# Kohonen Network Study of Aromatic Compounds Based on Electronic and Nonelectronic Structure Descriptors

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Received August 11, 2004

Atoms in Molecules (AIM) and Electron Localization Function (ELF) methodologies were applied to describe the electronic structure of 88 aromatic compounds. The analyzed database contains molecules substituted by nucleophilic and electrophilic groups which are responsible for electron density distribution in the molecule and further for its reactivity. Radial Distribution Function (RDF), Weighted Holistic Invariant Molecular (WHIM), Three-Dimensional Molecule Representation of Structures based on Electron Diffraction (3D-MoRSE) and Geometry, Topology and Atom-Weights Assembly (GETAWAY) descriptors were taken into account describing the structures of the analyzed molecules. According to generated descriptor space the classification of the molecules has been subsequently performed using unsupervised learning strategy and Kohonen network. The final step of descriptor space testing was supervised learning of Counter-Propagation Artificial Neural Network (CPANN) using *n*-octanol/water partition coefficient (logP), dipole moment (DM) and molecular refractivity (MR) as target values.

## 1. INTRODUCTION

Molecular similarity is one of the most widely invoked chemical concepts. We recognize the idea of functional groups, even if a rigorous quantum-chemical approach requires treating a molecule with all its nuclei and electrons as a whole, described by its wave function. The recent years brought, however, new theoretical developments such as topological analyses of electron density (Atoms In Molecules method, AIM<sup>1</sup>) or electron localization function (ELF<sup>2</sup>). These approaches indicate that even in the quantum world the concept of functional groups can be upheld and that for such groups there exists a marked degree of transferability of properties from one molecule to another.<sup>3,4</sup> Molecular similarity in its more refined sense constitutes a powerful base for rational drug and material design.<sup>5</sup> There is a broad variety of techniques used to study relations among molecular properties, from linear regression methods (Multiple Linear Regression – MLR, Partial Least Squares – PLS), Principal Component Analysis (PCA) and Regression (PCR) to the artificial intelligence (AI). Probably the most spectacular group of AI methods are neural networks.<sup>6</sup> They are capable of self-organization, pattern recognition and learning. The latter can be either supervised (with a set of previously defined correct answers such as experimental data to be reproduced) or unsupervised (during which the network seeks by itself for regularities and correlations in the data set). An important feature of a well-trained neural network is its ability to generalize: given an unknown set of data, the network should be able to classify the object into one of the classes formed during learning procedure. Neural networks are able to cope with both large data sets and large descriptor spaces. Two of the classical problems of MLR, PLS or PCA methods are managing correlations between descriptors and avoiding linear dependence - both of these become more and more important with growing a data set or number of parameters. Neural networks are less liable to these phenomena, which explains the large interest in this group of mathematical models.6 Versatility of neural networks is matched by the number of architectures used for their design. One of the approaches is the counter-propagation artificial neural network (CPANN) of the Kohonen type,<sup>7</sup> which was used in our study. Aromatic compounds are very well suited for molecular similarity study. Delocalized electrons of the aromatic ring act as excellent carriers of substituent effects over the whole molecule. The most obvious example is the orienting effect of certain functional groups on the electrophilic substitution, studied recently8 with the topological ELF method. Physicochemical properties and biological activity of aromatic compounds depend not only on the substituents but also on their relative position, as shown in the case of polychlorinated biphenyls (PCBs). These persistent organic pollutants have been and still are subjects of numerous structure-activity investigations. 9,10 Our study, however, was based on a more diverse set of compounds: monosubstituted derivatives of benzene, naphthalene, anthracene and phenanthrene (substituents: -F, -Cl, -Br, -OH, -NH<sub>2</sub>, -NO<sub>2</sub>, -CH<sub>3</sub>). There are many different molecular descriptors tailored for aromatic compounds,11 and we decided to base our investigations on quantum-chemical parameters, some of them computed in the framework of AIM and ELF methods. The obtained descriptors were combined with a set of selected nonelectronic parameters derived from RDF, WHIM, 3D-MoRSE and GETAWAY classes. The main goal of the study was the classification of similar compounds using the Kohonen network and unsupervised learning strategy. Additionally, the supervised learning was performed

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Figure 1. Selected structures of investigated molecules.

