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Atomic polarization justified Fukui indices and the affinity indicators in aromatic heterocycles and nucleobases

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ABSTRACT

Atomic Fukui indices have been calculated by integration of the polarization justified Fukui functions over the atomic basins. Resulting indices have been explored in the definition of the atomic and group affinity indicator and softnesses on the ground of the formal analysis of the polarization effect. These indicators combine the effect of the atomic charge and atomic Fukui index. They are potentially applicable in testing a sensing effect on a molecule induced by an approaching point agent, nucleophilic (−) or electrophilic (+), at a distance in the order of v.d. Waals radii. Calculated atomic and group affinity and softness indicators have been proved to be consistent with the well established trends of reactivity for a control group of the five-atom-ring heterocycles (imidazole, oxazole, thiazole). The indices have been applied to the set of 5 nucleobases (adenine, guanine, cytosine, thymine, uracyl), whose diverse reactivity towards electrophiles has been recognized as a key factor determining the sensitivity of DNA to cytotoxic agents. The pairing effect of the nucleobases bases in the DNA chain and the experimental trends of the site reactivity of these molecules have been properly accounted for by the calculated indicators.

1. Introduction

The Fukui indices for bonded atoms have been common representation of the local Fukui functions $f(\mathbf{r}) = (\partial\rho(\mathbf{r})/\partial N)_v$, tailored for the prospective use in the chemical practice [1–3]. Though many approaches for calculation of the atomic FF indices have been proposed since the benchmark paper introducing the idea of the Fukui function $f(\mathbf{r})$ [4], they have not been given a coherent theoretical analysis until the work by Ayers et al. [5,6] These authors convincingly demonstrated, how the actual atomic FF indices depend on the arbitrary method of condensing the electron density to atoms, according to the taste of the inventors. Bultinck et al. [7] demonstrated the drawbacks of any computational scheme for the atomic Fukui indices, due to the inevitable assumptions e.g. the arbitrary atom partitioning method. The recent general discussion of the Fukui indices given by Ayers et al. [6] has made it quite clear that "*transforming chemical DFT from a descriptive theory to a predictive theory requires developing tools for discerning when the Fukui function is the relevant reactivity indicator, and when something else is.*" This present work represents a step in this direction, aiming at calculation of the atomic Fukui indices based on existing polarization Fukui functions (PF) and transforming them to the novel reactivity indices within the rigor of conceptual DFT.

The polarization justified Fukui functions have been recently proposed and tested in this laboratory [8,9]. The underlying concept was to explore the polarization effect of the electron density in calculation of the Fukui function formulated as the derivative of the chemical potential μ over the external electrostatic potential $v(\mathbf{r})$, rather than the derivative of the density itself over N (Eq. (1)). The two approaches are strictly equivalent on the level of the Conceptual Density Functional Theory [10].

$$f(\mathbf{r}) = \left(\frac{\delta\mu}{\delta v(\mathbf{r})}\right)_N = \left(\frac{\partial\rho(\mathbf{r})}{\partial N}\right)_v \tag{1}$$

The chemical potential is given as:

$$\mu \equiv \frac{\delta E_v[\rho]}{\delta\rho(\mathbf{r})} = \left(\frac{\partial E}{\partial N}\right)_v \cong -\frac{1}{2}(I + A) \tag{2}$$

I and A stand for the ionization potential and electron affinity, respectively. The polarization effect on the electron density by the electric field $\boldsymbol{\varepsilon}$ is computable through the vector of local polarization $\boldsymbol{\alpha}(\mathbf{r})$:

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$$\alpha_i(\mathbf{r}) \equiv -\left(\frac{\partial\rho(\mathbf{r})}{\partial\varepsilon_i}\right)_N \qquad (i = x, y, z) \tag{3}$$

Developing a relation between $f(\mathbf{r})$ and $\boldsymbol{\alpha}(\mathbf{r})$ calls for an approximation for the softness kernel $s(\mathbf{r},\mathbf{r}') = -[\delta\rho(\mathbf{r})/\delta v(\mathbf{r}')]_\mu$; two approaches have been analyzed. For atoms, the local approximation of Vela and Gazquez [11] produced very promising results [8,9,12]. For molecules, the original and more advanced nonlocal relation for $s(\mathbf{r},\mathbf{r}')$ was necessary [13]. The extension of the work by Garza and Robles [14] and Li and Evans [15] has been proposed for that purpose. This led to the working relation between the local polarization vector $\vec{\alpha}(\mathbf{r})$ and the Fukui function $f(\mathbf{r})$ that serves as the definition of the polarization justified Fukui function:

$$\boldsymbol{\alpha}(\mathbf{r}) = Kf(\mathbf{r})\left[\mathbf{r} - \mathbf{M}_e^{(N)}\right] + b\rho(\mathbf{r})[\mathbf{M}_e - N\mathbf{r}] \tag{4}$$

The vectors $\left[\mathbf{r} - \mathbf{M}_e^{(N)}\right]$ and $[\mathbf{M}_e - N\mathbf{r}]$ are translationally invariant. The result contains two adjustable parameters (K,b), and also well defined global quantities for the system: the electron dipole moment $\mathbf{M}_e$ and its derivative, $\mathbf{M}_e^{(N)}$ [8]:

$$\mathbf{M}_e = \int \rho(\mathbf{r})\mathbf{r}d\mathbf{r} \qquad \text{and}$$

$$\mathbf{M}_e^{(N)} = (\partial\mathbf{M}_e/\partial N)_v = (\partial\mu/\partial\boldsymbol{\varepsilon})_N = \int f(\mathbf{r})\mathbf{r}d\mathbf{r} \tag{5}$$

Of necessity, the finite difference approximation to the chemical potential μ is hidden behind $\mathbf{M}_e^{(N)}$ quantity that serves as a global parameter of the computational scheme. This however, does not affect the local properties of the resulting $f(\mathbf{r})$ function; this is exclusively dependent on the local character of the density $\rho(\mathbf{r})$ and its derivative $\boldsymbol{\alpha}(\mathbf{r})$ (Eq. (3)), both well defined in every point in space. This approach relates the Fukui functions obtained by this method to the gradient expansion method by Chattaraj et al. [16], including the cusp condition requirement met.

