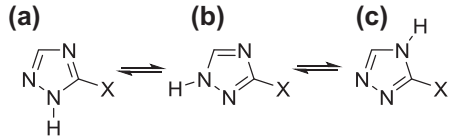


Scheme 3 Tautomerism of C5-substituted 1,2,3-triazoles: (a) 1*H*-, (b) 2*H*-, (c) 3*H*- forms.

two carbon atoms are substituted by two different substituents, three different tautomers for 1,2,3- as well as for 1,2,4-triazoles become possible (Scheme 3).

A computational study on the tautomerism of C5-substituted 1,2,3-triazole derivatives showed that, regardless of the substituent attached to the ring, the 2*H*- tautomer appeared to be the most stable (2003JMS(651-3)697). Except in three cases, with BH_2, BF_2, and COOH substituents, the second stable tautomer is the 3*H*- form, whereas the least stable are the 1*H*- tautomers. Similarly to C5-substituted derivatives of pyrazole and imidazole, the 1,2,3-triazole ring is in an analogous way affected by some substituents acting in a completely different way on the benzene ring, e.g., NH_2 and NO_2 groups. The relative stability of tautomers is influenced by intramolecular interactions (both attractive and repulsive) between the substituent and the proton located either at the N1 or N3 atom. The dependence of a rotation of COOH and $CONH_2$ groups located at the C5 position in 1,2,3-triazoles on the relative energy of these systems was analyzed. For all studied molecules, the Gibbs free energy at 0 and 298 K was estimated. The same type of molecules (C5-substituted 1,2,3-triazole derivatives) were used for the introduction of a new aromaticity index π electron-donor—acceptor descriptor (pEDA), which is a sum of occupation of $2p_z$ orbitals at all atoms constituting the ring (2009JPOC(22)769).

Similar analyses carried out for C5-substituted 1,2,4-triazoles (2004JMST(680)107) revealed that in these derivatives electron-withdrawing substituents and the C5-substituted anion stabilize the 1*H*-tautomer, whereas electron-donating substituents favor the 2*H*- tautomer (Scheme 4). The 4*H*- form of the C5-substituted molecules is the least stable tautomer.



Scheme 4 1*H*-, 2*H*-, and 4*H*- tautomers (a, b, c) of C5-substituted 1,2,4-triazoles.

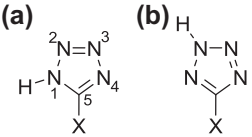
The influence of substituent nature on the CH acidity of 4-substituted 1,2,3-triazoles in tetrahydrofuran (THF) and dimethyl sulfoxide (DMSO) solutions has been studied (2010T(66)3415). Good correlations between substituent parameters and pK_a values were found using the Hammett, Swain and Lupton (1968JACS(90)4328), and Jaffe (1953CR(53)191) approaches. The latter method allows to the prediction the CH acidity of triazoles in the best way due to the consideration of a mixture of the substituent constants σ_m and σ_p. It was shown that the effect of the substituent in position 4 of 1,2,3-triazoles is predominantly inductive and similar to the effect of a meta-group in the benzene ring. The calculated pK_a values in THF and DMSO solutions are close to each other and correlates well with experimental data (1978MI1). The obtained results were also used to interpret an ability of *N*-alkyl-4-nitro-1,2,3-triazoles to undergo the mercuration. It was found that *N*1-substituted isomers undergo mercuration more easily than *N*2-substituted compounds under the same conditions. This agrees with the calculated CH acidity, which is significantly lower for *N*2-isomers than for *N*1–ones.

2.1.2 Tetrazoles

There are two tautomers, 1*H*- and 2*H*- (Scheme 5, X = H), differing in the position of the proton at the nitrogen atom and in consequence in the scheme of double bonds. Thus, we can expect a difference in the π-electron delocalization of their rings.

First, consider substituent effects on the tautomeric equilibria in C5-substituted tetrazole derivatives (Scheme 5). The substituent X acts not only on neighboring nitrogen atoms but also on other atoms. It can be assumed that the location of the proton depends on the electronic structure of the substituent, which can influence the ability of nitrogen atoms to accept the proton.

For unsubstituted tetrazole, the energy difference between 1*H*- and 2*H*-forms is equal to 2.91 kcal/mol, whereas for C5-substituted species the relative energy varies between 0.94 and 5.24 kcal/mol (for methoxy- and fluoro-derivatives, respectively) (2001JOC(66)8737). As it was confirmed



Scheme 5 C5-substituted 1*H*- (a) and 2*H*-tetrazoles (b).

by theoretical and experimental data in the gas phase, the 2*H*- form of tetrazole is more stable than the 1*H* isomer regardless of the substituent (2004JMST(668)123, 2007JMST(822)33).

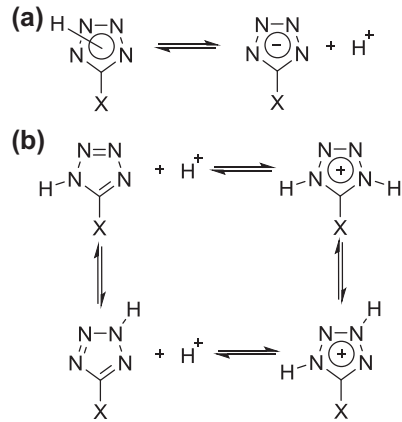
The study of the charge distribution in C5-X tetrazoles (with X = H, Me, CMe_3, Ph, Cl, CF_3, and NO_2) revealed that all substituents lead to changes in the electronic structure of the tetrazole ring (2004JMST(668)123). Therefore, further investigation of the substituent effect on the aromatic character of these systems was undertaken. For this purpose the most common π-electron delocalization indices were used, i.e., HOMA, NICS, and ASE. The obtained values of aromaticity indices showed that substituted 2*H*-tetrazole derivatives are more aromatic than their less stable 1*H*- forms (2001JOC(66)8737) and (2007JMST(822)33). The largest range of variability was found for the ASE parameter. For less aromatic substituted 1*H*-tetrazoles, values of ASE are in the range between 5.67 kcal/mol (for -F) and 16.6 kcal/mol (for $-BH_2$), whereas for 2*H*-tetrazoles ASE varies from 20.4 to 28.46 kcal/mol for $-NH_2$ and -Cl, respectively (2001JOC(66)8737). However, no relationship between the properties of the substituent and the aromaticity of the ring was found.

Chermahini et al. (2007JMST(822)33) also studied substituent effects on the aromaticity (expressed by HOMA and NICS indices) of anionic and protonated forms of C5-X tetrazole derivatives (with X = NH_2, OH, OMe, SMe_3, H, Me, F, Cl, BH_2, CF_3, CN, NO, and NO_2). They have shown that the stability order of protonated forms is related to the nature of the substituent. For electron-withdrawing substituents, the stability follows the sequence: 1,3-H > 1,4-H > 2,3-H > 1,2-H, but in the case of electron-donating groups the order of the stability changes to 1,4-H > 1,3-H > 1,2-H > 2,3-H. NICS(0) values suggest that the anionic forms of tetrazoles are less aromatic than 1*H*- tautomers, whereas the obtained NICS(1) and HOMA values indicate that the aromaticity of anionic forms lies between those found for 1*H*- and 2*H*- tautomeric forms. In the case of protonated tetrazole derivatives, the most aromatic are the 2,3-H forms, whereas 1,4-H tautomers are the least aromatic. Based on the HOMA index analysis the authors concluded that the aromaticity of protonated systems can be related to the nature of the substituent. However, a closer look on their results suggests that the π-electron delocalization of all the studied protonated systems hardly depends on the nature of the substituent at the position C5.

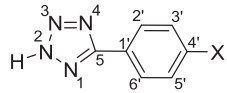
Very similar investigations have been carried out by Trifonov et al. (2004JMST(668)123). In addition to two neutral tautomers, deprotonated

and protonated 1,3-H and 1,4-H forms of C5-X tetrazole derivatives were also chosen. Energies of protonation and deprotonation (Scheme 6) for C5-X substituted derivatives gave a good correlation with the substituent constant σ_p. The aromaticity of their rings, estimated by the Pozharski index (1986KGS717), strongly depends on the position of the proton, but it is rather weakly associated with the nature of the substituent. In contrast, the substituent can strongly affect the balance between 1,3-H and 1,4-H cations. The stability order of the protonated systems agrees with that described above (2007JMST(822)33). In the case of electron-withdrawing substituents, the most preferred form for the conjugated acid is the 1,3-H form.

Apart from aromaticity studies, the acidity of C5-substituted tetrazoles and para-substituted phenyltetrazoles (see Scheme 7) has been investigated using the atomic electrostatic potential (2008JPCA(112)10017). In both types of compound, excellent correlations were found between the potential at the acidic hydrogen atom and the free energy of dissociation, with correlations coefficients (cc) of -0.958 and -0.984 for tetrazole and phenyltetrazoles, respectively. These potentials also correlate with the Hammett substituent constants. According to the slopes of linear trends, it is clear that the sensitivity to the substituent effect in the tetrazole series is greater than in the phenyltetrazole one. It is noteworthy that the electrostatic potentials at all individual atoms of studied systems are mutually highly correlated ($cc > 0.96$) except for the C5 atom in tetrazoles and the C4 atom in phenyltetrazoles, which are directly related to the substituent ($cc < 0.56$).



Scheme 6 Deprotonation (a) and protonation (b) of C5-X substituted tetrazole derivatives (with X = H, Me, CMe_3, Ph, Cl, CF_3, and NO_2).



Scheme 7 Substituted phenyltetrazoles. Only the dissociating hydrogen atom is shown.

Properties of these atoms correlate with the substituent's characteristics rather than with properties of the rest of the molecule.

The substituent effect in C5-substituted 2*H*-tetrazoles has also been studied in terms of the cSAR concept (2008PJC(82)935) (the original acronym was qSAR, but to avoid confusion and any misunderstanding with QSAR (quantitative structure-activity relationships) it was changed to cSAR (2014JOC(79)7321)). The cSAR(X) index is defined as the sum of atomic charges at the substituent and the *ipso* carbon atom, i.e., $cSAR(X) = q(X) + q(C_{ipso})$ (2008PJC(82)935). For 20 tetrazole derivatives, the obtained cSAR(X) values are highly correlated with σ_p constants ($cc = -0.933$) and well correlated with the calculated free energies of dissociation ($cc = 0.882$). It is important to note that similar correlations with only the substituent charges (i.e., without the charge of C_{ipso}) are very poor, $cc = -0.131$ and 0.260, respectively.

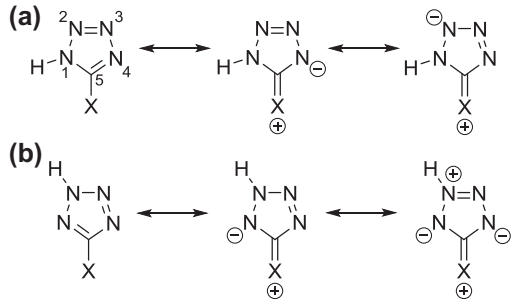
In turn, sums of charges on pairs of neighboring atoms, $q(N1 + N2)$ and $q(N3 + N4)$, are also well correlated with σ_p ($cc = 0.92$) and with each other ($cc = 0.987$). If instead of σ_p the obtained cSAR(X) values are used then the *cc* values are even higher (approximately −0.99). It was therefore concluded that the substituent and the *ipso* carbon atom in the tetrazole ring must be treated as one entity, the charge of which determines many properties of the substituted molecule, including the acidity.

A comparison of the substituent effects in monosubstituted tetrazole systems and benzene derivatives has been presented (2011T(67)6316). For this purpose the pEDA index (2009JPOC(22)769), defined as the sum of the occupation of $2p_z$ orbitals at all atoms of the ring minus 6, has been used as a substituent descriptor. In all three cases (substituted benzenes, 1*H*- and 2*H*-tetrazole derivatives) the pEDA index, which illustrates the π-electron transfer from the substituent to the ring or vice versa, is well correlated with σ_p^+ constants. A more detailed analysis revealed that the dependence of $2p_z$ occupancies at the carbon atoms of benzene in either ortho- or para-positions on pEDA values are represented by linear trends with $cc = 0.971$ and 0.968, respectively. In contrast, the same correlation for the carbon atom in the meta-position is worse ($cc = -0.791$) and with a small

opposite slope. This observation is consistent with a classical view of substituent effects in benzenes, i.e., the meta-position is affected to a greater degree by the field effect. Therefore, $2p_z$ orbitals of the meta carbon atom are less sensitive than in the case of ortho and para carbon atoms. Similar correlations were found for both 1*H*- and 2*H*-tetrazole derivatives. Occupations of the $2p_z$ orbitals of all nitrogen atoms, except N3, correlate nicely with pEDA values ($cc \geq 0.95$). The lack of the correlation with the $2p_z$ occupation at the N3 atom may suggest that this position in 1*H*- and 2*H*-tetrazoles resembles to some extent the meta-position in the benzene series.

