

Impact of the Substituents on the Electronic Structure of the Four Most Stable Tautomers of Purine and Their Adenine Analogues

Anna Jezuita,* Halina Szatyłowicz,* and Tadeusz M. Krygowski



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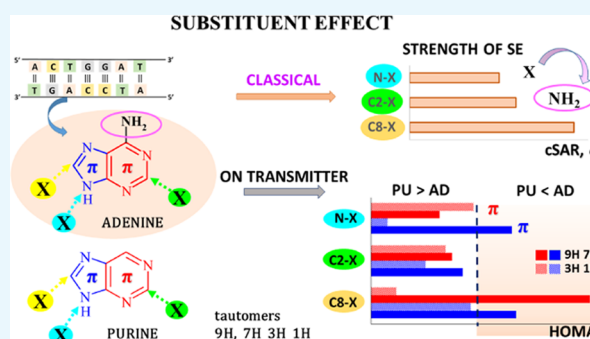


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ABSTRACT: Substituent effects at the C2-, C8-, and N-positions of adenine and purine on the structural and π -electronic changes in their four tautomers were studied using the B97D3/aug-cc-pvdz computational level. The effect of various substituents (NO₂, CN, CHO, Cl, F, H, Me, OMe, OH, and NH₂) was characterized by the charge of the substituent active region (cSAR) approach and Hammett substituent constants σ . It has been found that for both adenine and purine derivatives, substituents from the C8-X position have a stronger influence on their electronic structure than from the C2-X and N-X positions. The presence of the amino group in adenine enhances the substituent effect compared to that which occurs in purine. In addition, its electronic structure is more sensitive to the effect of the substituent in 3H and 1H than in the 9H and 7H adenine tautomers. For a given substituent, a large variation in cSAR(X) values is observed, strongly dependent on the substitution position. For 7H and 9H adenine tautomers for C8-X systems, substituents reduce the aromaticity of the five-membered rings but increase the aromaticity of the six-membered rings.

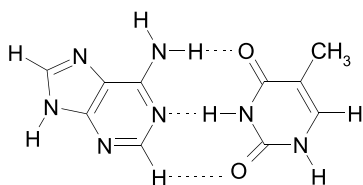


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INTRODUCTION

Adenine (AD) is one of the five important DNA and RNA components¹ and differs from purine (PU) only by the presence of the amino group in position 6. In the helices of DNA and RNA, adenine interacts by means of H-bonding with thymine,^{2,3} in which a 2p_{xy} lone pair at N1 and N-H in the amino group is involved (Scheme 1).

Scheme 1. Adenine–Thymine Watson–Crick Base Pair



Adenine in helices also interacts in a spatial way by stacking with other nucleic acid bases.^{4,5} Therefore, the problem of the electronic structure of adenine and the role of the amino group are essential. This is illustrated by comparison with the data of purine. The question arises how the amino group affects the electronic structure of purine molecule, which is just a parent system for adenine. They are both aromatic^{6,7} and may exist in several prototropic tautomers.⁸ The complete adenine tautomeric mixture consists of 23 tautomers (9 amine and 14 imino forms), while purine can exist in the form of 9 tautomers (4 NH and 5 CH isomers). Structural parameters and energetic stabilities of all adenine^{9–11} and purine^{12–14}

tautomers were studied in detail using quantum chemistry methods, taking into account both various oxidation states and environments. In the case of neutral purine in the gas phase, the stability of tautomers decreases in the following order: 9H, 7H, 3H, and 1H. The first three tautomers are also the most stable for adenine. Therefore, this study is focused on the four most stable purine tautomers and their adenine analogues, as presented in Scheme 2.