The resulting PF functions have been successfully tested in the series of preceding works. Characteristic feature of the PF functions for atoms are very clear regions of negative PF (radial) close to the nucleus [8]. These regions are considerably smaller for cations; isoelectronic species show very similar PF radial functions [9]. They produce reasonable correlation with the global hardness, when integrated with the electronic hardness kernel $\eta(\mathbf{r},\mathbf{r}') \cong |\mathbf{r} - \mathbf{r}'|^{-1}$ [9]. The consequences of the basic assumptions for the softness kernel have been verified separately and led to the first modeling approach for the softness and hardness kernels for an atom [12]. PF calculation for a series of small molecules (LiH, HF, CO, N_2, H_2CO) demonstrated rough qualitative agreement with the standard approximation $f_\pm(\mathbf{r}) = 1/2[\rho^-(\mathbf{r}) - \rho^+(\mathbf{r})]$ at intermediate distances from the nuclei, and show remarkable negative regions close to the nuclei [13]. The predictive power of the PF for chemistry have been analyzed on the group of five member ring heterocycles: imidazole, oxazole and thiazole, whose diverse reactivity trends are well recognized [17]. The maps of the PF function in this planar molecules very properly reflect the differences in the reactivity of the ring atoms, as well as the overall varieties of the ring systems.

Although producing the PF maps is attractive in computational studies, the practically oriented chemists require more condensed information. Producing the atomic PF indices appeared to be the first necessary next step.

The molecules selected for this study are aromatic heterocycles characterized by the polarization effect dominated by their π electrons. First group are again small isoelectronic rings showing considerable reactivity variety among the ring sites: imidazole, oxazole and thiazole [17]. Second group of molecules are the natural nucleobases: adenine, cytosine, guanine, thymine and uracyl. They are all heterocyclic aromatics, famous for their "affinity at a distance": selective pairing property as they show in DNA double helix.

Each nucleobase ring contains a number of atoms prone to electrophilic attack. Such reactions have great biological significance, since covalent modification of nucleobases is directly linked with mutagenicity and carcinogenicity [18,19]. Furthermore, biological consequences of these processes are often determined by site-selectivity of the attack.

Several studies on the site reactivity of nucleobases have been pursued on the ground of the DFT related parameters. The atomic Fukui indices calculated classically as the difference between atomic populations in neutral and ionic states (+1, 0, −1) confirmed the notable variety in the electron density of the ring atoms in nucleobases but led to no conclusion [20,21]. Attempts to quantify the properties of atoms by their softness parameters calculated from the orbitally resolved hardness tensor (ORHT) were in vain [22]. The study on the electrophilicity parameter changing with the external electric field demonstrated the essential role of the polarization effects in these molecules [23]. PF indices presented in this work open a new perspective in this direction.

2. Methods: from the Fukui indices to the affinity indicators

The present work focuses on the analysis and the prospective use of the polarization justified Fukui functions condensed to atoms or molecular fragments by the method introduced by Bader [24] (AIM): atoms are confined to the mathematically well defined, non-overlapping regions that reproduce atomic volumes matching those from experimental refractions [25,26]. The basic Bader method has been explored at the level described by Bultinck et al. as FMR (Fragment of Molecular Response approach) [7], i.e. retaining the atomic basins identified from the density in neutral molecule, well in accord with the finite field procedure explored in computations of the density polarization effect, extrapolated to zero electric field $\boldsymbol{\varepsilon} \to 0$.

The basic equation for calculation of the polarizability justified Fukui functions (Eq. (4)) is readily integrated over individual atomic basin a–th (AIM, [24]) to give:

$$\boldsymbol{\alpha}_a = K\left[\mathbf{M}_{e,a}^{(N)} - f_a\mathbf{M}_e^{(N)}\right] + bN_a[\mathbf{M}_e - N\mathbf{M}_{e,a}] \tag{6}$$

The sum over all atomic basins vanishes; K and b parameters are global and have to be calculated once, for the whole system [13], the electron dipole moments for the atomic basins $(\mathbf{M}_{e,a}, \mathbf{M}_{e,a}^{(N)})$ are defined identically as for the whole system (Eq. (5)). Eq. (6) serves as formal definition of the atomic Fukui index for an atomic basin a.

The resulting Fukui indices are additive. Known the long-lasting paradigm of the transferable atomic electron polarizabilities, one might suppose, that the resulting Fukui indices may be transferable as well. This, however, is not the case. The electron dipole polarizability is by definition:

$$\alpha_e = \frac{1}{3}\mathrm{Tr}\int \boldsymbol{\alpha}(\mathbf{r})\mathbf{r}d\mathbf{r} \tag{7}$$

When this is integrated over an atomic basin, the Fukui index of the basin will not appear in the result, since $\int_a f(\mathbf{r})\mathbf{r}d\mathbf{r} = \mathbf{M}_{e,a}^{(N)}$ (cf. Eq. (5)). The atomic Fukui indices as defined by Eq. (6) are uniquely characteristic for atoms in a given molecule. Notably, while the auxiliary vector quantities in Eq. (6) $(\mathbf{M}_e, \mathbf{M}_e^{(N)}, \mathbf{M}_{e,a}, \mathbf{M}_{e,a}^{(N)})$ vary upon transformation of the coordinate system [8], the scalar quantities (f_a, N_a, K, b) do not depend on the choice of the origin.

Calculation of the atomic PF indices according to Eq. (6) provides a potential tool to describe local reactivity of molecular

system leading to the charge transfer. This is an interaction typical for the soft–soft combination of the reagents. It has long been know, however, that in the hard-hard combination, the reaction is controlled by the electrostatic effects (atomic charges) rather that by the Fukui function [27,28]. Hence, the novel affinity indicator is needed to combine the electrostatic and electronic effect in the intermolecular interactions. The polarization nature of the proposed index opens the promising perspective to this point.

The atomic Fukui indices resulted from integration of $f(\mathbf{r})$ over atomic basin will be used in the DFT formalism, according to the assumed model process: disturbing the molecular density (hence changing the chemical potential) by an external electric field. The proper function minimized upon the change of external potential for a system of atoms potentially exchanging electrons is the thermodynamical potential $\Omega\,[\mu, v(\mathbf{r})] = E - N\mu$. To the first order:

$$d\Omega^{(1)} = -Nd\mu + \int \rho(\mathbf{r})\delta v(\mathbf{r})d\mathbf{r} \tag{8}$$

Using $d\mu = \eta dN + \int f(\mathbf{r})\delta v(\mathbf{r})d\mathbf{r}$ and considering stable number of electrons in the whole system (N = const.) we get:

$$d\Omega^{(1)} = \int [\rho(\mathbf{r}) - Nf(\mathbf{r})]\delta v(\mathbf{r})d\mathbf{r} \tag{9}$$

The second order term in the differential of the thermodynamical potential can also be approached on the similar way:

$$d\Omega^{(2)} = \frac{1}{2}\left[\left(\frac{\partial^2\Omega}{\partial\mu^2}\right)_v (d\mu)^2 + 2d\mu\frac{\partial}{\partial\mu}\int\left(\frac{\delta\Omega}{\delta v(\mathbf{r})}\right)_\mu \delta v(\mathbf{r})d\mathbf{r} + \iint\left(\frac{\delta^2\boldsymbol{\Omega}}{\delta v(\mathbf{r}')\delta v(\mathbf{r})}\right)_\mu \delta v(\mathbf{r}')\delta v(\mathbf{r})d\mathbf{r}'d\mathbf{r}\right] \tag{10}$$

