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Similarity Based on Atomic Electrostatic Potential in Heterocyclic Molecules: Acidity of Tetrazoles

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The multidimensional similarity measure, operating in the space spanned by potential values, and introduced recently for benzoic acids and monosubstituted benzenes, was applied to tetrazoles, hydrogenated tetrazoles, and phenyltetrazoles. High correlation of potentials at individual atoms constituting five-membered ring in tetrazoles was also found in hydrogenated tetrazoles despite the loss of aromatic character of the latter. Quality of the similarity measure was estimated by correlating it with Hammett constants and with free energy of dissociation for tetrazoles and phenyltetrazoles and methylation reactions for tetrazoles in gas phase. The correlations with the similarity measure were likened to correlations with the potentials at corresponding single atoms in the molecules. As the latter correlations were as good as (or even better than) the correlations with the multidimensional similarity introduced previously, we propose that potentials at the nuclei of congener molecules can be used as the simplest similarity measures. In addition to other systems where potentials at single atoms (sites of binding) were proven to be good reactivity descriptors, this investigation expands their applicability over some heterocyclic systems. Particularly, when similarity of acidic molecules is quantified by the potential at the dissociating hydrogen, it is a good measure of the acid strength both in gas phase as well as in water.

1. Introduction

Similarity is not a physical observable; however, the concept of similarity has been arousing much interest for a long time. When an estimation of similarity is to be attempted, the first problem which can be identified is what measure should be used for the similarity?

The assumption, that through using the data of the molecule's chemical or biological activity we can predict the activity of another closely related molecule by merely comparing how similar the original molecule is to the other one, forms the basis of molecular similarity postulate. Molecular similarity calculations can be especially useful in the study of processes with mechanisms that are complicated or partly or even completely unknown.

Similarity measure is a rather intuitive property and what follows is that its quantification is not straightforward and there is no generally agreed algebraic expression of this property. Yet the concept of similarity can be found in a such popular notion as the functional group. The molecules which are similar can differ, for example, in replacement of a functional group in a molecule by another group in another molecule. Many techniques have been proposed to measure similarity of molecules, and a variety of similarity indexes have been proposed in the literature.[1,2] Some of them are based on the properties of molecular wave functions, and we shall mention only these, i.e., the so-called quantum-mechanical similarity measures. They employ ab initio or DFT calculations and are based on the information which can be drawn from the wave function. The beginnings of this approach date back to 1980 and the work of Carbó[3] who assumed that similar molecules must have similar electron distributions. A resembling index, also based on electron density, was presented by Hodgkin and Richards.[4] The formula given in refs 1 and 2 and in the following papers[5,6] compare the shapes of charge distribution rather than magnitudes. A thorough overview of similarity indexes based on electron density is presented in ref 1 (a review). Determination of similarity based on electron density must meet the requirement of a proper alignment of molecules A and B, because it depends on mutual position of the molecules in space. The indexes were criticized on account of requiring a time-consuming three-dimensional integration and of the excessive importance of the conformation of the molecules.[7−9] To avoid these difficulties, the use of an autocorrelation function was proposed with a combination of an analysis of the principal components operating on electron density, as well as on electrostatic potential and local softness.[9] Other measures based on electron densities are referred to in literature.[10−15]

Recently, we presented a novel quantum similarity measure in potential space.[16] The similarity was measured by a distance in the space spanned by potentials at different atoms of the compared molecules. The space has a number of dimensions equivalent to the number of corresponding atoms selected for the purpose of comparison. The approach was applied to benzene rings in monosubstituted benzenes and in para-substituted benzoic acids. The expression for the similarity measure based on the distance $d_{A,B}$ between molecules of two benzoic acids, A and B, based on the ring carbon atoms and the atoms of the COOH group was

$$d_{A,B} = \left[\sum_{i=1}^{6}(V_{Ci,A}-V_{Ci,B})^2 + (V_{C7,A}-V_{C7,B})^2 + (V_{O1,A}-V_{O1,B})^2 + (V_{O2,A}-V_{O2,B})^2 + (V_{Hac,A}-V_{Hac,B})^2\right]^{1/2} \qquad (1)$$

where $V_{Ci,A}$ and $V_{Ci,B}$ denote electrostatic potential at the *i*th carbon atom in the rings of molecules A and B, and the remaining terms represent potentials at atoms of the COOH