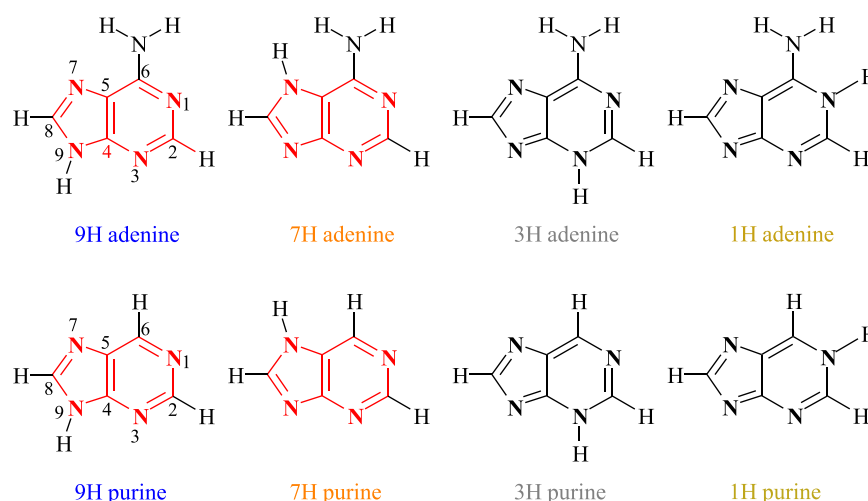
It has been accepted for a long time that five- and six-membered rings (R5 and R6, respectively) are just imidazole and pyrimidine moieties fused together into molecules of adenine or purine. Very recently, it was shown¹⁵ that this is correct only in the case of tautomers 7H and 9H. In these cases, both rings contain six π -electrons; thus, they follow the Hückel 4N + 2 rule and demonstrate proper π -electron delocalization for aromatic systems.¹⁶ For this reason, these rings are abbreviated as H+, i.e., fulfilling the Hückel rule (red in Scheme 2). In contrast, the rings R5 and R6 in tautomers 1H and 3H do not follow this rule. They contain either five or seven π -electrons, exhibit different π -electronic properties, and are abbreviated as H- (black in Scheme 2). Hence, tautomers

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Scheme 2. Structures and Numbering of Atoms in the Studied Tautomers of Adenine and Purine^a

^aRings following the Hückel $4N + 2$ rule (H+) marked in red and not meeting this rule (H-) marked in black; the colors used to label the tautomers are used in the figures and tables.

Table 1. Slopes of the Obtained Linear Dependences $cSAR(X)$ vs σ_p and σ_m for C8-X, C2-X, and N-X Substitutions of Adenine (AD) and Purine (PU) Derivatives

		C8-X		C2-X		N-X	
		<i>a</i>	<i>R</i> ²	<i>a</i>	<i>R</i> ²	<i>a</i>	<i>R</i> ²
$cSAR(X)$ vs σ_p							
AD	9H	-0.201	0.961	-0.182	0.983	-0.137	0.830
	7H	-0.194	0.967	-0.177	0.959	-0.139	0.809
	3H	-0.211	0.985	-0.194	0.986	-0.137	0.804
	1H	-0.204	0.985	-0.189	0.962	-0.128	0.791
PU	9H	-0.186	0.975	-0.182	0.987	-0.134	0.831
	7H	-0.184	0.979	-0.178	0.986	-0.144	0.826
	3H	-0.200	0.989	-0.181	0.980	-0.105	0.662
	1H	-0.195	0.990	-0.174	0.972	-0.120	0.756
$cSAR(X)$ vs σ_m							
AD	9H	-0.303	0.809	-0.284	0.880	-0.232	0.886
	7H	-0.291	0.800	-0.266	0.873	-0.239	0.890
	3H	-0.320	0.835	-0.296	0.847	-0.233	0.865
	1H	-0.310	0.837	-0.287	0.825	-0.212	0.807
PU	9H	-0.280	0.819	-0.281	0.870	-0.227	0.884
	7H	-0.277	0.820	-0.275	0.873	-0.242	0.863
	3H	-0.301	0.828	-0.275	0.832	-0.185	0.765
	1H	-0.295	0.837	-0.264	0.831	-0.203	0.798

7H and 9H in purine are significantly more stable than 1H and 3H.¹⁵ In adenine, this rule is somewhat perturbed by the interaction of rings with the amino group. These properties, substituent effects on the interactions between the amino group and various parts of the π -electron structure of adenine, and a comparison with the data of purine are subject of this report.

Recently, numerous studies have been carried out on the classical SE for meta- and para-disubstituted benzene series,^{17–21} cyclohexa-1,3-diene,²² and bicyclo[2.2.2]-octane^{23,24} derivatives with different reaction sites ($Y = NO_2$, $COOH$, OH , NH_2) and a wide range of substituents X properties. For the above-mentioned systems, it has been documented that quantum-chemical models of the SE (charge of the substituent active region (cSAR), substituent effect

stabilization energy (SESE), pi/sigma electron donor–acceptor (pEDA/sEDA); explanation and references are given in the **Methodology** section) show good compatibility with substituent constants and allow us to compare the electronic structures of X and Y. Therefore, it is very important to establish how such approaches work in heterocyclic systems composed of different π -electron rings, as in the case of adenine and purine structures. The use of substituent effect stabilization energy (SESE)^{25–27} to describe the effect of a substituent on the stability of adenine and purine tautomers has been shown recently.²⁸ This work is mainly devoted to the effect of substituents on the electronic structure of title systems.