**Figure 2.** Numbering scheme used in this study.

using n-octanol/water partition coefficient (logP), dipole moment (DM) and molecular refractivity (MR) values as targets in order to test the suitability of a generated descriptor space in reproducing the values of dependent variable. The outline of the article is the following: in Sections 2 and 3 there are given details of the database and computational methodology, respectively, followed by the results and discussion in Section 4. Conclusions are presented in Section

## 2. DATABASE

The database which has been taken into account in this study consists of 81 aromatic compounds such as benzene, naphthalene, antracene and phenanthrene substituted in ortho-, meta-, and para- positions using chosen atoms from the 17th group of the periodic table (F, Cl, Br), -CH<sub>3</sub>, -NH<sub>2</sub>, −NO<sub>2</sub> and −OH groups as substituents (see Figures 1 and 2). Seven additional compounds (benzoic acid, phenylnitrile, ethylbenzene, 1- and 2-ethylnaphthalene, 1- and 2-naphthoyl acid) were considered in further stages for testing the models but did not enter the initial database. The choice of compounds was not serendipity but was dictated by their common usage as chemicals. Their diverse reactivity and biological activity have been widely reported in the literature. 12-17 In accordance with the Hohenberg-Kohn

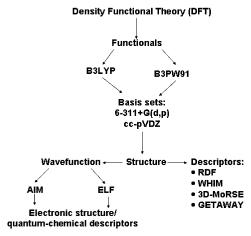


Figure 3. The scheme of calculations of analyzed database.

theorem, the electron density distribution is responsible for all the molecular properties.<sup>18</sup> Detailed discussion of the electron density topology in the framework of the AIM theory has been already presented in the case of compounds with  $\pi$ -electron delocalization and nucleophilic or electrophilic substituents. 19 Another approach applied to investigate the substituent influence on the molecular electronic structure was the Electron Localization Function (ELF) theory, which was found to reproduce an orienting effect of functional groups on the electrophilic substitution.<sup>8,20</sup> Recently Popelier<sup>21</sup> proposed to use AIM-derived parameters of bond critical points (BCPs) as OSAR/OSPR quantum-chemical descriptors. In our case the quantum-chemical descriptors were generated according to AIM and ELF theories. To show small method- and basis set dependence of AIM and ELF properties as opposed to Mulliken-type electronic structure analyses, four different level of theory (see Figure 3) were used thus producing four databases. For further enrichment of the mathematical representation of molecular structure, the Radial Distribution Function (RDF), Weighted Holistic Invariant Molecular (WHIM), Three-Dimensional Molecule Representation of Structures based on Electron Diffraction (3D-MoRSE) and Geometry, Topology and Atom-Weights Assembly (GETAWAY) descriptors were generated.<sup>22–25</sup> Three additional properties were also calculated for all the investigated compounds: n-octanol/water partition coefficient (logP) was obtained according to the Moriguchi algorithm, <sup>26</sup> dipole moment (DM) was extracted from electronic structure calculations (see below) and molecular refractivity (MR) was derived from the Ghose-Crippen formulas.<sup>27</sup> These parameters were however used further not as molecular descriptors but as target values in a supervised learning procedure. In the next step both descriptors and target values were normalized to the [0,1] range using Predata program.<sup>28</sup> Additionally, the preselection of independent variables (exclusion of the descriptors with constant values) was performed. Finally, prepared for further investigations, descriptor space contained 305 various parameters. The Kohonen network was used as a tool to classify compounds based on the full database of 305 descriptors and in the next step also for reduction of the descriptor space dimensionality and once more for classification of compounds according to the smaller set of 49 descriptors.