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group in both molecules. Alternatively, similarity based on the limited number of atoms, e.g. only the ring carbon atoms, or atoms of the COOH group, was also calculated. These measures, calculated between individual molecules and a reference molecule, being the first of the sequence (similarly to the procedure applied in ref 8), were successfully correlated with the Hammett sigma constants, with the values of free energy of dissociation and with the values of free energies of nitration in the gas phase. The results for *p*-benzoic acids indicated that the distance calculated based on the ring carbon atoms and the distance based on atoms of the COOH group reproduced the sequence of Hammett constants very well (the latter with higher correlation coefficient). The still satisfactory results were obtained when the distance was calculated for all atoms of the two groups jointly. The results suggested that the calculated atomic potentials in molecules under comparison are relevant for the molecules' similarity studies.

It appeared, however, that equally good or even better correlations were obtained for benzoic acids when potential at only one atom, being an atom of the COOH group or a ring atom, was applied. The distances based on potentials at individual atoms were at least as effective as the distances calculated for larger sets of nuclear potentials, when dissociation was a reference reaction. The same effect was found for the monosubstituted benzenes, when nitration was used as a reference reaction. This time the correlation of free energy of the reaction with the Hammett constants σ_p set was better after reduction of the distance in the potential space to one atom solely. These results correspond with the finding of Galabov and co-workers[17] that the potential at C_{para} in monosubstituted benzenes is highly correlated with the σ_p constants.

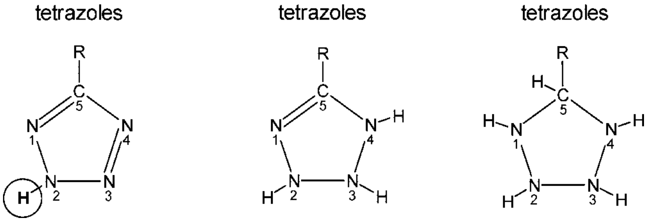
Thus, the dimensionality of the similarity measure, equal to the number of atoms taken into consideration, could be reduced to a smaller group of atoms (e.g., for benzoic acids, only atoms of COOH group or only ring atoms) or even to a single atom. In other words, the potential at a single atom, common to a series of homologous series of molecules, could be used as a similarity measure between individual molecules. It can be applied as a reactivity descriptor in other reactions, such as, for instance, hydrogen bonding,[18−21] alkaline hydrolysis,[22] or electrophilic attack.[23]

The results also suggested that the potential values at individual atoms in a molecule are highly correlated with each other, and thus comparable results were obtained in cases when eq 1 was reduced to only one pair of potential values at one atomic center in two molecules under comparison. What follows, potentials at individual atoms could serve as the simplest similarity measures. In this way, dimensionality of the potential space could be reduced from a dozen or so to one.

One could expect that high synchronization of potentials at individual atoms occurs chiefly in benzene derivatives due to the specific properties of benzene rings. Therefore, it seemed interesting to compare the results obtained for two groups of benzene derivatives[16] with results for another group of compounds. For the comparison we selected a group of 5C-tetrazole derivatives.

Tetrazole can exist in two tautomeric forms, namely 1H and 2H. The experimental[24,25] and theoretical[26] data showed that in the gas phase, the 2H tautomers are of lower energy, and here all calculations were made for them. The C-substituted tetrazoles, R-CN_4H, have acidic properties and the pK_a values of tetrazoles are comparable with those of benzoic acids.[27] Although the tetrazole system does not occur in nature, it is applied very widely in the pharmaceutical chemistry.[27] Chart 1 presents the numbering of atoms in the C5-substituted 2*H*-tetrazoles.

CHART 1[a]



[a] Dissociating hydrogen atom is surrounded by a ring.