This is readily simplified by using standard identities [29–31]:

$$\left(\frac{\delta\Omega}{\delta v(\mathbf{r})}\right)_\mu = \rho(\mathbf{r}) \quad \left[\frac{\partial\Omega}{\partial\mu}\right]_v = -N \quad \left[\frac{\partial^2\Omega}{\partial\mu^2}\right]_v = -\left[\frac{\partial N}{\partial\mu}\right]_v = -S \tag{10a}$$

$$\left[\frac{\partial}{\partial\mu}\left(\frac{\delta\Omega}{\delta v(\mathbf{r})}\right)_\mu\right]_v = \left[\frac{\partial\rho(\mathbf{r})}{\partial\mu}\right]_v = s(\mathbf{r}) \tag{10b}$$

$$\left(\frac{\delta^2\Omega}{\delta v(\mathbf{r})\delta v(\mathbf{r}')}\right)_\mu = \left(\frac{\delta\rho(\mathbf{r})}{\delta v(\mathbf{r}')}\right)_\mu = -s(\mathbf{r},\mathbf{r}') \tag{10c}$$

$S = (I - A)^{-1}$ is the global softness, $s(\mathbf{r})$ is the local softness and $s(\mathbf{r},\mathbf{r}')$ is the softness kernel. The second order term becomes:

$$d\Omega^{(2)} = \frac{1}{2}\left[-S(d\mu)^2 + 2d\mu\int s(\mathbf{r})\delta v(\mathbf{r})d\mathbf{r} - \iint s(\mathbf{r}',\mathbf{r})\delta v(\mathbf{r}')\delta v(\mathbf{r})d\mathbf{r}'d\mathbf{r}\right] \tag{11}$$

Substituting $d\mu = \int f(\mathbf{r})\delta v(\mathbf{r})d\mathbf{r}$ and reducing the last term to tractable form by the crude local approximation [8] $s(\mathbf{r}',\mathbf{r}) = s(\mathbf{r})\delta(\mathbf{r}' - \mathbf{r})$ leads to the simplified result:

$$d\Omega^{(2)} = \frac{S}{2}\left[\left(\int f(\mathbf{r})\delta v(\mathbf{r})d\mathbf{r}\right)^2 - \int f(\mathbf{r})[\delta v(\mathbf{r})]^2 d\mathbf{r}\right] \tag{12}$$

The total perturbation of the system due to an external potential may be decomposed into atomic contributions by combining Eqs. (9) and (12). Introducing the atomic Fukui indices f_a and populations N_a by integration of $f(\mathbf{r})$ and $\rho(\mathbf{r})$ over atomic basins, with the external potential change at the point atoms approximated by some average change ΔV_a, lead to the simple result:

$$\Delta\Omega^{(1)} + \Delta\Omega^{(2)} = \sum_a [-N_a + Nf_a]\Delta V_a + \frac{S}{2}\sum_a f_a[f_a - 1](\Delta V_a)^2 \tag{13}$$

To bring the expression closer to chemical practice, the DFT potential from a charge q at r ($v = -q/r$) has been replaced by the standard electrostatic definition of the potential ($V = q/r$). The global change of the thermodynamical potential due to the external field must still be completed by adding the nuclear interaction term $\Delta\Omega_n = \sum_a Z_a\Delta V_a$ The final result in atomic resolution reads:

$$\Delta\Omega = \Delta\Omega^{(1)} + \Delta\Omega^{(2)} + \Delta\Omega_n = \sum_a [Q_a + Nf_a]\Delta V_a + \frac{S}{2}\sum_a f_a[f_a - 1](\Delta V_a)^2 \tag{14}$$

where $Q_a = Z_a - N_a$. For a point charge q approaching a molecular site from a distance of the order of the sum of van Waals radii (no electron exchange), the interaction energy $\Delta\Omega$ is approximated by a sum of atomic contributions. Each atomic contribution is quadratic function of an external electrostatic potential change at a-th atom, with a maximum (the second term is negative, if only $f_a > 0$). The contribution from an atom a to a nucleophilic or electrophilic type of a reaction will be naturally described by the derivative $d\Omega/dV_a$ approximated here by the ratio $\Delta\Omega/\Delta V_a$:

$$\frac{\Delta\Omega}{\Delta V_a} = (Q_a + Nf_a) + Sf_a(f_a - 1)\Delta V_a \tag{15}$$

At infinitely small disturbing potentials this reduces to an individual affinity indicator for each atom in a system:

$$A_a = \lim_{\Delta V_a\to 0}\frac{\Delta\Omega}{\Delta V_a} = (Q_a + Nf_a) \tag{16}$$

Eq. (14) also hints to an approximation for the second derivative of the thermodynamical potential: $d^2\Omega/dV_a^2 \approx \Delta^2\Omega/\Delta V_a^2$. This derivative hides very clear interpretation as a local (atomic) softness descriptor (Eq. 10c): the diagonal atomic softness kernel [29] s_{aa}:

$$\frac{\Delta^2\Omega}{\Delta V_a^2} = \frac{\Delta N_a}{\Delta V_a} = -s_{aa} = Sf_a(f_a - 1) < 0 \tag{17}$$

$s_{aa} > 0$ is an interesting parameter complementary to the affinity indicator as it describes the first effect of an approaching external agent on the electron content at the site attacked – a contact atom while the system becomes polarized. Combining Eqs. (14), (16) and (17) gives an attractively simple, albeit crude, approximation for an atomic contribution to the energy change of a system disturbed by an interaction with a charge at a distance:

$$\Delta\Omega_a = A_a\Delta V_a - \frac{1}{2}s_{aa}(\Delta V_a)^2 \tag{18}$$

The energy change due to the atomic charge/Fukui index effect is determined mainly by the sign of the $A_a\Delta V_a$ product as discussed above. The second term represents the contribution from the atomic softness; it is definitely stabilizing, the more so, the softer is the attacked system as a whole (S, cf. Eq. (17)) and the higher the product $f_a(f_a - 1)$ with a maximum at $f_a = 0.5$. The total effect of a charge approaching to a system will be the sum of atomic contributions:

$$\Delta\Omega = \sum_a A_a\Delta V_a - \frac{1}{2}\sum_a s_{aa}(\Delta V_a)^2. \tag{19}$$

3. Calculations and results

The Fukui functions have been calculated on the basis of Eq. (4), using the method described in the preceding paper [13]. The electron density has been calculated by the Gaussian 03 code [32], the DFT B3LYP method using the *aug-cc-pvqz* basis set. The local polarizability vector $\vec{\alpha}(\mathbf{r})$ (Eq. (2)) has been calculated by the finite field

Table 1
Calculated atomic Fukui indices of atoms in the test heterocyclic rings. (For the number of atoms see Fig. 1.)