## 3. COMPUTATIONAL METHODOLOGY

Structural Calculations and Descriptor Space Generation. Geometry optimization for all 88 studied molecules was performed using Density Functional Theory (DFT) with the three-parameter hybrid functional proposed by Becke. 18,29 Electron correlation was described either by the formula of Lee, Yang and Parr<sup>30</sup> or of Perdew and Wang.<sup>31</sup> The two choices of an exchange-correlation formula will be henceforth denoted as B3LYP and B3PW91. Two different Gaussian basis set schemes were used during the calculations. First, a triple- $\zeta$  valence basis set<sup>32,33</sup> augmented with polarization functions on all atoms and diffuse functions on non-hydrogen atoms was denoted according to Pople's nomenclature as 6-311+G(d,p). Second, the correlationconsistent double- $\zeta$  valence basis set was denoted as ccpVDZ, which includes polarization functions by default and is carefully designed for efficiency in electron correlation description.34 These two basis sets, based on different contraction schemes, should therefore allow for a similarly good description of molecular orbitals. The combination of two DFT functionals and two basis sets gives as a result four levels of theory and four separate databases as is mentioned in the Database section. Additionally, for each compound the harmonic frequency calculations were performed confirming that the final structures were minima on the potential energy surface (PES). This part of the calculations was performed using the Gaussian 98 suite of programs.<sup>35</sup> In the next step, the two series of quantum-chemical descriptors were generated using advanced theoretical methods of electronic structure analysis. Those obtained in the Atoms in Molecules (AIM) framework (partial atomic charges) were obtained with AIMPAC suite of programs developed by R. F. W. Bader's group.<sup>36</sup> As a tool to obtain the second class of such a type of descriptors (bond populations), the Electron Localization Function (ELF) theory was used. The original TopMod package generated the properties to be included in the database.<sup>37</sup> In our case there were 50 descriptors connected with electronic structure. To generate nonelectronic parameters strictly connected with the composition of the molecules the RDF, WHIM, 3D-MoRSE and GETAWAY descriptors were calculated using Dragon software of R. Todeschini et al.38 resulting in additional 255 parameters. The Dragon package was also used for generation of logP and molecular refraction (MR) values used in the supervised learning, while the dipole moment (DM) was extracted from DFT calculations.

**Kohonen Network.** The Kohonen network was proposed by Kohonen<sup>7</sup> with the special purpose of mapping objects from an m-dimensional into a 1- or (in our case) 2-dimensional space. An additional feature is the preservation of topological distance, i.e., similar objects are located in the same or similar neurons. It is not necessary to have a set of *correct* answers — the Kohonen network is suitable for unsupervised learning and also object clustering.<sup>6</sup> The network consists of one layer of neurons, and each of them has as many weights as there are descriptors. The weights are modified according to the training set of objects. Kohonen network training is divided into learning epochs. One epoch consists of presenting every object exactly once to the network. The criteria used for the training quality assessment are as follows: average error at one object and average error

27	9	11	8	4	3	20
10	5	6	2	1	3	2
2	1	2	1	1	2	4
6	7	10	5	4	9	4
5	7	2	14	9	6	3
4	8	2	6	12	8	7
4	3	3	17	6	6	4

**Figure 4.** Number of descriptors assigned to each neuron in the descriptor space reduction process. Yellow: neurons with electronic and nonelectronic descriptors; orange — neurons with only electronic parameters.

at one weight. The latter is not dependent on the descriptor space dimensionality, while the former grows when the number of descriptors is increased. Since two different dimensionalities (305 and 49) are used in this work for unsupervised learning, the average error at one weight was used as the quality criterion. The comparison is facilitated by the fact that descriptors (described by weights) are normalized into the [0,1] range. The following network dimensions were tested: 9  $\times$  9, 10  $\times$  10 and 11  $\times$  11 neurons. The modeling was performed with the assumption of periodic boundary conditions at the network edge, while lateral neuron interactions were described with a triangular function extending for up to 5 neurons away. The number of learning epochs varied between 1 and 300. This broad range was dictated by our aim to show the details of the training process. The training was performed using a CPANN set of programs developed at the National Institute of Chemistry, Ljubljana, Slovenia.<sup>39</sup> After each training with the database of 81 compounds, also the seven compounds of the test set were presented to the trained network to be located on the Kohonen layer.