2. Calculations. All calculations reported in the present study were carried out using the density functional theory (DFT)[28] and B3LYP functional,[29,30] as implemented in the Gaussian 98 program package.[31] The initial three-dimensional structures of the compounds were built using the SpartanPro software,[32] followed by a preliminary semiempirical geometry optimization at the AM1 level. Subsequently, geometries were optimized and energies calculated using the Dunning's correlation-consistent cc-pVDZ basis set, followed by the calculation of vibrational frequencies at the same level. Whenever, from the energetic viewpoint, the existence of two conformers of a given substituted compound was possible, their energies differed by no more that 0.2 kcal/mol. All the reported properties were calculated for both conformers, and their average was applied in the correlations displayed in the tables. Using the B3LYP/cc-pVDZ wave functions, the atomic charges derived from natural population analysis[33] were calculated at the same level. The potentials together with a set of charges derived from them were calculated according to the CHelpG scheme.[34] AIM charges were calculated with the AIM package.[35] The substituents in phenyltetrazoles were the same as in the previous investigation involving benzoic acids (NO_2, CN, Cl, F, H, CH_3, OCH_3, NH_2, $N(CH_3)_2$, OH, $COCH_3$, CF_3, $C(CH_3)_3$, SO_2CH_3, and COOH). The same set for tetrazoles but without the OH substituent was taken because it is known that tetrazole substituted by the OH group at C5 is not stable and undergoes rearrangement to a ketone derivative.[27]

The σ_p and σ_m sets were taken from March's monograph[36] (Table 4 in Chapter 9) except for the constants of the OH group, which were taken as determined by Hine.[8,37]

3. Results

By analogy with the procedure applied to benzoic acids and other benzene derivatives, the corresponding equation for the distance in the potential space is:

$$d_{A,B} = \left[\sum_{i=1}^{4} (V_{Ni,A} - V_{Ni,B})^2 + (V_{C,A} - V_{C,B})^2 + (V_{H,A} - V_{H,B})^2 \right]^{1/2} \qquad (2)$$

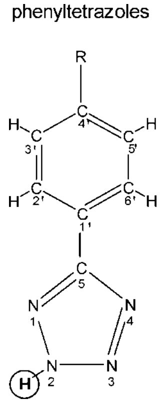
where $V_{Ni,A}$ and $V_{Ni,B}$ denote electrostatic potential at *i*th nitrogen atom in the molecules A and B. $V_{C,A}$ and $V_{C,B}$ denote electrostatic potential at C5 carbon atom in the molecules, whereas $V_{H,A}$ and $V_{H,B}$ denote electrostatic potential at the hydrogen connected to N2. When A and B cover all compounds taken into consideration, one obtains a two-dimensional table of the $d_{A,B}$ values. In order to have a one-dimensional set of data we took the similarity values between all molecules and a

TABLE 1: Correlation Coefficients of Linear Plots of Hammett Constants σ_m, Free Energies of Dissociation (ΔG_{dissoc}), and Free Energies of Methylation at N2 (ΔG_{meth}) against Two Similarity Measures (distances in potential space), *d*(4N,C,H) and *d*(4N,H), as well as against Potentials at Individual Atoms in Tetrazoles[a]

	d(4N,C,H)	*d*(4N,H)	V_{N1}	V_{N2}	V_{N3}	V_{N4}	V_{C5}	V_H
σ_m	0.955	0.978	0.951	0.970	0.989	0.979	**0.614**[b]	0.969
ΔG_{dissoc}	−0.933	−0.968	−0.964	−0.950	−0.969	−0.967	**−0.438**	−0.958
ΔG_{meth}	−0.982	−0.990	−0.993	−0.971	−0.979	−0.991	**−0.620**	−0.989

[a] Numbering of atoms is shown in Chart 1 as well as dissociating hydrogen in tetrazole ring. [b] Poor correlations between potential at C5 and other variables, standing out against the rest of very good correlations, are marked in bold.

CHART 2[a]



[a] Dissociating hydrogen atom is surrounded by a ring.

reference molecule, being the first of the sequence, similarly to the procedure applied in ref 8. The reference molecule chosen was the one substituted by $N(CH_3)_2$.

