

## Why is the Topological Approach in Chemistry so Successful?

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Graph theory has been used in chemistry to describe molecular structures, chemical reactions, and it has been particularly widely used in studies of the structure property relationship. On the other hand, the quantum mechanical approach to the molecular structure also leads to expressions that offer descriptions of molecular properties. Little effort was made in the past to combine the two approaches and investigate how an approximate description of molecular properties relates to the electronic structure of chemical compounds as computed from the quantum chemical stand point. We present a graph theoretical scheme for calculation of the heat of formation of saturated compounds, based on quantum mechanically calculated atomic charges.

### INTRODUCTION

Incremental methods are popular in describing molecular properties as arising from the contributions from the constituent atoms and other fragments of the molecular structure.<sup>1</sup> Many molecular properties are expressed as atom and bond additive, although occasionally other molecular fragments may make contributions. Contribution of each individual fragment or atomic group is usually additive to the total value of the molecular property. Two different approaches have been considered in order to improve the quality

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of the property investigated. Either the atomic and bond parameters used are slightly modified to accommodate variations in the immediate atomic environment or additional descriptors are used, usually corresponding to larger molecular fragments. In both cases, one ends with a statistical scheme accompanied by an increased number of parameters. In the former case, there are many different numerical values that describe the same atomic center, depending on the number and kind of nearest neighbors, the second nearest neighbors, *etc.*, (*e.g.*, Benson<sup>2</sup>).

These variations in the description of an atom in different environment reflect the role of the neighbors on the electronic structure of the atomic center considered. Therefore, the electronic structure of the molecule, and the local electronic surrounding around each atom, should be used to derive a model that will predict variation in molecular properties. Solving the quantum mechanical eigenvalue problem within semi-empirical or *ab initio* quantum chemistry is still a time consuming step and nor practical for many molecules of intermediate size. The calculated electronic structure will depend on the basis set used, on the level of simplifications inherent in the approximate hamiltonian, and on the type of the population analysis performed after the total molecular wave function has been generated. The last step is, however, the least difficult. Nowadays, very simple and fast procedures are available for generating atomic charge distributions from the electronegativity of the atoms connected in the molecule.

We feel that it is highly desirable to provide improvement in the empirical incremental scheme for a physicochemical molecular property by introducing descriptors that can be related to more sophisticated molecular models or methods. In this way one can circumvent a troublesome, often non unique, parametrization which should differentiate variations in local atomic environments for the same kind of atoms.

## ENERGY PARTITIONING

Contributions to the total energy of a molecule calculated by the quantum mechanical methods arise from the components involving from one to four atomic centers.<sup>3</sup> Many semi-empirical MO-methods usually implement the zero differential overlap approximation, which results in neglecting all of the 3- and 4-center two-electron integrals. This results in partitioning of the energy contributions within the orbital basis set to 1-center and 2-center terms, which can be viewed as atomic and bond contributions (taking that the overlap of atomic orbitals between distant centers is zero). In the simple Hückel Molecular Orbital (HMO) method Eq. (1), the orbital energy Eq. (2), and the total energy Eq. (4) are composed of energy components involving only atoms and bonds. The corresponding quantities that can be extracted from the electronic structure (density matrix) are the electron density ( $q_r$ ) and the bond order ( $p_{rs}$ ) Eq. (5). The one electron energies of atoms are the

coulomb integrals ( $\alpha_r$ ) and those of the bonds the resonance integrals ( $\beta_{rs}$ ) Eq. (6). They have to be multiplied by the density matrix to generate the energy components.

$$\text{HMO, LCAO } \Psi_i = \sum_r c_{ir} \varphi_r \quad (1)$$

$$E_i = \langle \Psi_i / H / \Psi_i \rangle = \sum_r c_{ir}^2 H_{rr} + 2 \sum_{r<s} c_{ir} c_{is} H_{rs} \quad (2)$$

$$\text{with } H_{rs} = \langle \varphi_r / H / \varphi_s \rangle \Rightarrow \alpha_r \text{ or } \beta_{rs} \quad (3)$$

$$E = \sum_i \rho_i E_i = \sum_i \rho_i \sum_r c_{ir}^2 \alpha_r + 2 \sum_i \rho_i \sum_{r<s} c_{ir} c_{is} \beta_{rs} \quad (4)$$

$$= \sum_r \sum_i \rho_i c_{ir}^2 \alpha_r + 2 \sum_{r<s} \sum_i \rho_i c_{ir} c_{is} \beta_{rs}$$

$$\text{with } \sum_i \rho_i c_{ir}^2 = q_r \text{ and } \sum_i \rho_i c_{ir} c_{is} = p_{rs} \quad (5)$$

$$E = \sum_r q_r \alpha_r + 2 \sum_{r<s} p_{rs} \beta_{rs} \quad (6)$$

Within the Hückel Molecular Orbital approach, the electron densities and bond orders are those quantities which directly relate the electron distribution to the stability of the molecule. Because of this simple topological nature of the HMO method, the analogy to the empirical scheme is evident. The approach justifies the inherent additivity of empirical approaches: one calculates the molecular energy by summing up the atomic and the bonding contributions Eq. (6). Therefore, in the topological approaches in chemistry, one is justified in neglecting the »through space« non-bonding interactions and view the model as involving only »through bond« interactions.