Scheme 8 describes these facts based on simple canonical structures: single-excited resonance structures allow localization of a negative charge only at the N2 and N4 in 1*H*-tetrazoles and at the N1 in 2*H*-tetrazoles, in a manner similar to carbon atoms in the ortho- and para-positions of a benzene ring (2007JPOC(20)297). A good correlation with the occupation at N4 in 2*H*-tetrazole can be illustrated when a double-excited structure is taken into account. In both cases, the smallest occupation at the N3 atom is in line with the lack of appropriate canonical structures.

Finally, it is useful to consider the other kind of the substituent effect, namely the effect of introducing of nitrogen atom(s) to pyrrole. The effect of aza-substitution on the aromaticity of azoles was studied by Ramsden (2010T(66)2696). It was shown that the aromaticity of the azoles, estimated by NICS, ASE, and HOMA indices is in a regular way dependent on the number of nitrogen atoms and their particular positions. Additionally, changes in σ- and π-electron structures, introduced by the number and position of incorporated nitrogen atoms to the pyrrole moiety were analyzed separately (2011JMM(17)1427). The obtained results support a general rule, i.e., if the σ-structure becomes richer in electrons then the



Scheme 8 Resonance structures of 1*H*- (a) and 2*H*-tetrazoles (b) describing the effect of electron-donating substituents.

π-structure has to lose them. However, changes in the σ/π relationships depend on the number of pyridine-type nitrogen atoms and their location. The aromaticity of azoles, expressed by the NICS(1) index, correlates linearly with the number of nitrogen atoms and NN bonds ($cc = -0.992$).

2.2 Six-Membered Rings

The growing interest in nitrogen-containing six-membered heterocyclic compounds is due to their abundance in nature and the variety of their applications. They are potential and essential candidates for the stabilization of metal ions in coordination chemistry (2014JPCA(118)6216). Such heterocycles are characterized by rather high electron density, high positive heats of formation, and good thermal stability (2004ACIE(43)4924, 2005JACS(127)12537). Apart from organic and structural chemistry, nitrogen-containing heterocycles are used in medicinal and pharmaceutical chemistry (2006MP(3)745).

Unlike cyclic five-membered nitrogen-containing systems, all the nitrogen atoms in the aza-analogs of benzene are of the same electron structure, valence, and electronegativity. There are four aspects of the substituent effect in this kind of π-electron system: (1) the basicity of the nitrogen atom(s) in the ring as well as its (their) reactivity; (2) the π-electron delocalization in the ring and hence the whole ring properties; (3) the stability of tautomers, when they exist; and (4) the participation of the nitrogen atom(s) in intermolecular interactions.

It should be stressed that most of the published papers concerning heterocyclic systems deal with the nitrogen-containing cycles, but some of them compare properties between analogous systems with other heteroatoms and these results are presented in Section 3.

Pyridine is considered as one of the commonest heterocycles among nitrogen-containing heterocyclic compounds. Substituent effects in meta- and para-X-substituted pyridines (with X = OMe and Me) on their basicity have been studied in water and ionic liquid (IL, 1-buthyl-3-methylimidazolium hexafluorophosphate) (2010JOC(75)3912). The equilibrium constants were evaluated by spectrophotometric titration of pyridine solution with trifluoroacetic acid. The results of the Hammett approach (Eqn (1)), applied to all studied systems, allow one to state that pyridine basicity is almost twice as less sensitive to the substituent effect in IL than in water (Figure 2).

Additionally, substituent effects and their additivity on the proton affinity and gas phase basicity have been studied for 11 substituents, namely NO_2,

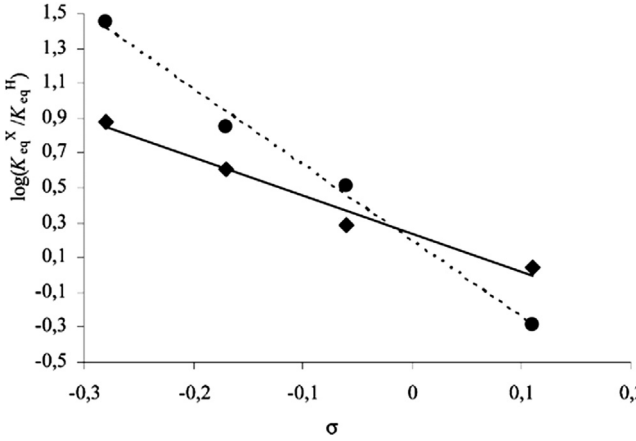


Figure 2 Hammett plots for the equilibrium of the reaction between 3- and 4-X-substituted pyridines (with X = OMe and Me) and trifluoroacetic acid in IL ($\rho = -2.17$, solid line) and water ($\rho = -4.53$, dotted line). *Reprinted with permission from (2010JOC(75)3912). Copyright 2010 American Chemical Society.*

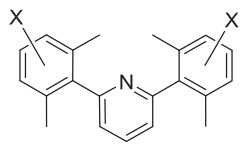
CN, CHO, F, Cl, Br, H, Me, NH_2, NHMe, and NMe_2, in mono-, di-, and trisubstituted pyridine derivatives (2011CTC(966)31). The Hammett plots, $\log(K/K_0)$ versus σ, for mono-, di-, and trisubstituted species gave the slopes of −5.1, −5.0, and −4.4, respectively. The negative slopes (ρ) indicate the increase of the protonation by electron-donating substituents and its decrease by the electron-withdrawing ones. The ρ values suggest that the sensitivity of this process decreases with the increasing number of substituents. However, no statistical analysis was performed to verify the significance of the difference between slopes (the first two are very close to each other). The correlation coefficients for individual correlations are also missing. For all 27 substituted systems the slope is −4.7 ($R^2 = 0.97$). For di- and trisubstituted systems, the total σ constants were calculated by summing up Hammett parameters (σ_p or σ_m) for all substituents present in the molecule. Therefore, it could be concluded that the effect of substituents on the studied properties is additive. This was confirmed by good correlations between proton affinities and the molecular electrostatic potentials around the nitrogen atom as well as the electron densities at bond critical point (BCP) of the N−H bond for some groups of polysubstituted pyridines.

The protonation of polysubstituted pyridines (from di- to penta-) was also investigated for halogen (Cl or Br) derivatives (2007JMGM(26)740). The obtained acidity constants (pK_a) show a good correlation ($cc = 0.99$) with the experimental values. Additionally, the experimental pK_a values

are also roughly correlated with the nucleophilicity parameter (*n*) and the charges on the nitrogen atom of pyridines.

A synthesis of 2,6-diarylpyridines allowed the experimental measurement of the pyridine fragment pK_a in substituted phenyl systems (see Scheme 9; 2014CEJ(20)6268). For para-substituted systems the obtained pK_a values (measured in DMSO) are strongly correlated with the Hammett σ_p ($cc = 0.99$). In the case of the methoxy group, its position in the ring (para- or meta-) does not influence the acidity of the substituted pyridine. The calculated proton affinity energies in the gas phase and DMSO (effect of solvation was simulated by the conductor-like screening model (COSMO)) are also nicely correlated with σ constants. The obtained slopes (ρ) amount to -11.0 and -1.8, respectively. This indicates that the pyridinium cation interacts with the substituents located at the distant para-position of phenyl rings more strongly in the gas phase than in DMSO.

The effect of monosubstitution on the geometric and electronic properties of neutral and protonated ortho-, meta-, and para-X-pyridine derivatives has been studied for a broad range of substituents. In particular, substituents containing atoms of the second and third row of the periodic table (X = H, Li, BeH, BH_2, Me, NH_2, OH, F, Na, MgH, AlH_2, SiH_3, PH_2, SH, and Cl) were taken into consideration (2008SC(19)339). The effect of substituents was described by changes in the π-electron delocalization of the pyridine ring. For this purpose NICS(0), NICS(1), HOMA indices and the electron density at ring critical point (RCP) (2007CEJ(13)7996) were used. The aromaticity of the pyridine ring increases with the increasing atomic number of the substituent for both rows of the periodic table when the HOMA index is applied; however, no such clear picture was found for NICS(1) values. The application of the electron density at RCP to both neutral and protonated species revealed their mutual, good linear correlations, separately for meta- and para-substituted derivatives. The slopes, 0.567 and 0.593, respectively, indicate that the aromaticity of the neutral derivatives is slightly less sensitive to the substituent effect than the protonated species. Moreover, very good correlations between substituent effects,



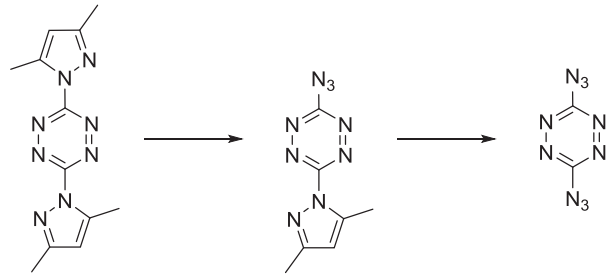
Scheme 9 Substituted 2,6-diarylpyridines, with X = H, *p*-OMe, *p*-Me, *p*-F, *p*-Cl, and *m*-OMe.

described by HOMA and NICS(0) indices, for benzene derivatives and those for pyridines were found for meta- and para-substituted systems ($cc > 0.98$).

Heterocyclic rings (five- and six-membered) can also be considered as functional groups, known as heteroaryl groups. In the case of pyridine, three substituents should be taken into account: 2-, 3-, and 4-pyridyl. The electronic effects of heteroaryl groups on the C═N−N unit of the five different hydrazone derivatives of aldehydes have been investigated (2008JPOC(21)173) by ^{13}C and ^{15}N NMR (nuclear magnetic resonance) chemical shifts, together with a natural bond orbital (NBO) analysis (1985JCP(83)735). The ^{15}N chemical shifts of the C═N and C═N−N fragments and the NBO charges at C═N−N unit correlate with the substituent constants σ (1981PPOC(13)119) of the heteroaryl groups. ^{13}C NMR chemical shifts of the C═N bond of *N*,*N*-dialkylhydrazones of the heteroarenecarbaldehydes can be described by a dual parameter possessing the polar substituent constant σ^* of the heteroaryl group (1991CR(91)165) and the electronegativity of the heteroatom as variables. It was found that the observed electronic effects of the heteroaryl groups or substituted phenyls on the hydrazone fragment are very similar.

Particular attention has been directed to "energetic organic compounds" with a high-nitrogen content due to their unique properties and thus numerous applications have been described (for details see (2005JACS(127)12537) and references therein). Very interesting results were obtained for 3,6-diazido-1,2,4,5-tetrazine. The normalized heat of formation ($N\Delta H_f$, determined experimentally) was found to have the highest positive value compared to all other organic molecules (2005JACS(127)12537). Moreover, properties of tetrazine derivatives can be changed by a substituent or tautomeric preferences. As presented in Scheme 10, azido substituents dramatically enhance the energy content of the system. Replacement by the first N_3 increases $N\Delta H_f$ by 19.21 kJ/atom, whereas the second N_3 increases $N\Delta H_f$ by an additional 54.45 kJ/atom. Appropriate changes of the redox potential, $\Delta(E_{1/2})$, correspond to 0.472 and 0.663 V, respectively. Therefore, the first substitution occurs more easily than the second one, which was found to be consistent with synthetic results.

The azido-tetrazolo tautomerization and the tetrazolo transformation have been investigated by ^{13}C NMR and cyclic voltammetry studies. Results of the latter suggested that the conversion of the azido form to the tetrazolo structure is electronically favored (see Scheme 11). However, the experimental data revealed that the last transformation presented in



ΔH_f=+615 kJ/mol
NΔH_f=+18.09 kJ/atom

ΔH_f=+858 kJ/mol
NΔH_f=+37.30 kJ/atom

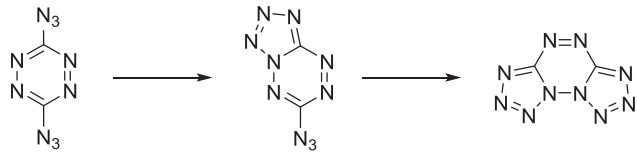
ΔH_f=+1101 kJ/mol
NΔH_f=+91.75 kJ/atom

Scheme 10 Substituent effect on energetic properties of 1,2,4,5-tetrazine derivatives.

Scheme 11 has a substantial activation energy barrier and can occur in DMSO when the temperature is at least 80 °C.

Since pyridine can be a part of drug structures, analysis of the substituent effect on the permeability of the parent pyridine and 14 monosubstituted derivatives across Caco-2 monolayers has been investigated (2006MP(3)745). The comparison of molecular descriptors from computational chemistry (solvent free energy, solvent accessible surface area, polar surface area, cavitation energy) with Hansch-based molecular descriptors (1995MI) revealed that the first method can better describe the observed substituent effect than the Hansch approach. The results indicate that pyridine itself is highly permeable and the introduction of a substituent significantly reduces this property (almost 20 times), as presented in Figure 3. Moreover, computational descriptors suggest that the desolvation of pyridines from water dictates the substituent effect on the permeability.

In addition, the study of the first hyperpolarizabilties (β) of triazine derivatives (2004JPOC(17)169) showed their growth with increasing the electron-donating power of the substituent and giving an excellent correlation with the gas-phase σ^+ constants (1996BCSJ(69)2009). Moreover, β values are larger when the conjugation length between the ring and the



$E_{1/2}$ = +0.518 V

$E_{1/2}$ = -0.106 V

$E_{1/2}$ = -0.472 V

Scheme 11 Voltammetric data for tautomeric forms of 3,6-diazido-1,2,4,5-tetrazine.