It has been recently observed that, as far as electrostatic properties in the group of monosubstituted benzenes or the group of substituted benzoic acids are concerned, the C_{ipso} atom differs from the rest of C atoms in the benzene ring.[38] The properties of the C_{ipso} atom also differ from those of the rest of atoms in the tetrazole ring.[39] What follows, we used as well a similarity measure with only nitrogen atoms of the ring and H atom connected to N2 taken into consideration. In that case eq 2 assumes the following form:

$$d_{A,B} = \left[\sum_{i=1}^{4} (V_{Ni,A} - V_{Ni,B})^2 + (V_{H,A} - V_{H,B})^2\right]^{1/2} \qquad (3)$$

The calculated $d_{A,B}$ values thus obtained were named *d*(4N,C,H) and (4N,H), according to eqs 2 or 3, respectively.

Previously, quality of the similarity measure for benzene derivatives was estimated by correlating it with Hammett constants. Since their introduction in the 1930s,[40] Hammett constants (σ) have been used as a measure of electron perturbation in the substituted benzene ring, resulting in the substituents' impact on dissociation and hundreds of other chemical reactions.[36,41−43] The constants were defined from the experimental pK_a values of benzoic acids in water,[36,40,44] but they were also successful in correlating experimental and calculated dissociation constants in gas phase.[45−47]

The extension of the Hammett equation to systems other than substituted benzoic acids produced quite good results in case of monosubstituted anilines and aliphatic amines, where the NH_3+ group is regarded as the acidic center.[48,49] However, papers devoted to acidity/basicity of other nitrogen-containing organic molecules in the gas phase, especially heterocyclic, are rather scarce. One can mention here those dealing with triazoles[50] and tetrazoles.[50,51] Charton found that the correlation of the experimental pK_a values for tetrazoles in water with the Hammett equation produced a correlation coefficient as high as 0.993.[52] Similar findings for tetrazoles were also reported.[53] A very good linear relationship between the acidity constants and the substituent constants was also observed when the dissociating tetrazole ring was connected to the substituent through a benzene ring.[54] These and other protolytic equilibria in tetrazoles were summarized[55] A recent review on tetrazole derivatives can also be useful.[56]

3.1. Tetrazoles. First, *d*(4N,C,H) and *d*(4N,H) variables were correlated both with para and meta Hammett constants. The correlations with the meta set were better, and only those are considered later. The values were also correlated with the free energies of dissociation (ΔG_{dissoc}) and free energies of methylation (ΔG_{meth}) in gas phase. The correlation coefficients (cc's) of these linear plots are displayed in Table 1. In both reactions the hydrogen at N2 was involved. Data in the table reflect the fact that values of cc's improve with the use of *d*(4N,H) as compared to *d*(4N,C,H). Taking into consideration that excellent results were obtained for benzoic acids when only potentials at one atom in the compared molecules were used,[17] Table 1 comprises results of the correlations with the potentials at individual N, C, and H atoms as well. Inspection of Table 1 shows that the correlations with both ΔG_{dissoc} and ΔG_{meth} are approximately equally good when the similarity measure *d*(4N,H) defined by eq 3 is used, and when potentials at single individual atoms are applied instead. Namely, values of cc's with $V_{N1}-V_{N4}$ and V_H are more or less as good as those with *d*(4N,H). On the other hand, correlations of σ_m, ΔG_{dissoc}, and ΔG_{meth} with V_{C5} are considerably poorer. These poor correlations are analogous to those for benzoic acids, where the correlations of σ_p with potentials at C_{ipso} were much lower than those with the rest of atoms of the ring and of the COOH group (Table 3 in ref 16).

Therefore, one might expect that the individual potentials at N1, N2, N3, N4, and H are mutually correlated. Table 2 displays cc's of the mutual correlations of the potentials at the individual atoms in the set of 14 molecules of tetrazole derivatives. In Table 2, results of correlations of potentials at all atoms and similarity measures calculated by using these potentials, *d*(4N,H), are also displayed. The values of cc's between *d*(4N,H) and potentials at individual atoms are on average slightly better than of cc's between the latter.