Imidazole		Oxazole		Thiazole	
Atom	Fukui index	Atom	Fukui index	Atom	Fukui index
C4	0.1049	C4	0.2013	C4	0.1407
C5	0.1021	C5	0.0545	C5	0.1546
N3	0.1216	N3	0.1596	N3	0.2045
C2	0.0731	C2	0.0846	C2	0.1207
N1	0.2445	O1	0.1569	S1	0.3287
H1	0.0949	–	–	–	–
H2	0.0768	H2	0.0663	H2	0.0165
H4	0.0718	H4	0.0888	H4	0.0179
H5	0.1102	H5	0.1880	H5	0.0164

procedure. Fukui functions have been integrated over the atomic basins identified by means of the Bader algorithm [33]. Resulting atomic indices for the entire set of molecules under study have been shown in Tables 1 and 2. Calculated indices are positive and are properly normalized to unity. The only meaningful exceptions are C6 in cytosine, thymine and in uracyl. These atoms are uniquely located within the –NH–CH–C< entity, the small negative values of their Fukui index are compensated by the extraordinary high positive Fukui indices of the vicinal hydrogen, to produce overall positive Fukui index for the CH group (0.1012, 0.0445 and 0.0713 respectively).

The atomic Fukui indices have been used in calculation of the atomic affinity indicator A_a (Eq. (16)) and the atomic softness kernel s_{aa} (Eq. (17)). The number of electrons in final equations N (Eqs. (13)–(16)) is crucial for determining numerical values of the affinity indicator A_a. In these equations N appears to be a parameter introduced by the form of the thermodynamical potential $\Omega\ [\mu, v] = E[v] - N\mu$. Since the polarization effect is considered "from a distance", it represents rather small perturbation to $\Delta\Omega$. Yet it's magnitude directly depends on the number of electrons in the system that are relevant for the actual perturbation, ($Nf_a\Delta V_a$ in Eq. (14)). Most naturally, this number must be limited to the electrons associated with a particular atom a and responding to a given perturbation ΔV_a. It is the matter of an educated guess of a chemist, what should be a reasonable choice of N parameter, to warrant the affinity indicator plays a predictive role for various types of systems.

Parr and Yang [10] noted, that their idea is coherent with the frontier electron concept by K. Fukui, and in fact the Fukui functions provided by the densities of frontier orbitals (ρ^{HOMO}, ρ^{LUMO}) are widely considered as very reasonable. This tends to suggest the HOMO electrons as playing the leading role. However, the polarization effect is determined by all valence electrons. There is a class of molecules, though, where discerning the polarizable group of electrons is most natural: the aromatic systems with their delocalized π-orbitals. In order to investigate the practical meaning of the proposed affinity indicator, the group of aromatics has been selected for this present study. The number of electrons N has been arbitrarily set on the number of π-electrons within the aromatic ring system.

The atomic affinity indicator is additive, since both atomic charges and atomic Fukui indices are additive for the AIM. This allows for calculation of the group indices by simple summation:

$$A_G = \sum_{a\in G}(Q_a + Nf_a) = Q_G + Nf_G \tag{20}$$

Calculation of the atomic softness kernel for a group required a two step procedure: first the Fukui indices for a group $f_G = \sum_{a\in G} f_a$, then $s_{GG} = Sf_G(1 - f_G)$. The interesting case of a group is the molecule as a whole: then $f_M = 1$ and $Q_M = 0, A_M = N, s_{MM} = 0$, the second term in Eq. (14) vanishes and the equation reduces to the trivial $N\Delta V$, exposing the essence of the polarization approximation that led to Eq. (14). The choice of N as the number of aromatic π-electrons becomes rationalized.

The diagrammatic representation of the calculated data has been proposed. Two informations have been coded in the presented set of figures: the atomic (group) affinity indicator A is given by the intensity of a color of atom, while the diameter of the circle designating an atom has been set proportional to the s_{aa}, in accord with the past discussion of the relation between the atomic softness and volume [34,35]. The diagrams have been shown in Figs. 1–3.

Additional two diagrams represent the results for the nucleobases set in two complementary pairs in the geometry typical for the DNA chain, in order to expose the characteristics of the contact atoms within the pair geometry. They are shown in Figs. 4 and 5 for the AT and GC pairs, respectively. The hydrogen bonds bridging the molecules are clearly reflected by the A parameters calculated for the isolated molecules in this work. The connecting atoms form either the (−+ |−) pattern (A–T: N6/H6′/O4, N1/H3/N3, G–C: O6/H4/N4), or the (++|−) pattern (G–C: N1/H1/N3, N2/H2′/O2), the weak C2/H2/O2 bond in A–T pair also belongs to this group,

Table 2
Calculated atomic Fukui indices of atoms in the purine and pyrimidine nucleobases. (For the number of atoms see Fig. 2 for pyrimidines and Fig. 3 for purines.)

Purines				Pyrimidines					
Adenine		Guanine		Uracyl		Thymine		Cytosine	
Atom	Fukui index	Atom	Fukui index	Atom	Fukui index	Atom	Fukui index	Atom	Fukui index
N1	0.0797	N1	0.1726	N1	0.2239	N1	0.1396	N1	0.1610
–	–	H1	0.0284	H1	0.0887	H1	0.0472	H1	0.0660
C2	0.0451	C2	0.0744	C2	−0.0046	C2	0.0271	C2	0.0039
H2	0.0238	N2	0.1631	O2	0.0933	O2	0.1626	O2	0.1201
–	–	H2	0.0209	N3	0.0237	N3	0.0742	N3	0.1129
–	–	H2′	0.0228	H3	0.0481	H3	0.0231	–	–
N3	0.0814	N3	0.1147	C4	0.0010	C4	0.0347	C4	0.0401
C4	0.0103	C4	0.0146	O4	0.1006	O4	0.1391	N4	0.0558
C5	0.0127	C5	0.0440	–	–	–	–	H4	0.0288
C6	0.0399	C6	0.0214	–	–	–	–	H4′	0.0270
N6	0.0763	O6	0.1123	C5	0.2506	C5	0.1192	C5	0.1968
H6	0.0089	–	–	–	–	C5′	0.0678	–	–
H6′	0.0132	–	–	H5	0.1034	H5	0.0430	H5	0.0864
N7	0.1251	N7	0.0641	–	–	H5′	0.0348		
C8	0.1370	C8	0.0485	–	–	H5″	0.0431		
H8	0.0490	H8	0.0215	C6	−0.1282	C6	−0.0640	C6	−0.0712
N9	0.2649	N9	0.0642	H6	0.1995	H6	0.1085	H6	0.1724
H9	0.0328	H9	0.0124	–	–	–	–	–	–