The Kohonen network was used also for the purpose of the descriptor space reduction. The 305 descriptors were clustered by the networks of a steadily diminishing size (with the number of epochs also between 1 and 300) until a map with no empty neurons was found (the critical size was  $7 \times 7$ , see Figure 4). The first descriptor of each neuron was then included in a reduced-size database of 49 parameters.

Counter-Propagation Neural Network. The counterpropagation artificial neural network (CPANN) is a multilayer network. It is composed of a Kohonen input layer and counter-propagation output layer. The combination of these motifs allows for the supervised learning of CPANN, i.e., the network is able to reproduce target values, such as experimental data, on the basis of input data (the descriptor space). The details of CPANN architecture are described in ref 6. In case of our study, the target values were logP, DM and MR molecular properties, while the reduced descriptor space of 49 variables was used as an input. The  $9 \times 9$ ,  $10 \times 10$  and  $11 \times 11$  network sizes were tested for each of the three target properties with the number of learning epochs ranging from 1 to 300. Lateral interactions were treated with a triangular function. In difference from the Kohonen network, the average error at one target was used as the quality criterion. An additional step - recall test - was performed including an additional seven compounds not present in the initial database. In this test the target values were reproduced by the previously trained network. This allowed us to supplement property-based clustering results

J. Chem. Inf. Model., Vol. 45, No. 2, 2005

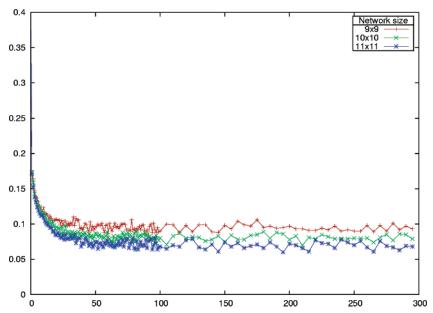
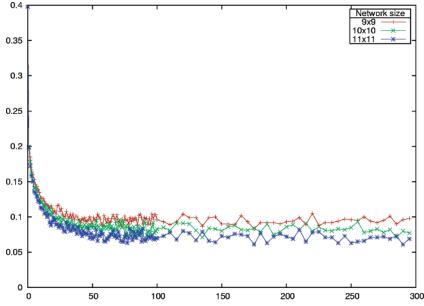


Figure 5. Network training with full descriptor space (305 variables). Average error at one weight (Y axis) as a function of the number of learning epochs (X axis) and network size.



**Figure 6.** Network training with reduced descriptor space (49 variables). Average error at one weight (*Y* axis) as a function of the number of learning epochs (*X* axis) and network size.

with a test of the predictive power of our reduced descriptor space.

## 4. RESULTS AND DISCUSSION

The database of 88 aromatic compounds was analyzed using the Kohonen network as a tool for classification and clustering. The network training process has shown that all four combinations of the DFT functional and basis set gave essentially the same results with only minor variations of error values. Therefore from now on, only the results from the best database, built at the B3LYP/cc-pVDZ level of theory, will be reported. The obtained significant results are divided into the two parts and are presented in this section.

**Kohonen Network Training.** Results of the training process are depicted in Figures 5 and 6, respectively, for the full descriptor space (305 variables) and the space

reduced to 49 variables by the selection procedure (see Figure 4 and Table 1). In both cases the average error at one weight quickly stabilizes at similar values, thus showing that the procedure for descriptor selection was efficient and also did not remove any significant variables. The error stopped to decrease substantially after 50 learning epochs, and after 100 epochs it was fully converged but still showed marked, visible fluctuations. The classification quality increases also with the growing network size. Our chosen dimensions,  $9 \times 9$ ,  $10 \times 10$  and  $11 \times 11$ , did not produce fully occupied Kohonen maps (full occupation could indicate possible crowding and artificial clustering), but neither did they contain too many empty neurons. From each combination of the descriptor space and network dimension there was chosen one model with the least error possible. The statistical data of six obtained models 1-6 are presented in the Table 2.