The potentials of all atoms mentioned in the table (except C5) vary synchronously from one molecule to another. Correlations with potentials at the C5 atom evidently differ from those with the potentials at the rest of the atoms, in accordance with the results concerning correlations of other properties (Table 1).

The properties of C5 are correlated with those of the substituent attached to it rather than with the properties of the rest of the molecule.[39] Yet all the remaining atoms in Table 2 are somewhat similar to each other with regard to the fact that their potentials harmonize.

3.2. Hydrogenated Tetrazoles. The tetrazole ring possesses a certain, fairly high degree of aromatic character[57,58] due to

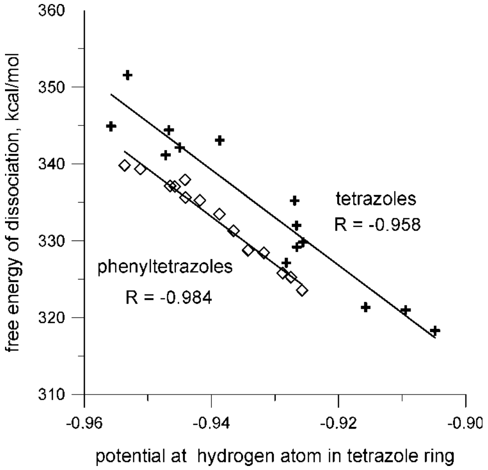


Figure 1. Plots of free energy of dissociation calculated in the gas phase against the potential at the acidic hydrogen in tetrazoles and phenyltetrazoles.

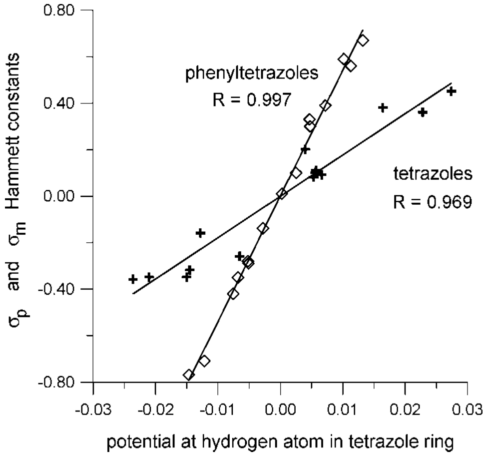


Figure 2. Plot of σ_m constants against the potential of the acidic hydrogen in tetrazoles and plot of σ_p constants against the potential of the acidic hydrogen in phenyltetrazoles. For clarity, the σ_m, σ_p, and potential data are centered.

TABLE 2: Mutual Correlations of Potentials at Individual Atoms in Tetrazoles[a]

	V_{N1}	V_{N2}	V_{N3}	V_{N4}	V_{C5}	V_H
V_{N1}	1					
V_{N2}	0.985	1				
V_{N3}	0.993	0.976	1			
V_{N4}	0.997	0.984	0.991	1		
V_H	0.986	0.968	0.983	0.985	1	
V_{C5}	**0.557**	**0.560**	**0.464**	**0.539**	**0.544**	1
d(4N,C,H)	0.985	0.969	0.972	0.978	**0.619**	0.976
d(4N,H)	0.999	0.985	0.997	0.998	**0.524**	0.987

[a] Poor correlations between potential at C and those at other atoms, standing out against the rest of very good correlations, are marked in bold.

TABLE 3: Mutual Correlation Coefficients of Potentials at Individual Atoms in Semihydrogenated Tetrazoles as well as Correlation Coefficients of Linear Plots of the Potentials with the Two Similarity Measures *d*(4N,3H,C) and *d*(4N,3H)[a]