RESULTS AND DISCUSSION

The results of the application of the quantum chemistry-based descriptors of the substituent effect (cSAR, charge flow index (CFI), harmonic oscillator model of aromaticity (HOMA), and pEDA/sEDA) to C8-X-, C2-X-, and N-X-substituted adenine (AD) and purine (PU) tautomers are presented in Tables S1–S16 (Supporting Information).

A comparison of the relationships between the cSAR(X) values obtained for adenine and those for purine gives a good insight into understanding the basic relations for electronic characteristics between these two molecular systems. It should be noted that the cSAR(X) values, as SE characteristics, are usually well correlated with the Hammett σ constants,^{29–31} mainly σ_{para} and σ_{meta} (abbreviated as σ_p and σ_m , respectively) constants. However, it should be stressed that the substituent constant values are determined for particular reference systems. In the case of the Hammett σ constants, they describe exactly the electronic properties of substituents only in meta- and para-substituted benzoic acids.^{32,33} When they are used as SE characteristics for other systems, similarity models are applied by means of linear regressions of a given physicochemical property P(X) plotted against given σ 's. The differences in the electronic properties of substituents attached to various systems in question are expressed by the slopes of the linear regression and the precision of the similarity model by the determination coefficient R^2 (where $100 \times R^2$ describes the percentage by which the similarity models describe variability of P(X) in a given sample).³⁴ In the case of our studies, the σ_p constants are more suitable than σ_m , as presented in Table 1.

For the C-X (both C8-X and C2-X) substitution, the determination coefficients for cSAR(X) on σ_p dependences are always higher than 0.96, indicating a high similarity for the interaction discussed. They are significantly worse for N-X systems, always below 0.831, for both adenine and purine systems and particularly worse for PU 1H and 3H tautomers $R^2 < 0.756$. In general, the slopes are (as absolute values) slightly larger for AD tautomers than for PU ones, but the differences seem to be insignificant. This may be understood as a high similarity for the substituent effect in PU and AD for 2- and 8-substituted systems. This conclusion is not as clear for N-X substitution for 1H and particularly for 3H tautomers. Nevertheless, it can be concluded that the cSAR(X) approach could be successfully applied to the investigation of SE in PU- and AD-like systems.

Classical Substituent Effect. The application of the classical interpretation of the SE allows us to consider how the substituent may affect the properties of the reaction site, in our case the distinguished group NH_2 . For this purpose, a Hammett-type linear equation is used, in which the slope (also known as reaction constant) describes the sensitivity of the reaction site on the impact of substituents X. In adenine, a good example of the classical approach is illustrated by dependences of cSAR(NH_2) on substituent constants, σ_m and σ_p , as presented in Table S17 and Figure 1. The number of bonds between C6, where the NH_2 group is attached, and C2 and C8 positions of attachment of the substituent X is two and three, respectively. This resembles the well-known situation for meta- and para-substituted benzene derivatives,³⁵ in which σ_m and σ_p are used in similarity models, respectively.³⁶ This analogy between meta- and para-substituted benzene deriva-

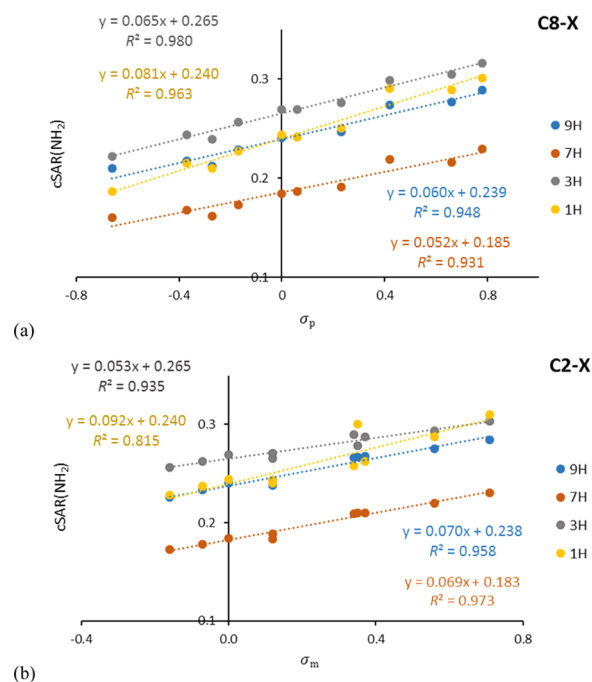


Figure 1. Correlations of cSAR(NH_2) on σ_p for (a) C8-X- and cSAR(NH_2) on σ_m for (b) C2-X-substituted derivatives of adenine.

tives and C2- and C8-substituted adenine derivatives is very well shown by the data in Table S17.