### THE PARAMETRIZATION SCHEME

From Eq. (6) we saw that the atomic energy contribution to the total energy of a molecule depends linearly on the electron density of atoms. We know that empirical correlations of energies in single atoms with respect to the number of electrons lead to a parabolic fit (see Figure 1).<sup>4</sup> Using  $Q$  as a label for atomic charge, we may then write Eq. (7):

$$-H_{rr} = I(Q) = A + BQ + CQ^2 \quad (7)$$

The slope in Figure 1 is the electronegativity Eq. (8) of the atom, derived by Parr<sup>5</sup> from the Density Functional Theory (DFT).

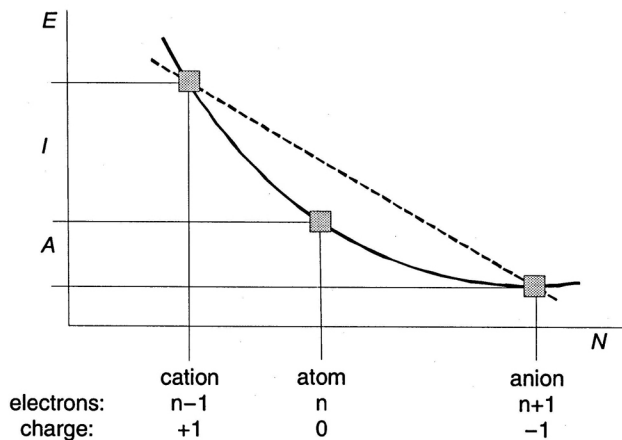


Figure 1. Atomic energy with respect to the number of electrons

$$\chi = -\frac{\partial E}{\partial n} \quad (8)$$

This corresponds to the Mulliken orbital electronegativity.

$$\chi = 1/2 (I + A) \quad (9)$$

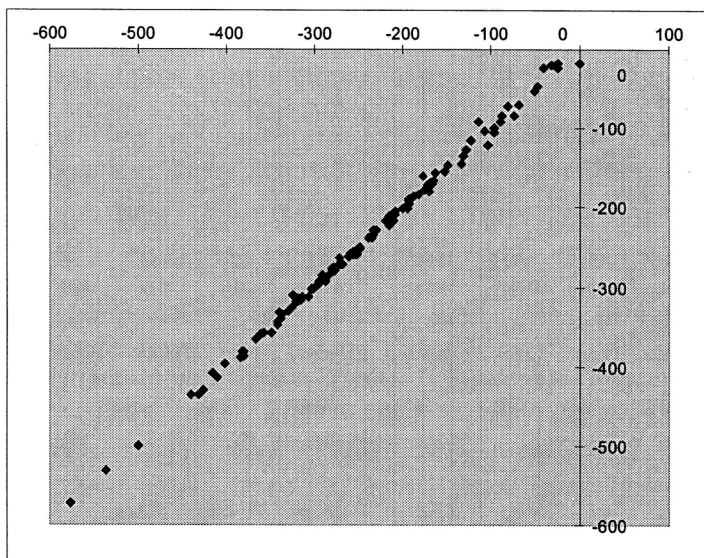


Figure 2. Correlation between the calculated and experimental heats of formation

In this work, we will examine the parametrization for the heat of formation of a series of amines, hydrocarbons, ethers, alcohols, and carbonyls. We have selected only compounds having localized bonds (*e.g.*, no conjugation) because we want to use a simple algorithm to calculate the charge distribution in the molecules. The atomic charges were calculated by the Partial Equalization of Orbital Electronegativity (PEOE) formalism.<sup>6</sup> The procedure is based on the topology of the compound. We started from the valence structural formula (2D structure) using the program StrukEd<sup>7</sup> on a PC with MS Windows, which internally generates the graph theoretical description of atoms (vertices) and bonds (edges) in the form of a connection table (CT). As input, one can simply use chemical drawing for the compounds and continue to calculate the desired PEOE atomic charges.

