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Quantitative Structure–Property Relationship: XIV.[1] Properties of Derivatives of Saturated Hydrocarbons and Benzene, Containing Several Polar Groups

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Abstract — The previously suggested quantitative structure–property relationship was applied to estimate the properties of derivatives of saturated hydrocarbons and benzene, containing several polar groups. The boiling points, $\log P$ values (where P is the distribution factor in the octanol–water system), and solvatochromic parameters were calculated for a series of polyhydric alcohols, polyphenols, and isoelectronic chloro derivatives of saturated hydrocarbons and benzene. The calculated values are in good agreement with the experiment. A satisfactory correlation between these properties allows in some cases estimation of properties using a quantitative property–property relationship instead of a structure–property relationship.

In the previous papers [2–5], we described a quantitative structure–property relationship describing various properties of diverse classes of organic compounds with a good accuracy. If saturated hydrocarbon molecules are considered as systems consisting of similar fragments that do not noticeably interact with each other, then their properties can be estimated using a small number of parameters. In going to compounds differing from saturated hydrocarbons by the presence of a certain polar group X, a "nonuniformity" arises which, however, can be described by introducing a few additional parameters. In this case, all intramolecular interactions appear to be weak, and the intermolecular interactions of polar groups X···X, though being stronger, give a small number of contributions, so that local perturbations brought about by one group X can be described fairly simply. However, the pattern becomes different in molecules containing several polar groups X: Strong X···X interactions alter the set of equilibrium conformers as compared to the corresponding saturated hydrocarbons, so that it becomes necessary not only to introduce parameters describing the contributions of groups X, but also to redetermine all the parameters for the hydrocarbon moiety, i.e., to solve a new problem. Furthermore, experimental data for such molecules are often insufficient or lacking.

In this work we apply the quantitative structure–property relationship to estimate various properties of polyhydric alcohols and isoelectronic chloro derivatives of saturated hydrocarbons, and also of the related aromatic compounds. It is appropriate to divide the general problem of estimating properties of such compounds into several independent subproblems, some of which can be solved using the previous experience: (1) for molecules with a constant relative arrangement of polar groups and variable hydrocarbon moiety; (2) for molecules in which the polar groups are arranged along the whole hydrocarbon chain; (3) for molecules containing two polar groups in different positions; (4) for molecules containing several polar groups irregularly arranged in the hydrocarbon chain; and (5) for benzene derivatives with several polar groups in different positions.

Molecules with a constant relative arrangement of polar groups can be considered as R–Y molecules, where Y is the moiety containing polar groups (e.g., Y = –XCH–XCH–). The solution of a similar problem was described in [5]. Using this solution, we estimated certain properties of R_1–CHX–CHX–R_2 molecules. The representation of properties is described in Table 1, and the boiling points, $\log P$ values (P is the distribution factor in the octanol–water system), and solvatochromic parameters $E_T(30)$ for some diols, and also the boiling points of isoelectronic alkylene dichlorides are given in Table 2. The experimental data are reproduced with a good accuracy using a simple approach.

It is interesting to compare the boiling points of isoelectronic molecules. The boiling points of hydrocarbons and their chloro derivatives vary in the same

[1] For communication XIII, see [1].

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Table 1. Representation of properties of molecules with a constant arrangement of polar groups (R_1–CHX–CHX–R_2)

No.	Molecule	Property
1	$CH_2X–CH_2X$	A
2	$CH_2X–CHX–CH_3$	$A + \alpha^*$
3	$CH_3–CHX–CHX–CH_3$	$A + 2\alpha^*$
4	$CH_2X–CHX–CH_2–CH_3$	$A + \alpha^* + \gamma$
5	$CH_3–CHX–CHX–CH_2CH_3$	$A + 2\alpha^* + \gamma$

direction, increasing as the molecular size grows, whereas the boiling points of diols vary in a different manner. This may be due to the following fact. The Cl atoms, like CH_3 groups, only weakly interact with any groups of surrounding molecules, whereas intra- and intermolecular interactions between the OH groups are much stronger. The boiling point depends on intermolecular interactions of OH groups. A CH_3 group introduced into a 1,2-ethanediol molecule (to obtain 1,2-propanediol) sterically hinders interaction of the adjacent OH groups with the environment. As a result, the intermolecular interactions become weaker, and the boiling point decreases. Introduction of two CH_3 groups (2,3-butanediol) enhances this effect. Further increase in the length of the hydrocarbon radical does not cause stronger shielding of the OH groups and does not noticeably affect the conditions for interaction with the environment, but the intermolecular interactions involving the hydrocarbon moiety become stronger, and the boiling points increase. Similar trends are observed with monohydric aliphatic alcohols: *tert*-butanol boils at a lower temperature than *n*-butanol, which also reflects changes in intermolecular interactions. In hydrocarbons and their chloro derivatives, this trend is less pronounced. Except 1,2-ethanediol whose isoelectronic analogs are 1,2-dichloroethane and *n*-butane, all the isoelectronic molecules listed in Table 2 are branched. Their boiling points are lower than those of the linear isomers, because branching alters the conditions for interaction of various groups with the environment. This trend, however, is less pronounced than with alcohols.