The mean R^2 value for regression lines cSAR(NH_2) vs σ_p for C8-X substitution is 0.955, and for C2-X vs σ_m , it is 0.920. Excluding the deviating point for CHO, the average R^2 value is 0.947. Therefore, σ_p should be used for describing C8-X-substituted systems, while σ_m should be used for the C2-X ones. For N-X-substituted systems, no clear conclusion can be drawn. This is most probably due to the fact that the lone pair at the substituted nitrogen may interact strongly with the substituents, particularly with the electron-attracting ones. In addition, for C8-X-substituted adenine derivatives, the obtained slope values (Table S17) reveal a greater impact of the electronic structure of the amino group on the substituent effect in 3H and 1H tautomers than in 9H and 7H series.

The impact of substituent on the amino group in adenine can be also presented by the linear equation cSAR(NH_2) vs cSAR(X), which reveals the interactions between two substituents through the heterocyclic π -system. For comparison, also shown are the appropriate dependences of cSAR(C6H in purine) on C2-X and C8-X. The obtained results of linear correlations are presented in Table 2 and shown in Figure S1.

The advantage of this approach is that there is no need to distinguish between meta- and para-type interactions because the relationships between cSAR(X) and cSAR(NH_2) or cSAR(C6H) automatically take into account differences in the nature of these interactions. In almost all cases, regressions have good or at least acceptable determination coefficients, with the only exception being the N-X-substituted 1H PU tautomer ($R^2 = 0.670$). In all cases, the slopes (their absolute values) are greater for regression for the cSAR(NH_2) equation than cSAR(C6H), indicating the important role of the participation of the lone pair at NH_2 in the interactions under consideration. It is important to note that for adenine the correlation trends in both cases are similar; the slopes are

Table 2. Slopes of the Obtained Linear Dependences cSAR(NH₂) vs cSAR(X) and cSAR(C6H) vs cSAR(X) for C8-X-, C2-X-, and N-X-Substituted Derivatives of Adenine and Purine

		C8-X		C2-X		N-X	
		<i>a</i>	<i>R</i> ²	<i>a</i>	<i>R</i> ²	<i>a</i>	<i>R</i> ²
cSAR(NH ₂) vs cSAR(X)							
AD	9H	-0.297	0.989	-0.222	0.913	-0.166	0.902
	7H	-0.269	0.987	-0.234	0.904	-0.300	0.890
	3H	-0.308	0.984	-0.153	0.805	-0.272	0.885
	1H	-0.399	0.984	-0.313	0.941	-0.348	0.896
average		-0.318		-0.230			
cSAR(C6H) vs cSAR(X)							
PU	9H	-0.173	0.987	-0.125	0.796	-0.106	0.940
	7H	-0.154	0.994	-0.116	0.948	-0.145	0.843
	3H	-0.222	0.977	-0.113	0.937	-0.135	0.887
	1H	-0.232	0.973	-0.159	0.911	-0.132	0.670
average		-0.195		-0.128			

substantially steeper for the C8-X substitution (mean value, -0.318) compared to the C2-X-substituted systems (mean value, -0.230). Similar relations are found for purine. For regression cSAR(CH₆) vs cSAR(X), the mean slope values are -0.195 and -0.128, respectively. This indicates a stronger SE when the number of bonds between the substituent and the amino group (or H in purines) is odd (C8 vs C6) rather than even (C2 vs C6). This strongly supports our previously suggested rule, presented in ref 35. In addition, for C8-X adenine and purine derivatives, the 3H and 1H tautomers are more sensitive to the impact of substituent than the 9H and 7H ones.

Reverse Substituent Effect. In addition to the correlations presented above, it should be emphasized that the same substituent X in a different position in adenine may have a quite different cSAR(X) value. Moreover, the same picture is observed for purine. This is due to the fact that various positions in adenine or purine have different abilities for electron attraction or donation. Hence, cSAR(X) may be considered as a numerical measure of these properties in given chemical moieties. In other words, cSAR(X) can be used to measure the reverse substituent effect, describing changes of the electronic properties of the substituent, either due to the position in the transmitting moiety or due to the nature of the fixed group (reaction site).

The analysis of the data in Tables S1–S4 allows us to show the ranges of variability of cSAR(X) values dependent on the position of substitution (C8-X, C2-X), taking into account all types of tautomers (9H, 7H, 3H, and 1H). Table 3 presents the ranges of cSAR(X) values for particular substituents for adenine and purine tautomers. This changeability is usually more strongly expressed in adenine than in purine tautomers. It should be emphasized again that the variability of cSAR(X) is in contradiction with the traditional concept of using the fixed values of substituent constants $\sigma(X)$ and reveals a new type of substituent properties.