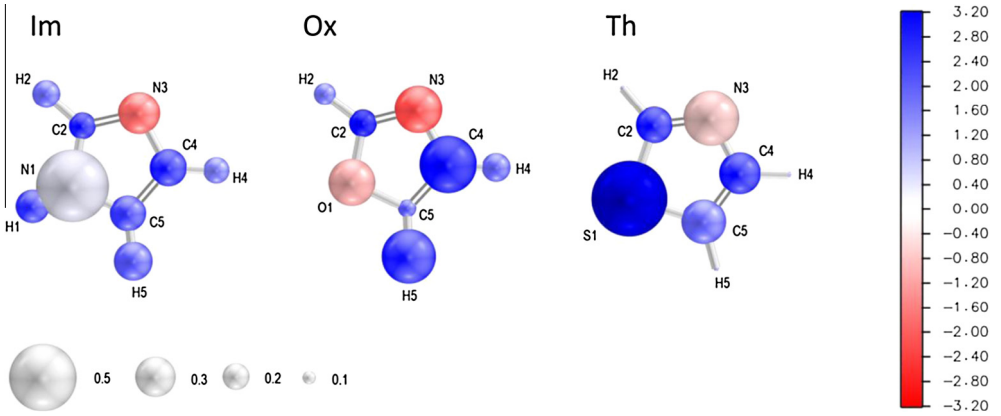

Fig. 1. Calculated atomic affinity indicators (colored *A* scale) and softness kernels (s_{aa}, the diameter scale) for the imidazole ring systems: imidazole (Im), oxazole (Ox), thiazole (Th). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

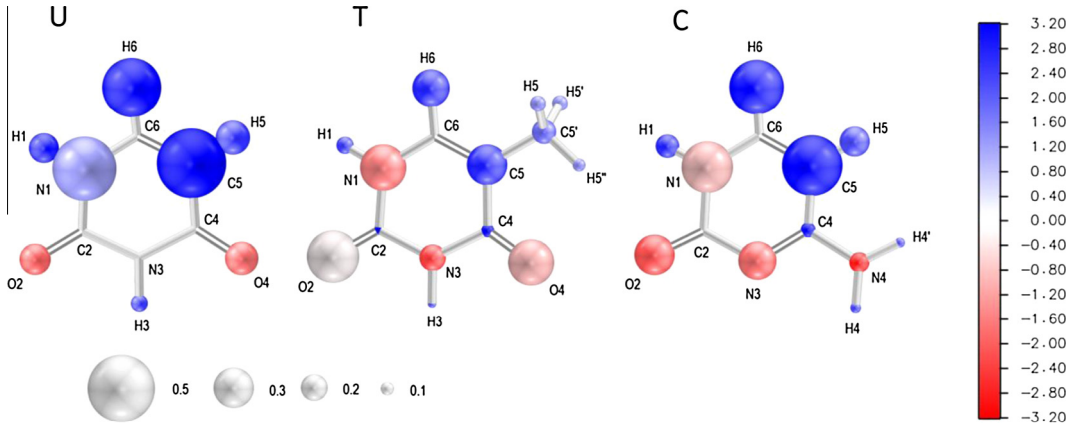

Fig. 2. Calculated atomic affinity indicators (colored *A* scale) and softness kernels (s_{aa}, the diameter scale) for the pyrimidine nucleobases: uracyl (U), thymine (T), cytosine (C). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

indicating, that the strength of a bond goes parallel to the atomic reactivity indices of connected atoms (For the thymine O2 atom the index is very low $A_{O2} = -0.02$). The bridging pattern of the atomic softness in a sequence of bridging atoms confirms the electrostatic nature of the hydrogen bonds (Figs. 4 and 5): the hard and positive atom trapped in between two softer atoms.

4. Discussion and conclusions

The proposed affinity indicator A_a (Eq. (16)) contains a balanced effect of two factors for each bonded atom: its charge Q_a and its Fukui index f_a. Since $f_a > 0$, the result of interaction with a test point charge is non-symmetric. By approaching an electrophilic point-agent ($\Delta V_a > 0$), the contribution of an atom to the energy change of a system as a result of initial contact is stabilizing ($\Delta\Omega < 0$), when the site is characterized by the negative $A_a < 0$. This is the case when the atomic charge is negative ($Q_a < 0$), however, the affinity indicator contains also a polarization effect that makes the energy gain smaller (the $Nf_a > 0$ term in Eq. (16)); the Fukui index for an atom in question acts in the opposite direction than its charge. The balance between the two factors is controlled by the assumed *N* parameter.

An external point nucleophile introduces $\Delta V_a < 0$, hence, it will introduce a stabilizing effect on a system when approaching sites characterized by a positive charge ($Q_a > 0$), but also when $Q_a \cong 0$, if only its Fukui index happens to be considerable high due to $Nf_a > 0$ component. Both factors (the charge and the Fukui index) act in the same direction. Site sensitivity to a nucleophile is likely to be sufficiently reflected by the affinity index *A*.

The proposed affinity indicator appears to provide a hint of first preferences to accommodate an electrophile or a nucleophile at a given molecular site, when applied with necessary caution. The response of a system even to a test point charge comes from interaction of a number of vicinal atoms and consideration of the group index may be necessary. Also, due to the arbitrary parameter *N*, the meaning of the *A* index may only be considered as a relative measure possibly useful in ordering the affinity tendency.

The first test for the power of the descriptors proposed in this work is possible in the set of 3 model member ring heterocycles. They show common feature as far as the substitution to the carbon atoms is concerned: C5 and C4 carbons are sensitive to an electrophilic attack, while the nucleophiles go into C2 position exclusively [17].

By the diagram in Fig. 1 the action of a nucleophile on C2 is understood as the combined effect of its positive *A* and considerably negative (or lower) *A* for its nearest ring neighbors (X1 = NH, O, S; and N3), Table 1. This conclusion is in harmony with the observations [17]: nucleophilic substitution is easy for Im, less common for Ox and rare for Th. It may be important to note, that the site C2 is relatively hard in all these molecules.

