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Molecular Descriptors of the Reactivity in Hydrogenation Reaction of 2-Substituted Nitrobenzenes

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Abstract—Molecular descriptors of the reactivity of 2-substituted nitrobenzenes in the hydrogenation reaction were estimated. It was shown that the use of such values as the electron affinity and the number of substituents in the 2-position allows obtaining a model with good prognostic characteristics.

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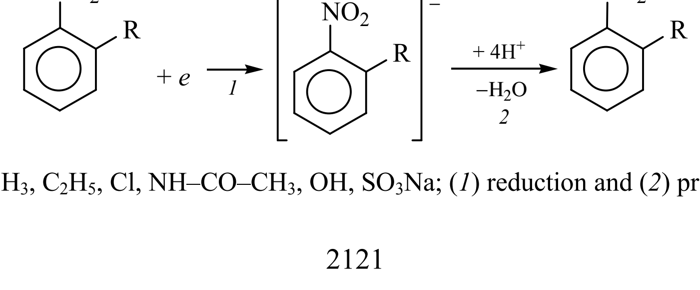
Finding relationships between structure and properties of substances is among the major challenges of chemistry now. Such relationships allow predicting the specific properties for new, not yet synthesized, compounds and can also be used to search for the substances with given parameters.

Quantitatively, the relationship between the structures of substances and their properties can be expressed in mathematic equations reflecting the dependence of a set of numbers responsible for the properties of a compound, against the another set, representing its structure [1]. A property of a molecule can be expressed in numerical form relatively easy. For example, the reaction rate constants can be quantified experimentally. For the numerical expression of the structure of chemical compounds, now are widely used the descriptors of molecular structure.

Descriptor is a parameter characterizing structure of an organic compound so that to notice certain structural features. In recent decades has been proposed a number of different descriptors, which describe the features of the geometrical structure (branching, shape) of molecules, as well as take into account the distribution of electron density, molecular surface, substituent size, etc. [2, 3]. One should keep in mind that often the crucial role in a chemical reaction play individual fragments of molecules, and the compound structure at the identifying the structure–property relationships often is described fragmentwise [4].

This paper examines the relationship between the structure of 2-nitrobenzene derivatives and their reactivity in the liquid phase catalytic hydrogenation to the corresponding primary amines. The reaction system at the liquid phase catalytic hydrogenation is very complicated: the process involves hydrogen, solvent, substrate and catalyst [5–10]. The overall reaction rate is affected by the diffusion of reactants to the catalyst surface, adsorption on this surface, the chemical reaction, desorption of reaction products and their diffusion into the reaction mixture [11]. At present is assumed that in the course of reduction the molecules of nitro compounds form anion-radicals, which are able to pass into solution and react with any form of hydrogen on the catalyst surface or with a hydrogen ion in solution (the scheme) [11–14]. In this regard, one can use the energy of the electron affinity



R = H, CH_3, C_2H_5, Cl, NH–CO–CH_3, OH, SO_3Na; (*1*) reduction and (*2*) protonation.

The effective rate constants of hydrogenation of the 2-substituted nitrobenzenes on palladium catalysts, electron affinity, and the volume of the substituent in the 2-substituted nitrobenzenes ($2-RC_6H_4NO_2$)

Run no.	R	K_{eff} [5]			V_{sub}, Å^3	EA, eV
		AB-17-8-Pd	AH-1-Pd	Pd/C		
1	H	2.200	2.000	3.500	5.54	0.252
2	CH_3	0.140	0.370	0.870	71.13	0.221
3	C_2H_5	0.170	0.140	0.650	88.73	0.248
4	Cl	0.370	0.310	0.750	79.74	0.492
5	$NH–CO–CH_3$	0.300	0.280	0.630	102.99	0.787
6	OH	0.018	0.012	0.070	24.86	0.001
7	SO_3Na	0.020	0.015	0.066	55.67	1.243

(*EA*) as a molecular descriptor: the smaller *EA*, the easier proceeds formation of the anion-radical. If the electron transfer in the step of the radical-anion formation proceeds rapidly, one should expect that at higher *EA* the hydrogenation rate is lower. If the formation of the radical anion is the limiting step, then the relationship must be reciprocal.