**Table 1.** Names of the 49 Descriptors Chosen from the Full Database of 305 Parameters by the Selection Procedure Based on the Kohonen Network

category	name					
RDF	RDF010u	RDF020u	RDF030u	RDF035u	RDF045u	
RDF	RDF065u	RDF070u	RDF075u	RDF090u	RDF095u	
RDF	RDF020m	RDF035m	RDF045m	RDF050m	RDF070m	
RDF	RDF010v	RDF040v	RDF045v	RDF065v	RDF085v	RDF010e
3D-MoRSE	Mor07u	Mor18u	Mor21u	Mor25u	Mor08v	Mor06e
3D-MoRSE	Mor02m	Mor05m	Mor06m	Mor13m	Mor15m	
WHIM	G1u	G2u	G3u	L2m		
GETAWAY	ISH	H0u	HATSv			
AIM	q1	q7	q12	q17		
ELF	n(1-2)	n(2-3)	n(11-13)	n(2-8)	n(3-9)	n(16-19)

**Table 2.** Statistical Parameters of the Best Models Obtained in the  $Study^a$ 

model	descriptor space	network size	learning epochs	error/ object	error/ weight
1	full	9 × 9	91	1.453	0.083
2	full	$10 \times 10$	65	1.208	0.069
3	full	$11 \times 11$	195	1.040	0.060
4	reduced	$9 \times 9$	175	0.581	0.083
5	reduced	$10 \times 10$	135	0.498	0.071
6	reduced	$11 \times 11$	175	0.424	0.061

 $<sup>^{\</sup>it a}$  The last two columns are average error at one object and at one weight.

The data presented in Table 2 show that indeed the average error at one weight is not dependent on the descriptor space size. The claim of equal accuracy and suitability of both descriptor spaces is also supported by only negligible differences in the error per weight of mutually coupled models (1 and 4 etc.) meaning that no essential information was lost during the transition from 305 to 49 descriptors. If there was such a loss, remaining parameters (weights) would be less suitable for the classification process thus increasing the error per weight.

**Clustering Results.** The three parameters of discussed compounds which could possibly most affect their clustering

were analyzed. They were as follows: number of rings (1-3), substitution place and the type of substituent. Color-coded representations of Kohonen maps are presented in Figures 7-12 for models 1-6, respectively.

The most notable feature of the Kohonen maps is that the number of rings (and implicitly size of the molecule) is the primary clustering factor, which does not depend on the model, network size or descriptor space dimensionality. All the drawings exhibit distinct regions occupied by derivatives of benzene, naphthalene and both antracene and phenanthrene. Moreover, the red region of one-ring molecules is in most cases surrounded by the green area of naphthalene derivatives separating them from three-ring compounds (when examining Figures 7-12 take note that the network was constructed with periodic boundary conditions, so the clusters divided by the network edge are in fact adjacent). On the other hand, the substituent position and type are both secondary clustering factors. Their role clearly depends on the network size. While both  $9 \times 9$  models 1 and 4 exhibit well-resolved areas for a given substituent type, the largest models 3 and 6 are rather inclined to assign the compounds according to the substituent location. The differences however are delicate, and both criteria are of almost the same significance. There is no evident disagreement between

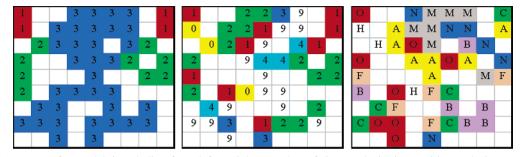
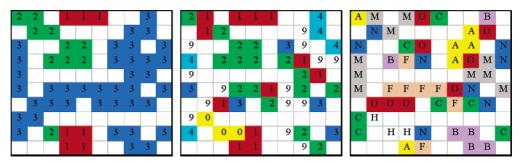


Figure 7. Kohonen map for model 1. Labeling from left to right: number of rings; substitution position; substituent type. Substituent codes: H = -H; F = -F; C = -Cl; B = -Br;  $M = -CH_3$ ;  $A = -NH_2$ ;  $N = -NO_2$ ; O = -OH.