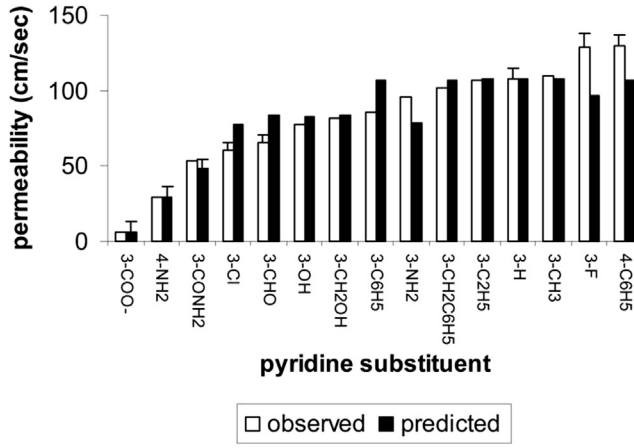
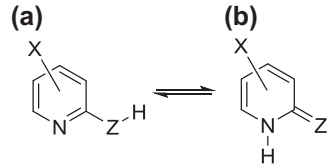


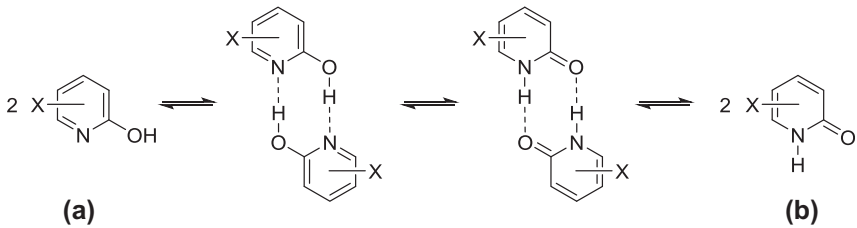
Figure 3 Observed and predicted permeability values for substituted pyridines. *Reprinted with permission from (2006MP(3)745). Copyright 2006 American Chemical Society.*

substituent becomes longer. This is probably caused by greater electron delocalization which leads to a decrease of the highest occupied molecular orbital − lowest unoccupied molecular orbital (HOMO-LUMO) energy gap. Therefore, the susceptibility of β to the donor strength increases with increasing the elongation of a substrate.

Next, the substituent effect on the tautomeric preference should be considered. For example, ortho-derivatives of pyridine with substituents which have an acidic proton may participate in prototropic tautomerism (Scheme 12; 2002A(11)198). Stability of the particular tautomeric form depends on an additional substituent and intermolecular H-bonding (Scheme 13). Moreover, tautomeric preferences can be changed by a solvent. For 6-X substituted 2-hydroxypyridines, the tautomeric equilibrium is strongly affected by substituents which can change the π-electron structure of fragments involved in the prototropy. For example, it was found that 2-hydroxy-6-chloro- and 2-hydroxy-6-methoxy-pyridines exist mainly in the aromatic form **a**



Scheme 12 Prototropic equilibrium in some derivatives of pyridine. Z = O, S, NX.



Scheme 13 Influence intra- and intermolecular interactions on tautomeric equilibrium. X = H, 6-Cl, 6-NH_2, 6-OCH_3, 5-NO_2.

(Scheme 13), whereas 2-hydroxy-6-methyl-pyridines prefer form **b**. An X-ray diffraction study of 2-hydroxy-5-nitropyridine revealed that its oxo-form **b** is more stable in the solid state, while in solution both forms may exist.

At this point it is important to note that in organometallic chemistry, pyridine is considered as a common and relatively strong σ-donating ligand. The substituent effect on the emission, excitation spectra, quantum yields, and emission lifetimes for the mixed ligand systems of bis-(2,2′-bipyridine) ruthenium(II) complexes having 4-Y-substituted pyridines (L) and non-chromophoric groups X ($X = PPh_3$, Cl^- and NO_2^-) as monodentate ligands has been reported (2014JPCA(118)6216). The following ligands L were used in the study: (1) isonicotinamide (isnc), (2) 4,4′-bipyridine (bipy), (3) pyridine (py), (4) 4-phenylpyridine (phpy), (5) 1,2-bis(4-pyridyl) ethane (bpa), (6) 4-picoline (mepy), (7) 4-aminopyridine (apy), and (8) 4-dimethylaminopyridine (ampy). All measurements were performed in 4:1 EtOH−MeOH solution at 77 K. The idea of these studies is nicely summarized in Figure 4; 2014JPCA(118)6216). The Hammett relations (ν_{00} versus σ_p, Figure 5) illustrate the influence of the substituents on the emission spectra parameter. The slopes of these correlation lines (for different ligands X) are nearly the same, indicating that the impact of nonchromophoric ligands X and 4-substituted pyridine ligands L on the metal-to-ligand charge transfer excited state are independent and additive.

It has also been demonstrated that the substituent located in the para-position in the pyridine moiety influences the Cr−N bond in the $Cr(CO)_5$-pyridine complex (Scheme 14; 2007JOC(692)3866). Electron-withdrawing substituents stabilize the Cr−N bond, whereas the electron-donating substituents weaken it, mainly affecting the π-component of the Cr−N bond. Mutual interrelation between geometrical and electronic properties of the Cr−N bond and the considered substituent constants illustrate the complexity of the metal−ligand bonding.

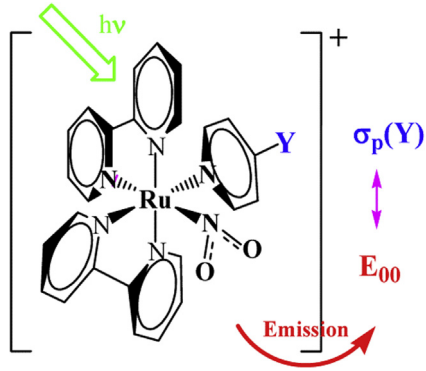


Figure 4 Substituent effect of 4-Y-substituted pyridines as ligands on photophysical properties of bis-bipyridyl nitro complexes of ruthenium (II). *Reprinted with permission from (2014JPCA(118)6216). Copyright 2014 American Chemical Society.*

Finally in this section, relations between substituents' properties and characteristics of intermolecular interactions are discussed. Analysis of the experimental geometries of H-bonded complexes of variously substituted pyridine and pyridinium derivatives (taken from *The Cambridge Structural*

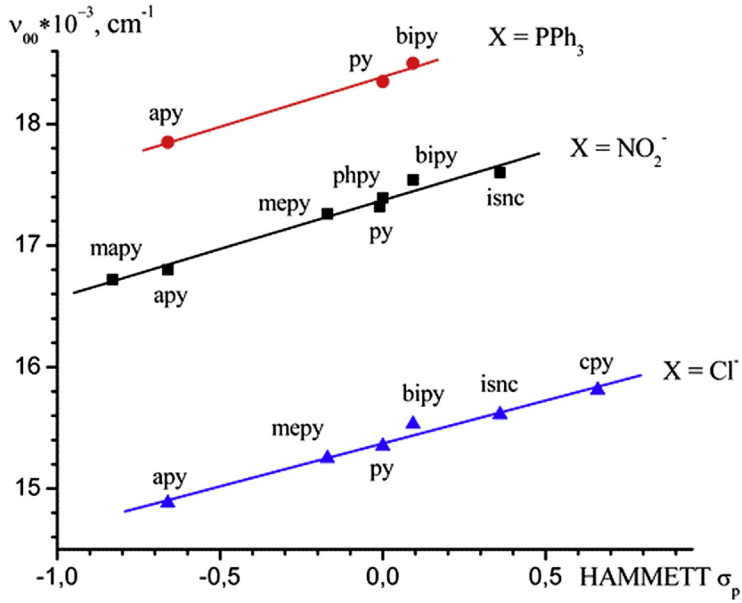
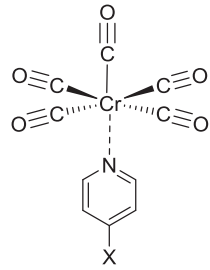


Figure 5 The substituent effect on the emission spectra parameter for the series of complexes *cis*-$[Ru(bpy)_2(L)(X)]^{n+}$ in EtOH-MeOH (4:1) at 77 K (X = PPh3, NO_2^-, and Cl^-). *Reprinted with permission from (2014JPCA(118)6216). Copyright 2014 American Chemical Society.*

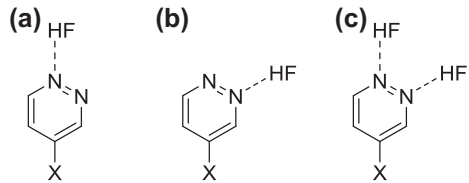


Scheme 14 The para-X-substituted $Cr(CO)_5$-pyridine complex (with X = NO, NO_2, CN, CHO, F, H, Me, OMe, OH, and NH_2).

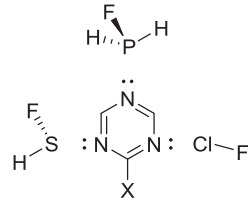
Database) revealed a very small variation of all bond lengths in the ring but substantial changes in the values of α (*ipso*) and β bond angles near the nitrogen atom (2005JOC(70)8859). Since the X-ray structural analysis does not give a reliable position of the proton, the *ipso* angle at the nitrogen atom was proposed as a valuable indicator of the proton location in the H-bond interaction: N···H or N—H.

Energy decomposition analysis (by the symmetry adapted perturbation theory (SAPT) approach) was performed for the N···HF interactions in the X-pyridazine···HF and X-pyridazine···$(HF)_2$ complexes (Scheme 15; 2012APC362608). It was found that the binding energies of the latter complexes (**c**) correlate well with the total Hammett constants ($\sigma_p + \sigma_m$). Electron-donating substituents increase the strength of interactions, whereas for electron-withdrawing ones the trend is opposite. The results of the SAPT analysis showed that the electrostatic component is dominant in interactions taking place in X-pyridazine···HF systems. Interaction energies for para-complexes (**a**) correlate well with σ_p, whereas for meta-complexes (**b**) only the electrostatic energy correlates with σ_m, indicating different electronic interactions for these two cases.

Substituent effects on weak noncovalent interactions (pnicogen, chalcogen, and halogen bonding) (2013SC(24)1705) in complexes of X-substituted



Scheme 15 The para-X-pyridazine complexes with HF, X = NMe_2, NHMe, NH_2, Et, Me, OMe, OH, CN, OF, NO_2, F, Br, and Cl.



Scheme 16 Possible pnicogen (P···N), chalcogen (S···N), and halogen (Cl···N) bonding in X-substituted s-triazine (X-TAZ···Y, X = CN, F, Cl, Br, H, Me, OH, and NH_2; Y = P, S, and Cl).

s-triazine (X-TAZ···Y, see Scheme 16) have been studied using quantum theory atoms in molecules (QTAIM) (1994MI) and NBO methods.

A linear correlation was found between the binding energies and the sum of the Hammett substituent constants for X-TAZ···Y complexes. Linear dependences between electron densities at BCP and the appropriate interatomic distances are satisfied, but the slopes of these lines are different, indicating variable sensitivity of the noncovalent interactions to the substituent effects (see Figure 6).

A comprehensive *ab initio* study of geometric and energetic properties of halogen-bonded complexes between two aromatic moieties (pyridine and

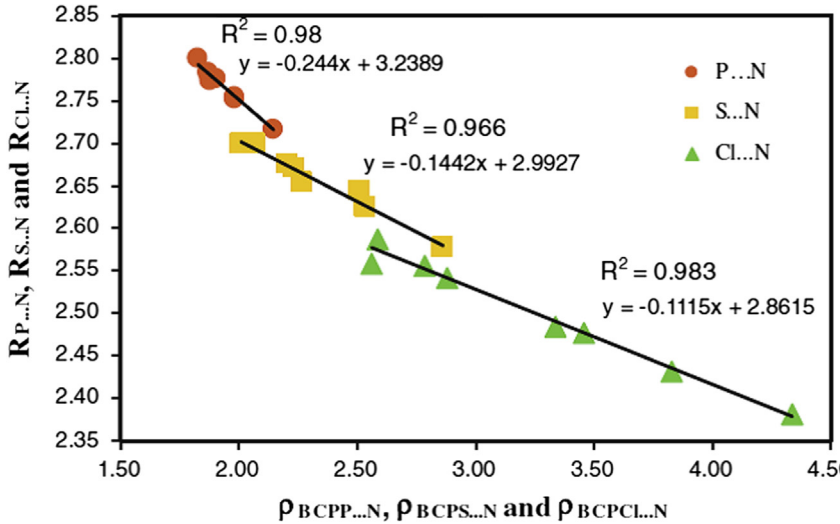


Figure 6 Relationships between the electron density at BCPs of pnicogen, chalcogen, and halogen bonds and their length in X-TAZ···Y complexes. BCP, bond critical point. *Reproduced from (2013SC(24)1705) with kind permission from Springer Science and Business Media.*

benzene derivatives) was performed by Bauza et al. (2011PCCP(13)20371). Substituent effects in both rings (halogen-bond donor and acceptor molecules) and in two different electron-donor molecules (pyridine and cyanobenzene) were considered. Relations between interaction energies and substituent constants for the complexes of pyridine with *p*-substituted iodotetrafluorobenzenes and for the complexes of *p*-substituted pyridines with iodotetrafluorobenzene are shown in Figure 7. The slopes of both regression plots are similar in magnitude but obviously of opposite sign (−1.2 and 1.3, respectively). Therefore, the influence of the substituents on the interaction strength is similar in either the halogen-bond donor or acceptor aromatic molecules.