Here, we will consider solely the role of atomic contributions in prediction of the heats of formation. This approach amounts to the partitioning of bond contributions to the atoms forming the bonds. Contributions of the chemical bonds are neglected simply by summing up atomic energies belonging to individual atoms, which depend on the type of element, its hybridization, and the calculated charge. The parameters *A*, *B* and *C* of Eq. (7) were optimized to reproduce the experimental values of the heat of formation on a series of 122 chemical compounds (see Table I).

The compounds considered have only four different kinds of atoms: carbon, hydrogen, oxygen and nitrogen. Carbon atom appears in two different hybridizations,  $sp^3$  and  $sp^2$ , and oxygen arises as singly bonded  $-O-$  and doubly bonded  $=O$ . The adapted parameters for the kinds of atoms considered and their hybridizations are listed in Table II. The mean error in the estimated heat of formation is  $3.85 \text{ kJ mol}^{-1}$ , in surprisingly good relation to the original empirical Benson's scheme.<sup>2</sup>

In the next step, we optimized iteratively the PEOE parameter and the *A*, *B* and *C* parameters for the best reproduction of the experimental values. After the optimization the mean error was reduced to  $2.25 \text{ kJ mol}^{-1}$  (for individual errors see Table I, column delta 2). There are only a few compounds with an increase of deviation from the experimental values. The calculated atomic charges of the modified PEOE procedure are quite similar to the original ones.

We can see from the fit parameters (*A*, *B* and *C*) that the quadratic term *C* is very small. This is the consequence of selecting only neutral molecules for our study ( $|Q| < 1$ ). Hence, in the case of neutral molecules, one can in the future reduce the approach for the energy contribution to a linear regression depending on the atomic charge as already found from energy partitioning. Due to neglecting all contribution from bonds in the model, we cannot expect to interpret the fitting parameters as pure atomic quantities. The value of *B* should be the one-electron energy ( $H_{rr}$ ) of that atom and should be always negative. Parameter *A* counts for the relation between the total energy and heat of formation.

TABLE I

Comparison of calculated and experimental heat of formation ( $\text{kJ mol}^{-1}$ )

No.	$H_{\text{calc.}}$	$H_{\text{exp.}}^2$	$D_1$	$D_2$	compound
0	-23.84	-23	0.84	-0.20	Methylamine
1	-47.80	-47.4	0.40	2.84	Ethylamine
2	-31.86	-18.6	13.26	2.39	Dimethylamine
3	-69.24	-70.2	-0.96	1.02	1-Propylamine
4	-74.23	-83.8	-9.57	-2.46	2-Propylamine
5	-40.70	-23.7	17.00	-7.89	Trimethylamine
6	-90.08	-92	-1.92	0.00	1-Butylamine
7	-95.89	-104.9	-9.01	-2.41	2-Butylamine
8	-102.94	-120.9	-17.96	-5.57	2-Methyl-2-propylamine
9	-80.00	-72.5	7.50	4.66	Diethylamine
10	-95.89	-98.7	-2.81	3.79	2-Methylpropylamine
11	-114.20	-92.8	21.40	8.54	Triethylamine
12	-122.56	-116.1	6.46	2.97	Dipropylamine
13	-133.77	-144	-10.23	-3.28	Diisopropylamine
14	-167.09	-171	-3.91	-5.39	<i>N</i> -(2-Methylpropyl)-1-butylamine
15	-163.56	-156.6	6.96	3.80	Dibutylamine
16	-170.62	-179.2	-8.58	-8.39	Diisobutylamine
17	-177.63	-161	16.63	3.12	Tripropylamine
18	-25.12	-17.6	7.52	2.85	1,2-Ethandiamine
19	-51.70	-53.6	-1.90	-0.87	1,2-Propanediamine
20	0.68	-17.7	-18.38	-0.75	<i>N,N,N',N'</i> -Tetramethylmethandiamine
21	-87.33	-83.8	3.53	0.73	Ethane
22	-107.72	-103.9	3.82	1.16	Propane
23	-128.32	-126.2	2.12	-0.41	<i>n</i> -Butane
24	-131.00	-134.6	-3.60	-3.95	<i>i</i> -Butane
25	-148.81	-146.5	2.31	-0.06	<i>n</i> -Pentane
26	-151.82	-154.6	-2.78	-3.04	2-Methyl-butane
27	-169.17	-167.3	1.87	-0.25	<i>n</i> -Hexane
28	-172.21	-174.4	-2.19	-2.24	2-Methyl-pentane
29	-172.53	-171.7	0.83	0.71	3-Methyl-pentane
30	-175.54	-177.9	-2.36	-0.39	2,3-Dimethyl-butane
31	-189.39	-187.9	1.49	-0.29	<i>n</i> -Heptane
32	-192.45	-195.1	-2.65	-2.38	2-Methyl-hexane
33	-192.79	-192.4	0.39	0.55	3-Methyl-hexane
34	-196.16	-199.4	-3.24	-1.11	2,3-Dimethyl-pentane
35	-195.53	-202.1	-6.57	-4.29	2,4-Dimethyl-pentane
36	-193.14	-189.9	3.24	3.28	3-Ethyl-Pentane