A clear illustration of the reverse substituent effect is shown by comparing the cSAR(X) values for C8-X, C2-X, and N-X substitution in adenine with those in purine (Table 4). The obtained slope values, depending on the type of tautomer and substitution position, illustrate changes in the properties of substituents at different reaction sites NH₂ and H.

Table 3. Ranges of cSAR(X) Values for Substituents for Adenine and Purine C8-X- and C2-X-Substituted Tautomers^a

	cSAR(X)			
	C8-X		C2-X	
	AD	PU	AD	PU
NO ₂	0.061	0.036	0.044	0.045
CN	0.048	0.021	0.034	0.028
CHO	0.054	0.025	0.036	0.032
Cl	0.056	0.031	0.058	0.053
F	0.041	0.022	0.042	0.037
H	0.039	0.019	0.032	0.028
Me	0.050	0.027	0.049	0.045
OMe	0.066	0.026	0.055	0.050
OH	0.047	0.022	0.047	0.043
NH ₂	0.020	0.013	0.061	0.035
range	0.046	0.023	0.029	0.025
average	0.048	0.024	0.046	0.040
SD	0.013	0.006	0.010	0.009

^aEntries in bold underline the obtained values for unsubstituted adenine and purine tautomers.

These data indicate a slightly greater impact of the NH₂ group on the electronic properties of the substituent in adenine compared to its properties in purine.

Substituent Effect on Transmitting Moiety. Interactions between the amino group with other substituents, from different positions, cause changes in π -electron delocalization in the adenine rings. However, no valuable correlations between HOMA values for five- or six-membered rings and cSAR(X) are obtained, as shown for adenine and purine systems in Table S18. The reason may be both small variability of HOMA values in these systems and proximity effects (interactions with adjacent atoms or lone electron pair). However, if substituents are considered in two subgroups, i.e., electron-donating and electron-attracting, the correlations become clearer, especially for C8-substituted adenine derivatives (Table S18). In this series, for 9H and 7H tautomers, π -electron delocalization of the five-membered ring decreases, while that of the six-membered ring increases, both with decreasing electron-attracting and increasing electron-donating abilities of substituents (i.e., slopes are negative and positive,

Table 4. Slopes of the Obtained Linear Dependences of $cSAR(X)_{AD}$ vs $cSAR(X)_{PU}$ for C8-X, C2-X, and N-X Substitution

	$cSAR(X)_{AD}$ vs $cSAR(X)_{PU}$					
	C8-X		C2-X		N-X	
	a	R^2	a	R^2	a	R^2
9H	1.089	0.995	1.001	0.998	1.018	0.998
7H	1.063	0.997	0.964	0.996	1.004	0.986
3H	1.057	0.997	1.067	0.996	1.144	0.932
1H	1.045	0.996	1.091	0.995	1.033	0.991

respectively). In addition, the aromaticity of six-membered rings increases more with electron-attracting substituents than with electron donors.

Much more informative is the consideration of the substituent effect on HOMA for five- and six-membered rings when comparisons are carried out between adenine and purine derivatives. The slopes of the linear regressions and their determination coefficients are summarized in Table S19.

The data in Figure 2a show that for C8-X systems, imidazole-like rings are more sensitive to C8 substituents on

for C8-X systems, the slopes for 9H and 7H tautomers are much greater than those for the two other tautomers, and their R^2 values are between 0.75 and 0.80. Thus, for 9H and 7H tautomers and C8-X substitution, the adenine amino group enhances the substituent effect on the π -electron delocalization of both rings (in these cases, slopes > 1.0).

In contrast to these data, the linear regressions of $HOMA(6)_{AD}$ vs $HOMA(6)_{PU}$ for C2-X series (Figure 2b) have good or at least acceptable R^2 (0.861), and the slopes are always less than 1.0 (between 0.513 and 0.755), indicating a smaller sensitivity of the aromatic character of the six-membered rings in all tautomers in adenine than in purine.