Rationalizing the result of an electrophilic attack on the test heterocycles requires a broader analysis. For the $(CH)_2$ group as a whole, the electrophilic substitution is apparently driven by the high softness of this group (close to the maximum possible value),

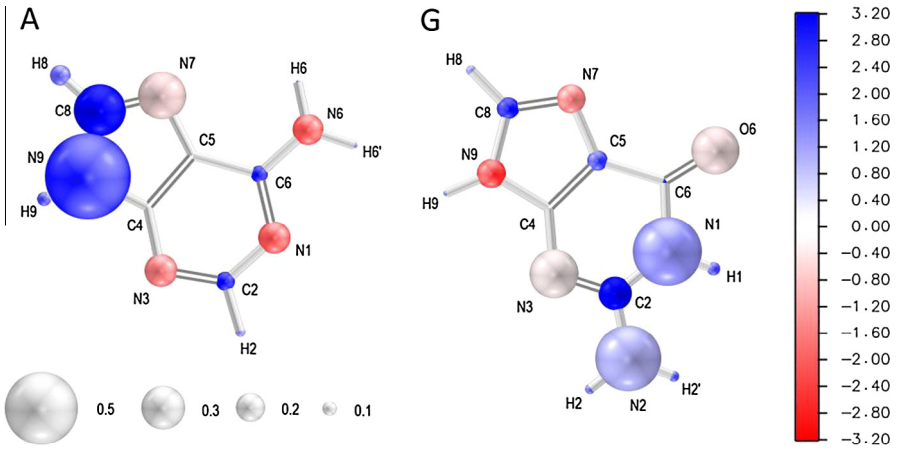

Fig. 3. Calculated atomic affinity indicators (colored *A* scale) and softness kernels (s_{aa}, the diameter scale) for the purine nucleobases: adenine (A), guanine (G). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

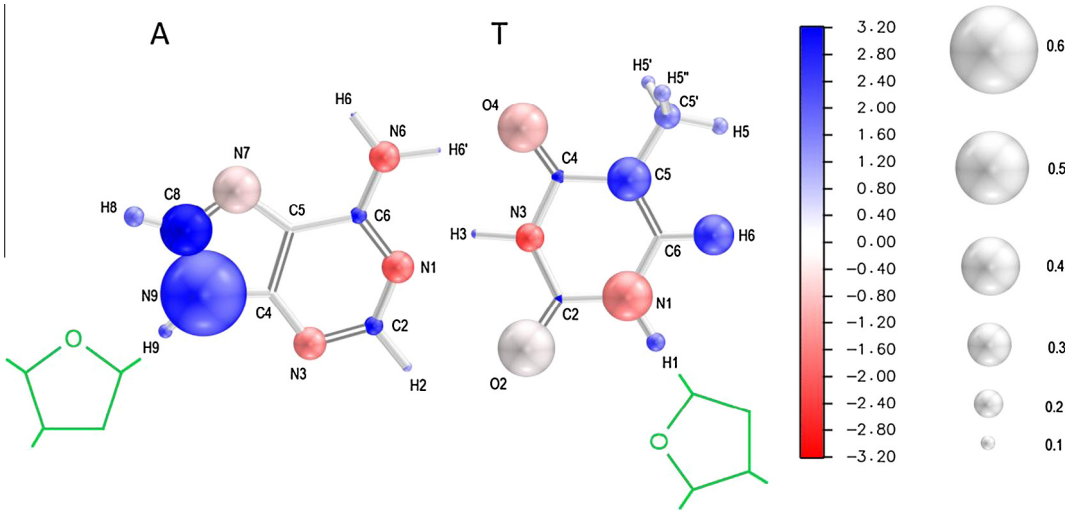

Fig. 4. Calculated atomic affinity indicators (colored *A* scale) and softness kernels (s_{aa}, the diameter scale) for the coupled nucleobases: Adenine–Thymine (AT). The point of attachment of the glycoside bonds has been indicated schematically. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

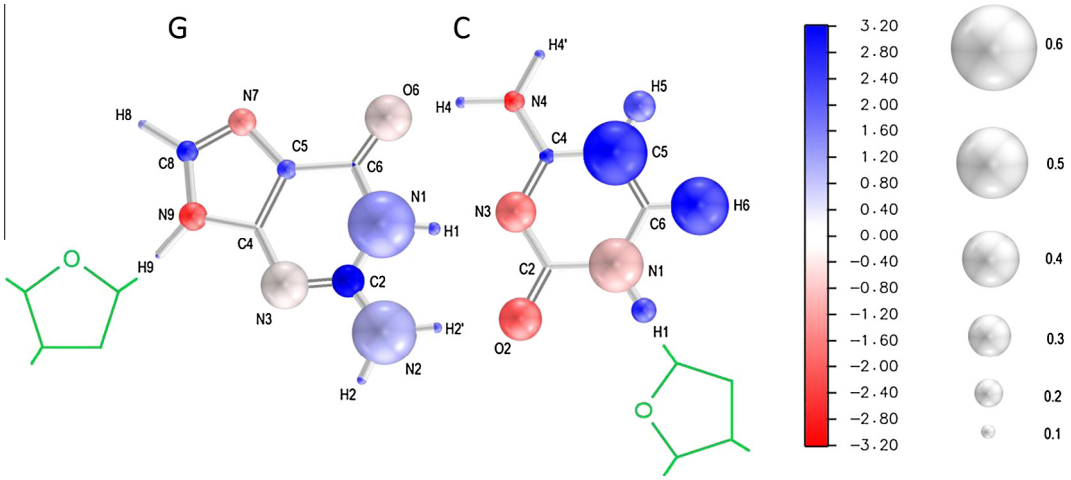

Fig. 5. Calculated atomic affinity indicators (colored *A* scale) and softness kernels (s_{aa}, the diameter scale) for the coupled nucleobases: Guanine–Cytosine (GC). The point of attachment of the glycoside bonds has been indicated. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 3
Atomic affinity indicators of selected atoms and group in the test heterocyclic rings.

	Index	C2	X1		N3	$(CH)_2$
Imidazole	A	1.41	(N1)	0.06	−0.59	3.37
	s_{aa}	0.20		0.66	0.31	0.70
Oxazole	A	1.90	(O1)	−0.27	−0.78	4.21
	s_{aa}	0.20		0.35	0.35	0.65
Thiazole	A	1.38	(S1)	3.18	−0.15	2.45
	s_{aa}	0.27		0.56	0.41	0.56

Table 4
Atomic affinity indicators of selected atoms in pyrimidine bases.

	Index	N1	N3	O2	O4
Uracyl	A	0.33	−1.41	−0.61	−0.55
	s_{aa}	0.48	0.06	0.23	0.26
Thymine	A	−0.46	−0.83	−0.02	−0.23
	s_{aa}	0.34	0.20	0.39	0.34
Cytosine	A	−0.19	−0.54	−0.71	(N4) −1.14
	s_{aa}	0.38	0.28	0.30	0.15

Table 5
Atomic affinity indicators of selected atoms in purine bases.