37	-209.48	-208.6	0.88	-0.48	<i>n</i> -Octane
38	-212.55	-215.6	-3.05	-2.36	2-Methyl-heptane
39	-212.90	-212.8	0.10	0.67	3-Methyl-heptane
40	-212.92	-212.2	0.72	1.25	4-Methyl-heptane
41	-216.30	-214.1	2.20	4.68	2,3-Dimethyl-hexane
42	-215.98	-219.6	-3.62	-1.04	2,4-Dimethyl-hexane
43	-215.62	-222.8	-7.18	-4.46	2,5-Dimethyl-hexane
44	-216.64	-213.1	3.54	5.92	3,4-Dimethyl-hexane
45	-213.26	-211	2.26	2.68	3-Ethyl-hexane
46	-219.69	-217.6	2.09	6.50	2,3,4-Trimethyl-pentane
47	-216.66	-211.3	5.36	7.70	2-Methyl-3-Ethyl-pentane
48	-229.43	-229.2	0.23	-0.61	<i>n</i> -Nonane
49	-232.51	-229.2	3.31	4.50	2-Methyl-octane
50	-249.25	-249.5	-0.25	-0.49	Decane
51	-252.34	-259.9	-7.56	-5.78	2-Methylnonane
52	-252.72	-258.6	-5.88	-4.27	5-Methylnonane
53	-268.93	-270.9	-1.97	-1.53	Undecane
54	-288.48	-289.7	-1.22	-0.01	Dodecane
55	-200.17	-201.3	-1.13	-0.81	Methanol
56	-234.09	-235.2	-1.11	-0.92	Ethanol
57	-257.01	-256.6	0.41	-1.01	Propanol
58	-269.76	-272.6	-2.84	-1.54	<i>iso</i> -Propanol
59	-278.14	-274.9	3.24	1.45	<i>n</i> -Butanol
60	-292.91	-292.8	0.11	-0.28	2-Butanol
61	-282.71	-283.4	-0.69	-1.55	<i>iso</i> -Butanol
62	-307.00	-312.8	-5.80	-2.75	<i>tert</i> -Butanol
63	-298.99	-298.9	0.09	-1.75	<i>n</i> -Pentanol
64	-314.00	-312.7	1.30	0.52	2-Pentanol
65	-315.96	-317.2	-1.24	-3.28	3-Pentanol
66	-304.07	-302.7	1.37	0.08	2-Methyl-1-butanol
67	-302.14	-302.3	-0.16	-0.16	3-Methyl-1-butanol
68	-318.84	-315.2	3.64	3.69	3-methyl-2-butanol
69	-330.37	-329.9	0.47	1.72	2-Methyl-2-butanol
70	-319.70	-317.8	1.90	0.11	1-Hexanol
71	-340.26	-332	8.26	6.63	1-Heptanol
72	-360.69	-360.1	0.59	-0.80	1-Octanol
73	-366.41	-365.5	0.91	-0.48	2-Ethyl-1-hexanol
74	-380.99	-387.2	-6.21	-7.28	1-Nonanol
75	-401.15	-396.4	4.75	4.10	Decanol
76	-441.06	-436.6	4.46	4.90	1-Dodecanol
77	-181.70	-184.1	-2.40	-0.60	Dimethylether
78	-215.55	-216.4	-0.85	0.26	Methoxyethane
79	-341.52	-348.4	-6.88	-0.25	Dimethoxymethane