At the hydrogenation of 2-nitrobenzene derivatives the substituent is in close proximity to the reaction center, the nitro group. Therefore, it should be taken into account steric hindrances, which can be reflected through such molecular descriptor as the substituent volume (V_{sub}). This descriptor was shown to work well in the prediction of other properties of molecules [2, 3] and can easy be calculated.

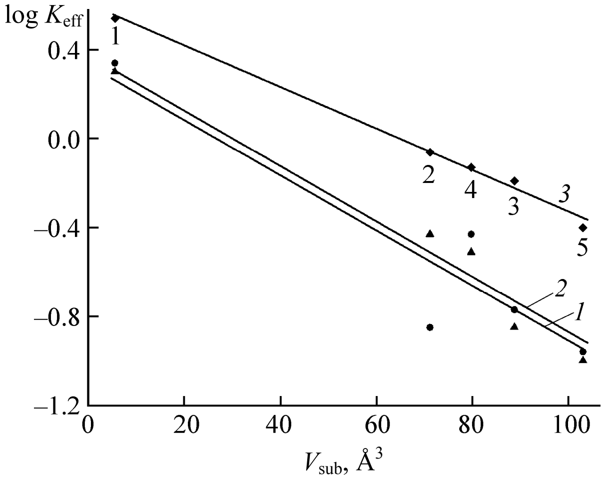


Fig. 1. The logarithm of the observed rate constants vs. the volume of substituent in the 2-position of nitrobenzene (the numbering corresponds to the 2-nitrobenzene table). (*1*) AB-17-8-Pd, log K_{eff} = (0.374±0.225) – (0.013±0.001)V_{sub}, $n = 5$, $r = 0.93$; (*2*) AH-1-Pd, log K_{eff} = (0.415±0.116) – (0.013±0.001)V_{sub}, $n = 5$, $r = 0.98$; (*3*) Pd/C, log K_{eff} = (0.600±0.034) – (0.009±0.000)V_{sub}, $n = 5$, $r = 0.99$.

In this work the molecular descriptors $V_{sub.}$ and *EA* were estimated by quantum-chemical calculations and compared with the experimental data on the hydrogenation of 2-nitrobenzenes [5, 6].

Estimation of the volume of a substituent in 2-position. In 2-nitrobenzene derivatives the substituent is located in close proximity to the nitro group. Therefore, on the one hand, its electronic effects are more pronounced (e.g., halogens, hydroxyl, carboxylic and sulphonic acid groups are in direct conjugation with the reaction center of the molecule, that is, with the nitro group), and on the other hand, the substituent screens the nitro group and thus reduces the rate of hydrogenation (alkyl, acetamido group).

We have studied the influence of the substituent in the 2-position of nitrobenzene on the rate of its hydrogenation in the presence of some palladium catalysts (see the table).

It turned out that with an increase in the volume of the substituent in 2-position relative to the NO_2 group, the rate of hydrogenation of the substituted 2-nitrobenzene decreases. Two points only, corresponding to 2-nitrophenol (see the table, no. 6) and 2-nitrobenzenesulfoacid sodium salt (see the table, no. 7) drop out of the total dependence. This is probably due to the formation of intramolecular hydrogen bonds between the nitro group and the substituent, which is confirmed by published data [15]. Correlation analysis revealed the presence of linear relationships between the logarithm of the observed rate constants of hydrogenation and the volume of the substituent in the 2-position (Fig. 1).