**Figure 8.** Kohonen map for model **2**. Labeling from left to right: number of rings; substitution position; substituent type. For substituent codes see Figure 7.

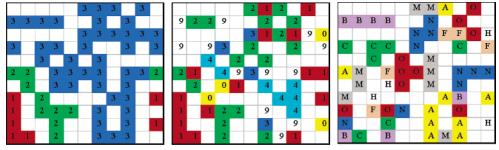


Figure 9. Kohonen map for model 3. Labeling from left to right: number of rings; substitution position; substituent type. For substituent codes see Figure 7.

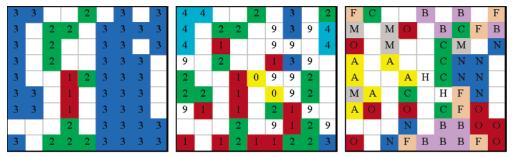


Figure 10. Kohonen map for model 4. Labeling from left to right: number of rings; substitution position; substituent type. For substituent codes see Figure 7.

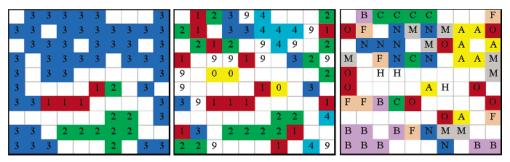


Figure 11. Kohonen map for model 5. Labeling from left to right: number of rings; substitution position; substituent type. For substituent codes see Figure 7.

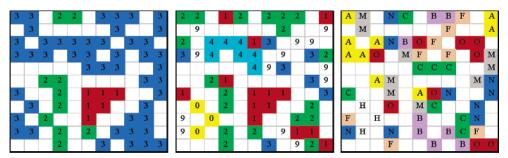


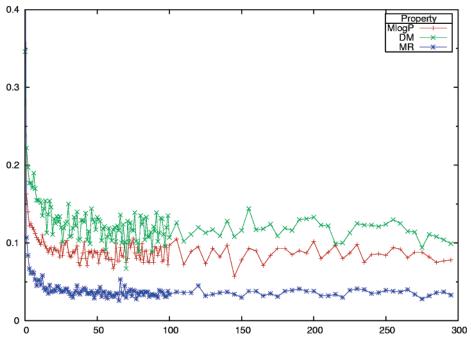
Figure 12. Kohonen map for model 6. Labeling from left to right: number of rings; substitution position; substituent type. For substituent codes see Figure 7.

models of different descriptor space dimensionality (e.g. 1 and 4). This fact once more shows that full, unreduced descriptor space contained undesired redundancies.

The Kohonen network classifies the objects according to their similarity, i.e., similar compounds should be located in topologically near neurons. Analysis of Figures 7–10 shows that phenols (O) and amines (A) are usually found in neighboring locations. They are often surrounded by methyl derivatives (M). On the other hand, halogen compounds are also grouped together, especially -Br (B) and -Cl (C) derivatives, while fluorocompounds (F) are more distributed across the network. The last group of substitutions, nitro compounds (N), seem to form a region of their own, and it

is difficult to decide which neighborhood they prefer. These results are in agreement with chemical reasoning, because both -NH2 and -OH substituents strongly activate the aromatic ring, while  $-NO_2$  is strongly deactivating. In most cases these two groups are separated by substituents of more moderate action (-CH<sub>3</sub>, halogens). However, one should note that, for example, basic and acidic properties of amines and phenols were not recognized by the network - in that case these types of compounds would be separated. The classification is thus based more on the strength of perturbation in the aromatic ring.

The seven compounds of the test set were chosen in such a way that their position in the Kohonen maps should be



**Figure 13.** Accuracy of property prediction with reduced descriptor space (49 variables). Average error of normalized target value (*Y* axis) as a function of the number of learning epochs (*X* axis) for logP, dipole moment and molecular refractivity.