80	-249.37	-252.4	-3.03	-2.65	Diethylether
81	-238.56	-237.9	0.66	0.06	Methyl-Propyl-ether
82	-251.14	-252.2	-1.06	0.58	Methyl-isopropyl-ether
83	-383.82	-389.7	-5.88	-0.31	1,1-Dimethoxyethane
84	-536.20	-531.6	4.60	2.34	Trimethoxymethane
85	-288.27	-293.1	-4.83	-2.04	<i>tert</i> -Butyl-methyl-ether
86	-259.78	-258.1	1.68	0.64	1-Methoxybutane
87	-272.30	-272.2	0.10	-1.19	1-Methoxypropane
88	-426.35	-429.3	-2.95	0.96	2,2-Dimethoxypropane
89	-410.16	-414.8	-4.64	-0.28	Diethoxymethane
90	-576.81	-572.4	4.41	-1.72	1,1,1-Trimethoxyethane
91	-295.12	-293.1	2.02	-0.88	Dipropylether
92	-320.47	-319	1.47	2.79	Diisopropylether
93	-415.30	-408.2	7.10	3.32	1,2-Diethoxyethane
94	-357.56	-357.6	-0.04	2.35	<i>tert</i> -Butyl-isopropylether
95	-431.74	-436.2	-4.46	-2.87	1,3-Diethoxypropane
96	-337.02	-334.11	2.91	-0.54	Dibutylether
97	-499.93	-501.3	-1.37	-2.19	Dibutoxymethane
98	-383.31	-381.1	2.21	1.99	1-Methoxydecane
99	-165.58	-166.1	-0.52	0.00	Acetaldehyde
100	-188.44	-185.6	2.84	0.63	Propanal
101	-211.13	-217.3	-6.17	0.73	Acetone
102	-209.49	-204.9	4.59	1.77	Butyraldehyde
103	-214.13	-215.8	-1.67	-4.21	2-Methylpropanol
104	-234.93	-238.7	-3.77	0.46	2-Butanone
105	-258.83	-257.9	0.93	2.56	3-Pentanone
106	-256.05	-259	-2.95	0.60	2-Pentanone
107	-261.51	-262.5	-0.99	2.97	3-Methyl-2-butanone
108	-230.32	-228.5	1.82	-1.07	Pentanal
109	-276.87	-279.8	-2.93	0.52	2-Hexanone
110	-279.85	-278.3	1.55	2.57	3-Hexanone
111	-291.39	-286.1	5.29	0.85	2-Methyl-3-pentanone
112	-271.52	-263.8	7.72	5.06	Heptanal
113	-325.18	-311.3	13.88	2.32	2,4-Dimethyl-3-pentanone
114	-297.64	-299.6	-1.96	-5.52	2-Ethylhexanal
115	-342.09	-344.9	-2.81	-2.47	5-Nonanone
116	-349.92	-357.6	-7.68	-5.56	2,6-Dimethyl-4-heptanone
117	-338.42	-340.7	-2.28	1.58	2-Nonanone
118	-382.50	-387.4	-4.90	-3.90	6-Undecanone
119	-212.47	-212	0.47	1.14	Ethanedial
120	-271.76	-271	0.76	-0.23	1,2-Propandione
121	-325.99	-327.1	-1.11	-0.57	2,3-Butandione
122	-380.49	-380.6	-0.11	-0.30	2,4-Pentandione



The PEOE calculated atomic charges include all influence of the actual bonding situation in the molecule. Even by neglecting specific contributions of the bonds, we can approximate the heat of formation by only taking into account the atomic charges. From the definition of the electronegativity of atoms we know the relation between energy and charge, which for small changes can be reduced to a linear approach (slope in Figure 1).

## DISCUSSION

A close look at the calculated and experimental heats of formation shows one significant difference between the results for amines (compounds 1–20) and the rest of the compounds. With the exception of 1-heptanol (compound #71) and 2,4-dimethyl-3-pentanone (compound # 113), for all hydrocarbons, aldehydes and ketones, alcohols, ethers the standard error, for the calculated heats of formation is below  $7.70 \text{ kJ mol}^{-1}$ , (twice the standard error). However, among twenty amines, half of the molecules have an error exceeding twice the standard error. The difference between the computed and the experimental heat of formation in several cases exceeds three times the standard error approaching, in the case of triethylamine (compound # 11), even four times the standard error. All this clearly indicates that the particular theoretical calculations associated with nitrogen atoms are less satisfactory than those involving hydrogen, carbon or oxygen.

Hence, the agreement between the experimental and computed heats of formation for all compounds, except for amines, is even better than suggested by Table II. It seems appropriate to consider the four classes of compounds of Table I separately just to see what kind of agreement one obtains in predicting the heats of formation within each class. In Figures 3a–3f and in Table III, we show the regressions of experimental and calculated heats of formation for the four classes of compounds studied. From the table, we see that in all cases the correlation coefficient  $r$  is very close to 1, even the value  $r = 0.95$  for amides appears satisfactory. The reason for  $r$  approaching