	V_{N1}	V_{N2}	V_{N3}	V_{N4}	V_{C5}	V_{H2}	V_{H3}	V_{H4}
V_{N1}	1							
V_{N2}	0.990	1						
V_{N3}	0.962	0.982	1					
V_{N4}	0.907	0.938	0.985	1				
V_{C5}	**0.383**	**0.482**	**0.601**	**0.705**	1			
V_{H2}	0.996	0.996	0.966	0.911	**0.410**	1		
V_{H3}	0.952	0.975	0.999	0.990	**0.625**	0.957	1	
V_{H4}	0.878	0.909	0.969	0.996	**0.738**	0.877	0.974	1
d(4N,3H,C)	0.863	0.890	0.925	0.943	**0.719**	0.867	0.928	0.944
d(4N,3H)	0.991	0.995	0.987	0.951	**0.410**	0.991	0.981	0.928
σ_m	0.953	0.973	0.983	0.956	**0.583**	0.953	0.977	0.939

[a] Numbering of atoms is shown in Chart 1.

the number of π-electrons in the ring that is close to six (slightly different for different derivatives). High correlation of potentials at the individual atoms was previously found for benzene rings[16] and presently for atoms constituting the five-membered ring in tetrazoles. One may ask whether the correlation of potentials at individual atoms is a property of aromatic systems. To see if it is true we calculated the potentials in two other sets: the first consisted of the same tetrazole derivatives, having a single bond, instead of a double one, between nitrogens N3 and N4, and the second, having totally hydrogenated ring (derivatives of tetrazidine, CN_4H_5). Models of the compounds belonging to the two sets are shown in Chart 1. For both sets the similarity measures were calculated analogously as for tetrazoles, taking into consideration all atoms of the ring together with hydrogens attached to the nitrogen atoms, or considering all the atoms except C5. In the first case they are named (4N,3H,C) and *d*(4N,4H,C), respectively; in the second case they are named (4N,3H) and *d*(4N,4H). The results of the mutual correlation of potentials, as well as correlations between the potentials and the similarity measures on the one hand and the Hammet σ_m constants on the other, are displayed in Tables 3 and 4. The potentials at all atoms mentioned in both tables (except C5) also vary synchronously from one molecule to another. It is evident that inclusion of the C5 atom to the calculated distances resulted in deterioration of the correlations.

Data in the tables prove that in the set of derivatives of tetrazole with one hydrogenated double bond (Table 3) as well as in the set of the derivatives of tetrazidine (Table 4), good or even very good correlations are conserved between the *d*(4N,3H) and *d*(4N,4H) variables and the atomic potentials, as well as between the atomic potentials themselves. The cc's for the two groups of compounds between multidimensional similarity measures and atomic potentials at four ring nitrogen atoms are higher than those between the individual atomic potentials on average (similarly as in the derivatives of "aromatic" tetrazole, Table 2). Therefore, the loss of aromatic character in the hydrogenated tetrazole derivatives did not influence synchronization of potential at nitrogen atoms of the ring and at hydrogens attached to it. In all cases C5 (C_{ipso} in tetrazoles) was the unit which was excluded from the harmonization of atomic potentials. It was shown that charges of C5 atoms are synchronized rather with the charge of substituents,[39] similarly as at C_{ipso} in benzene derivatives.[38]

3.3. Phenyltetrazoles. Data in Table 1 proved that in the derivatives of tetrazole V_{N1} and V_H correlated equally well with the free energies of two reactions, ΔG_{dissoc} and $\Delta G_{meth,}$ as the *d*(4N,H) distance did. We wanted to test similar correlations in another group of compounds, namely tetrazoles bearing a phenyl attachment with the same substituents in the phenyl ring as used previously, in the para position to the tetrazole ring (Chart 2), plus an OH substituent. In this group of compounds, the substituent, influencing their acidic properties, is far more (ca. 4.3 Å) distant from the atoms of the tetrazole unit than in the set of tetrazoles.