Five- and six-membered rings in adenine and purine tautomers may contain five (3H, 1H, five-membered rings), six (9H, 7H, both rings), or seven (3H, 1H, six-membered rings) π -electrons. The pEDA approach allows the determination of these quantities for all particular cases, as documented in ref 15. It should be stressed that substituents do not change this picture in a significant way, as shown in Figures 3, S2, and S3 (Supporting Information). In addition, the presented relationships between pEDA and $cSAR(X)$ indicate that the values of pEDA increase with increasing

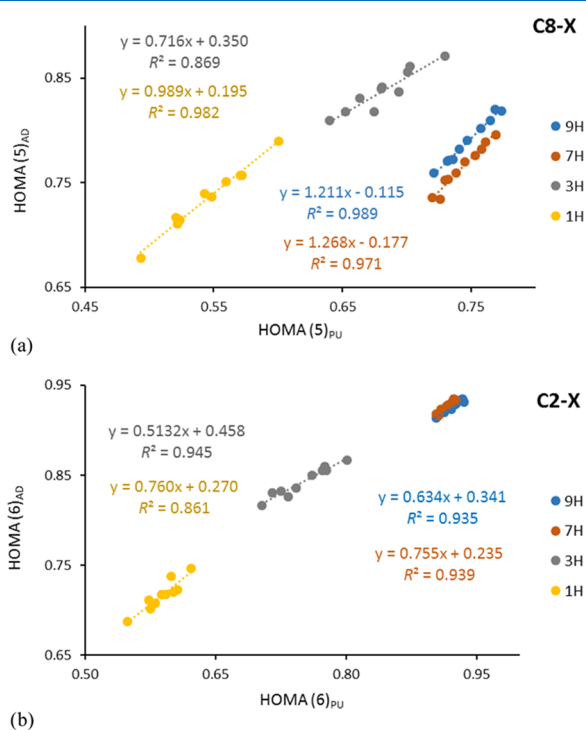


Figure 2. Dependence of $HOMA(5)_{AD}$ vs $HOMA(5)_{PU}$ for C8-X (a) and $HOMA(6)_{AD}$ vs $HOMA(6)_{PU}$ for C2-X (b) substitution of adenine and purine.

9H and 7H tautomers (the slopes are higher than those for 3H and 1H tautomers). Thus, the enhancement of SE by the amino group ($a > 1.0$) is observed only for cases where the substituent is attached to the five-membered ring in the neighborhood of the NH group (7H, 9H). The data for C2-X are not conclusive due to too low R^2 values.

The data in Table S19 also allow for a comparison of the HOMA values of six-membered rings ($HOMA(6)$) in AD and PU moieties. The slopes are very differentiated, but unfortunately, the precision of regressions is rather low ($R^2 < 0.8$); hence, deeper interpretation is not allowed. Nevertheless,

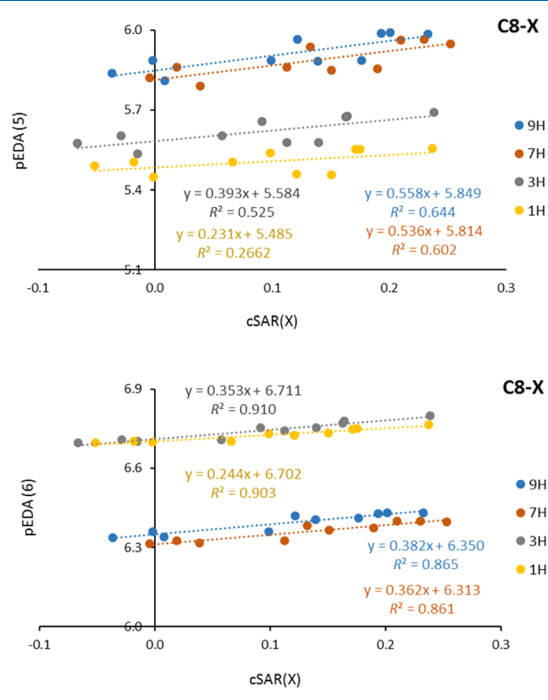


Figure 3. Dependence of pEDA vs $cSAR(X)$ for five- (a) and six-membered (b) rings of adenine tautomers for C8-X derivatives.

Table 5. Slopes of the Obtained Linear Dependences of CFI_{AD} vs CFI_{PU} for C8-X-, C2-X-, and N-X-Substituted Series

	CFI _{AD} vs CFI _{PU}					
	C8-X		C2-X		N-X	
	<i>a</i>	<i>R</i> ²	<i>a</i>	<i>R</i> ²	<i>a</i>	<i>R</i> ²
9H	1.205	0.995	1.092	0.998	1.084	0.998
7H	1.292	0.992	1.054	0.996	1.069	0.965
3H	1.132	0.997	1.056	0.996	1.150	0.956
1H	1.187	0.994	1.230	0.984	1.231	0.989

electron-donating ability of the substituent. The values of sEDA do not clearly correlate with cSAR(X) (low *R*² values).