Molecules in which the polar groups are arranged along the whole hydrocarbon chain, i.e., molecules of the type $XCH_2–(CHX)_n–CH_2–X$, can be considered as linear molecules consisting of similar fragments. Estimation of properties of such molecules is described in detail in [2, 3], and any property can be represented in the following form:

$$P(n) = n\alpha + (n - 1)\beta + (n - 2)\gamma + (n - 3)\delta + \ldots \quad , (1)$$

where n is the number of fragments in the molecule; α, single-fragment contribution to a property; β, con-

Table 2. Properties of molecules with a constant arrangement of polar groups (R_1–CHX–CHX–R_2)

Compound,[a] parameter	X = OH						X = Cl, T_b, °C		X = CH_3, T_b, °C, experiment [6, 7]
	T_b, °C		log P		$E_T(30)$				
	experiment [6, 7]	this work	experiment [8]	this work	experiment [9]	this work	experiment [10]	this work	
1	198	198	–1.36	–1.36	55.4	55.6	83.5	83.5	–0.5
2	189	189	–0.92	–0.93	54.1	53.8	98.0	99.2	27.8
3	180	180	(–0.50)[b]	–0.50	51.8	52.0	116.0	114.9	49.7
4	192	192	(–0.50)[b]	–0.50	52.6	52.6	125.0	123.9	64.0
5							138.5	139.6	89.8
r		1.000		0.9999		0.9891		0.9987	
s		0		0.0082		0.4082		1.5916	
A		198.0 ± 0		–1.3567 ± 0.0075		55.5667 ± 0.3727		83.4667 ± 1.3630	
α^*		–9.0 ± 0		0.4300 ± 0.0058		–1.8000 ± 0.2887		15.7000 ± 1.0066	
γ		3.0 ± 0		0.4267 ± 0.0094		–1.1667 ± 0.9714		29.7333 ± 1.5377	

[a] Compound numbers are the same as in Table 1. [b] Values accepted by us; they are close to those calculated using the approach described in [11].

Table 3. Boiling points and distribution factors in the octanol–water system of molecules in which the polar groups X are arranged along the whole hydrocarbon chain

Molecule, parameter	X = OH				X = Cl,	
	T_b, °C		log P		T_b, °C	
	experiment [6, 7]	this work	experiment [8]	this work	experiment [10]	this work
CH_3X	65	65	–0.74	–0.74	–24.2	–24.2
$XCH_2–CH_2X$	198	206	–1.36	–1.34	83.5	84.9
$XCH_2–CHX–CH_2X$	290 (dec.)	273	–1.76	–1.80	156.0	153.2
$XCH_2–(CHX)_2–CH_2X$	330	338	–2.29	–2.27	220.0	221.4
r		0.9946		0.9989		0.9998
s		21.22		0.0531		3.4701
α		65.0000 ± 21.2289		–0.7400 ± 0.0531		–24.2000 ± 3.4701
β		76.6667 ± 46.6714		0.1417 ± 0.1167		133.3167 ± 7.6290
γ		–75.6667 ± 38.7585		0.1333 ± 0.0969		–40.8667 ± 6.3355

tribution corresponding to interaction of fragments i and $i + 1$; γ, contribution corresponding to interaction of fragments i and $i + 2$; etc. Unfortunately, we found in the literature only four test examples for polyhydric alcohols. Therefore, Eq. (1) should not contain more than three parameters. The estimates of properties of $XCH_2–(CHX)_n–CH_2X$ molecules (X = OH or Cl) obtained in this approximation are listed in Table 3. The calculated properties are well consistent with the experiment, except the boiling points of polyhydric alcohols. Glycerol and erythritol occur as equilibrium mixtures of conformers characterized by different possibilities for intra- and intermolecular hydrogen bonding, which, apparently, makes it necessary to consider 1···4 interactions; is impossible here because of the lack of the experimental data.