The same distance *d*(4N,C,H) as that in Table 1 was calculated, as well as the *d*(4N,C,H,5C) distance including potentials at the five carbon atoms (C1′, C2′, C3′, C5′, and C6′)

TABLE 4: Mutual Correlation Coefficients of Potentials at Individual Atoms in Hydrogenated Tetrazoles as Well as Correlation Coefficients of Linear Plots of the Potentials with the Two Similarity Measures *d*(4N,3H,C) and *d*(4N,4H)[a]

	V_{N1}	V_{N2}	V_{N3}	V_{N4}	V_{C5}	V_{H1}	V_{H2}	V_{H3}	V_{H4}
V_{N1}	1								
V_{N2}	0.954	1							
V_{N3}	0.957	0.991	1						
V_{N4}	0.958	0.954	0.982	1					
V_{C5}	**0.735**	**0.746**	**0.677**	**0.588**	1				
V_{H1}	0.984	0.942	0.927	0.908	**0.829**	1			
V_{H2}	0.924	0.993	0.976	0.935	**0.759**	0.924	1		
V_{H3}	0.935	0.973	0.987	0.978	**0.621**	0.888	0.970	1	
V_{H4}	0.974	0.955	0.950	0.936	**0.732**	0.957	0.944	0.944	1
d(4N,4H,C)	0.941	0.937	0.938	0.930	**0.743**	0.945	0.925	0.937	0.960
d(4N,4H)	0.988	0.979	0.983	0.976	**0.721**	0.967	0.966	0.972	0.984
σ_m	0.976	0.941	0.964	0.971	**0.638**	0.935	0.917	0.951	0.947

[a] Numbering of atoms is shown in Chart 1.

TABLE 5: Correlation Coefficients of Linear Plots of Hammett Constants σ_p and Free Energies of Dissociation (ΔG_{dissoc}) against Two Similarity Measures *d*(4N,C,H) and *d*(4N,C,H,5C) as well as against Potentials at Individual Atoms in Phenyltetrazoles[a]

			potentials at atoms of tetrazole ring			potentials at atoms of benzene ring			
	d(4N,C,H)	*d*(4N,C,H,5C)[b]	V_{N1}	V_{N2}	V_H	$V_{C1'}$	$V_{C2'}$	$V_{C3'}$	$V_{C4'}$
σ_p	0.995	0.982	0.998	0.983	0.997	0.996	0.950	0.968	0.060
ΔG_{dissoc}	−0.979	−0.980	−0.982	−0.976	−0.984	−0.984	−0.953	−0.975	−0.103

[a] Numbering of atoms is shown in Chart 2 as well as the dissociating hydrogen in tetrazole ring. [b] *d*(4N,C,H,5C) is the similarity calculated taking into consideration all atoms of the tetrazole ring (4N,C,H) and five carbon atoms of the phenyl ring (C1′, C2′, C3′, C5′, and C6′).

TABLE 6: Mutual Correlations of Potentials at Individual Atoms in Phenyltetrazoles[a]

	V_{N1}	V_{N2}	V_{N3}	V_{N4}	V_{C5}	V_H	$V_{C1'}$	$V_{C2'}$	$V_{C3'}$	$V_{C4'}$
V_{N1}	1									
V_{N2}	0.993	1								
V_{N3}	0.998	0.992	1							
V_{N4}	0.996	0.998	0.997	1						
V_{C5}	0.998	0.995	0.998	0.998	1					
V_H	0.999	0.994	1.000	0.998	0.999	1				
$V_{C1'}$	0.998	0.995	0.998	0.998	1.000	0.999	1			
$V_{C2'}$	0.963	0.957	0.958	0.960	0.971	0.963	0.966	1		
$V_{C3'}$	0.975	0.973	0.973	0.976	0.982	0.977	0.980	0.990	1	
$V_{C4'}$	**0.103**	**0.094**	**0.086**	**0.091**	**0.123**	**0.095**	**0.103**	**0.344**	**0.247**	1
d(4N,C,H)	0.997	0.996	0.997	0.999	0.997	0.998	0.998	0.956	0.974	**0.075**
d(4N,C,H,5C)[b]	0.987	0.981	0.987	0.985	0.988	0.987	0.986	0.968	0.968	**0.184**

[a] Poor correlations between potential at $C_{4'}$ and those at other atoms, standing out against the rest of very good correlations, are marked in bold. [b] *d*(4N,C,H,5C) is the similarity calculated taking into consideration all atoms of the tetrazole ring (4N,C,H) and five carbon atoms of the phenyl ring (C1′, C2′, C3′, C5′, and C6′).