Strong correlations were also found for the complexes of cyanobenzene with *p*-substituted iodotetrafluorobenzenes and for the complexes of *p*-substituted cyanobenzenes with iodotetrafluorobenzene. In this case the slopes are different in magnitude (−1.0 and 0.7, respectively), indicating a smaller substituent effect on the interaction energy in *p*-substituted cyanobenzenes than in *p*-substituted iodotetrafluorobenzenes. The halogen bond in the benzene complexes is weaker compared to the pyridine complexes because the aromatic nitrogen atom is a better acceptor than the nitrile group.

The interaction of *p*-X-substituted pyridine derivatives with atomic chlorine (Scheme 17) has been investigated (2015MP(doi)). The existence of an intermolecular N···Cl interaction was confirmed by topological parameters from QTAIM (1994MI). Moreover, their values suggested a partially covalent character of the N···Cl bonding in all studied complexes. The obtained binding energies ranged between −42.08 kJ/mol (4-NO_2-pyridine···Cl) and −53.96 kJ/mol (4-NH_2-pyridine···Cl) and were found

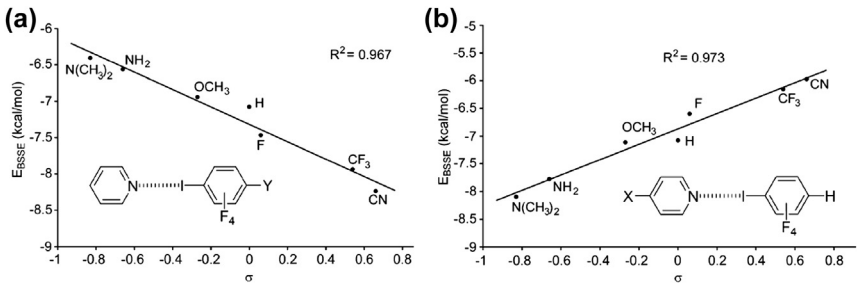
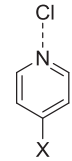


Figure 7 Hammett's relation for pyridine···C_6F_4I-Y complexes (a) and X-pyridine···C_6HF4I complexes (b). *Reproduced from (2011PCCP(13)20371) with permission from the PCCP Societies.*



Scheme 17 Para-X-pyridine···chlorine complexes (with X = H, NH_2, Me, F, CN, and NO_2).

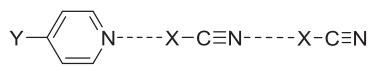
to correlate with the proton affinity and the ionization potential of the studied pyridines.

It should also be noted that a substituent in a heterocycle can influence the cooperativity of halogen bonding. This effect was analyzed in ternary complexes of 4-substituted pyridine derivatives (Scheme 18; 2013JPCA(117)5551). For all complexes the obtained values of the cooperativity are negative, indicating that the ternary complex is more stable than the sum of two isolated binary ones. Furthermore, a linear relationship was found between the cooperativity and the total stabilization energy as well as the Hammett constant (see Figure 8). The most stable complexes exhibit the larger absolute values of the cooperativity and they are formed by derivatives with electron-donating substituents.

2.3 Polycyclic Systems

The description of works concerning substituent effects in polycyclic compounds containing nitrogen atom(s) can be divided into four parts: (1) benzo-fused analogs of nitrogen-containing five-membered rings (indole, indazole, benzimidazole); (2) benzo-fused analogs of nitrogen-containing six-membered rings (quinoline, isoquinoline, quinoxaline, quinazoline); (3) benzo-fused analogs of nitrogen-containing seven-membered rings (benzodiazepine); and (4) other polycyclic systems consisting of two or more nitrogen-containing rings.

First, for aza analogs of indole (Scheme 19), the substituent effects on the π-electron delocalization of mono- and disubstituted derivatives have been considered (2010JMST(951)72). Electronic aromaticity indices (average of two center indices (ATI) and FLU) indicate that the aromaticity of both rings in substituted derivatives is lower than the local aromaticity in their



Scheme 18 Halogen-bonded ternary complexes of 4-substituted pyridine derivatives, Y = H, F, OH, OMe, Me, NH_2, NO_2, CN; X = Cl and Br.

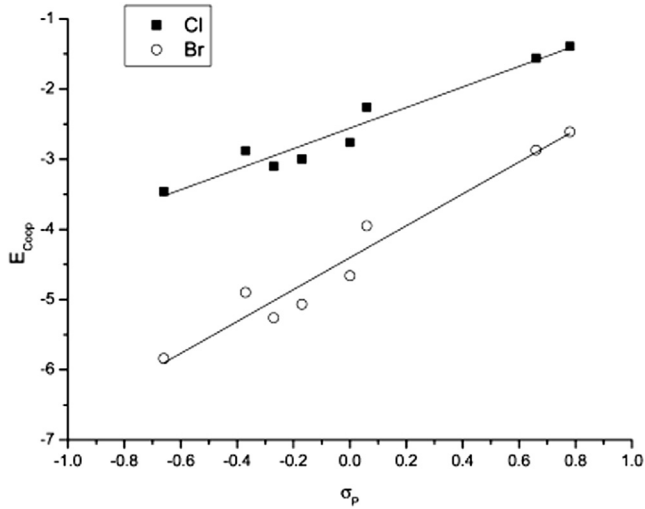
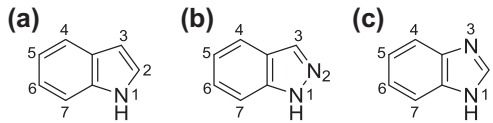


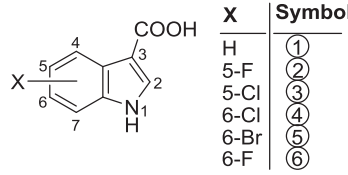
Figure 8 Relationships between cooperative energy (in kJ/mol) and the Hammett constants σ_p for 4-Y-pyridine···XCN···XCN systems (X = Cl or Br). *Reprinted with permission from (2013JPCA(117)5551). Copyright 2013 American Chemical Society.*

unsubstituted counterparts, regardless of whether the substituent is of electron-donating or electron-withdrawing nature. In disubstituted derivatives, the π-electron delocalization is significantly lower than in the monosubstituted ones. It was also found that the position of the substituent has a significant influence on the aromaticity. As a rule, structures with the position of substituents leading to maximum aromatic character are favored. For example, the introduction of substituents in the positions 4 and 7 of the benzene ring provides the structures with the smallest decrease of the aromaticity in the five-membered ring compared to the parent unsubstituted ring.

The substituent effect of halogen atoms on the crystal structure of indole-3-carboxylic acid derivatives (Scheme 20) has been investigated experimentally (2013CEC(15)7490). Different types of atoms or their positions have a significant effect on the crystal structure, molecular π···π stacking motives and the types of intermolecular interactions. The results



Scheme 19 Numbering of atoms in 1*H*-indole (a), 1*H*-indazole (b), and 1*H*-benzo[*d*] imidazole (c).



X	Symbol
H	①
5-F	②
5-Cl	③
6-Cl	④
6-Br	⑤
6-F	⑥

Scheme 20 Structure of indole-3-carboxylic acid derivatives (see Figures 9 and 10).

obtained reveal that the C6 position substituted with halogen atoms strengthens the hydrogen bond interactions (OH···H and NH···H) as well as π···π intermolecular interactions between the benzene ring and the pyrrole ring of the different indole structures. In contrast, the structures with a substituted C5 position usually weaken the OH···H and π···π interactions. The effect of an F atom is greater than Cl and Br atoms, which is ascribed to its high electronegativity and a small radius.

It is interesting to note that the substituent effects described above have been visualized by the molecular Hirshfeld surfaces (2007CGD(7)755, 2007CEC(9)728). The H···H interactions contribute the most to the total Hirshfeld surface followed by the OH···O and XH···π (X = F, Cl, Br) interactions (Figure 9). Moreover, it was found that the melting points of

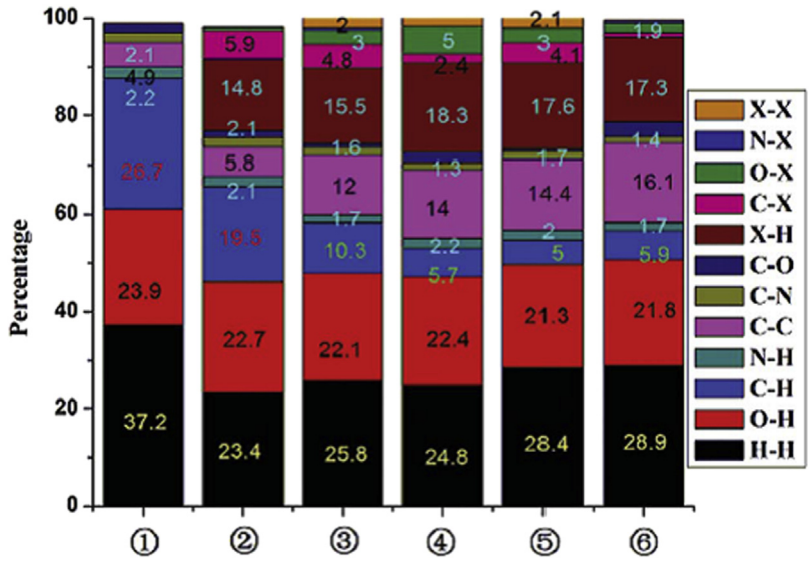


Figure 9 The percentage contributions from the individual intermolecular interactions to the Hirshfeld surface of compounds **1**–**6**; X represents halogen atoms. *Reproduced from (2013CEC(15)7490) with permission from The Royal Society of Chemistry.*

all the studied compounds are well correlated with the contributions of these interactions (see Figure 10).

Second, the substituent effect on the stability and the aromaticity of substituted aza analogs of naphthalene should be considered. Different mono- and disubstituted derivatives of aza- and diazanaphthalenes (with F, Cl, OH, OCH_3, and CN substituents) have been studied theoretically (2010JPOC(23)440, 2011CTC(963)263). Electronic (para-delocalization index (PDI), ATI, and FLU), magnetic (NICS), and structural (HOMA) aromaticity indices have been used to describe the local π-electron delocalization. It has been pointed out that the decrease of the aromaticity of diazanaphthalene can be compensated by the introduction of an

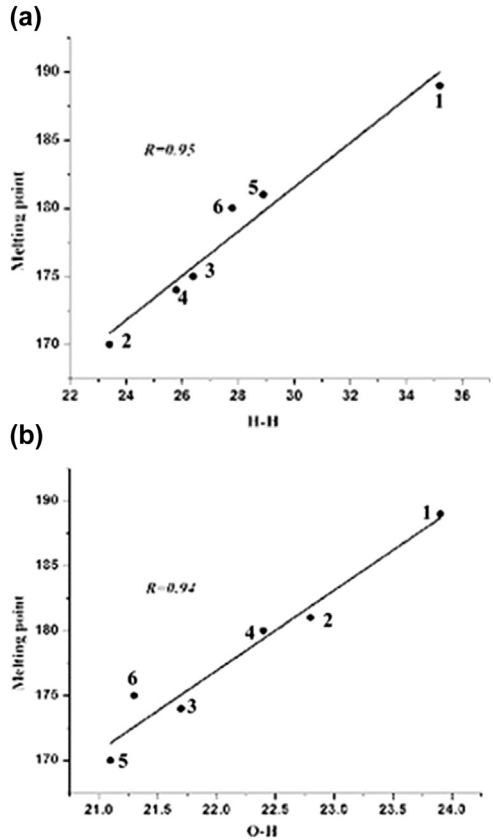
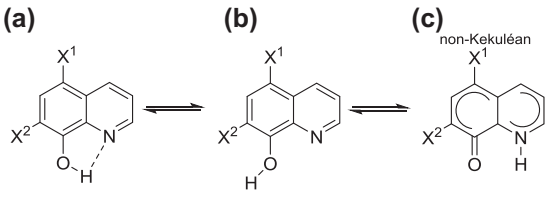


Figure 10 Correlations between the melting points (°C) and percentage contributions of the H···H (a) and OH···O (b) intermolecular interactions to the Hirshfeld surface for compounds **1**–**6**. *Reproduced from (2013CEC(15)7490) with permission from The Royal Society of Chemistry.*

electronegative atom attached to a ring carbon atom. The aromaticity can vary significantly depending on the relative position of the substituent, ortho-, meta-, or para- to the heteroatom. The systems become more aromatic when the electronegative atoms or groups are located closer to the aza points.