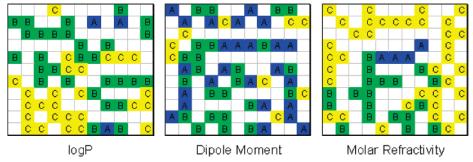


Figure 14. Clustering of compounds in  $11 \times 11$  networks according to the property value (color coding described in the text). From left to right: logP-trained network after 145 learning epochs, DM-trained network after 70 epochs and MR-trained network after 65 epochs.

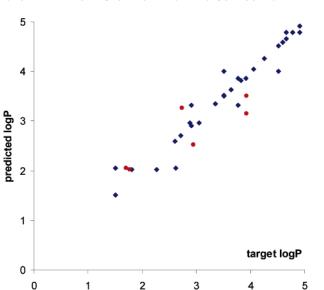
another test of similarity-recognition abilities of the trained networks. The results for the model 6 (Figure 12) will be described as representative for other models as well. The neuron positions are given as [x,y] coordinates. The benzoic acid is located in the [6,4] neuron, correctly among the benzene derivatives and close to aniline and phenol. Ethylbenzene (neuron [6,5]) is surprisingly located in the same neuron as aniline, but phenylnitrile ([8,5]) shares its location with nitrobenzene and is adjacent to phenol; thus the model recognizes strong perturbations of the electronic density in these classes of compounds. Both 1- and 2-naphthoyl acid molecules are located in [3,5] which is empty but adjacent to the naphthalene derivatives with  $-NH_2$  ([3,6]) and -OH([4,4]) groups. 1-Ethylnaphthalene ([4,7]) is found one neuron above 1-methylnaphthalene, while the 2-ethyl derivative ([2,6]) is near 2-naphthylamine ([3,6]). The results show that the network in some cases classified a new compound in an empty neuron but always in the correct neighborhood with the number of rings being the most important parameter while substituent type and location play a secondary role.

**Supervised Learning Results.** The reduced descriptor space of 49 variables was found to reproduce target properties for the investigated compounds quite well but with different accuracy, MR models having the most while DM – the least predictive power (see Figures 13–17). This fact is visible

also in the Kohonen top-maps of the best models (Figure 14), where the areas of differing classes are most uniform for MR and rather scattered for DM. For the purpose of the neuron labeling in this figure, the compounds were divided into three classes according to the property value. For the logP parameter the classes were defined as follows: A: logP <2.5; B: logP <4.0; C: logP  $\geqslant$ 4.0. For the dipole moment the classes were as follows: A: DM <1.5; B: DM <3.5; C: DM  $\geqslant$ 3.5. For the MR the classes were partitioned as A: MR <35; B: logP <60; C: logP  $\geqslant$ 60.

The errors reported in Figure 13 are taken from the whole data set of 81+7 compounds. The training is equally fast as in the case of the Kohonen network (compare Figures 5, 6 and 13). The best models in terms of statistical parameters (average error of the target value) are obtained with the  $11 \times 11$  network size. The three models for the three considered properties will be discussed below.

The best model for logP prediction was obtained with the  $11 \times 11$  network size after 145 learning epochs. The average error of logP prediction is  $\pm 0.057$  (in normalized values, which corresponds to  $\pm 0.19$  in original logP data), which is significantly better than the  $9 \times 9$  and  $10 \times 10$  network errors (0.073 and 0.070 respectively). In all cases the molecules are distributed among the neurons in such a way that there is no occurrence of a close contact between most

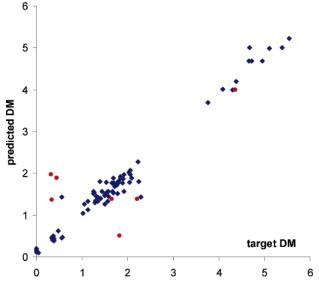


**Figure 15.** Results of the logP recall test after 145 epochs of supervised learning of a  $11 \times 11$  network. Blue markers: training set, red dots: test set.