of the phenyl ring. The results are presented in Table 5. In this case better correlations were obtained with the Hammet σ_p constants than with σ_m constants, and in the table only cc's with the first are shown. Correlations of σ_p and ΔG_{dissoc} with the two similarity measures are more or less as good as with the potentials at the individual ring atoms. Therefore, this finding provided motivation to test the correlation between potentials at individual atoms. The results are displayed in Table 6, yet although they show that the correlations are very good, better correlations, on average, are found between potentials at atoms belonging to the same ring than between potentials at atoms belonging to different rings (i.e., one atom to the benzene ring, and the other atom to the tetrazole ring).

4. Conclusions

When studying Table 5, attention should be paid to the substantial cc value (0.997) between the potential at the acidic hydrogen, V_H, and the Hammett σ_p constant. Previously equally good correlations were reported between potentials at the acidic H of the COOH group in the para-substituted benzoic acids and the same σ_p constants as well as between the potentials and free energies of dissociation, ΔG_{dissoc}.[16] The present results prove that the potential at the acidic H atom may be a good measure of the acidity of molecules other than benzoic acids (here tetrazoles and phenyltetrazoles). It also correlates very well with the ΔG_{meth} value, free energy of methylation at the same site.

It is worth bearing in mind that in all four sets of tetrazole derivatives, whether of aromatic character or not, potentials at all atoms taken into consideration (Tables 2−4, 6) are mutually highly correlated. The correlation is broken at the atom which is immediately connected to a substituent, C5 in tetrazoles and C4′ in phenyltetrazoles.

Results in Tables 1 and 5 show that the complex, multidimensional similarity measure based on potentials evaluated at atoms constituting the five-membered ring in tetrazoles (eq 3) or at the five-membered tetrazole and benzene rings in phenyltetrazoles is no more helpful in determination of reactivities of the molecules under consideration than the monodimensional sets of potential values at individual atomic sites. On the grounds of present and previous results[16] we may propose the following inductive conclusion: As far as the similarity is quantified by chemical, or perhaps biological, activity of molecules, the electrostatic potential of the atom constituting reaction site provides a very good similarity measure. The statement may be extended to potentials at other atoms because the potentials at the atoms of a molecule (except atoms bridging substituents with the rest of a molecule) are strongly correlated.

Figure 1 plots free energy of dissociation, $\Delta G_{\mathrm{dissoc}}$, against potential at acidic hydrogen in tetrazoles and phenyltetrazoles. The correlation coefficient is higher for phenyltetrazoles than for tetrazoles but in both cases is highly significant. However, correlation coefficients between free energy of dissociation in the gas phase for tetrazoles and phenyltetrazoles (-0.958 and -0.984, respectively) were somewhat lower than the corresponding correlation coefficients for benzoic acid (-0.992).[16]

At this point there arises a question whether the good correlations with V_{H} would also hold for acidity of the compounds in water. Reactivity with respect to dissociation can be represented by the Hammett constants values. The corresponding correlations for tetrazoles and phenyltetrazoles are displayed in Figure 2. It turned out that the correlation was better for the phenyltetrazoles, just as for data in the gas phase (Figure 1). A possible reason for the lower cc in the case of tetrazoles is that their reactivity may not be perfectly represented by σ_{m} Hammet constants. When V_{H} was correlated with pK_{a} values of tetrazoles, a higher cc, namely -0.989, was obtained (however, only five compounds were used for the correlation, because of the scarcity of available data concerning the investigated tetrazoles, as the pK_{a} values found in the literature[59] were those for the parent compound and that substituted by NH_2, CH_3, Cl, NO_2, and Br groups. Of these, the latter could not have been used because the procedure applied did not allow for the potentials in molecules containing Br to be calculated). Nevertheless these scarce data and data displayed in Figures 1 and 2 prove that as long as similarity of the molecules is evaluated by the potential at V_{H}, it corresponds well with the molecules' acidity in gas phase and in aqueous solution as well.

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