TABLE II  
Elements, range of charges and optimized parameters

Element	Code	$Q_{\min}$	$Q_{\max}$	No. Atoms	A	B	C
C $sp^3$	64	-0.06826	0.27872	685	9.259	-1.129	0.001
C $sp^2$	63	0.12945	0.15476	28	1133.26	-25.959	-0.109
-H	11	0.02275	0.21079	1640	-33.114	-10.805	0.001
N $sp^2$	73	-0.33324	-0.29659	24	122.966	-6.626	-0.066
-O-	82	-0.39956	-0.33101	55	-118.719	0.026	0.002
=O	81	-0.31660	-0.24819	28	0.000	-11.611	0.032

Figure 3. Correlation between the calculated and experimental heats of formation: (a) Amines; (b) alkanes; (c) alcohols; (d) ethers; (e) aldehydes; (f) all

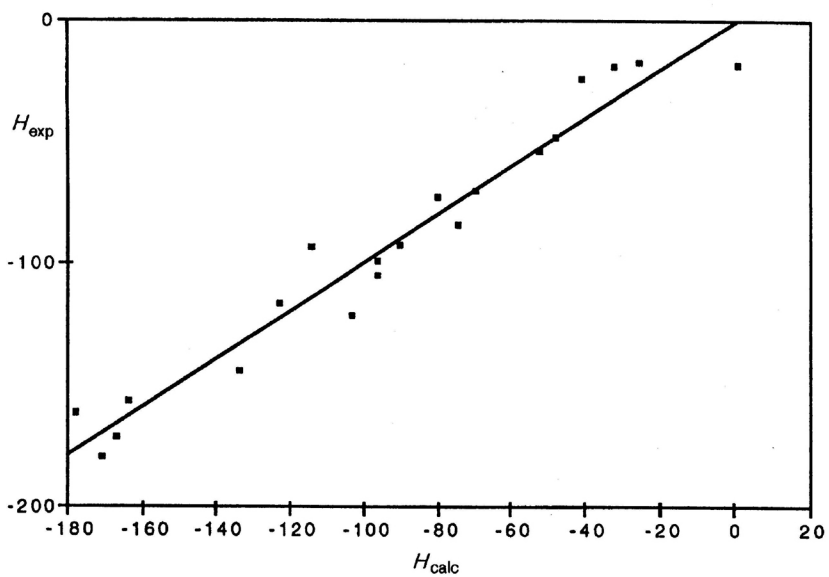


Figure 3a.

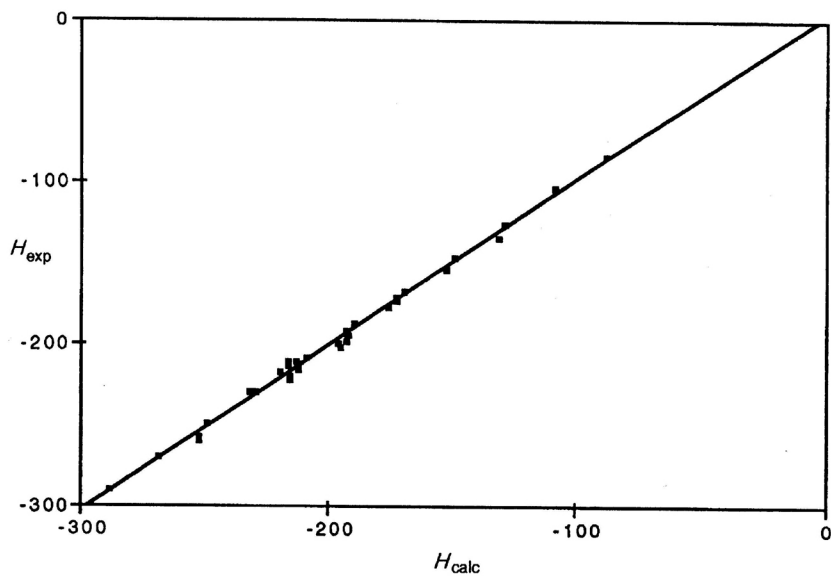


Figure 3b.