Particular attention has been paid to hydroxyquinolines (HQs) due to their widespread use in medicine, agriculture, and other areas. HQ may exists in the form of different structural isomers (2HQ−8HQ), tautomers (OH or NH), and conformers (OH group rotation). Their structures, relative stabilities, and aromaticity, calculated using the HOMA index, have been investigated theoretically (2011CTC(972)48). The NH-tautomer of the 2HQ molecule was found to be the most stable of all studied systems because exocyclic groups (C═O and N−H) form a cyclic amide structure. For all other HQs, the OH-tautomers are preferred. The aromaticity of both rings in OH-tautomers is high (HOMA > 0.75) and varies only slightly with the OH position, while in some NH-tautomers the aromaticity can be reduced up to 0.1 HOMA units. For 8-hydroxyquinoline, the effect of introducing two extra substituents was studied in details (2010JMST(961)101). Regardless of the substitution, the form **a** (Scheme 21) with an intramolecular OH•••N hydrogen bond has been found as the most stable. Based on a QTAIM analysis it was shown that this H-bond is the weakest in unsubstituted 8HQ, whereas the strongest one is in nitroxolin (Scheme 21, $X^1 = NO_2$, $X^2 = H$). The obtained σ- and π-electron populations of the valence orbitals in each ring suggest that the halogens act as the σ-electron-withdrawing and the π-electron-donating substituents, whereas the NO_2 group is the σ- and π-electron-withdrawing substituent. Moreover, the σ substituent effect is local (i.e., influences only the substitution site), while the π substituent effect is extended over the pyridine ring.

The third group of polycyclic N-containing compounds is represented by derivatives of benzodiazepine. In particular, the substituent effect in

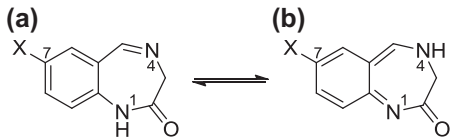


X^1	X^2	Compound name
H	H	8-Hydroxyquinoline
Cl	Cl	Chloroxine
Cl	I	Clioquinol
I	I	Iodoquinol
NO_2	H	Nitroxoline

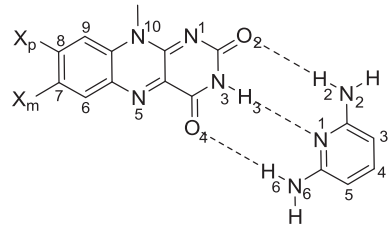
Scheme 21 Tautomeric equilibria and pharmaceutical names of 8-hydroxyquinoline derivatives.

benzodiazepinone derivatives, which have wide pharmaceutical application, has been analyzed in the gas phase and in water (simulated by the IEF-PCM method) (2012CTC(993)13). A variety of substituents covering a large range of the electron-donating/electron-withdrawing properties have been considered. The N1H tautomers were found to be more stable than the N4H ones (Scheme 22), both in the gas phase and water, and their stability depends on the π-electron abilities of the substituent (in terms of the pEDA descriptor). The aromaticity of both rings, expressed by the HOMA index, was found to be the main reason for the relative instability of the N4H form; its benzo ring is less aromatic and the diazepinone ring is more antiaromatic than for the N1H tautomer. The correlations between topological parameters and the substituent descriptors σ electron-donor—acceptor descriptor (sEDA) and pEDA revealed that the modification of the pharmaceutical activity of benzodiazepinones can be partially controlled by attaching a substituent with appropriate donor—acceptor properties in the C7 position (Scheme 22).

Among representatives of the last group of polycyclic systems, flavin and its meta- and para-substituted derivatives have been studied systematically (2006JMST(758)107, 2008JMST(856)112). It is known that conformations of flavins are dependent on their oxidation states. Oxidized flavins are planar regardless of a type of a substituent. The fully reduced flavin is bent along the N5-N10 axis. It was found that the planarity of the reduced flavins is affected by substituents. Electron-withdrawing substituents located at the C7 and C8 positions (Scheme 23) induce reduced flavins to be more planar, whereas electron-donating substituents make them more bent. The reduction potentials of variously substituted flavin derivatives in aqueous solution have been calculated (2008JMST(856)112) and compared with the experimental values (the average deviation was less than 0.06 eV) (1998JACS(120)2251). Two parameters (σ_m and σ_p) of the Hammett-type relationship were proposed to estimate the reduction potentials in substituted flavins. It was suggested that introduction of different substituents at the C7 or C8 positions allows



Scheme 22 Tautomeric equilibrium between N1H (a) and N4H (b) tautomers of C7-X substituted 1,3-dihydro-benzo[*e*][1,4]diazepin-2-ones; X = NH_2, OH, SH, F Cl, Br, Me, Ph, H, CN, COOH, NO_2, CHO, NO, and BH_2.

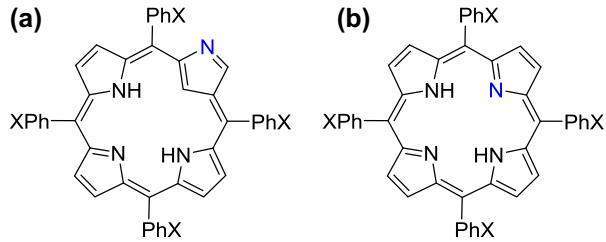


Scheme 23 Complex of flavins with 2,6-diaminopyridine.

regulation of the reduction potentials of flavins, which can find application in biochemistry. The estimated ionization potentials and proton affinities are also well correlated with the appropriate Hammett substituent constants.

Interactions between substituted flavins and diaminopyridine have also been investigated (2006JMST(758)107). Complexes with para-substituted flavins are always more stable than with the corresponding meta-derivatives (Scheme 23). Since the flavin molecule acts as an electron donor through O2···H2N2 and O4···H6N6 hydrogen bonds, electron-donating groups will shorten and strengthen these bonds and simultaneously elongate and weaken the N3H3···N1 H-bond.

Porphyrins, which are macrocyclic organic compounds widely applied in medicine and chemistry, can be considered as a particular type of system with several N-containing heterocycles. The effect of meso-aryl substituents on acid–base properties of N-confused porphyrins (see Scheme 24) was examined by both spectrophotometric methods and theoretical calculations (2015JPCA(119)1013). It was shown that the acidity and basicity of N-confused porphyrins are higher than that exhibited by the corresponding regular congeners. Moreover, individual basicities of the studied N-confused porphyrins are directly related to the inductive effect of para-substituents on the meso-phenyl groups: pK_a values are correlated with the Hammett σ_p substituent constants.

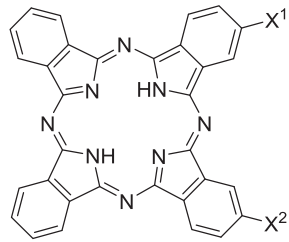


Scheme 24 Structures of N-confused (a) and regular (b) porphyrines with para-X-substituted phenyl rings (X = H, Me, OMe, CF_3, CN, SO_3).

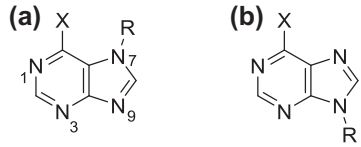
Other compounds structurally related to porphyrins are the phthalocyanines which have been investigated also from the viewpoint of their sensitivity to substituent effects. Since they can be used in optoelectronic devices, the study of substituent effects on their electronic properties is of great interest. The effect of substitution on the HOMO level energy was studied in the metal-free phthalocyanine (Scheme 25) and, for comparison, in naphthalene (2010CP(367)7). The results reveal that there is a rough linear dependence of the HOMO energy on substituent constants for naphthalene while no strong linear correlation exists for phthalocyanine, although it was noted that electron-donating substituents cause an increase of the HOMO energy, whereas electron-withdrawing substituents decrease the HOMO level compared to unsubstituted species.

2.4 DNA/RNA Bases and Their Analogs

Purine derivatives, particularly substituted at position 6, play a significant role in medicinal chemistry and are important intermediates for synthesis of biologically active nucleoside analogs, which can exhibit antiviral or antitumor properties (2006BMC(14)3987). The nature and position of the substituents, which can be reflected in the NMR chemical shifts and nuclear spin–spin coupling constants, determine the reactivity and biological activity. An experimental study of 6-halopurines (2010PCCP(12)5126) revealed an insensitivity of the spin–spin coupling constants to substitution; therefore, further investigation of two isomers (7*H* and 9*H*) of 6-substituted purines (Scheme 26; 2011PCCP(13)15854) was focused solely on the variation in the chemical shifts caused by substituents. It was found that only chemical shifts of the N3 atom correlate satisfactorily with the Hammett constants σ_p, regardless of the substituent nature, as well as with calculated natural population analysis (NPA) charges on N3. Changes in other chemical shifts do not lead to any correlations with substituent properties.



Scheme 25 Substituted metal-free phthalocyanine (X^1, X^2 = H, OH, NH_2, Me, OMe, $SiMe_3$, Ph, F, Cl, COOH, OCOMe, CF_3, CN, NO_2).



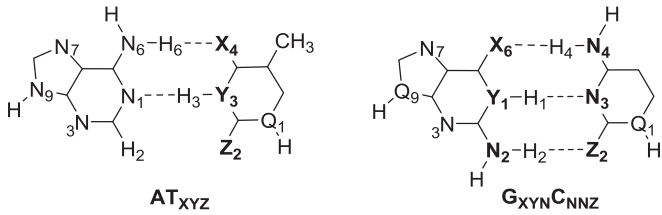
Scheme 26 Structures of 6-substituted purines: (a) 7*H*-tautomer and (b) 9*H*-tautomer (X = NH_2, NHMe, NMe_2, OMe, Me, CCH and CN; R = CH_3, benzyl).

Purine derivatives substituted by NH_2, NO_2, and $NHNO_2$ groups have been investigated from the viewpoint of their application as high energy density compounds (2012JMM(18)3501, 2013JMM(19)3491). Commonly, the introduction of a nitro group makes the molecule more explosive, whereas the introduction of an amino group reduces this drawback, because this group can form intra- and intermolecular interactions that stabilize the molecule and simultaneously lead to an increase of a crystal density. All studied purine derivatives have high positive heats of formation which increase with the number of the NO_2 or $NHNO_2$ groups. However, their close location and consequently the strong repulsion between two such groups lower the thermodynamic stability of the molecule.

Generally, most publications concerning substituent effects or other structural changes in nucleobases provide information on effects observed in the base pairs. Therefore, the most frequently studied systems are structurally modified Watson–Crick base pairs, i.e., adenine–thymine (AT) and guanine–cytosine (GC) pairs.

The substituent effect on hydrogen bonds in the nucleobase pairs can be considered in three ways: (1) substitution in the hydrogen bonding fragment; (2) remote substitution, i.e., at positions not directly involved in hydrogen bonding; and (3) supramolecular substitution (2006MI).

First, substitution of O by F in NH···O and of NH by CH in N···HN hydrogen bonds in AT and GC Watson–Crick pairs causes weakening and elongation of these hydrogen bonds (2004CPC(5)481, 2006IJQC(106)2428). More precisely, these effects depend on the number and location of substituted hydrogen bonds in AT and GC pairs (Scheme 27). In the case of AT and its mimics, the replacement of one of the two hydrogen bonds by a weak H-bond has a small effect on the strength of the second hydrogen bond, which almost preserves its original strength (Table 3). In the case of GC, replacement of one of the three hydrogen bonds by a weak one also has a slight effect on the strength of the second hydrogen bond; however, the replacement of a second hydrogen bond significantly weakens the third, still unchanged, H-bond (Table 4). As expected, the



Scheme 27 AT and GC Watson–Crick pairs and their mimics in which C=O and N–H bonds in T, G, and C have been replaced by C–F and C–H (X, Z = O, F, H; Y, Q = N, C).

substitution of the O2 atom in thymine by H or F almost does not change this H-bond energy, because atom Z2 is not involved in any stabilizing interaction as previously pointed out (1999CEJ(5)3581). In general, weakening of the hydrogen bonds can be explained by electronic properties of the interacting groups; in particular, the fluorine atom and CH group are poorer proton acceptor and donor, respectively, than the oxygen atom and NH group.

The substitution of the O atom by an S atom in NH···O hydrogen bond has also been investigated in AT and GC pairs (2008CEJC(6)15). This leads to the elongation and a slight weakening of this bond. Interestingly, the single-substituted base pairs remain planar, whereas the double-substituted pairs become propeller-like twisted around the N1–N3 bond with dihedral angles equal to 30.6° and 31.2° for AT and GC, respectively.

The second type of substitution by different electron-donating or electron-withdrawing groups in positions which are distant from hydrogen

Table 3 H-bond distances (Å) and energies (kcal/mol) for natural and substituted AT pairs computed at BP86/TZ2P

Pairs	*N**	N6H6···X4	N1···H3Y3	H2···Z2	ΔE_{HB}
AT	0	2.85	2.81	2.80	−13.0
AT_{FNO}	1	3.18	2.84	2.44	−8.8
AT_{OCH}	1	2.80	3.33	4.19	−8.9
AT_{OCF}	1	2.81	3.29	4.10	−8.9
AT_{FCH}	2	3.15	3.47	4.04	−2.7
AT_{FCO}	2	3.68	3.31	3.28	−2.0
AT_{SO}	1	3.35	2.86	2.35	−11.1
AT_{OS}	1	2.83	2.85	2.84	−12.6
AT_{SS}	2	3.34	2.89	2.83	−9.2

AT, adenine–thymine Watson–Crick base pair.
* *N* denotes the number of modified H-bonds.
Data taken from (2004CPC(5)481) and (2008CEJC(6)15).