Another view on changes of the transmitting properties caused by SE is shown by the charge flow index (CFI) values presented in Tables S7 and S8. The slopes of linear regression between CFI for adenine and purine tautomers, shown in Table 5, indicate that the transmission of the substituent effect is more significant in adenine than in purine tautomers. The slopes are greater than ~1.1, which evidently shows an increase of charge flow in adenine due to the impact of the amino group.

CONCLUSIONS

The use of cSAR, quantum-chemical-based descriptors of the substituent effect, allows us to show the influence of the substituent on the electronic structure of adenine and purine.

A comparison of the relationships between cSAR(X) and Hammett σ constants reveals that for carbon-substituted systems (C2-X, C8-X), better correlations are found with σ_{para} than with σ_{meta} , while for N-X-substituted series, better correlations are found with σ_{meta} .

The undoubted advantage of the cSAR(X) descriptor is that it describes the electronic structure of the X substituent regardless of the system to which X is attached. It is worth noting that the cSAR characteristic, in contrast to the traditional substituent constants (σ), shows the variability of the electronic properties of a given substituent, depending on the type of tautomers and the position of substitution in adenine and purine.

The results of the classical substituent effect analysis indicate stronger interactions of substituents from C8-X position than from C2-X and N-X positions, both in adenine and purine derivatives.

The changes induced by substituents in the π -electron structure of the rings are almost similar in adenine and purine, as estimated by the HOMA index. However, the presence of the NH₂ group in adenine enhances the substituent effect compared to that found in purine.

A more pronounced effect of the substituent on HOMA values is observed for C8-X-substituted systems. In addition, in the case of 7H and 9H tautomers that follow the Hückel rule, substituents reduce the aromaticity of the five-membered rings but increase it for the six-membered rings.

The results of the pEDA analysis for the five- and six-membered rings in adenine and purine tautomers indicate that the substituents do not significantly change the π -electron population for both "Hückel" (9H, 7H) and "anti-Hückel" (3H, 1H) tautomers.

The more effective transmission of the substituent effect in adenine than in purine tautomers is also shown by CFI.

METHODOLOGY

To investigate the substituent effects in C2-X-, C8-X-, and N-X-substituted derivatives of the four most stable purine tautomers and their adenine analogues, various substituents X (where X = NO₂, CN, CHO, Cl, F, H, Me, OMe, OH, and NH₂) were used (Scheme 2).

For all studied systems, optimization without any symmetry constraints was performed using the Gaussian 09 program.³⁷ Based on the experience from our previous research,³⁸ the density functional theory (DFT)-D method was applied, that is, functionals B97D3³⁹ with Dunning's⁴⁰ aug-cc-pvdz basis set. The harmonic vibrational frequencies were calculated at the same level of theory to confirm that all obtained structures correspond to the minima on the potential energy surface. No imaginary frequencies were found for the obtained series. In the case of asymmetric substituents (CHO, OMe, and OH), a lower-energy rotamer was considered.

The electronic properties of substituents in adenine and purine were characterized by the charge of the substituent active region (cSAR) parameter.^{29,30} The Hirshfeld method was used to calculate all cSAR values.⁴¹ The cSAR descriptor was calculated as a sum of charges at all atoms of the substituent X and the charge at the ipso carbon atom

$$\text{cSAR}(X) = q(X) + q(\text{C}_{\text{ipso}}) \quad (1)$$

In this study, the cSAR(X) in N-X substitution was calculated as the sum of charges at all atoms of the substituent X and the charge at the ipso nitrogen atom for individual tautomers

$$\text{cSAR}(X)_{\text{N-X}} = q(X) + q(\text{N}_{\text{ipso}}) \quad (2)$$

The effect of the SE on the electronic structure of the system was described by a charge flow index (CFI), defined as

$$\text{CFI} = \text{cSAR}(Y) - \text{cSAR}(X) \quad (3)$$

where Y = NH₂ for adenine and Y = H for purine tautomers.

The effect of substituents on the π -electron delocalization of the adenine and purine rings was investigated by a geometry-based aromaticity index harmonic oscillator model of aromaticity (HOMA).^{42,43} HOMA is defined as a normalized sum of squared deviations of bond lengths from the values of a system assumed to be fully aromatic. The appropriate expression is presented by eq 4

$$\text{HOMA} = 1 - \frac{1}{n} \sum_{j=1}^n \alpha_i (d_{\text{opt},i} - d_{i,j})^2 \quad (4)$$

where *n* is the number of bonds taken into account when carrying out the summation, *i* means the type of bond (CC or CN), α_i is an empirical normalization constant (for CC and CN bonds, $\alpha_{\text{CC}} = 257.7$ and $\alpha_{\text{CN}} = 93.52$) chosen to give

HOMA = 0 for nonaromatic system, and HOMA = 1 for the system where all bonds are equal to the optimal value $d_{\text{opt},i}$ assumed to be realized for full aromatic systems (for CC and CN bonds, $d_{\text{opt},\text{CC}} = 1.388 \text{ \AA}$ and $d_{\text{opt},\text{CN}} = 1.334 \text{ \AA}$), and $d_{i,j}$ are the bond lengths taken into calculation.