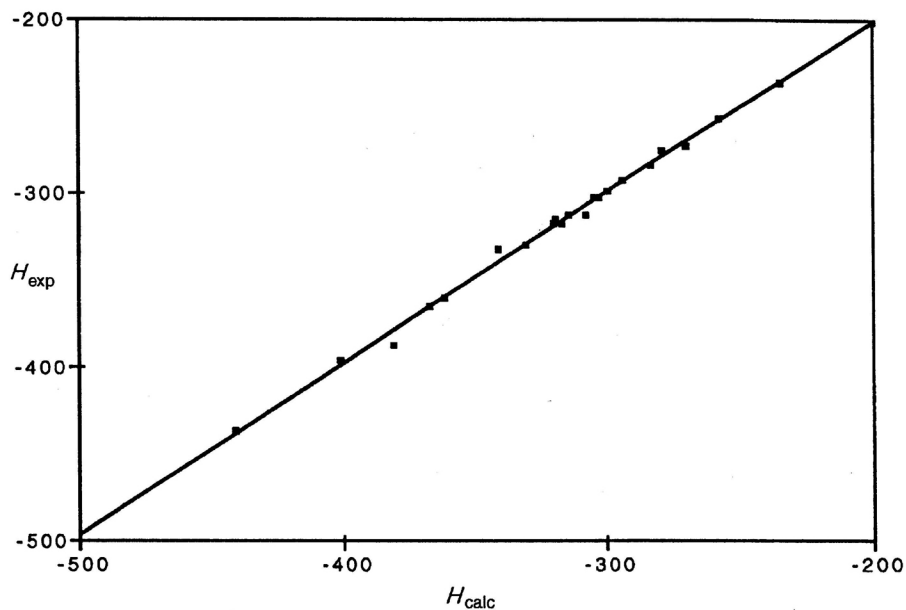


Figure 3c.

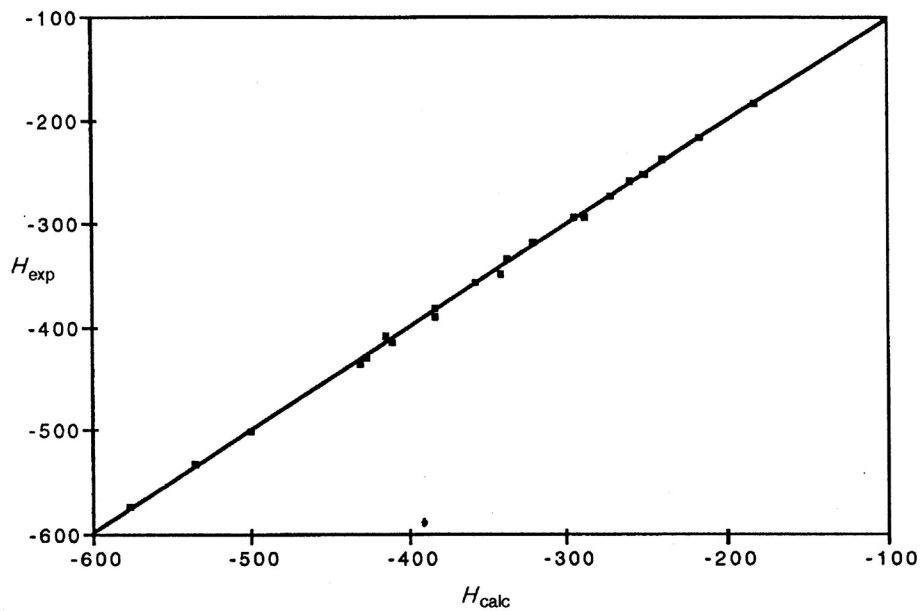


Figure 3d.

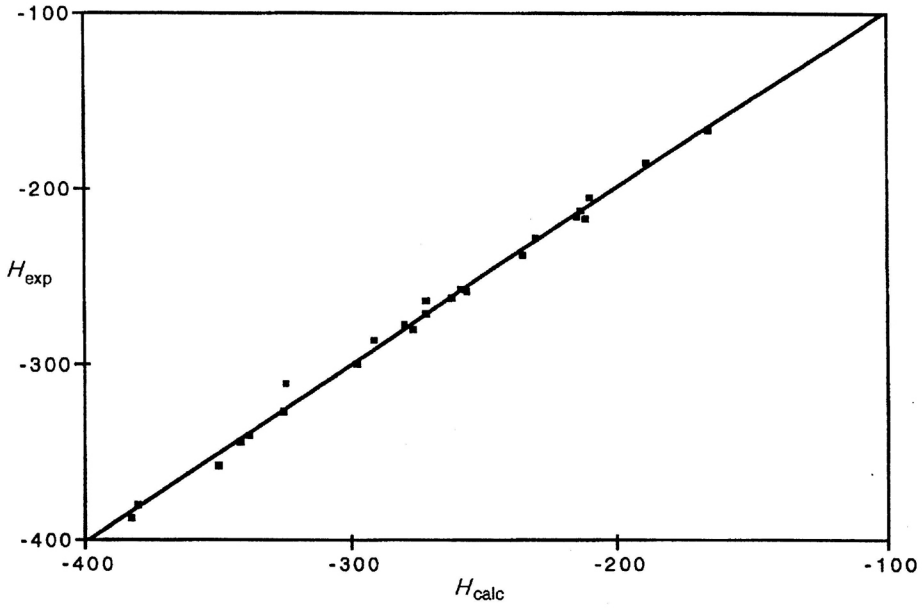


Figure 3e.