For molecules containing two polar groups in different positions, it is necessary to take into account both interaction of these groups and possible changes in the conformations of the hydrocarbon moiety. Apparently, the intra- and intermolecular X···X interactions will be different in different molecules. For example, the preferable intramolecular H bonds in 1,3-propanediol significantly differ from the H bonds in 1,2-ethanediol and 1,4-butanediol. At present, there are no clear theoretical concepts concerning the dependence of the correction for interaction of polar groups on their mutual arrangement, so that specific parameters should be determined in each particular case. This is impossible because of the lack of the required set of experimental data. To circumvent these problems, we considered a property of an $X–R_1–R_2–X$ molecule as follows:

$$P_{X–R_1–R_2–X} = P_{H–R_1–X} + P_{H–R_2–X} + \beta + n_{13}\gamma + n_{14}\delta, \quad (2)$$

where $R_1 + R_2 = R$ is the hydrocarbon part of the molecule; $P_{H–R_i–X}$, property of the $H–R_i–X$ molecule; β, correction for interaction of the adjacent (i and $i + 1$) C atoms forming the bond between R_1 and R_2; γ, correction for 1···3 interaction of the same atoms, etc.; and n_{13} (n_{14}), number of γ (δ) contributions.

Since in R–X molecules the correction for introduction of group X is not constant and decreases as R is increased, in Eq. (2) the contribution of interaction of groups X will be different even at constant β, γ, and other parameters. Using this approach, we calculated the boiling points and log P values for certain dihydric alcohols in which the OH groups are located at different distances from each other, and also for the corresponding dichloro derivatives. The results (Table 4) show that Eq. (2) allows estimation of the properties of such molecules with a good accuracy.

The problem of estimating the properties of molecules containing several polar groups irregularly arranged along the hydrocarbon chain will not be considered in this work because of the lack of the required experimental data.

Whereas estimation of properties of saturated hydrocarbon derivatives involves problems associated with the existence of several conformers, each characterized by specific values of all the corrections starting from δ, in such "rigid" molecules as benzene derivatives these corrections are equal, and therefore this class of compounds is better suited for demonstrating

Table 4. Boiling points and distribution factors in the octanol–water system of molecules containing two polar groups X in different positions

Molecule, parameter	X = OH				X = Cl, T_b, °C	
	T_b, °C		log P			
	experiment [6, 7]	this work	experiment [8]	this work	experiment [10]	this work
XCH_2–CH_2X	198	197	–1.36	–1.34	83.5	84.6
XCH_2–CH_2–CH_2X	213	215	–1.04	–1.08	125.0	122.9
XCH_2–$(CH_2)_2$–CH_2X	232	214	–0.83	–0.81	162.0	161.2
XCH_2–$(CH_2)_3$–CH_2X	242	241	–0.40	–0.40	178.0	181.7
XCH_2–$(CH_2)_4$–CH_2X	250	250			204.0	202.2
r		0.9993		0.9979		0.9987
s		1.1339		0.0449		3.4048
β		197.4286 ± 1.0321		–1.3417 ± 0.0410		89.5571 ± 3.0993
γ		17.2143 ± 0.7667		0.2650 ± 0.0318		38.3286 ± 2.3021
δ		4.2875 ± 0.7667		0.4117 ± 0.0608		20.4714 ± 2.3021

the potentialities of the suggested quantitative structure–property relationship. By analogy with [4], we calculated the boiling points and log P values for hydroxy and chloro derivatives of benzene (Table 5); the results are in good agreement with the experiment.

Thus, application of the quantitative structure–property relationship to estimating certain properties of polyhydric alcohols, polyphenols, and isoelectronic chloro derivatives of saturated hydrocarbons and benzene involved the greatest problems in the case of molecules containing two polar groups in different positions, which made us to look for a way around. To avoid such situations, we can take advantage of the

Table 5. Boiling points and distribution factors in the octanol–water system of benzene derivatives containing polar groups X in various positions

Molecule,[a] parameter	X = OH				X = Cl			
	T_b, °C		log P		T_b, °C		log P	
	experiment [6, 7]	this work	experiment [8]	this work[b]	experiment [12]	this work	experiment [8]	this work[b]
BZ	80.1	80.8	2.1	2.2/2.1	80.1	84.3	2.1	2.2/2.1
1-XBZ	182	180	1.5	1.4/1.4	132	130	3.0	2.8/2.9
1,2-X_2BZ	243	244	0.9	0.9/1.0	181	177	3.4	3.5/3.7
1,3-X_2BZ	279	279	0.8	0.8/0.7	172	171	3.5	3.5/3.4
1,4-X_2BZ	286	286	0.6	0.6/0.7	174	170	3.4	3.4/3.5
1,2,3-X_3BZ	309	308	0.7	0.7/0.5	218	219	4.0	4.0/4.1
1,2,4-X_3BZ					213	212	4.0	4.0/4.0
1,3,5-X_3BZ					208	207	4.0	4.1/4.0
1,2,3,4-X_4BZ					254	254	4.6	4.5/4.6
1,2,3,5-X_4BZ					246	248	4.7	4.6/4.5
1,2,4,5-X_4BZ					243	247	4.5	4.5/4.4
X_5-BZ					277	284	5.0	5.0/4.9
X_6-BZ					322	315	5.5	5.5/5.6

Table 5. (Contd.)