The pi/sigma electron donor–acceptor (pEDA/sEDA) models⁴⁴ were used to show the electronic structures of five- and six-membered rings in adenine and obtained according to eqs 5 and 6

$$s\text{EDA} = \sum_{i=1}^n \sigma_X^i \quad (5)$$

$$p\text{EDA} = \sum_{i=1}^n \pi_X^i \quad (6)$$

where for the planar part (in XY plane) of the system in question, σ_X^i denotes the sum of occupancies of 2s, 2p_x and 2p_y sigma orbitals, π_X^i means the occupancy of the 2p_z pi orbital of the *i*-th atom in the structure (for C and N atoms in adenine rings, respectively), and *n* denotes the sum of atoms, i.e., for adenine six-membered ring (6): *n* = 6, five-membered ring (5): *n* = 5. To obtain occupancy of individual orbitals, an analysis of natural bond orbital (NBO)⁴⁵ was performed using the Gaussian program (with the use of NBO 6.0 module).⁴⁶ Unlike in the original paper,⁴⁴ in this report, pEDA and sEDA were not standardized.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.0c00820>.

cSAR(X) and cSAR(NH₂) values for C8–X and C2–X substitution of adenine (Tables S1 and S2); cSAR(X) and cSAR(C6H) values for C8–X and C2–X substitution of purine (Tables S3 and S4); cSAR(X) and cSAR(NH₂) values for N–X substitution of adenine (Table S5); cSAR(X) and cSAR(C6H) values for N–X substitution of adenine (Table S6); CFI values for C8–X and C2–X substitution for adenine and purine tautomers (Tables S7 and S8); HOMA for imidazole (5) and pyrimidine (6) rings for C8–X, C2–X, and N–X of adenine (Tables S9, S10, and S11); HOMA for imidazole (5) and pyrimidine (6) rings for C8–X, C2–X, and N–X of purine (Tables S12, S13, and S14); pEDA and sEDA values for C8–X substitution for adenine tautomers (Tables S15 and S16); slopes of the linear dependences of cSAR(NH₂) on substituent constants σ_p , σ_m for C8–X-, C2–X-, and N–X-substituted derivatives of adenine (Table S17); dependence HOMA vs cSAR(X) for all substituents and with separation on EA and ED substituents for all types of substitution for five- and six-membered rings of adenine and purine tautomers (Table S18); slopes of the obtained linear dependences of HOMA(5)_{AD} vs HOMA(5)_{PU} for C8–X, C2–X, and N–X substitution (Table S19); Cartesian coordinates of equilibrium geometries of C8–X- and C2–X-substituted adenine and purine 9H, 7H, 3H, and 1H tautomers (Tables S20 and S22); Cartesian coordinates of equilibrium geometries of NX-substituted adenine and purine 9H, 7H, 3H, and 1H tautomers (Tables S21 and S23); dependences of cSAR(NH₂) vs cSAR(X) for C8–X-,

C2–X-, and N–X (c)-substituted derivatives of adenine (Figure S1); dependence of pEDA vs cSAR(X) for five- and six-membered rings of adenine tautomers for C2–X derivatives (Figure S2); and dependence of pEDA vs cSAR(X) for five- and six-membered rings of adenine tautomers for NX derivatives (Figure S3) (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Anna Jezuita – Faculty of Chemistry, Opole University, 45-052 Opole, Poland; Email: ajezuita@uni.opole.pl

Halina Szatyłowicz – Faculty of Chemistry, Warsaw University of Technology, 00-664 Warsaw, Poland; orcid.org/0000-0002-7034-6985; Email: halina@ch.pw.edu.pl

Author

Tadeusz M. Krygowski – Faculty of Chemistry, University of Warsaw, 02-093 Warsaw, Poland

Complete contact information is available at: <https://pubs.acs.org/10.1021/acsomega.0c00820>

Notes

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■ DEDICATION

Dedicated to our friend, professor Jerzy Błażejowski, outstanding Polish chemist, on the occasion of his 75th birthday.

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