	Index	N1	N3	N7	(NH) N9	C8
Adenine	A	−0.71	−0.49	−0.11	1.17	2.40
	s_{aa}	0.22	0.22	0.33	0.59	0.36
Guanine	A	(NH) 0.39	−0.04	−0.45	−0.98	1.61
	s_{aa}	0.47	0.34	0.20	0.20	0.15

despite the high values of their A indicators, Table 3. This should be compared with the indicators for the N3 atom, the site of primary electrophilic substitution in this set of molecules. It becomes evident, that the electrophilic attack on N3 is driven by the primary electrostatic factors represented by A, while in the attack of an electrophile on the $(CH)_2$ entity (the double bond) the polarization term in Eq. (14) plays the decisive role due to the high softness parameter, very well in line with the property of the π electrons.

The above discussion opens a way to correlate the properties of nucleobases with the atomic indices introduced in this work (A, s_{aa}). In all the bases there are three types of electronegative heteroatoms, namely three- and twofold coordinated nitrogens and carbonyl oxygen atoms. The first two types illustrate the physical effects captured by the presented softness parameters. The twofold coordinated nitrogens donate their $2p_z$ electron to the aromatic system and retain the lone pair directed away from the ring. When a point charge approaches this atom the lone pair serves as an internal degree of freedom, hence the atom's polarization response is only local and atomic softness' of these atoms are small, Table 4.

Polarization response of the threefold coordinated nitrogens is dominated by the aromatic π electrons and as such spreads across a larger region. For this reason threefold coordinated nitrogens are characterized by large softness values. Exceptions from this trend are the N3 atoms of uracil and thymine placed between two carbonyl groups which prevent electron delocalization over the rest of the ring, Table 4.

Experimental studies for pyrimidine bases show that, despite large electronegativity of oxygen atoms, various electrophiles attack these molecules on nitrogens, with preferences towards N1 [36–39]. While the A values of nitrogen atoms are comparable to or lower than those of oxygens (Table 4), the N1 atom is distinctly different with its high softness in all three molecules, which appears to be the key factor favoring the electrophilic attack.

In the case of adenine, attack on N1 and N7 atoms is observed experimentally [40–47]. The set of parameters for the nitrogen atoms collected in Table 5 very well reflects this phenomenon, considering the introductory hints gained from the analysis of the test heterocycles. Electrophilic attack on N1 is driven by the electrostatic effect (low negative A value), while the site sensitivity of N7 atom is due to its considerable softness. The reactivity toward an electrophile at even softer, but threefold coordinated N9 atom in adenine is apparently obstructed by the positive A of that atom. The same effect is confirmed for guanine: atoms N7 and N9 are indicated as the favorable sites for an electrophilic attack by their low negative A and combined with moderate softness. In the DNA structure, the N9 is blocked by the glycoside bond. The twofold coordinated N7 atom (high negative A) not the twofold coordinated N3 (softer) is known to be the most reactive towards electrophilic attack in DNA molecules.

Only the evident and principal trends of reactivity of the nucleobases have been indicated here, in order to test correlations with the proposed atomic indices, calculated for the most thermodynamically stable forms of these molecules. The most important single factor affecting the results is a variety of forms of these molecules in various reaction conditions. The effect of tautomeric conversion in guanine is responsible for the dramatic difference in the parameters for the 5-member ring atoms in adenine an guanine (Fig. 3): extremely soft group in adenine, rather hard in guanine (keton). This equilibrium is very likely to be responsible for the known DNA sensitivity to alkylation at guanine N7 (by nitrogen mustards and cis-platin) and at N1/O6 (by chloroethylnitrosoureas, CENU) [23].

The reactivity of nucleobases emphasizes also the problematic nature of ambidente organic chemistry [48]. Very often, especially for thermodynamically controlled reactions, single-reactant reactivity criteria are not sufficient to explain the observed reaction products. In such cases, specific interactions between reactants, e.g. hydrogen bonds, or steric factors, are responsible for the regioselectivity.

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References

[1] P. Geerlings, F. De Proft, W. Langenaeker, Conceptual density functional theory, Chem. Rev. 103 (2003) 1793–1873.
[2] R.F. Nalewajski, J. Korchowiec, Charge Sensitivity Approach to Electronic Structure and Chemical Reactivity, Advances Series in Physical Chemistry, vol. 8, World Scientific, Singapore, 1997.
[3] R. Balawender, L. Komorowski, Atomic Fukui function and local softness ab initio, J. Chem. Phys. 109 (1998) 5203–5211.
[4] R.G. Parr, W. Yang, Density functional approach to the frontier-electron theory of Chemical Reactivity, J. Am. Chem. Soc. 106 (1984) 4049–4050.
[5] P.W. Ayers, R.C. Morrison, R.K. Roy, Variational principles for describing chemical reactions: condensed reactivity indices, J. Chem. Phys. 116 (2002) 8731–8744.
[6] P.W. Ayers, W. Yang, L.J. Bartolotti, Fukui functions, in: P.K. Chattaraj (Ed.), Chemical Reactivity Theory. A Density Functional View, CRC Press, Boca Raton, 2009.
[7] P. Bultinck, S. Fias, C. Van Alsenoy, P.W. Ayers, R. Carbó-Dorca, Critical thoughts on computing atom condensed Fukui functions, J. Chem. Phys. 127 (2007) 034102. 1-11.