Molecule,[a] parameter	X = OH				X = Cl			
	T_b, °C		log P		T_b, °C		log P	
	experiment [6, 7]	this work	experiment [8]	this work[b]	experiment [12]	this work	experiment [8]	this work[b]
r		0.9999		0.9976/0.9860		0.9982		0.9980/0.9940
s		2.6750		0.0925/0.1107		4.6449		0.0705/0.1030
A		80.7687 ± 2.5901		2.1531 ± 0.0896		84.2564 ± 3.9201		2.1817 ± 0.0595
α^*		99.0250 ± 2.6750		–0.7625 ± 0.0925		46.1153 ± 2.2785		0.6546 ± 0.0346
γ_o		–34.9812 ± 2.5901		0.2981 ± 0.0896		0.8471 ± 1.7020		–0.0405 ± 0.0258
γ_m		0.4500 ± 3.7830		0.1950 ± 0.1308		–5.2216 ± 1.6495		–0.0233 ± 0.0250
γ_p		7.6813 ± 4.5847		–0.0381 ± 1.1585		–6.4566 ± 2.6200		–0.0823 ± 0.0398

[a] The formulas of benzene and its derivatives are given in the simplified form [13]: benzene is denoted as BZ, and the locants indicate the positions of polar groups X in the benzene ring. [b] The log P values calculated using the property–property relationship log $P = k_1 + k_2 T_b$ (k_1 = 2.6600 ± 0.1402, k_2 = –0.0068 ± 0.0006 for hydroxybenzenes; k_1 = 1.0015 ± 0.1025, k_2 = 0.0142 ± 0.0005 for chlorobenzenes) are given in the denominator.

fact that the properties of these malecules show a good mutual correlation (Tables 1–5). For example, the coefficient of the correlation between log P and boiling point for 1,3-ethanediol, glycerol, and erythritol molecules (Table 3) is 0.9787; for 1,2-ethanediol, 1,3-propanediol, 1,4-butanediol, 1,5-pentanediol, and 1,6-hexanediol molecles (Table 4), it is 0.9856; and for polyphenols (Table 5), it is 0.9860. This means that, if the boiling points are known, we can estimate with a reasonable accuracy the log P values for these molecules and their other properties. In Table 5 we give as example the log P values calculated by the relationship log $P = k_1 + k_2 T_b$. These values are also in good agreement with the experiment. Thus, when it is difficult to determine certain parameters, we can estimate the property of interest using, instead of a structure–property relationship, a property–property relationship which implicitly takes into account all these parameters.

REFERENCES

1. Golovanov, I.B. and Zhenodarova, S.M., *Zh. Obshch. Khim.*, 2003, vol. 73, no. 4, p. 553.
2. Golovanov, I.B. and Tsygankova, I.G., *Zh. Obshch. Khim.*, 1999, vol. 69, no. 8, p. 1275.
3. Golovanov, I.B. and Zhenodarova, S.M., *Zh. Obshch. Khim.*, 2003, vol. 73, no. 1, p. 90.
4. Golovanov, I.B. and Zhenodarova, S.M., *Zh. Obshch. Khim.*, 2003, vol. 73, no. 2, p. 260.
5. Golovanov, I.B. and Zhenodarova, S.M., *Zh. Obshch. Khim.*, 2003, vol. 73, no. 3, p. 400.
6. Stull, D.R., Westrum, E.F., and Sinke, G.C., *The Chemical Thermodynamics of Organic Compounds*, New York: Wiley, 1969.
7. *CRC Handbook of Chemistry and Physics*, Lide, D.R., Ed., Boca Raton: CRC, 1993–1994, sect. 3.
8. Hansch, C., Leo, A., and Hoekman, D., *Exploring QSAR*, Washington: Am. Chem. Soc., 1995, vol. 2.
9. Reichardt, Ch., *Solvents and Solvent Effects in Organic Chemistry*, Weinheim: VCH, 1988.
10. *Beilsteins Handbuch der organischen Chemie*, Berlin: Springer, 1918, vol. 1, pp. 105–144.
11. Golovanov, I.B., Ivanitskii, G.R., and Tsygankova, I.G., *Dokl. Ross. Akad. Nauk*, 1998, vol. 359, no. 6, p. 823.
12. *Beilsteins Handbuch der organischen Chemie*, Berlin: Springer, 1918, vol. 5, pp. 201–205.
13. Kier, L.B. and Hall, L.H., *Molecular Connectivity in Chemistry and Drug Research*, New York: Academic, 1976.