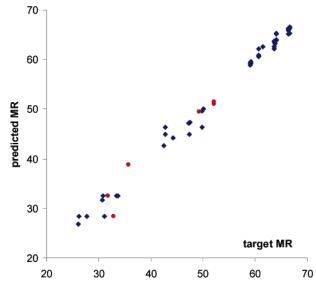
differing logP classes (A and C, see Figure 14). Compounds belonging to a given class are located in close proximity, in agreement with earlier nonsupervised learning calculations. Interestingly, the most hydrophilic compounds (A) are located in just three neurons. The recall and prediction test results for logP (Figure 15) indicate that there are no instances of a wrong classification: the logP prediction is qualitatively correct. The agreement is slightly worse in the hydrophilic region (low logP), most probably because of the specific interactions (hydrogen bonds) which are important for solubility but not included in the models. It must be mentioned that the empirical schemes of logP prediction<sup>26</sup> usually do not distinguish between isomers, e.g. 1- and 2-naphthol, but the experimental logP data are unfortunately available for only some of the investigated compounds. Therefore, an empirical Moriguchi scheme was applied in our study. The neural network technique with the descriptor space described above should perform even better for a set of experimental logP values, because it is able to distinguish between isomers, as was shown in the Kohonen network clustering analysis.

The best model for dipole moment prediction was obtained after 70 learning epochs with 11 × 11 network. The classes of compounds do not form distinct areas on the Kohonen map (Figure 14). The average error of DM prediction is  $\pm 0.067$  in normalized values ( $\pm 0.33$  D), which is again better than the errors of smaller  $9 \times 9$  and  $10 \times 10$  networks (0.098) and 0.089, respectively). The recall-and-prediction test (Figure 16) shows however that the test set molecules are not described as well as the compounds used in training. Obviously the dipole moment depends on the spatial orientation of strongly polar groups (-CN, -COOH) and is not easy to reproduce using a "local descriptor space" containing electronic structure parameters of only a common fragment of the molecules considered. However, also in this case the CPANN network is able to make a qualitative prediction of the molecular polarity.

Finally, the best model for molecular refractivity prediction was obtained after 65 learning epochs with  $11 \times 11$  network. The MR prediction average error is  $\pm 0.026$  in normalized



**Figure 16.** Results of the dipole moment recall test after 70 epochs of supervised learning of a  $11 \times 11$  network. Blue markers: training set, red dots: test set.



**Figure 17.** Results of the molecular refractivity recall test after 65 epochs of supervised learning of a  $11 \times 11$  network. Blue markers: training set, red dots: test set.

values ( $\pm 1$  au), as compared to 0.035 and 0.031 for smaller  $9 \times 9$  and  $10 \times 10$  networks. These values are much lower than for the logP and DM, which is also apparent on the prediction test graph (Figure 17). This fact is connected with the additive nature of MR - it is dependent on the molecular size, which was found to be a primary clustering factor in this study.

The results of the supervised learning show that the descriptor space used in this study preserves information about molecular similarity and also enables at least a semi-quantitative prediction of three various physicochemical properties, despite some limitations in case of the compounds containing strongly polar groups.

## 5. CONCLUSIONS

The Kohonen network turned out to be very useful in the classification and clustering of an investigated set of aromatic compounds similar in geometrical, topological and electronic

sense. It was also successful in a suitable reduction of dimensionality of descriptor space from 305 to 49 variables without visible loss of information and performance. Final remarks are that in most cases both secondary clustering factors are in operation, and it is difficult to separate their respective influences. Nevertheless, the constructed descriptor space containing AIM, ELF and nonquantum-chemical parameters was successfully able to recognize molecular similarities in a set of 81+7 compounds. The recall test of the supervised learning showed that the descriptor space was able to reproduce calculated logP, DM and MR values with good accuracy.

## ACKNOWLEDGMENT

The authors would like to thank Professor Bernard Silvi, Pierre et Marie Curie University, Paris 6, for stimulating discussions and valuable remarks. Authors gratefully acknowledge the Wrocław Centre for Networking and Supercomputing (WCSS) and Academic Computer Center CY-FRONET-KRAKÓW (Grants KBN/SGI/UWrocl/029/1998 and KBN/SGI/UWrocl/078/2001) for providing computer time and facilities.

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CI049752T