Estimation of electron affinity. As mentioned above, reduction of nitro compounds on palladium

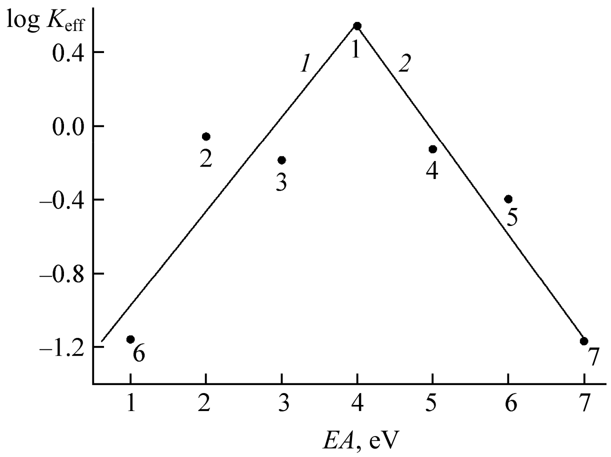


Fig. 2. The logarithm of the observed rate constants vs. the electron affinity of 2-substituted nitrobenzenes in liquid-phase catalytic hydrogenation in the presence of Pd/C catalyst. (*1*) *EA* of substituted 2-nitrobenzene < *EA* nitrobenzene, $\log K_{\text{eff}} = (-1.18 \pm 0.36) + (5.32 \pm 1.71)EA$, $n = 4$, $r = 0.91$; (*2*) *EA* of substituted 2-nitrobenzene > *EA* nitrobenzene, $\log K_{\text{eff}} = (0.84 \pm 0.16) + (1.63 \pm 0.20)EA$, $n = 4$, $r = 0.99$. Numbering of dots corresponds to the table.

catalysts proceeds by the reduction–protonation mechanism through a stage of formation of anion-radicals.

The dependence of the logarithm of observed rate constants on the electron affinity of 2-nitrobenzene in the liquid-phase catalytic hydrogenation in the presence of the Pd/C catalyst (Fig. 2) indicates that the rate of hydrogenation of 2-substituted nitrobenzenes falls down compared to nitrobenzene. The studied substrates consist of two groups showing opposite tendencies. In the first group consisting of nitrobenzene, 2-alkylnitrobenzenes and 2-nitrophenol an increase in the *EA* value leads to increase in the reaction rate. In the second group, on the contrary, increase in the *EA* value decreases the reaction rate. The data obtained suggest that the limiting stages of reduction of 2-substituted nitrobenzenes are different. In the first case the rate-limiting step is the formation of anion-radical, while in the second case the protonation. With the catalysts AB-17-8-Pd, AH-1-Pd the dependence is similar.

Comparison of the results of quantum-chemical calculations with experimental data shows that if the value of *EA* is less than that of nitrobenzene, the substrate should be included to the first group, if more, then to the second. Thus, using the *EA* as a molecular descriptor one can not only predict the rate of hydrogenation, but also to clarify the mechanism of reduction of some aromatic nitro compounds.

EXPERIMENTAL

Molecular descriptors were evaluated based on the values of geometric and energetic characteristics of the compounds, obtained by quantum chemical calculations. The calculations were performed with full geometry optimization (the norm of the gradient does not exceed 0.001 kcal mol^{-1}) using the *ab initio* (6-31G**) (UHF) method within the HyperChem software package [16]. In the course of calculations was carried out monitoring of the type of stationary point on the potential energy surface. To do this, we calculated the spectra of normal vibrations of molecules. The absence of negative frequencies allowed us to conclude that the geometry optimization reached the minimum on the potential energy surface.

The electron affinity (*EA*) was determined using the following formula [17].

$$EA = E^1_{\text{total}} - E^2_{\text{total}}.$$

Here E^1_{total} is the total energy of the neutral molecule, E^2_{total} is the total energy of the molecule in the anionic form.

The values of volumes of the substituents in 2 position of nitrobenzene was determined taking into account the van der Waals atomic radii with the QSAR properties program in the HyperChem package.

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