Table 4 H-bond distances (Å) and energies (kcal/mol) for natural and substituted GC pairs computed at BP86/TZ2P

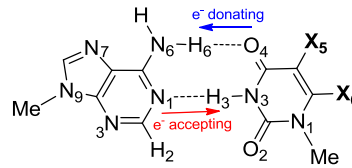
Pairs	*N**	X6···H4N4	Y1H1···N3	N2H2···Z2	ΔE_{HB}
GC	0	2.73	2.88	2.87	−26.1
$G_{FNN}C$	1	3.00	2.99	2.90	−18.1
GC_{NNF}	1	2.78	3.03	3.02	−16.2
$G_{FCN}C$	2	3.53	3.26	3.05	−8.8
$G_{FNN}C_{NNF}$	2	3.02	3.09	3.05	−10.2
$G_{FCN}C_{NNF}$	3	3.26	3.42	3.52	−4.1
G_SC	1	3.22	3.10	2.77	−24.0
GC_S	1	2.68	3.09	3.30	−24.1
G_SC_S	2	3.20	3.12	3.29	−21.0

GC, guanine–cytosine Watson–Crick base pair.
* *N* denotes the number of modified H-bonds.
Data taken from (2004CPC(5)481) and (2008CEJC(6)15).

bonding has a weak effect on hydrogen bond distances and energies in comparison with the previous type of the substitution (directly in the H-bond). In particular, remote substitution usually affects the hydrogen bond strength by less than 1 kcal/mol in both AT and GC pairs (2005SC(16)211).

Theoretical studies on substituent effects have been performed for methylated AU and GC pairs. Substitutions at the N6 or C8 positions of adenine (2001JPCA(105)3894); C5 or C6 of uracil (1999JPCA(103)8516, 2002JMST(588)29); N2 or C8 of guanine (2002JPCA(106)3207); and N4, C5, or C6 of cytosine (2001JPCA(105)10596) were examined separately. Only in adenine derivatives was no remarkable trend observed in the relationship between substituent properties and the strength of H-bonds. In the case of uracil substitution (Scheme 28), H-bond energies are strengthened by introduction of electron-withdrawing groups (NO_2, CN, F) and attenuated in the presence of electron-donating groups (NH_2, NMe_2). This tendency found for the AT pair suggests that the N1···H3N3 bond plays a more important role in this system.

For the GC pair, a substitution at the position C5 of 1-methylcytosine and the position C8 in 9-methylguanine has an opposite effect (Figure 11).



Scheme 28 Electron transfer during substitution in the methylated AU pair.

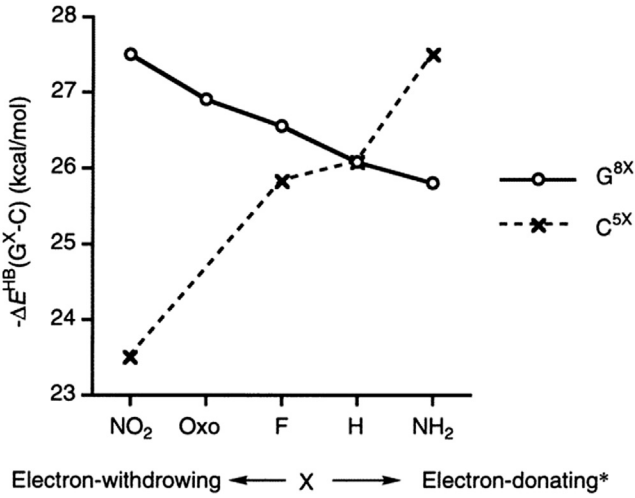


Figure 11 Substituent effects on H-bond energy in methylated GC pair. GC, guanine–cytosine Watson–Crick base pair. *Reproduced with permission from (2002JPCA(106)3207). Copyright 2002 American Chemical Society.*

In general, introduction of electron-withdrawing groups at the C8, C9 position or at the *exo*-cyclic amino group of guanine leads to stronger H-bonds between G and C in comparison with the natural base pair, whereas the presence of electron-donating groups at the N1, C5, or C6 position in cytosine helps to form more stable GC pairs (2002JPCA(106)3207, 2008JPCB(112)5257, 2010JCAMD(24)409). A similar trend was obtained by Moser et al. (2009TCA(122)179), who found that halogens, pyridine, pyrimidine, formyl, cyano, nitro, etc. at the C5 position of cytosine decrease binding energy by 1–3 kcal/mol. In aqueous solution (the COSMO model), these changes are even smaller.

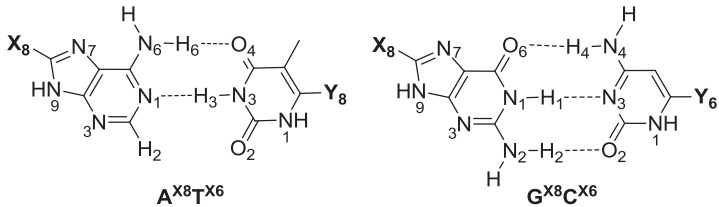
The substituent effects of CH_3, OCH_3, F, and NO_2 groups have also been investigated in substituted cationic GC pairs (2005CP(308)117) and were compared with the neutral pairs (2003CPL(373)72). The results show that the dependence of H-bond strength on the nature of substituents for neutral pairs is similar to that observed in previous studies. Ionization leads to a significant increase of the stabilization energies for all substituted base pairs. This increase has been attributed to the strengthening of only those H-bonds in which the ionized monomer acts as a proton donor. An NPA revealed that the HOMO orbital of the neutral pairs and the LUMO orbital of the corresponding cationic derivatives consist of $2p_z$ and $3p_z$ orbitals of atoms from the guanine moiety. This

indicates that the ionized electron goes from the HOMO orbital of the neutral pairs.

The effect of the remote substitution by halogen atoms (F, Cl, Br) has been considered in detail on the basis of the electron density distribution and the stabilization of the orbitals in the halogen-substituted bases. Replacing the hydrogen atom by more electronegative halogen atoms causes a redistribution of the electron density in all systems. The front H atoms become more positively charged, which strengthens the electrostatic attraction in appropriate H-bond, while the N and O front atoms become less negatively charged, which leads to the opposite effect. The stabilization of σ^*_{N-H} acceptor orbitals reduces the energy gap between interacting orbitals and causes the strengthening of the donor—acceptor orbital interaction in the appropriate H-bond, whereas the stabilization of orbitals with the N or O lone pairs increases the energy gap and weakens the orbital interaction in other bonds. For example, substitution of adenine in position X8 promotes the N6H6···O4 bond to become shorter and stronger, while N1···H3N3 becomes longer and weaker. Substitution of thymine in the position X6 causes the opposite effect (Scheme 29).

Additionally, the theoretical analysis of AT and GC pairs with neutral (-OH, $-NH_2$), anionic ($-O^-$, $-NH^-$), and cationic ($-OH_2^+$, $-NH_3^+$) substituents has shown that it is possible to build a supramolecular switch, based on the DNA bases, which can be chemically switched between three states differing in (1) H-bond strength (weak, intermediate, and strong) and (2) the geometrical form (Figure 12; 2006CPC(7)1971, 2006CEJ(12)3032). However, it was found that the switching behavior of the AT pair is less systematic and less evident than that of the GC pair.

The neutral substituents hardly affect the H-bonds, whereas the presence of charged substituents leads to more pronounced effects. In general, the insertion of an anionic substituent reduces the H-bond donating and increases the H-bond accepting capabilities of a DNA base. In the case of a cationic substituent the opposite effects are observed. Moreover, it has



Scheme 29 Adenine—thymine and guanine—cytosine pairs with remote substituents.

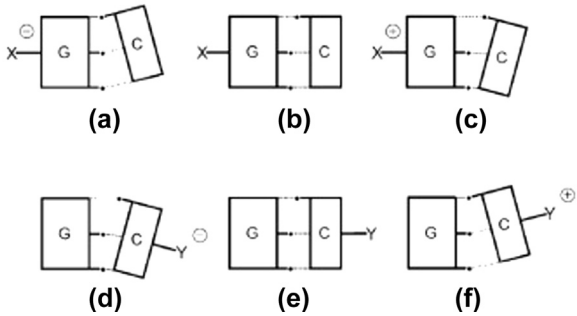


Figure 12 Schematic representation of substituent effects on hydrogen bonds in the GC pair. GC, guanine–cytosine Watson–Crick base pair. *Reproduced with permission from (2006CEJ(12)3032). Copyright 2006 John Wiley and Sons.*

been reported that the GC system presented above works if a substituent is separated from guanine by up to 3 nm through a $-(C{\equiv}C)_n-$ linker (2011CEJ(17)8816).

Additionally, for the GC pair with either modified cytosine or guanine, quantitative models using the multiple linear regression method with QTAIM descriptors to predict the interaction energy between nucleobases have been suggested by Xue and Popelier (2008JPCB(112)5257, 2009JPCB(113)3245). The best linear models were achieved using two descriptors, namely $\lambda_{3,C4-N4}$ and ε_{C4-C5} for GC^{5X} pairs and $\varepsilon_{C6=O6}$ and G_{N2-H2} for $G^{8X}C$ pairs. Good statistical parameters shown in Figure 13 confirmed that the proposed models can be used to estimate the interaction energies in modified GC pairs.

Summing up, remote substitution (2003EJOC2577) influences the H-bond energy depending on two separate factors: the electron-donating/electron-withdrawing power of the substituent and its location. Such chemical modification of nucleobases can be used to control the stability of unnatural base pairs.

As a particular case of the substitution in nucleic acid bases, the insertion/addition of a benzene ring to the natural bases can be considered (Scheme 30; 2006JPCA(110)12249). The analysis of the local aromaticity, expressed by HOMA, NICS, FLU, and PDI indices, revealed notable differences in the aromatic character of the natural and size-expanded bases. Insertion/addition of the benzene ring reduces aromaticity of six-membered rings in natural bases as well as the aromatic character of the benzene ring. An inverse correlation between the HOMO-LUMO gap and the aromaticity of the fused benzene ring was also found. Therefore, it has been suggested that

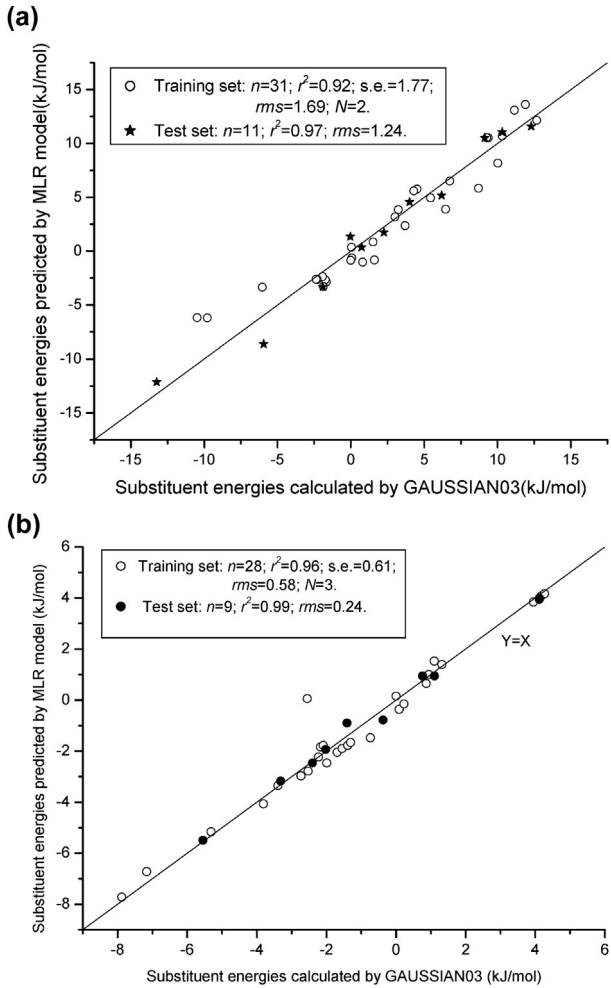
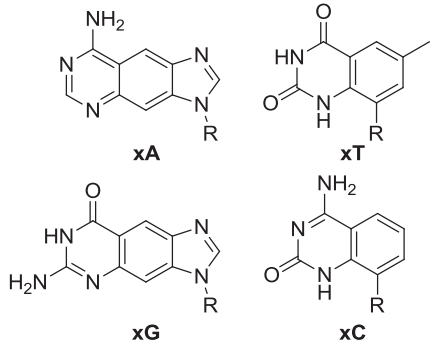


Figure 13 Correlations between H-bond energies in GC^{5X} (a) and $G^{8X}C$ (b) predicted by MLR model based on two quantum chemical topology (QCT) descriptors versus energies calculated by supramolecular method: $\Delta E_{HB} = E(GC^X) - \{E(G) + E(C^X)\}$. MLR, multiple linear regression. *Reproduced with permission from (2008JPCB(112)5257) and (2009JPCB(113)3245). Copyright 2008 and 2009 American Chemical Society.*

by introducing the appropriate chemical modifications in the benzene ring, it is possible to modulate the HOMO-LUMO gap without affecting the H-bond recognition properties, which could be useful in the design of modified DNA duplexes with altered properties.