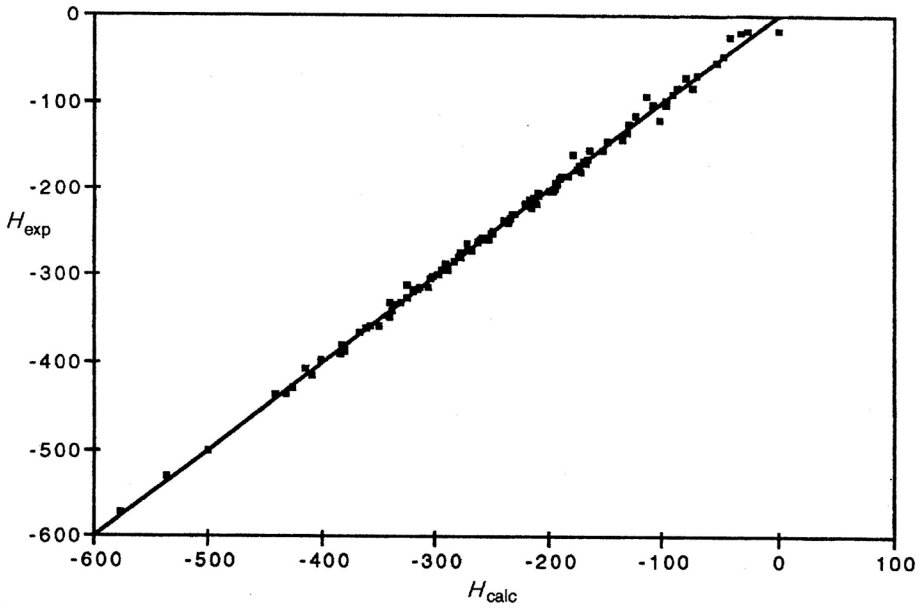


Figure 3f.

TABLE III  
Regression statistics

	<i>n</i>	<i>r</i>	<i>s</i>	<i>F</i>
amides	18	0.9512	11.62	372
alkanes	32	0.9973	3.37	5883
alcohols	20	0.9983	3.16	5961
ethers	20	0.9994	3.64	17187
aldehydes	22	0.9971	4.70	3804
all	120	0.9986	5.67	43284

Regression equation

amides	0.9875 H - 0.5647
alkanes	1.0209 H + 3.4617
alcohols	0.9817 H - 5.2060
ethers and ketones	0.9915 H - 3.4639
aldehydes	1.0084 H + 2.2931
all	0.9995 H - 0.1944

1 is that in each class of compounds there are structures of considerably different size; thus, the calculated and experimental values span large domains, resulting in good coefficients of correlation. However, if we compare the standard errors, then it is immediately clear that amides have not been adequately predicted. The same is again visible if we compare Fisher *F* ratio which is for the class of amines considered relatively small relative to *F* values for other classes of compounds. Overall regression statistics looks fine but it obscures the limited reproducibility of the experimental heats of formation for amines.

As it can be seen, except for amines, the correlation between the calculated and experimental heats of formation is very satisfactory. Amines clearly present a challenge. We expect that future work may bring some clarification as to why this particular group of compounds does not produce a better correlation.

### CONCLUDING REMARKS

From theoretical methods of quantum mechanics, we derived the relation between the charge distribution and the molecular energy. Within the topological approach we proposed an additive scheme<sup>8</sup> of only atomic data for the parametrization of molecular heats of formation. The error of this model is in the same order as those derived from purely empirical para-

metrizations. The main advantage will be realized in the extension of this procedure to include other elements.

We hope to improve the model on the basis of physically derived quantities of the chemical bonds here not explicitly included in the approach.

## REFERENCES

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## SAŽETAK

### Zašto je topološki pristup u kemiji tako uspješan?

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Teorija grafova upotrebljava se u kemiji za opis struktura molekula, kemijskih reakcija i u istraživanjima odnosa između strukture i svojstava. S druge strane, kvantno-kemijski pristup molekulskoj strukturi također daje izraze za opis molekulskih svojstava. Dosad je malo učinjeno na povezivanju tih dvaju pristupa i istraživanju odnosa između približnog opisa molekulskih svojstava i elektronske strukture kemijskih spojeva izračunane kvantno-mehanički. Predstavljamo grafteorijsku shemu za izračunavanje toplina stvaranja zasićenih spojeva zasnovanu na atomskim nabojima izračunanim kvantno-mehanički.