[8] L. Komorowski, J. Lipiński, P. Szarek, Polarization justified Fukui functions, J. Chem. Phys. 131 (2009) 124120. 1-9.
[9] P. Szarek, L. Komorowski, J. Lipiński, Fukui functions for atoms and ions: polarization justified approach, Int. J. Quant. Chem. 110 (2010) 2315–2319.
[10] R.G. Parr, W. Yang, Density-Functional Theory of Atoms and Molecules, Oxford University Press, New York, 1989.
[11] A. Vela, J.L. Gazquez, A relationship between the Static Dipole Polarizability, the Global Softness, and the Fukui Function, J. Am Chem. Soc. 112 (1990) 1490–1492.
[12] P. Szarek, L. Komorowski, Modeling the electron density kernels, J. Comp. Chem. 32 (2011) 1721–1724.
[13] L. Komorowski, J. Lipiński, P. Szarek, P. Ordon, Polarization justified Fukui functions: the theory and applications for molecules, J. Chem. Phys. 135 (2011) 014109. 1-8.
[14] J. Garza, J. Robles, Density-functional-theory softness kernel, Phys. Rev. 47 (1993) 2680–2685.
[15] Y. Li, N.S. Evans, The Fukui function: a key concept linking frontier molecular orbital theory and the hard-soft-acid-base principle, J. Am. Chem. Soc. 117 (1995) 7756–7759.
[16] P. Chattaraj, A. Cedillo, R.G. Parr, Fukui function from a gradient expansion formula, and estimate of hardness and covalent radius for an atom, J. Chem. Phys. 103 (1995) 10621–10626.
[17] W. Beker, P. Szarek, L. Komorowski, J. Lipiński, Reactivity patterns of imidazole, oxazole, and thiazole as reflected by the polarization justified Fukui functions, J. Phys. Chem. A 117 (2013) 1596–1600.
[18] S.J. Enoch, M.T.D. Cronin, A review of the electrophilic reaction chemistry involved in covalent DNA binding, Crit. Rev. Toxicol. 40 (2010) 728–748.
[19] M.P. Stone, H. Huang, K.L. Brown, G. Shanmugam, Chemistry and structural biology of DNA damage and biological consequences, Chem. Biodivers. 8 (2011) 1571–1615.
[20] D. Sivanesan, V. Subramanian, B. Unni Nair, Quantification of reactive sites in DNA bases using condensed Fukui functions, J. Mol. Struct. (Theochem) 544 (2001) 123–139.
[21] D. Mishra, S. Pal, Ionization potential and structure relaxation of adenine, thymine, guanine and cytosine bases and their base pairs: a quantification of reactive sites, J. Mol. Struct. (Theochem) 544 (2009) 123–139.
[22] T. Mineva, N. Russo, Atomic Fukui indices and orbital hardness' of adenine, thymine, uracil, guanine and cytosine from density functional computations, J. Mol. Struct. (Theochem) 943 (2010) 71–76.
[23] B.J. Dutta, P.Kr. Bhattacharyya, Reactivity and aromacity of nucleobases are sensitive toward external electric field, J. Phys. Chem. B 118 (2014) 9573–9582.
[24] R.F.W. Bader, Atoms in Molecules. A Quantum Theory, Clarendon Press, Oxford, 1990.
[25] L. Komorowski, Empirical evaluation of chemical hardness, Chem. Phys. Lett. 134 (1987) 536–540.
[26] L. Komorowski, Hardness indices for free and bonded atoms, in: Chemical hardness, in: K.D. Sen (Ed.), Structure and Bonding, vol. 80, Springer-Verlag, 1993, pp. 45–70.
[27] P.K. Chattaraj, Chemical reactivity and selectivity: Local HSAB principle versus frontier orbital theory, J. Phys. Chem. A 105 (2001) 511–513.
[28] F. Nalewajski, Electrostatic effects in interactions between hard (soft) acids and bases, J. Am. Chem. Soc. 106 (1984) 944–945.
[29] P. Ordon, The effect of molecular deformations on the chemical DFT indices, Dissertation, Wrocław University of Technology, Poland, 2003.
[30] P. Ordon, L. Komorowski, DFT energy derivatives and their renormalization in molecular vibrations, Int. J. Quant. Chem. 101 (2005) 703–713.
[31] L. Komorowski, P. Ordon, Anharmonicity of a molecular oscillator, Int. J. Quant. Chem. 99 (2004) 153–160.
[32] M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, J.A. Montgomery Jr., T. Vreven, K.N. Kudin, J.C. Burant et al. Gaussian 03, Revision C.01, Gaussian Inc, Wallingford, 2004.
[33] A. Arnaldsson, W. Tang, S. Chill, G. Henkelman, Bader Charge Analysis, Version 0.28a.
[34] L. Komorowski, Electronegativity and hardness in the chemical approximation, Chem. Phys. 114 (1987) 55–71.
[35] L. Komorowski, S.L. Boyd, R.J. Boyd, Electronegativity and hardness of disjoint and transferable molecular fragments, J. Phys. Chem. 100 (1996) 3448–3453.
[36] J.L. Wong, D.S. Fuchs, Reactivities and electronic aspects of nucleic acid heterocycles. II. Diazomethane methylation of uracil and its methyl derivatives, J. Org. Chem. 36 (1971) 848–850.
[37] K. Yamauchi, M. Kinoshita, N-alkylation of thymine and uracil with trialkyl phosphates, J. Chem. Soc. Perkin Trans. 1 (1973) 391–392.
[38] K. Zhao, H.-J. Gi, Y. Xiang, R.F. Schinazi, Synthesis of dihydroisoxazole nucleoside and nucleotide analogs, J. Org. Chem. 62 (1997) 88–92.
[39] A. Akanni, K. Tabakovic, Y.J. Abul-Hajj, Estrogen-nucleic acid adducts: reaction of 3,4-estrone o-quinone with nucleic acid bases, Chem. Res. Toxicol. 10 (1997) 477–481.
[40] B. Reiner, S. Zamenhof, Studies on the chemically reactive groups of deoxyribonucleic acids, J. Biol. Chem. 228 (1957) 475–486.
[41] W. Xue, A. Siner, M. Rance, K. Jayasimhulu, G. Talaska, et al., A metabolic activation mechanism of 7H-dibenzo[c, g]carbazole via o-quinone. Part 2: covalent adducts of 7H-dibenzo[c, g]carbazole-3,4-dione with nucleic acid bases and nucleosides, Chem. Res. Toxicol. 15 (2002) 915–921.
[42] A.J. Pawłowicz, T. Munter, Y. Zhao, L. Kronberg, Formation of acrolein adducts with 2'-deoxyadenosine in calf thymus DNA, Chem. Res. Toxicol. 19 (2006) 571–576.
[43] N. Balu, W.T. Padgett, G.R. Lambert, A.E. Swank, A.M. Richard, et al., Identification and characterization of novel stable deoxyguanosine and deoxyadenosine adducts of benzo[a]pyrene-7,8-quinone from reactions at physiological pH, Chem. Res. Toxicol. 17 (2004) 827–838.
[44] X. Lu, J.M. Heilman, P. Blans, J.C. Fishbein, The structure of DNA dictates purine atom site selectivity in alkylation by primary diazonium ions, Chem. Res. Toxicol. 18 (2005) 1462–1470.
[45] R.C. Moschel, W.R. Hudgins, A. Dipple, Selectivity in nucleoside alkylation and aralkylation in relation to chemical carcinogenesis, J. Org. Chem. 44 (1979) 3324–3328.
[46] C. Qian, A. Dipple, Different mechanisms of aralkylation of adenosine at the N1- and N6-positions, Chem. Res. Toxicol. 8 (1996) 389–395.
[47] R.E. Royer, T.A. Lyle, G.G. Moy, G.H. Daub, D.L. Vander Jagt, Reactivity-selectivity properties of reactions of carcinogenic electrophiles with biomolecules. Kinetics and product of the reaction of benzo[a]-6-methyl cation with nucleosides and deoxynucleosides, J. Org. Chem. 44 (1979) 3202–3207.
[48] A. Stachowicz-Kuśnierz, Polarizable force fields from a perspective of the Charge Sensitivity Analysis, Dissertation, Jagiellonian University, Cracow (Poland), 2013.