Finally, it was suggested that not only the substituents chemically bound to nucleobases can affect the hydrogen bonds characteristics, but

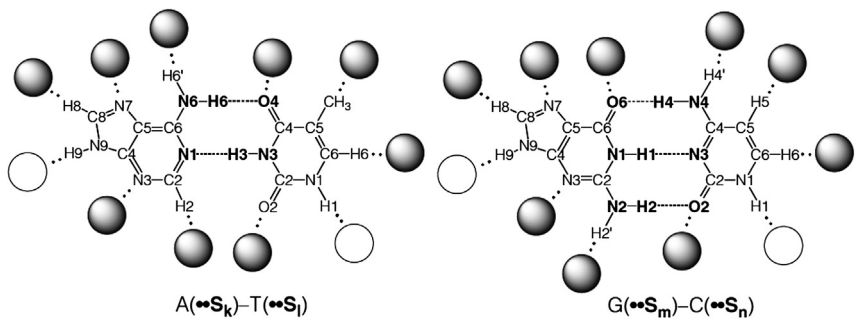


Scheme 30 Benzo-fused derivatives of natural nucleobases.

also the substituents interacting with nucleobases through hydrogen bonds; the so-called supramolecular substituents (Scheme 31; 2006MI). As examples of such substituents, water molecules, counterions, or other nucleobases can be considered (1999ACIE(38)2942, 2000JACS(122)4117, 2002CGD(2)239). It has also been shown that this effect may be of the same magnitude as that caused by the usual substituents described above. For example, water molecules and Na^+ cation alter H-bond length order in GC pairs from short-long-long (2.73, 2.88, and 2.87 Å) to long-long-short (2.88, 2.95, and 2.85 Å).

3. SYSTEMS WITH OXYGEN, SULFUR, AND OTHER HETEROATOMS

Similarly to the previous part devoted to the substituent effect in N-containing heterocycles, systems presented here will be divided into three



Scheme 31 Supramolecular substituents in adenine–thymine and guanine–cytosine pairs. *Reproduced from (2006MI) with kind permission from Springer Science and Business Media.*

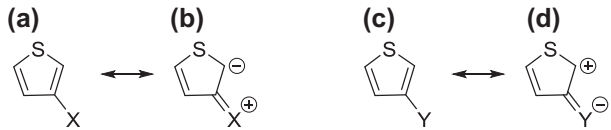
groups: (1) five-membered rings, (2) six-membered rings, and (3) systems with two or more fused rings.

3.1 Five-Membered Rings

An analysis of substituent effects on the thermochemistry of monosubstituted thiophene derivatives revealed that 3-substituted isomers are more stable in comparison with their 2-counterparts if the substituent has strong π-electron-donating ($\sigma_R < 0$) or strong σ-electron-accepting properties (large σ_I) (2012JPCA(116)4363). The effect of substituents in 3-substituted thiophenes can be illustrated by resonance structures presented in Scheme 32. The sulfur atom in thiophene is positively charged, and therefore the stabilization of the system **b** is greater than that of the system **d**.

Ab initio studies of the conformational equilibria of 2-substituted furan and thiophene carbonyl derivatives (Scheme 33) revealed that electron-withdrawing substituents favor the *cis* conformer in furan carbonyls but the *trans* form in thiophene derivatives. These effects in the *cis* forms are ascribed to a decrease in electrostatic repulsive interaction between two oxygen atoms in furan systems and attractive interactions between oxygen and sulfur atoms in thiophene carbonyls (1996TCA(93)199). Solvent effects only slightly influence the absolute value of the energy differences between conformers but can lead to the reverse order of the stability. The *cis* conformer with higher dipole moment is more stable in solution than the *trans* conformer.

Complementary to the previous work, the effect of substituents located in a five-membered ring on the conformational equilibrium between planar forms of furfural has also been studied. The results obtained show that not only properties of a substituent but also its position have an important effect on the equilibrium between *OO-cis* and *OO-trans* isomers (2004JCC(25)429). The electron-donating substituents at position 4 stabilize the *OO-trans* conformer, whereas the electron-withdrawing substituents show the opposite effect (Scheme 33). In turn, the effect of substituents at position 5 is contrary to that typical for the position 4.



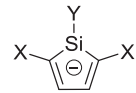
Scheme 32 Resonance structures for 3-substituted thiophene with π-donating (X) and π-withdrawing (Y) substituents.

Scheme 33 *Cis* (a) and *trans* (b) conformers (X = H, Me, Cl, F; Y = O, S) of carbonyl derivatives of furan and thiophene.

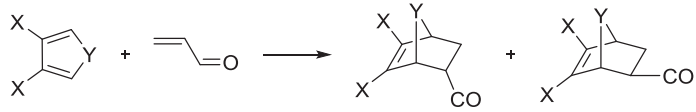
Various substituted silole derivatives were also investigated, mostly in terms of an inversion barrier, planarity of structure, and aromatic character (1998JPCA(102)10530, 2014SC(25)377). The silacyclopentadienyl anion has a significantly low aromaticity (1995ACIE(34)337) due to the pyramidal geometry of the Si atom which prevents conjugation between the lone electron pair of the Si atom and the π-electron system of the ring. However, its electronic structure can be modified by introducing appropriate substituents either at the Si atom or at a carbon atom of the ring (Scheme 34). It was found that substituents on the Si atom hardly affect the aromaticity of the five-membered ring, whereas electron-withdrawing groups on the α-carbon atoms reduce substantially the inversion barrier and stabilize the planar geometry in a manner similar to the case of phosphole derivatives (1995JPC(99)586). All these factors lead to an increase of the aromaticity of the ring.

In addition to studies of effects in individual molecules there are also works concerning substituent impact on chemical reactions. For example, an investigation of the Diels–Alder reaction between substituted pyrrole, phosphole, furan, and thiophene rings with acrolein (Scheme 35) has shown that equilibrium constants of the reaction are sensitive to the nature of the substituent located on the diene (2004JMST(672)35). The reaction enthalpy ΔH^0 also linearly depends on the Hammett constants σ_m and σ_p. The increase of exothermicity with the increasing electron-donating power of the substituents is connected with the changes of the HOMO energy of the diene.

Substituent effects on the nucleophilic substitution of 2-methoxy-3-X-5-nitrothiophenes have also been reported (2014IJCK(46)470). Changes in reactivity caused by the differing natures of the 3-X substituents were



Scheme 34 Structure of substituted silacyclopentadienyl anion (X = F, BH_2, AlH_2, CH_3, SiH_3, vinyl; Y = F, CH_3, SiH_3, vinyl, phenyl).



Scheme 35 Diels–Alder reaction of five-membered heterocycles with acrolein (X = NMe_2, OMe, COOMe, CN; Y = NH, O, PH, S).

found to correlate with the σ_p^- constant. A linear correlation, shown in Figure 14, between the electrophilicity parameter *E* and the σ_p^- constant was also observed for systems with X = SO_2CH_3 (1a), CO_2CH_3 (1b), $CONH_2$ (1c), and H (1d). Moreover, this trend was used to estimate the unknown *E* values, in particular for structures with X = CN, NO_2, and $COCH_3$.

Apart from studies of the substituent effect on properties of heterocycles, the latter can be also considered as substituents which may influence the stability and reactivity of many organic molecules (2008JPOC(21)173). The substituents furyl, thienyl, and pyrrolyl can demonstrate a dual character. They are electron-withdrawing inductively (large σ_I and *F*) but also able to donate electrons via resonance ($\sigma_R < 0$) (1991CR(91)165). It has been found that electronic effects of five-membered heteroaromatic rings on the C=N–N fragment of hydrazone derivatives are analogous to the effects of substituted phenyl groups.

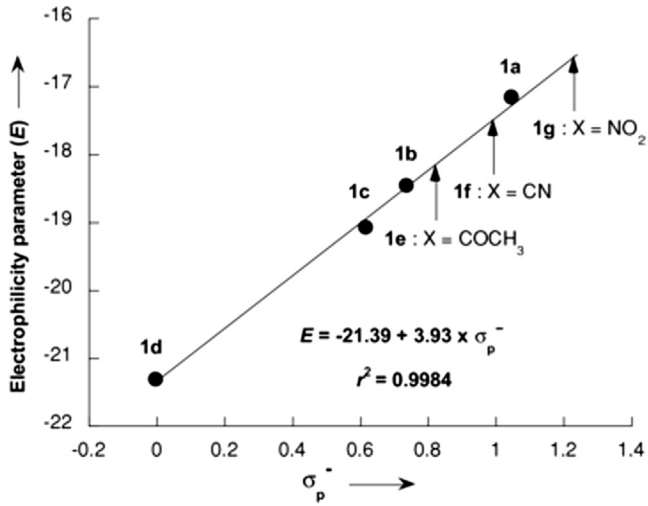


Figure 14 Correlation between the electrophilicity parameter and substituent constants for 2-methoxy-3-X-5-nitrothiophene. *Reproduced with permission from (2014IJCK(46)470). Copyright 2006 John Wiley and Sons.*

3.2 Six-Membered Rings

It can be assumed that structural analogs of benzene with one heteroatom will demonstrate similar physicochemical properties and reactivity. The nitrogen-containing heterocycles are the most studied among them. However, information about the substituent effect in other six-membered heterocycles is limited.

A comparative analysis of magnetic properties (the absolute shielding and the NICS index) for ortho- and para-substituted benzene, silabenzene, pyridine, and phosphabenzene revealed good correlations between absolute shieldings and σ_p^+ values (2010MRC(48)532). According to the slopes of these linear trends, the sensitivity to the substituent effect increases in the following order: benzene < Si-benzene < N-benzene < P-benzene (see Table 5). The resistance of the high aromatic benzene ring to the substituents of different nature has already been reported (2004JOC(69)6634). Interestingly, silabenzene is less sensitive, albeit its π-system is delocalized to a lesser degree compared to other studied heterocycles. In general, electron-donating groups increase the aromaticity of heterocycles, while electron-withdrawing groups decrease their aromatic character.

The effects of nitro and amino substitution on structural and energetic characteristics of heteroanalogs of benzene have been examined (2013SC(24)725). Substitution at the positions 2, 3, and 4 in C_5H_5X systems with X = N, P, As, O^+, S^+, Se^+, SiH, GeH was taken into consideration. The aromaticity of substituted heterobenzenes was compared with the aromatic character of the benzene ring and unsubstituted parent heterocycles (2011PCCP(13)20536). It was found that aromaticity of amino-derivatives is usually lower than the aromaticity of nitro-derivatives. According to the aromaticity descriptors applied in this study (ASE, Bird's index I_a (1986T(42)89), and NICS), N-containing nitro-derivatives are the most aromatic followed by nitrothio- and nitroselelopyrylium cations. The nitro-substituted pyrylium cation and germabenzene are the least aromatic. In turn, amino-derivatives show quite different behavior. Although

Table 5 Statistics of dependences of absolute shieldings on σ^+ values

Derivatives	Intercept	Slope	R^2
Benzene	1.03	−8.05	0.944
Silobenzene	1.33	−21.52	0.950
Pyridine	2.59	−25.25	0.962
Phosphabenzene	6.42	−50.48	0.960

Data taken from (2010MRC(48)532).

aminopyridines are still the most aromatic, ortho-, and para-substituted thio- and selenopyrylium cations are significantly less aromatic compared to their unsubstituted species. Finally, the least aromatic rings were found for ortho- and para-aminopyrylium compounds.

Substituent effects on the relative stability of different isomers of the above heterocycles were also studied (2011PCCP(13)20536). For amino-derivatives of N, O, S, Se-benzenes, the ortho- and para-isomers are preferred, whereas in the case of P, As, Si, Ge-benzenes, the meta-isomer is more stable. Differences in the energy for nitro-derivatives are smaller compared to the amino-systems indicating a smaller substituent effect of the nitro-group and the relatively resistant π-electron structure of the quite aromatic nitro-substituted heterocycles.

It was also found that among the studied systems, the ortho- and para-amino derivatives of charged heterocycles, i.e., substituted pyrylium and chalcogenopyrylium cations, undergo the greatest changes in structure, aromaticity, and relative stability in comparison with other hetero- and carbocyclic derivatives. This has been explained by a strong pull—push effect that rises from the high electronegativity of the charged heteroatom and the π-donating electronic effect of the amino group. The behavior of such systems appears to be similar to that of disubstituted benzenes with π-donor and π-acceptor substituents (2012SC(23)1585).

Phosphinines are used as ligands in coordination chemistry and even a minor structural modification in the central ring can cause a significant change in their photophysical properties. In particular, the possibility to tune optoelectronic properties of phosphinines by introducing an additional donor substituent in the ortho-positions to the P atom was shown for different pyridyl-, thienyl-, and phenyl-substituted phosphinines (2007CEJ(13)4548). It has been demonstrated that the electronic properties of 2,4,6-triarylphosphinine derivatives can also be modulated by introducing additional substituents into the para-position of the phenyl ring (2014CC(50)8842). In particular, these compounds, presented in Figure. 15(a), can show strong π-donating properties originating from a significant mesomeric effect of the substituents. Indeed, introducing the CH_3S-group destabilizes the frontier orbital compared to the unsubstituted compound and increases the π-donating properties of triarylphosphinine.

3.3 Polycyclic Systems

The electronic effects of meta- and para-substituents located in the phenyl ring have been studied for aryl-substituted benzothiophenes (Scheme 36(a)).

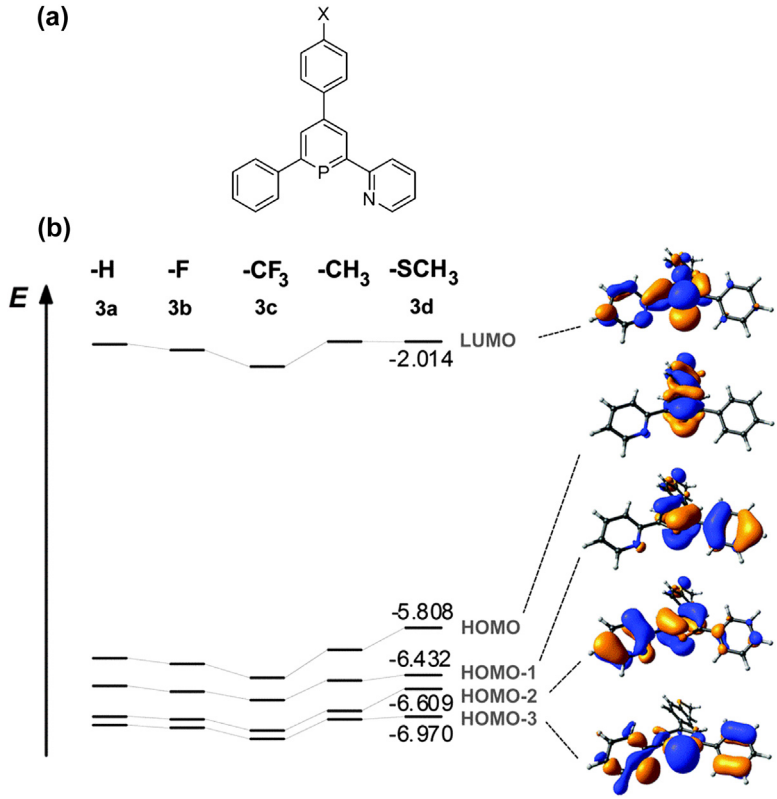
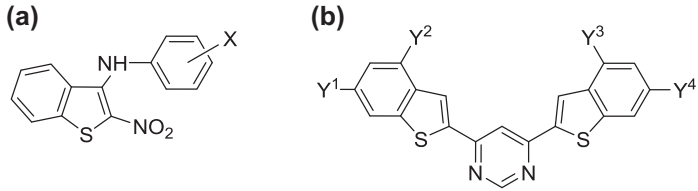


Figure 15 Substituted 2,4,6-triarylphosphinines (a) and their frontier orbitals (b). *Reproduced from (2014CC(50)8842) with permission from The Royal Society of Chemistry.*

Based on the experimentally measured redox properties (2001T(57)1857) of the studied compounds, it was noted that the tendency to reduction is strongly dependent on the electronic nature of substituent. The half-wave potentials ($\Delta E_{1/2}$) of the meta- and para-substituted derivatives are well correlated with Hammett substituent constants. Relatively high values of the reaction constant ρ indicate a good ability of the —NH— bridge to transmit the substituent effects. Similar results have been observed in studies of the



Scheme 36 Substituted benzothiophene derivatives.

substituent-induced ^{13}C NMR chemical shifts for the same series of compounds (1995MRC(33)883).

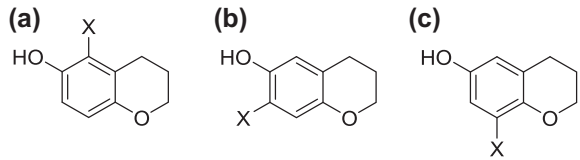
It has been reported that the direct substitution of the benzene ring of benzothiophene in such compounds can be used as a tool for modification of electronic and photophysical properties of π-conjugated materials. In particular, the substituent effect on HOMO/LUMO energies, ionization potentials, electron affinities, and reorganization energies have been described for 4,6-di(thiophen-2-yl)pyrimidine derivatives (Scheme 36(b); 2014CTC(1031)76).

Effect of ortho- and meta-substituents on bond dissociation enthalpies (BDE) of the OH bond in chromane-6-ol derivatives (Scheme 37), which possess antioxidant properties, have been investigated (2011CTC(965)114). A protective role of antioxidants is realized by the hydrogen atom transfer mechanism (2001JACS(123)1173). The results show that electron-donating substituents decrease the BDE of the OH bond, whereas electron-withdrawing groups have the opposite effect. Moreover, substituents in ortho-positions cause greater BDE changes compared to those in meta-positions. Interestingly, effects of the meta-substituent on BDE were found to be larger in water (PCM (polarizable continuum model)) than in the gas phase. This was ascribed to unequal stabilization/destabilization effects in the parent molecule and the corresponding radical in solution.

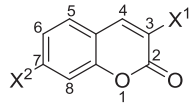
Coumarin derivatives are highly fluorescent molecules whose photophysical properties are influenced by the nature and position of substituents (1995JL(63)203). In particular, introducing electron-donating groups at position 3 leads to fluorescence and the opposite effect is observed in the case of the electron-withdrawing groups (Scheme 38). In addition, the electron-donating acetoxy group at position 7 seems to increase the luminescence of coumarin derivatives to a greater extent (2010SAPA(75)1610).

4. SYSTEMS WITH VARIOUS HETEROATOMS

Among systems with two and more various heteroatoms in the ring, thiazole, oxazole, and their derivatives attract attention because of the interesting physicochemical properties and significant biological activity



Scheme 37 Ortho- (a,b) and meta-substituted (c) chroman-6-ol derivatives.

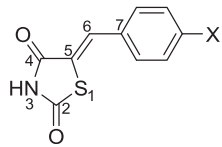


Scheme 38 Substituted coumarin derivatives.

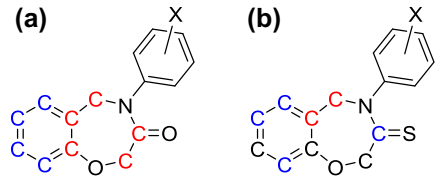
(2010MD(8)2755). The aromaticity of thiazoles and oxazoles (described by NICS, ASE, and HOMA indices) depends in a regular way on the number of nitrogen atoms and their particular positions (2010T(66)2695), in a manner similar to the case of aza-substituted pyrrole derivatives.

Experimental and theoretical studies of the substituent effect on ^{13}C NMR chemical shifts, as well as on the NBO atomic charges, of 5-arylidene-2,4-thiazolidinedione derivatives (Scheme 39; 2013JMS(1049)59) have been reported. Three approaches were used to describe the substituent effect: (1) a single substituent parameter (SSP), when σ_p or σ_p^+ were considered; (2) a dual substituent parameter (DSP) using the Reynolds planar regression with inductive (σ_F) and resonance (σ_R) substituent constants (1983CJC(61)2376); and (3) the Yukawa–Tsuno model (1959BCSJ(32)971). Correlations between chemical shifts at the C5 and C7 atoms and the substituent constants σ_p/σ_p^+ are excellent, indicating an electronic origin of the substituent effect. However, the correlation for the C6 atom has an opposite sign. Trends for the calculated NBO charges and the substituent constants are similar to those observed for the chemical shifts. The comparison of correlation results for the molecules investigated and seven structurally related styrenes revealed a better performance of the Yukawa–Tsuno model; however, good agreement between the interpretation of the substituent effect via the Yukawa–Tsuno and the DSP approaches was also shown.

Compounds with a wide spectrum of biological activities are derivatives of benzoxazepine (Scheme 40). The results of experimental and theoretical studies of ^{13}C NMR chemical shifts in X-substituted phenyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(*2H*)-ones (thiones) were analyzed using the SSP (the Hammett-type) and the DSP (the Reynolds model) linear



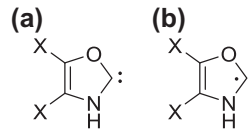
Scheme 39 Chemical structure of 5-arylidene-2,4-thiazolidinediones, where X is: H, Me, iPr, OMe, OEt, OH, NH_2, NMe_2, Cl, Br, and NO_2.



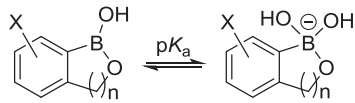
Scheme 40 X-substituted phenyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(*2H*)-ones (a) and X-substituted phenyl-4,5-dihydrobenzo[*f*][1,4]oxazepin-3(*2H*)-thiones (b); blue (dark gray in print versions), red (gray in print versions), and black carbon atoms denote positive slope, negative slope, and no DSP correlations, respectively.

equations (2013JMC(1053)61). Both approaches lead to similar conclusions: a substituent significantly influences the chemical shifts of carbon atoms in the oxazepine unit. Furthermore, it was shown that the sign of the slope for correlations between the chemical shifts and the substituents constants depends on the position of the carbon atom in the ring (Scheme 40), indicating their different sensitivities to the substituent effect. Additionally, using the Reynolds approach, the ρ_F/ρ_R ratio for each carbon atom was determined indicating the prevalence either of the polar (inductive and field) or the resonance effect. The obtained values of the ρ_F/ρ_R ratio are in the range 0.031 and 2.445 for ketones and from 0.529 to 2.728 for thiones.

The next very interesting systems with various heteroatoms are the substituted five-membered heterocyclic carbenes (Scheme 41), which are especially important in organic synthesis as well as in polymer and organometallic chemistry (2008JPCA(112)8775). Their relative stability, reactivity, singlet-triplet gap (ΔE_{ST}), lifetime, and other properties appear to be dependent on the substituents. It has been shown that electron-withdrawing substituents at the C4 and C5 positions of the 1,3-oxazol-2-ylidene ring decrease ΔE_{ST}, electron-donating substituents have little effect, whereas a methyl group on the N atom increases ΔE_{ST}. Substituent effects on 1,2-rearrangements of 1,3-oxazol-2-ylidenes to 1,3-oxazoles have also been studied. Electron-withdrawing groups at the C4 and C5 atoms lower the activation barriers and promote the 1,2-rearrangements of the singlet 1,3-oxazol-2-ylidenes to 1,3-oxazoles (2008JPCA(112)8775).



Scheme 41 Singlet (a) and triplet (b) 1,3-oxazol-2-ylidenes (X = H, Me, F, Cl, Br).



Scheme 42 Acid–base equilibrium of X-substituted benzoxaboroles.

Benzoxaboroles are an important boron-containing pharmacophore. The effect of aryl substitution on the ionization of the boronic acid moiety (Scheme 42) has been studied experimentally (2012ACSMCL(3)48). It was noted that all the studied systems, mono- and multisubstituted, follow the Hammett relationship (pK_a versus σ). Moreover, aromatic substitution can also affect the binding of benzoxaboroles to saccharides. Indeed, an increase of binding constants with increasing σ values was observed. This has been explained by the stabilization of anionic tetrahedral products by removal of electron density at the boron atom.

5. CONCLUSIONS

The phenomena known as substituent effects are one of the most important issues in chemistry, biochemistry, and related fields. Their influences on chemical/physicochemical properties and pharmaceutical activity of heterocyclic systems are mainly described through the use of the Hammett substituent constants. Only in a few cases have other physicochemical descriptors been used for this purpose. However, even in those cases, their applicability is verified by the comparison of the "new" correlations with the one obtained by using the classical approach. Among new physicochemical concepts of the substituent effect, the most promising seems to be the cSAR approach (2014JOC(79)7321).

LIST OF ABBREVIATIONS

ASE	Aromatic stabilization energy
AT	Adenine-thymine Watson–Crick base pair
ATI	Average of two center indices
BCP	Bond critical point
BDE	Bond dissociation enthalpies
COSMO	Conductor-like screening model
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DSP	Dual substituent parameter
EDA	Energy of decomposition analysis
pEDA	π electron-donor–acceptor descriptor
sEDA	σ electron-donor–acceptor descriptor
FLU	Aromatic fluctuation index

GC	Guanine–cytosine Watson–Crick base pair
HOMA	Harmonic oscillator model of aromaticity
HOMO	Highest occupied molecular orbital
HQ	Hydroxyquinoline
LUMO	Lowest unoccupied molecular orbital
MCI	Multicenter bond index
MLCT	Metal-to-ligand charge transfer
MLR	Multiple linear regression
NBO	Natural bonding orbital method
NICS	Nucleus independent chemical shift
NMR	Nuclear magnetic resonance
NPA	Natural population analysis
PCM	Polarizable continuum model
PDI	Para-delocalization index
QTAIM	Quantum theory of atoms in molecules
RCP	Ring critical point
RNA	Ribonucleic acid
cSAR	Charge of a substituent active region
SSP	Single substituent parameter
THF	Tetrahydrofuran

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